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(54) **CARDIAC PRESSURE OVERLOAD ASSOCIATED GENES**

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C12M 1/34 (2006.01)

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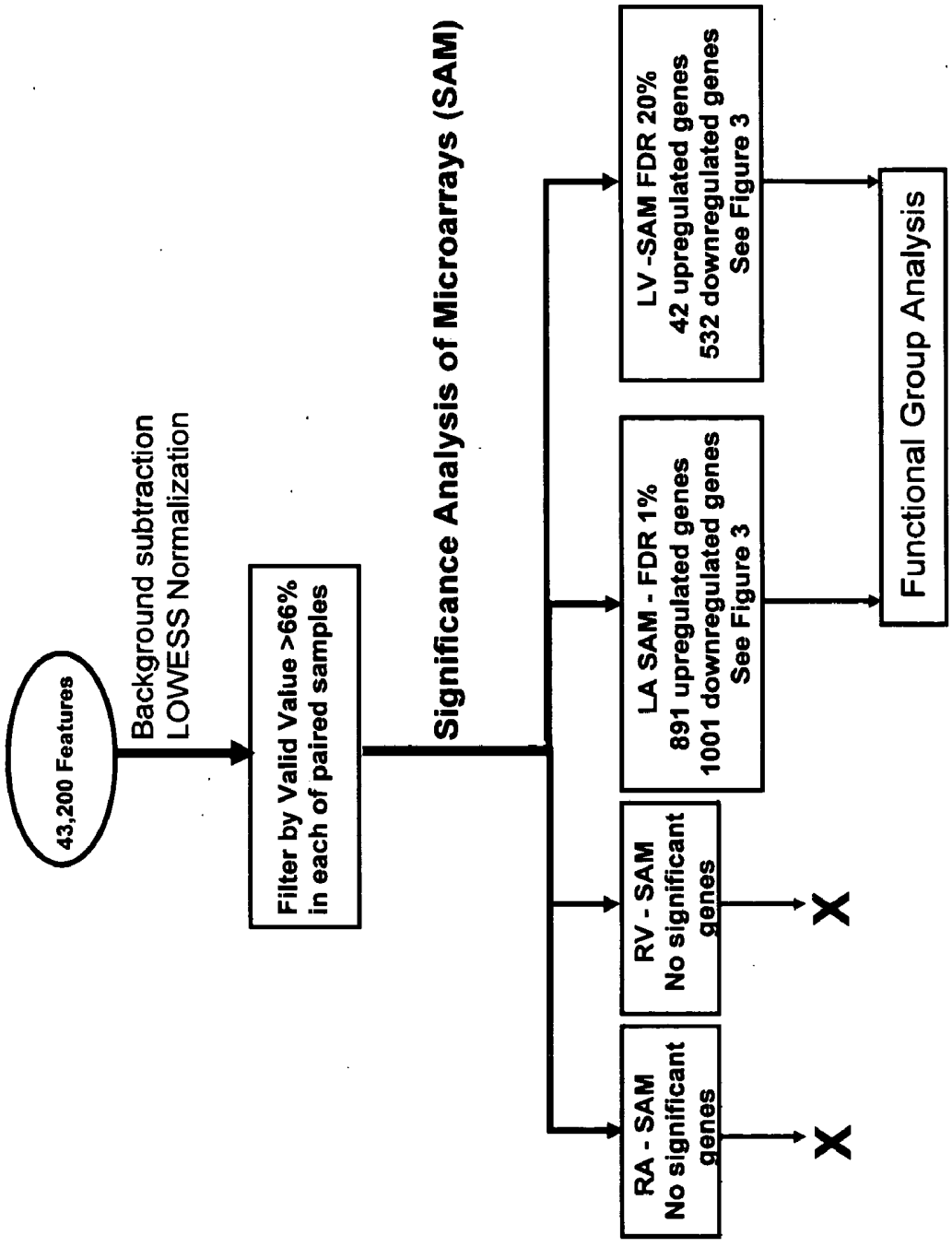
(57) **ABSTRACT**

The present invention identifies genes whose gene products are differentially expressed pressure overload of the heart. The invention provides methods for diagnosing or assessing an individual's susceptibility to heart failure from many etiologies, as well as the presence and severity of hypertrophy, chamber enlargement, or systolic heat failure. Also provided are therapeutic methods for treating a heart patient or methods for prophylactically treating an individual susceptible to heart failure. Additionally, the invention describes screening methods for identifying agents that can be administered to treat individuals that have suffered a heart attack or are at risk of heart failure.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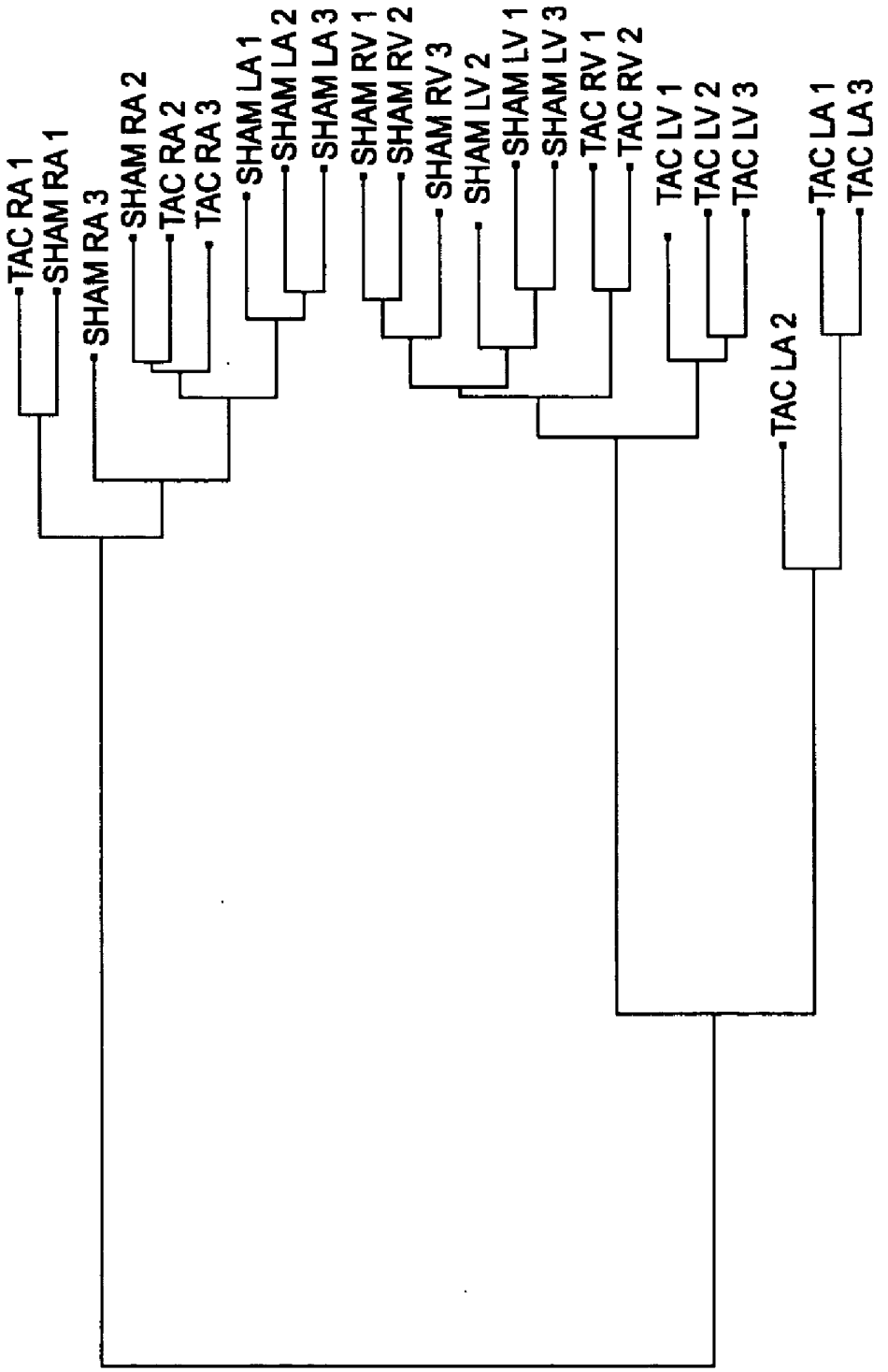
in each of paired samples
Significance Analysis of Microarrays (SAM)
LV -SAM FDR 20%
42 upregulated genes
532 downregulated genes
See Figure 3
LA SAM - FDR 1%
891 upregulated genes
1001 downregulated genes
See Figure 3
RV - SAM
No significant
genes
RA - SAM
No significant
genes
Functional Group Analysis

FIG. 1

FIG. 2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SHAM RA 3
SHAM RA 2
TAC RA 2
TAC RA 3
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SHAM LV 2
SHAM LV 1
SHAM LV 3
TAC RV 1
TAC RV 2
TAC LV 1
TAC LV 2
TAC LV 3
TAC LA 2
TAC LA 1
TAC LA 3

Heatmap LA	Top 50 Positive Significant Genes - Increased Transcription TAC LA FDR 0.01			
TAC LA SHAM LA	Gene Name	Gene ID	Score(d)	Fold Increase
[redacted]	bone morphogenetic protein 4	AA498724	26.255	5.68709
	RIKEN cDNA 1110007F23 gene	AV083352	25.741	9.37273
	neuropilin	BG073453	24.320	3.32496
	EST	AW547583	22.959	7.725
	adrenomedullin	BG063461	21.136	2.44953
	EST	AW550960	19.855	9.11485
	Unsequenced EST	412394	18.330	4.03427
	frizzled related protein	AV089650	15.649	5.14052
	hypoxia inducible factor 1, alpha subunit	AV068685	15.091	2.53258
	expressed sequence C80501	BG066820	14.537	1.7801
	procollagen, type IV, alpha 2	AV021908	14.059	8.2334
	matrix metalloproteinase 23	AV015188	13.705	2.613
	ribosome binding protein 1	AV012322	13.692	1.83212
	epithelial membrane protein 1	X98403	13.587	5.24265
	neuroblastoma, supression of tumorigenicity 1	AI325886	13.277	2.60809
	ESTs	AV032403	12.615	2.31331
	Unsequenced EST	410619	12.577	1.97239
	DNA segment, Chr 8, Brigham & Women's Genetic's 111	AV083741	12.395	4.11124
	guanylate cyclase 1, soluble, beta 3	AV029404	12.251	2.41285
	ESTs	BG073461	11.903	4.05199
	Unsequenced EST	433064	11.815	1.44531
	tubulin, beta 5	AV109614	11.657	1.99179
	insulin-like growth factor binding protein 7	AV013851	11.614	3.032
	chemokine (C-X-C) receptor 4	D87747	11.407	4.14082

FIG. 3A

	EST	W33396	11.403	1.61638
	EST	BG071255	11.228	2.05956
	mesenchyme homeobox 1	AV307023	11.160	2.7277
	PDZ and LIM domain 1 (elfin)	BG064108	11.025	2.26198
	adenylate cyclase 7	AA797434	10.995	1.96661
	frizzled-related protein	AV089650	10.881	6.12984
	mannosidase 1, alpha	AV026219	10.738	2.23747
	Harvey rat sarcoma oncogene, subgroup R	AA123466	10.696	1.67121
	annexin A5	AV087971	10.635	2.44345
	RIKEN cDNA 1110007F23 gene	BG074573	10.540	8.20649
	RAB7, member RAS oncogene family	AV032302	10.508	1.66445
	EST	AV036347	10.471	1.81269
	calponin 2	AV025199	10.466	3.671
	Mus musculus, clone IMAGE:2647796, mRNA	AV011175	10.451	1.64082
	**N-acetylated alpha-linked acidic dipeptidase	BG069303	10.260	2.13623
	eukaryotic translation initiation factor 4E	AV094728	9.891	2.36476
	extracellular matrix protein 1	AV085019	9.887	2.46146
	RIKEN cDNA 2610528A15 gene	BG073520	9.883	1.87944
	amyloid beta (A4) precursor protein	AV028985	9.791	2.57737
	serine (or cysteine) proteinase inhibitor, clade I (neuros...)	AV052090	9.790	2.31567
	transforming growth factor beta 1 induced transcript 1	AV006479	9.758	2.79512
	RIKEN cDNA 3230402E02 gene	AV140438	9.698	1.91583
	granulin	AV134035	9.674	2.56818
	RIKEN cDNA 1110020C13 gene	AV071424	9.658	1.6748
	Unsequenced EST	413096	9.650	1.65344
	extracellular matrix protein 1	BG075104	9.603	1.96784
	fibulin 2	BG073227	9.535	5.40206

FIG. 3B

FIG. 3C

Heatmap LA	Top 50 Negative Significant Genes - Decreased Transcription TAC LA FDR 0.01			
TAC LA SHAM LA	Gene Name	Gene ID	Score(d)	Fold Decrease
	Unsequenced EST	411432	-20.537	1.668
	RIKEN cDNA 1810036J22 gene	AV113916	-19.446	2.089
	RIKEN cDNA 0610025I19 gene	AV085433	-17.568	4.519
	zinc finger protein 216	BG066068	-17.411	1.797
	EST	AV084337	-15.846	4.456
	RIKEN cDNA 1110020I04 gene	AV051530	-14.920	3.256
	cold inducible RNA binding protein	BG073558	-14.830	2.634
	RIKEN cDNA 6720475J19 gene	BG073712	-13.956	4.144
	EST	BG065742	-13.009	1.761
	serologically defined colon cancer antigen 28	BG065578	-12.464	5.362
	FK506 binding protein 3 (25kD)	AV134155	-12.241	2.153
	ESTs	AI840562	-12.067	2.037
	ESTs	AI839959	-11.808	3.839
	lipoprotein lipase	AV006290	-11.425	2.334
	synaptobrevin like 1	AV113528	-11.352	2.060
	RIKEN cDNA 6030457N17 gene	AV094720	-11.180	2.092
	Unsequenced EST	411277	-11.089	2.781
	RIKEN cDNA 1500004O06 gene	AV084141	-10.933	1.861
	nuclear distribution gene C homolog (Aspergillus)	BG073422	-10.863	1.775
	ESTs	AV087279	-10.847	2.700
	RIKEN cDNA 2310079PP10 gene	BG069582	-10.795	3.197
	EST	AV092327	-10.731	2.454
	Unsequenced EST	412922	-10.702	2.732
	peroxiredoxin 3	AA168985	-10.690	2.396

FIG. 3D

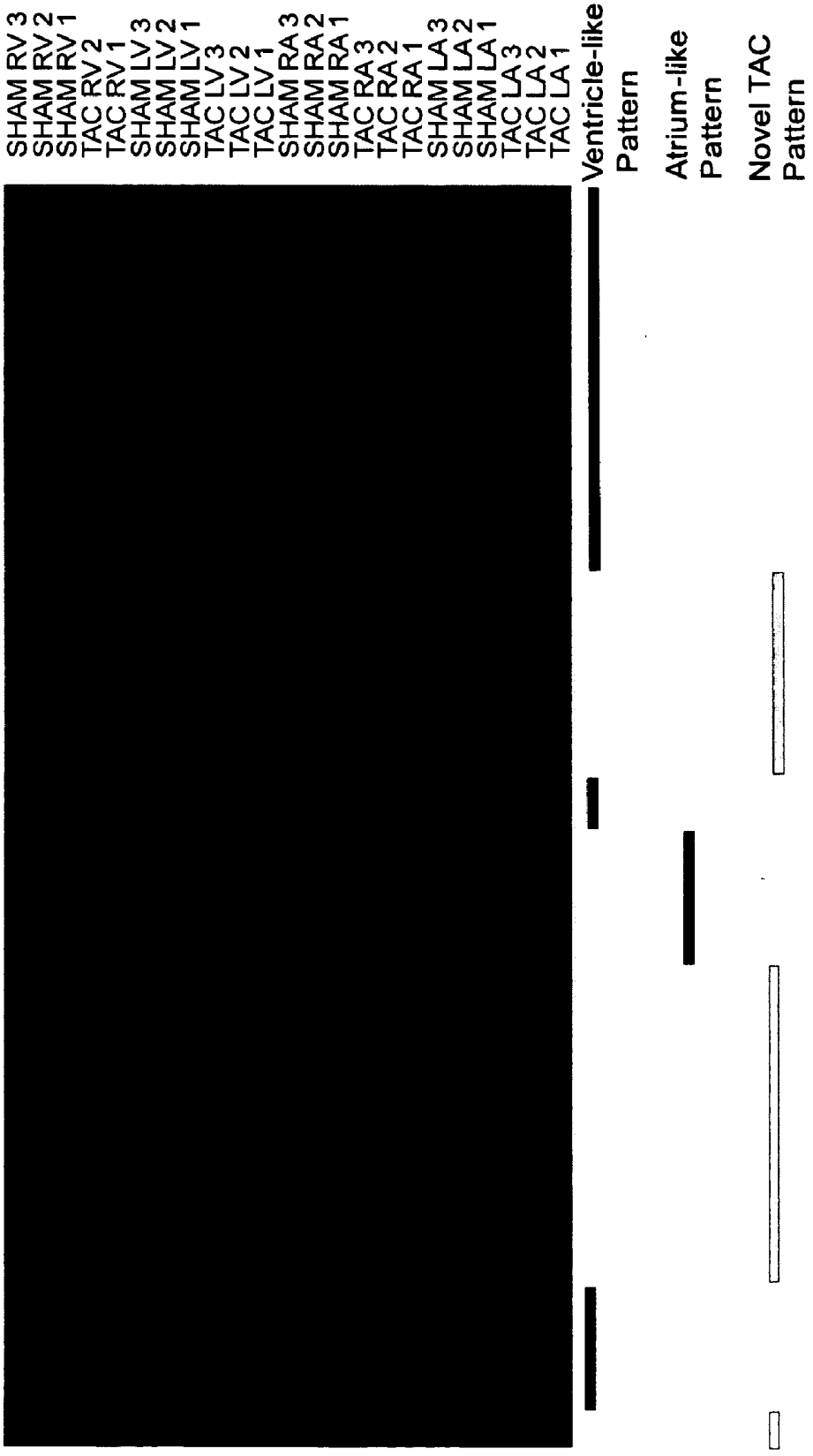
	RIKEN cDNA 2310039H15 gene	AV088685	-10.655	2.360
	RIKEN cDNA 5830498C14 gene	AV012853	-10.643	2.256
	receptor-associated protein of the synapse, 43 kDa	AV061434	-10.619	2.413
	ESTs	BG073667	-10.485	1.791
	steroid 5 alpha-reductase 2-like	AV084563	-10.289	2.146
	Unsequenced EST	432064	-10.137	3.743
	RIKEN cDNA 4933411H20 gene	AV094491	-10.133	4.209
	cardiac Abnormality/abnormal facies (CATCH22),microdel...	AV041840	-9.984	2.474
	phytanoyl-CoA hydroxylase	AV084314	-9.878	3.516
	Mus musculus 10 day old male pancrease cDNA, RIKEN full–	AV058496	-9.867	2.324
	carboxylesterase 3	BG072503	-9.855	5.735
	DNA primase, p49 subunit	AV113083	-9.822	2.021
	RIKEN cDNA 1200015P04 gene Homeodomain-only (Hop)	AV068725	-9.796	4.485
	expressed sequence AI314967	BG075147	-9.700	1.700
	H2A histone family, member Y	C75971	-9.633	3.334
	RIKEN cDNA 2310001N14 gene	AV083256	-9.471	2.820
	RIKEN cDNA 1810018M11 gene	AV018921	-9.416	1.649
	RIKEN cDNA 4933436C10 gene	AI854103	-9.222	3.913
	cytochrome c oxidase, subunit VIc	AV149855	-9.193	2.687
	RIKEN cDNA 2610041P16 gene	BG063943	-9.172	2.553
	heme oxygenase (decycling) 1	AV083964	-9.130	1.736
	acetyl-Coenzyme A dehydrogenase, long-chain	BG066557	-9.091	2.493
	solute carrier family 1, member 7	AV006313	-9.007	1.846
	cytochrome c oxidase subunit VIIb	AV093625	-8.988	2.538
	ATP synthase, H+ transporting, mitochondrial F0 complex	AV088674	-8.968	2.061
	Unsequenced EST	412659	-8.871	4.094
	RIKEN cDNA 2610028H24 gene	AU041304	-8.838	2.331

FIG. 3E

Heatmap LV		Top 42 Positive Significant Genes Increased Transcription TAC LV - FDR 0.20			
TAC LV	Sham LV	Gene Name	Gene ID	Score(d)	Fold Increase
		Unsequenced EST	432492	8.881	1.80763
		RIKEN cDNA 2700083B06 gene	AV050682	8.310	2.07196
		Unsequenced EST	411923	7.401	1.52787
		adenylate cyclase 7	BG063167	7.400	2.41092
		frizzled-related protein	AV089650	6.686	1.83742
		procollagen C-proteinase enhancer protein	AV084561	6.562	1.98521
		**N-acetylated alpha-linked acidic dipeptidase 2	BG069303	6.359	1.22554
		EST	U20156	6.130	2.27447
		RIKEN cDNA 1110054M18 gene	AV015246	6.071	2.74743
		ESTs, Weakly similar to D2045.2.p [Caenorhabditis elegans] [C.elegans]	AI851039	6.060	1.34369
		N-acetylated alpha-linked acidic dipeptidase 2	BG066563	5.867	1.42168
		EST	AW547864	5.473	1.61217
		low density lipoprotein receptor-related protein 1	BG071948	5.453	2.3717
		RIKEN cDNA 2510010F10 gene	AV141532	5.194	2.35768
		expressed sequence AW494241	BG070007	5.178	1.71397
		Unsequenced EST	413203	5.165	2.04177
		four and a half LIM domains 1	AV083596	5.152	2.71956
		Mus musculus uridindiphosphoglucosepyrophosphorylase 2 (Ugp2) mRNA, c	AV085874	5.057	1.87525
		epithelial membrane protein 1	AI838613	5.049	4.46827
		ets variant gene 6 (TEL oncogene)	AV059438	5.016	3.0627
		RIKEN cDNA 1300018J16 gene	AI836568	4.923	2.66342
		**actin, gamma, cytoplasmic	BG072752	4.871	2.21337
		transforming growth factor, beta 2	BG067564	4.857	2.60932
		integrin beta 4 binding protein	BG073319	4.851	1.56309
		gap junction membrane channel protein beta 1	AV057141	4.834	1.4246
		**expressed sequence AU018638	BG072998	4.833	2.22487
		expressed sequence C79946	C79946	4.724	2.72331
		retinol binding protein 1, cellular	AA087526	4.670	2.12653
		RIKEN cDNA 2410002J21 gene	AI322274	4.590	1.60908
		Unsequenced EST	412218	4.527	1.59785
		small EDRK-rich factor 2	AV093704	4.505	1.5842
		heat shock protein, 70 kDa 3	AV223941	4.492	1.97766
		RIKEN cDNA 2510010F10 gene	AI851067	4.454	1.8533
		Mus musculus, clone IMAGE:3589087, mRNA, partial cds	BG065584	4.428	2.0797
		dystonin	AV083262	4.410	1.52849
		transforming growth factor, beta 2	AI574416	4.408	2.33766
		Unsequenced EST	413419	4.382	1.41333
		matrix metalloproteinase 2	AI836311	4.366	1.61224
		actin, alpha 2, smooth muscle, aorta	AV077699	4.343	2.09809
		EST	AW537378	4.319	1.35016
		heterogeneous nuclear ribonucleoprotein C	AW551778	4.299	2.14689
		prion protein dublet	BG073284	4.283	4.52034

FIG. 3F

Heatmap LV	Top 50 Negative Significant Genes Decreased Transcription TAC LV - FDR 0.20				
TAC LV Sham LV	Gene Name	Gene ID	Score(d)	Fold Decrease	
	granzyme B	AV038272	-23.621	1.82	
	Unsequenced EST	202908	-9.850	2.11	
	acetyl-Coenzyme A dehydrogenase, long-chain	AV029241	-9.704	1.74	
	RIKEN cDNA 2310005N03 gene	AV133799	-9.589	1.69	
	regulator of G-protein signaling 2	BG068533	-9.142	3.69	
	ESTs, Weakly similar to ZINC FINGER PROTEIN MLZ-4 [M.musculus]	AV086783	-9.097	1.46	
	Unsequenced EST	410956	-8.910	2.08	
	RIKEN cDNA 0610038N19 gene	BG066600	-8.805	1.40	
	RIKEN cDNA 2310079P10 gene	BG069582	-8.438	1.52	
	ESTs	BG076327	-8.423	2.38	
	glutathione S-transferase, mu 6	BG075231	-8.194	1.60	
	diacylglycerol O-acyltransferase 2	AV084679	-7.907	2.05	
	sorbitol dehydrogenase 1	AV103136	-7.628	1.64	
	target of myb1 homolog (chicken)	AV089758	-7.566	1.36	
	dodecenoyl-Coenzyme A delta isomerase (3,2 trans-enoyl-Coenzyme A isom	AV106338	-7.414	1.91	
	diacylglycerol O-acyltransferase 2	AI847556	-7.333	2.31	
	EST	AV032087	-7.206	2.05	
	RIKEN cDNA 0610005A07 gene	BG072517	-6.970	1.86	
	expressed sequence AW555814	BG065375	-6.920	2.11	
	tubulin, alpha 4	AA168671	-6.742	2.75	
	RIKEN cDNA 1200015P04 gene Homeodomain-only	AV067337	-6.719	2.13	
	syntrophin, acidic 1	AI838964	-6.675	1.47	
	EST	AV092810	-6.603	1.60	
	RIKEN cDNA 1810015C04 gene	BG070063	-6.455	1.89	
	Ly1 antibody reactive clone	AV034129	-6.393	1.78	
	RIKEN cDNA 2810403D23 gene	AV140294	-6.303	2.17	
	carnitine palmitoyltransferase 2	AV006197	-6.149	1.73	
	2,4-dienoyl CoA reductase 1, mitochondrial	AV088048	-6.148	2.07	
	Mus musculus, clone MGC:41265 IMAGE:1364804, mRNA, complete cds	AV049896	-6.124	1.54	
	RIKEN cDNA 0610033L03 gene	BG074425	-6.116	1.24	
	phospholipase A2, group V	BG063219	-5.905	2.19	
	RIKEN cDNA 2310032D16 gene	BG068791	-5.903	1.87	
	isovaleryl coenzyme A dehydrogenase	AV088137	-5.872	2.18	
	expressed sequence AU022809	AU022809	-5.728	1.22	
	RIKEN cDNA 2610207I16 gene	AV030438	-5.715	1.65	
	Unsequenced EST	333639	-5.650	1.83	
	CD59a antigen	AV133920	-5.638	1.63	
	methylmalonyl-Coenzyme A mutase	AV031545	-5.605	1.44	
	growth factor, erv1 (S. cerevisiae)-like (augmenter of liver regeneration)	AV140416	-5.596	1.77	
	suppressor of initiator codon mutations, related sequence 1 (S. cerevisiae)	AV042274	-5.592	1.54	
	basic FGF repressed, Zic binding protein	AV095032	-5.540	1.55	
	Unsequenced EST	413604	-5.535	2.19	
	EST	AW554432	-5.518	1.66	
	microtubule-associated protein 1 light chain 3	BG072065	-5.515	1.26	
	methylcrotonoyl-Coenzyme A carboxylase 1 (alpha)	AV057294	-5.451	1.33	
	RIKEN cDNA 2410004D18 gene	BG071211	-5.432	1.51	
	Unsequenced EST	201604	-5.391	1.28	
	signal transducer and activator of transcription 5B	AI838314	-5.389	1.30	
	adenylate cyclase 9	BG072288	-5.388	1.33	
	RIKEN cDNA 2600013N14 gene	AV033628	-5.388	1.26	
	transcription elongation factor A (SII), 3	AI322966	-5.355	1.59	
	lens epithelial protein	BG075251	-5.313	1.34	
	expressed sequence C76711	C76711	-5.290	2.77	
	RIKEN cDNA 1810073P09 gene	AV061385	-5.273	1.95	
	cell division cycle 37 homolog (S. cerevisiae)-like	AV042062	-5.260	1.70	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TAC RA 2
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SHAM LA 3
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Ventricle-like Pattern
Atrium-like Pattern
Novel TAC Pattern

FIG. 4

FIG. 5A

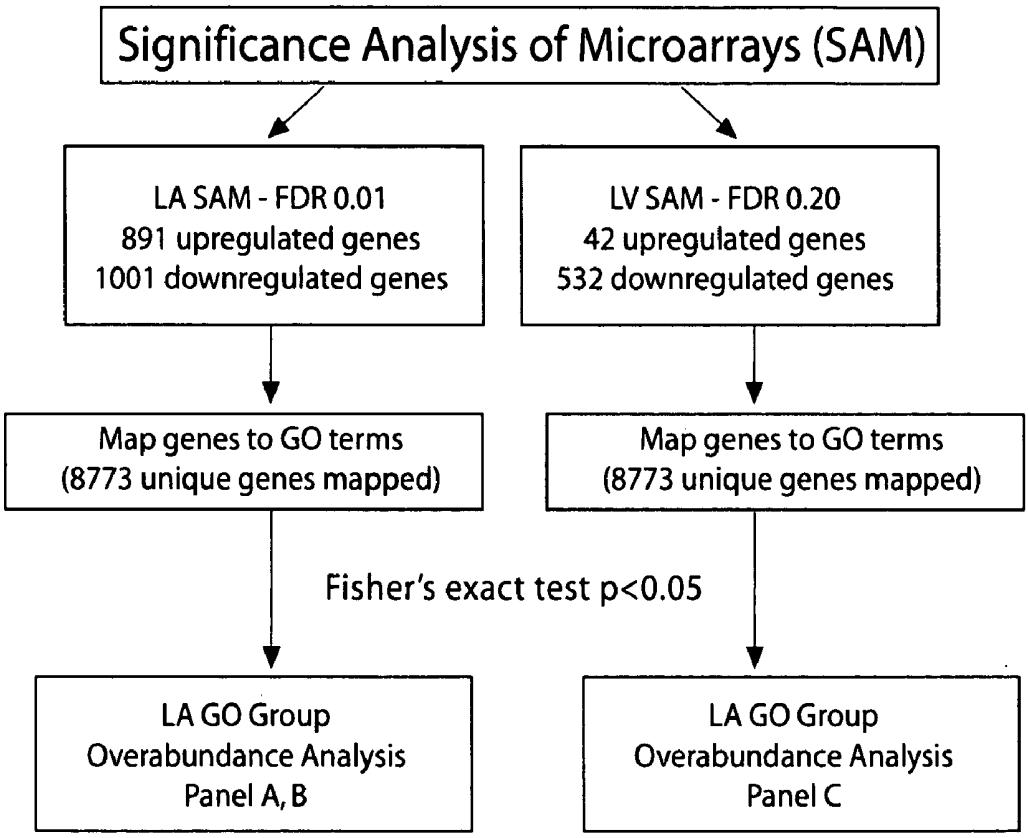

Significance Analysis of Microarrays (SAM)
LA SAM - FDR 0.01
891 upregulated genes
1001 downregulated genes
LV SAM - FDR 0.20
42 upregulated genes
532 downregulated genes
Map genes to GO terms
(8773 unique genes mapped)
Map genes to GO terms
(8773 unique genes mapped)
Fisher's exact test p<0.05
LA GO Group
Overabundance Analysis
Panel A, B
LA GO Group
Overabundance Analysis
Panel C

FIG. 5B

Biological Process Upregulated TAC LA	Total#	# Up	P.Value
cell adhesion	347	41	<0.0001
actin cytoskeleton organization and biogenesis	74	14	<0.0001
blood vessel development	51	12	<0.0001
morphogenesis	877	80	<0.0001
intracellular signaling cascade	632	62	<0.0001
organogenesis	775	70	<0.0001
development	1341	110	<0.0001
cell communication	1822	148	<0.0001
signal transduction	1451	121	<0.0001
cell surface receptor linked signal transduction	608	58	<0.0001
cell motility	244	28	0.0001
cell growth and/or maintenance	2678	183	0.0001
small GTPase mediated signal transduction	181	22	0.0003
Rho protein signal transduction	28	7	0.0006
cytoskeleton organization and biogenesis	298	30	0.0008
response to nutrients	9	4	0.0009
cell-matrix adhesion	49	9	0.0011
amine/polyamine transport	49	9	0.0011
organelle organization and biogenesis	411	37	0.0016
regulation of cell migration	19	5	0.0029
beta-1,3 glucan biosynthesis	2	2	0.003
MAPKKK cascade	46	8	0.003
response to extracellular stimulus	12	4	0.003
integrin-mediated signaling pathway	37	7	0.0033
regulation of cell cycle	328	30	0.0035
protein amino acid glycosylation	70	10	0.0043
G1/S transition of mitotic cell cycle	49	8	0.0045
negative regulation of adenylate cyclase activity	7	3	0.0047
circulation	71	10	0.0048
O-linked glycosylation	14	4	0.0056
regulation of cell shape	22	5	0.0057
lymph gland development	22	5	0.0057
glycoprotein biosynthesis	74	10	0.0064
amino acid transport	43	7	0.0079
4-hydroxyproline metabolism	3	2	0.0085
G-protein coupled receptor protein signaling pathway	278	25	0.009
transmembrane receptor protein serine/threonine kin	55	8	0.0092
TGFbeta receptor signaling pathway	45	7	0.0101
heart develope	35	6	0.0106
cell proliferation	824	60	0.0109
RAS protein signal transduction	26	5	0.0118

FIG. 5C

Biological Process Downregulated TAC LA	Total#	#Down	P.Value
energy pathways	200	38	<0.0001
protein-disulfide reduction	24	12	<0.0001
mitochondrial electron transport, NADH to ubiquinone	19	10	<0.0001
oxidative phosphorylation	30	16	<0.0001
ATP synthesis coupled electron transport	22	12	<0.0001
electron transport	385	45	<0.0001
ATP biosynthesis	27	8	<0.0001
nucleoside phosphate metabolism	27	8	<0.0001
energy derivation by oxidation of organic compounds	146	20	0.0001
proton transport	72	12	0.0003
ribonucleoside triphosphate biosynthesis	37	8	0.0005
apoptosis	295	29	0.0007
fatty acid oxidation	22	6	0.0007
phosphorylation	458	40	0.0008
tricarboxylic acid cycle	31	7	0.0009
nucleoside triphosphate biosynthesis	40	8	0.0009
programmed cell death	302	29	0.001
purine ribonucleotide biosynthesis	52	9	0.0013
fatty acid metabolism	119	15	0.0013
coenzymes and prosthetic group metabolism	136	16	0.0018
lipid metabolism	390	34	0.0021
respiratory gaseous exchange	19	5	0.0024
mitochondrial genome maintenance	6	3	0.0025
purine nucleotide biosynthesis	58	9	0.0028
phosphate metabolism	552	44	0.0029
cellular respiration	21	5	0.0038
apoptotic program	41	7	0.0048
aerobic respiration	15	4	0.0063
ribonucleotide metabolism	66	9	0.0069
mitochondrial electron transport, ubiquinol to cytochrome c	3	2	0.0078
monocyte differentiation	3	2	0.0078
metamorphosis	3	2	0.0078
regulation of translation	57	8	0.0089
organic acid metabolism	310	26	0.0109

FIG. 5D

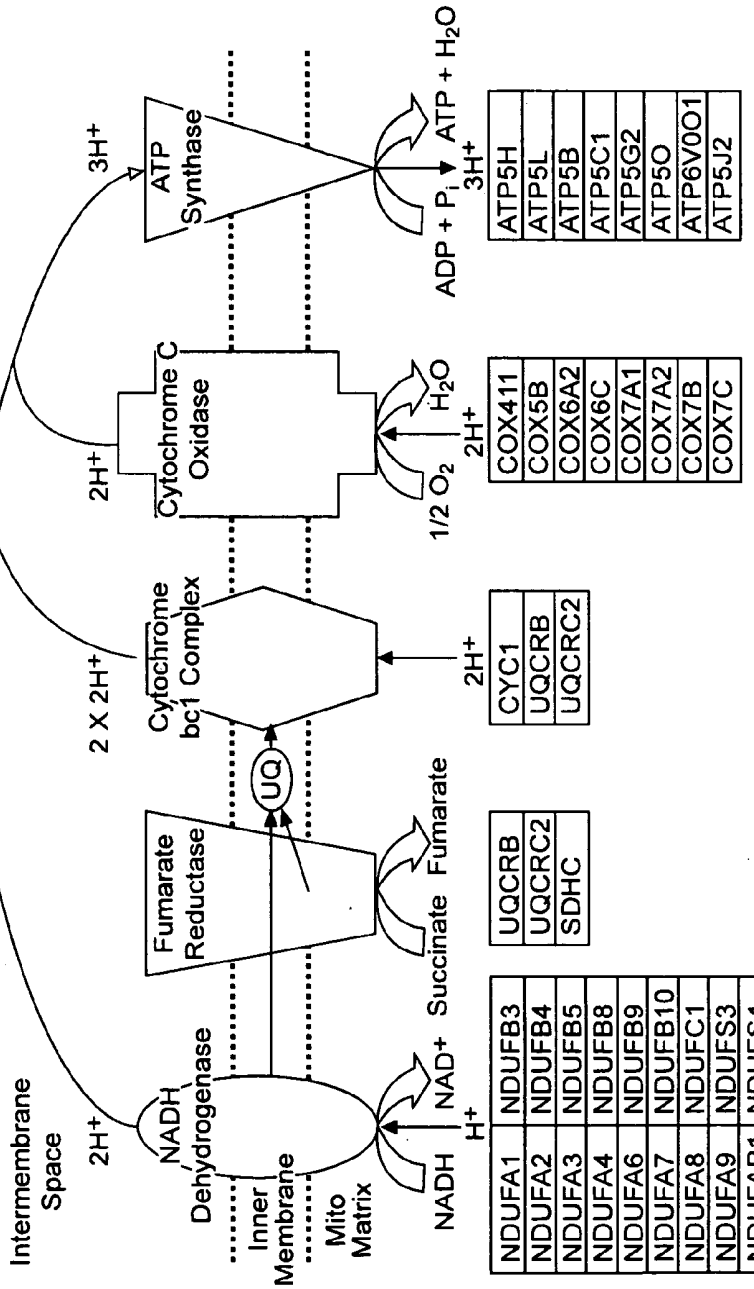
Biological Process Upregulated TAC LA	Total#	# Up	P.Value
fatty acid oxidation	22	6	<0.0001
tricarboxylic acid cycle	31	7	<0.0001
energy pathways	200	20	<0.0001
organic acid metabolism	310	27	<0.0001
lipid metabolism	390	25	<0.0001
coenzymes and prosthetic group metabolism	136	13	<0.0001
main pathways of carbohydrate metabolism	92	10	<0.0003
electron transport	385	23	0.0006
proton transport	72	8	0.001
amino acid and derivative metabolism	190	14	0.0011
oxidative phosphorylation	30	5	0.0015
alcohol metabolism	179	13	0.0018
branched chain family amino acid metabolism	10	3	0.0024
energy derivation by oxidation of organic compounds	146	11	0.0031
ATP synthesis coupled electron transport	22	4	0.0032
amine metabolism	214	14	0.0033
cation transport	262	16	0.0035
peroxisome organization and biogenesis	23	4	0.0038
protein-disulfide reduction	24	4	0.0044
ornithine metabolism	4	2	0.0047
nonprotein amino acid metabolism	4	2	0.0047
ion transport	356	19	0.0065
ATP biosynthesis	27	4	0.0068
nucleoside phosphate metabolism	27	4	0.0068
glucose metabolism	80	7	0.0078
monovalent inorganic cation transport	165	11	0.008
acylglycerol metabolism	17	3	0.0117
gluconeogenesis	17	3	0.0117
iron ion homeostasis	18	3	0.0137
microtubule stabilization	7	2	0.0156
mitochondrial electron transport, NADH to ubiquinon	19	3	0.016
ribonucleoside triphosphate biosynthesis	37	4	0.0206
metabolism	4858	155	0.0224
carbohydrate metabolism	324	16	0.0235
intra-Golgi transport	22	3	0.0238
nucleotide metabolism	123	8	0.0246
ribonucleotide biosynthesis	59	5	0.0263
regulation of muscle contraction	23	3	0.0269
monosaccharide metabolism	105	7	0.0307

Energy Pathway Genes Downregulated in TAC LA
hsa00190 Oxidative phosphorylation
ATP5H; ATP synthase, H+ transporting, mitochondrial F0 complex, subunit d [EC3.6.3.14]
ATP5L; ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g [EC3.6.3.14]
COX411; cytochrome c oxidase subunit IV isoform 1 [EC:1.9.3.1]
COX5B; cytochrome c oxidase subunit Vb [EC:1.9.3.1]
COX6A2; cytochrome c oxidase subunit VIIa polypeptide 2 [EC:1.9.3.1]
COX6C; cytochrome c oxidase subunit VIc [EC:1.9.3.1]
COX7A1; cytochrome c oxidase subunit VIIa polypeptide 1 (muscle) [EC:1.9.3.1]
COX7A2; cytochrome c oxidase subunit VIIa polypeptide 2 (liver) [EC:1.9.3.1]
COX7B; cytochrome c oxidase subunit VIIb [EC:1.9.3.1]
COX7C; cytochrome c oxidase subunit VIIc [EC:1.9.3.1]
CYC1; cytochrome c-1 [EC:1.10.2.2]
NDUFA1; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1, 7.5kDa [EC:1.6.5.3 1.6.99.3]
NDUFA2; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 2, 8kDa [EC:1.6.5.3 1.6.99.3]
NDUFA3; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa [EC:1.6.5.3 1.6.99.3]
NDUFA4; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa [EC:1.6.5.3 1.6.99.3]
NDUFA6; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6, 14kDa [EC:1.6.5.3 1.6.99.3]
NDUFA7; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7, 14.5kDa [EC:1.6.5.3 1.6.99.3]
NDUFA8; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 8, 19kDa [EC:1.6.5.3 1.6.99.3]
NDUFA9; NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 9, 39kDa [EC:1.6.5.3 1.6.99.3]
NDUFAB1; NADH dehydrogenase (ubiquinone) 1 alpha/beta subcomplex, 1, 8kDa [EC:1.6.5.3 1.6.99.3]
NDUFB2; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa [EC:1.6.5.3 1.6.99.3]
NDUFB3; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 3, 12kDa [EC:1.6.5.3 1.6.99.3]
NDUFB4; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa [EC:1.6.5.3 1.6.99.3]
NDUFB5; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa [EC:1.6.5.3 1.6.99.3]
NDUFB8; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 8, 19kDa [EC:1.6.5.3 1.6.99.3]
NDUFB9; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9, 22kDa [EC:1.6.5.3 1.6.99.3]
NDUFB10; NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10, 22kDa [EC:1.6.5.3 1.6.99.3]
NDUFC1; NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 1, 6kDa [EC:1.6.5.3 1.6.99.3]
NDUFS3; NADH dehydrogenase (ubiquinone) 1,Fe-S protein 3, 30kDa (NADH-coQ reductase) [EC:1.6.5.3 1.6.99.3]
NDUFS4; NADH dehydrogenase (ubiquinone) 1,Fe-S protein 4, 18kDa (NADH-coQ reductase) [EC:1.6.5.3 1.6.99.3]
NDUFS5; NADH dehydrogenase (ubiquinone) 1,Fe-S protein 5, 15kDa (NADH-coQ reductase) [EC:1.6.5.3 1.6.99.3]
ATP5B, ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide [EC:3.6.3.14]
ATP5C1, ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1 [EC:3.6.3.14]
ATP5F1, ATP synthase, H+ transporting, mitochondrial F0 complex, subunit b, isoform 1 [EC:3.6.3.14]
ATP5G2, ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c, isoform 2 [EC:3.6.3.14]
ATP5O, ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit [EC:3.6.3.14]
SDHC, succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa [EC1.3.5.1]
UQCRB, ubiquinol-cytochrome c reductase binding protein [EC.1.10.2.2]
UQCRC2, ubiquinol-cytochrome c reductase core protein II [EC.1.10.2.2]
ATP6V0D1; ATPase, H+ transporting, lysosomal 38kDa, V0 subunit d isoform 1 [EC:3.6.3.14]
ATP5J2; ATP synthase, H+ transporting, mitochondrial F0 complex, subunit f, isoform 2 [EC:3.6.3.14]

FIG. 6A

hsa00020 Citrate cycle (TCA cycle)
DLST; dihydrolipoamide S-succinyltransferase (E2 component of 2-oxo-glutarate complex) [EC:2.3.1.61]
IDH3A; isocitrate dehydrogenase 3 (NAD+) alpha [EC:1.1.1.41]
IDH3B; isocitrate dehydrogenase 3 (NAD+) beta [EC:1.1.1.41]
SDHC, succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa [EC:1.3.5.1]
SUCLG2, succinate-CoA ligase, GDP-forming, beta subunit [EC:6.2.1.4]
hsa00071 Fatty acid metabolism
ACAA2, acetyl-Coenzyme A acyltransferase 2 (mitochndrial 3-oxoacyl-Coenzyme A thiolase) [EC:2.3.1.16]
CPT2, carnitine palmitotransferase II [EC:2.3.1.21]
DCI; dodecenoyl-Coenzyme A delta isomerase (3,2 trans-enoyl-Coenzyme A isomerase) [EC:5.3.3.8]
FACL2; fatty-acid-Coenzyme A ligase, long-chain 2 [EC:6.2.1.3]
HADH2; hydroxyacyl-Coenzyme A dehydrogenase, type II [EC:1.1.1.35]
HADHSC, L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain [EC:1.1.1.35]
ACADL; acyl-Coenzyme A dehydrogenase, long chain [EC:1.3.99.13]
ACADM; acyl-Coenzyme A dehydrogenase, C-4 toC-12 straight chain [EC:1.3.99.3]
hsa001193 ATP synthesis
ATP5H; ATP synthase, H+ transporting, mitochondrial F0 complex, subunit d [EC:3.6.3.14]
ATP5L; ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g [EC:3.6.3.14]
ATP5B; ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide [EC:3.6.3.14]
ATP5C1; ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1 [EC:3.6.3.14]
ATP5F1; ATP synthase, H+ transporting, mitochondrial F0 complex, subunit b, isoform 1 [EC:3.6.3.14]
ATP5G2; ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c, isoform 2 [EC:3.6.3.14]
ATP5O; ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit [EC:3.6.3.14]
ATP6V0D1; ATPase, H+ transporting, lysomal 38kDa, V0 subunit d isoform 1 [EC:3.6.3.14]
ATP5J2; ATP synthase, H+ transporting, mitochondrial F0 complex, subunit f isoform 2 [EC:3.6.3.14]
hsa00220 Urea cycle and metabolism of amino groups
CKMT2; creatine kinase, mitochondrial 2 (sarcomeric) [EC:2.7.3.2]
hsa00620 Pyruvate metabolism
PDHA1; pyruvate dehydrogenase (lipoamide) alpha 1 [EC:1.2.4.1]

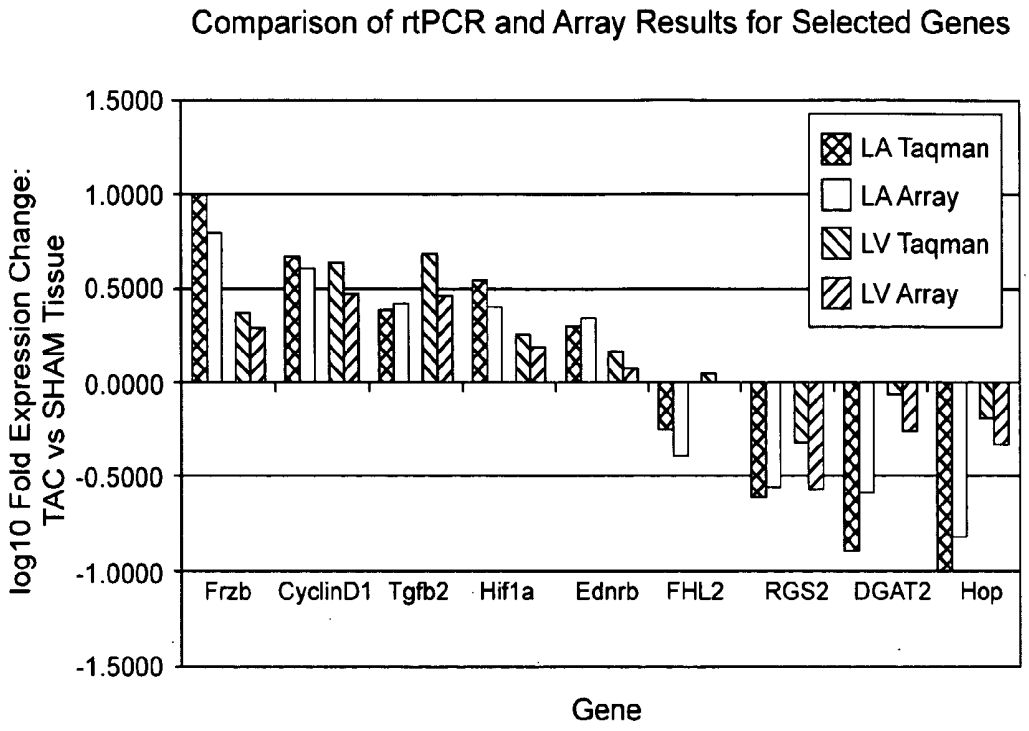
FIG. 6B



Oxidative Phosphorylation genes downregulated in TAC LA by Complex

FIG. 6C

FIG. 7


Comparison of rtPCR and Array Results for Selected Genes
log10 Fold Expression Change: TAC vs SHAM Tissue
1.5000
1.0000
0.5000
0.0000
-0.5000
-1.0000
-1.5000
LA Taqman
LA Array
LV Taqman
LV Array
Frzb
CyclinD1
Tgfb2
Hif1a
Ednrb
FHL2
RGS2
DGAT2
Hop
Gene

CARDIAC PRESSURE OVERLOAD ASSOCIATED GENES

INTRODUCTION

[0001] Heart failure is the leading cause of morbidity in western cultures. Congestive heart failure (CHF) develops when plasma volume increases and fluid accumulates in the lungs, abdominal organs (especially the liver), and peripheral tissues. In many forms of heart disease, the clinical manifestations of HF may reflect impairment of the left or right ventricle. Left ventricular (LV) failure characteristically develops in coronary artery disease, hypertension, cardiac valvular disease, many forms of cardiomyopathy, and with congenital defects. Right ventricular (RV) failure is most commonly caused by prior LV failure, which increases pulmonary venous pressure and leads to pulmonary arterial hypertension and tricuspid regurgitation. Heart failure is manifest by systolic or diastolic dysfunction, or both. Combined systolic and diastolic abnormalities are common.

[0002] In systolic dysfunction, primarily a problem of ventricular contractile dysfunction, the heart fails to provide tissues with adequate circulatory output. A wide variety of defects in energy utilization, energy supply, electrophysiologic functions, and contractile element interaction occur, which appear to reflect abnormalities in intracellular Ca^{++} modulation and adenosine triphosphate (ATP) production. Systolic dysfunction has numerous causes; the most common are coronary artery disease, hypertension, valvular disease, and dilated cardiomyopathy. Additionally, there are many known and probably many unidentified causes for dilated myocardiopathy, e.g. virus infection, toxic substances such as alcohol, a variety of organic solvents, certain chemotherapeutic drugs (e.g., doxorubicin), β-blockers, Ca blockers, and antiarrhythmic drugs.

[0003] Diastolic dysfunction accounts for 20 to 40% of cases of heart failure. It is generally associated with prolonged ventricular relaxation time, as measured during isovolumic relaxation. Resistance to filling directly relates to ventricular diastolic pressure; this resistance increases with age, probably reflecting myocyte loss and increased interstitial collagen deposition. Diastolic dysfunction is presumed to be dominant in hypertrophic cardiomyopathy, circumstances with marked ventricular hypertrophy, e.g. hypertension, advanced aortic stenosis, and amyloid infiltration of the myocardium. Without intervention, hypertrophic cardiomyopathy and diastolic dysfunction often progress to systolic dysfunction and overt, symptomatic heart failure in the natural course of the disease.

[0004] The mammalian heart responds to pressure overload by undergoing left ventricular hypertrophy (LVH) and left atrial enlargement (LAE). These adaptive responses to increases in hemodynamic overload involve many alterations in myocardial structure and function. Although these responses are necessary in the short term to maintain cardiac output in the face of increased afterload, LVH and LAE are associated with increased risk for sudden death and progression to heart failure, the leading cause of morbidity in western cultures. A detailed understanding of the molecular events accompanying these changes is an important step toward the ability to interrupt or reverse their progression.

[0005] While the LV takes the brunt of the pressure insult, during pressure overload the left atrium faces physiological challenges due to mitral regurgitation and increased wall stress, which result in enlargement and remodeling. Many of the most important clinical complications of hypertrophic cardiomyopathy, valvulvar heart disease, and congestive heart failure are due to atrial enlargement, and include atrial fibrillation and other electrophysiological disturbances, as well as hemodynamic compromise caused by decreased ventricular filling. In humans, the hemodynamic and electrophysiological sequelae of left atrial enlargement are nearly as important as those stemming from LVH.

[0006] In view of the importance of cardiomyopathy for human mortality and morbidity, the identification of genes involved in the disease, and development of methods of treatment is of great interest.

SUMMARY OF THE INVENTION

[0007] The present invention provides methods and compositions for the diagnosis and treatment of heart diseases relating to pressure overload, including but not limited to those which lead to heart failure. Among other pathologies, pressure overload induces the development of left ventricular hypertrophy (LVH) and left atrial enlargement (LAE) in the mammalian heart.

[0008] Specifically, genes are identified and described herein that are differentially expressed following induced pressure overload of the heart. The detection of the coding sequence and/or polypeptide products of these genes provides useful methods for early detection, diagnosis, staging, and monitoring of conditions leading to hypertrophy and enlargement of the heart, e.g. by the analysis of blood samples, biopsy material, in vivo imaging, metabolic assays for enzymatic activities, and the like. Expression signatures of a set of genes in heart tissue may also be evaluated for conditions indicative of pressure overload of the heart.

[0009] The invention also provides methods for the identification of compounds that modulate the expression of genes or the activity of gene products in heart diseases involving pressure overload, as well as methods for the treatment of disease by administering such compounds to individuals exhibiting heart failure symptoms or tendencies.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **FIG. 1**. Summary of data analysis. After background subtraction and dye bias normalization, poor quality features with low signal intensity were excluded from further analysis. Features with valid values in at least 66% of the experiments for each pairwise comparison (e.g., LA>66% AND TAC LA>66%) were retained for further analysis using SAM and t-test. Lists of genes identified as up-or downregulated by SAM were then mapped to GO terms and Fisher's exact test used to identify biological process groups with significant groupwide regulation.

[0011] **FIG. 2**. Hierarchical clustering. Left atria from TAC animals cluster more closely with ventricles than atria.

[0012] **FIGS. 3A-3B**. SAM analysis. Heatmaps of the top most significantly up- and downregulated genes in TAC LA(a) and LV(b). The order of the genes reflects decreasing SAM score, or d-statistic.

[0013] **FIG. 4**. Heatmap of the 891 upregulated and 1001 downregulated genes identified by SAM in the TAC LA.

Blocks of genes with ventricle-like, atrial-like, and novel TAC expression patterns are highlighted. Red color denotes high expression, green denotes low expression level.

[0014] **FIG. 5A-5C**. Top statistically significantly regulated gene ontology biological process groups for TAC LA(a and b) and LV(c). The figure lists the biological process group, the total number of annotated genes in that group on the array, the number of genes identified by SAM as up- or downregulated in the group, and the one sided Fisher's exact p-value for differential regulation of each group.

[0015] **FIG. 6**. Energy pathway genes downregulated in TAC LA. This figure shows the breadth of downregulation of the TCA cycle, fatty acid metabolism, and oxidative phosphorylation genes that occur in response to pressure overload in the LA. Downregulated genes from each oxidative phosphorylation complex are listed in the graphic. A similar number of genes is downregulated in the TAC LV.

[0016] **FIG. 7**. Comparison of microarray and qRT-PCR results. Expression is plotted as log(10) fold expression change versus sham operated control for LA and LV tissues. This figure illustrates that fold changes in expression are usually greater in the LA than LV. Results are shown for the 9 regulated genes (frizzled-related protein (Frzb), cyclin D1, TGFβ2, HIF1a, endothelin receptor b (Ednrb), four-and-a-half LIM domains 2 (FHL2), regulator of G-protein signaling 2 (RGS2), diacylglycerol O-acyltransferase 2 (DGAT2), and homeodomain-only protein (Hop)) for which qRT-PCR validation was performed.

[0017] Table I pg. 1-pg. 26 provides a list of genetic sequences differentially expressed following transverse aortic constriction. The Stanford Gene ID refers to the internet address of genome-www5.stanford.edu, which provides a database including Genbank accession numbers. Pages 1-12 provide for significantly upregulated genes, and pages 13-26 provide for significantly down-regulated genes. Table IA pg. 1-pg. 3 provides a subset of upregulated genes of interest, and includes under the heading "UGRepAcc [A]" the accession numbers for representative genetic sequences available at Genbank. Under the heading "LLRepProtAcc [A]" are provided accession numbers for representative protein sequences at Genbank. Table IB provides a further subset of sequences of interest, similarly annotated. The sequences of Table IA or Table IB pg. 1-pg. 2 may be further sub-divided according to their representation in Tables II, III or IV.

[0018] Table II pg. 1-pg. 4 provides a list of genetic sequences set forth in Table I, which are differentially expressed following transverse aortic constriction, which are of interest for serologic assays. Table II further provides Genbank accession numbers, Genbank accession numbers of human homologs, and whether the gene is upregulated in transverse aortic constriction in the left atrium (designated UP TAC LA) and/or the left ventricle (designated UP TAC LV).

[0019] Table III pg. 1-pg. 4 provides a list of genetic sequences set forth in Table I, differentially expressed following transverse aortic constriction, which are of interest for imaging assays. Table III further provides Genbank accession numbers, Genbank accession numbers of human homologs, and whether the gene is upregulated in transverse aortic constriction in the left atrium (designated UP TAC LA) and/or the left ventricle (designated UP TAC LV).

[0020] Table IV pg 1-pg. 3 provides a list of genetic sequences set forth in Table I, differentially expressed following transverse aortic constriction, which are of interest for metabolic assays. Table IV further provides Genbank accession numbers, Genbank accession numbers of human homologs, and whether the gene is upregulated in transverse aortic constriction in the left atrium (designated UP TAC LA) and/or the left ventricle (designated UP TAC LV).

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0021] Methods and compositions for the diagnosis and treatment of heart diseases involving pressure overload, including but not limited to cardiomyopathies; heart failure; and the like, are provided. The invention is based, in part, on the evaluation of the expression and role of genes that are differentially expressed in response to pressure overload, e.g. during left atrial enlargement and left ventricular hypertrophy. The right chambers may have similar changes in gene expression in association with pathologies such as pulmonary hypertension, etc. Such sequences are useful in the diagnosis and monitoring of cardiac disease. The gene products are also useful as therapeutic targets for drug screening and action.

[0022] To systematically investigate the transcriptional changes that mediate these processes, a genome-wide transcriptional profiling of each of the four heart chambers was performed following transverse aortic constriction. It is shown herein that during enlargement, the left atrium undergoes radical changes in gene transcription. Structural changes in the LA and LV are correlated with significant changes in the transcriptional profile of these chambers. Statistical analysis of the results identified biological process groups with significant group-wide changes, including angiogenesis, fatty acid oxidation, oxidative phosphorylation, cytoskeletal and matrix reorganization, and G-protein coupled receptor signaling. The genes thus identified, and their classification into biological process groups, are provided in Table I. Subsets of the upregulated genes are provided in Tables IA and IB. Table IA is a subset of Table I, and Table IB is a subset of Table IA.

[0023] For some methods of the invention, a panel of sequences will be selected, comprising, for example, at least one, at least two, at least three, at least four, at least five, at least ten, at least 15, at least 20, and may include substantially all the sequences of a specific Table (I, IA, IB; and/or II, III, IV), or may be limited to not more than about 100 distinct sequences, not more than about 50 distinct sequences, not more than about 25 distinct sequences, and the like. The selection of sequences for inclusion in arrays, use in diagnostic panels, and the like may be based on representation of a sequence in one or more of the subtables, e.g. selecting sequences present in Table IA or Table IB; representation of a sequence in both Table IB and Table II; Table IB and Table III; Table IB and Table IV, and the like. The use of human homologs of the sequences is of particular interest. Selection of sequences may alternatively be based on a cut-off for significance or for fold-change in expression, e.g. those sequences have a fold-change of at least about 3, at least about 6, at least 10, or more. Selection of sequences may also be based on biological activity grouping, e.g. using the grouping as set forth in **FIG. 5**, genes can be divided into energy pathways, cell adhesion, cell communication, signal transduction, etc., where

[0024] The identification of pressure overload associated genes provides diagnostic and prognostic methods, which detect the occurrence of a disorder, e.g. cardiomyopathy; atrial enlargement; myocardial hypertrophy; etc., particularly where such a disorder is indicative of a propensity for heart failure; or assess an individual's susceptibility to such disease, by detecting altered expression of pressure overload associated genes. Early detection of genes or their products can be used to determine the occurrence of developing disease, thereby allowing for intervention with appropriate preventive or protective measures.

[0025] Various techniques and reagents find use in the diagnostic methods of the present invention. In one embodiment of the invention, blood samples, or samples derived from blood, e.g. plasma, serum, etc. are assayed for the presence of polypeptides encoded by pressure overload associated genes, e.g. cell surface and, of particular interest, secreted polypeptides. Such polypeptides may be detected through specific binding members. The use of antibodies for this purpose is of particular interest. Various formats find use for such assays, including antibody arrays; ELISA and RIA formats; binding of labeled antibodies in suspension/solution and detection by flow cytometry, mass spectroscopy, and the like. Detection may utilize one or a panel of antibodies. A subset of genes and gene products of interest for serologic assays are provided in Table II. These sequences may be further defined by reference to the sequences set forth in Table IA and/or Table IB, i.e. sequences that are present in both Table II, and Table IA or Table IB, may be of particular interest for serologic assays.

[0026] In another embodiment, in vivo imaging is utilized to detect the presence of pressure overload associated gene on heart tissue. Such methods may utilize, for example, labeled antibodies or ligands specific for cell surface pressure overload associated gene products. Included for such methods are gene products differentially expressed on chambers of the heart, which can be localized by in situ binding of a labeled reagent. In these embodiments, a detectably-labeled moiety, e.g., an antibody, ligand, etc., which is specific for the polypeptide is administered to an individual (e.g., by injection), and labeled cells are located using standard imaging techniques, including, but not limited to, magnetic resonance imaging, computed tomography scanning, and the like. Detection may utilize one or a cocktail of imaging reagents. A subset of genes and gene products of interest for imaging assays are provided in Table III. These sequences may be further defined by reference to the sequences set forth in Table IA and/or Table IB, i.e. sequences that are present in both Table III, and Table IA or Table IB, may be of particular interest for imaging assays.

[0027] In another embodiment, metabolic tests are performed, e.g. with a labeled substrate, to determine the level of enzymatic activity of a pressure overload associated gene product. Gene products of interest for such assays include enzymes whose reaction product is readily detected, e.g. in blood samples. It is shown herein, for example, that oxidative phosphorylation is markedly downregulated during left ventricular hypertrophy and atrial enlargement, and provides a marker for risk of heart failure. A subset of genes and gene products of interest for metabolic assays are provided in Table IV. These sequences may be further defined by reference to the sequences set forth in Table IA and/or Table IB, i.e. sequences that are present in both Table IV and Table IA or Table IB may be of particular interest for metabolic assays.

[0028] In another embodiment, an mRNA sample from heart tissue, preferably from one or more chambers affected by pressure overload, is analyzed for the genetic signature indicating pressure overload, and diagnostic of a tendency to heart failure. Expression signatures typically utilize a panel of genetic sequences, e.g. a microarray format; multiplex amplification, etc., coupled with analysis of the results to determine if there is a statistically significant match with a disease signature.

[0029] Functional modulation of pressure overload associated genes and their products provides a point of intervention to block the pathophysiologic processes of hypertrophy and enlargement, and also provides therapeutic intervention in other cardiovascular system diseases with similar pathophysiologies. These genes and their products can also be used to prevent, attenuate or reduce damage in prophylactic strategies in patients at high-risk of heart failure. Genes whose expression is altered during development of hypertrophy or enlargement may be cardiodamaging. Agent(s) that inhibit the activity or expression of cardiodamaging genes can be used as a therapeutic or prophylactic agent. The agent that acts to decrease such gene product activity can be an anti-sense or RNAi nucleic acid that includes a segment corresponding a cardiodamaging gene, or any agent that acts as a direct or indirect inhibitor of the gene product, e.g. a pharmacological agonist, or partial agonist.

Disease Conditions

[0030] Heart failure is a general term that describes the final common pathway of many disease processes. Heart failure is usually caused by a reduction in the efficiency of cardiac muscle contraction. However, mechanical overload with normal or elevated cardiac contraction can also cause heart failure. This mechanical overload may be due to arterial hypertension, or stenosis or leakage of the aortic, mitral, or pulmonary valves, or other causes. The initial response to overload is usually hypertrophy (cellular enlargement) of the myocardium to increase force production, returning cardiac output (CO) to normal levels. Typically, a hypertrophic heart has impaired relaxation, a syndrome referred to as diastolic dysfunction. In the natural history of the disease, compensatory hypertrophy in the face of ongoing overload is followed by thinning, dilation, and enlargement, resulting in systolic dysfunction, also commonly known as heart failure. This natural progression typically occurs over the course of months to many years in humans, depending on the severity of the overload stimulus. Intervention at the hypertrophy stage can slow or prevent the progression to the clinically significant systolic dysfunction stage. Thus, diagnosis in the early hypertrophy stage provides unique therapeutic opportunities. The most common cause of congestive heart failure is coronary artery disease, which can cause a myocardial infarction (heart attack), which forces the heart to carry out the same work with fewer heart cells. The result is a pathophysiological state where the heart is unable to pump out enough blood to meet the nutrient and oxygen requirements of metabolizing tissues or cells.

[0031] in LV failure, CO declines and pulmonary venous pressure increases. Elevated pulmonary capillary pressure to

levels that exceed the oncotic pressure of the plasma proteins (about 24 mm Hg) leads to increased lung water, reduced pulmonary compliance, and a rise in the O_2 cost of the work of breathing. Pulmonary venous hypertension and edema resulting from LV failure significantly alter pulmonary mechanics and, thereby, ventilation/perfusion relationships. When pulmonary venous hydrostatic pressure exceeds plasma protein oncotic pressure, fluid extravasates into the capillaries, the interstitial space, and the alveoli.

[0032] Increased heart rate and myocardial contractility, arteriolar constriction in selected vascular beds, venoconstriction, and Na and water retention compensate in the early stages for reduced ventricular performance. Adverse effects of these compensatory efforts include increased cardiac work, reduced coronary perfusion, increased cardiac preload and afterload, fluid retention resulting in congestion, myocyte loss, increased K excretion, and cardiac arrhythmia.

[0033] The mechanism by which an asymptomatic patient with cardiac dysfunction develops overt CHF is unknown, but it begins with renal retention of Na and water, secondary to decreased renal perfusion. Thus, as cardiac function deteriorates, renal blood flow decreases in proportion to the reduced CO, the GFR falls, and blood flow within the kidney is redistributed. The filtration fraction and filtered Na decrease, but tubular resorption increases.

[0034] Although symptoms and signs, for example exertional dyspnea, orthopnrea, edema, tachycardia, pulmonary rales, a third heart sound, jugular venous distention, etc. have a diagnostic specificity of 70 to 90%, the sensitivity and predictive accuracy of conventional tests are low. Elevated levels of B-type natriuretic peptide may be diagnostic. Adjunctive tests include CBC, blood creatinine, BUN, electrolytes (eg, Mg, Ca), glucose, albumin, and liver function tests. ECG may be performed in all patients with HF, although findings are not specific.

[0035] Patients diagnosed as being at risk for heart failure by the methods of the invention may be appropriately treated to reduce the risk of heart failure. Drug treatment of systolic dysfunction primarily involves diuretics, ACE inhibitors, digitalis, and β-blockers; most patients are treated with at least two of these classes. Addition of hydralazine and isosorbide dinitrate to standard triple therapy of HF may improve hemodynamics and exercise tolerance and reduce mortality in refractory patients. The angiotensin II receptor blocker losartan has effects similar to those of ACE inhibitors.

[0036] Digitalis preparations have many actions, including weak inotropism, and blockade of the atrioventricular node. Digoxin is the most commonly prescribed digitalis preparation. Digitoxin, an alternative in patients with known or suspected renal disease, is largely excreted in the bile and is thus not influenced by abnormal renal function.

[0037] With careful administration of β-blockers, some patients, especially those with idiopathic dilated cardiomyopathy, will improve clinically and may have reduced mortality. Carvedilol, a 3rd-generation nonselective β-blocker, is also a vasodilator with α blockade and an antioxidant activity. Vasodilators such as nitroglycerin or nitroprusside improve ventricular function by reducing systolic ventricular wall stress, aortic impedance, ventricular chamber size, and valvular regurgitation.

[0038] Arterial hypertension, or the elevation of systolic and/or diastolic BP, either primary or secondary, is frequently associated with pressure overload of the heart, and is an important risk factor for heart failure. Hypertensive patients may be analyzed by the diagnostic methods of the invention, in order to determine whether there is a concurrent development of hypertrophy, diastolic dysfunction, and a tendency to heart failure. Criteria for hypertension is typically over about 140 mm Hg systolic blood pressure, and/or diastolic blood pressure of greater than about 90 mm Hg.

[0039] Primary (essential) hypertension is of unknown etiology; its diverse hemodynamic and pathophysiologic derangements are unlikely to result from a single cause. Heredity is a predisposing factor, but the exact mechanism is unclear. The pathogenic mechanisms can lead to increased total peripheral vascular resistance by inducing vasoconstriction and to increased cardiac output.

[0040] While no early pathologic changes occur in primary hypertension, ultimately, generalized arteriolar sclerosis develops. Left ventricular hypertrophy and, eventually, dilation develop gradually. Coronary, cerebral, aortic, renal, and peripheral atherosclerosis are more common and more severe in hypertensives because hypertension accelerates atherogenesis.

[0041] Valvular disease, including stenosis or insufficiency of the aortic, mitral, pulmonary, or tricuspid valves, is also frequently associated with overload of the heart, and is another important risk factor for heart failure. Patients with valvular disease may be analyzed by the diagnostic methods of the invention, in order to determine whether other is a concurrent development of hypertrophy, diastolic dysfunction, and a tendency to heart failure. Valvular disease is typically diagnosed by echocardiographic measurement of significant valvular stenoses or insufficiencies. Valvular heart disease has many etiologies, including but not limited to rheumatic heart disease, congenital valve defects, endocarditis, aging, etc. The pathogenic mechanism whereby valvular disease leads to heart failure is the obstruction of blood outflow from various chambers of the heart, thus increasing load.

[0042] Cardiomyopathy refers to a structural or functional abnormality of the ventricular myocardium. Cardiomyopathy has many causes. Pathophysiologic classification (dilated congestive, hypertrophic, or restrictive cardiomyopathy) by means of history, physical examination, and invasive or noninvasive testing may be performed. If no cause can be found, cardiomyopathy is considered primary or idiopathic.

[0043] Dilated congestive cardiomyopathies include disorders of myocardial function with heart failure, in which ventricular dilation and systolic dysfunction predominate. The most common identifiable cause in temperate zones is diffuse coronary artery disease with diffuse ischemic myopathy. Most commonly, at presentation there is chronic myocardial fibrosis with diffuse loss of myocytes. Diagnosis depends on the characteristic history and physical examination and exclusion of other causes of ventricular failure. The ECG may show sinus tachycardia, low-voltage QRS, and nonspecific ST segment depression with low-voltage or inverted T waves.

[0044] Hypertrophic cardiomyopathies are congenital or acquired disorders characterized by marked ventricular

hypertrophy with diastolic dysfunction that may develop in the absence of increased afterload. The cardiac muscle is abnormal with cellular and myofibrillar disarray, although this finding is not specific to hypertrophic cardiomyopathy. The interventricular septum may be hypertrophied more than the left ventricular posterior wall (asymmetric septal hypertrophy). In the most common asymmetric form of hypertrophic cardiomyopathy, there is marked hypertrophy and thickening of the upper interventricular septum below the aortic valve. During systole, the septum thickens and the anterior leaflet of the mitral valve, already abnormally oriented due to the abnormal shape of the ventricle, is sucked toward the septum, producing outflow tract obstruction. Clinical manifestations may occur alone or in any combination: Chest pain is usually typical angina related to exertion. Syncope is usually exertional and due to a combination of cardiomyopathy, arrhythmia, outflow tract obstruction, and poor diastolic filling of the ventricle. Dyspnea on exertion results from poor diastolic compliance of the left ventricle, which leads to a rapid rise in left ventricular end-diastolic pressure as flow increases. Outflow tract obstruction, by lowering cardiac output, may contribute to the dyspnea.

[0045] Restrictive cardiomyopathies are characterized by rigid, noncompliant ventricular walls that resist diastolic filling of one or both ventricles, most commonly the left. The cause is usually unknown. Amyloidosis involving the myocardium is usually systemic, as is iron infiltration in hemochromatosis. Sarcoidosis and Fabry's disease involve the myocardium, and nodal conduction tissue can be involved. Löffler's disease (a subcategory of hypereosinophilic syndrome with primary cardiac involvement) is a cause of restrictive cardiomyopathy. It occurs in the tropics. It begins as an acute arteritis with eosinophilia, with subsequent thrombus formation on the endocardium, chordae, and atrioventricular valves, progressing to fibrosis. Endocardial fibrosis occurs in temperate zones and involves only the left ventricle. The main hemodynamic consequence of these pathologic states is diastolic dysfunction with a rigid, noncompliant chamber with a high filling pressure. Systolic function may deteriorate if compensatory hypertrophy is inadequate in cases of infiltrated or fibrosed chambers. Mural thrombosis and systemic emboli can complicate the restrictive or obliterative variety.

Identification of Genes Associated With Pressure Overload

[0046] In order to identify pressure overload associated genes, tissue was taken from the chambers of the heart following transverse aortic constriction, or from control, unaffected tissue. RNA, either total or mRNA, is isolated from such tissues. See, for example, Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, New York; and Ausubel, F. M. et al., eds., 1987-1993, Current Protocols in Molecular Biology, John Wiley & Sons, Inc., New York, both of which are incorporated herein by reference in their entirety. Differentially expressed genes are detected by comparing gene expression levels between the experimental and control conditions. Transcripts within the collected RNA samples that represent differentially expressed genes may be identified by utilizing a variety of methods known to those of skill in the art, including differential screening, subtractive hybridization, differential display, or hybridization to an array comprising a plurality of gene sequences.

[0047] "Differential expression" as used herein refers to both quantitative as well as qualitative differences in the genes' temporal and/or tissue expression patterns. Thus, a differentially expressed gene may have its expression activated or inactivated in normal versus disease conditions, or in control versus experimental conditions. Preferably, a regulated gene will exhibit an expression pattern within a given tissue or cell type that is detectable in either control or disease subjects, but is not detectable in both. Detectable, as used herein, refers to an RNA expression pattern or presence of polypeptide product that is detectable via the standard techniques of differential display, reverse transcription-(RT-) PCR and/or Northern analyses, ELISA, RIA, metabolic assays, etc., which are well known to those of skill in the art. Generally, differential expression means that there is at least a 20% change, and in other instances at least a 2-, 3-, 5- or 10-fold difference between disease and control tissue expression. The difference usually is one that is statistically significant, meaning that the probability of the difference occurring by chance (the P-value) is less than some predetermined level (e.g., 5%). Usually the confidence level (P value) is <0.05, more typically <0.01, and in other instances, <0.001.

[0048] Table I provides a list of sequences that have significantly altered expression in hypertrophic cardiomyopathy, which genes may be induced or repressed as indicated in the table. Table IA provides a subset of upregulated genes of interest. Table IB provides a further subset of upregulated sequences of interest. The sequences of Table IA or Table IB may be further sub-divided according to their representation in Tables II, III or IV. In some embodiments, the sequences of interest have a "fold change" as set forth in Table I, of at least about 4; of a least about 5, of at least about 6, or more.

Nucleic Acids

[0049] The sequences of pressure overload associated genes find use in diagnostic and prognostic methods, for the recombinant production of the encoded polypeptide, and the like. A list of pressure overload associated genetic sequences is provided in Table I, and in the sub-tables thereof. The nucleic acids of the invention include nucleic acids having a high degree of sequence similarity or sequence identity to one of the sequences provided in Table 1, and also include homologs, particularly human homologs, examples of which are provided in Tables II, III and IV. Sequence identity can be determined by hybridization under stringent conditions, for example, at 50° C. or higher and 0.1×SSC (9 mM NaCl/0.9 mM Na citrate). Hybridization methods and conditions are well known in the art, see, e.g., U.S. Pat. No. 5,707,829. Nucleic acids that are substantially identical to the provided nucleic acid sequence, e.g. allelic variants, genetically altered versions of the gene, etc., bind to one of the sequences provided in Table I and sub-tables thereof under stringent hybridization conditions. Further specific guidance regarding the preparation of nucleic acids is provided by Fleury et al. (1997) *Nature Genetics* 15:269-272; Tartaglia et al., PCT Publication No. WO 96/05861; and Chen et al., PCT Publication No. WO 00/06087, each of which is incorporated herein in its entirety.

[0050] The genes listed in Table I and sub-tables thereof may be obtained using various methods well known to those

skilled in the art, including but not limited to the use of appropriate probes to detect the genes within an appropriate cDNA or genomic DNA library, antibody screening of expression libraries to detect cloned DNA fragments with shared structural features, direct chemical synthesis, and amplification protocols. Libraries are preferably prepared from nerve cells. Cloning methods are described in Berger and Kimmel, Guide to Molecular Cloning Techniques, Methods in Enzymology, 152, Academic Press, Inc. San Diego, Calif.; Sambrook, et al. (1989) Molecular Cloning—A Laboratory Manual (2nd ed) Vols. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, N.Y.; and Current Protocols (1994), a joint venture between Greene Publishing Associates, Inc. and John Wiley and Sons, Inc.

[0051] The sequence obtained from clones containing partial coding sequences or non-coding sequences can be used to obtain the entire coding region by using the RACE method (Chenchik et al. (1995) CLONTECHniques (X) 1: 5-8). Oligonucleotides can be designed based on the sequence obtained from the partial clone that can amplify a reverse transcribed mRNA encoding the entire coding sequence. Alternatively, probes can be used to screen cDNA libraries prepared from an appropriate cell or cell line in which the gene is transcribed. Once the target nucleic acid is identified, it can be isolated and cloned using well-known amplification techniques. Such techniques include the polymerase chain reaction (PCR) the ligase chain reaction (LCR), Qβ-replicase amplification, the self-sustained sequence replication system (SSR) and the transcription based amplification system (TAS). Such methods include, those described, for example, in U.S. Pat. No. 4,683,202 to Mullis et al.; PCR Protocols A Guide to Methods and Applications (Innis et al. eds) Academic Press Inc. San Diego, Calif. (1990); Kwoh et al. (1989) Proc. Natl. Acad. Sci. USA 86: 1173; Guatelli et al. (1990) Proc. Natl. Acad. Sci. USA 87: 1874; Lomell et al. (1989) J. Clin. Chem. 35: 1826; Landegren et al. (1988) Science 241: 1077-1080; Van Brunt (1990) Biotechnology 8: 291-294; Wu and Wallace (1989) Gene 4: 560; and Barringer et al. (1990) Gene 89: 117.

[0052] As an alternative to cloning a nucleic acid, a suitable nucleic acid can be chemically synthesized. Direct chemical synthesis methods include, for example, the phosphotriester method of Narang et al. (1979) Meth. Enzymol. 68: 90-99; the phosphodiester method of Brown et al. (1979) Meth. Enzymol. 68: 109-151; the diethylphosphoramidite method of Beaucage et al. (1981) Tetra. Left., 22: 1859-1862; and the solid support method of U.S. Pat. No. 4,458,066. Chemical synthesis produces a single stranded oligonucleotide. This can be converted into double stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. While chemical synthesis of DNA is often limited to sequences of about 100 bases, longer sequences can be obtained by the ligation of shorter sequences. Alternatively, subsequences may be cloned and the appropriate subsequences cleaved using appropriate restriction enzymes.

[0053] The nucleic acids can be cDNAs or genomic DNAs, as well as fragments thereof. The term "cDNA" as used herein is intended to include all nucleic acids that share the arrangement of sequence elements found in native mature mRNA species, where sequence elements are exons and 3' and 5' non-coding regions. Normally mRNA species have contiguous exons, with the intervening introns, when present, being removed by nuclear RNA splicing, to create a continuous open reading frame encoding a polypeptide of the invention.

[0054] A genomic sequence of interest comprises the nucleic acid present between the initiation codon and the stop codon, as defined in the listed sequences, including all of the introns that are normally present in a native chromosome. It can further include the 3' and 5' untranslated regions found in the mature mRNA. It can further include specific transcriptional and translational regulatory sequences, such as promoters, enhancers, etc., including about 1 kb, but possibly more, of flanking genomic DNA at either the 5' or 3' end of the transcribed region. The genomic DNA flanking the coding region, either 3' or 5', or internal regulatory sequences as sometimes found in introns, contains sequences required for proper tissue, stage-specific, or disease-state specific expression, and are useful for investigating the up-regulation of expression in tumor cells.

[0055] Probes specific to the nucleic acid of the invention can be generated using the nucleic acid sequence disclosed in Table I and sub-tables thereof. The probes are preferably at least about 18 nt, 25 nt, 50 nt or more of the corresponding contiguous sequence of one of the sequences provided in Table I and sub-tables thereof, and are usually less than about 2, 1, or 0.5 kb in length. Preferably, probes are designed based on a contiguous sequence that remains unmasked following application of a masking program for masking low complexity, e.g. BLASTX. Double or single stranded fragments can be obtained from the DNA sequence by chemically synthesizing oligonucleotides in accordance with conventional methods, by restriction enzyme digestion, by PCR amplification, etc. The probes can be labeled, for example, with a radioactive, biotinylated, or fluorescent tag.

[0056] The nucleic acids of the subject invention are isolated and obtained in substantial purity, generally as other than an intact chromosome. Usually, the nucleic acids, either as DNA or RNA, will be obtained substantially free of other naturally-occurring nucleic acid sequences, generally being at least about 50%, usually at least about 90% pure and are typically "recombinant," e.g., flanked by one or more nucleotides with which it is not normally associated on a naturally occurring chromosome.

[0057] The nucleic acids of the invention can be provided as a linear molecule or within a circular molecule, and can be provided within autonomously replicating molecules (vectors) or within molecules without replication sequences. Expression of the nucleic acids can be regulated by their own or by other regulatory sequences known in the art. The nucleic acids of the invention can be introduced into suitable host cells using a variety of techniques available in the art, such as transferrin polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated DNA transfer, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, gene gun, calcium phosphate-mediated transfection, and the like.

[0058] For use in amplification reactions, such as PCR, a pair of primers will be used. The exact composition of the primer sequences is not critical to the invention, but for most applications the primers will hybridize to the subject

sequence under stringent conditions, as known in the art. It is preferable to choose a pair of primers that will generate an amplification product of at least about 50 nt, preferably at least about 100 nt. Algorithms for the selection of primer sequences are generally known, and are available in commercial software packages. Amplification primers hybridize to complementary strands of DNA, and will prime towards each other. For hybridization probes, it may be desirable to use nucleic acid analogs, in order to improve the stability and binding affinity. The term "nucleic acid" shall be understood to encompass such analogs.

Polypeptides

[0059] Polypeptides encoded by pressure overload associated genes are of interest for screening methods, as reagents to raise antibodies, as therapeutics, and the like. Such polypeptides can be produced through isolation from natural sources, recombinant methods and chemical synthesis. In addition, functionally equivalent polypeptides may find-use, where the equivalent polypeptide may be a homolog, e.g. a human homolog, may contain deletions, additions or substitutions of amino acid residues that result in a silent change, thus producing a functionally equivalent gene product. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved. "Functionally equivalent", as used herein, refers to a protein capable of exhibiting a substantially similar in vivo activity as the polypeptide encoded by an pressure overload associated gene, as provided in Table I and sub-tables thereof.

[0060] Peptide fragments find use in a variety of methods, where fragments are usually at least about 10 amino acids in length, about 20 amino acids in length, about 50 amino acids in length, or longer, up to substantially full length. Fragments of particular interest include fragments comprising an epitope, which can be used to raise specific antibodies. Soluble fragment of cell surface proteins are also of interest, e.g. truncated at transmembrane domains.

[0061] The polypeptides may be produced by recombinant DNA technology using techniques well known in the art. Methods that are well known to those skilled in the art can be used to construct expression vectors containing coding sequences and appropriate transcriptional/translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques and in vivo recombination/genetic recombination. Alternatively, RNA capable of encoding the polypeptides of interest may be chemically synthesized.

[0062] Typically, the coding sequence is placed under the control of a promoter that is functional in the desired host cell to produce relatively large quantities of the gene product. An extremely wide variety of promoters are well-known, and can be used in the expression vectors of the invention, depending on the particular application. Ordinarily, the promoter selected depends upon the cell in which the promoter is to be active. Other expression control sequences such as ribosome binding sites, transcription termination sites and the like are also optionally included. Constructs that include one or more of these control sequences are termed "expression cassettes." Expression can be achieved in prokaryotic and eukaryotic cells utilizing promoters and other regulatory agents appropriate for the particular host cell. Exemplary host cells include, but are not limited to, *E. coli,* other bacterial hosts, yeast, and various higher eukaryotic cells such as the COS, CHO and HeLa cells lines and myeloma cell lines.

[0063] In mammalian host cells, a number of viral-based expression systems may be used, including retrovirus, lentivirus, adenovirus, adeno associated virus, and the like. In cases where an adenovirus is used as an expression vector, the coding sequence of interest can be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing differentially expressed or pathway gene protein in infected hosts.

[0064] Specific initiation signals may also be required for efficient translation of the genes. These signals include the ATG initiation codon and adjacent sequences. In cases where a complete gene, including its own initiation codon and adjacent sequences, is inserted into the appropriate expression vector, no additional translational control signals may be needed. However, in cases where only a portion of the gene coding sequence is inserted, exogenous translational control signals must be provided. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc.

[0065] In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells that possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, W138, etc.

[0066] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines that stably express the differentially expressed or pathway gene protein may be engineered. Rather than using expression vectors that contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements, and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines.

This method may advantageously be used to engineer cell lines that express the target protein. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that affect the endogenous activity of the differentially expressed or pathway gene protein. A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase, hypoxanthine-guanine phosphoribosyltransferase, and adenine phosphoribosyltransferase genes. Antimetabolite resistance can be used as the basis of selection for dhfr, which confers resistance to methotrexate; gpt, which confers resistance to mycophenolic acid; neo, which confers resistance to the aminoglycoside G-418; and hygro, which confers resistance to hygromycin.

[0067] The polypeptide may be labeled, either directly or indirectly. Any of a variety of suitable labeling systems may be used, including but not limited to, radioisotopes such as ^{125}I; enzyme labeling systems that generate a detectable calorimetric signal or light when exposed to substrate; and fluorescent labels. Indirect labeling involves the use of a protein, such as a labeled antibody, that specifically binds to the polypeptide of interest. Such antibodies include but are not limited to polyclonal, monoclonal, chimeric, single chain, Fab fragments and fragments produced by an Fab expression library.

[0068] Once expressed, the recombinant polypeptides can be purified according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, ion exchange and/or size exclusivity chromatography, gel electrophoresis and the like (see, generally, R. Scopes, Protein Purification, Springer—Verlag, N.Y. (1982), Deutscher, Methods in Enzymology Vol. 182: Guide to Protein Purification, Academic Press, Inc. N.Y. (1990)).

[0069] As an option to recombinant methods, polypeptides and oligopeptides can be chemically synthesized. Such methods typically include solid-state approaches, but can also utilize solution based chemistries and combinations or combinations of solid-state and solution approaches. Examples of solid-state methodologies for synthesizing proteins are described by Merrifield (1964) J. Am. Chem. Soc. 85:2149; and Houghton (1985) Proc. Natl. Acad. Sci., 82:5132. Fragments of a CARDIOPROTECTIVE protein can be synthesized and then joined together. Methods for conducting such reactions are described by Grant (1992) Synthetic Peptides: A User Guide, W.H. Freeman and Co., N.Y.; and in "Principles of Peptide Synthesis," (Bodansky and Trost, ed.), Springer-Verlag, Inc. N.Y., (1993).

Arrays

[0070] Arrays provide a high throughput technique that can assay a large number of polynucleotides or polypeptides in a sample. In one aspect of the invention, an array is constructed comprising one or more of the pressure overload associated genes, gene products, binding members specific for the gene product, etc., as set forth in Table I and sub-tables thereof, preferably comprising at least 4 distinct genes or gene products, at least about 8, at least 10, at least about 15, at least about 25, or more of these sequences, which array may further comprise other sequences known to be up- or down-regulated in heart tissue.

[0071] This technology can be used as a tool to test for differential expression. Arrays can be created by spotting polynucleotide probes, antibodies, polypeptides, etc. onto a substrate (e.g., glass, nitrocellulose, etc.) in a two-dimensional matrix or array having bound probes. The probes can be bound to the substrate by either covalent bonds or by non-specific interactions, such as hydrophobic interactions. Techniques for constructing arrays and methods of using these arrays are described in, for example, Schena et al. (1996) *Proc Natl Acad Sci USA.* 93(20):10614-9; Schena et al. (1995) *Science* 270(5235):467-70; Shalon et al. (1996) *Genome Res.* 6(7):639-45, U.S. Pat. No. 5,807,522, EP 799 897; WO 97/29212; WO 97/27317; EP 785 280; WO 97/02357; U.S. Pat. No. 5,593,839; U.S. Pat. No. 5,578,832; EP 728 520; U.S. Pat. No. 5,599,695; EP 721 016; U.S. Pat. No. 5,556,752; WO 95/22058; and U.S. Pat. No. 5,631,734.

[0072] The probes utilized in the arrays can be of varying types and can include, for example, synthesized probes of relatively short length (e.g., a 20-mer or a 25-mer), cDNA (full length or fragments of gene), amplified DNA, fragments of DNA (generated by restriction enzymes, for example), reverse transcribed DNA, peptides, proteins, antibodies or fragments thereof, and the like. Arrays can be utilized in detecting differential expression levels.

[0073] Arrays can be used to, for example, examine differential expression of genes. For example, arrays can be used to detect differential expression of pressure overload associated genes, where expression is compared between a test cell and control cell. Exemplary uses of arrays are further described in, for example, Pappalarado et al. (1998) *Sem. Radiation Oncol.* 8:217; and Ramsay. (1998) *Nature Biotechnol.* 16:40. Furthermore, many variations on methods of detection using arrays are well within the skill in the art and within the scope of the present invention. For example, rather than immobilizing the probe to a solid support, the test sample can be immobilized on a solid support which is then contacted with the probe. Additional discussion regarding the use of microarrays in expression analysis can be found, for example, in Duggan, et al., Nature Genetics Supplement 21:10-14 (1999); Bowtell, Nature Genetics Supplement 21:25-32 (1999); Brown and Botstein, Nature Genetics Supplement 21:33-37 (1999); Cole et al., Nature Genetics Supplement 21:38-41 (1999); Debouck and Goodfellow, Nature Genetics Supplement 21:48-50 (1999); Bassett, Jr., et al., Nature Genetics Supplement 21:51-55 (1999); and Chakravarti, Nature Genetics Supplement 21:56-60 (1999).

[0074] For detecting expression levels, usually nucleic acids are obtained from a test sample, and either directly labeled, or reversed transcribed into labeled cDNA. Alternatively, a protein sample, e.g. a serum sample, may be used, and labeled following binding to the array. The test sample containing the nucleic acids or proteins is then contacted with the array. After allowing a period sufficient for any nucleic acid or protein present in the sample to bind to the probes, the array is typically subjected to one or more washes to remove unbound sample and to minimize non-specific binding to the probes of the arrays. Binding of labeled sequences is detected using any of a variety of commercially available scanners and accompanying software programs.

[0075] For example, if the nucleic acids from the sample are labeled with fluorescent labels, hybridization intensity can be determined by, for example, a scanning confocal

microscope in photon counting mode. Appropriate scanning devices are described by e.g., U.S. Pat. No. 5,578,832 to Trulson et al., and U.S. Pat. No. 5,631,734 to Stern et al. and are available from Affymetrix, Inc., under the GeneChip™ label. Some types of label provide a signal that can be amplified by enzymatic methods (see Broude, et al., *Proc. Natl. Acad. Sci. U.S.A.* 91, 3072-3076 (1994)). A variety of other labels are also suitable including, for example, radioisotopes, chromophores, magnetic particles and electron dense particles.

[0076] Those locations on the probe array that are bound to sample are detected using a reader, such as described by U.S. Pat. No. 5,143,854, WO 90/15070, and U.S. Pat. No. 5,578,832. For customized arrays, the hybridization pattern can then be analyzed to determine the presence and/or relative amounts or absolute amounts of known species in samples being analyzed as described in e.g., WO 97/10365.

Specific Binding Members

[0077] The term "specific binding member" or "binding member" as used herein refers to a member of a specific binding pair, i.e. two molecules, usually two different molecules, where one of the molecules (i.e., first specific binding member) through chemical or physical means specifically binds to the other molecule (i.e., second specific binding member). The complementary members of a specific binding pair are sometimes referred to as a ligand and receptor; or receptor and counter-receptor. For the purposes of the present invention, the two binding members may be known to associate with each other, for example where an assay is directed at detecting compounds that interfere with the association of a known binding pair. Alternatively, candidate compounds suspected of being a binding partner to a compound of interest may be used.

[0078] Specific binding pairs of interest include carbohydrates and lectins; complementary nucleotide sequences; peptide ligands and receptor; effector and receptor molecules; hormones and hormone binding protein; enzyme cofactors and enzymes; enzyme inhibitors and enzymes; lipid and lipid-binding protein; etc. The specific binding pairs may include analogs, derivatives and fragments of the original specific binding member. For example, a receptor and ligand pair may include peptide fragments, chemically synthesized peptidomimetics, labeled protein, derivatized protein, etc.

[0079] In a preferred embodiment, the specific binding member is an antibody. The term "antibody" or "antibody moiety" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The specific or selective fit of a given structure and its specific epitope is sometimes referred to as a "lock and key" fit. The archetypal antibody molecule is the immunoglobulin, and all types of immunoglobulins, IgG, IgM, IgA, IgE, IgD, etc., from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammal, chicken, other avians, etc., are considered to be "antibodies." Antibodies utilized in the present invention may be polyclonal antibodies, although monoclonal antibodies are preferred because they may be reproduced by cell culture or recombinantly, and can be modified to reduce their antigenicity.

[0080] Polyclonal antibodies can be raised by a standard protocol by injecting a production animal with an antigenic composition, formulated as described above. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In one such technique, an antigen comprising an antigenic portion of the protein target is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). When utilizing an entire protein, or a larger section of the protein, antibodies may be raised by immunizing the production animal with the protein and a suitable adjuvant (e.g., Freund's, Freund's complete, oil-in-water emulsions, etc.) When a smaller peptide is utilized, it is advantageous to conjugate the peptide with a larger molecule to make an immunostimulatory conjugate. Commonly utilized conjugate proteins that are commercially available for such use include bovine serum albumin (BSA) and keyhole limpet hemocyanin (KLH). In order to raise antibodies to particular epitopes, peptides derived from the full sequence may be utilized. Alternatively, in order to generate antibodies to relatively short peptide portions of the protein target, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as ovalbumin, BSA or KLH. The peptide-conjugate is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

[0081] Alternatively, for monoclonal antibodies, hybridomas may be formed by isolating the stimulated immune cells, such as those from the spleen of the inoculated animal. These cells are then fused to immortalized cells, such as myeloma cells or transformed cells, which are capable of replicating indefinitely in cell culture, thereby producing an immortal, immunoglobulin-secreting cell line. The immortal cell line utilized is preferably selected to be deficient in enzymes necessary for the utilization of certain nutrients. Many such cell lines (such as myelomas) are known to those skilled in the art, and include, for example: thymidine kinase (TK) or hypoxanthine-guanine phosphoriboxyl transferase (HGPRT). These deficiencies allow selection for fused cells according to their ability to grow on, for example, hypoxanthine aminopterinthymidine medium (HAT).

[0082] Preferably, the immortal fusion partners utilized are derived from a line that does not secrete immunoglobulin. The resulting fused cells, or hybridomas, are cultured under conditions that allow for the survival of fused, but not unfused, cells and the resulting colonies screened for the production of the desired monoclonal antibodies. Colonies producing such antibodies are cloned, expanded, and grown so as to produce large quantities of antibody, see Kohler and Milstein, 1975 Nature 256:495 (the disclosures of which are hereby incorporated by reference).

[0083] Large quantities of monoclonal antibodies from the secreting hybridomas may then be produced by injecting the clones into the peritoneal cavity of mice and harvesting the ascites fluid therefrom. The mice, preferably primed with pristane, or some other tumor-promoter, and immunosuppressed chemically or by irradiation, may be any of various suitable strains known to those in the art. The ascites fluid is harvested from the mice and the monoclonal antibody

purified therefrom, for example, by CM Sepharose column or other chromatographic means. Alternatively, the hybridomas may be cultured in vitro or as suspension cultures. Batch, continuous culture, or other suitable culture processes may be utilized. Monoclonal antibodies are then recovered from the culture medium or supernatant.

[0084] Monoclonal antibodies against the protein targets of the invention may be currently available from commercial sources. These antibodies are suitable for use in the compositions of the present invention.

[0085] In addition, the antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with the standard hybridoma procedure, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from the immune spleen cells or hybridomas is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host (e.g. bacteria, insect cells, mammalian cells, or other suitable protein production host cell.). When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

[0086] In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab', $F(ab')_2$, or other fragments) are useful as antibody moieties in the present invention. Such antibody fragments may be generated from whole immunoglobulins by ficin, pepsin, papain, or other protease cleavage. "Fragment," or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by linking a variable light chain region to a variable heavy chain region via a peptide linker (e.g., poly-glycine or another sequence which does not form an alpha helix or beta sheet motif).

[0087] In addition, derivatized immunoglobulins with added chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, substrates, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. For convenience, the term "antibody" or "antibody moiety" will be used throughout to generally refer to molecules which specifically bind to an epitope of the protein targets, although the term will encompass all immunoglobulins, derivatives, fragments, recombinant or engineered immunoglobulins, and modified immunoglobulins, as described above.

Diagnostic and Prognostic Methods

[0088] The differential expression of pressure overload associated genes indicates that these sequences can serve as markers for diagnosis, and in prognostic evaluations to detect individuals at risk for cardiac pathologies, including atrial enlargement, ventricular hypertrophy, heart failure, etc. Prognostic methods can also be utilized to monitor an individual's health status prior to and after an episode, as well as in the assessment of the severity of the episode and the likelihood and extent of recovery.

[0089] In general, such diagnostic and prognostic methods involve detecting an altered level of expression of pressure overload associated genes or gene products in the cells or tissue of an individual or a sample therefrom, to generate an expression profile. A variety of different assays can be utilized to detect an increase in pressure overload associated gene expression, including both methods that detect gene transcript and protein levels. More specifically, the diagnostic and prognostic methods disclosed herein involve obtaining a sample from an individual and determining at least qualitatively, and preferably quantitatively, the level of a pressure overload associated genes product expression in the sample. Usually this determined value or test value is compared against some type of reference or baseline value.

[0090] The term expression profile is used broadly to include a genomic expression profile, e.g., an expression profile of mRNAs, or a proteomic expression profile, e.g., an expression profile of one or more different proteins. Profiles may be generated by any convenient means for determining differential gene expression between two samples, e.g. quantitative hybridization of mRNA, labeled mRNA, amplified mRNA, cRNA, etc., quantitative PCR, ELISA for protein quantitation, and the like.

[0091] The expression profile may be generated from a biological sample using any convenient protocol. While a variety of different manners of generating expression profiles are known, such as those employed in the field of differential gene expression analysis, one representative and convenient type of protocol for generating expression profiles is array based gene expression profile generation protocols. Following obtainment of the expression profile from the sample being assayed, the expression profile is compared with a reference or control profile to make a diagnosis regarding the susceptibility phenotype of the cell or tissue from which the sample was obtained/derived. Typically a comparison is made with a set of cells from an unaffected, normal source. Additionally, a reference or control profile may be a profile that is obtained from a cell/tissue known to be predisposed to heart failure, and therefore may be a positive reference or control profile.

[0092] In certain embodiments, the obtained expression profile is compared to a single reference/control profile to obtain information regarding the phenotype of the cell/tissue being assayed. In yet other embodiments, the obtained expression profile is compared to two or more different reference/control profiles to obtain more in depth information regarding the phenotype of the assayed cell/tissue. For example, the obtained expression profile may be compared to a positive and negative reference profile to obtain confirmed information regarding whether the cell/tissue has the phenotype of interest.

[0093] The difference values, i.e. the difference in expression in the presence and absence of radiation may be performed using any convenient methodology, where a variety of methodologies are known to those of skill in the

array art, e.g., by comparing digital images of the expression profiles, by comparing databases of expression data, etc. Patents describing ways of comparing expression profiles include, but are not limited to, U.S. Pat. Nos. 6,308,170 and 6,228,575, the disclosures of which are herein incorporated by reference. Methods of comparing expression profiles are also described above. A statistical analysis step is then performed to obtain the weighted contribution of the set of predictive genes.

[0094] In one embodiment of the invention, blood samples, or samples derived from blood, e.g. plasma, serum, etc. are assayed for the presence of polypeptides encoded by pressure overload associated genes, e.g. cell surface and, of particular interest, secreted polypeptides. Such polypeptides may be detected through specific binding members. The use of antibodies for this purpose is of particular interest. Various formats find use for such assays, including antibody arrays; ELISA and RIA formats; binding of labeled antibodies in suspension/solution and detection by flow cytometry, mass spectroscopy, and the like. Detection may utilize one or a panel of specific binding members, e.g. specific for at least about 2, at least about 3, at least about 5, at least about 10 or more different gene products. A subset of genes and gene products of interest for serologic assays are provided in Table II.

[0095] In another embodiment, in vivo imaging is utilized to detect the presence of pressure overload associated gene on heart tissue. Such methods may utilize, for example, labeled antibodies or ligands specific for cell surface pressure overload associated gene products. Included for such methods are gene products differentially expressed on chambers of the heart, which can be localized by in situ binding of a labeled reagent. In these embodiments, a detectably-labeled moiety, e.g., an antibody, ligand, etc., which is specific for the polypeptide is administered to an individual (e.g., by injection), and labeled cells are located using standard imaging techniques, including, but not limited to, magnetic resonance imaging, computed tomography scanning, and the like. Detection may utilize one or a cocktail of imaging reagents e.g. imaging reagents specific for at least about 2, at least about 3, at least about 5, at least about 10 or more different gene products. A subset of genes and gene products of interest for imaging assays are provided in Table III.

[0096] In another embodiment, metabolic tests are performed, e.g. with a labeled substrate, to determine the level of enzymatic activity of a pressure overload associated gene product. Gene products of interest for such assays include enzymes whose reaction product is readily detected, e.g. in blood samples. It is shown herein, for example, that oxidative phosphorylation is markedly downregulated during atrial enlargement, and provides a marker for risk of heart failure. A subset of genes and gene products of interest for metabolic assays are provided in Table IV. Assays may be directed to one or more metabolic activities

[0097] In another embodiment, an mRNA sample from heart tissue, preferably from one or more chambers affected by pressure overload, is analyzed for the genetic signature indicating pressure overload, and diagnostic of a tendency to heart failure. Expression signatures typically utilize a panel of genetic sequences, e.g. a microarray format; multiplex amplification, etc., coupled with analysis of the results to determine if there is a statistically significant match with a disease signature.

[0098] Nucleic acids or binding members such as antibodies that are specific for polypeptides derived from the sequence of one of the sequences provided in Table I and sub-tables thereof can be used to screen patient samples for increased expression of the corresponding mRNA or protein. Samples can be obtained from a variety of sources. For example, since the methods are designed primarily to diagnosis and assess risk factors for humans, samples are typically obtained from a human subject. However, the methods can also be utilized with samples obtained from various other mammals, such as primates, e.g. apes and chimpanzees, mice, cats, rats, and other animals. Such samples are referred to as a patient sample.

[0099] Samples can be obtained from the tissues or fluids of an individual, as well as from cell cultures or tissue homogenates. For example, samples can be obtained from whole blood, heart tissue biopsy, serum, saliva, tears, urine, fecal material, sweat, buccal, skin, etc. Also included in the term are derivatives and fractions of such cells and fluids. Where cells are analyzed, the number of cells in a sample will often be at least about 10^2, usually at least 10^3 and may be about 10^4 or more. The cells may be dissociated, in the case of solid tissues, or tissue sections may be analyzed. Alternatively a lysate of the cells may be prepared.

[0100] Diagnostic samples are collected any time after an individual is suspected to have cardiomyopathy, atrial enlargement, ventricular hypertrophy, etc. or has exhibited symptoms that predict such pathologies. In prophylactic testing, samples can be obtained from an individual who present with risk factors that indicate a susceptibility to heart failure, which risk factors include high blood pressure, obesity, diabetes, etc. as part of a routine assessment of the individual's health status.

[0101] The various test values determined for a sample from an individual believed to suffer pressure overload, cardiac hypertrophy, diastolic dysfunction, and/or, a tendency to heart failure typically are compared against a baseline value to assess the extent of increased or decreased expression, if any. This baseline value can be any of a number of different values: In some instances, the baseline value is a value established in a trial using a healthy cell or tissue sample that is run in parallel with the test sample. Alternatively, the baseline value can be a statistical value (e.g., a mean or average) established from a population of control cells or individuals. For example, the baseline value can be a value or range that is characteristic of a control individual or control population. For instance, the baseline value can be a statistical value or range that is reflective of expression levels for the general population, or more specifically, healthy individuals not susceptible to stroke. Individuals not susceptible to stroke generally refer to those having no apparent risk factors correlated with heart failure, such as high blood pressure, high cholesterol levels, diabetes, smoking and high salt diet, for example.

Nucleic Acid Screening Methods

[0102] Some of the diagnostic and prognostic methods that involve the detection of a pressure overload associated gene transcript begin with the lysis of cells and subsequent

purification of nucleic acids from other cellular material, particularly mRNA transcripts. A nucleic acid derived from an mRNA transcript refers to a nucleic acid for whose synthesis the mRNA transcript, or a subsequence thereof, has ultimately served as a template. Thus, a cDNA reverse transcribed from an mRNA, an RNA transcribed from that cDNA, a DNA amplified from the cDNA, an RNA transcribed from the amplified DNA, are all derived from the mRNA transcript and detection of such derived products is indicative of the presence and/or abundance of the original transcript in a sample. Thus, suitable samples include, but are not limited to, mRNA transcripts of pressure overload associated genes, cDNA reverse transcribed from the mRNA, cRNA transcribed from the cDNA, DNA amplified from pressure overload associated nucleic acids, and RNA transcribed from amplified DNA.

[0103] A number of methods are available for analyzing nucleic acids for the presence of a specific sequence, e.g. upregulated expression. The nucleic acid may be amplified by conventional techniques, such as the polymerase chain reaction (PCR), to provide sufficient amounts for analysis. The use of the polymerase chain reaction is described in Saiki et al. (1985) *Science* 239:487, and a review of techniques may be found in Sambrook, et al. *Molecular Cloning: A Laboratory Manual,* CSH Press 1989, pp. 14.2-14.33.

[0104] A detectable label may be included in an amplification reaction. Suitable labels include fluorochromes, e.g. fluorescein isothiocyanate (FITC), rhodamine, Texas Red, phycoerythrin, allophycocyanin, 6-carboxyfluorescein(6-FAM),2,7-dimethoxy4,5-dichloro-6-carboxyfluorescein (JOE), 6-carboxy-X-rhodamine (ROX), 6-carboxy-2,4,7,4,7-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM) or N,N,N,N-tetramethyl-6-carboxyrhodamine (TAMRA), radioactive labels, e.g. ^{32}P, ^{35}S, ^{3}H; etc. The label may be a two stage system, where the amplified DNA is conjugated to biotin, haptens, etc. having a high affinity binding partner, e.g. avidin, specific antibodies, etc., where the binding partner is conjugated to a detectable label. The label may be conjugated to one or both of the primers. Alternatively, the pool of nucleotides used in the amplification is labeled, so as to incorporate the label into the amplification product.

[0105] The sample nucleic acid, e.g. amplified, labeled, cloned fragment, etc. is analyzed by one of a number of methods known in the art. Probes may be hybridized to northern or dot blots, or liquid hybridization reactions performed. The nucleic acid may be sequenced by dideoxy or other methods, and the sequence of bases compared to a wild-type sequence. Single strand conformational polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), and heteroduplex analysis in gel matrices are used to detect conformational changes created by DNA sequence variation as alterations in electrophoretic mobility. Fractionation is performed by gel or capillary electrophoresis, particularly acrylamide or agarose gels.

[0106] In situ hybridization methods are hybridization methods in which the cells are not lysed prior to hybridization. Because the method is performed in situ, it has the advantage that it is not necessary to prepare RNA from the cells. The method usually involves initially fixing test cells to a support (e.g., the walls of a microtiter well) and then permeabilizing the cells with an appropriate permeabilizing solution. A solution containing labeled probes for a pressure overload associated gene is then contacted with the cells and the probes allowed to hybridize with the nucleic acids. Excess probe is digested, washed away and the amount of hybridized probe measured. This approach is described in greater detail by Harris, D. W. (1996) Anal. Biochem. 243:249-256; Singer, et al. (1986) Biotechniques 4:230-250; Haase et al. (1984) Methods in Virology, vol. VII, pp. 189-226; and Nucleic Acid Hybridization: A Practical Approach (Hames, et al., eds., 1987).

[0107] A variety of so-called "real time amplification" methods or "real time quantitative PCR" methods can also be utilized to determine the quantity of pressure overload associated gene mRNA present in a sample. Such methods involve measuring the amount of amplification product formed during an amplification process. Fluorogenic nuclease assays are one specific example of a real time quantitation method that can be used to detect and quantitate pressure overload associated gene transcripts. In general such assays continuously measure PCR product accumulation using a dual-labeled fluorogenic oligonucleotide probe—an approach frequently referred to in the literature simply as the "TaqMan" method.

[0108] The probe used in such assays is typically a short (ca. 20-25 bases) polynucleotide that is labeled with two different fluorescent dyes. The 5' terminus of the probe is typically attached to a reporter dye and the 3' terminus is attached to a quenching dye, although the dyes can be attached at other locations on the probe as well. For measuring a pressure overload associated gene transcript, the probe is designed to have at least substantial sequence complementarity with a probe binding site on a pressure overload associated gene transcript. Upstream and downstream PCR primers that bind to regions that flank the pressure overload associated gene are also added to the reaction mixture.

[0109] When the probe is intact, energy transfer between the two fluorophors occurs and the quencher quenches emission from the reporter. During the extension phase of PCR, the probe is cleaved by the 5' nuclease activity of a nucleic acid polymerase such as Taq polymerase, thereby releasing the reporter dye from the polynucleotide-quencher complex and resulting in an increase of reporter emission intensity that can be measured by an appropriate detection system.

[0110] One detector which is specifically adapted for measuring fluorescence emissions such as those created during a fluorogenic assay is the ABI 7700 manufactured by Applied Biosystems, Inc. in Foster City, Calif. Computer software provided with the instrument is capable of recording the fluorescence intensity of reporter and quencher over the course of the amplification. These recorded values can then be used to calculate the increase in normalized reporter emission intensity on a continuous basis and ultimately quantify the amount of the mRNA being amplified.

[0111] Additional details regarding the theory and operation of fluorogenic methods for making real time determinations of the concentration of amplification products are described, for example, in U.S. Pat. No. 5,210,015 to Gelfand, U.S. Pat. No. 5,538,848 to Livak, et al., and U.S. Pat. No. 5,863,736 to Haaland, as well as Heid, C. A., et al., Genome Research, 6:986-994 (1996); Gibson, U. E. M, et

al., Genome Research 6:995-1001 (1996); Holland, P. M., et al., Proc. Natl. Acad. Sci. USA 88:7276-7280, (1991); and Livak, K. J., et al., PCR Methods and Applications 357-362 (1995), each of which is incorporated by reference in its entirety.

Polypeptide Screening Methods

[0112] Screening for expression of the subject sequences may be based on the functional or antigenic characteristics of the protein. Various immunoassays designed to quantitate proteins encoded by the sequences corresponding to the sequences provided in Table I and sub-tables thereof may be used in screening. Functional, or metabolic, protein assays have proven to be effective screening tools. The activity of the encoded protein in oxidative phosphorylation assays, etc., may be determined by comparison with unaffected individuals.

[0113] Detection may utilize staining of cells or histological sections, performed in accordance with conventional methods, using antibodies or other specific binding members that specifically bind to the pressure overload associated polypeptides. The antibodies or other specific binding members of interest, e.g. receptor ligands, are added to a cell sample, and incubated for a period of time sufficient to allow binding to the epitope, usually at least about 10 minutes. The antibody may be labeled with radioisotopes, enzymes, fluorescers, chemiluminescers, or other labels for direct detection. Alternatively, a second stage antibody or reagent is used to amplify the signal. Such reagents are well known in the art. For example, the primary antibody may be conjugated to biotin, with horseradish peroxidase-conjugated avidin added as a second stage reagent. Final detection uses a substrate that undergoes a color change in the presence of the peroxidase. The absence or presence of antibody binding may be determined by various methods, including flow cytometry of dissociated cells, microscopy, radiography, scintillation counting, etc.

[0114] An alternative method for diagnosis depends on the in vitro detection of binding between antibodies and the polypeptide corresponding to a sequence of Table I and sub-tables thereof in a blood sample, cell lysate, etc. Measuring the concentration of the target protein in a sample or fraction thereof may be accomplished by a variety of specific assays. A conventional sandwich type assay may be used. For example, a sandwich assay may first attach specific antibodies to an insoluble surface or support. The particular manner of binding is not crucial so long as it is compatible with the reagents and overall methods of the invention. They may be bound to the plates covalently or non-covalently, preferably non-covalently.

[0115] The insoluble supports may be any compositions to which polypeptides can be bound, which is readily separated from soluble material, and which is otherwise compatible with the overall method. The surface of such supports may be solid or porous and of any convenient shape. Examples of suitable insoluble supports to which the receptor is bound include beads, e.g. magnetic beads, membranes and microtiter plates. These are typically made of glass, plastic (e.g. polystyrene), polysaccharides, nylon or nitrocellulose. Microtiter plates are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples.

[0116] Patient sample lysates are then added to separately assayable supports (for example, separate wells of a microtiter plate) containing antibodies. Preferably, a series of standards, containing known concentrations of the test protein is assayed in parallel with the samples or aliquots thereof to serve as controls. Preferably, each sample and standard will be added to multiple wells so that mean values can be obtained for each. The incubation time should be sufficient for binding, generally, from about 0.1 to 3 hr is sufficient. After incubation, the insoluble support is generally washed of non-bound components. Generally, a dilute non-ionic detergent medium at an appropriate pH, generally 7-8, is used as a wash medium. From one to six washes may be employed, with sufficient volume to thoroughly wash non-specifically bound proteins present in the sample.

[0117] After washing, a solution containing a second antibody is applied. The antibody will bind to one of the proteins of interest with sufficient specificity such that it can be distinguished from other components present. The second antibodies may be labeled to facilitate direct, or indirect quantification of binding. Examples of labels that permit direct measurement of second receptor binding include radiolabels, such as ^{3}H or ^{125}I, fluorescers, dyes, beads, chemiluminescers, colloidal particles, and the like. Examples of labels that permit indirect measurement of binding include enzymes where the substrate may provide for a colored or fluorescent product. In a preferred embodiment, the antibodies are labeled with a covalently bound enzyme capable of providing a detectable product signal after addition of suitable substrate. Examples of suitable enzymes for use in conjugates include horseradish peroxidase, alkaline phosphatase, malate dehydrogenase and the like. Where not commercially available, such antibody-enzyme conjugates are readily produced by techniques known to those skilled in the art. The incubation time should be sufficient for the labeled ligand to bind available molecules. Generally, from about 0.1 to 3 hr is sufficient, usually 1 hr sufficing.

[0118] After the second binding step, the insoluble support is again washed free of non-specifically bound material, leaving the specific complex formed between the target protein and the specific binding member. The signal produced by the bound conjugate is detected by conventional means. Where an enzyme conjugate is used, an appropriate enzyme substrate is provided so a detectable product is formed.

[0119] Other immunoassays are known in the art and may find use as diagnostics. Ouchterlony plates provide a simple determination of antibody binding. Western blots may be performed on protein gels or protein spots on filters, using a detection system specific for the pressure overload associated polypeptide as desired, conveniently using a labeling method as described for the sandwich assay.

[0120] In some cases, a competitive assay will be used. In addition to the patient sample, a competitor to the targeted protein is added to the reaction mix. The competitor and the pressure overload associated polypeptide compete for binding to the specific binding partner. Usually, the competitor molecule will be labeled and detected as previously described, where the amount of competitor binding will be proportional to the amount of target protein present. The concentration of competitor molecule will be from about 10 times the maximum anticipated protein concentration to about equal concentration in order to make the most sensitive and linear range of detection.

[0121] The detection methods can be provided as part of a kit. Thus, the invention further provides kits for detecting the presence of an mRNA corresponding to a sequence of Table I, II, or III, and/or a polypeptide encoded thereby, in a biological sample. Procedures using these kits can be performed by clinical laboratories, experimental laboratories, medical practitioners, or private individuals. The kits of the invention for detecting a polypeptide comprise a moiety that specifically binds the polypeptide, which may be a specific antibody. The kits of the invention for detecting a nucleic acid comprise a moiety that specifically hybridizes to such a nucleic acid. The kit may optionally provide additional components that are useful in the procedure, including, but not limited to, buffers, developing reagents, labels, reacting surfaces, means for detection, control samples, standards, instructions, and interpretive information.

Imaging In Vivo

[0122] In some embodiments, the methods are adapted for imaging use in vivo, e.g., to locate or identify sites where pressure overload associated genes are expressed. In these embodiments, a detectably-labeled moiety, e.g., an antibody, which is specific for the pressure overload associated polypeptide is administered to an individual (e.g., by injection), and labeled cells are located using standard imaging techniques, including, but not limited to, magnetic resonance imaging, computed tomography scanning, and the like.

[0123] For diagnostic in vivo imaging, the type of detection instrument available is a major factor in selecting a given radionuclide. The radionuclide chosen must have a type of decay that is detectable by a given type of instrument. In general, any conventional method for visualizing diagnostic imaging can be utilized in accordance with this invention. Another important factor in selecting a radionuclide for in vivo diagnosis is that its half-life be long enough that it is'still detectable at the time of maximum uptake by the target tissue, but short enough that deleterious radiation of the host is minimized. A currently used method for labeling with ^{99m}Tc is the reduction of pertechnetate ion in the presence of a chelating precursor to form the labile ^{99m}Tc-precursor complex, which, in turn, reacts with the metal binding group of a bifunctionally modified chemotactic peptide to form a ^{99m}Tc-chemotactic peptide conjugate.

[0124] The detectably labeled antibody is used in conjunction with imaging techniques, in order to analyze the expression of the target. In one embodiment, the imaging method is one of PET or SPECT, which are imaging techniques in which a radionuclide is synthetically or locally administered to a patient. The subsequent uptake of the radiotracer is measured over time and used to obtain information about the targeted tissue. Because of the high-energy (γ-ray) emissions of the specific isotopes employed and the sensitivity and sophistication of the instruments used to detect them, the two-dimensional distribution of radioactivity may be inferred from outside of the body.

[0125] Among the most commonly used positron-emitting nuclides in PET are included ^{11}C, ^{13}N, ^{15}O, and ^{18}F. Isotopes that decay by electron capture and/or y emission are used in SPECT, and include ^{123}I and ^{99m}Tc.

Time Course Analyses

[0126] Certain prognostic methods of assessing a patient's risk of heart failure involve monitoring expression levels for a patient susceptible to heart failure, to track whether there is a change in expression of a pressure overload associated gene over time. An increase in expression over time can indicate that the individual is at increased risk for heart failure. As with other measures, the expression level for the patient at risk for heart failure is compared against a baseline value. The baseline in such analyses can be a prior value determined for the same individual or a statistical value (e.g., mean or average) determined for a control group (e.g., a population of individuals with no apparent neurological risk factors). An individual showing a statistically significant increase in pressure overload associated expression levels over time can prompt the individual's physician to take prophylactic measures to lessen the individual's potential for heart failure. For example, the physician can recommend certain life style changes (e.g., medication, improved diet, exercise program) to reduce the risk of heart failure.

Databases of Expression Profiles

[0127] Also provided are databases of expression profiles of phenotype determinative genes. Such databases will typically comprise expression profiles of various cells/tissues having susceptible phenotypes, negative expression profiles, etc., where such profiles are further described below.

[0128] The expression profiles and databases thereof may be provided in a variety of media to facilitate their use. "Media" refers to a manufacture that contains the expression profile information of the present invention. The databases of the present invention can be recorded on computer readable media, e.g. any medium that can be read and accessed directly by a computer. Such media include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media. One of skill in the art can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising a recording of the present database information. "Recorded" refers to a process for storing information on computer readable medium, using any such methods as known in the art. Any convenient data storage structure may be chosen, based on the means used to access the stored information. A variety of data processor programs and formats can be used for storage, e.g. word processing text file, database format, etc.

[0129] As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the information of the present invention. The minimum hardware of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based system are suitable for use in the present invention. The data storage means may comprise any manufacture comprising a recording of the present information as described above, or a memory access means that can access such a manufacture.

[0130] A variety of structural formats for the input and output means can be used to input and output the information in the computer-based systems of the present invention. Such presentation provides a skilled artisan with a ranking of similarities and identifies the degree of similarity contained in the test expression profile.

Therapeutic/Prophylactic Treatment Methods

[0131] Agents that modulate activity of pressure overload associated genes provide a point of therapeutic or prophylactic intervention. Numerous agents are useful in modulating this activity, including agents that directly modulate expression, e.g. expression vectors, antisense specific for the targeted gene; and agents that act on the protein, e.g. specific antibodies and analogs thereof, small organic molecules that block catalytic activity, etc.

[0132] The genes, gene fragments, or the encoded protein or protein fragments are useful in therapy to treat disorders associated with defects in expression. From a therapeutic point of view, modulating activity may have a therapeutic effect on a number of degenerative disorders. For example, expression can be upregulated by introduction of an expression vector, enhancing expression, providing molecules that mimic the activity of the targeted polypeptide, etc.

[0133] Antisense molecules can be used to down-regulate expression in cells. The antisense reagent may be antisense oligonucleotides (ODN), particularly synthetic ODN having chemical modifications from native nucleic acids, or nucleic acid constructs that express such antisense molecules as RNA. The antisense sequence is complementary to the mRNA of the targeted gene, and inhibits expression of the targeted gene products. Antisense molecules inhibit gene expression through various mechanisms, e.g. by reducing the amount of mRNA available for translation, through activation of RNAse H, or steric hindrance. One or a combination of antisense molecules may be administered, where a combination may comprise multiple different sequences.

[0134] Antisense molecules may be produced by expression of all or a part of the target gene sequence in an appropriate vector, where the transcriptional initiation is oriented such that an antisense strand is produced as an RNA molecule. Alternatively, the antisense molecule is a synthetic oligonucleotide. Antisense oligonucleotides will generally be at least about 7, usually at least about 12, more usually at least about 20 nucleotides in length, and not more than about 500, usually not more than about 50, more usually not more than about 35 nucleotides in length, where the length is governed by efficiency of inhibition, specificity, including absence of cross-reactivity, and the like.

[0135] Antisense oligonucleotides may be chemically synthesized by methods known in the art (see Wagner et al. (1993) supra. and Milligan et al., supra.) Preferred oligonucleotides are chemically modified from the native phosphodiester structure, in order to increase their intracellular stability and binding affinity. A number of such modifications have been described in the literature, which alter the chemistry of the backbone, sugars or heterocyclic bases.

[0136] In one embodiment of the invention, RNAi technology is used. As used herein, RNAi technology refers to a process in which double-stranded RNA is introduced into cells expressing a candidate gene to inhibit expression of the candidate gene, i.e., to "silence" its expression. The dsRNA is selected to have substantial identity with the candidate gene. In general such methods initially involve transcribing a nucleic acids containing all or part of a candidate gene into single- or double-stranded RNA. Sense and anti-sense RNA strands are allowed to anneal under appropriate conditions to form dsRNA. The resulting dsRNA is introduced into cells via various methods. Usually the dsRNA consists of two separate complementary RNA strands. However, in some instances, the dsRNA may be formed by a single strand of RNA that is self-complementary, such that the strand loops back upon itself to form a hairpin loop. Regardless of form, RNA duplex formation can occur inside or outside of a cell.

[0137] dsRNA can be prepared according to any of a number of methods that are known in the art, including in vitro and in vivo methods, as well as by synthetic chemistry approaches. Examples of such methods include, but are not limited to, the methods described by Sadher et al. (Biochem. Int. 14:1015, 1987); by Bhaltacharyya (Nature 343:484, 1990); and by Livache, et al. (U.S. Pat. No. 5,795,715), each of which is incorporated herein by reference in its entirety. Single-stranded RNA can also be produced using a combination of enzymatic and organic synthesis or by total organic synthesis. The use of synthetic chemical methods enable one to introduce desired modified nucleotides or nucleotide analogs into the dsRNA. dsRNA can also be prepared in vivo according to a number of established methods (see, e.g., Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd ed.; Transcription and Translation (B. D. Hames, and S. J. Higgins, Eds., 1984); DNA Cloning, volumes I and II (D. N. Glover, Ed., 1985); and Oligonucleotide Synthesis (M. J. Gait, Ed., 1984, each of which is incorporated herein by reference in its entirety).

[0138] A number of options can be utilized to deliver the dsRNA into a cell or population of cells. For instance, RNA can be directly introduced intracellularly. Various physical methods are generally utilized in such instances, such as administration by microinjection (see, e.g., Zernicka-Goetz, et al. (1997) Development 124:1133-1137; and Wianny, et al. (1998) Chromosoma 107: 430-439). Other options for cellular delivery include permeabilizing the cell membrane and electroporation in the presence of the dsRNA, liposome-mediated transfection, or transfection using chemicals such as calcium phosphate. A number of established gene therapy techniques can also be utilized to introduce the dsRNA into a cell. By introducing a viral construct within a viral particle, for instance, one can achieve efficient introduction of an expression construct into the cell and transcription of the RNA encoded by the construct.

Compound Screening

[0139] Compound screening may be performed using an in vitro model, a genetically altered cell or animal, or purified protein corresponding to any one of the provided pressure overload associated genes. One can identify ligands or substrates that bind to, inhibit, modulate or mimic the action of the encoded polypeptide.

[0140] The polypeptides include those encoded by the provided genetic sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants

thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, a phosphorylation site or an acetylation site, or to minimize misfolding by substitution or deletion of one or more cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (e.g., a functional domain and/or, where the polypeptide is a member of a protein family, a region associated with a consensus sequence). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Fragments of interest will typically be at least about 10 aa to at least about 15 aa in length, usually at least about 50 aa in length, and can be as long as 300 aa in length or longer, but will usually not exceed about 500 aa in length, where the fragment will have a contiguous stretch of amino acids that is identical to a polypeptide encoded by a pressure overload associated gene, or a homolog thereof.

[0141] Transgenic animals or cells derived therefrom are also used in compound screening. Transgenic animals may be made through homologous recombination, where the normal locus corresponding to a pressure overload associated gene is altered. Alternatively, a nucleic acid construct is randomly integrated into the genome. Vectors for stable integration include plasmids, retroviruses and other animal viruses, YACs, and the like. A series of small deletions and/or substitutions may be made in the coding sequence to determine the role of different domains. Of interest is the use of pressure overload associated genes to construct transgenic animal models for heart failure. Specific constructs of interest include antisense sequences that block expression of the targeted gene and expression of dominant negative mutations. A detectable marker, such as lac Z may be introduced into the locus of interest, where up-regulation of expression will result in an easily detected change in phenotype. One may also provide for expression of the target gene or variants thereof in cells or tissues where it is not normally expressed or at abnormal times of development. By providing expression of the target protein in cells in which it is not normally produced, one can induce changes in cell behavior.

[0142] Compound screening identifies agents that modulate function of the pressure overload associated gene. Of particular interest are screening assays for agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, and the like. Knowledge of the 3-dimensional structure of the encoded protein, derived from crystallization of purified recombinant protein, could lead to the rational design of small drugs that specifically inhibit activity. These drugs may be directed at specific domains.

[0143] The term "agent" as used herein describes any molecule, e.g. protein or pharmaceutical, with the capability of altering or mimicking the physiological function of a pressure overload associated associated gene. Generally a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a differential response to the various concentrations. Typically one of these concentrations serves as a negative control, i.e. at zero concentration or below the level of detection.

[0144] Candidate agents encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 50 and less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof.

[0145] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides and oligopeptides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means, and may be used to produce combinatorial libraries. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, amidification, etc. to produce structural analogs. Test agents can be obtained from libraries, such as natural product libraries or combinatorial libraries, for example. A number of different types of combinatorial libraries and methods for preparing such libraries have been described, including for example, PCT publications WO 93/06121, WO 95/12608, WO 95/35503, WO 94/08051 and WO 95/30642, each of which is incorporated herein by reference.

[0146] Where the screening assay is a binding assay, one or more of the molecules may be joined to a label, where the label can directly or indirectly provide a-detectable signal. Various labels include radioisotopes, fluorescers, chemiluminescers, enzymes, specific binding molecules, particles, e.g. magnetic particles, and the like. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin, etc. For the specific binding members, the complementary member would normally be labeled with a molecule that provides for detection, in accordance with known procedures.

[0147] A variety of other reagents may be included in the screening assay. These include reagents like salts, neutral proteins, e g. albumin, detergents, etc that are used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions. Reagents that improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc. may be used. The mixture of components are added in any order that provides for the requisite binding. Incubations are performed at any suitable temperature, typically between 4 and 40° C. Incubation periods are selected for optimum activity,

but may also be optimized to facilitate rapid high-throughput screening. Typically between 0.1 and 1 hours will be sufficient.

[0148] Preliminary screens can be conducted by screening for compounds capable of binding to a pressure overload associated gene product, as at least some of the compounds so identified are likely inhibitors. The binding assays usually involve contacting a protein with one or more test compounds and allowing sufficient time for the protein and test compounds to form a binding complex. Any binding complexes formed can be detected using any of a number of established analytical techniques. Protein binding assays include, but are not limited to, methods that measure co-precipitation, co-migration on non-denaturing SDS-polyacrylamide gels, and co-migration on Western blots. The protein utilized in such assays can be naturally expressed, cloned or synthesized.

[0149] Compounds that are initially identified by any of the foregoing screening methods can be further tested to validate the apparent activity. The basic format of such methods involves administering a lead compound identified during an initial screen to an animal that serves as a model for humans and then determining if an pressure overload associated gene is in fact differentially regulated. The animal models utilized in validation studies generally are mammals. Specific examples of suitable animals include, but are not limited to, primates, mice, and rats.

[0150] Active test agents identified by the screening methods described herein can serve as lead compounds for the synthesis of analog compounds. Typically, the analog compounds are synthesized to have an electronic configuration and a molecular conformation similar to that of the lead compound. Identification of analog compounds can be performed through use of techniques such as self-consistent field (SCF) analysis, configuration interaction (CI) analysis, and normal mode dynamics analysis. Computer programs for implementing these techniques are available. See, e.g., Rein et al., (1989) Computer-Assisted Modeling of Receptor-Ligand Interactions (Alan Liss, New York).

[0151] Once analogs have been prepared, they can be screened using the methods disclosed herein to identify those analogs that exhibit an increased ability to modulate gene product activity. Such compounds can then be subjected to further analysis to identify those compounds that appear to have the greatest potential as pharmaceutical agents. Alternatively, analogs shown to have activity through the screening methods can serve as lead compounds in the preparation of still further analogs, which can be screened by the methods described herein. The cycle of screening, synthesizing analogs and re-screening can be repeated multiple times.

[0152] Compounds identified by the screening methods described above and analogs thereof can serve as the active ingredient in pharmaceutical compositions formulated for the treatment of various disorders, including a propensity for heart failure. The compositions can also include various other agents to enhance delivery and efficacy. The compositions can also include various agents to enhance delivery and stability of the active ingredients.

[0153] Thus, for example, the compositions can also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers of diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, buffered water, physiological saline, PBS, Ringer's solution, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation can include other carriers, adjuvants, or non-toxic, nontherapeutic, nonimmunogenic stabilizers, excipients and the like. The compositions can also include additional substances to approximate physiological conditions, such as pH adjusting and buffering agents, toxicity adjusting agents, wetting agents and detergents.

[0154] The composition can also include any of a variety of stabilizing agents, such as an antioxidant for example. When the pharmaceutical composition includes a polypeptide, the polypeptide can be complexed with various well-known compounds that enhance the in vivo stability of the polypeptide, or otherwise enhance its pharmacological properties (e.g., increase the half-life of the polypeptide, reduce its toxicity, enhance solubility or uptake). Examples of such modifications or complexing agents include sulfate, gluconate, citrate and phosphate. The polypeptides of a composition can also be complexed with molecules that enhance their in vivo attributes. Such molecules include, for example, carbohydrates, polyamines, amino acids, other peptides, ions (e.g., sodium, potassium, calcium, magnesium, manganese), and lipids.

[0155] Further guidance regarding formulations that are suitable for various types of administration can be found in Remington's Pharmaceutical Sciences, Mace Publishing Company, Philadelphia, Pa., 17th ed. (1985). For a brief review of methods for drug delivery, see, Langer, Science 249:1527-1533 (1990).

[0156] The pharmaceutical compositions can be administered for prophylactic and/or therapeutic treatments. Toxicity and therapeutic efficacy of the active ingredient can be determined according to standard pharmaceutical procedures in cell cultures and/or experimental animals, including, for example, determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD_{50}/ED_{50}. Compounds that exhibit large therapeutic indices are preferred.

[0157] The data obtained from cell culture and/or animal studies can be used in formulating a range of dosages for humans. The dosage of the active ingredient typically lines within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized.

[0158] The pharmaceutical compositions described herein can be administered in a variety of different ways. Examples include administering a composition containing a pharmaceutically acceptable carrier via oral, intranasal, rectal, topical, intraperitoneal, intravenous, intramuscular, subcutaneous, subdermal, transdermal, and intrathecal methods.

[0159] Formulations suitable for parenteral administration, such as, for example, by intraarticular (in the joints),

intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

[0160] The components used to formulate the pharmaceutical compositions are preferably of high purity and are substantially free of potentially harmful contaminants (e.g., at least National Food (NF) grade, generally at least analytical grade, and more typically at least pharmaceutical grade). Moreover, compositions intended for in vivo use are usually sterile. To the extent that a given compound must be synthesized prior to use, the resulting product is typically substantially free of any potentially toxic agents, particularly any endotoxins, which may be present during the synthesis or purification process. Compositions for parental administration are also sterile, substantially isotonic and made under GMP conditions.

Experimental

[0161] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0162] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

[0163] The present invention has been described in terms of particular embodiments found or proposed by the present inventor to comprise preferred modes for the practice of the invention. It will be appreciated by those of skill in the art that, in light of the present disclosure, numerous modifications and changes can be made in the particular embodiments exemplified without departing from the intended scope of the invention. For example, due to codon redundancy, changes can be made in the underlying DNA sequence without affecting the protein sequence. Moreover, due to biological functional equivalency considerations, changes can be made in protein structure without affecting the biological action in kind or amount. All such modifications are intended to be included within the scope of the appended claims.

[0164] The mammalian heart responds to pressure overload by undergoing left ventricular hypertrophy (LVH) and left atrial enlargement (LAE). The response to pressure overload is mediated in large part by alterations in gene transcription, and previous studies using standard molecular biological, computational, and, recently, microarray techniques have identified a number of genes involved in the pathophysiology of LVH. Many of the differentially expressed genes identified in these earlier studies are involved in cytoskeletal and matrix remodeling, myosin isoform switching (MHCα to MHCβ), TGFβ signaling, and a general reactivation of fetal gene expression patterns. Transcriptional downregulation of components of the fatty acid oxidation pathway in the hypertrophic LV has also been noted, though there has been little previous evidence of alterations in other energy metabolism pathways.

[0165] While previous studies have examined transcriptional changes in the LV, almost no attention has been paid to the changes which occur in the other heart chambers in response to pressure overload.

[0166] Transverse aortic constriction (TAC) was used to induce LVH and LAE in young adult mice, and then performed genome-wide transcriptional profiling on each of the four heart chambers from TAC and sham operated animals. Transcription of thousands of genes is significantly altered in the hypertrophic LV and enlarged LA, with an unexpectedly dramatic shift in the transcriptional profile of the TAC LA. No significant transcriptional changes are seen in the right atrium or right ventricle. Using Gene Ontology group enrichment analysis, we identified biological process groups with significant changes in group-wide expression, and found major new and unexpected changes in energy metabolism, cell cycle regulation, and signaling pathways in the LA and LV which may profoundly affect our understanding of the molecular basis of the heart's response to pressure overload.

Materials and Methods

[0167] Animal surgery, RNA preparation and hybridization. Twenty male FVB mice, age 8 weeks, underwent transverse aortic constriction performed as described by Nakamura et al. (2001) Am J Physiol Heart Circ Physiol. 281:H1104-12; and Rockman et al. (1991) Proc Natl Acad Sci USA. 1991;88:8277-81. Twenty male age matched littermates underwent the identical surgical procedure without placement of the aortic band and served as sham-operated controls.

[0168] Hearts were harvested 20 days after operation. Chambers from 15 TAC and 15 sham hearts were divided into three independent pools for RNA isolation (5 mice per pool) to obtain sufficient RNA to perform three biological replicate microarray hybridizations for each chamber. Heart harvest, chamber dissection, RNA preparation, and array hybridizations were performed as previously described in Tabibiazar et al. (2003) *Circ Res.*

[0169] Microarray construction. The Mouse Transcriptome Microarray used in this study was constructed in our laboratory in collaboration with the Stanford Functional Genomics Facility. Briefly, the microarray is composed of 43,200 mouse cDNA probes representing ~25,000 unique genes and ESTs. It is composed of the National Institutes of Aging 15 k developmental gene set, the Riken 22 k gene set, and approximately 5,000 other unique clones chosen for their biological interest.

[0170] Data acquisition, processing, and statistical analysis. Image acquisition, processing, and normalization of the mouse cDNA microarray data was performed as described previously. Microarray experiments were performed using three biological replicates for each tissue and control. Features with values significantly above background in at least two out of three biological replicates were used for two-group statistical comparisons.

[0171] The Significance Analysis of Microarrays (SAM) algorithm was employed to identify genes with statistically different expression levels between TAC and sham for each of the chambers. Hierarchical clustering was performed using a set of variable genes (ANOVA, $p<0.005$ across all experiments) as described by Tabibiazar et al. (2003), supra. Heat maps were prepared using Heatmap Builder, Version 1. The approach to data analysis is summarized in **FIG. 1**.

[0172] Statistical analysis of over- and under-representation within Gene Ontology categories was performed by applying Fisher's exact test to SAM flagged genes using GoMiner analysis software.

[0173] Quantitative real-time reverse transcriptase-polymerase chain reaction. Primers and probes for 9 representative genes were obtained from Applied Biosystems' Assays-on-Demand. Quantitative rtPCR was performed as described by Tabibiazar et al. (2003), supra.

Results

[0174] Induction of cardiac hypertrophy. Hearts were harvested 20 days after operative intervention at a point when LV hypertrophy and echocardiographic indices had reached equilibrium (Nakamura et al. (2001) *Am J Physiol Heart Circ Physiol.* 281:H1104-12). Transverse aortic constriction induced an increase in heart weight of ~50% (TAC 0.192±0.03 g, sham 0.133±0.007 g, $p<0.03$), and an increase in heart to body weight ratio of 11% (TAC 5.27+/-0.69, sham 4.72+/-0.32, $p<0.03$), as expected. On inspection, the left atria and left ventricles of TAC operated animals were visibly greatly enlarged, and the left ventricular wall thickness was increased.

[0175] Overview of gene expression patterns—clustering analysis. Twenty-four heart chamber mRNA samples derived from 30 individual animals were labeled and hybridized in triplicate to microarrays containing 42,300 elements, totaling over 1 million gene expression measurements. Hierarchical clustering of the data revealed a large change in the transcriptional profile of the TAC left atria, (**FIG. 2**) resulting in their clustering more closely with ventricles than with atria. The remainder of the atrial samples clustered as expected, with the sham LA tissues in one subgroup, and TAC and sham RA tissues in another. Left ventricles from TAC mice formed a distinct subcluster within the ventricular group, while the TAC RV and sham RV and LV cluster more closely together, suggesting there is little transcriptional change from the ventricular baseline in these tissues. These clustering results show that the most significant changes in transcription take place in the LA and LV, the two heart chambers most directly affected by increased afterload.

[0176] Differential gene expression in the left atria and left ventrcles of TAC mice. Using SAM, we identified 891 upregulated and 1001 downregulated genes in the TAC LA (false detection rate (FDR) <0.01) (**FIG. 3a**). A heatmap of these variable genes highlights genes whose expression in the TAC LA was similar to the ventricular pattern (**FIG. 4**). In the LV, SAM identified 42 upregulated and 532 downregulated genes (FDR<0.20)(**FIG. 3*b***). Overall, the differentially regulated genes, and their direction of change in expression, are similar in the LA and LV. SAM analysis of RV and RA data demonstrated that there are no significant differences in gene expression in these tissues. T-tests identified only a small number of genes in the RA and RV with differential expression that trended toward significance.

[0177] GO functional group enrichment analysis of differentially regulated genes demonstrates coordinated regulation of biological processes. We applied Fisher's exact test to the 8773 unique GO annotated genes on the array to identify statistically significantly enriched and depleted GO groups in the TAC LA and LV. (**FIG. 5**). In the TAC LA, among the most significantly upregulated processes were signaling pathway activation, blood vessel development/angiogenesis, cell matrix and adhesion, and cytoskeletal organization. Downregulated processes were dominated in both the TAC LA and LV by energy pathways, including downregulation of genes involved in fatty acid oxidation, the TCA cycle, and oxidative phosphorylation. Because of the small number of upregulated genes in the TAC LV, statistical GO group analysis was not considered to be valid.

[0178] Transcriptional regulation of signaling pathways. The physiological stresses of pressure overload must be transduced into molecular signals to actuate compensatory mechanisms in cardiac cells. Deciphering which genes and pathways are involved in this transduction is of central importance, since they are some of the most interesting targets for further investigation and, potentially, drug development. In this study, we have identified many specifically regulated genes from a number of signaling pathways that have not previously been implicated in the pressure overload response.

[0179] Signaling through the transforming growth factor-β superfamily pathways is thought to modulate the cardiac response to stress, but the role of many of the downstream molecules has not been well characterized. We found significant increases in the transcription of TGF-β82, BMP2, BMP4, BMP receptor 1A, and endoglin, a component of the TGF-β receptor complex involved in angiogenesis and vessel identity. In addition, transcription of many downstream genes, including TGF-β induced transcript 1, latent transforming growth factor-β binding protein 3, activin receptor-like kinase 1, and SMADs 2, 5, 6, and 7 was significantly increased in the TAC LA, implicating them in the pressure response.

[0180] G-protein coupled receptor (GPCR) signaling pathways play a key role in the cardiac response to pressure overload. The most striking finding was the 3.6-fold downregulation of regulator of G-protein signaling 2 (RGS2) in both the LA and LV of banded mice. This gene is critically important in the regulation of blood pressure and vascular smooth muscle relaxation. Expression of the related genes RGS 3, 4, and 5 was significantly upregulated (~2-fold) in the TAC LA but not LV. Other modifiers of GPCR signaling, the Rho small GTPases, are also specifically regulated in pressure overload. Expression of Rho A2, C, D, and G is highly significantly increased, and Rho GDP dissociation inhibitor alpha, which disrupts cardiac morphogenesis when overexpressed in the heart, is upregulated by 2.5-fold. In total, 7 of 28 annotated Rho signal transduction genes and 22 of 181 small GTPase signal transduction genes are upregulated, suggesting that this signaling pathway is integrally involved in the pressure overload response.

[0181] Transcription of several pathways involved in cell-cell signaling and physiological regulation is also dramatically impacted in pressure overload. For example, many components of angiogenic signaling pathways including VEGF A, VEGF C, VEGF-D (fos induced growth factor), neuropilin, TIE 1 tyrosine kinase receptor, angiopoietin 2, endoglin, PDGF receptor beta polypeptide, MCAM, protein O-fucosyltransferase 1, integrin alpha V, endothelial PAS domain protein 1 (HIF 2 alpha), and hypoxia inducible factor 1a are upregulated in the LA, as is chemokine receptor

CXCR 4, a transcript directly induced by HIF. Altered hemodynamics in the LA also leads to regulation of a number of vasoactive peptides; transcription of endothelin receptor b was upregulated by 2-fold, while transcription of endothelin itself was downregulated 2-fold. Angiotensin converting enzyme (3,4-fold), angiotensin receptor-like 1 (Apelin receptor)(2,3-fold), adrenomedullin (2.5fold), and myotrophin (3,4-fold) were also upregulated in the LA, suggesting that the left atrium may be especially important in sensing and responding to volume conditions.

Transcriptional Regulation of Downstream Processes

[0182] Matrix and cytoskeletal remodeling. In response to the signals documented above, the pressure overloaded heart undergoes substantial tissue and cellular remodeling. Since much of this remodeling is maladaptive, and drugs which interrupt the process promote survival, (Jessup and Brozena (2003) *N Engl J Med.* 348:2007-18) it is important to understand which specific genes are involved. Many matrix and cell adhesion genes are highly differentially regulated, with expression differences from 5-15 fold. Expression of specific collagens is upregulated (types I, III, IV, V, VI, VIII, XV, XVI, XVIII) or downregulated (types II, IX, XI, XIV, as are specific MMPs (2 and 23 upregulated, 3, 8, 13, and 16 downregulated). One of the most highly regulated ECM genes is osteoblast specific factor 2, which has also been identified in other surveys of pressure overload. In all, more than 40 cell adhesion genes are upregulated in the TAC LA (**FIG. 5**).

[0183] Dynamic cytoskeletal remodeling also occurs in response to pressure overload. Transcription of a large number of actins and other cytoskeletal proteins is highly upregulated in the TAC tissues, including beta cytoplasmic actin, catenin beta, cofilin 1 (non-muscle), alpha actinin 1, coronin, dynein cytoplasmic light chain 1, thymosin beta 4 and 10, tropomodulin 3, calponin 2, destfin, drebrin, epithelial protein lost in neoplasm, vinculin, LIM and SH-3 protein 1, actin related protein complex 2/3 subunits 1B and 3, glia maturation factor beta, moesin, and the atypical, myosins Ic, Va, and X (**FIG. 1*a***). Transcription of several actin related genes including α2 smooth muscle actin, γ-cytoplasmic actin, and four-and-a-half LIM domains 1 is also upregulated in the TAC LV. In the overabundance analyses, 30 of 298 annotated cytoskeletal and structural genes are upregulated in the TAC LA (**FIG. 5**). This highly specific regulation of a broad range of matrix and cytoskeletal genes demonstrates that the significant remodeling that is taking place is following a precise molecular script.

[0184] There are many points at which this maladaptive process be interrupted, such as specific inhibition of matrix metalloproteinases or potentiation of TIMPs, which can provide treatment of new aspects of the disease process.

[0185] Precisely regulated expression of cell cycle factors. Another prominent downstream target of signaling in pressure overload is the cell cycle machinery. Over 30 of 328 cell cycle genes are upregulated in the TAC LA; importantly, these genes are a clearly delineated subset of the G1 cell cycle machinery. Transcription of the early G1 cyclins D1 and D2 is elevated 2.4-to 4.7-fold in both the TAC LA and LV while there is no change in the late G1 cyclin E, necessary for entry into S-phase, or cyclin B, necessary for the G2/M phase transition. Inhibition of cyclin D expression or the downstream E2F in primary cardiomyocyte culture has been shown to prevent the development of cardiomyocyte hypertrophy. Thus, it appears that cyclin D/CDK activity without cell cycle progression promotes the hypertrophic response by facilitating increased transcription of prohypertrophic genes. Our finding that this mechanism is active in vivo in the LA and LV indicates that targeted inhibition of D-type cyclin activity provides another therapeutic approach to hypertrophy.

[0186] Altered regulation of energy metabolism. One of the most prominent and interesting targets of signaling in the pressure overloaded heart is energy metabolism. In both the LA and LV, there is a major downregulation of mitochondrial oxidative phosphorylation, the TCA cycle, and fatty acid oxidation in the TAC LA and LV. Transcription of over 40 genes associated with complexes (I-V) of the mitochondrial oxidative phosphorylation and respiratory chain machinery is dramatically downregulated, as are 7 TCA cycle genes and a large number of lipid metabolism and fatty acid oxidation pathway genes. (**FIGS. 5, 6**) These metabolic alterations have profound implications in a signaling feedback mechanism which may perpetuate hypertrophy.

[0187] Differential expression of hundreds of uncharacterized ESTs. A major benefit of performing microarray analyses is the ability to recognize new, uncharacterized genes which may be involved in disease processes. We have identified over 200 upregulated and 400 downregulated ESTs which respond to pressure overload. Further analysis of these novel genes can provide unique insights into the biology of the cardiac response to stress.

[0188] Quantitative realtime polymerase chain reaction confirmation of array results. Quantitative realtime polymerase chain reaction (qRT-PCR) was performed using primers for nine representative genes involved in the major processes discussed to verify that array results represent true expression differences. Each of the genes was shown to be regulated similarly in the qRT-PCR and array measurements, with the qRT-PCR data showing slightly larger measured differences in most cases (**FIG. 7**).

[0189] Heart failure is the leading cause of morbidity in western cultures. Commonly, the disease process begins with the development of LVH and LAE due to an increase in afterload, often as the result of systemic hypertension or aortic valve disease. We have used microarray profiling of the TAC mouse model of pressure overload to obtain a more comprehensive view of the genes and processes involved in the heart's response to increased afterload.

[0190] Previous studies of cardiac pressure overload have focused on only one heart chamber, the left ventricle, and have used significantly smaller microarrays. By using more comprehensive microarrays and improved statistical techniques to analyze transcription in the LV, we have been able identify important and previously unrecognized genes, pathways, and processes which mediate changes in the hypertrophic LV.

[0191] While the LV takes the brunt of the pressure insult, we know that during pressure overload the left atrium faces physiological challenges due to mitral regurgitation and increased wall stress which result in enlargement and remodeling. Many of the most important clinical complications of hypertrophic cardiomyopathy, valvulvar heart disease, and congestive heart failure are due to atrial enlargement, and include atrial fibrillation and other electrophysiological disturbances, as well as hemodynamic compromise caused by decreased ventricular filling. Knowing which genes and processes are associated with the atrial response may give us important clues about how to intervene in this disease process, but no studies have previously

examined the transcriptional changes in the left atrium in this setting. Surprisingly, the transcriptional changes in the enlarged LA are tremendous, and much greater in scope and magnitude than the changes in the LV at this timepoint.

[0192] Similarly, no previous studies have examined whether increased pulmonary capillary wedge pressure or systemic neurohumoral changes due to left sided stresses induce transcriptional changes in the right ventricle and atrium. By examining transcription in the RA and RV, we have shown that at this point in the process, which is characterized by substantial left ventricular hypertrophy and left atrial enlargement, transcription in the RA and RV is essentially unchanged.

[0193] Our findings provide answers to a number of intriguing questions about the biology of heart failure. We know that physiological stresses such as stretch, shear, and hypoxia must be transduced into cellular signals. The data indicate that a number of different pathways are utilized in specific ways. For example, we see evidence for activation of TGFβ superfamily pathways from the extracellular space (TGFβ2, BMP2 and 4), to cell surface receptors (endoglin, BMP receptor 1a , ACVRL), to downstream transcription factors (SMADs). While the participation of TGFβ itself in the response to pressure overload has been suspected for some time, this is the first demonstration that BMPs and their receptors are involved. Mutations in the BMP pathways may be responsible for inherited cardiomyopathies, and whether targeted myocardial overexpression predisposes the heart to hypertrophy. If so, components of these BMP pathways may be tempting targets for the development of drugs aimed at interrupting the hypertrophic response.

[0194] Another unique observation from these investigations is that angiogenic signaling pathways are upregulated in the TAC LA, from extracellular VEGFs A, C and D, to receptors (Tie1, neuropilins), to transcription factors (Hif1α). This is likely the result of increased workload that leads to myocardial hypoxia followed a by robust angiogenic response.

[0195] Energy generation in the normal adult myocardium is primarily dependent on oxidative metabolism of long-chain fatty acids through the TCA cycle and mitochondrial oxidative phosphorylation, all of which we find to be dramatically transcriptionally downregulated in both the LA and LV. Though a metabolic substrate switch from fatty acids to glucose in LV hypertrophy is a well known phenomenon, there has been little previous evidence of altered expression of mitochondrial respiratory chain genes with only a few instances of decreased transcription (COX I and IV, adenine nucleotide transporter 1, F1ATPase α and β) or protein levels (ANT1, F1 ATPase α and β cytochrome c oxidase, cytochrome b5) in stressed hearts reported. We find that transcription of more than 40 genes coding for multiple components of all five complexes of the respiratory chain is dramatically downregulated in both the TAC LA and LV (**FIG. 5**). This concerted metabolic switch from oxygen intensive fatty acid oxidation and oxidative phosphorylation (4.1 mole ATP/1 mole O_2) to glycolysis (6.3 mole ATP/1 mole O_2) probably represents a response to relative hypoxia resulting from increased myocardial work and increased oxygen extraction. This response, however, leads to lower energy production in the form of ATP.

[0196] What are the potential effects of this energy deficit on the myocardium? We know that a number of mutations in disparate energy pathway genes such as the mitochondrial fatty acid importer CD36, very long chain acyl-CoA dehydrogenase, adenine nucleotide translocator-1, and mitochondrial tRNA result in inefficient ATP production and lead to hypertrophic cardiomyopathy. Another major class of inherited cardiomyopathies is due to sarcomeric protein mutations, many of which result in inefficient ATP utilization. This has led to the development of a model in which end-systolic ATP depletion prevents effective cytosolic calcium clearance by the SERCA2 pump, which is exquisitely sensitive to ATP levels. Prolonged cytosolic calcium transients then activate calcium sensitive mediators such as calcineurin, calmodulin, and CaM kinase, leading to hypertrophic stimulation.

[0197] The dramatic downregulation of oxidative phosphorylation observed herein certainly also leads to decreased ATP production in accordance with this model. The likely proximate cause for downregulation of ox-phos in the pressure overloaded and hypoxic tissues is to prevent the production of immediately toxic reactive oxygen species; unfortunately, this leads to a cycle-of hypertrophy, increased oxygen demand, ATP depletion, and further hypertrophic signaling. (**FIG. 8**)

[0198] The response to cardiac pressure overload requires the coordinated regulation of transcription of thousands of genes in the left atrium and left ventricle. Microarray transcription profiling and rigorous and innovative statistical techniques are used to identify the specific genes and the general biological processes which are modulated in a standard mouse model of LV hypertrophy and LA enlargement. Transcriptional patterns demonstrate significant alterations in energy metabolism, cell cycle regulation, remodeling, and signaling transduction. This study provides important insights into the pathophysiology of LVH and LAE, and identifies numerous new targets diagnosis and therapy.

TABLE I

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

S0 percentile	0.03
False Significant Number (Median, 90 percentile)	(19.57943, 55.64681)
False Discovery Rate (Median, 90 percentile)	(1.03485, 2.94116)
Pi0Hat	0.51525

Gene Name	Gene ID	Score(d)	Fold Change
768 Positive Significant Genes_Upregulated			
**CD8 antigen, beta chain	BG073140	4.935952744	1.62458
**DNA segment, Chr 1, ERATO Doi 471, expressed	BG067625	6.679778765	2.17829
**ESTs, Weakly similar to CG1_HUMAN CG1 PROTEIN [*H. sapiens*]	BG072335	5.639596521	2.12391

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

**expressed sequence AI324259	AA030895	5.862670201	2.27914
**expressed sequence AW986256	AW908312	4.547379287	1.76174
**guanine nucleotide binding protein, alpha 13	BG073165	5.298455537	1.78085
**itchy	BG074097	5.958778311	1.78255
**lymphoid blast crisis-like 1	BG063325	5.481956898	1.83237
**N-acetylated alpha-linked acidic dipeptidase 2	BG069303	10.26035569	2.13623
**ribophorin 2, related sequence 1	BG065724	4.279942955	1.63117
**RIKEN cDNA 1110005E01 gene	BG072956	6.320481699	2.65102
**RIKEN cDNA 2210419I08 gene	BG072630	4.443289031	2.74871
**RIKEN cDNA 9130023P14 gene	BG073847	4.898954283	2.03363
**secreted acidic cysteine rich glycoprotein	BG065013	4.305756425	5.37944
**selected mouse cDNA on the X	BG075333	5.40756834	1.96253
a disintegrin and metalloproteinase domain 15 (metargidin)	AI841353	6.418564533	1.69879
A kinase (PRKA) anchor protein 2	AV024684	9.339968419	2.37728
A20 binding inhibitor of NF-kappaB activation-2	AV051979	4.833606233	1.36115
actin related protein 2/3 complex, subunit 1B (41 kDa)	AV000246	5.339644842	3.15358
actin related protein 2/3 complex, subunit 3 (21 kDa)	AV103730	4.357179662	1.72106
actin, alpha 1, skeletal muscle	AV085882	4.680715563	2.52776
actin, alpha 2, smooth muscle, aorta	AA815993	4.742146264	2.50123
adaptor protein complex AP-1, sigma 1	AV133937	5.115943193	1.75715
adenylate cyclase 7	BG063167	5.836599536	1.97081
ADP-ribosylation factor 2	AV030860	4.970811116	1.83182
ADP-ribosylation factor 4	AV103043	4.859284926	1.70300
ADP-ribosylation-like factor 6 interacting protein 5	AV032992	5.254319701	1.99125
adrenomedullin	BG063461	21.13558162	2.44953
aldehyde dehydrogenase family 1, subfamily A1	BG073939	5.362174526	2.10401
alpha actinin 4	AA000257	8.732257466	2.60533
alpha glucosidase 2, alpha neutral subunit	BG074747	6.505408498	2.20388
amyloid beta (A4) precursor protein	AV028985	9.791283359	2.57737
amyloid beta (A4) precursor protein-binding, family B, member 2	BG074998	4.702942915	1.59024
amyloid beta (A4) precursor-like protein 2	AV070218	5.099119145	1.98500
anaphase-promoting complex subunit 5	AV162432	4.760379367	2.04115
angiopoietin 2	BG176309	8.307441471	1.96272
angiotensin converting enzyme	AV043404	6.765684823	3.37500
angiotensin receptor-like 1	AV025146	5.137112984	2.30047
ankyrin repeat hooked to zinc finger motif	AV233612	5.258631025	2.31219
annexin A3	AV218319	5.580106736	2.46726
annexin A5	AV087971	10.63486669	2.44345
annexin A7	AV083120	6.629951533	1.67612
antigen identified by monoclonal antibody MRC OX-2	AV070419	9.074059959	3.86021
aquaporin 1	AV025941	4.616039959	1.60363
ATPase, Cu++ transporting, alpha polypeptide	AV173744	4.546259988	1.99187
ATPase, H+ transporting, lysosomal 34 kD, V1 subunit D	AU044566	8.432452913	2.47791
ATPase, H+ transporting, lysosomal 70 kD, V1 subunit A, isoform 1	AV031502	4.300354342	1.50397
ATP-binding cassette, sub-family G (WHITE), member 1	U34920	4.75251549	2.19022
basigin	BG064525	4.767661651	1.91891
Bcl-2-related ovarian killer protein	AV086475	4.864063728	3.01715
beclin 1 (coiled-coil, myosin-like BCL2-interacting protein)	AV104535	5.149891952	1.43711
benzodiazepine receptor, peripheral	AV087921	6.339980832	1.76235
beta-2 microglobulin	X01838	4.818860152	1.51526
biglycan	AV170826	4.23050528	9.77739
binder of Rho GTPase 4	AV033754	5.435925244	1.57561
biregional cell adhesion molecule-related/down-regulated by oncogene	AV140458	6.223050315	1.90841
block of proliferation 1	AV055176	4.462862768	2.03097
bone morphogenetic protein 1	BG072809	5.076200526	1.75397
bone morphogenetic protein 2	AV087036	6.312534538	1.97717
bone morphogenetic protein 4	AA498724	26.25531622	5.68709
bone morphogenetic protein receptor, type 1A	D16250	4.802550091	1.70860
bridging integrator 3	AV041000	5.021149627	1.50525
calcium binding protein P22	BG069892	6.038426191	2.12398
calcium binding protein, intestinal	AV089105	5.424073635	2.85345
calcium channel, voltage-dependent, beta 3 subunit	BG072964	6.261620208	2.92954
calponin 2	AV025199	10.46579777	3.67100
calreticulin	AV105953	5.781249515	2.81549
calumenin	AV103772	8.556760191	2.53735
capping protein alpha 1	AV001105	6.759727509	2.71943
caspase 6	AV078409	4.712305758	1.66628
catalase 1	AV006202	4.789401928	1.58530
catenin beta	AA116287	4.625727547	3.51804
cathepsin D	X52886	6.073458864	2.36142
CCR4-NOT transcription complex, subunit 8	AV086227	4.323085101	1.52705
CD 81 antigen	AV171867	5.345211432	1.62394
CD24a antigen	BG076069	4.489826052	2.69550
CD34 antigen	AI893233	5.242368789	1.99835

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

Cd63 antigen	AI838302	7.516141528	1.57199
CD97 antigen	AI325851	4.612899255	1.49007
cell line NK14 derived transforming oncogene	AV085072	7.267896568	1.89454
cellular retinoic acid binding protein I	AV109555	4.284820548	6.21775
chemokine (C-X-C) receptor 4	D87747	11.40652967	4.14082
cholinergic receptor, nicotinic, epsilon polypeptide	AV043279	6.325648118	2.37315
citrate synthase	AV006320	4.319928146	1.74608
CLIP associating protein 1	AV043798	7.870330961	2.45765
coagulation factor II (thrombin) receptor	BG067569	6.360824121	3.46932
coatomer protein complex, subunit gamma 1	AV031224	4.96823225	1.90246
cofilin 1, non-muscle	AV170788	4.418502562	3.52909
cut-like 1 (*Drosophila*)	AV138233	4.699208238	1.90631
cyclin D1	AA111722	8.105067906	4.69475
cyclin D2	AV112821	4.804290349	2.37763
cyclin-dependent kinase 9 (CDC2-related kinase)	BG073423	4.447615705	1.37304
cyclin-dependent kinase inhibitor 1A (P21)	AA184368	4.925894578	2.03325
cystatin C	AV149987	4.597603564	1.69061
cytochrome P450, 2j6	AV147446	5.623033193	1.75987
damage specific DNA binding protein 1 (127 kDa)	BG063543	5.159414426	1.74271
degenerative spermatocyte homolog (*Drosophila*)	AV037185	5.957462607	1.73960
destrin	BG073428	4.348798505	2.67946
diaphanous homolog 1 (*Drosophila*)	U96963	5.838659607	1.91987
diaphorase 1 (NADH)	BG067095	4.899045494	4.08856
dimethylarginine dimethylaminohydrolase 2	BG073732	5.137410647	1.81856
DNA segment, Chr 10, ERATO Doi 398, expressed	BG075070	6.143626337	1.70405
DNA segment, Chr 17, human D6S45	AV133629	4.211882115	1.59857
DNA segment, Chr 5, Bucan 26 expressed	AV069614	5.864980176	1.33431
DNA segment, Chr 6, Wayne State University 116, expressed	AV025747	4.17734088	1.78077
DNA segment, Chr 6, Wayne State University 157, expressed	BG063319	4.778791053	1.37298
DNA segment, Chr 6, Wayne State University 176, expressed	BG074174	5.06659014	1.61445
DNA segment, Chr 8, Brigham & Women's Genetics 1112 expressed	AV083741	12.39491386	4.11124
DnaJ (Hsp40) homolog, subfamily B, member 11	AV103429	4.762415879	1.59127
dolichyl-di-phosphooligosaccharide-protein glycotransferase	BG074138	5.614640775	1.93040
downstream of tyrosine kinase 1	BG075775	4.518520078	3.49959
drebrin 1	AI893388	6.85211633	2.36141
dual adaptor for phosphotyrosine and 3-phosphoinositides 1	AV026192	4.455231001	2.98196
E26 avian leukemia oncogene 1, 5' domain	BG065072	4.66168427	1.92560
ectonucleotide pyrophosphatase/phosphodiesterase 1	BG065640	4.820720624	2.12344
elastin	AV019210	4.312030037	9.08198
ELAV (embryonic lethal, abnormal vision, *Drosophila*)-like 1 (Hu antige⑦	AV066211	6.879063154	1.62078
ELK3, member of ETS oncogene family	BE624428	5.107654756	2.38162
elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeas⑦	AV050518	4.418412743	2.30385
embigin	AV140302	4.484360869	5.19130
endoglin	AV086531	6.471940695	2.94673
endothelial cell-selective adhesion molecule	AV104213	5.050052051	1.60966
endothelial PAS domain protein 1	AV024401	8.285911089	3.72721
endothelin receptor type B	AA646322	6.145920718	2.12895
enhancer of rudimentary homolog (*Drosophila*)	AV109613	6.553746708	1.82896
enigma homolog (*R. norvegicus*)	AV032832	4.944256052	3.43678
epithelial membrane protein 1	X98403	13.58738841	5.24265
epithelial protein lost in neoplasm	AV111531	4.531493283	1.48848
EST	AW550960	19.85526024	9.11485
EST	AW547583	22.95866337	7.72500
EST	AV025040	4.957687972	6.04194
EST	AW549166	4.595440753	3.33061
EST	AW554082	6.275568831	3.30960
EST	S78355	4.608423503	3.25394
EST	AV109453	4.819280814	2.92748
EST	AW540995	4.418897593	2.81516
EST	AW558227	5.708451876	2.56659
EST	AW546256	5.04488313	2.47766
EST	AV087039	5.166733239	2.46773
EST	AW544349	6.584770327	2.44220
EST	AV039967	7.723950024	2.43554
EST	AW536421	4.60287571	2.31306
EST	AV111465	8.781751248	2.25221
EST	AV088410	8.109631088	2.25135
EST	AV140901	6.233643771	2.22461
EST	AV000446	7.438718341	2.15361
EST	AV171584	4.477396404	2.15320
EST	BG071255	11.22819532	2.05956
EST	AW557711	4.212906527	2.05094
EST	AW537424	4.462581095	2.00188
EST	AV042683	4.743621075	1.97510

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

EST	BG063099	4.292752601	1.91866
EST	AV083993	4.328607976	1.88436
EST	AV058573	5.408477871	1.87775
EST	AV070393	6.250654238	1.86022
EST	AV111580	5.931170364	1.85750
EST	AW552177	4.265679471	1.83036
EST	U20156	5.993089117	1.81293
EST	AV036347	10.47139823	1.81269
EST	AV060165	4.411955396	1.76104
EST	AV094706	4.494165965	1.66259
EST	AV039638	4.503534771	1.65226
EST	AW550705	4.519430775	1.64943
EST	AV034332	7.596671753	1.62595
EST	W33396	11.40348429	1.61638
EST	AV011166	5.154200811	1.52498
EST	BI076464	5.448788539	1.48872
EST	AI840788	5.913183312	1.47325
EST	AW548208	4.180285767	1.45699
EST	AV311582	4.533520381	1.45416
EST	AV106736	4.242664931	1.43099
EST	AV015464	4.465624384	1.38793
EST	AV057158	5.371258736	1.37442
EST AA087124	AV087918	4.883999133	1.86715
EST, Moderately similar to A57474 extracellular matrix protein 1 precu⑦	AV087499	7.921172215	2.38462
ESTs	AV024412	4.73782118	8.19962
ESTs	BG073461	11.90278678	4.05199
ESTs	AV033798	4.672511285	2.61520
ESTs	BG064580	5.626668637	2.59721
ESTs	BG067879	8.66729916	2.54050
ESTs	BG076276	6.300156668	2.48193
ESTs	BG071739	8.847636772	2.45591
ESTs	AV032403	12.61514085	2.31331
ESTs	AV078400	4.837085255	2.27415
ESTs	BG073799	8.280866889	2.22741
ESTs	BG076404	4.634204251	2.19874
ESTs	AV014607	4.307653699	2.06730
ESTs	BG073713	6.561139463	1.99167
ESTs	BG071422	7.424409835	1.98279
ESTs	BI076812	5.205004314	1.85616
ESTs	AV013722	5.134325271	1.84817
ESTs	AV011768	4.642319657	1.81806
ESTs	BG068597	5.106651008	1.80365
ESTs	BG070087	4.392989325	1.71777
ESTs	AW548360	4.447121798	1.70141
ESTs	AU040159	5.202446948	1.64202
ESTs	AV059238	4.787621426	1.56132
ESTs	BG071674	5.550982071	1.54806
ESTs, Highly similar to KIAA0356 [*H. sapiens*]	AU043034	5.516554107	1.52378
ESTs, Highly similar to tyrosine phosphatase [*H. sapiens*]	AV085816	4.575361973	2.50854
ESTs, Moderately similar to AAK1 RAT 5'-AMP-ACTIVATED PROTEIN	AV109623	5.911406841	2.27280
ESTs, Moderately similar to AF188634 1 F protein [*D. melanogaster*]	AV083375	4.568649007	1.95386
ESTs, Moderately similar to KIAA0337 [*H. sapiens*]	BG074691	4.825337515	1.56164
ESTs, Moderately similar to S12207 hypothetical protein [*M. musculus*]	AV024981	6.277067603	1.92645
ESTs, Moderately similar to T17285 hypothetical protein DKFZp434N0⑦	BG070270	4.175752257	1.47554
ESTs, Moderately similar to T46312 hypothetical protein DKFZp434J1⑦	BG063981	5.614233932	1.55378
ESTs, Weakly similar to ATPase, class 1, member a; ATPase 8A2, p t⑦	AV021942	5.948732902	2.18491
ESTs, Weakly similar to DnaJ (Hsp40) homolog, subfamily B, member	AV055460	4.218301895	1.86141
ESTs, Weakly similar to SELX_MOUSE SELENOPROTEIN X 1 (SELE⑦	AA016799	4.24930929	2.59695
ESTs, Weakly similar to TUBULIN ALPHA-2 CHAIN [*M. musculus*]	BG069637	7.697591957	2.61021
ESTs, Weakly similar to TYROSINE-PROTEIN KINASE JAK3 [M. musc⑦	BG064647	4.824734913	1.86704
ESTs, Weakly similar to Y43F4B.7.p [*Caenorhabditis elegans*] [C. eleg⑦	AV016534	7.020227711	2.36673
ESTs, Weakly similar to ZINC FINGER PROTEIN ZFP-90 [M. musculu⑦	AV010028	4.601968235	2.80189
ETL1	AV025841	5.647091648	1.71244
eukaryotic translation initiation factor 4A1	BG063879	4.650336504	2.14899
eukaryotic translation initiation factor 4E	AV094728	9.89111267	2.36476
expressed sequence AA408208	BG068911	4.94103443	1.20099
expressed sequence AA408225	BG064180	5.374291641	2.50821
expressed sequence AA408783	AV140475	4.763802282	2.25681
expressed sequence AA409156	BG063366	8.910555681	2.10904
expressed sequence AA414969	AV024857	5.458866268	2.29391
expressed sequence AA517451	BG068828	5.023811923	1.49100
expressed sequence AA589574	AV013217	4.283226237	1.80346
expressed sequence AA960365	BG063068	6.815863912	1.66690
expressed sequence AA986889	AV059924	4.234542123	2.92099

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

expressed sequence AI115505	AV025730	7.461892397	1.96667
expressed sequence AI316797	BG072659	4.914587425	2.36058
expressed sequence AI448102	AV024096	4.73415826	1.77000
expressed sequence AI450948	AW554840	4.372618811	2.43030
expressed sequence AI451006	BG064999	5.00890408	2.04887
expressed sequence AI452336	AV025047	4.324732341	1.54836
expressed sequence AI480459	BG072798	4.542252847	1.93882
expressed sequence AI481106	AV025042	4.89209432	2.42812
expressed sequence AI504145	AV033704	6.252282603	1.96397
expressed sequence AI645998	AV058892	6.153140191	1.71074
expressed sequence AI790744	BG075363	4.48367478	1.83228
expressed sequence AI836219	AV069461	6.473474892	1.26115
expressed sequence AI852829	AV009918	7.894529871	2.08611
expressed sequence AL024047	AV103290	4.73722655	1.67508
expressed sequence AU022349	BG074257	4.17594653	1.59209
expressed sequence AU022349	AV140471	4.330667996	1.40070
expressed sequence AU022549	AV037769	4.734643112	2.21919
expressed sequence AU024550	AV026341	8.658717009	1.91059
expressed sequence AV218468	AV162214	4.845939783	2.30456
expressed sequence AW146116	AV087220	4.922111816	1.82565
expressed sequence AW229038	BG073479	6.074272086	5.58416
expressed sequence AW547365	BG075520	4.708552985	1.82784
expressed sequence AW553532	BG074525	5.208390615	1.92628
expressed sequence C79946	C79946	4.443093726	3.00389
expressed sequence C80501	BG066820	14.53712728	1.78010
expressed sequence C86807	BG067580	5.813108082	1.63424
expressed sequence C87251	AV010913	5.434787975	1.62230
expressed sequence R74732	BG072984	5.028448407	1.92281
expressed sequence R74732	AV051721	5.134983785	1.74936
extracellular matrix protein 1	AV085019	9.887151966	2.46146
F-box only protein 25	AV049438	4.694542333	1.44710
fibrillin 1	AA000350	4.873526108	3.58211
fibroblast growth factor receptor 1	AW476537	5.283837041	1.38006
fibronectin 1	BG072878	8.392583287	9.10080
fibulin 2	BG073227	9.534808735	5.40206
FK506 binding protein 9	AV059445	6.405950764	1.82419
flightless I homolog (*Drosophila*)	AV103121	4.923074719	2.02616
follistatin-like 3	BG063294	4.93440651	2.16520
frizzled-related protein	AV089650	10.88058362	6.12984
frizzled-related protein	AV089650	15.64907314	5.14052
FXYD domain-containing ion transport regulator 6	AV086002	5.73258712	3.32687
G1 to phase transition 1	BG066535	4.937695403	1.78801
GA repeat binding protein, beta 1	AV041052	5.78517292	2.14048
gamma-aminobutyric acid (GABA-B) receptor, 1	AI838468	4.537301802	1.60145
glia maturation factor, beta	BG066438	4.287951378	1.91477
glucose regulated protein, 58 kDa	AV073997	5.138344434	2.95017
glutathione S-transferase, mu 2	BG076504	8.932482655	1.89118
glycoprotein galactosyltransferase alpha 1, 3	BG067028	4.369235979	2.77433
glycoprotein m6b	AV033394	4.391593098	2.33415
GPI-anchored membrane protein 1	AV025862	4.623471043	2.55428
granule cell differentiation protein - Myotrophin	AV038957	6.096480398	3.36270
granulin	AV001464	5.834497342	2.84047
growth arrest and DNA-damage-inducible 45 alpha	AV035081	5.53017267	1.97603
guanine nucleotide binding protein, alpha inhibiting 2	BG072092	5.46262511	2.36297
guanine nucleotide binding protein, beta 1	BG063447	4.468078137	2.09860
guanosine diphosphate (GDP) dissociation inhibitor 1	AV114180	5.31572224	1.87795
guanosine diphosphate (GDP) dissociation inhibitor 3	AV141729	4.336524933	1.59962
guanylate cyclase 1, soluble, beta 3	AV029404	12.25096825	2.41285
H2A histone family, member Y	C75971	4.826283805	1.60582
hairy/enhancer-of-split related with YRPW motif-like	BG063796	7.73742705	2.82845
Harvey rat sarcoma oncogene, subgroup R	AA123466	10.69644502	1.67121
heterogeneous nuclear ribonucleoprotein C	AW551778	6.086651332	4.39239
heterogeneous nuclear ribonucleoprotein K	AV111538	5.420454646	2.03602
histocompatibility 2, D region locus 1	X00246	4.796300997	1.83908
histone deacetylase 1	AV023621	6.399471146	1.72915
HLS7-interacting protein kinase	BG064733	7.536386645	2.10383
homer, neuronal immediate early gene, 3	AV041850	4.333653316	1.39983
human immunodeficiency virus type I enhancer binding protein 1	AI847832	5.466729403	1.52844
hypothetical protein MGC32441	AV103742	5.697047099	1.61848
hypothetical protein MGC7474	AV025840	4.417451505	1.54831
hypothetical protein, MGC: 6943	AV003921	4.389090449	1.53375
hypoxia inducible factor 1, alpha subunit	AV068685	15.09148684	2.53258
immunoglobulin kappa chain variable 4 (V4)	AV133863	5.61971492	1.92740
immunoglobulin superfamily containing leucine-rich repeat	AV084844	4.489385861	3.04893

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

inhibitor of DNA binding 2	BG071421	5.645525734	2.61535
inositol 1,4,5-triphosphate receptor5	AI526630	5.500524188	1.77221
insulin-like growth factor binding protein 5	AV012617	4.210617115	1.98780
insulin-like growth factor binding protein 7	AV013851	11.6136427	3.03200
integral membrane protein 2B	AV010401	4.761131048	1.49528
integrin alpha 6	AV078295	4.48185886	2.35403
integrin beta 1 (fibronectin receptor beta)	BG074422	9.178922865	2.31509
integrin beta 5	BF100414	7.042785682	4.40899
interferon (alpha and beta) receptor 2	AV006514	6.206846171	1.36667
interleukin 17 receptor	AV074586	8.887484487	2.61352
interleukin 6 signal transducer	BG070387	4.905276993	3.42328
kit ligand	AV031540	4.359720807	2.07255
lactate dehydrogenase 1, A chain	AV094945	5.610828808	2.11934
lamin A	AV057135	4.451745488	1.91029
laminin, gamma 1	AA059779	5.285143506	2.71396
latent transforming growth factor beta binding protein 3	AV057100	7.691066971	2.61620
lectin, galactose binding, soluble 8	AV042964	9.342070728	1.55241
leptin receptor	AV054666	4.245977332	1.75594
leukemia-associated gene	AV134166	5.334752619	2.63905
leukotriene B4 receptor 1	AV104152	4.916931994	2.25628
LIM and SH3 protein 1	AV094974	5.827389871	2.57319
LIM-domain containing, protein kinase	AV306359	5.736847323	1.49652
low density lipoprotein receptor-related protein 1	BG075361	8.628798235	2.60739
LPS-induced TNF-alpha factor	AV051386	4.348912358	2.73900
lymphocyte antigen 6 complex, locus A	AV162270	4.19767661	2.80421
lymphocyte antigen 6 complex, locus E	AV036454	4.26829469	1.80785
lysyl oxidase-like	AV094998	6.168991293	3.19925
macrophage migration inhibitory factor	AV099090	4.445056769	1.46008
MAD homolog 6 (*Drosophila*)	AA451501	5.16784027	3.86816
manic fringe homolog (*Drosophila*)	AV117035	7.32646913	2.04230
mannosidase 1, alpha	AV026219	10.73847163	2.23747
matrilin 2	AV156534	4.577038874	1.52149
matrix metalloproteinase 2	M84324	7.727668489	2.67602
matrix metalloproteinase 23	BG067807	5.424531301	1.87576
melanoma cell adhesion molecule	BG075377	6.156732011	3.94572
membrane-bound transcription factor protease, site 1	BG072908	4.810623416	1.93507
mesenchyme homeobox 1	AV307023	11.15999865	2.72770
mesothelin	BG074344	6.369636518	1.59146
metastasis associated 1-like 1	AV048589	4.923977579	2.01067
methionine aminopeptidase 2	AV058243	5.461974898	2.45077
methyl-CpG binding domain protein 1	AV029255	7.661952699	2.16378
microfibrillar associated protein 5	AV113097	6.373883783	2.56881
microtubule-associated protein 4	AV025133	6.033347949	1.84371
milk fat globule-EGF factor 8 protein	AV094498	6.951638445	2.53495
milk fat globule-EGF factor 8 protein	AV088358	4.283989729	1.84505
mitogen activated protein kinase 1	D10939	4.874268557	1.57936
mitogen activated protein kinase 3	BE197033	6.398420263	1.53070
moesin	BG066632	6.70779398	1.86464
MORF-related gene X	AV094989	5.633228762	2.01584
Mus musculus, clone IMAGE: 2647796, mRNA	AV016890	6.338916212	1.87032
Mus musculus, clone IMAGE: 2647796, mRNA	BG070357	6.047190914	1.74898
Mus musculus, clone IMAGE: 2647796, mRNA	AV011175	10.4511173	1.64082
Mus musculus, clone IMAGE: 3597827, mRNA, partial cds	BG071066	6.312665533	2.57700
Mus musculus, clone IMAGE: 3597827, mRNA, partial cds	AV090253	4.407933409	1.70877
Mus musculus, clone IMAGE: 4913219, mRNA, partial cds	AI837764	4.190999025	1.74159
Mus musculus, clone IMAGE: 5066061, mRNA, partial cds	AV025927	4.487832407	1.99689
Mus musculus, clone IMAGE: 5251262, mRNA, partial cds	AV043496	4.810808264	2.82307
Mus musculus, clone MGC: 19042 IMAGE: 4188988, mRNA, complete ⓒ	AV073489	4.221423402	1.62803
Mus musculus, clone MGC: 27672 IMAGE: 4911158, mRNA, complete ⓒ	AV057440	4.818077648	1.96209
Mus musculus, clone MGC: 36911 IMAGE: 4945500, mRNA, complete ⓒ	BG067972	4.567256641	1.61513
Mus musculus, clone MGC: 37634 IMAGE: 4990983, mRNA, complete ⓒ	BG063958	5.175320148	2.15206
Mus musculus, clone MGC: 6357 IMAGE: 3493883, mRNA, complete c ⓒ	BG074005	4.309867406	2.13653
Mus musculus, clone MGC: 7530 IMAGE: 3492114, mRNA, complete c ⓒ	BG074684	4.762369358	1.93980
Mus musculus, clone MGC: 7734 IMAGE: 3498403, mRNA, complete c ⓒ	BG073500	4.341923916	2.21105
Mus musculus, Similar to cytoskeleton-associated protein 4, clone IMA	BG073772	5.451341006	3.42885
Mus musculus, Similar to gene overexpressed in astrocytoma, clone I ⓒ	BG065693	6.47734946	2.38394
Mus musculus, Similar to huntingtin interacting protein 1, clone MGC: 2	BG074730	7.373282071	1.94462
Mus musculus, Similar to hypothetical protein BC014916, clone MGC: 3	AU040965	5.633541364	2.13415
Mus musculus, Similar to hypothetical protein FLJ12806, clone MGC: 6	AV013963	4.728290073	2.06908
Mus musculus, Similar to hypothetical protein FLJ20244, clone MGC: 3	BG064625	6.805628105	1.67661
Mus musculus, Similar to hypothetical protein FLJ20335, clone MGC: 2	AV041795	4.238385	1.55944
Mus musculus, Similar to hypothetical protein MGC2555, clone MGC: 2	AV089816	5.349671441	10.06282
Mus musculus, Similar to hypothetical protein MGC3178, clone MGC: 2	BG065641	6.163853471	3.84895
Mus musculus, Similar to KIAA1741 protein, clone IMAGE: 5133740, m	BG066559	4.277183806	1.72731

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Mus musculus, Similar to KIAA1741 protein, clone IMAGE: 5133740, m	AV074072	5.188066436	1.54141
Mus musculus, Similar to pituitary tumor-transforming 1 interacting pro?	BG066621	6.439863345	2.07579
Mus musculus, Similar to Protein P3, clone MGC: 38638 IMAGE: 53558	AV162286	4.452893786	2.08569
Mus musculus, Similar to Rho GTPase activating protein 1, clone MGC?	AV009002	8.688394673	2.37995
Mus musculus, Similar to xylosylprotein beta1, 4-galactosyltransferase,	BG064673	4.407048366	1.51119
myeloid-associated differentiation marker	BG072632	7.785489825	1.99411
myosin lc	AW543748	4.939976544	1.62146
myosin Va	X57377	4.179971164	2.18490
myosin X	BG065453	4.207672452	1.44525
myristoylated alanine rich protein kinase C substrate	BG072584	8.486813472	3.67023
N-acetylated alpha-linked acidic dipeptidase 2	BG066563	5.295722761	1.55776
nestin	BG066228	4.927494432	2.81873
neural proliferation, differentiation and control gene 1	AV061081	7.40303682	1.97029
neuroblastoma ras oncogene	BG074219	4.631012268	2.22671
neuroblastoma, suppression of tumorigenicity 1	AI325886	13.27653071	2.60809
neuropilin	AV005825	7.420796498	4.00358
nidogen 1	BG063616	4.874231512	1.63136
Niemann Pick type C2	BG072810	5.871734028	2.05727
nischarin	AV024779	4.627785218	1.86577
nitric oxide synthase 2, inducible, macrophage	M92649	6.098182317	1.74329
NK2 transcription factor related, locus 5 (*Drosophila*)	AA530575	4.45779765	2.08311
N-myc downstream regulated 3	AV002395	6.665100729	1.93402
non-POU-domain-containing, octamer binding protein	BG064006	4.621685867	1.97153
Notch gene homolog 1, (*Drosophila*)	BF182158	4.667460187	2.06267
Notch gene homolog 3, (*Drosophila*)	BF136770	4.691872797	2.76353
novel nuclear protein 1	AV030823	6.412898231	1.45599
nuclear factor of kappa light chain gene enhancer in B-cells 1, p105	AV011539	7.627479907	1.72959
nucleobindin	BG067101	6.471783836	2.20795
O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglu?	AV026079	4.76043905	1.79532
origin recognition complex, subunit 2 homolog (*S. cerevisiae*)	AV032582	4.712779251	1.52315
osteoblast specific factor 2 (fasciclin I-like)	AV084876	6.69600179	4.83838
parathyroid hormone receptor	AV145718	4.402641605	2.07806
parotid secretory protein	BG074915	4.353877483	1.96222
PDZ and LIM domain 1 (elfin)	AV093772	4.260472685	2.39615
peptidylprolyl isomerase A	BG065164	4.33669464	1.87201
peptidylprolyl isomerase C-associated protein	AV059520	5.448607935	2.69065
peripheral myelin protein, 22 kDa	AV113888	7.6004572	1.83675
phosphatase and tensin homolog	AI840761	4.468842663	1.49890
phosphatidylinositol glycan, class Q	AV006019	4.310623965	1.57576
phosphatidylinositol transfer protein	AV086045	9.123016634	1.84353
phosphofructokinase, liver, B-type	BG064930	5.928386214	2.36933
phosphoglycerate mutase 1	BG064823	4.737973813	1.87748
phosphoprotein enriched in astrocytes 15	BG064035	4.268230432	2.97109
platelet derived growth factor receptor, beta polypeptide	AV112983	4.553128201	3.77585
platelet-activating factor acetylhydrolase, isoform 1b, alpha1 subunit	AV090194	5.288964722	1.60210
pleckstrin homology, Sec7 and coiled/coil domains 3	AV053270	5.577033188	2.02770
plexin B2	AW544029	4.422870765	1.98924
poly A binding protein, cytoplasmic 1	AV112724	4.782371155	3.15594
polycystic kidney disease 1 homolog	AV234882	5.358502717	2.22470
polydomain protein	AI327133	7.858540607	3.84128
procollagen C-proteinase enhancer protein	AV084561	8.995793312	3.95693
procollagen C-proteinase enhancer protein	BG074851	7.005456302	3.30109
procollagen, type IV, alpha 1	AV009300	4.799631432	6.90333
procollagen, type IV, alpha 2	BG074718	6.556955707	8.64733
procollagen, type XV	AV015595	4.255615327	1.63778
procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxyla?	AW548258	4.72698998	2.16626
programmed cell death 10	AV134945	4.45010746	1.49911
proline arginine-rich end leucine-rich repeat	BG069745	5.296255508	4.80791
prolyl 4-hydroxylase, beta polypeptide	BG073750	4.854848183	2.62046
prosaposin	BE307724	4.281458018	1.86208
prostaglandin-endoperoxide synthase 2	AV025665	6.86188836	1.97886
protective protein for beta-galactosidase	AV088011	4.408757905	1.91973
protein kinase C and casein kinase substrate in neurons 2	BG074185	5.12487867	1.71964
protein kinase C, delta	AA276844	5.711302904	2.37450
protein kinase C, eta	AI787844	5.059946731	1.93754
protein kinase, cAMP dependent regulatory, type I, alpha	BG075240	4.751171639	2.91943
protein phosphatase 1, regulatory (inhibitor) subunit 14B	AV087756	4.95678378	1.55296
protein tyrosine phosphatase, non-receptor type 2	AA693053	9.43234409	2.53086
protein tyrosine phosphatase, receptor type, E	BG070083	4.670895434	1.80602
protein tyrosine phosphatase, receptor type, S	BG074663	5.119471562	1.71380
proteolipid protein 2	AI893212	4.640045123	1.95153
protocadherin 13	BG073000	4.667531323	1.89233
protocadherin alpha 1	AV033049	7.668542332	1.68190
PTK2 protein tyrosine kinase 2	BG065137	4.202113544	1.69356

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purine-nucleoside phosphorylase	AU042511	4.450485386	1.59343
Rab6 interacting protein 1	AW554976	4.29655828	1.83268
RAB7, member RAS oncogene family	BG074292	8.190446914	2.03505
RAD51 homolog (*S. cerevisiae*)	AV140483	4.533421842	1.88562
radixin	AV040247	4.443038978	2.29201
ras homolog 9 (RhoC)	AV140333	6.458308062	1.82988
ras homolog A2	AA008793	5.650216452	1.97274
ras homolog D (RhoD)	AU041357	8.369273714	1.74085
ras homolog G (RhoG)	AV104284	5.754236727	1.75346
RAS p21 protein activator 3	AV090329	4.515734577	1.43582
Ras suppressor protein 1	BG064612	4.223689279	1.66992
regulator of G-protein signaling 19 interacting protein 1	AV086128	5.478596342	2.14051
regulator of G-protein signaling 3	AU040596	6.449998123	1.32466
regulator of G-protein signaling 4	AV088379	9.080281445	2.31400
regulator of G-protein signaling 5	AV012999	6.01259402	2.00387
reticulon 4	AV084219	8.227919039	2.29694
retinal short-chain dehydrogenase/reductase 1	BG073341	7.334494325	1.84661
retinoblastoma binding protein 7	AW544081	4.911862441	3.01012
retinoid-inducible serine caroboxypetidase	AV083867	7.654642812	1.89865
retinol binding protein 1, cellular	AV140184	8.194434932	2.71765
reversion-inducing-cysteine-rich protein with kazal motifs	AV024396	6.204698809	2.25801
Rho guanine nucleotide exchange factor (GEF) 3	AV025023	4.811921398	2.10195
Rho interacting protein 3	AV074565	9.03990222	2.07373
rhotekin	AV170878	4.913811275	1.99649
ribosomal protein L13a	AV029954	7.60434309	1.79277
ribosomal protein L35	AW558719	8.648199166	1.79930
ribosome binding protein 1	BG063638	4.422386381	2.03374
RIKEN cDNA 0610013I17 gene	AW538766	7.435056738	1.78394
RIKEN cDNA 0610031J06 gene	BG064127	5.847627156	1.61255
RIKEN cDNA 0610039A15 gene	AV133782	4.264872953	1.68391
RIKEN cDNA 0610040B21 gene	AV140189	4.391354632	1.62500
RIKEN cDNA 0610040B21 gene	BG073889	4.768851518	1.58153
RIKEN cDNA 0610041E09 gene	AV017582	5.484190523	1.75496
RIKEN cDNA 0710001O03 gene	AV032734	5.007378039	2.30051
RIKEN cDNA 1100001D10 gene	BG064565	5.81906433	1.83095
RIKEN cDNA 1110003M08 gene	AV007276	4.843292995	2.03155
RIKEN cDNA 1110006G06 gene	AV056387	4.243506473	1.74607
RIKEN cDNA 1110007A10 gene	BG063682	5.612559572	2.02026
RIKEN cDNA 1110007A14 gene	AV058524	9.424689462	1.84586
RIKEN cDNA 1110007F23 gene	AV083352	25.74086099	9.37273
RIKEN cDNA 1110007F23 gene	BG074573	10.53962237	8.20649
RIKEN cDNA 1110020C13 gene	AV071424	9.657620902	1.67480
RIKEN cDNA 1110020C13 gene	BG067962	4.551573598	1.64600
RIKEN cDNA 1110059L23 gene	AV133706	5.93034392	1.95157
RIKEN cDNA 1110067B02 gene	AV016765	4.568660885	1.62828
RIKEN cDNA 1110070A02 gene	AV048556	4.545063428	2.14508
RIKEN cDNA 1190017B18 gene	AV020346	4.203168452	1.41632
RIKEN cDNA 1200002H13 gene	AV091707	4.572821208	1.60106
RIKEN cDNA 1200003O06 gene	AV086520	4.356732374	2.11517
RIKEN cDNA 1200013F24 gene	BG064285	4.963857029	1.46712
RIKEN cDNA 1200015A22 gene	AV088097	5.486213183	1.89786
RIKEN cDNA 1200015E15 gene	BG073318	5.415048311	2.58596
RIKEN cDNA 1200015E15 gene	AV081663	6.747503344	2.47340
RIKEN cDNA 1200015E15 gene	AV133998	7.301986486	2.26073
RIKEN cDNA 1200015G06 gene	BG075983	5.637931395	1.36193
RIKEN cDNA 1300012G16 gene	BG074142	4.667358199	1.78865
RIKEN cDNA 1300013C10 gene	AV025369	6.120894601	2.76926
RIKEN cDNA 1300018J16 gene	AI838568	4.828416466	3.43289
RIKEN cDNA 1500019E20 gene	BG075290	4.570907379	1.56867
RIKEN cDNA 1600013L13 gene	AV084040	4.956392552	1.78135
RIKEN cDNA 1600019O04 gene	AV036591	6.674797485	1.66154
RIKEN cDNA 1600025D17 gene	AV093668	5.107066557	1.47692
RIKEN cDNA 1810004P07 gene	AV060319	5.037144115	2.13161
RIKEN cDNA 1810009F10 gene	AV060194	5.765496546	4.45887
RIKEN cDNA 1810013K23 gene	AV141499	4.997925821	1.60819
RIKEN cDNA 1810048P08 gene	AV103510	5.525945988	2.01813
RIKEN cDNA 1810049K24 gene	AV058250	4.203974492	2.26156
RIKEN cDNA 1810061M12 gene	AV060180	5.135166258	1.83261
RIKEN cDNA 1810073N04 gene	BG075130	4.747837421	2.97518
RIKEN cDNA 2010012O16 gene	AV065962	4.19570901	2.00840
RIKEN cDNA 2010209O12 gene	BG067525	4.873273183	1.71182
RIKEN cDNA 2210404D11 gene	BG075242	4.395009347	1.71187
RIKEN cDNA 2210412K09 gene	AV087410	4.178520626	1.36176
RIKEN cDNA 2210417O06 gene	BG063700	4.902542854	1.82425

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RIKEN cDNA 2300002L21 gene	AV088022	5.028858918	1.63333
RIKEN cDNA 2310003C10 gene	AV083528	4.203309799	1.68513
RIKEN cDNA 2310003C10 gene	AV085418	4.271031125	1.54570
RIKEN cDNA 2310008D10 gene	AV086327	7.029577134	2.03788
RIKEN cDNA 2310008M10 gene	AV084553	6.227559729	1.57439
RIKEN cDNA 2310010I22 gene	AV086049	6.078943346	1.64346
RIKEN cDNA 2310010I22 gene	BG075721	4.268018658	1.53406
RIKEN cDNA 2310028N02 gene	AV087181	5.021775951	1.85309
RIKEN cDNA 2310047O13 gene	AV056495	4.76990036	1.63158
RIKEN cDNA 2310058J06 gene	BG071334	6.684567202	2.01084
RIKEN cDNA 2410001H17 gene	AV085104	4.601565596	1.72648
RIKEN cDNA 2410004M09 gene	AV085387	4.721414349	1.72715
RIKEN cDNA 2410006F12 gene	AV140116	5.917743128	1.71626
RIKEN cDNA 2410008K03 gene	AV103791	4.43380025	1.43239
RIKEN cDNA 2410043F08 gene	BG063619	8.445139044	2.28280
RIKEN cDNA 2410043F08 gene	AV112735	9.085975215	1.93280
RIKEN cDNA 2500002L14 gene	AV103348	5.594034154	1.57808
RIKEN cDNA 2500002L14 gene	BG071504	4.443376161	1.40983
RIKEN cDNA 2510025F08 gene	AV133838	4.683564778	1.90121
RIKEN cDNA 2510049I19 gene	AV065538	4.458739741	1.25154
RIKEN cDNA 2600001C03 gene	AV109257	6.600191843	1.75703
RIKEN cDNA 2600015J22 gene	AI847883	4.509126103	2.02467
RIKEN cDNA 2610001A11 gene	AV111320	4.231568249	2.73739
RIKEN cDNA 2610001E17 gene	BG074158	5.479986902	1.93419
RIKEN cDNA 2610002H11 gene	BG067332	4.238835621	4.00913
RIKEN cDNA 2610002H11 gene	AV111526	4.489291561	3.74398
RIKEN cDNA 2610007A16 gene	BG063373	5.350241939	1.76553
RIKEN cDNA 2610007K22 gene	BG063903	4.537443323	1.74250
RIKEN cDNA 2610009E16 gene	BG070614	4.459754931	1.78302
RIKEN cDNA 2610027H02 gene	BG073064	4.855351496	1.90289
RIKEN cDNA 2610040E16 gene	AV094630	4.215693303	1.44224
RIKEN cDNA 2610042L04 gene	AV134021	7.569249596	2.12844
RIKEN cDNA 2610209F03 gene	AV040010	4.807860846	1.52011
RIKEN cDNA 2610301D06 gene	AV094921	4.599529029	1.48585
RIKEN cDNA 2610301D06 gene	BG072779	4.193665179	1.27258
RIKEN cDNA 2610306D21 gene	BG067397	4.20266368	1.41549
RIKEN cDNA 2610528A15 gene	BG073520	9.882601001	1.87944
RIKEN cDNA 2700083B06 gene	AV050682	5.341326624	1.42328
RIKEN cDNA 2810002E22 gene	AV133755	5.013779545	2.42777
RIKEN cDNA 2810404D13 gene	AV134953	5.074203389	1.71177
RIKEN cDNA 2810417D08 gene	AV141703	4.850126949	1.89762
RIKEN cDNA 2810482I07 gene	AV024973	5.179744306	1.54763
RIKEN cDNA 3110023E09 gene	AV053955	4.54999042	1.87698
RIKEN cDNA 3110079L04 gene	AV140192	8.178677607	1.66774
RIKEN cDNA 3230402E02 gene	AV140438	9.69822229	1.91583
RIKEN cDNA 4432404K01 gene	AV025421	6.884470549	2.73483
RIKEN cDNA 4833439O17 gene	BG075582	4.750554365	1.76219
RIKEN cDNA 4921531N22 gene	AV052379	6.930339773	1.83146
RIKEN cDNA 4921531N22 gene	AV060478	5.199122927	1.77508
RIKEN cDNA 4930415K17 gene	AV032599	5.240194387	1.73203
RIKEN cDNA 5031406P05 gene	AV061276	6.411675128	1.56308
RIKEN cDNA 5033421K01 gene	BG070713	4.782136451	1.43323
RIKEN cDNA 5133400A03 gene	BG070551	4.353282877	1.71061
RIKEN cDNA 5430400P17 gene	AA060086	6.044644227	1.82388
RIKEN cDNA 5730403E06 gene	AV020551	4.347632496	1.84263
RIKEN cDNA 5730414C17 gene	AV016743	4.369181842	2.10883
RIKEN cDNA 5730461F13 gene	BG075436	6.351981125	1.92385
RIKEN cDNA 5730518J08 gene	AV056350	4.249685748	1.61971
RIKEN cDNA 5730591C18 gene	AV085942	4.867612034	1.87048
RIKEN cDNA 6030455P07 gene	BG076243	5.979146053	2.90914
RIKEN cDNA 6330414G21 gene	BG076505	4.813930193	2.19023
RIKEN cDNA 6720474K14 gene	AV085966	4.822592598	2.07363
RIKEN cDNA 9130005N14 gene	AV060665	4.252358329	2.54257
RIKEN cDNA B430104H02 gene	AV000213	9.138694463	2.32483
RIKEN cDNA C330007P06 gene	AV029419	5.722192826	1.77950
ring finger protein 13	AV072479	5.989110349	1.56109
RNA polymerase II 1	AV018343	4.489707981	1.82930
roundabout homolog 1 (*Drosophila*)	AV128328	5.524511639	1.85130
roundabout homolog 4 (*Drosophilia*)	BE377723	4.981917421	2.15467
RuvB-like protein 2	AV109340	4.2446986	1.65863
S-adenosylmethionine decarboxylase 1	AV121939	5.707603849	1.64498
sarcoglycan, epsilon	BG072850	4.370750746	1.50031
scavenger receptor class B1	U37799	4.50358952	2.46176
secreted acidic cysteine rich glycoprotein	AW988741	5.549292892	6.14126

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

secreted frizzled-related sequence protein 2	AV021712	4.238424177	3.26213
sema domain, immunoglobulin domain (Ig), short basic domain, secret	BG074382	5.028318471	2.13790
septin 2	AV116832	7.212302484	2.33584
serine (or cysteine) proteinase inhibitor, clade F (alpha-2 antiplasmin, ⑦	BG074697	8.856683533	3.35898
serine (or cysteine) proteinase inhibitor, clade H (heat shock protein 47⑦	AV104522	4.258740241	5.50558
serine (or cysteine) proteinase inhibitor, clade I (neuroserpin), member	AV052090	9.790229028	2.31567
serine palmitoyltransferase, long chain base subunit 1	AV062462	9.24035025	1.73956
serine protease inhibitor 6	AV035785	4.308010944	1.41468
serum/glucocorticoid regulated kinase	AI315589	4.359268623	2.04271
serum-inducible kinase	AV056942	8.688448107	3.20116
SH3 domain protein D19	BG076318	4.83286573	1.72859
shroom	BG072834	4.460051279	2.66437
sialyltransferase 1 (beta-galactoside alpha-2,6-sialyltransferase)	D16106	6.392086396	1.92378
sialyltransferase 4C (beta-galactosidase alpha-2,3-sialytransferase)	AI385650	6.610358353	1.97374
signal transducer and activator of transcription 6	L47650	6.315908147	1.91050
signal transducing adaptor molecule (SH3 domain and ITAM motif) 2	AV046859	4.327158168	1.76305
signal-induced proliferation associated gene 1	AV088479	4.550408961	2.31046
small GTPase, homolog (*S. cerevisiae*)	BG067356	4.586503857	1.50828
solute carrier family 29 (nucleoside transporters), member 1	BG075739	4.337648607	1.39981
sorting nexin 4	AV055722	4.473535794	1.46762
sprouty homolog 4 (*Drosophila*)	AA499432	6.438240138	2.13976
SRY-box containing gene 18	AA261240	5.111004932	1.78753
stanniocalcin 2	AV094416	4.405714011	1.46040
stromal cell derived factor 1	BG073593	4.24723061	2.11053
stromal cell derived factor 4	AV048780	4.802035607	1.43164
superoxide dismutase 3, extracellular	U38261	7.250231972	3.29160
suppressor of white apricot homolog 2-pending	AV162195	4.994355697	1.70716
surfeit gene 4	AV074505	4.815569801	1.79779
survival motor neuron	AV133987	6.539797582	1.39888
SWI/SNF related, matrix associated, actin dependent regulator of chro⑦	AV298569	4.355370118	2.60646
syndecan 3	BG064265	6.613530318	2.88308
synovial sarcoma translocation, Chromosome 18	AV033310	5.408808458	1.80124
syntaxin binding protein 2	BG075753	5.004233958	1.65309
TAR (HIV) RNA binding protein 2	AV040847	6.423086255	2.01946
thymic stromal-derived lymphopoietin, receptor	AV070805	8.547082806	2.02117
torsin family 3, member A	AV057827	7.477887867	2.27552
transcription factor 4	AV000162	8.345957891	2.23130
transcription factor Dp 1	AV053081	4.329499465	1.34063
transcription factor E2a	AA030885	6.525307406	1.75147
transcription factor UBF	AV095317	4.895225679	1.62658
transforming growth factor beta 1 induced transcript 1	AV006479	9.758134935	2.79512
transforming growth factor, beta 2	AV135894	5.173585005	2.73350
transient receptor protein 2	AV002597	5.333447366	2.68369
transmembrane domain protein regulated in adipocytes 40 kDa	AV083947	5.088665302	1.28986
transmembrane protein with EGF-like and two follistatin-like domains 1⑦	AA023493	5.206812136	1.93718
tropomodulin 3	AV026409	5.07481845	1.77695
tubby like protein 4	AW552694	4.530630076	1.78186
tubby-like protein 3	AV139648	5.616340312	1.85776
tubulin, alpha 1	AV093632	6.193575886	3.07888
tubulin, alpha 4	AA408725	7.155536699	2.13397
tubulin, beta 5	AV109614	11.6573826	1.99179
tumor necrosis factor	X02611	6.428930694	1.53428
tumor necrosis factor receptor superfamily, member 1a	L26349	6.392431179	2.39873
tumor necrosis factor, alpha-induced protein 1 (endothelial)	AV024570	4.370295461	1.75306
tumor-associated calcium signal transducer 1	AV089835	6.791092517	3.32950
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation pr⑦	AV104266	6.100287629	1.55178
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation pr⑦	U57311	6.573928853	1.87425
tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation pr⑦	AV130451	8.350838932	2.79631
tyrosine kinase receptor 1	AA838996	6.050255188	3.70273
U1 small nuclear ribonucleoprotein 70 kDa polypeptide A	AV035403	5.218365194	1.76839
ubiquitin carboxy-terminal hydrolase L1	BG074009	4.758072234	2.59745
UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1	BG062994	4.784175093	1.63427
UDP-glucuronate decarboxylase 1	BG073697	4.651857039	1.53280
UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosam	AI893181	4.61960655	1.98472
UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosam	BG071100	5.251330578	2.12686
Unsequenced EST	413107	6.273291655	7.53126
Unsequenced EST	413273	4.31807147	5.78325
Unsequenced EST	412394	18.32998763	4.03427
Unsequenced EST	411467	4.357834225	3.38896
Unsequenced EST	411755	4.951849941	3.34666
Unsequenced EST	412745	4.568501936	3.27897
Unsequenced EST	432151	4.774738602	2.87892
Unsequenced EST	432603	4.333142623	2.85312
Unsequenced EST	431006	6.562712284	2.77119

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Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

Unsequenced EST	411350	9.505971157	2.72549
Unsequenced EST	411609	4.71354952	2.66098
Unsequenced EST	412246	5.633966439	2.61787
Unsequenced EST	411505	5.901191293	2.55842
Unsequenced EST	432010	5.557544512	2.54505
Unsequenced EST	410993	4.939733861	2.50496
Unsequenced EST	412701	4.209083529	2.47011
Unsequenced EST	411885	6.186881729	2.40448
Unsequenced EST	412021	4.902811974	2.39953
Unsequenced EST	410761	4.924640447	2.39667
Unsequenced EST	431651	5.237876041	2.38955
Unsequenced EST	199450	5.780625675	2.37856
Unsequenced EST	412588	4.795004918	2.37853
Unsequenced EST	411923	8.396940653	2.33231
Unsequenced EST	410840	4.457849585	2.31171
Unsequenced EST	430732	5.597887132	2.30696
Unsequenced EST	412675	4.815014954	2.22233
Unsequenced EST	410968	5.153844667	2.19677
Unsequenced EST	412594	5.824024683	2.19605
Unsequenced EST	410746	5.973693751	2.18081
Unsequenced EST	431888	8.608487166	2.15587
Unsequenced EST	431920	5.682201344	2.12745
Unsequenced EST	410743	4.439738415	2.12029
Unsequenced EST	197104	8.383105866	2.09296
Unsequenced EST	430919	4.794214749	2.08514
Unsequenced EST	431706	6.304117743	2.08389
Unsequenced EST	410654	8.351953022	2.05228
Unsequenced EST	206956	5.237784101	2.04248
Unsequenced EST	193306	4.945515669	2.02954
Unsequenced EST	431072	5.684602565	2.00932
Unsequenced EST	413009	6.614854617	1.99915
Unsequenced EST	411412	4.868030026	1.99180
Unsequenced EST	431050	6.699411715	1.98252
Unsequenced EST	410619	12.57706405	1.97239
Unsequenced EST	411013	4.960471191	1.96703
Unsequenced EST	411635	6.118763105	1.95047
Unsequenced EST	431767	5.521076531	1.94831
Unsequenced EST	411464	5.02732744	1.94358
Unsequenced EST	410545	6.37147916	1.89709
Unsequenced EST	411329	5.294206879	1.88701
Unsequenced EST	411969	4.92425749	1.86985
Unsequenced EST	411285	4.3570354	1.86488
Unsequenced EST	432326	7.966893738	1.84998
Unsequenced EST	412447	4.260473196	1.83558
Unsequenced EST	431082	4.937632166	1.82592
Unsequenced EST	431540	6.428336919	1.82275
Unsequenced EST	196552	5.793122078	1.81776
Unsequenced EST	410789	4.550275542	1.81343
Unsequenced EST	412803	4.176585206	1.80861
Unsequenced EST	411561	4.605900103	1.80665
Unsequenced EST	413042	4.676182648	1.78983
Unsequenced EST	412220	5.167673303	1.78385
Unsequenced EST	207914	5.173303361	1.76367
Unsequenced EST	412958	4.871233065	1.72164
Unsequenced EST	410773	5.107733423	1.71129
Unsequenced EST	432024	4.432735142	1.70615
Unsequenced EST	412011	4.742393759	1.69693
Unsequenced EST	411472	4.490487626	1.69603
Unsequenced EST	411765	4.556559515	1.69434
Unsequenced EST	412337	4.770108721	1.69362
Unsequenced EST	410698	4.340616492	1.69179
Unsequenced EST	413591	4.59016315	1.68542
Unsequenced EST	412313	4.490810017	1.67931
Unsequenced EST	410920	6.621227261	1.66619
Unsequenced EST	412612	6.354130371	1.65767
Unsequenced EST	413096	9.649532409	1.65344
Unsequenced EST	411309	5.855658163	1.65342
Unsequenced EST	431982	4.428555085	1.63322
Unsequenced EST	411222	4.524397103	1.63149
Unsequenced EST	412210	4.357035656	1.60479
Unsequenced EST	413582	6.172475352	1.59892
Unsequenced EST	413181	5.247839338	1.59329
Unsequenced EST	432273	5.284928181	1.57465
Unsequenced EST	411229	4.606022357	1.55993

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Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

Unsequenced EST	432889	6.86044512	1.54569
Unsequenced EST	411240	4.931389088	1.54312
Unsequenced EST	411256	4.370621835	1.53806
Unsequenced EST	431197	5.553558202	1.51658
Unsequenced EST	411384	4.226502978	1.51562
Unsequenced EST	433064	11.81517212	1.44531
Unsequenced EST	411576	4.557199497	1.41029
Unsequenced EST	430683	4.395744711	1.40057
Unsequenced EST	207209	5.462293397	1.39444
Unsequenced EST	413286	6.146895859	1.38486
Unsequenced EST	411904	4.653902177	1.37670
Unsequenced EST	333870	4.973207701	1.33528
Unsequenced EST	413172	4.587654857	1.20891
uridine phosphorylase	D44464	4.407420784	3.33647
valosin containing protein	BG074307	4.582529317	1.50710
vanilloid receptor-like protein 1	BG064510	5.54598292	1.95257
vascular endothelial growth factor A	AW913188	8.832564999	2.38847
vascular endothelial growth factor C	BE376968	6.23701522	1.95868
vasodilator-stimulated phosphoprotein	AW538871	5.171791268	1.99901
vinculin	AI385712	4.203457851	1.61965
v-rel reticuloendotheliosis viral oncogene homolog A, (avian)	AV095204	4.443651896	1.71953
WD repeat domain 1	BG064839	5.053585228	2.13577
zinc finger protein 103	AV224747	5.236448071	1.82055
zinc finger protein 106	AV071915	5.082827154	2.05709
zinc finger protein 36	AV103195	4.444107655	2.24632
zyxin	AV166088	6.273023884	1.64875
896 Negative Significant Genes - Repressed in Hypertrophic Cardiomyopathy			
**DNA segment, Chr 13, ERATO Doi 332, expressed	BG066890	−5.396062055	0.45499
**DNA segment, Chr 2, ERATO Doi 542, expressed	BG073740	−6.995498483	0.57935
**DNA segment, Chr 2, Wayne State University 85, expressed	BG062980	−4.136751331	0.61115
**DNA segment, Chr 8, Brigham & Women's Genetics 1112 expressed?	BG064137	−4.174714082	0.64681
**ESTs	BG074866	−5.813263409	0.54492
**guanine nucleotide binding protein, alpha 13	BG068913	−5.745250343	0.64597
**methionine aminopeptidase 2	BG074258	−5.880170454	0.70541
***Mus musculus*, clone IMAGE: 5361283, mRNA, partial cds	AA072842	−4.13161274	0.58861
**proteasome (prosome, macropain) 26S subunit, ATPase 3	AA163174	−5.040496567	0.46827
**RIKEN cDNA 2310075M17 gene	AI840674	−5.823426143	0.68802
**RIKEN cDNA 3110052N05 gene	BG072585	−4.203653088	0.68898
**RIKEN cDNA 3930401B19 gene	BG076041	−4.221966232	0.69199
**RIKEN cDNA 6720463E02 gene	BG067712	−5.527362247	0.42232
**RIKEN cDNA 6720475J19 gene	BG071484	−7.674685475	0.26086
**RNA polymerase II 4 (14 kDa subunit)	BG073536	−4.407989935	0.64966
**small nuclear ribonucleoprotein N	AI841348	−4.56247846	0.50950
**succinate-Coenzyme A ligase, GDP-forming, beta subunit	BG075548	−4.444081173	0.49038
**suppressor of initiator codon mutations, related sequence 1 (S. cere?	BG064153	−5.434802411	0.46790
**ubiquinol-cytochrome c reductase core protein 1	AI841290	−4.554338409	0.51911
6-pyruvoyl-tetrahydropterin synthase	BG072031	−4.902929092	0.56213
acetyl-Coenzyme A dehydrogenase, long-chain	BG066557	−9.090909676	0.40106
acetyl-Coenzyme A dehydrogenase, medium chain	AI840666	−8.398490697	0.43686
acyl-Coenzyme A dehydrogenase, very long chain	AI839605	−6.18762928	0.59203
acylphosphatase 2, muscle type	AA120674	−7.657983239	0.33130
adaptor-related protein complex AP-4, sigma 1	BG069322	−4.138928716	0.48502
adenylate cyclase 6	AA727732	−5.870740066	0.47590
ADP-ribosylation-like 3	AV134034	−4.98247219	0.45712
ADP-ribosylation-like 4	AA003086	−4.452096978	0.45981
adrenergic receptor kinase, beta 1	BG072616	−5.951311824	0.60538
aldo-keto reductase family 1, member B3 (aldose reductase)	AV133992	−5.029352566	0.74821
aminolevulinate, delta-, dehydratase	BG063937	−4.245991722	0.51637
amino-terminal enhancer of split	AA968065	−4.942847825	0.72701
angiopoietin	BF538875	−4.881730093	0.32339
apoptotic chromatin condensation inducer in the nucleus	BG071714	−4.62623729	0.47419
ATP synthase, H+ transporting mitochondrial F1 complex, beta subunit?	AV006369	−4.695530788	0.53925
ATP synthase, H+ transporting, mitochondrial F0 complex, subunit b, is?	AI836064	−6.423143997	0.45158
ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (s?	AV095153	−7.430215562	0.48878
ATP synthase, H+ transporting, mitochondrial F0 complex, subunit c (s?	AV056821	−4.424102615	0.52819
ATP synthase, H+ transporting, mitochondrial F0 complex, subunit f, is?	BG073062	−4.492001119	0.50909
ATP synthase, H+ transporting, mitochondrial F0 complex, subunit g	BG069449	−6.684865638	0.39574
ATP synthase, H+ transporting, mitochondrial F1 complex, gamma pol?	BG072870	−5.347883074	0.52850
ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit	AV133927	−5.352698253	0.47237
ATP synthase, H+ transporting, mitochondrial F1F0 complex, subunit ?	BG072635	−4.819618354	0.41437
ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	AI837797	−5.834521502	0.53249
ATPase, H+ transporting, lysosomal 70 kD, V1 subunit A, isoform 1	AW545296	−4.280719124	0.75002
AU RNA binding protein/enoyl-coenzyme A hydratase	AV095181	−8.782972174	0.53747

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

baculoviral IAP repeat-containing 4	AV073504	−5.130039053	0.68359
bromodomain-containing 4	AV085802	−5.786610727	0.71518
cadherin EGE LAG seven-pass G-type receptor 2	BG074441	−4.154879365	0.71952
calcyclin binding protein	BG069742	−8.690706344	0.65713
capping protein alpha 3	AV039134	−5.081582357	0.42546
carbonic anhydrase 14	AV014385	−5.82139814	0.40180
carbonyl reductase 1	AI323923	−5.260736815	0.63722
carboxylesterase 3	BG072503	−9.855339495	0.17436
cardiac Abnormality/abnormal facies (CATCH22), microdeletion syndrc⑦	AV041840	−9.98418961	0.40426
carnitine palmitoyltransferase 2	AV006197	−5.312556125	0.62582
caspase 1	AA672522	−5.482885752	0.50832
caspase 14	AJ007750	−4.270794528	0.59138
catenin src	C77281	−5.060897945	0.55404
cathepsin F	AV085152	−5.325513355	0.51925
Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-termina⑦	BG069399	−4.222038294	0.49555
CDC-like kinase	BG065099	−4.390363621	0.71405
cell division cycle 5-like (S. pombe)	BG069455	−4.117820871	0.62771
citrate lyase beta like	AV028854	−4.199225491	0.53480
cleavage and polyadenylation specific factor 2, 100 kD subunit	AV111435	−4.800913152	0.49169
coagulation factor III	AA879919	−6.686739114	0.58633
cold inducible RNA binding protein	BG073558	−14.8302043	0.37969
complexin 2	AV149907	−4.775702769	0.37946
copper chaperone for superoxide dismutase	AV093569	−5.248357511	0.59552
cornichon-like (*Drosophila*)	AV150049	−5.432444546	0.56343
creatine kinase, mitochondrial 2	AV085004	−4.742066271	0.61057
cysteine-rich protein 3	AV087451	−4.266568219	0.39188
cytochrome c oxidase subunit VIIb	AV093625	−8.988138804	0.39401
cytochrome c oxidase, subunit IVa	AV005997	−4.487420289	0.41076
cytochrome c oxidase, subunit Vb	AV088644	−4.949569116	0.46997
cytochrome c oxidase, subunit VI a, polypeptide 2	AV001082	−4.842370725	0.31139
cytochrome c oxidase, subunit VI a, polypeptide 2	AV030529	−4.152568557	0.33572
cytochrome c oxidase, subunit VIc	AV149855	−9.192827977	0.37223
cytochrome c oxidase, subunit VIIa 1	AV086493	−4.364923988	0.27457
cytochrome c oxidase, subunit VIIa 3	AV133935	−5.936847157	0.47440
cytochrome c oxidase, subunit VIIa 3	BG072912	−4.12193731	0.53257
cytochrome c oxidase, subunit VIIc	BG063960	−5.099803728	0.37129
cytochrome c oxidase, subunit XVII assembly protein homolog (yeast)	AV081105	−7.938746128	0.46201
cytochrome c, somatic	AV086888	−5.722105998	0.42669
cytochrome c-1	AV093672	−5.446589149	0.68598
cytochrome P450, 17	AV042908	−4.426517275	0.37805
DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 13 (RNA helicase A)	AV106868	−6.374954218	0.67058
DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 20	BG071005	−4.145761402	0.69357
death associated protein 3	BG065205	−6.784949232	0.48820
deleted in polyposis 1	AA032557	−4.19567949	0.40696
desmocollin 2	BG063370	−6.637675079	0.34694
diacylglycerol kinase, alpha (80 kDa)	AV069373	−4.808213153	0.58075
diacylglycerol O-acyltransferase 2	BG072524	−5.216696741	0.26003
diaphanous homolog 1 (*Drosophila*)	AV134828	−4.349910406	0.64965
DiGeorge syndrome critical region gene 6	BG071919	−4.99953028	0.52770
dipeptidylpeptidase 4	AA266854	−5.003475925	0.66937
DNA fragmentation factor, 40 kD, beta subunit	AV109088	−4.25080084	0.65806
DNA primase, p49 subunit	AV113083	−9.821814843	0.49491
DNA segment, Chr 14, ERATO Doi 574, expressed	BG068808	−7.416007266	0.52173
DNA segment, Chr 9, Wayne State University 149, expressed	AV135842	−4.165273935	0.56300
DnaJ (Hsp40) homolog, subfamily A, member 3	AW540988	−6.542750844	0.45648
DnaJ (Hsp40) homolog, subfamily A, member 3	AV050059	−6.311708326	0.48336
DnaJ (Hsp40) homolog, subfamily B, member 9	AV041142	−4.594900976	0.65180
DnaJ (Hsp40) homolog, subfamily C, member 1	AV057225	−5.477300649	0.51634
dodecenoyl-Coenzyme A delta isomerase (3,2 trans-enoyl-Coenyme A⑦	AA108563	−7.017480503	0.35225
down-regulated by Ctnnb1, a	BG068535	−4.586302098	0.59629
dynein, axon, heavy chain 11	AA039110	−4.619323446	0.41136
dystonin	BG070533	−4.583900131	0.55822
dystroglycan 1	BE137475	−4.960612662	0.55724
E2F transcription factor 6	AV126035	−4.440266193	0.57132
ectodermal-neural cortex 1	BG065122	−5.705275017	0.55060
endothelial monocyte activating polypeptide 2	BG076119	−4.974086698	0.59151
endothelin 1	AA511462	−4.919891156	0.50725
enigma homolog (*R. norvegicus*)	AV086590	−4.495935882	0.46027
enoyl coenzyme A hydratase 1, peroxisomal	BG074113	−6.80582581	0.36476
Eph receptor A4	AV089919	−4.344159052	0.34405
ephrin A2	AA036231	−5.071477425	0.55979
EST	AV084337	−15.84609455	0.22443
EST	AV089256	−7.821945704	0.32354
EST	AV088222	−6.000803756	0.34203

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Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

EST	BG067237	−5.60660002	0.37931
EST	AV092327	−10.7313156	0.40744
EST	BG067593	−5.308733795	0.40771
EST	AV104735	−4.234815034	0.41649
EST	AV107204	−4.79899725	0.41907
EST	AV090230	−4.529261068	0.42529
EST	AV032077	−5.739628612	0.44260
EST	BI076847	−5.256943225	0.44584
EST	BG066574	−7.127384551	0.45000
EST	AW558245	−5.478409371	0.45389
EST	AV089999	−5.190665501	0.45408
EST	AW554432	−5.896214411	0.46163
EST	AV006409	−5.964082052	0.46864
EST	AV058135	−4.521649529	0.47454
EST	AI836950	−5.937211188	0.47461
EST	AV092810	−5.241936126	0.47602
EST	AV112960	−4.617628152	0.47834
EST	AW545825	−6.727669546	0.48212
EST	AV085516	−4.842648477	0.48488
EST	AW538191	−5.153458917	0.48631
EST	AU024393	−4.895288583	0.49035
EST	AI836065	−4.7755092	0.49306
EST	AA855859	−4.331305958	0.50195
EST	BG068314	−5.199228334	0.50230
EST	AV043406	−6.09893817	0.51042
EST	AV066234	−4.254484662	0.51985
EST	AW537378	−4.704989436	0.52235
EST	BI076614	−5.172671539	0.52412
EST	C78728	−4.342469046	0.52937
EST	AV106287	−4.157198249	0.53067
EST	AV084802	−5.166639576	0.53424
EST	AV113584	−5.364282201	0.53477
EST	AV073557	−4.506325346	0.54223
EST	AV058085	−8.095910962	0.54278
EST	AV087849	−6.671209615	0.54694
EST	AV087838	−8.769144558	0.54700
EST	AV113429	−6.64494074	0.54723
EST	AI854089	−4.234523551	0.55638
EST	AW539454	−4.298537333	0.56091
EST	AV054545	−6.94654287	0.56151
EST	BG065742	−13.00933301	0.56794
EST	BG067648	−8.683396149	0.57773
EST	AW537634	−5.324519908	0.57869
EST	AW538620	−5.025049378	0.58142
EST	AW554258	−5.832400646	0.59289
EST	AW558391	−4.257365597	0.59868
EST	AV065563	−4.768348545	0.60682
EST	AW542440	−4.491683933	0.62565
EST	AW558803	−5.020329084	0.63071
EST	AW558059	−4.281910751	0.63476
EST	BG067262	−5.922809848	0.63861
EST	AW556930	−4.246241225	0.65183
EST	BG069129	−4.137277132	0.66716
EST	BG068320	−4.21521866	0.67052
EST	BG063124	−4.343859108	0.67655
EST	AV124902	−6.244482147	0.68098
EST	AV066141	−4.258530103	0.70579
EST	AW546201	−5.334334206	0.71851
ESTs	AV013380	−8.675110287	0.12285
ESTs	AI839959	−11.80827248	0.26051
ESTs	AV087279	−10.84738974	0.37033
ESTs	BG074584	−4.991848058	0.41016
ESTs	BG071766	−7.140449539	0.41412
ESTs	BG064317	−5.723777122	0.42958
ESTs	BG071847	−5.928135678	0.43532
ESTs	AW558570	−4.480154195	0.45840
ESTs	BG069296	−5.240917448	0.46577
ESTs	AV028938	−4.151541241	0.48718
ESTs	AI840562	−12.06683549	0.49094
ESTs	AV026027	−4.506939508	0.49232
ESTs	AV006522	−4.613819892	0.52324
ESTs	AV083513	−4.828251577	0.53129
ESTs	BG073031	−4.566306264	0.53403
ESTs	BG075173	−5.028506537	0.53874

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Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

ESTs	BG063906	−8.089370979	0.54039
ESTs	BG066954	−4.782615457	0.54260
ESTs	BG067242	−6.82332378	0.54553
ESTs	BG072934	−5.228313195	0.54677
ESTs	AI854088	−4.159598239	0.55320
ESTs	BG073667	−10.48492722	0.55826
ESTs	BG065948	−4.860061653	0.56492
ESTs	AV031990	−6.549327409	0.56848
ESTs	BG067986	−7.07452791	0.58210
ESTs	BG067553	−5.000443636	0.59575
ESTs	AV033253	−4.213052314	0.59746
ESTs	BG066080	−7.178865626	0.60242
ESTs	AV094549	−5.448465601	0.61795
ESTs	BG069475	−5.197976115	0.63287
ESTs	BG073483	−5.580896625	0.63556
ESTs	AU043006	−6.902027048	0.63790
ESTs	AW557124	−4.400332672	0.67259
ESTs	BG071818	−6.164734724	0.67323
ESTs	AV087922	−5.463551198	0.68467
ESTs	BG073793	−5.556289784	0.69451
ESTs	AV029719	−4.64572808	0.70854
ESTs	AU040991	−4.656330027	0.71007
ESTs	AV123079	−4.487953887	0.79323
ESTs	AA219953	−4.928476302	0.81818
ESTs, Highly similar to NUMM MOUSE NADH-UBIQUINONE OXIDOR?	AV053614	−4.892019315	0.42037
ESTs, Highly similar to SR68_HUMAN SIGNAL RECOGNITION PART?	AA044456	−5.779140415	0.63127
ESTs, Moderately similar to CENC MOUSE CENTROMERE PROTEIN?	BG070887	−6.937133122	0.49208
ESTs, Moderately similar to COXM MOUSE CYTOCHROME C OXIDA?	BG073133	−4.382614329	0.38552
ESTs, Moderately similar to hypothetical protein MGC2217 [Homo sap?	AV140202	−5.884098532	0.42443
ESTs, Moderately similar to put. gag and pol gene product [M. musculu?	AU017598	−4.66917538	0.61340
ESTs, Moderately similar to T29098 microtubule-associated protein 4,	AV085051	−4.652120447	0.41777
ESTs, Moderately similar to TSC1_RAT HAMARTIN (TUBEROUS SCI?	BG073522	−4.528364031	0.57654
ESTs, Moderately similar to unnamed protein product [*H. sapiens*]	BG069242	−5.864025522	0.48855
ESTs, Weakly similar to 17-beta hydroxysteroid dehydrogenase type 2	AV012778	−5.99546057	0.29569
ESTs, Weakly similar to A48133 pre-mRNA splicing SRp75 [*H. sapiens*?	BG068996	−8.42767335	0.41807
ESTs, Weakly similar to COXD MOUSE CYTOCHROME C OXIDASE	AV088683	−4.686650535	0.38315
ESTs, Weakly similar to DIA3_MOUSE Diaphanous protein homolog 3	BG066491	−5.603551357	0.42357
ESTs, Weakly similar to F-actin binding protein b-Nexilin [*R. norvegicus*?	AU022020	−5.030069452	0.55649
ESTs, Weakly similar to FOR4 MOUSE FORMIN 4 [*M. musculus*]	BG068457	−5.127410189	0.51270
ESTs, Weakly similar to proline rich protein 2 [*Mus musculus*] [M. musc?	BG068802	−6.578307544	0.63820
ESTs, Weakly similar to S33477 hypothetical protein 1 —rat [R. norvegi?	BG063187	−4.666226794	0.59621
ESTs, Weakly similar to S48081 GRSF-1 protein [*H. sapiens*]	AV074326	−4.328278109	0.58441
ESTs, Weakly similar to SNAP190 [*H. sapiens*]	AV094673	−4.368590902	0.62151
ESTs, Weakly similar to testis derived transcript 3 [*Mus musculus*] [M. r?	BG065317	−5.144519948	0.39289
ESTs, Weakly similar to TLM MOUSE TLM PROTEIN [*M. musculus*]	AV092958	−6.150403741	0.45074
eukaryotic translation elongation factor 1 delta (guanine nucleotide exc?	AA253918	−4.186569986	0.57143
eukaryotic translation elongation factor 2	BG067570	−6.371044444	0.65020
eukaryotic translation initiation factor 2 alpha kinase 3	AV095205	−5.059393319	0.56401
eukaryotic translation initiation factor 3, subunit 2 (beta, 36 kD)	AV094437	−4.601527312	0.45547
excision repair cross-complementing rodent repair deficiency, complen?	BG063161	−5.547050872	0.63136
expressed sequence AA407270	BG063148	−5.93566094	0.40575
expressed sequence AA407270	AV024203	−5.771368225	0.55519
expressed sequence AA408168	BG066580	−7.720142458	0.42173
expressed sequence AA408877	AV009485	−7.331843342	0.44266
expressed sequence AA408877	BG063884	−7.549736289	0.69757
expressed sequence AA959758	BG070652	−6.210569504	0.69281
expressed sequence AA959857	AV109470	−6.111199231	0.57250
expressed sequence AA960047	AV033573	−4.632811011	0.71552
expressed sequence AI197390	BG064453	−4.447429392	0.65801
expressed sequence AI256693	AV083357	−7.061594227	0.44924
expressed sequence AI256693	BG062933	−6.84069401	0.50397
expressed sequence AI314967	BG075147	−9.700426666	0.58836
expressed sequence AI315037	AV014911	−4.168917128	0.46734
expressed sequence AI414265	BG063334	−5.374078873	0.35065
expressed sequence AI428506	AV032231	−4.312084153	0.46225
expressed sequence AI428794	BG076075	−4.228379709	0.69144
expressed sequence AI450287	BG065344	−6.167875756	0.74403
expressed sequence AI451892	AV032341	−4.405035852	0.58191
expressed sequence AI452301	BI076508	−8.197208043	0.54245
expressed sequence AI462702	BG068253	−6.418310883	0.57868
expressed sequence AI480535	AV083879	−5.187049508	0.47634
expressed sequence AI504630	AV015284	−5.888394236	0.56047
expressed sequence AI595366	AV086025	−7.209264922	0.54969
expressed sequence AI604911	BG063457	−6.27869333	0.60458

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expressed sequence AI746547	BG073543	−4.303474374	0.66202
expressed sequence AI838773	AV013448	−5.430320297	0.51111
expressed sequence AU022809	AU022809	−6.877820253	0.37946
expressed sequence AU040217	AV006387	−4.601437144	0.37921
expressed sequence AU043990	AV085893	−4.61060875	0.61610
expressed sequence AV006127	AV006127	−4.968478814	0.55637
expressed sequence AV028368	AV010507	−4.92003212	0.42417
expressed sequence AW122032	BG071778	−5.449835828	0.53237
expressed sequence AW125446	BG070892	−6.504525167	0.53458
expressed sequence AW215868	BG069736	−4.284651389	0.71600
expressed sequence AW495846	BG076492	−4.461876137	0.66865
expressed sequence AW545363	AV060425	−4.699771388	0.68385
expressed sequence AW554339	AW554339	−4.990896506	0.68667
expressed sequence AW555814	BG065375	−5.729264312	0.37042
expressed sequence C76711	C76711	−4.673701033	0.54362
expressed sequence C78643	C78643	−4.923270952	0.57835
expressed sequence C79026	BG066389	−4.28748357	0.68151
expressed sequence C81189	BG066971	−5.597395275	0.41821
expressed sequence C85317	BG067152	−5.135834608	0.52423
expressed sequence C86676	BG069605	−5.566957046	0.59228
expressed sequence C87882	BG067895	−5.351181214	0.51928
expressed sequence R74645	AV032243	−4.837023248	0.46405
Fas-activated serine/threonine kinase	BG074856	−4.217025613	0.45434
fatty acid binding protein 3, muscle and heart	AV006024	−7.308756431	0.40356
fatty acid Coenzyme A ligase, long chain 2	AV006061	−4.941866769	0.48297
FBJ osteosarcoma oncogene B	BG076079	−7.042746377	0.52580
f-box and leucine-rich repeat protein 12	BG067545	−4.400264381	0.77610
fibroblast growth factor receptor 4	AI385693	−5.90785626	0.48522
FK506 binding protein 3 (25 kD)	AV134155	−12.24059879	0.46456
forkhead box C1	A1415347	−4.299584893	0.64530
four and a half LIM domains 2	BG065614	−4.837322463	0.40643
G protein-coupled receptor kinase 7	AV005838	−5.282517048	0.50864
galactokinase	AV108357	−4.391030016	0.47824
gamma-glutamyl transpeptidase	AA162908	−4.562953433	0.41377
gelsolin	AV170949	−7.811644475	0.39819
gene rich cluster, C8 gene	C81126	−7.15072821	0.68777
genes associated with retinoid-IFN-induced mortality 19	BG073545	−6.967346166	0.40268
glioblastoma amplified sequence	AV082190	−7.336574711	0.44947
glucocorticoid-induced leucine zipper	W33468	−4.377977394	0.39408
glutamate oxaloacetate transaminase 1, soluble	BG066689	−5.113196958	0.41673
glutamine synthetase	AV009064	−5.494322506	0.38899
glutathione S-transferase, alpha 4	AV084880	−5.620268508	0.49942
glutathione S-transferase, mu 1	BG074268	−4.904981635	0.48909
glycosylphosphatidylinositol specific phospholipase D1	AV086924	−6.085890514	0.44720
granzyme B	AV038272	−4.606881006	0.42438
growth factor receptor bound protein 2-associated protein 1	BG063323	−4.173021249	0.73731
guanosine monophosphate reductase	AV103032	−4.121459006	0.49495
H2A histone family, member Y	C75971	−9.632930002	0.29998
heat shock 10 kDa protein 1 (chaperonin 10)	AV055529	−4.14388602	0.66410
heat shock protein, 70 kDa 3	AV223941	−4.717867523	0.42727
heme oxygenase (decycling) 1	AV083964	−9.130108662	0.57613
hemoglobin, beta adult major chain	AV108710	−6.575328842	0.48588
histidine ammonia lyase	AV022721	−5.357960558	0.44637
histidine rich calcium binding protein	BG073810	−7.723374649	0.29908
histidine triad nucleotide binding protein	AA154889	−4.936798282	0.68692
histocompatibility 47	AV036651	−7.347503305	0.63359
homeo box C4	AA245472	−4.46392246	0.41142
homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiqu?	AV086303	−4.450795031	0.32623
hydroxysteroid (17-beta) dehydrogenase 10	BG073539	−5.757417226	0.49471
hypothetical protein, MGC: 6943	AV085351	−4.547811108	0.62294
hypothetical protein, MGC: 6989	AV031846	−4.932452886	0.38973
hypothetical protein, MGC: 7550	AV087882	−8.375970889	0.61973
immediate early responses 5	BG069628	−4.158460406	0.56982
immunoglobulin superfamily, member 7	AV073565	−7.864977871	0.52541
insulin-like growth factor binding protein 4	AV005795	−5.368416582	0.18068
insulin-like growth factor binding protein 5	AV087798	−6.367247348	0.43614
integrin binding sialoprotein	AV171934	−4.99290928	0.34304
interferon activated gene 204	AV015208	−7.701331319	0.64560
interferon activated gene 205	AV058630	−8.015190946	0.34982
interferon-related developmental regulator 1	AA107115	−4.366931288	0.67719
iroquois related homeobox 4 (*Drosophila*)	AV006035	−6.23099642	0.58603
isocitrate dehydrogenase 2 (NADP+), mitochondrial	AV089252	−5.278687285	0.45360
isocitrate dehydrogenase 3 (NAD+) alpha	BG068774	−4.55487821	0.45957
isocitrate dehydrogenase 3 (NAD+) beta	AA036340	−4.162269318	0.47460

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isovaleryl coenzyme A dehydrogenase	BG070984	−8.767935605	0.30518
Janus kinase 1	BG067874	−7.25451775	0.65078
Janus kinase 2	AA153109	−5.307586645	0.64858
keratin associated protein 6-2	AV013499	−5.525131815	0.38744
keratin complex 2, basic, gene 16	AA738772	−4.266087447	0.51812
keratin complex 2, basic, gene 18	AV086522	−4.989188404	0.40787
keratin complex 2, basic, gene 6g	AV008410	−5.481104059	0.33635
L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain	AA122758	−7.489259426	0.44349
lactate dehydrogenase 2, B chain	AV171750	−4.652580719	0.33146
leucine zipper-EF-hand containing transmembrane protein 1	AV083103	−4.847170719	0.65147
LIM domain binding 3	AV088371	−4.401196368	0.41447
lipin 1	AV022047	−4.914016394	0.52166
lipoprotein lipase	AV084650	−4.839334145	0.42555
lipoprotein lipase	AV006290	−11.42464459	0.42847
low density lipoprotein receptor-related protein 2	BG064854	−4.220186803	0.59503
lurcher transcript 1	BG074415	−6.244274361	0.41951
lysosomal apyrase-like 1	AV086322	−6.775781299	0.65322
lysosomal membrane glycoprotein 2	BG074453	−6.248153587	0.74154
malate dehydrogenase, soluble	AV093576	−5.202957456	0.32039
MAP kinase-activated protein kinase 2	AA030342	−7.597964206	0.59516
MAP kinase-activated protein kinase 5	AA616241	−6.281175594	0.51661
maternal embryonic leucine zipper kinase	AV140411	−5.56058333	0.51604
membrane-associated protein 17	AV060358	−4.806294256	0.39397
methyl-CpG binding domain protein 4	AV032932	−4.628918539	0.55652
methylmalonyl-Coenzyme A mutase	AV031545	−5.467911803	0.50168
microsomal glutathione S-transferase 3	AV056432	−4.333591334	0.41688
microtubule-associated protein tau	BG066372	−4.116954726	0.42329
mitochondrial ribosomal protein 64	AV094889	−4.490503004	0.63412
mitochondrial ribosomal protein L15	BG064987	−5.229142603	0.54936
mitochondrial ribosomal protein L16	BG075780	−4.148872464	0.60350
mitochondrial ribosomal protein L23	BG071604	−7.059249111	0.49751
mitochondrial ribosomal protein L39	AV150063	−6.943179503	0.67150
mitochondrial ribosomal protein L43	AV094774	−4.968939433	0.69126
mitochondrial ribosomal protein S17	BG071752	−5.227257781	0.42507
mitochondrial ribosomal protein S25	BG065867	−6.463001045	0.47504
mitochondrial ribosomal protein S31	AV058185	−4.943328985	0.52131
mitogen activated protein binding protein interacting protein	AV134069	−5.084504328	0.63511
mitogen-activated protein kinase kinase kinase 7 interacting protein 2	AV011185	−5.269766834	0.51165
MLN51 protein	AW556296	−6.239103687	0.56037
Mus musculus 10 day old male pancreas cDNA, RIKEN full-length enri?	AV058496	−9.867161529	0.43027
Mus musculus 10, 11 days embryo whole body cDNA, RIKEN full-leng?	BG075565	−6.173663343	0.72665
Mus musculus brain and reproductive organ-expressed protein (Bre) m?	AV073509	−4.883581812	0.51095
Mus musculus methyl-CpG binding domain protein 3-like protein 2 (Mb?	BG071308	−5.716981372	0.53500
Mus musculus QIL1 (Qil1) mRNA, complete cds	BG072356	−5.841602916	0.46840
Mus musculus, clone IMAGE: 3491909, mRNA, partial cds	BG071756	−4.496303875	0.65826
Mus musculus, clone IMAGE: 4482598, mRNA	AA034560	−4.150299072	0.31779
Mus musculus, clone IMAGE: 5357662, mRNA, partial cds	AV042520	−4.408584942	0.60396
Mus musculus, clone MGC: 11691 IMAGE: 3962417, mRNA, complete ?	AV084848	−5.490316133	0.52085
Mus musculus, clone MGC: 36369 IMAGE: 4982239, mRNA, complete?	AV094465	−5.44774435	0.49239
Mus musculus, clone MGC: 6816 IMAGE: 2648797, mRNA, complete c?	AV014114	−4.282850534	0.53438
Mus musculus, clone MGC: 7480 IMAGE: 3490700, mRNA, complete c?	AV034637	−5.987456834	0.50215
Mus musculus, clone MGC: 7530 IMAGE: 3492114, mRNA, complete c?	AV089939	−6.833387684	0.58423
Mus musculus, H4 histone family, member A, clone MGC: 30488 IMAG?	AV113959	−4.622426446	0.45955
Mus musculus, hypothetical protein MGC11287 similar to ribosomal p?	AV031726	−5.584850445	0.70092
Mus musculus, Similar to 3-hydroxyisobutyrate dehydrogenase, clone I	AI854120	−5.249848661	0.50351
Mus musculus, Similar to ATPase, Na+/K+ transporting, alpha 1a.1 po?	AA063844	−4.712431921	0.52469
Mus musculus, Similar to chromosome 18 open reading frame 1, clone?	BG070238	−4.251926511	0.72193
Mus musculus, Similar to electron-transfer-flavoprotein, alpha polypep?	AV088774	−5.68750046	0.47951
Mus musculus, Similar to glutamate rich WD repeat protein GRWD, c?	BG071389	−4.464168152	0.69603
Mus musculus, Similar to hypothetical protein BC004409, clone MGC: ?	AV086576	−5.211455456	0.54638
Mus musculus, Similar to hypothetical protein MGC4368, clone MGC: 2	BG065643	−4.140909089	0.53064
Mus musculus, Similar to hypothetical protein MGC4368, clone MGC: 2	AV005807	−4.448246934	0.54984
Mus musculus, Similar to hypothetical protein, clone MGC: 19257 IMA?	AV055251	−5.964031565	0.71353
Mus musculus, Similar to mannosyl (alpha-1,3-)-glycoprotein beta-1,4-?	BG063179	−4.963893564	0.68444
Mus musculus, Similar to metallothionein 1, clone MGC: 27821 IMAGE:?	AV149953	−5.009409882	0.38263
Mus musculus, Similar to MIPP65 protein, clone MGC: 18783 IMAGE: 4	AV109599	−4.769020513	0.62297
Mus musculus, Similar to PTD015 protein, clone MGC: 36240 IMAGE: 5	AV088778	−4.30312782	0.51111
Mus musculus, Similar to secretory leukocyte protease inhibitor, clone	AV089194	−5.393553048	0.56725
Mus musculus, Similar to transmembrane protein 5, clone MGC: 28135?	AV095048	−4.755442646	0.65205
myeloblastosis oncogene	AV222464	−5.594373043	0.63770
myeloid leukemia factor 1	AV042698	−6.286060346	0.36555
myosin binding protein C, cardiac	AV005840	−4.40479052	0.56183
myosin light chain, alkali, cardiac atria	AV005821	−7.047964424	0.31699
N-acetyltransferase ARD1 homolog (*S. cerevisiae*)	AI841645	−4.230855583	0.72328

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 2	AV016078	−6.793461475	0.40427
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 2	AV093541	−5.380207421	0.51264
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1	AV140287	−7.671234989	0.49739
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4	AV050140	−4.641798789	0.43550
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14 kD, B1⑦	AV106199	−5.540201021	0.41067
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14 kD, B1⑦	AV087995	−4.857759692	0.46752
NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (14.5 kD, B⑦	AV133797	−4.463338846	0.45989
NADH dehydrogenase (ubiquinone) 1 beta subcomplex 5	AV057902	−6.33345429	0.40844
NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9	BG075174	−5.525039706	0.44325
NADH dehydrogenase (ubiquinone) 1, subcomplex Unsequenced EST⑦	AV088122	−4.47328854	0.43713
NADH dehydrogenase (ubiquinone) Fe—S protein 3	BG076060	−7.829252699	0.40260
NADH dehydrogenase (ubiquinone) Fe—S protein 4	BG066265	−4.786795598	0.56585
nebulin-related anchoring protein	AV013274	−4.709864985	0.31656
neurotensin receptor 2	AV032954	−6.394790155	0.34827
Niemann Pick type C1	AV012796	−5.818245482	0.57019
N-myc downstream regulated 2	AV149939	−4.956548973	0.47960
non MHC restricted killing associated	BG076189	−5.906532297	0.56544
N-sulfotransferase	AV051308	−4.548362727	0.41566
nuclear distribution gene C homolog (*Aspergillus*)	BG073422	−10.8626569	0.56353
nuclear receptor coactivator 6 interacting protein	AV113681	−6.148669995	0.34592
nuclear receptor interacting protein 1	AI840578	−4.612742367	0.59793
nuclear receptor subfamily 2, group F, member 1	BG071238	−4.980625532	0.35648
nuclear transcription factor-Y beta	AV016446	−6.246444283	0.41297
olfactomedin 1	BG073096	−7.286235688	0.39555
oxysterol binding protein-like 1A	BG073162	−6.812913131	0.57590
p53 apoptosis effector related to Pmp22	BG065306	−4.678975404	0.40269
p53 regulated PA26 nuclear protein	BG076140	−5.448306149	0.55541
paired box gene 6	AV032892	−4.488629951	0.61857
pantophysin	AV091203	−4.149100799	0.69535
PCTAIRE-motif protein kinase 1	AV157322	−5.035290036	0.46140
pellino 1	BG063809	−6.156617986	0.49251
peptidase 4	U51014	−4.3323071	0.47568
peptidylprolyl isomerase (cyclophilin)-like 1	AV015645	−4.821247351	0.32093
periplakin	BG074644	−4.757437218	0.33818
peroxiredoxin 3	AA168985	−10.6903742	0.41739
peroxiredoxin 6	AV052763	−4.530139145	0.54965
peroxisomal membrane protein 2, 22 kDa	BG073687	−5.266196231	0.36957
peroxisomal membrane protein 3, 35 kDa	BG075110	−4.851555962	0.58487
peroxisome proliferative activated receptor, gamma, coactivator 1	AF049330	−5.741819935	0.48224
phosphate cytidylyltransferase 1, choline, alpha isoform	BG071157	−8.214581306	0.56759
phosphatidylinositol 3 kinase, regulatory subunit, polypeptide 4, p150	BG069962	−5.634662461	0.72045
phosphofructokinase, muscle	AV012100	−4.863378338	0.31668
phospholipase A2 group VII (platelet-activating factor acetylhydrolase,	AV033702	−4.176805214	0.45211
phospholipase A2, group IB, pancreas	AV085478	−7.151034427	0.68461
phosphoribosylglycinamide formyltransferase	AV009977	−6.77843399	0.62257
phytanoyl-CoA hydroxylase	AV084314	−9.87801812	0.28442
platelet-derived growth factor receptor-like	BG068957	−5.060999551	0.39457
polymyositis/scleroderma autoantigen 2	BG063453	−5.530726571	0.44618
potassium voltage-gated channel, Shal-related family, member 2	BG075283	−4.752089401	0.48273
pre-B-cell colony-enhancing factor	AV108470	−4.183827947	0.53050
prefoldin 2	AU020724	−6.551694173	0.50227
pregnancy upregulated non-ubiquitously expressed CaM kinase	AI391204	−4.976455425	0.67410
programmed cell death 5	BG063248	−4.346750922	0.47631
proteasome (prosome, macropain) 26S subunit, non-ATPase, 4	AV111455	−4.786266311	0.70045
proteasome (prosome, macropain) subunit, alpha type 7	AV093698	−7.206924146	0.71542
proteasome (prosome, macropain) subunit, beta type 6	AV093807	−4.135275065	0.73806
protein kinase inhibitor, gamma	BG073627	−5.407677293	0.66327
protein kinase, AMP-activated, gamma 1 non-catalytic subunit	BG067722	−5.174284179	0.48660
protein phospatase 3, regulatory subunit B, alpha isoform (calcineurin⑦	AV006032	−4.245876461	0.32451
protein tyrosine phosphatase, non-receptor type 9	AV114744	−4.237859546	0.58064
pyruvate dehydrogenase E1 alpha 1	BG068736	−6.333567491	0.40029
quaking	BG068631	−4.93071726	0.57698
Rab acceptor 1 (prenylated)	BG072002	−5.608012206	0.48144
RAN guanine nucleotide release factor	AV133777	−4.36279612	0.59926
RAS-homolog enriched in brain	AV095119	−4.879211565	0.53004
RAS-related C3 botulinum substrate 1	BG076502	−6.040933852	0.60293
receptor (calcitonin) activity modifying protein 2	AV085507	−5.303383378	0.54970
receptor-associated protein of the synapse, 43 kDa	AV061434	−10.61862114	0.41436
regulator of G-protein signaling 2	BG068533	−4.835282956	0.27907
reticulon 2 (Z-band associated protein)	AV088718	−5.623316329	0.44935
retinoic acid induced 1	AV012729	−4.290030308	0.63998
retinoid X receptor gamma	AV089219	−5.822213161	0.49561
ribosomal protein L27a	AV013292	−4.437253914	0.49756
ribosomal protein L30	BG065356	−4.252974113	0.68577

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ribosomal protein L37a	AI837822	−5.154049385	0.59292
ribosomal protein S25	AV093430	−4.658335514	0.58295
ribosomal protein S29	L31609	−6.110664766	0.45134
RIKEN cDNA 0610006N12 gene	AA110681	−6.75185087	0.40291
RIKEN cDNA 0610007H07 gene	BG072309	−4.126129022	0.60173
RIKEN cDNA 0610009D10 gene	AA154397	−7.08466256	0.34713
RIKEN cDNA 0610009I16 gene	AV086609	−7.236199669	0.35051
RIKEN cDNA 0610010E03 gene	AI841340	−6.802249485	0.47787
RIKEN cDNA 0610010I17 gene	AV056903	−5.538754596	0.46727
RIKEN cDNA 0610010I23 gene	AV051596	−4.328819955	0.61515
RIKEN cDNA 0610011B04 gene	BG073700	−6.555996854	0.38623
RIKEN cDNA 0610011L04 gene	BG072552	−5.054443334	0.37549
RIKEN cDNA 0610025I19 gene	AV085433	−17.56809908	0.22127
RIKEN cDNA 0610033L03 gene	AV093484	−7.039284704	0.41225
RIKEN cDNA 0610039N19 gene	AV083519	−5.406448324	0.41668
RIKEN cDNA 0610039N19 gene	BG066600	−5.330882468	0.45065
RIKEN cDNA 0610040D20 gene	AV004247	−4.512757398	0.63567
RIKEN cDNA 0710008D09 gene	AW558029	−4.729146692	0.46971
RIKEN cDNA 1010001M12 gene	AV086467	−7.48040813	0.44085
RIKEN cDNA 1010001N11 gene	AV133828	−4.686104019	0.46207
RIKEN cDNA 1100001F19 gene	BG070073	−5.288822697	0.68489
RIKEN cDNA 1110001A12 gene	BG070781	−4.703835715	0.64679
RIKEN cDNA 1110001I24 gene	AV140151	−6.052802797	0.36840
RIKEN cDNA 1110001J03 gene	AV065564	−4.192297591	0.32893
RIKEN cDNA 1110001O19 gene	AV056481	−4.314017396	0.56079
RIKEN cDNA 1110003P16 gene	BG075816	−4.46363954	0.51085
RIKEN cDNA 1110003P16 gene	AV057754	−4.970604264	0.55663
RIKEN cDNA 1110004A22 gene	BG071279	−4.457797204	0.48172
RIKEN cDNA 1110007A04 gene	AV055217	−4.969107085	0.47342
RIKEN cDNA 1110007C09 gene	AV051158	−4.118786157	0.53859
RIKEN cDNA 1110008L20 gene	AV018091	−4.697507959	0.52248
RIKEN cDNA 1110013H04 gene	AV052337	−6.788162338	0.45818
RIKEN cDNA 1110013H04 gene	BG068276	−6.06832892	0.56841
RIKEN cDNA 1110018B13 gene	AV028535	−4.615083855	0.43160
RIKEN cDNA 1110018B13 gene	AV084595	−5.97322181	0.57666
RIKEN cDNA 1110020I04 gene	AV051530	−14.92032087	0.30711
RIKEN cDNA 1110020I04 gene	BG063739	−4.463807689	0.47696
RIKEN cDNA 1110020J08 gene	AW550860	−4.614727887	0.61323
RIKEN cDNA 1110021D01 gene	AV071376	−4.58410245	0.79871
RIKEN cDNA 1110028A07 gene	AV085772	−6.174919065	0.39958
RIKEN cDNA 1110031C13 gene	AV041472	−5.028419389	0.46491
RIKEN cDNA 1110031I02 gene	AU043030	−4.403755369	0.51919
RIKEN cDNA 1110036H21 gene	AV012479	−5.160074727	0.45281
RIKEN cDNA 1110054G21 gene	AV014368	−5.027901058	0.49410
RIKEN cDNA 1110063J16 gene	AV078407	−5.999746891	0.59492
RIKEN cDNA 1110065A22 gene	AV016366	−4.92541762	0.51442
RIKEN cDNA 1190002A23 gene	AV024081	−5.535759516	0.60154
RIKEN cDNA 1190002L16 gene	BG071000	−6.490599379	0.52952
RIKEN cDNA 1190006F07 gene	AI839764	−6.766591842	0.28987
RIKEN cDNA 1190006F07 gene	BG072458	−4.615357067	0.47455
RIKEN cDNA 1190006L01 gene	BG076352	−6.238204432	0.38844
RIKEN cDNA 1190017B19 gene	AV022384	−4.286049069	0.61201
RIKEN cDNA 1200006O19 gene	BG071963	−4.904434126	0.49222
RIKEN cDNA 1200006O19 gene	AV074439	−4.359926363	0.57055
RIKEN cDNA 1200007E24 gene	BG075635	−5.547606302	0.54461
RIKEN cDNA 1200009K13 gene	BG069392	−4.497346028	0.66746
RIKEN cDNA 1200015P04 gene	AV065655	−6.152236946	0.15180
RIKEN cDNA 1200015P04 gene	AV067337	−8.636968452	0.18033
RIKEN cDNA 1200015P04 gene	AI840878	−8.089636915	0.18339
RIKEN cDNA 1200015P04 gene	AV068725	−9.796466054	0.22295
RIKEN cDNA 1300002C13 gene	BG064110	−6.428715365	0.48112
RIKEN cDNA 1300013G12 gene	BG076497	−6.939802129	0.53379
RIKEN cDNA 1300013J15 gene	AV082636	−4.431683442	0.42023
RIKEN cDNA 1300017C12 gene	BG069813	−5.158800113	0.47198
RIKEN cDNA 1300019P08 gene	AV094927	−6.036452338	0.46761
RIKEN cDNA 1500001L03 gene	BG067671	−4.740520776	0.33865
RIKEN cDNA 1500004O06 gene	AV084141	−10.93331411	0.53732
RIKEN cDNA 1500004O06 gene	AV095102	−4.337275885	0.59115
RIKEN cDNA 1500010M16 gene	AV162350	−4.399118243	0.53491
RIKEN cDNA 1500012D08 gene	AV094880	−5.354092617	0.47779
RIKEN cDNA 1500032E05 gene	AI894110	−5.272445403	0.58956
RIKEN cDNA 1500034J20 gene	AV111483	−8.495755577	0.49446
RIKEN cDNA 1500036F01 gene	AV074483	−4.169290222	0.23080
RIKEN cDNA 1600014J01 gene	AV051090	−6.532850795	0.57481

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RIKEN cDNA 1600023A02 gene	AV002462	−4.735699762	0.55362
RIKEN cDNA 1700006F03 gene	BG071686	−6.491908138	0.57462
RIKEN cDNA 1700013G20 gene	BG067233	−5.577143706	0.50168
RIKEN cDNA 1700016D08 gene	BG073980	−4.295578649	0.66457
RIKEN cDNA 1700029P11 gene	AV043746	−4.981358021	0.38488
RIKEN cDNA 1700029P11 gene	AV043137	−8.428540481	0.48877
RIKEN cDNA 1810004I06 gene	AV050264	−5.021183923	0.33763
RIKEN cDNA 1810004I06 gene	AV070272	−4.335500464	0.53518
RIKEN cDNA 1810008A14 gene	BG063535	−8.636021346	0.63781
RIKEN cDNA 1810011O01 gene	AV070830	−5.421078504	0.43645
RIKEN cDNA 1810013D10 gene	BG067851	−4.892379863	0.54634
RIKEN cDNA 1810013K23 gene	AW539206	−4.282626641	0.50783
RIKEN cDNA 1810017G16 gene	AV087873	−7.888058385	0.46376
RIKEN cDNA 1810017G16 gene	AV051238	−4.521324967	0.51059
RIKEN cDNA 1810017G16 gene	AV070773	−4.128355653	0.68677
RIKEN cDNA 1810018M11 gene	AV018921	−9.416192926	0.60647
RIKEN cDNA 1810020E01 gene	AV032033	−5.136798775	0.45741
RIKEN cDNA 1810029B16 gene	BG069652	−6.038729723	0.56189
RIKEN cDNA 1810030E18 gene	AV140504	−5.27469245	0.67706
RIKEN cDNA 1810030E20 gene	BG064141	−4.932956216	0.58007
RIKEN cDNA 1810030E20 gene	BG063825	−4.229066461	0.64290
RIKEN cDNA 1810033A19 gene	AV054886	−5.043468074	0.60235
RIKEN cDNA 1810035L17 gene	BG072596	−5.548484127	0.58195
RIKEN cDNA 1810036J22 gene	AV113916	−19.44625479	0.47866
RIKEN cDNA 1810036J22 gene	AV084361	−5.973172086	0.50101
RIKEN cDNA 1810036J22 gene	AV086261	−5.281464813	0.52027
RIKEN cDNA 1810036J22 gene	BG064173	−5.173272699	0.59456
RIKEN cDNA 1810055D05 gene	AV140588	−5.31258747	0.39893
RIKEN cDNA 1810055D05 gene	AV065469	−4.676521256	0.43368
RIKEN cDNA 1810055D05 gene	AV059067	−5.706489038	0.56482
RIKEN cDNA 2010003O02 gene	BG066308	−4.636818478	0.52627
RIKEN cDNA 2010004E11 gene	AV066070	−5.293676718	0.58290
RIKEN cDNA 2010100O12 gene	BG075840	−5.184355736	0.56372
RIKEN cDNA 2010100O12 gene	AV088623	−7.043681229	0.61838
RIKEN cDNA 2010107E04 gene	BG076108	−4.676770221	0.48870
RIKEN cDNA 2010110I09 gene	BG072417	−8.047056971	0.50518
RIKEN cDNA 2010110M21 gene	AV031008	−4.152271601	0.62642
RIKEN cDNA 2010110M21 gene	AV006309	−5.174330603	0.63652
RIKEN cDNA 2210008F15 gene	AV085342	−6.760958652	0.43695
RIKEN cDNA 2210008F15 gene	AV140597	−4.976752904	0.50033
RIKEN cDNA 2210009K14 gene	AV074534	−4.244231808	0.58997
RIKEN cDNA 2210016H18 gene	AW556974	−4.695260223	0.48019
RIKEN cDNA 2210415M14 gene	AV063132	−4.15138579	0.41701
RIKEN cDNA 2210415M14 gene	AV123133	−6.866891309	0.46633
RIKEN cDNA 2210415M14 gene	BG072853	−5.89983116	0.46756
RIKEN cDNA 2210418G03 gene	AV081301	−7.382877216	0.59853
RIKEN cDNA 2310001N14 gene	AV083256	−9.471464778	0.35457
RIKEN cDNA 2310002J21 gene	BG063238	−4.177926076	0.64768
RIKEN cDNA 2310005O14 gene	AV104008	−5.644497912	0.55170
RIKEN cDNA 2310015J09 gene	AV085812	−5.079301158	0.32950
RIKEN cDNA 2310016E22 gene	AV085956	−4.508187361	0.53050
RIKEN cDNA 2310016M24 gene	AV109219	−6.174685479	0.45223
RIKEN cDNA 2310020D23 gene	AA087197	−4.989916277	0.70975
RIKEN cDNA 2310020H20 gene	BG063177	−4.162978542	0.49609
RIKEN cDNA 2310021J10 gene	AV086427	−5.249829896	0.41447
RIKEN cDNA 2310026J01 gene	AV087038	−6.224052995	0.18088
RIKEN cDNA 2310034L04 gene	AV088072	−4.857617607	0.43830
RIKEN cDNA 2310039H15 gene	AV103530	−5.762586781	0.37401
RIKEN cDNA 2310039H15 gene	AV088685	−10.65523915	0.42365
RIKEN cDNA 2310039H15 gene	AV006258	−4.770080482	0.48698
RIKEN cDNA 2310042M24 gene	AV089703	−4.957830613	0.70818
RIKEN cDNA 2310042N02 gene	AV089174	−5.227461526	0.44265
RIKEN cDNA 2310045A07 gene	AV089574	−5.794732203	0.36180
RIKEN cDNA 2310051E17 gene	AV090635	−5.386354388	0.39477
RIKEN cDNA 2310056B04 gene	BG074855	−4.928886112	0.54397
RIKEN cDNA 2310058J06 gene	AV171032	−5.566735601	0.50412
RIKEN cDNA 2310066N05 gene	AV109445	−4.136380251	0.71050
RIKEN cDNA 2310067L22 gene	AV085162	−6.065666962	0.43059
RIKEN cDNA 2310076O14 gene	AV093026	−5.288222969	0.46965
RIKEN cDNA 2310079P10 gene	BG069582	−10.79467049	0.31277
RIKEN cDNA 2400003N08 gene	BG068322	−5.831862696	0.57334
RIKEN cDNA 2400006N03 gene	AV095106	−5.022967582	0.63521
RIKEN cDNA 2400010D15 gene	BG070770	−5.425606132	0.50504
RIKEN cDNA 2400010D15 gene	AV014412	−5.422633849	0.58352

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RIKEN cDNA 2400010G15 gene	AV087844	−5.241042761	0.59067
RIKEN cDNA 2410004H02 gene	AV095143	−4.661273681	0.52258
RIKEN cDNA 2410004H02 gene	BG065078	−4.425936465	0.60061
RIKEN cDNA 2410005O16 gene	AV085399	−4.304045051	0.66223
RIKEN cDNA 2410011G03 gene	BG072634	−7.102554029	0.34324
RIKEN cDNA 2410011G03 gene	AV140158	−7.412258554	0.53256
RIKEN cDNA 2410016F19 gene	BG066198	−4.153805722	0.67772
RIKEN cDNA 2410030A14 gene	AV095185	−4.882546338	0.56335
RIKEN cDNA 2410043G19 gene	AV056739	−5.579786915	0.39668
RIKEN cDNA 2410066K11 gene	BG074815	−4.189499593	0.65618
RIKEN cDNA 2410166I05 gene	BG076161	−7.746565635	0.56369
RIKEN cDNA 2510027N19 gene	BG063257	−4.424035337	0.64005
RIKEN cDNA 2510048K03 gene	AV050186	−7.214847749	0.39540
RIKEN cDNA 2600001N01 gene	BG065115	−4.622808402	0.65666
RIKEN cDNA 2610002K22 gene	AV095125	−4.222224194	0.65841
RIKEN cDNA 2610003B19 gene	AV077867	−5.392435801	0.50676
RIKEN cDNA 2610020H15 gene	BG067911	−4.33184907	0.50925
RIKEN cDNA 2610028H24 gene	AU041304	−8.837908474	0.42891
RIKEN cDNA 2610034N03 gene	AV104092	−4.334279184	0.60381
RIKEN cDNA 2610041P16 gene	BG063943	−9.171542327	0.39169
RIKEN cDNA 2610041P16 gene	AV086193	−4.437390523	0.53171
RIKEN cDNA 2610205H19 gene	AV149977	−5.075180419	0.54297
RIKEN cDNA 2610509H23 gene	BG073333	−4.529188732	0.67762
RIKEN cDNA 2610529I12 gene	AV112870	−4.147133165	0.55866
RIKEN cDNA 2700018N07 gene	AI327124	−4.29762364	0.56436
RIKEN cDNA 2700033I16 gene	AV060239	−4.362623219	0.48215
RIKEN cDNA 2700049M22 gene	AU022477	−6.242566156	0.56361
RIKEN cDNA 2700055K07 gene	AV086940	−5.809367054	0.33093
RIKEN cDNA 2700094L05 gene	BG070651	−6.743245025	0.63558
RIKEN cDNA 2810403A07 gene	BG064481	−4.939425861	0.70126
RIKEN cDNA 2810403L02 gene	AI838447	−5.476484495	0.79272
RIKEN cDNA 2810417D04 gene	AV141701	−4.439903075	0.53864
RIKEN cDNA 2810422J05 gene	BG064518	−5.097975531	0.54326
RIKEN cDNA 2810432N10 gene	BG070211	−4.811203049	0.51703
RIKEN cDNA 2810468K05 gene	BG071137	−5.342157238	0.70066
RIKEN cDNA 2900010I05 gene	AV056021	−4.774554089	0.48993
RIKEN cDNA 2900055D03 gene	AV140126	−4.271457143	0.50891
RIKEN cDNA 3110004H13 gene	BG071859	−6.046421631	0.54200
RIKEN cDNA 3110005M08 gene	AV108251	−4.206377049	0.72772
RIKEN cDNA 3200001M24 gene	AV093570	−4.129969377	0.55745
RIKEN cDNA 3200001M24 gene	BG074430	−4.354466269	0.66040
RIKEN cDNA 3230402N08 gene	AV089737	−4.465701864	0.65941
RIKEN cDNA 3830417M17 gene	BG076225	−4.421284948	0.67375
RIKEN cDNA 4432406C05 gene	AV085137	−6.099053061	0.44504
RIKEN cDNA 4631426G04 gene	BG068677	−4.625459494	0.56033
RIKEN cDNA 4632432J16 gene	AV060454	−4.617958369	0.47517
RIKEN cDNA 4633402N23 gene	AA408693	−5.506478686	0.57523
RIKEN cDNA 4833415N24 gene	AV086029	−4.306972542	0.46627
RIKEN cDNA 4833417L20 gene	BG070225	−4.161297063	0.53534
RIKEN cDNA 4930422J18 gene	BG074133	−6.542937211	0.63785
RIKEN cDNA 4930438D12 gene	AV114186	−5.788046741	0.45307
RIKEN cDNA 4930564D15 gene	AW539497	−6.195679798	0.63818
RIKEN cDNA 4933411H20 gene	AV094491	−10.13251578	0.23760
RIKEN cDNA 4933436C10 gene	AI854103	−9.22185596	0.25555
RIKEN cDNA 4933436C10 gene	AV043801	−7.145276072	0.26851
RIKEN cDNA 5430432N15 gene	AV023999	−5.168897494	0.42754
RIKEN cDNA 5730591C18 gene	AV087450	−4.292004125	0.52004
RIKEN cDNA 5830417I10 gene	BG066100	−4.264697524	0.71856
RIKEN cDNA 5830457J20 gene	AV140522	−5.873234067	0.57518
RIKEN cDNA 5830498C14 gene	AV012853	−10.64307472	0.44318
RIKEN cDNA 5830498C14 gene	BG066452	−4.63710017	0.72557
RIKEN cDNA 6030457N17 gene	AV094720	−11.17974002	0.47794
RIKEN cDNA 6430411K18 gene	AV023331	−6.558273485	0.55220
RIKEN cDNA 6530416A09 gene	BG071475	−6.13803934	0.53936
RIKEN cDNA 6720475J19 gene	BG073712	−13.95563601	0.24131
RIKEN cDNA 6720475J19 gene	BG073481	−7.39081553	0.26541
RIKEN cDNA 9030421L11 gene	BG075528	−4.628327246	0.54551
RIKEN cDNA 9130012G04 gene	BG073930	−6.693464096	0.54126
RIKEN cDNA A930018B01 gene	AV073463	−4.81629501	0.73761
RIKEN cDNA E130105L11 gene	BG075577	−5.960051773	0.51388
ring finger protein 11	AV084728	−4.227540819	0.54992
ring-box 1	AV053017	−5.363684395	0.58013
RNA polymerase 1–3 (16 kDa subunit)	AV134053	−4.479915258	0.59561
S100 calcium binding protein A1	AV003587	−4.795563356	0.51956

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

sacsin	AV013617	−4.705249687	0.67220
S-adenosylmethionine decarboxylase 1	BG075459	−6.575072123	0.38803
SEC61, gamma subunit (*S. cerevisiae*)	AV133876	−4.885488937	0.76946
secretory carrier membrane protein 3	AV094492	−4.979251312	0.43904
serine/threonine kinase 23	AA170153	−4.185610913	0.46751
serine/threonine kinase 25 (yeast)	AA146115	−6.421699669	0.54596
serologically defined colon cancer antigen 28	BG065578	−12.46409454	0.18651
serum response factor	AV014460	−4.179789629	0.60298
signal recognition particle 14 kDa (homologous Alu RNA binding protei⑦	AV005775	−7.122752178	0.78602
small inducible cytokine A11	BE137080	−4.753939259	0.43931
small proline rich-like 7	AV072477	−4.143398782	0.31871
soggy 1	AV087775	−4.59725695	0.41376
solute carrier family 1, member 7	AV006313	−9.007262827	0.54179
solute carrier family 16 (monocarboxylic acid transporters), member 2	AA199215	−4.248424723	0.57730
solute carrier family 25 (mitochondrial carrier; adenine nucleotide trans⑦	AV087780	−4.501100977	0.35837
solute carrier family 25 (mitochondrial carrier; oxoglutarate carrier), me⑦	AV094940	−7.980202556	0.45584
solute carrier family 27 (fatty acid transporter), member 2	AA154831	−6.128882484	0.52385
Son cell proliferation protein	BG071049	−6.036472623	0.57640
sortilin-related receptor, LDLR class A repeats-containing	AA673962	−4.841253747	0.44436
special AT-rich sequence binding protein 1	BG065579	−6.042197612	0.44733
spermine synthase	AV113836	−4.915770722	0.55802
sphingomyelin phosphodiesterase 2, neutral	BG063429	−4.588922541	0.53816
split hand/foot deleted gene 1	AV134049	−4.646755588	0.56217
steroid 5 alpha-reductase 2-like	AV084563	−10.28926678	0.46589
sterol carrier protein 2, liver	AA146030	−5.055773043	0.61558
succinate-Coenzyme A ligase, GDP-forming, beta subunit	AV087975	−4.401153724	0.54934
superoxide dismutase 1, soluble	BG074045	−4.775499706	0.57536
suppressor of initiator codon mutations, related sequence 1 (S. cerevis⑦	AV042274	−5.892946224	0.47109
surfactant associated protein A	AV024739	−6.312755463	0.44949
synaptobrevin like 1	AV113528	−11.35230657	0.48532
TAR (HIV) RNA binding protein 2	BG069749	−4.479592469	0.60506
T-box 5	AA198841	−5.929892933	0.50092
T-cell receptor beta, variable 13	AV015100	−5.567729981	0.54115
TGF-beta1-induced anti-apoptotic factor 1	AV078541	−5.048008293	0.68665
thioredoxin 2	AA116866	−4.64110901	0.58741
thioredoxin-like (32 kD)	AV070815	−4.571951113	0.54871
thioredoxin-like 2	AV016790	−5.561621744	0.50942
thyroid hormone receptor interactor 13	AV094724	−4.603203665	0.52873
tight junction protein 1	BG073399	−7.525877699	0.67799
tissue inhibitor of metalloproteinase 3	NM_011595	−7.557159513	0.56285
transcription elongation factor A (SII), 3	AI322966	−4.159841646	0.34762
transducer of ERBB2, 2	BG074926	−5.987030543	0.45199
transforming growth factor beta 1 induced transcript 4	AV140519	−4.616859427	0.74969
transforming growth factor, beta 1	AA049522	−8.01904204	0.45450
tubulointerstitial nephritis antigen	AV066552	−4.635666571	0.61805
tumor differentially expressed 1, like	AV083974	−4.20155329	0.64214
tumor necrosis factor (ligand) superfamily, member 10	U37522	−7.159468126	0.44011
tumor necrosis factor receptor superfamily, member 19	BG072211	−4.140657689	0.34852
tumor necrosis factor, alpha-induced protein 3	AA572306	−4.133144105	0.60638
ubiquitin-conjugating enzyme E2B, RAD6 homology (*S. cerevisiae*)	AV095421	−4.659707734	0.55089
ubiquitin-like 3	BG072313	−4.13814274	0.55812
Unsequenced EST	413125	−8.22561445	0.22295
Unsequenced EST	412659	−8.870617869	0.24426
Unsequenced EST	432064	−10.13653121	0.26718
Unsequenced EST	410956	−4.818374482	0.26969
Unsequenced EST	410595	−5.430746949	0.29232
Unsequenced EST	431252	−5.030312199	0.29553
Unsequenced EST	411369	−8.60777606	0.29715
Unsequenced EST	413333	−4.28197017	0.32070
Unsequenced EST	413297	−6.333308867	0.33170
Unsequenced EST	411987	−4.70742313	0.33375
Unsequenced EST	411660	−8.229104928	0.33965
Unsequenced EST	411054	−5.207650574	0.34062
Unsequenced EST	410682	−5.274633509	0.34330
Unsequenced EST	431081	−5.546409705	0.34658
Unsequenced EST	206294	−4.181652187	0.35033
Unsequenced EST	412975	−5.605640895	0.35576
Unsequenced EST	432689	−5.97281453	0.35787
Unsequenced EST	411277	−11.08897728	0.35956
Unsequenced EST	412922	−10.70236842	0.36608
Unsequenced EST	431286	−4.773151093	0.36615
Unsequenced EST	410681	−5.539678826	0.36806
Unsequenced EST	410961	−5.922086756	0.36889
Unsequenced EST	412082	−5.502268659	0.37358

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

Unsequenced EST	411260	−7.318521913	0.37963
Unsequenced EST	413169	−8.824803866	0.38149
Unsequenced EST	431574	−7.915188019	0.38774
Unsequenced EST	201627	−4.705533576	0.39533
Unsequenced EST	411524	−5.524062307	0.39648
Unsequenced EST	207603	−4.355050407	0.39946
Unsequenced EST	411380	−7.305463236	0.40609
Unsequenced EST	412118	−5.556347655	0.40838
Unsequenced EST	412779	−5.441554043	0.40976
Unsequenced EST	413183	−4.193228901	0.41145
Unsequenced EST	412186	−5.014710177	0.41232
Unsequenced EST	412432	−6.021307948	0.41525
Unsequenced EST	202131	−4.528895291	0.42149
Unsequenced EST	411977	−5.552286122	0.42892
Unsequenced EST	411945	−5.19632995	0.43045
Unsequenced EST	412392	−5.259013295	0.43294
Unsequenced EST	411789	−5.942433491	0.43374
Unsequenced EST	411605	−4.341117607	0.43784
Unsequenced EST	412744	−7.339592203	0.43951
Unsequenced EST	413539	−4.989934344	0.44370
Unsequenced EST	195728	−6.178492322	0.44536
Unsequenced EST	413134	−6.241885103	0.45027
Unsequenced EST	411383	−5.401353982	0.45800
Unsequenced EST	411085	−4.137943214	0.46202
Unsequenced EST	412790	−4.941794716	0.46286
Unsequenced EST	412128	−4.173237872	0.46629
Unsequenced EST	412515	−4.302837338	0.47046
Unsequenced EST	411160	−4.39905373	0.47073
Unsequenced EST	431843	−4.915899211	0.47188
Unsequenced EST	412684	−4.241205638	0.47318
Unsequenced EST	412861	−8.341188453	0.47330
Unsequenced EST	412655	−7.654529341	0.47341
Unsequenced EST	412947	−5.987474705	0.47730
Unsequenced EST	431845	−6.589036532	0.47756
Unsequenced EST	412605	−4.545499757	0.47830
Unsequenced EST	412852	−5.666295082	0.48040
Unsequenced EST	412719	−6.436286215	0.48313
Unsequenced EST	412846	−6.379601248	0.48331
Unsequenced EST	411516	−4.186279748	0.48381
Unsequenced EST	430640	−8.543745358	0.48480
Unsequenced EST	413600	−4.901398844	0.48861
Unsequenced EST	410665	−5.244586119	0.48898
Unsequenced EST	412580	−4.121077374	0.49239
Unsequenced EST	412961	−6.883843851	0.49284
Unsequenced EST	410750	−4.49336413	0.49891
Unsequenced EST	413575	−8.092713979	0.49917
Unsequenced EST	412258	−4.851281671	0.50038
Unsequenced EST	413527	−5.132468462	0.50202
Unsequenced EST	339227	−5.039795897	0.50472
Unsequenced EST	412794	−4.990410609	0.50493
Unsequenced EST	413170	−4.535280662	0.50708
Unsequenced EST	412554	−5.450841531	0.51085
Unsequenced EST	411061	−4.769542333	0.51494
Unsequenced EST	413191	−4.260493159	0.51664
Unsequenced EST	411529	−4.146671502	0.51863
Unsequenced EST	201438	−5.686498384	0.51877
Unsequenced EST	412188	−5.828768851	0.53010
Unsequenced EST	412687	−4.271665088	0.53249
Unsequenced EST	411735	−4.468462406	0.53596
Unsequenced EST	432195	−4.335845288	0.53607
Unsequenced EST	431862	−6.165660675	0.54297
Unsequenced EST	431724	−4.338553681	0.54756
Unsequenced EST	202908	−5.418394672	0.54969
Unsequenced EST	413323	−4.184245611	0.55110
Unsequenced EST	411704	−5.096046224	0.55200
Unsequenced EST	412581	−5.269737426	0.55208
Unsequenced EST	412585	−4.659918123	0.55273
Unsequenced EST	431810	−4.180748837	0.55450
Unsequenced EST	413365	−4.2659871	0.55605
Unsequenced EST	433229	−4.517254893	0.56214
Unsequenced EST	411979	−4.346159953	0.56235
Unsequenced EST	413165	−4.62951073	0.56443
Unsequenced EST	192693	−5.043346885	0.56552
Unsequenced EST	431411	−4.213334563	0.56581

TABLE I-continued

Significant Genes List - Significantly Altered Expression in Hypertrophic Cardiomyopathy

Unsequenced EST	413343	−4.858667556	0.56811
Unsequenced EST	431024	−4.530557713	0.57100
Unsequenced EST	411004	−5.585263324	0.57150
Unsequenced EST	412778	−4.958457315	0.57369
Unsequenced EST	411679	−4.397694818	0.57591
Unsequenced EST	412092	−4.601171247	0.57736
Unsequenced EST	411187	−5.420404234	0.57748
Unsequenced EST	412049	−4.182454971	0.57918
Unsequenced EST	411739	−5.261687986	0.57938
Unsequenced EST	412792	−5.800493052	0.58184
Unsequenced EST	430792	−4.281087478	0.58252
Unsequenced EST	412248	−6.65590185	0.58382
Unsequenced EST	411820	−5.940618083	0.58997
Unsequenced EST	412944	−5.470273005	0.59317
Unsequenced EST	413551	−4.582248971	0.59406
Unsequenced EST	411432	−20.53697874	0.59957
Unsequenced EST	410575	−5.303084684	0.60532
Unsequenced EST	412300	−4.818706528	0.61404
Unsequenced EST	413127	−4.268879629	0.61420
Unsequenced EST	413147	−4.834386905	0.61435
Unsequenced EST	431502	−4.610470753	0.61626
Unsequenced EST	412669	−6.722369522	0.62754
Unsequenced EST	205043	−4.492534174	0.62848
Unsequenced EST	411951	−4.241151187	0.63106
Unsequenced EST	410855	−7.411266903	0.63325
Unsequenced EST	431873	−4.381828532	0.64516
Unsequenced EST	413577	−4.117483105	0.64824
Unsequenced EST	412322	−5.050800613	0.65809
Unsequenced EST	431604	−4.652721214	0.65891
Unsequenced EST	410853	−5.906498521	0.67231
Unsequenced EST	410873	−5.013976686	0.68258
Unsequenced EST	411493	−5.338523882	0.68321
Unsequenced EST	411809	−4.799364595	0.70861
Unsequenced EST	431869	−5.019525302	0.70973
Unsequenced EST	410832	−4.976967369	0.72665
Unsequenced EST	413270	−4.343167788	0.75177
upregulated during skeletal muscle growth 5	AV088589	−4.446982985	0.45597
vesicle-associated membrane protein 2	AW911135	−4.74028883	0.67738
vesicle-associated membrane protein 3	AV085364	−4.433657569	0.34943
voltage-dependent anion channel 1	BG073650	−4.530236983	0.55543
wingless-related MMTV integration site 3A	AA000971	−5.545510401	0.58208
Y box protein 2	BG066570	−4.568246796	0.43028
Yamaguchi sarcoma viral (v-yes-1) oncogene homolog	AA509398	−4.224596131	0.55530
zinc finger protein 106	AV013127	−4.399813491	0.43000
zinc finger protein 216	BG066068	−17.41108393	0.55649

⑦ indicates text missing or illegible when filed

[0199]

TABLE IA

Gene Name	Gene Description	UGRepAcc [A]	LLRepProtAc⑦
AA068104	transforming growth factor, beta 2	NM_009367	NP_033393
AA098349	lysyl oxidase-like	AK078512	
AA498724	bone morphogenetic protein 4	NM_007554	NP_031580
AA646363	endoglin	NM_007932	NP_031958
AI323974	neuropilin	NM_008737	NP_032763
AI327133	polydomain protein	NM_022814	NP_073725
AI841353	a disintegrin and metalloproteinase domain 15 (metar	NM_009614	NP_033744
AV012617	insulin-like growth factor binding protein 5	NM_010518	NP_034648
AV015188	matrix metalloproteinase 23	NM_011985	NP_036115
AV019210	elastin	NM_007925	NP_031951
AV021712	secreted frizzled-related sequence protein 2	NM_009144	NP_033170
AV024396	reversion-inducing-cysteine-rich protein with kazal m⑦	NM_016678	NP_057887
AV029310	superoxide dismutase 3, extracellular	NM_011435	NP_035565
AV059520	peptidylprolyl isomerase C-associated protein	NM_011150	NP_035280
AV070218	amyloid beta (A4) precursor-like protein 2	NM_009691	NP_033821
AV070419	antigen identified by monoclonal antibody MRC OX-2	NM_010818	NP_034948
AV083867	retinoid-inducible serine caroboxypetidase	NM_029023	NP_083299

TABLE IA-continued

Gene Name	Gene Description	UGRepAcc [A]	LLRepProtAc
AV084876	osteoblast specific factor 2 (fasciclin I-like)	NM_015784	NP_056599
AV085019	extracellular matrix protein 1	NM_007899	NP_031925
AV104097	basigin	BI106083	
AV104213	endothelial cell-selective adhesion molecule	NM_027102	NP_081378
AV109513	stromal cell derived factor 1	NM_013655	NP_068350
AV113097	microfibrillar associated protein 5	NM_015776	NP_056591
AV117035	manic fringe homolog (*Drosophila*)	NM_008595	NP_032621
AV149987	cystatin C	NM_009976	NP_034106
AV156534	matrilin 2	NM_016762	NP_058042
AV170826	biglycan	NM_007542	NP_031568
AW476537	fibroblast growth factor receptor 1	NM_010206	NP_034336
AW988741_	secreted acidic cysteine rich glycoprotein		
BE376968	vascular endothelial growth factor C	NM_009506	NP_033532
BF136770	Notch gene homolog 3, (*Drosophila*)	NM_008716	NP_032742
BG063294	follistatin-like 3	NM_031380	NP_113557
BG063616	nidogen 1	NM_010917	NP_035047
BG064180	expressed sequence AA408225	NM_009868	NP_033998
BG065640	ectonucleotide pyrophosphatase/phosphodiesterase	NM_008813	NP_032839
BG066563	N-acetylated alpha-linked acidic dipeptidase 2	NM_028279	NP_082555
BG073227	fibulin 2	NM_007992	NP_032018
BG074344	mesothelin	NM_018857	NP_061345
BG074382	sema domain, immunoglobulin domain (Ig), short bas	NM_011349	NP_035479
BG074663	protein tyrosine phosphatase, receptor type, S	NM_011218	NP_035348
BG075377	melanoma cell adhesion molecule	NM_023061	NP_075548
D16250	bone morphogenetic protein receptor, type 1A	BC042611	NP_033888
L26349	tumor necrosis factor receptor superfamily, member 1	NM_011609	NP_035739
U38261	superoxide dismutase 3, extracellular	NM_011435	NP_035565
X52886	cathepsin D	NM_009983	NP_034113
AI838311	matrix metalloproteinase 2	NM_008610	NP_032636
AI851067	RIKEN cDNA 2510010F10 gene	NM_175833	NP_787027
BG071948	low density lipoprotein receptor-related protein 1	NM_008512	NP_032538
BG072998	expressed sequence AU018638	NM_008524	NP_032550
AI838613	epithelial membrane protein 1		
AI893233	CD34 antigen	NM_133654	NP_598415
AV001464	granulin	NM_008175	NP_032201
AV006514	interferon (alpha and beta) receptor 2	NM_010509	NP_034639
AV022379	serine (or cysteine) proteinase inhibitor, clade F (alph	NM_011340	NP_035470
AV025941	aquaporin 1	NM_007472	NP_031498
AV070805	thymic stromal-derived lymphopoietin, receptor	NM_016715	NP_057924
AV223941	heat shock protein, 70 kDa 3	M12571	
AW537378	EST		
AA673390	fibronectin 1	AK090130	
AI325851	CD97 antigen	NM_011925	NP_036055
AI325886	neuroblastoma, suppression of tumorigenicity 1	NM_008675	NP_032701
AI385650	sialyltransferase 4C (beta-galactosidase alpha-2,3-si	NM_009178	NP_033204
AI838302	Cd63 antigen	NM_007653	NP_031679
AI838568	RIKEN cDNA 1300018J16 gene	NM_029092	NP_083368
AV007183	latent transforming growth factor beta binding protein	NM_023912	NP_076401
AV007276	RIKEN cDNA 1110003M08 gene	AK090329	
AV009300	procollagen, type IV, alpha 1	J04694	
AV010312	procollagen, type IV, alpha 2	J04695	
AV011166	EST	NM_080463	NP_536711
AV013988	procollagen, type VI, alpha 1	NM_009933	NP_034063
AV015595	procollagen, type XV	NM_009928	NP_034058
AV016743	RIKEN cDNA 5730414C17 gene	NM_133680	NP_598441
AV025665	prostaglandin-endoperoxide synthase 2	NM_011198	NP_035328
AV036454_	lymphocyte antigen 6 complex, locus E		
AV037769	expressed sequence AU022549	NM_007904	NP_031930
AV048780	stromal cell derived factor 4	NM_011341	NP_035471
AV050682	RIKEN cDNA 2700083B06 gene	NM_026531	NP_080807
AV052090	serine (or cysteine) proteinase inhibitor, clade I (neur	NM_009250	NP_033276
AV053955	RIKEN cDNA 3110023E09 gene	NM_026522	NP_080798
AV057827	torsin family 3, member A	NM_023141	NP_075630
AV058250	RIKEN cDNA 1810049K24 gene	NM_030209	NP_084485
AV059445	FK506 binding protein 9	NM_012056	NP_036186
AV059924	expressed sequence AA986889	NM_134102	NP_598863
AV061081	neural proliferation, differentiation and control gene 1	NM_008721	NP_032747
AV062071	CD24a antigen	NM_009846	NP_033976
AV066211	ELAV (embryonic lethal, abnormal vision, *Drosophila*)	NM_010485	NP_034615
AV073997	glucose regulated protein, 58 kDa	NM_007952	NP_031978
AV083352	RIKEN cDNA 1110007F23 gene	NM_029568	NP_083844
AV084561	procollagen C-proteinase enhancer protein	NM_008788	NP_032814
AV084844	immunoglobulin superfamily containing leucine-rich r	NM_012043	NP_036173
AV086002	FXYD domain-containing ion transport regulator 6	NM_022004	NP_071287

TABLE IA-continued

Gene Name	Gene Description	UGRepAcc [A]	LLRepProtAc?
AV087039	EST	NM_008885	NP_032911
AV087220	expressed sequence AW146116	NM_133352	NP_835359
AV087499	EST, Moderately similar to A57474 extracellular matri	NM_007899	NP_031925
AV087921	benzodiazepine receptor, peripheral	NM_009775	NP_033905
AV089105	calcium binding protein, intestinal	NM_009787	NP_033917
AV093463	serine (or cysteine) proteinase inhibitor, clade H (hea?	NM_009825	NP_033955
AV094498	milk fat globule-EGF factor 8 protein	NM_008594	NP_032620
AV103290	expressed sequence AL024047	NM_134151	NP_598912
AV104157	dolichyl-di-phosphooligosaccharide-protein glycotrans	NM_007838	NP_031864
AV109555	cellular retinoic acid binding protein I	AK090130	
AV111526	RIKEN cDNA 2610002H11 gene	NM_133721	NP_598482
AV112983	platelet derived growth factor receptor, beta polypepti?	NM_008809	NP_032835
AV133755	RIKEN cDNA 2810002E22 gene	NM_133859	NP_598620
AV134035	granulin	NM_008175	NP_032201
AV140189	RIKEN cDNA 0610040B21 gene	NM_025334	NP_079610
AV140901	EST	NM_010368	NP_034498
AV162270	lymphocyte antigen 6 complex, locus A	NM_027015	NP_081291
AV171867	CD 81 antigen	NM_133655	NP_598416
AW548258	procollagen-proline, 2-oxoglutarate 4-dioxygenase (p?	BC009654	
AW551778	heterogeneous nuclear ribonucleoprotein C	NM_016884	NP_058580
BF100414	integrin beta 5	NM_010580	NP_034710
BF182158	Notch gene homolog 1, (*Drosophila*)	NM_008714	NP_032740
BG063167	adenylate cyclase 7	NM_007406	NP_031432
BG065103	lymphocyte antigen 6 complex, locus E	NM_008529	NP_032555
BG066621	*Mus musculus*, Similar to pituitary tumor-transforming	NM_145925	NP_666037
BG067569	coagulation factor II (thrombin) receptor	NM_010169	NP_034299
BG069745	proline arginine-rich end leucine-rich repeat	NM_054077	NP_473418
BG070083	protein tyrosine phosphatase, receptor type, E	NM_011212	NP_035342
BG070387	interleukin 6 signal transducer	NM_010560	NP_034690
BG072624	laminin, gamma 1	BC032194	NP_034813
BG072810	Niemann Pick type 02	NM_023409	NP_075898
BG072850	sarcoglycan, epsilon	NM_011360	NP_035490
BG072908	membrane-bound transcription factor protease, site 1	NM_019709	NP_062683
BG073140	CD8 antigen, beta chain	NM_009858	NP_033988
BG073341	retinal short-chain dehydrogenase/reductase 1	NM_011303	NP_035433
BG073479	expressed sequence AW229038	NM_133918	NP_598679
BG073729	prolyl 4-hydroxylase, beta polypeptide	J05185	
BG073750	prolyl 4-hydroxylase, beta polypeptide	J05185	
BG074142	RIKEN cDNA 1300012G16 gene	NM_023625	NP_076114
BG074174	DNA segment, Chr 6, Wayne State University 176 e?	NM_138587	NP_613053
BG074422	integrin beta 1 (fibronectin receptor beta)	AK088016	
BG074747	alpha glucosidase 2, alpha neutral subunit	NM_008060	NP_032086
BG074915	parotid secretory protein	NM_172261	NP_758465
BG075864	procollagen, type VI, alpha 2	NM_146007	NP_666119
C79946	expressed sequence C79946	AK080023	
U20156	EST		
U34920	ATP-binding cassette, sub-family G (WHITE), membe?	NM_009593	NP_033723
X00246	histocompatibility 2, D region locus 1	NM_010380	NP_034510
X01838	beta-2 microglobulin	NM_009735	NP_033865
AA087526	retinol binding protein 1, cellular	NM_011254	NP_035384
AI322274	RIKEN cDNA 2410002J21 gene	AK033091	
AI851039	ESTs, Weakly similar to D2045.2.p [*Caenorhabditis* e?	AK038775	
AV015246	RIKEN cDNA 1110054M18 gene	NM_175132	NP_780341
AV057141	gap junction membrane channel protein beta 1	NM_008124	NP_032150
AV059438	ets variant gene 6 (TEL oncogene)	BC009120	
AV077899	actin, alpha 2, smooth muscle, aorta	AK002886	
AV083262	dystonin	NM_134448	NP_604443
AV083596	four and a half LIM domains 1	NM_010211	NP_034341
AV085874	*Mus musculus* uridindiphosphoglucosepyrophosphor?	NM_139297	NP_647458
AV093704	small EDRK-rich factor 2	AK044479	
AW547864	EST		
BG065584	*Mus musculus*, clone IMAGE: 3589087, mRNA, partia	BF124761	
BG070007	?xpressed sequence AW494241	BC040467	
BG072752	actin, gamma, cytoplasmic	NM_013798	NP_038826
BG073284	prion protein dublet	NM_023043	NP_075530
BG073319	integrin beta 4 binding protein	NM_010579	NP_034709

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[0200]

TABLE IB

Gene Name	Gene Description	UGRepAcc [A]	LLRepProtAcc [A]
AA068104	transforming growth factor, beta 2	NM_009367	NP_033393
AA098349	lysyl oxidase-like	AK078512	
AA498724	bone morphogenetic protein 4	NM_007554	NP_031580
AA646363	endoglin	NM_007932	NP_031958
AI323974	neuropilin	NM_008737	NP_032763
AI327133	polydomain protein	NM_022814	NP_073725
AI841353	a disintegrin and metalloproteinase domain 15 (met?	NM_009614	NP_033744
AV012617	insulin-like growth factor binding protein 5	NM_010518	NP_034648
AV015188	matrix metalloproteinase 23	NM_011985	NP_036115
AV019210	elastin	NM_007925	NP_031951
AV021712	secreted frizzled-related sequence protein 2	NM_009144	NP_033170
AV024396	reversion-inducing-cysteine-rich protein with kazal n?	NM_016678	NP_057887
AV029310	superoxide dismutase 3, extracellular	NM_011435	NP_035565
AV059520	peptidylprolyl isomerase C-associated protein	NM_011150	NP_035280
AV070218	amyloid beta (A4) precursor-like protein 2	NM_009691	NP_033821
AV070419	antigen identified by monoclonal antibody MRC OX-?	NM_010818	NP_034948
AV083867	retinoid-inducible serine caroboxypetidase	NM_029023	NP_083299
AV084876	osteoblast specific factor 2 (fasciclin I-like)	NM_015784	NP_056599
AV085019	extracellular matrix protein 1	NM_007899	NP_031925
AV104097	basigin	BI106083	
AV104213	endothelial cell-selective adhesion molecule	NM_027102	NP_081378
AV109513	stromal cell derived factor 1	NM_013655	NP_068350
AV113097	microfibrillar associated protein 5	NM_015776	NP_056591
AV117035	manic fringe homolog (*Drosophila*)	NM_008595	NP_032621
AV149987	cystatin C	NM_009976	NP_034106
AV156534	matrilin 2	NM_016762	NP_058042
AV170826	biglycan	NM_007542	NP_031568
AW476537	fibroblast growth factor receptor 1	NM_010206	NP_034336
AW988741___2	secreted acidic cysteine rich glycoprotein		
BE376968	vascular endothelial growth factor C	NM_009506	NP_033532
BF136770	Notch gene homolog 3, (*Drosophila*)	NM_008716	NP_032742
BG063294	follistatin-like 3	NM_031380	NP_113557
BG063616	nidogen 1	NM_010917	NP_035047
BG064180	expressed sequence AA408225	NM_009868	NP_033998
BG065640	ectonucleotide pyrophosphatase/phosphodiesterase	NM_008813	NP_032839
BG066563	N-acetylated alpha-linked acidic dipeptidase 2	NM_028279	NP_082555
BG073227	fibulin 2	NM_007992	NP_032018
BG074344	mesothelin	NM_018857	NP_061345
BG074382	sema domain, immunoglobulin domain (Ig), short b?	NM_011349	NP_035479
BG074663	protein tyrosine phosphatase, receptor type, S	NM_011218	NP_035348
BG075377	melanoma cell adhesion molecule	NM_023061	NP_075548
D16250	bone morphogenetic protein receptor, type 1A	BC042611	NP_033888
L26349	tumor necrosis factor receptor superfamily, member?	NM_011609	NP_035739
U38261	superoxide dismutase 3, extracellular	NM_011435	NP_035565
X52886	cathepsin D	NM_009983	NP_034113
AI838311	matrix metalloproteinase 2	NM_008610	NP_032636
AI851067	RIKEN cDNA 2510010F10 gene	NM_175833	NP_787027
BG071948	low density lipoprotein receptor-related protein 1	NM_008512	NP_032538
BG072998	expressed sequence AU018638	NM_008524	NP_032550
AI838613	epithelial membrane protein 1		
AI893233	CD34 antigen	NM_133654	NP_598415
AV001464	granulin	NM_008175	NP_032201
AV006514	interferon (alpha and beta) receptor 2	NM_010509	NP_034639
AV022379	serine (or cysteine) proteinase inhibitor, clade F (al?	NM_011340	NP_035470
AV025941	aquaporin 1	NM_007472	NP_031498
AV070805	thymic stromal-derived lymphopoietin, receptor	NM_016715	NP_057924

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[0201]

TABLE II

Table II Genes of Use in Imaging Studies - Membrane Associated
Annotated Extracellular and Antigen genes Upregulated in TAC tissues - 149 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information						Human Homolog Information	
Gene ID	Gene Description	UGRepAcc	LLRepProtAcc	Up TAC LA	Up TAC LV	UGRepAcc	LLRepProtAcc
BG073140	**CD8 antigen, beta chain	NM_009858	NP_033988	UP TAC LA			
AI841353	a disintegrin and metalloproteinase domain 15 (metargidin)	NM_009614	NP_033744	UP TAC LA		AY560601	NP_997080
AV024684	A kinase (PRKA) anchor protein 2	NM_009649	NP_033779	UP TAC LA			
AA797434	adenylate cyclase 7	NM_007406	NP_031432	UP TAC LA		D25538	NP_001105
AV103043	ADP-ribosylation factor 4	NM_007479	NP_031505	UP TAC LA		BC016325	NP_001651
AV032992	ADP-ribosylation-like factor 6 interacting protein 5	NM_022992	NP_075368	UP TAC LA			
AV057752	amyloid beta (A4) precursor protein	NM_007471	NP_031497	UP TAC LA		BC018937	NP_958817
AV104479	amyloid beta (A4) precursor protein-binding, family B, member 2	AK004792		UP TAC LA			
AV070218	amyloid beta (A4) precursor-like protein 2	NM_009691	NP_033821	UP TAC LA		BX647107	NP_001633
AV043404	angiotensin converting enzyme			UP TAC LA			
AV025146	angiotensin receptor-like 1	NM_011784	NP_035914	UP TAC LA		AK075252	NP_005152
AV163403	antigen identified by monoclonal antibody MRC OX-2	NM_010818	NP_034948	UP TAC LA		BC022522	NP_005935
AV025941	aquaporin 1	NM_007472	NP_031498	UP TAC LA		NM_198098	NP_932766
AV173744	ATPase, Cu++ transporting, alpha polypeptide	NM_009726	NP_033856	UP TAC LA		NM_000052	NP_000043
AV031502	ATPase, H+ transporting, lysosomal 70 kD, V1 subunit A, isoform 1	BI100125		UP TAC LA		AK023063	NP_006326
U34920	ATP-binding cassette, sub-family G (WHITE), member 1	NM_009593	NP_033723	UP TAC LA		NM_207630	NP_997513
BG064525	basigin	BI106083		UP TAC LA		NM_001728	NP_940993
AV104535	beclin 1 (coiled-coil, myosin-like BCL2-interacting protein)	NM_026562	NP_080838	UP TAC LA			
AV087921	benzodiazepine receptor, peripheral	NM_009775	NP_033905	UP TAC LA		BX537892	NP_009295
X01838	beta-2 microglobulin	NM_009735	NP_033865	UP TAC LA		AK022379	NP_004039
AV140458	biregional cell adhesion molecule-related/ down-regulated by oncog	NM_172506	NP_766094	UP TAC LA		NM_033254	NP_150279
D16250	bone morphogenetic protein receptor, type 1A	BC042611	NP_033888	UP TAC LA		NM_004329	NP_004320
BG065470	catenin beta	NM_177589	NP_808257	UP TAC LA			
AV171867	CD 81 antigen	NM_133655	NP_598416	UP TAC LA		BM810055	NP_004347
AV062071	CD24a antigen	NM_009846	NP_033976	UP TAC LA			
AI893233	CD34 antigen	NM_133654	NP_598415	UP TAC LA		BX640941	NP_001764
BG073167	Cd63 antigen	NM_007653	NP_031679	UP TAC LA		BM701371	NP_001771
AI325851	CD97 antigen	NM_011925	NP_036055	UP TAC LA		NM_078481	NP_510966
AV300841	chemokine (C—X—C) receptor 4			UP TAC LA		NM_003467	NP_003458
BG067569	coagulation factor II (thrombin) receptor	NM_010169	NP_034299	UP TAC LA		NM_001992	NP_001983
AV031224	coatomer protein complex, subunit gamma 1	NM_017477	NP_059505	UP TAC LA			
AV147446	cytochrome P450, 2j6			UP TAC LA			
AV037185	degenerative spermatocyte homolog (*Drosophila*)	NM_007853	NP_031879	UP TAC LA		NM_003676	NP_659004
AV083741	DNA segment, Chr 8, Brigham & Women's Genetics 1112 express	NM_026002	NP_080278	UP TAC LA			
AV104157	dolichyl-di-phosphooligosaccharide-protein glycotransferase	NM_007838	NP_031864	UP TAC LA		NM_005216	NP_005207
BG075775	downstream of tyrosine kinase 1	NM_010070	NP_034200	UP TAC LA		AK055944	NP_001372
BG065640	ectonucleotide pyrophosphatase/ phosphodiesterase 1	NM_008813	NP_032839	UP TAC LA		NM_006208	NP_006199
AV050518	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, y	NM_019422	NP_062295	UP TAC LA		NM_022821	NP_073732
AV140302	embigin	NM_010330	NP_034460	UP TAC LA			
AV086531	endoglin	NM_007932	NP_031958	UP TAC LA		NM_000118	NP_000109
AV104213	endothelial cell-selective adhesion molecule	NM_027102	NP_081378	UP TAC LA			
AI838613	epithelial membrane protein 1			UP TAC LA	UP TAC LV	NM_001423	NP_001414
AV087039	EST	NM_008885	NP_032911	UP TAC LA		NM_000304	NP_696997
AV087918	EST AA087124	AA896198		UP TAC LA		NM_001759	NP_001750
AV021942	ESTs, Weakly similar to ATPase, class 1, member a; ATPase 8A2	AF156546		UP TAC LA		AB032963	NP_065185
AV016534	ESTs, Weakly similar to Y43F4B.7.p [*Caenorhabditis elegans*] [C.e	NM_153170	NP_694810	UP TAC LA			
AV113175	ETL1	NM_133222	NP_573485	UP TAC LA		AY358360	
BG064180	expressed sequence AA408225	NM_009868	NP_033998	UP TAC LA		NM_001795	NP_001786
BG072659	expressed sequence AI316797	NM_080563	NP_542130	UP TAC LA		NM_014746	NP_055561

TABLE II-continued

Table II Genes of Use in Imaging Studies - Membrane Associated
Annotated Extracellular and Antigen genes Upregulated in TAC tissues - 149 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information						Human Homolog Information	
Gene ID	Gene Description	UGRepAcc	LLRepProtAcc	Up TAC LA	Up TAC LV	UGRepAcc	LLRepProtAcc
AV033704	expressed sequence AI504145	NM_028990	NP_083266	UP TAC LA			
AV037769	expressed sequence AU022549	NM_007904	NP_031930	UP TAC LA		NM_000115	NP_003982
AV087220	expressed sequence AW146116	NM_133352	NP_835359	UP TAC LA			
BG066820	expressed sequence C80501	NM_009320	NP_033346	UP TAC LA		NM_003043	NP_003034
AW476537	fibroblast growth factor receptor 1	NM_010206	NP_034336	UP TAC LA		BC018128	NP_075599
BG072676	FXYD domain-containing ion transport regulator 6	NM_022004	NP_071287	UP TAC LA		AK092198	NP_071286
AI838468	gamma-aminobutyric acid (GABA-B) receptor, 1	NM_019439	NP_062312	UP TAC LA		AJ225028	NP_068705
AV057141	gap junction membrane channel protein beta 1	NM_008124	NP_032150		UP TAC LV	BF570961	NP_000157
BG067028	glycoprotein galactosyltransferase alpha 1, 3	NM_010283	NP_034413	UP TAC LA			
AV033394	glycoprotein m6b	NM_023122	NP_075611	UP TAC LA		AK095657	NP_005269
AV085916	GPI-anchored membrane protein 1	BU611749		UP TAC LA			
BG063447	guanine nucleotide binding protein, beta 1	NM_008142	NP_032168	UP TAC LA		AK123609	NP_002065
X00246	histocompatibility 2, D region locus 1	NM_010380	NP_034510	UP TAC LA			
BG064733	HLS7-interacting protein kinase	NM_147201	NP_671734	UP TAC LA		AK122664	NP_037524
AV010401	integral membrane protein 2B	NM_008410	NP_032436	UP TAC LA		BX537657	NP_068839
AV078295	integrin alpha 6	NM_008397	NP_032423	UP TAC LA		X53586	NP_000201
BG074422	integrin beta 1 (fibronectin receptor beta)	AK088016		UP TAC LA		NM_002211	NP_596867
BF100414	integrin beta 5	NM_010580	NP_034710	UP TAC LA		AK091595	NP_002204
AV006514	interferon (alpha and beta) receptor 2	NM_010509	NP_034639	UP TAC LA		L41944	NP_997468
AV074586	interleukin 17 receptor	BC037587		UP TAC LA			
BG070387	interleukin 6 signal transducer	NM_010560	NP_034690	UP TAC LA		BC071555	NP_786943
BG072624	laminin, gamma 1	BC032194	NP_034813	UP TAC LA		NM_002293	NP_002284
AV054666	leptin receptor	NM_175036	NP_778201	UP TAC LA			
BG075361	low density lipoprotein receptor-related protein 1	NM_008512	NP_032538	UP TAC LA		NM_002332	NP_002323
AV162270	lymphocyte antigen 6 complex, locus A	NM_027015	NP_081291	UP TAC LA			
BG065103	lymphocyte antigen 6 complex, locus E	NM_008529	NP_032555	UP TAC LA		BF969813	NP_002337
AV117035	manic fringe homolog (*Drosophila*)	NM_008595	NP_032621	UP TAC LA		U94352	NP_002396
AV026219	mannosidase 1, alpha	NM_008548	NP_032574	UP TAC LA			
BG075377	melanoma cell adhesion molecule	NM_023061	NP_075548	UP TAC LA		NM_006500	NP_006491
BG072908	membrane-bound transcription factor protease, site 1	NM_019709	NP_062683	UP TAC LA		NM_003791	NP_957720
AV025927	*Mus musculus*, clone IMAGE: 5066061, mRNA, partial cds	BC046959		UP TAC LA			
AV057440	*Mus musculus*, clone MGC: 27672 IMAGE: 4911158, mRNA, comp⑦	NM_144852	NP_659101	UP TAC LA		BC062565	NP_004164
BG066621	*Mus musculus*, Similar to pituitary tumor-transforming 1 interacting⑦	NM_145925	NP_666037	UP TAC LA			
BG064673	*Mus musculus*, Similar to xylosylprotein beta1,4-galactosyltransfer⑦	NM_146045	NP_666157	UP TAC LA		AK022566	NP_009186
BG072632	myeloid-associated differentiation marker	NM_016969	NP_058665	UP TAC LA		AF087882	NP_612382
BG072584	myristoylated alanine rich protein kinase C substrate	NM_008538	NP_032564	UP TAC LA		NM_002356	NP_002347
BG066563	N-acetylated alpha-linked acidic dipeptidase 2	NM_028279	NP_082555	UP TAC LA	UP TAC LV	AK075390	NP_005458
AV061081	neural proliferation, differentiation and control gene 1	NM_008721	NP_032747	UP TAC LA		AK054950	NP_056207
BG074219	neuroblastoma ras oncogene	NM_010937	NP_035067	UP TAC LA		X02751	NP_002515
AI323974	neuropilin	NM_008737	NP_032763	UP TAC LA			
BG063616	nidogen 1	NM_010917	NP_035047	UP TAC LA			
BF182158	Notch gene homolog 1, (*Drosophila*)	NM_008714	NP_032740	UP TAC LA		NM_017617	NP_060087
BF136770	Notch gene homolog 3, (*Drosophila*)	NM_008716	NP_032742	UP TAC LA		NM_000435	NP_000426
AV145718	parathyroid hormone receptor	NM_011199	NP_035329	UP TAC LA		AF495723	NP_000307
AV059520	peptidylprolyl isomerase C-associated protein	NM_011150	NP_035280	UP TAC LA			
AV006019	phosphatidylinositol glycan, class Q	NM_011822	NP_035952	UP TAC LA		NM_004204	NP_683721
BG064035	phosphoprotein enriched in astrocytes 15	NM_008556	NP_035193	UP TAC LA		NM_003768	NP_003759
AV112983	platelet derived growth factor receptor, beta polypeptide	NM_008809	NP_032835	UP TAC LA		BC032224	NP_002600
AV234882	polycystic kidney disease 1 homolog	NM_013630	NP_038658	UP TAC LA		L33243	NP_000287
AV009300	procollagen, type IV, alpha 1	J04694		UP TAC LA		NM_001845	NP_001836
BG074718	procollagen, type IV, alpha 2	J04695		UP TAC LA		NM_001846	NP_001837
AV025665	prostaglandin-endoperoxide synthase 2	NM_011198	NP_035328	UP TAC LA		NM_000963	NP_000954
BG067870	protein kinase C, delta	NM_011103	NP_035233	UP TAC LA		NM_006254	NP_997704
BG070083	protein tyrosine phosphatase, receptor	NM_011212	NP_035342	UP TAC LA		BX648180	NP_569119

TABLE II-continued

Table II Genes of Use in Imaging Studies - Membrane Associated
Annotated Extracellular and Antigen genes Upregulated in TAC tissues - 149 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information						Human Homolog Information	
Gene ID	Gene Description	UGRepAcc	LLRepProtAcc	Up TAC LA	Up TAC LV	UGRepAcc	LLRepProtAcc
	type, E						
BG074663	protein tyrosine phosphatase, receptor type, S	NM_011218	NP_035348	UP TAC LA		NM_002850	NP_570925
AI893212	proteolipid protein 2	NM_019755	NP_062729	UP TAC LA		BF214130	NP_002659
BG073000	protocadherin 13	NM_033576	NP_291054	UP TAC LA			
AV086128	regulator of G-protein signaling 19 interacting protein 1	NM_018771	NP_061241	UP TAC LA		NM_005716	NP_974223
AU040596	regulator of G-protein signaling 3	NM_019492	NP_062365	UP TAC LA		AK128127	NP_652760
AV084219	reticulon 4	NM_024226	NP_077188	UP TAC LA		NM_020532	NP_997404
BG073341	retinal short-chain dehydrogenase/ reductase 1	NM_011303	NP_035433	UP TAC LA		BX648476	NP_004744
AV024396	reversion-inducing-cysteine-rich protein with kazal motifs	NM_016678	NP_057887	UP TAC LA		BX648668	NP_066934
BG063638	ribosome binding protein 1	AK019964	NP_598329	UP TAC LA		AB037819	NP_004578
AW538766	RIKEN cDNA 0610013I17 gene	NM_029789	NP_084065	UP TAC LA		NM_012432	NP_036564
AV133782	RIKEN cDNA 0610039A15 gene	NM_175101	NP_780310	UP TAC LA			
AV007276	RIKEN cDNA 1110003M08 gene	AK090329		UP TAC LA		AK124975	NP_005818
AV058524	RIKEN cDNA 1110007A14 gene	NM_025841	NP_080117	UP TAC LA		AK093917	NP_006845
AV133706	RIKEN cDNA 1110059L23 gene	NM_134255	NP_599016	UP TAC LA		AL833001	NP_068586
AV086520	RIKEN cDNA 1200003O06 gene	NM_025813	NP_080089	UP TAC LA			
BG064285	RIKEN cDNA 1200013F24 gene	NM_025822	NP_080098	UP TAC LA			
AV088097	RIKEN cDNA 1200015A22 gene	NM_028766	NP_083042	UP TAC LA			
BG074142	RIKEN cDNA 1300012G16 gene	NM_023625	NP_076114	UP TAC LA			
AV086327	RIKEN cDNA 2310008D10 gene	NM_025858	NP_080657	UP TAC LA			
AV087181	RIKEN cDNA 2310028N02 gene	NM_025864	NP_080140	UP TAC LA			
AV085104	RIKEN cDNA 2410001H17 gene	NM_025889	NP_080165	UP TAC LA			
BG067332	RIKEN cDNA 2610002H11 gene	NM_133721	NP_598482	UP TAC LA		BX647350	NP_002198
BG073064	RIKEN cDNA 2610027H02 gene	BC027791		UP TAC LA			
AV061276	RIKEN cDNA 5031406P05 gene	NM_026669	NP_080945	UP TAC LA		AK130050	NP_003208
AV020551	RIKEN cDNA 5730403E06 gene	NM_027439	NP_081715	UP TAC LA			
AV016743	RIKEN cDNA 5730414C17 gene	NM_133680	NP_598441	UP TAC LA			
AV085966	RIKEN cDNA 6720474K14 gene	NM_175414	NP_780623	UP TAC LA			
BG072850	sarcoglycan, epsilon	NM_011360	NP_035490	UP TAC LA		NM_003919	NP_003910
AV087531	scavenger receptor class B1	NM_016741	NP_058021	UP TAC LA		AK023485	NP_005496
AV021712	secreted frizzled-related sequence protein 2	NM_009144	NP_033170	UP TAC LA		NM_003013	NP_003004
AV062462	serine palmitoyltransferase, long chain base subunit 1	NM_009269	NP_033295	UP TAC LA		NM_006415	NP_847894
D16106	sialyltransferase 1 (beta-galactoside alpha-2,6-sialyltransferase)	NM_145933	NP_666045	UP TAC LA			
AI385650	sialyltransferase 4C (beta-galactosidase alpha-2,3-sialytransferase⑦	NM_009178	NP_033204	UP TAC LA		AK128605	NP_006269
AV093704	small EDRK-rich factor 2	AK044479			UP TAC LV		
BG075739	solute carrier family 29 (nucleoside transporters), member 1	NM_022880	NP_075018	UP TAC LA		AK090615	NP_004946
AA499432	sprouty homolog 4 (*Drosophila*)	NM_011898	NP_036028	UP TAC LA		AF227516	NP_112226
AV074505	surfeit gene 4	NM_011512	NP_035642	UP TAC LA		NM_033161	NP_149351
AV111434	transient receptor protein 2	BF583628		UP TAC LA		BM701565	NP_852667
AV083947	transmembrane domain protein regulated in adipocytes 40 kDa	NM_011906	NP_036036	UP TAC LA			
AA023493	transmembrane protein with EGF-like and two follistatin-like domai⑦	AK079633		UP TAC LA		NM_003692	NP_003683
L26349	tumor necrosis factor receptor superfamily, member 1a	NM_011609	NP_035739	UP TAC LA		NM_001065	NP_001056
AV024570	tumor necrosis factor, alpha-induced protein 1 (endothelial)	NM_009395	NP_033421	UP TAC LA		BC003694	NP_066960
BG062994	UDP-GlcNAc: betaGal beta-1,3-N-acetylglucosaminyltransferase 1	NM_016888	NP_058584	UP TAC LA		BC047933	NP_150274
BG073697	⑦DP-glucuronate decarboxylase 1	NM_026430	NP_080706	UP TAC LA		BC035177	NP_079352
BG064510	vanilloid receptor-like protein 1	NM_011706	NP_035836	UP TAC LA		AK126996	NP_057197
BE376968	vascular endothelial growth factor C	NM_009506	NP_033532	UP TAC LA		NM_005429	NP_005420
AV103195	zinc finger protein 36	NM_133786	NP_598547	UP TAC LA		NM_005496	NP_005487

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TABLE III

Table III Genes of Use in Serologic Assays and/or Imaging Studies
Annotated Extracellular and Antigen genes Upregulated in TAC tissues - 169 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information						Human Homolog Information	
Gene ID	Gene Description	UGRepAcc	LLReProtA	Up TAC LA	Up TAC LV	Human UGRepA?	Human LLRep?
AI841353	a disintegrin and metalloproteinase domain 15 (metargidin)	NM_009614	NP_033744	UP TAC LA		AY560601	NP_997080
AV077899	actin, alpha 2, smooth muscle, aorta	AK002886			UP TAC LV		
BG072752	actin, gamma, cytoplasmic	NM_013798	NP_038826		UP TAC LV		
BG063167	adenylate cyclase 7	NM_007406	NP_031432	UP TAC LA	UP TAC LV	D25538	NP_001105
BG074747	alpha glucosidase 2, alpha neutral subunit	NM_008060	NP_032086	UP TAC LA			
AV070218	amyloid beta (A4) precursor-like protein 2	NM_009691	NP_033821	UP TAC LA		BX647107	NP_001633
AV070419	antigen identified by monoclonal antibody MRC OX-2	NM_010818	NP_034948	UP TAC LA		BC022522	NP_005935
AV025941	aquaporin 1	NM_007472	NP_031498	UP TAC LA		NM_198098	NP_932766
U34920	ATP-binding cassette, sub-family G (WHITE), member 1	NM_009593	NP_033723	UP TAC LA		NM_207630	NP_997513
AV104097	basigin	BI106083		UP TAC LA		NM_001728	NP_940993
AV087921	benzodiazepine receptor, peripheral	NM_009775	NP_033905	UP TAC LA		BX537892	NP_009295
X01838	beta-2 microglobulin	NM_009735	NP_033865	UP TAC LA		AK022379	NP_004039
AV170826	biglycan	NM_007542	NP_031568	UP TAC LA		BC004244	NP_001702
AA498724	bone morphogenetic protein 4	NM_007554	NP_031580	UP TAC LA		NM_001202	NP_570912
D16250	bone morphogenetic protein receptor, type 1A	BC042611	NP_033888	UP TAC LA		NM_004329	NP_004320
AV089105	calcium binding protein, intestinal	NM_009787	NP_033917	UP TAC LA			
X52886	cathepsin D	NM_009983	NP_034113	UP TAC LA		NM_001909	NP_001900
AV171867	CD 81 antigen	NM_133655	NP_598416	UP TAC LA		BM810055	NP_004347
AV062071	CD24a antigen	NM_009846	NP_033976	UP TAC LA			
AI893233	CD34 antigen	NM_133654	NP_598415	UP TAC LA		BX640941	NP_001764
AI838302	Cd63 antigen	NM_007653	NP_031679	UP TAC LA		BM701371	NP_001771
BG073140	CD8 antigen, beta chain	NM_009858	NP_033988	UP TAC LA			
AI325851	CD97 antigen	NM_011925	NP_036055	UP TAC LA		NM_078481	NP_510966
AV109555	cellular retinoic acid binding protein I	AK090130		UP TAC LA		NM_212482	NP_997647
BG067569	coagulation factor II (thrombin) receptor	NM_010169	NP_03429	UP TAC LA		NM_001992	NP_001983
AV149987	cystatin C	NM_009976	NP_034106	UP TAC LA		BX647523	NP_000090
BG074174	DNA segment, Chr 6, Wayne State University 176, expressed	NM_138587	NP_613053	UP TAC LA			
AV104157	dolichyl-di-phosphooligosaccharide-protein glycotransferase	NM_007838	NP_031864	UP TAC LA		NM_005216	NP_005207
AV083262	dystonin	NM_134448	NP_604443		UP TAC LV	NM_183380	NP_899236
BG065640	ectonucleotide pyrophosphatase/ phosphodiesterase 1	NM_008813	NP_032839	UP TAC LA		NM_006208	NP_006199
AV019210	elastin	NM_007925	NP_031951	UP TAC LA		BX537939	NP_000492
AV066211	ELAV (embryonic lethal, abnormal vision, *Drosophila*)-like 1 (H?	NM_010485	NP_034615	UP TAC LA		NM_001419	NP_001410
AA646363	endoglin	NM_007932	NP_031958	UP TAC LA		NM_000118	NP_000109
AV104213	endothelial cell-selective adhesion molecule	NM_027102	NP_081378	UP TAC LA			
AI838613	epithelial membrane protein 1			UP TAC LA	UP TAC LV	NM_001423	NP_001414
AV011166	EST	NM_080463	NP_536711	UP TAC LA		AF375884	NP_758436
AV087039	EST	NM_008885	NP_032911	UP TAC LA		NM_000304	NP_696997
AV140901	EST	NM_010368	NP_034498	UP TAC LA			
AW537378	EST			SAM DOWN	UP TAC LV		
AW547864	EST				UP TAC LV		
U20156	EST			UP TAC LA	UP TAC LV	BQ056329	NP_002406
AV087499	EST, Moderately similar to A57474 extracellular matrix protein?	NM_007899	NP_031925	UP TAC LA		AK097205	NP_073155
AI851039	ESTs, Weakly similar to D2045.2.p [*Caenorhabditis elegans*] [?	AK038775			UP TAC LV		
AV059438	ets variant gene 6 (TEL oncogene)	BC009120			UP TAC LV		
BG064180	expressed sequence AA408225	NM_009868	NP_033998	UP TAC LA		NM_001795	NP_001786
AV059924	expressed sequence AA986889	NM_134102	NP_598863	UP TAC LA		BX647516	NP_056984
AV103290	expressed sequence AL024047	NM_134151	NP_598912	UP TAC LA		AK125213	NP_003671
BG072998	expressed sequence AU018638	NM_008524	NP_032550		UP TAC LV	BG114678	NP_002336
AV037769	expressed sequence AU022549	NM_007904	NP_031930	UP TAC LA		NM_000115	NP_003982
AV087220	expressed sequence AW146116	NM_133352	NP_835359	UP TAC LA			

TABLE III-continued

Table III Genes of Use in Serologic Assays and/or Imaging Studies
Annotated Extracellular and Antigen genes Upregulated in TAC tissues - 169 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information						Human Homolog Information	
Gene ID	Gene Description	UGRepAcc	LLReProtA	Up TAC LA	Up TAC LV	Human UGRepA?	Human LLRep?
BG073479	expressed sequence AW229038	NM_133918	NP_598679	UP TAC LA		AL050138	NP_008977
BG070007	expressed sequence AW494241	BC040467			UP TAC LV		
C79946	expressed sequence C79946	AK080023		UP TAC LA	UP TAC LV		
AV085019	extracellular matrix protein 1	NM_007899	NP_031925	UP TAC LA		AK097205	NP_073155
AW476537	fibroblast growth factor receptor 1	NM_010206	NP_034336	UP TAC LA		BC018128	NP_075599
AA673390	fibronectin 1	AK090130		UP TAC LA		NM_212482	NP_997647
BG073227	fibulin 2	NM_007992	NP_032018	UP TAC LA		AY130459	NP_001004019
AV059445	FK506 binding protein 9	NM_012056	NP_036186	UP TAC LA		AK075331	NP_009201
BG063294	follistatin-like 3	NM_031380	NP_113557	UP TAC LA		BC005839	NP_005851
AV083596	four and a half LIM domains 1	NM_010211	NP_034341		UP TAC LV	AK122708	NP_001440
AV086002	FXYD domain-containing ion transport regulator 6	NM_022004	NP_071287	UP TAC LA		AK092198	NP_071286
AV057141	gap junction membrane channel protein beta 1	NM_008124	NP_032150		UP TAC LV	BF570961	NP_000157
AV073997	glucose regulated protein, 58 kDa	NM_007952	NP_031978	UP TAC LA		AK075455	NP_005304
AV001464	granulin	NM_008175	NP_032201	UP TAC LA		NM_002087	NP_002078
AV134035	granulin	NM_008175	NP_032201	UP TAC LA		NM_002087	NP_002078
AV223941	heat shock protein, 70 kDa 3	M12571		SAM DOWN	UP TAC LV	NM_005345	NP_005336
AW551778	heterogeneous nuclear ribonucleoprotein C	NM_016884	NP_058580	UP TAC LA	UP TAC LV	AK126950	NP_112604
X00246	histocompatibility 2, D region locus 1	NM_010380	NP_034510	UP TAC LA			
AV084844	immunoglobulin superfamily containing leucine-rich repeat	NM_012043	NP_036173	UP TAC LA		NM_005545.3	NP_005536.1
AV012617	insulin-like growth factor binding protein 5	NM_010518	NP_034648	UP TAC LA		NM_000599	NP_000590
BG074422	integrin beta 1 (fibronectin receptor beta)	AK088016		UP TAC LA		NM_002211	NP_596867
BG073319	integrin beta 4 binding protein	NM_010579	NP_034709		UP TAC LV	BQ278496	NP_852134
BF100414	integrin beta 5	NM_010580	NP_034710	UP TAC LA		AK091595	NP_002204
AV006514	interferon (alpha and beta) receptor 2	NM_010509	NP_034639	UP TAC LA		L41944	NP_997468
BG070387	interleukin 6 signal transducer	NM_010560	NP_034690	UP TAC LA		BC071555	NP_786943
BG072624	laminin, gamma 1	BC032194	NP_034813	UP TAC LA		NM_002293	NP_002284
AV007183	latent transforming growth factor beta binding protein 3	NM_023912	NP_076401	UP TAC LA		AK024477	NP_066548
BG071948	low density lipoprotein receptor-related protein 1	NM_008512	NP_032538		UP TAC LV	NM_002332	NP_002323
AV162270	lymphocyte antigen 6 complex, locus A	NM_027015	NP_081291	UP TAC LA		NM_001030	NP_001021
BG065103	lymphocyte antigen 6 complex, locus E	NM_008529	NP_032555	UP TAC LA		BF969813	NP_002337
AA098349	lysyl oxidase-like	AK078512		UP TAC LA		BC068542	NP_005567
AV117035	manic fringe homolog (*Drosophila*)	NM_008595	NP_032621	UP TAC LA		U94352	NP_002396
AV156534	matrilin 2	NM_016762	NP_058042	UP TAC LA		BX648291	NP_085072
AI838311	matrix metalloproteinase 2	NM_008610	NP_032636		UP TAC LV	AL832088	NP_004521
AV015188	matrix metalloproteinase 23	NM_011985	NP_036115	UP TAC LA			
BG075377	melanoma cell adhesion molecule	NM_023061	NP_075548	UP TAC LA		NM_006500	NP_006491
BG072908	membrane-bound transcription factor protease, site 1	NM_019709	NP_062683	UP TAC LA		NM_003791	NP_957720
BG074344	mesothelin	NM_018857	NP_061345	UP TAC LA		BC003512	NP_037536
AV113097	microfibrillar associated protein 5	NM_015776	NP_056591	UP TAC LA		NM_003480	NP_003471
AV094498	milk fat globule-EGF factor 8 protein	NM_008594	NP_032620	UP TAC LA		AK092157	NP_005919
AV085874	*Mus musculus* uridindiphosphoglucosepyrophosphorylase 2 (U?	NM_139297	NP_647458		UP TAC LV	BX537559	NP_006750
BG065584	*Mus musculus*, clone IMAGE: 3589087, mRNA, partial cds	BF124761			UP TAC LV		
BG066621	*Mus musculus*, Similar to pituitary tumor-transforming 1 interac?	NM_145925	NP_666037	UP TAC LA			
BG066563	N-acetylated alpha-linked acidic dipeptidase 2	NM_028279	NP_082555	UP TAC LA	UP TAC LV	AK075390	NP_005458
AV061081	neural proliferation, differentiation and control gene 1	NM_008721	NP_032747	UP TAC LA		AK054950	NP_056207
AI325886	neuroblastoma, suppression of tumorigenicity 1	NM_008675	NP_032701	UP TAC LA		NM_182744	NP_877421
AI323974	neuropilin	NM_008737	NP_032763	UP TAC LA			

TABLE III-continued

Table III Genes of Use in Serologic Assays and/or Imaging Studies
Annotated Extracellular and Antigen genes Upregulated in TAC tissues - 169 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information						Human Homolog Information	
Gene ID	Gene Description	UGRepAcc	LLReProtA	Up TAC LA	Up TAC LV	Human UGRepA?	Human LLRep?
BG063616	nidogen 1	NM_010917	NP_035047	UP TAC LA			
BG072810	Niemann Pick type C2	NM_023409	NP_075898	UP TAC LA		BQ896617	NP_006423
BF182158	Notch gene homolog 1, (*Drosophila*)	NM_008714	NP_032740	UP TAC LA		NM_017617	NP_060087
BF136770	Notch gene homolog 3, (*Drosophila*)	NM_008716	NP_032742	UP TAC LA		NM_000435	NP_000426
AV084876	osteoblast specific factor 2 (fasciclin I-like)	NM_015784	NP_056599	UP TAC LA			
BG074915	parotid secretory protein	NM_172261	NP_758465	UP TAC LA		AL713642	NP_115984
AV059520	peptidylprolyl isomerase C-associated protein	NM_011150	NP_035280	UP TAC LA			
AV112983	platelet derived growth factor receptor, beta polypeptide	NM_008809	NP_032835	UP TAC LA		BC032224	NP_002600
AI327133	polydomain protein	NM_022814	NP_073725	UP TAC LA			
BG073284	prion protein dublet	NM_023043	NP_075530		UP TAC LV	NM_012409	NP_036541
AV084561	procollagen C-proteinase enhancer protein	NM_008788	NP_032814	UP TAC LA	UP TAC LV	BM994449	NP_002584
AV009300	procollagen, type IV, alpha 1	J04694		UP TAC LA		NM_001845	NP_001836
AV010312	procollagen, type IV, alpha 2	J04695		UP TAC LA		NM_001846	NP_001837
AV013988	procollagen, type VI, alpha 1	NM_009933	NP_034063	UP TAC LA		NM_001848	NP_001839
BG075864	procollagen, type VI, alpha 2	NM_146007	NP_666119	UP TAC LA		AK128695	NP_478055
AV015595	procollagen, type XV	NM_009928	NP_034058	UP TAC LA		NM_001855	NP_001846
AW548258	procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-h?	BC009654		UP TAC LA		BX648829	NP_000908
BG069745	proline arginine-rich end leucine-rich repeat	NM_054077	NP_473418	UP TAC LA		NM_002725	NP_958505
BG073729	prolyl 4-hydroxylase, beta polypeptide	J05185		UP TAC LA		J02783	NP_000909
BG073750	prolyl 4-hydroxylase, beta polypeptide	J05185		UP TAC LA		J02783	NP_000909
AV025665	prostaglandin-endoperoxide synthase 2	NM_011198	NP_035328	UP TAC LA		NM_000963	NP_000954
BG070083	protein tyrosine phosphatase, receptor type, E	NM_011212	NP_035342	UP TAC LA		BX648180	NP_569119
BG074663	protein tyrosine phosphatase, receptor type, S	NM_011218	NP_035348	UP TAC LA		NM_002850	NP_570925
BG073341	retinal short-chain dehydrogenase/ reductase 1	NM_011303	NP_035433	UP TAC LA		BX648476	NP_004744
AV083867	retinoid-inducible serine caroboxypetidase	NM_029023	NP_083299	UP TAC LA			
AA087526	retinol binding protein 1, cellular	NM_011254	NP_035384		UP TAC LV	BF508021	NP_002890
AV024396	reversion-inducing-cysteine-rich protein with kazal motifs	NM_016678	NP_057887	UP TAC LA		BX648668	NP_066934
AV140189	RIKEN cDNA 0610040B21 gene	NM_025334	NP_079610	UP TAC LA			
AV007276	RIKEN cDNA 1110003M08 gene	AK090329		UP TAC LA		AK124975	NP_005818
AV083352	RIKEN cDNA 1110007F23 gene	NM_029568	NP_083844	UP TAC LA			
AV015246	RIKEN cDNA 1110054M18 gene	NM_175132	NP_780341		UP TAC LV		
BG074142	RIKEN cDNA 1300012G16 gene	NM_023625	NP_076114	UP TAC LA			
AI838568	RIKEN cDNA 1300018J16 gene	NM_029092	NP_083368	UP TAC LA	UP TAC LV		
AV058250	RIKEN cDNA 1810049K24 gene	NM_030209	NP_084485	UP TAC LA			
AI322274	RIKEN cDNA 2410002J21 gene	AK033091			UP TAC LV		
AI851067	RIKEN cDNA 2510010F10 gene	NM_175833	NP_787027		UP TAC LV		
AV111526	RIKEN cDNA 2610002H11 gene	NM_133721	NP_598482	UP TAC LA		BX647350	NP_002198
AV050682	RIKEN cDNA 2700083B06 gene	NM_026531	NP_080807	UP TAC LA	UP TAC LV		
AV133755	RIKEN cDNA 2810002E22 gene	NM_133859	NP_598620	UP TAC LA			
AV053955	RIKEN cDNA 3110023E09 gene	NM_026522	NP_080798	UP TAC LA			
AV016743	RIKEN cDNA 5730414C17 gene	NM_133680	NP_598441	UP TAC LA			
BG072850	sarcoglycan, epsilon	NM_011360	NP_035490	UP TAC LA		NM_003919	NP_003910
AW988741_2	secreted acidic cysteine rich glycoprotein			UP TAC LA		AK126525	NP_003109
AV021712	secreted frizzled-related sequence protein 2	NM_009144	NP_033170	UP TAC LA		NM_003013	NP_003004
BG074382	sema domain, immunoglobulin domain (Ig), short basic domain?	NM_011349	NP_035479	UP TAC LA		U38276	NP_004177
AV022379	serine (or cysteine) proteinase inhibitor, clade F (alpha-2 antipl?	NM_011340	NP_035470	UP TAC LA		BM918904	NP_002606
AV093463	serine (or cysteine) proteinase inhibitor, clade H (heat shock pr?	NM_009825	NP_033955	UP TAC LA		AK122936	NP_001226
AV052090	serine (or cysteine) proteinase inhibitor, clade I (neuroserpin),?	NM_009250	NP_033276	UP TAC LA		BC018043	NP_005016
AI385650	sialyltransferase 4C (beta-galactosidase alpha-2,3-sialytransfe?	NM_009178	NP_033204	UP TAC LA		AK128605	NP_006269
AV093704	small EDRK-rich factor 2	AK044479			UP TAC LV		
AV109513	stromal cell derived factor 1	NM_013655	NP_068350	UP TAC LA		BX647204	NP_954637

TABLE III-continued

Table III Genes of Use in Serologic Assays and/or Imaging Studies
Annotated Extracellular and Antigen genes Upregulated in TAC tissues - 169 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information						Human Homolog Information	
Gene ID	Gene Description	UGRepAcc	LLReProtA	Up TAC LA	Up TAC LV	Human UGRepA?	Human LLRep?
AV048780	stromal cell derived factor 4	NM_011341	NP_035471	UP TAC LA			
U38261	superoxide dismutase 3, extracellular	NM_011435	NP_035565	UP TAC LA		NM_003102	NP_003093
AV070805	thymic stromal-derived lymphopoietin, receptor	NM_016715	NP_057924	UP TAC LA			
AV057827	torsin family 3, member A	NM_023141	NP_075630	UP TAC LA		NM_022371	NP_071766
AA068104	transforming growth factor, beta 2	NM_009367	NP_033393	UP TAC LA		M19154	NP_003229
L26349	tumor necrosis factor receptor superfamily, member 1a	NM_011609	NP_035739	UP TAC LA		NM_001065	NP_001056
BE376968	vascular endothelial growth factor C	NM_009506	NP_033532	UP TAC LA		NM_005429	NP_005420

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TABLE IV

Table IV Genes of Use in Metabolic Assays
Annotated Metabolism Genes Downregulated in TAC tissues - 109 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information						Human Homolog Information	
Gene Name	Gene Description	UGRepAcc	LLRepProtA	Down TAC LA	Down TAC LV	UGRepAcc	LLRepProtAcc
BG066890	**DNA segment, Chr 13, ERATO Doi 332, expressed	NM_007749	NP_031775	DOWN TAC LA		BI118114	NP_001858
BG062980	**DNA segment, Chr 2, Wayne State University 85, expressed	U37501		DOWN TAC LA		NM_005560	NP_005551
AV025301	2,4-dienoyl CoA reductase 1, mitochondrial	NM_026172	NP_080448		DOWN TAC LV	BM920635	NP_001350
AV029241	acetyl-Coenzyme A dehydrogenase, long-chain	NM_007381	NP_031407	DOWN TAC LA	DOWN TAC LV	BC039063	NP_001599
AI840666	acetyl-Coenzyme A dehydrogenase, medium chain	NM_007382	NP_031408	DOWN TAC LA	DOWN TAC LV	NM_000016	NP_000007
AV004604	acetyl-Coenzyme A dehydrogenase, short chain	NM_007383	NP_031409		DOWN TAC LV	AK057021	NP_000008
AI839605	acyl-Coenzyme A dehydrogenase, very long chain	NM_017366	NP_059062	DOWN TAC LA		AK097243	NP_000009
AF006688	acyl-Coenzyme A oxidase 1, palmitoyl	NM_015729	NP_056544		DOWN TAC LV	BC008767	NP_009223
U07235	aldehyde dehydrogenase 2, mitochondrial	NM_009656	NP_033786		DOWN TAC LV	AL832043	NP_000681
AV006235	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	NM_009722	NP_033852		DOWN TAC LV	BX648282	NP_733765
BG074044	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	NM_009722	NP_033852	DOWN TAC LA	DOWN TAC LV	BX648282	NP_733765
AI837797	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	NM_009722	NP_033852	DOWN TAC LA		BX648282	NP_733765
AV095181	AU RNA binding protein/ enoyl-coenzyme A hydratase	NM_016709	NP_057918	DOWN TAC LA		AK124142	NP_001689
AI323918	branched chain ketoacid dehydrogenase E1, alpha polypeptide	NM_007533	NP_031559		DOWN TAC LV	BF206112	NP_000700
AV014385	?arbonic anhydrase 14	NM_146104	NP_666216	DOWN TAC LA	DOWN TAC LV		
AV170903	carbonic anhydrase 14	NM_146104	NP_666216		DOWN TAC LV		
AI323923	carbonyl reductase 1	NM_007620	NP_031646	DOWN TAC LA		BM810059	NP_001748
AV006197	carnitine palmitoyltransferase 2	NM_009949	NP_034079	DOWN TAC LA	DOWN TAC LV	NM_000098	NP_000089
AV093569	copper chaperone for superoxide dismutase	NM_016892	NP_058588	DOWN TAC LA		BM543741	NP_005116
AV085004	creatine kinase, mitochondrial 2	AK009042		DOWN TAC LA		NM_001825	NP_001816
AV005997	cytochrome c oxidase, subunit IVa	NM_009941	NP_034071	DOWN TAC LA		AK027136	NP_001852
AV095075	cytochrome c oxidase, subunit Va	NM_007747	NP_031773		DOWN TAC LV	BM911641	NP_004246
AV088644	cytochrome c oxidase, subunit Vb	NM_009942	NP_034072	DOWN TAC LA		BM912880	NP_001853

TABLE IV-continued

Table IV Genes of Use in Metabolic Assays
Annotated Metabolism Genes Downregulated in TAC tissues - 109 Unique genes
One example for each gene - Passed stringent SAM criteria

Mouse Gene Information							
Gene Name	Gene Description	UGRepAcc	LLRepProtA	Down TAC LA	Down TAC LV	UGRepAcc	LLRepProtAcc
AV001082	cytochrome c oxidase, subunit VI a, polypeptide 2	NM_009943	NP_034073	DOWN TAC LA	DOWN TAC LV	BM712970	NP_005196
AV149855	cytochrome c oxidase, subunit VIc	NM_053071	NP_444301	DOWN TAC LA	DOWN TAC LV	AK128382	NP_004365
AV086493	cytochrome c oxidase, subunit VIIa 1	NM_009944	NP_034074	DOWN TAC LA		BM726594	NP_001855
AV133935	cytochrome c oxidase, subunit VIIa 3	NM_009945	NP_034075	DOWN TAC LA	DOWN TAC LV	BF210089	NP_001856
BG063960	cytochrome c oxidase, subunit VIIc	NM_007749	NP_031775	DOWN TAC LA		BI118114	NP_001858
AV086888	cytochrome c, somatic	NM_007808	NP_031834	DOWN TAC LA		NM_018947	NP_061820
AV093672	cytochrome c-1	NM_025567	NP_079843	DOWN TAC LA		BF569085	NP_001907
AV095067	DNA segment, Chr 18, Wayne State University 181, expressed⑦	NM_138600	NP_613066		DOWN TAC LV	AK092507	NP_001173
AV083353	dodecenoyl-Coenzyme A delta isomerase (3,2 trans-enoyl-Coe⑦	NM_010023	NP_034153	DOWN TAC LA	DOWN TAC LV	BQ277959	NP_001910
BG074113	enoyl coenzyme A hydratase 1, peroxisomal	NM_016772	NP_058052	DOWN TAC LA		AK126566	NP_001389
AU022217	epoxide hydrolase 2, cytoplasmic	NM_007940	NP_031966		DOWN TAC LV	AK094393	NP_001970
BG067242	ESTs	BE988802		DOWN TAC LA		NM_002660	NP_877963
AV006522	ESTs	NM_028545	NP_082821	DOWN TAC LA			
AV095205	eukaryotic translation initiation factor 2 alpha kinase 3	NM_010121	NP_034251	DOWN TAC LA		NM_004836	NP_004827
AV109470	expressed sequence AA959857	BC048412		DOWN TAC LA		NM_005463	NP_112740
AV006061	fatty acid Coenzyme A ligase, long chain 2	NM_007981	NP_032007	DOWN TAC LA			
AV140552	fumarate hydratase 1	BC006048			DOWN TAC LV		
BG072359	fumarylacetoacetate hydrolase	NM_010176	NP_034306		DOWN TAC LV	BX537608	NP_000128
AI841654	G protein-coupled receptor 56	NM_018882	NP_061370		DOWN TAC LV	NM_201524	NP_958933
AV108357	galactokinase	NM_016905	NP_058601	DOWN TAC LA		BM471434	NP_000145
AA162908	gamma-glutamyl transpeptidase	NM_008116	NP_032142	DOWN TAC LA		BC035341	NP_038347
BG068200	GATA binding protein 6	AF179425			DOWN TAC LV	X95701	NP_005248
BG066689	glutamate oxaloacetate transaminase 1, soluble	NM_010324	NP_034454	DOWN TAC LA		BM994502	NP_002070
AV009064	glutamine synthetase	NM_008131	NP_032157	DOWN TAC LA		AL161952	NP_002056
AV134367	glutaryl-Coenzyme A dehydrogenase	NM_008097	NP_032123		DOWN TAC LV	BC002579	NP_039663
AV087315	guanosine monophosphate reductase	NM_025508	NP_079784		DOWN TAC LV	BM994423	NP_006868
AV022721	histidine ammonia lyase	NM_010401	NP_034531	DOWN TAC LA		NM_002108	NP_002099
BG073539	hydroxysteroid (17-beta) dehydrogenase 10	NM_016763	NP_058043	DOWN TAC LA		BQ940058	NP_004484
BG068774	isocitrate dehydrogenase 3 (NAD+) alpha	NM_029573	NP_083849	DOWN TAC LA	DOWN TAC LV	AK123316	NP_005521
AA036340	isocitrate dehydrogenase 3 (NAD+) beta	NM_130884	NP_570954	DOWN TAC LA		BQ051868	NP_777281
AV005828	L-3-hydroxyacyl-Coenzyme A dehydrogenase, short chain	NM_008212	NP_032238		DOWN TAC LV	AK096018	NP_005318
AV022047	lipin 1	NM_015763	NP_766538	DOWN TAC LA		AK127039	NP_663731
AV006290	lipoprotein lipase	NM_008509	NP_032535	DOWN TAC LA		NM_000237	NP_000228
BG064854	low density lipoprotein receptor-related protein 2	AK084165		DOWN TAC LA		NM_004525	NP_004516
AV088662	malic enzyme, supernatant	NM_008615	NP_032641		DOWN TAC LV		
AV057294	methylcrotonoyl-Coenzyme A carboxylase 1 (alpha)	NM_023644	NP_076133		DOWN TAC LV	BC042453	NP_064551
AA108913	methylmalonyl-Coenzyme A mutase	NM_008650	NP_032676		DOWN TAC LV	BX647789	NP_000246
AV006153	*Mus musculus*, clone MGC: 7898 IMAGE: 3582717, mRNA, com⑦	BF180657			DOWN TAC LV		
AI854120	*Mus musculus*, Similar to 3-hydroxyisobutyrate dehydrogenase,	NM_145567	NP_663542	DOWN TAC LA			
AV088774	⑦*Mus musculus*, Similar to electron-transfer-flavoprotein, alpha p⑦	NM_145615	NP_663590	DOWN TAC LA		BM907902	NP_000117
AV103083	NAD(P)H menadione oxidoreductase 2, dioxin inducible	NM_020282	NP_064678		DOWN TAC LV		
AA162428	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 2	NM_010885	NP_035015	DOWN TAC LA			
AV016078	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 2	NM_010885	NP_035015	DOWN TAC LA			
AV140287	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 1	NM_019443	NP_062316	DOWN TAC LA			
AV050140	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4	BQ044115		DOWN TAC LA		BX538277	NP_002480

TABLE IV-continued

Table IV Genes of Use in Metabolic Assays
Annotated Metabolism Genes Downregulated in TAC tissues - 109 Unique genes
One example for each gene - Passed stringent SAM criteria

		Mouse Gene Information					
Gene Name	Gene Description	UGRepAcc	LLRepProtA	Down TAC LA	Down TAC LV	UGRepAcc	LLRepProtAcc
AV106199	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 6 (14?	NM_025987	NP_080263	DOWN TAC LA	DOWN TAC LV	BM709562	NP_002481
AW555047	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 7 (14?	NM_023202	NP_075691	DOWN TAC LA	DOWN TAC LV	BM545518	NP_004992
AI836747	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 9	NM_023172	NP_075661	DOWN TAC LA		BM994434	NP_004996
BG076060	NADH dehydrogenase (ubiquinone) Fe—S protein 3	BU756147		DOWN TAC LA	DOWN TAC LV		
AV084172	ornithine aminotransferase	NM_016978	NP_058674		DOWN TAC LV	BC016928	NP_000265
BG073162	oxysterol binding protein-like 1A	NM_020573	NP_065598	DOWN TAC LA		BX647893	NP_579802
BG071157	phosphate cytidylyltransferase 1, choline, alpha isoform	AK083965		DOWN TAC LA		BC046355	NP_005008
AV033702	phospholipase A2 group VII (platelet-activating factor acetylhyd?	NM_013737	NP_038765	DOWN TAC LA		BC025674	NP_005075
BG068736	pyruvate dehydrogenase E1 alpha 1	NM_008810	NP_032836	DOWN TAC LA		AK092210	NP_000275
AV012729	retinoic acid induced 1	NM_011480	NP_035610	DOWN TAC LA		NM_030665	NP_109590
AA403731	RIKEN cDNA 0610009I16 gene	NM_026695	NP_080971	DOWN TAC LA		AL833205	NP_001976
AI841340	RIKEN cDNA 0610010E03 gene	NM_025321	NP_079597	DOWN TAC LA		BQ899032	NP_002992
BG072552	RIKEN cDNA 0610011L04 gene	NM_177470	NP_803421	DOWN TAC LA			
AV093484	RIKEN cDNA 0610033L03 gene	NM_026703	NP_080979	DOWN TAC LA	DOWN TAC LV	BM704035	NP_055037
AW558029	RIKEN cDNA 0710008D09 gene	NM_025650	NP_079926	DOWN TAC LA			
AV086467	RIKEN cDNA 1010001M12 gene	NM_025348	NP_079624	DOWN TAC LA		BM805609	NP_004533
AV133828	RIKEN cDNA 1010001N11 gene	NM_025358	NP_079634	DOWN TAC LA	DOWN TAC LV	BM546373	NP_004993
AV012912	RIKEN cDNA 1110038I05 gene	NM_134042	NP_598803		DOWN TAC LV	NM_005589	NP_005580
AV022384	RIKEN cDNA 1190017B19 gene	NM_023175	NP_075664	DOWN TAC LA			
AV114239	RIKEN cDNA 1200006L06 gene	NM_024181	NP_077143		DOWN TAC LV		
AV095102	RIKEN cDNA 1500004O06 gene	NM_025899	NP_080175	DOWN TAC LA		AK094006	NP_003357
AV052491	RIKEN cDNA 1810022C23 gene	NM_026947	NP_081223		DOWN TAC LV		
AV063132	RIKEN cDNA 2210415M14 gene	NM_026219	NP_080495	DOWN TAC LA		BC041005	NP_006285
AV081301	RIKEN cDNA 2210418G03 gene	AK008974		DOWN TAC LA			
AV085923	RIKEN cDNA 2310016C19 gene	NM_025862	NP_080138		DOWN TAC LV	AK125373	NP_055199
AV086427	RIKEN cDNA 2310021J10 gene	NM_025641	NP_079917	DOWN TAC LA			
AV103530	RIKEN cDNA 2310039H15 gene	NM_028177	NP_082453	DOWN TAC LA	DOWN TAC LV	BE547177	NP_004994
AV095143	RIKEN cDNA 2410004H02 gene	NM_145954	NP_666066	DOWN TAC LA			
BG063257	RIKEN cDNA 2510027N19 gene	NM_026330	NP_080606	DOWN TAC LA			
AV077867	RIKEN cDNA 2610003B19 gene	NM_028177	NP_082453	DOWN TAC LA		BE547177	NP_004994
BG067911	RIKEN cDNA 2610020H15 gene	NM_025638	NP_079914	DOWN TAC LA	DOWN TAC LV		
AV104092	RIKEN cDNA 2610034N03 gene	NM_025478	NP_079754	DOWN TAC LA			
BG063943	RIKEN cDNA 2610041P16 gene	NM_025641	NP_079917	DOWN TAC LA			
BG072165	RIKEN cDNA 2610205J15 gene	NM_152813	NP_690026		DOWN TAC LV		
AV030438	RIKEN cDNA 2610207I16 gene	NM_024255	NP_077217		DOWN TAC LV		
AV089737	RIKEN cDNA 3230402N08 gene	NM_021509	NP_067484	DOWN TAC LA		AY007239	NP_056344
AA154831	solute carrier family 27 (fatty acid transporter), member 2	NM_011978	NP_036108	DOWN TAC LA		D88308	NP_003636
AA673962	sortilin-related receptor, LDLR class A repeats-containing	AF031816		DOWN TAC LA		NM_003105	NP_003096
AA146030	sterol carrier protein 2, liver	BC018384		DOWN TAC LA	DOWN TAC LV	BX537619	NP_002970
AV088223	succinate-CoA ligase, GDP-forming, alpha subunit	NM_019879	NP_063932		DOWN TAC LV	AK125502	NP_003840
AV016790	thioredoxin-like 2	NM_023140	NP_075629	DOWN TAC LA		AJ010841	NP_006532

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What is claimed is:

1. A method for the diagnosis of pressure overload in the heart, the method comprising:

determining the differential expression in one or more of the sequences set forth in Table I.

2. The method according to claim 1, wherein said pressure overload is associated with atrial enlargement and/or ventricular hypertrophy.

3. The method according to claim 1, wherein said determining comprises:

contacting a biological sample comprising protein with an antibody that specifically binds to one or more of the proteins having amino acid sequences encoded by said pressure overload associated genes;

detecting the presence of a complex formed between said antibody and said protein;

wherein an alteration in the presence of said complex, compared to a control sample, is indicative of pressure overload in the heart.

4. The method according to claim 3, wherein said biological sample is blood or serum.

5. The method according to claim 4, wherein said biological sample is contacted with a panel of antibodies specific for pressure overload associated polypeptides.

6. The method according to claim 3, wherein said pressure overload associated genes are set forth in Table II.

7. The method according to claim 5, wherein said biological sample is cardiac cells.

8. The method according to claim 7, wherein said contacting is performed in vivo.

9. The method according to claim 8, the steps comprising:

a) administering to a patient an effective amount of an imaging composition comprising: an antibody that specifically binds to a pressure overload associated polypeptide, and increases contrast between an overloaded cardiac tissue and surrounding tissue in a visualization method; and

b) visualizing said imaging composition.

10. The method according to claim 7, wherein said pressure overload associated genes are set forth in Table III.

11. The method according to claim 1, wherein said determining comprises:

contacting a biological sample comprising protein with a labeled substrate for a metabolic reaction catalyzed by said pressure overload associated genes;

detecting the presence of the product of said metabolic reaction;

wherein an increase in the presence of said complex, compared to a control sample, is indicative of pressure overload in the heart.

12. The method according to claim 11, wherein said pressure overload associated gene is set forth in Table IV.

13. The method according to claim 1, wherein said determining step comprises:

contacting a biological sample comprising nucleic acids from a patient suspected of suffering from pressure overload with a probe that specifically binds to one or more of said sequences;

detecting the presence of a complex formed between said probe and said nucleic acid;

wherein an increase in the presence of said complex, compared to a control sample, is indicative of pressure overload of the heart.

14. The method according to claim 13, wherein said biological sample comprises nucleic acids specifically amplified with said sequences.

15. The method according to claim 13, wherein said biological sample is blood.

16. The method according to claim 13, wherein said biological sample is contacted with a panel of pressure overload associated gene sequences.

17. An array comprising two or more pressure overload associated genes as set forth in Table I, gene products, or antibodies specific for said gene products.

18. A method for identifying an agent that modulates activity of a pressure overload associated gene or gene product, the method comprising:

combining a candidate biologically active agent with any one of:

(a) a polypeptide encoded by any one of the sequences set forth in Table I;

(b) a cell comprising a nucleic acid encoding and expressing a polypeptide encoded by any one of the sequences set forth in Table I; or

(c) a non-human transgenic animal model for pressure overload associated gene function comprising one of: (i) a knockout of a gene corresponding to any one of the sequences set forth in Table I; (ii) an exogenous and stably transmitted mammalian gene sequence comprising any one of the sequences set forth in Table I; and

determining the effect of said agent on pressure overload induced molecular and cellular changes.

19. The method according to claim 18, wherein said biologically active agent upregulates activity.

20. The method according to claim 18, wherein said biologically active agent downregulates activity.

21. The method according to claim 20, wherein said biologically active agent binds to said polypeptide.

22. The method according to claim 1, wherein said sequence is set forth in Table IA.

23. The method according to claim 1, wherein said sequence is set forth in Table IB.

* * * * *

专利名称(译)	心脏压力超负荷相关基因		
公开(公告)号	US20060094038A1	公开(公告)日	2006-05-04
申请号	US11/231700	申请日	2005-09-20
[标]申请(专利权)人(译)	斯坦福大学		
申请(专利权)人(译)	THE利兰·斯坦福，齐齐哈尔大学董事会		
当前申请(专利权)人(译)	THE利兰·斯坦福，齐齐哈尔大学董事会		
[标]发明人	WAGNER ROGER A TABIBIAZAR RAYMOND QUERTERMOUS THOMAS		
发明人	WAGNER, ROGER A. TABIBIAZAR, RAYMOND QUERTERMOUS, THOMAS		
IPC分类号	C12Q1/68 G01N33/53 C12M1/34		
CPC分类号	C12Q1/6883 C12Q2600/158 G01N33/6893 G01N2800/32 G01N2800/325 C12Q2600/136		
优先权	60/611674 2004-09-20 US		
外部链接	Espacenet USPTO		

摘要(译)

本发明鉴定了其基因产物差异表达心脏压力超负荷的基因。本发明提供了用于诊断或评估个体对许多病因的心力衰竭易感性的方法，以及肥大，腔室扩大或收缩热衰竭的存在和严重性。还提供了用于治疗心脏病患者的治疗方法或用于预防性治疗易患心力衰竭的个体的方法。另外，本发明描述了用于鉴定可以施用以治疗患有心脏病发作或有心力衰竭风险的个体的药剂的筛选方法。

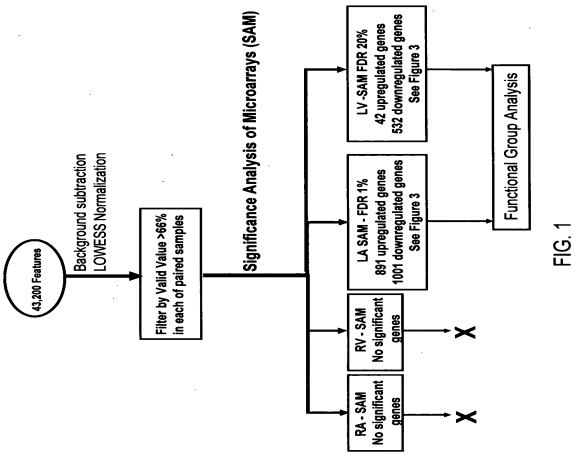

FIG. 1