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(54) **METHOD OF DIAGNOSING DEPRESSION**

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(57) **ABSTRACT**

This invention provides a novel method of diagnosing the conditions of depression of a patient in a simple, objective, and accurate manner. In this method, gene expression is analyzed using mRNA of a subject's peripheral blood to evaluate whether or not the subject is afflicted with depression, the type of depression of a subject who had been evaluated as being afflicted with depression is identified, and the conditions of depression are then diagnosed in accordance with the type of depression.

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Fig 1

Gene	Sample	#01	#02	#03	#04	#05	#06	#07	#08	#09	#10	#11	#12	#13	#14	#15	#16	#17	#18	#19	#20	#21	#22	#23	#24	#25	#26	#27	#28	#29	#30	#31	#32	#33					
Genes with lower expression level	ATP2A2	0.68	0.68	0.77	-0.83	-0.70	1.03	-0.33	-0.57	-0.95	-0.68	-0.77	-0.71	-0.78	-0.50	-0.52	-0.70	-0.64	1.16	-0.72	-0.74	-0.74	-0.86	-0.53	-0.93	-0.76	-0.58	-0.66	0.68	-0.97	0.61	1.10	-0.94						
	PRKCH	0.80	0.70	0.62	-0.88	-0.81	-0.80	-0.68	-0.60	-0.96	-0.74	1.04	-0.88	-0.68	-0.61	-0.78	-0.80	-0.83	1.08	1.00	1.23	-0.92	-0.88	-0.81	-0.89	-0.92	-0.85	-0.77	-0.61	1.15	0.93	-0.48	-0.72	-0.92					
	CHST2	0.68	1.64	-0.64	-0.68	1.03	-0.94	-0.80	-0.88	-0.80	-0.66	-0.76	-0.53	-0.53	-0.60	-0.76	-0.76	-0.83	1.09	-0.90	-0.81	-0.87	-0.79	-0.94	-0.88	-0.71	-0.69	-0.87	1.00	-0.75	-0.42	-0.84	-0.98						
	Genes with higher expression level	STIP1	0.68	0.78	-0.68	-0.83	-0.85	-0.80	-0.40	-0.92	-0.82	-0.68	-0.72	1.15	-0.37	-0.68	-0.82	1.02	1.84	-0.58	-0.80	-0.93	-0.97	-0.74	-0.75	-0.44	1.01	-0.68	-0.78	-0.38	-0.87	-0.89	-0.64	1.32	-0.77				
		PPARA	0.87	-0.76	-0.87	1.01	-0.82	-0.80	-0.88	-0.87	-0.95	1.15	-0.62	-0.68	-0.72	-0.71	-0.80	-0.82	1.45	-0.80	-0.65	-0.81	-0.67	1.12	-0.62	-0.76	-0.83	-0.80	-0.72	-0.83	-0.71	1.33	-0.80	-0.63	-0.87	-0.82			
		CDJ2	0.59	1.24	-0.51	1.40	-0.87	1.09	-0.88	-0.78	-0.80	-0.80	-0.80	1.16	-0.69	-0.38	-0.81	1.19	1.12	-0.61	-0.61	1.40	-0.74	1.04	-0.84	-0.82	-0.81	-0.85	-0.84	-0.57	-0.83	-0.78	1.04	-0.65	-0.48	-0.85	-0.69		
		NPR2L	0.77	0.70	-0.67	-0.76	-0.70	-0.68	-0.72	-0.75	-0.78	-0.78	-0.82	-0.82	-0.82	-0.82	-0.81	-0.81	1.19	1.12	-0.61	-0.61	1.40	-0.74	1.04	-0.84	-0.82	-0.85	-0.84	-0.57	-0.83	-0.78	1.04	-0.65	-0.48	-0.85	-0.69		
		NFATC3	0.80	-0.75	-0.89	-0.99	-0.79	-0.53	-0.80	-0.81	1.10	-0.78	-0.71	1.31	-0.56	1.11	-0.85	-0.62	-0.78	1.11	-0.85	-0.62	-0.78	-0.81	-0.85	-0.85	-0.99	1.36	-0.68	-0.68	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88		
		PSMC5	0.84	1.17	0.84	-0.99	-0.89	-0.77	-0.82	-0.82	-0.82	-0.82	-0.82	1.03	1.26	-0.88	-0.73	1.20	-0.73	1.08	1.19	-0.88	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82		
		LBC	0.68	1.02	1.07	-0.85	-0.81	1.28	-0.75	-0.82	1.38	-0.95	-0.97	1.31	-0.92	-0.80	-0.70	-0.72	1.03	-0.88	-0.75	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88		
		IPF1	0.85	1.47	1.56	-0.81	-0.98	1.28	-0.78	-0.84	1.04	-0.73	-0.83	1.04	-0.85	-0.86	-0.86	-0.86	1.02	1.17	1.23	-0.69	-0.89	-0.99	1.22	-0.78	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		TSC22	0.80	1.11	1.33	1.06	1.61	1.34	-0.51	-0.52	1.02	-0.88	-0.88	1.02	-0.88	-0.88	-0.88	-0.88	1.02	1.17	1.23	-0.69	-0.89	-0.99	1.22	-0.78	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		WNT1	0.80	0.82	-0.69	-0.75	-0.79	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	-0.82	1.02	1.17	1.23	-0.69	-0.89	-0.99	1.22	-0.78	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		TDR	0.80	0.90	0.91	-0.92	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	1.02	1.17	1.23	-0.69	-0.89	-0.99	1.22	-0.78	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		STAT3	0.70	0.72	-0.81	1.04	-0.71	1.02	-0.35	1.25	-0.88	-0.88	-0.88	1.02	-0.88	-0.88	-0.88	-0.88	1.02	1.17	1.23	-0.69	-0.89	-0.99	1.22	-0.78	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		UGT1A6	0.88	-0.76	-0.87	-0.86	-0.80	1.15	-0.68	-0.78	1.02	1.01	1.01	-0.88	-0.88	-0.88	-0.88	-0.88	1.02	1.17	1.23	-0.69	-0.89	-0.99	1.22	-0.78	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		CCND	1.15	-0.95	-0.82	-1.20	-0.78	1.34	-0.88	-0.78	1.07	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	1.02	1.17	1.23	-0.69	-0.89	-0.99	1.22	-0.78	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		ATRX	0.96	1.03	0.73	1.02	-0.98	-0.77	-0.68	-0.98	-0.98	-0.98	-0.98	1.27	1.47	-0.88	-0.71	-0.82	1.02	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		GRB10	1.31	1.19	1.14	1.24	1.16	1.93	1.12	1.19	-0.90	1.27	1.47	-0.88	-0.71	-0.82	1.02	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		ALDH8	1.93	1.00	1.22	0.91	1.10	-0.94	1.31	-0.87	1.24	1.18	1.75	1.08	1.54	-0.75	-0.75	1.48	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94	-0.94
		SCY45	1.68	2.10	1.66	0.92	1.48	3.54	2.08	1.35	1.97	1.49	2.03	1.03	1.42	-0.83	2.06	1.68	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88
		RBPS	1.59	1.20	1.54	1.05	1.10	1.41	1.58	-0.91	1.35	1.02	1.85	-0.94	1.08	-0.93	1.69	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88
		CASP8	1.80	1.14	1.42	1.13	1.12	1.94	1.69	-0.90	1.32	-0.91	1.35	-0.76	-0.90	1.14	-0.78	1.56	1.28	1.93	1.11	1.39	1.05	1.36	1.26	1.78	-0.88	1.44	1.18	1.00	1.40	1.00	1.08	1.79	1.84	1.31	1.64	1.31	
		CP2	1.47	1.04	1.20	0.82	1.76	1.46	1.42	-0.90	1.21	-0.91	1.35	-0.76	-0.90	1.00	-0.86	1.77	1.30	1.61	1.21	1.27	-0.84	1.39	1.07	1.73	-0.87	1.14	1.00	1.04	1.42	1.13	1.13	1.73	1.84	1.31	1.64	1.31	
		CYPBB1	1.20	1.06	1.21	1.05	1.28	1.51	1.48	-0.82	1.33	1.15	1.41	-0.85	1.08	-0.86	2.00	1.45	2.30	0.70	-0.87	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		TNFRSF9	1.29	1.41	1.20	1.20	1.15	1.70	1.48	-0.82	1.33	1.15	1.41	-0.85	1.08	-0.86	2.00	1.45	2.30	0.70	-0.87	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	-0.88	
		KARP1	1.37	1.48	1.32	0.84	1.18	1.20	1.35	-0.70	1.18	1.42	1.72	-0.64	-0.69	1.28	1.26	1.32	1.60	1.53	1.29	-0.85	1.05	1.22	1.52	1.69	-0.82	1.31	1.16	1.14	1.33	0.92	1.23	1.96	1.23	1.28	1.28		
		NFKBIA	1.57	1.28	1.31	1.21	1.26	1.10	1.81	1.07	1.21	1.32	1.12	-0.85	1.63	-0.94	1.72	1.09	1.49	1.59	1.13	-0.84	1.13	1.17	1.41	-0.82	1.28	1.28	1.28	1.28	1.28	1.28	1.28	1.28	1.28	1.28	1.28	1.28	
		CHST1	1.07	0.89	0.92	1.09	1.82	1.18	1.05	2.15	1.45	2.87	0.74	-0.28	1.09	1.98	1.58	2.40	2.16	2.13	-0.64	1.12	1.47	1.65	1.60	-0.88	1.88	1.15	3.73	1.23	3.36	1.56	1.72	1.69	0.96	0.96	0.96		
		IL1R2	0.80	0.83	1.39	1.52	1.69	1.13	1.57	1.02	1.02	2.39	1.08	-0.40	1.42	1.57	1.25	1.99	1.38	2.22	-0.78	-0.70	1.65	2.43	-0.48	1.72	2.36	2.29	3.64	1.67	1.11	1.18	2.22	2.66	0.96	0.96			
		SULT1C1	1.29	1.16	1.23	1.21	1.38	1.81	2.17	-0.84	1.21	1.16	1.37	1.28	-0.48	1.31	-1.00	1.00	-0.67	1.84	1.21	-0.94	-0.95	1.71	1.59	1.12	1.31	1.91	1.29	1.60	1.27	1.09	1.10	1.25	1.89	1.21	1.21		
		IGFBP5	1.09	1.16	1.23	1.21	1.38	1.81	2.17	-0.84	1.21	1.16	1.37	1.28	-0.48	1.31	-1.00	1.00	-0.67	1.84	1.21	-0.94	-0.95	1.71	1.59	1.12	1.31	1.91	1.29	1.60	1.27	1.09	1.10	1.25	1.89	1.21	1.21		
		SSS1	1.54	1.64	1.24	1.45	1.83	1.01	2.																														

Fig 2

Gene	PA group																	PB group																
	#01	#02	#03	#07	#12	#14	#15	#18	#21	#24	#25	#26	#28	#29	#31	#32	#33	#04	#05	#06	#08	#10	#11	#13	#15	#17	#19	#20	#22	#23	#25	#27	#30	
ADP1	1.01	1.05	1.09	0.65	1.38	1.70	-0.60	-0.82	-0.92	-0.43	-0.75	-0.84	-0.98	-0.45	-0.48	-0.94	1.32	1.15	1.39	1.55	1.19	1.63	1.25	1.16	1.51	1.55	1.59	1.70	3.65	1.43	1.71	1.14		
PAP	1.24	0.89	0.96	0.88	-0.88	1.43	0.06	-0.67	-0.67	-0.67	1.06	0.34	0.84	1.06	0.39	0.88	0.80	1.34	1.26	1.23	1.49	1.26	1.49	1.26	1.49	1.26	1.49	1.26	1.49	1.26	1.49	1.26	1.49	
P2Y5	2.92	1.09	0.96	1.11	0.79	1.40	1.00	-0.32	-0.92	-0.84	0.94	1.52	-0.87	0.93	0.92	1.25	1.97	1.81	1.66	1.39	1.36	1.45	2.05	1.24	1.60	2.66	4.21	2.54	1.26	2.03	6.31	1.34		
TAZF2	2.32	0.68	0.99	0.93	1.23	2.16	1.13	-0.37	-0.95	1.30	0.81	1.45	0.95	0.20	0.38	1.22	1.87	2.30	1.32	1.49	1.23	1.41	1.33	2.83	1.90	1.21	2.41	4.68	2.24	2.98	1.79	1.29		
POLR2B	1.06	0.71	0.75	0.69	1.10	1.00	1.43	0.43	0.72	0.78	0.72	0.73	0.84	0.75	1.22	1.14	1.19	1.19	1.03	1.47	0.96	1.16	1.32	0.91	1.28	1.24	1.35	2.45	1.21	1.29	0.92	1.16		
HSPD1	1.37	0.68	0.83	1.12	1.43	1.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43	0.43		
PKAC3	1.43	0.74	0.72	0.72	1.03	0.88	1.17	0.88	1.03	0.78	0.75	1.14	0.95	0.74	0.75	1.09	1.30	1.32	1.63	1.59	1.49	1.04	1.43	1.51	1.05	1.47	1.36	1.33	1.06	2.71	1.49	1.02	1.09	
COX7B	1.63	0.66	0.62	0.90	1.31	1.57	1.79	1.19	0.94	1.15	0.92	1.09	0.97	1.17	1.14	0.87	1.25	1.45	1.36	1.08	1.58	1.54	1.14	1.84	0.91	1.68	1.23	1.26	1.16	1.93	1.46	0.99	0.92	
COX5C	1.85	0.94	0.99	1.25	1.32	1.42	0.86	-0.83	-0.35	-0.87	1.05	0.71	0.78	0.78	0.50	1.14	1.02	1.96	1.63	2.37	0.85	4.01	1.32	1.75	3.56	3.11	1.89	1.83	4.63	2.51	0.83	0.99		
FNBP1	1.71	0.82	1.12	0.78	0.47	1.66	-0.82	-0.88	-1.11	-0.99	1.01	1.60	0.88	0.28	-0.44	1.03	1.80	1.84	1.55	3.59	2.08	1.91	1.11	1.57	1.93	1.03	1.27	1.99	2.35	1.83	3.58	1.38	1.07	
FNFRS16	1.38	0.71	0.71	0.99	0.66	1.84	0.72	1.04	0.63	1.23	1.48	2.52	0.68	0.28	-0.44	1.03	1.80	1.84	1.55	3.59	2.08	1.91	1.11	1.57	1.93	1.03	1.27	1.99	2.35	1.83	3.58	1.38	1.07	
RBP1	1.08	1.13	1.21	1.03	1.00	1.65	0.84	0.94	1.09	1.21	1.09	1.21	0.98	0.92	1.14	0.87	1.25	1.45	1.36	1.08	1.58	1.54	1.14	1.84	0.91	1.68	1.23	1.26	1.16	1.93	1.46	0.99	0.92	
CDG10	1.65	0.81	0.74	1.07	1.31	1.31	0.84	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	0.61	
NR1H4	0.86	0.94	0.74	1.12	1.24	0.93	0.86	0.83	0.82	0.82	0.88	1.04	0.96	0.73	0.41	0.90	1.57	1.44	0.87	2.43	1.57	1.43	1.05	1.24	1.42	1.21	1.43	1.69	1.89	1.65	1.10	0.88		
GNL10	1.80	0.58	0.81	0.51	0.22	0.98	0.90	1.07	1.34	0.83	1.14	0.73	0.84	0.70	0.72	0.99	1.20	1.31	1.15	1.01	-0.84	1.01	1.42	0.89	1.41	1.20	1.66	0.64	0.84	1.93	1.38	0.70	2.20	
TLR1	0.80	0.51	0.85	0.42	0.22	1.09	0.59	1.10	1.14	1.27	0.83	0.95	0.95	0.95	0.95	0.95	1.65	1.12	2.87	1.92	1.79	1.19	1.21	1.50	2.09	0.64	0.84	1.93	1.38	0.70	2.20	1.44		
PTEN	1.41	0.66	0.86	0.69	0.72	1.27	0.96	1.02	1.07	1.05	0.92	1.08	0.77	0.37	0.62	0.77	1.18	1.32	1.24	1.92	1.19	1.19	1.21	1.50	2.09	0.64	0.84	1.93	1.38	0.70	2.20	1.44		
HRSA	1.42	0.70	0.71	0.84	0.74	1.23	1.10	0.64	1.04	1.11	1.19	1.22	0.93	0.31	0.62	0.77	1.18	1.32	1.24	1.92	1.19	1.19	1.21	1.50	2.09	0.64	0.84	1.93	1.38	0.70	2.20	1.44		
TANK	1.22	0.77	0.80	0.63	1.03	1.20	1.26	1.13	1.11	0.98	0.92	1.19	0.85	0.92	1.14	0.87	1.25	1.45	1.36	1.08	1.58	1.54	1.14	1.84	0.91	1.68	1.23	1.26	1.16	1.93	1.46	0.99	0.92	
FNFR1	1.08	0.59	0.81	0.45	0.73	1.09	1.05	1.32	0.85	0.94	0.93	1.53	0.88	0.32	0.84	0.75	1.21	1.10	1.19	1.33	1.73	0.88	0.92	1.03	1.11	1.47	0.73	0.55	2.08	1.92	1.17	1.23	1.16	
CLDN1	1.19	1.40	1.12	0.29	0.86	1.36	0.67	0.63	0.58	1.84	0.72	1.16	0.78	0.38	0.84	0.75	1.21	1.10	1.19	1.33	1.73	0.88	0.92	1.03	1.11	1.47	0.73	0.55	2.08	1.92	1.17	1.23	1.16	
PTPRC	0.98	1.01	0.82	0.63	0.90	1.29	1.00	0.71	0.84	1.16	1.08	0.93	0.98	0.74	0.41	0.99	1.69	1.09	1.15	1.65	2.25	1.01	1.46	1.32	1.81	1.12	1.55	2.08	1.92	1.17	1.23	1.16		
PI3K	1.18	0.97	0.74	0.22	0.59	0.84	0.94	1.03	0.99	1.07	1.04	0.95	0.98	0.75	0.41	0.99	1.69	1.09	1.15	1.65	2.25	1.01	1.46	1.32	1.81	1.12	1.55	2.08	1.92	1.17	1.23	1.16		
ARNTL	1.03	0.68	0.58	0.47	1.46	1.09	0.93	1.09	0.67	0.90	1.10	1.04	0.99	1.07	1.04	0.99	1.69	1.09	1.15	1.65	2.25	1.01	1.46	1.32	1.81	1.12	1.55	2.08	1.92	1.17	1.23	1.16		
FNFR1	0.79	0.78	0.87	0.43	0.41	0.92	0.92	0.93	1.04	0.99	1.07	1.04	0.99	1.07	1.04	0.99	1.69	1.09	1.15	1.65	2.25	1.01	1.46	1.32	1.81	1.12	1.55	2.08	1.92	1.17	1.23	1.16		
FNFR1	0.78	1.30	1.02	0.32	0.11	0.74	0.67	1.30	0.68	1.07	0.72	0.90	0.97	0.74	0.41	0.99	1.69	1.09	1.15	1.65	2.25	1.01	1.46	1.32	1.81	1.12	1.55	2.08	1.92	1.17	1.23	1.16		
KRAS2	1.12	1.03	0.80	0.57	0.60	0.67	0.68	0.45	1.03	0.86	0.93	0.93	0.93	0.93	0.93	0.93	1.69	1.09	1.15	1.65	2.25	1.01	1.46	1.32	1.81	1.12	1.55	2.08	1.92	1.17	1.23	1.16		
PRK3A	0.90	0.97	0.90	0.66	0.72	1.04	0.67	0.87	1.02	0.96	0.92	0.96	0.96	0.96	0.96	0.96	1.69	1.09	1.15	1.65	2.25	1.01	1.46	1.32	1.81	1.12	1.55	2.08	1.92	1.17	1.23	1.16		
PCNG1	1.19	1.03	0.65	0.61	0.77	1.09	1.01	0.48	0.78	1.02	0.96	0.92	0.96	0.96	0.96	0.96	1.69	1.09	1.15	1.65	2.25	1.01	1.46	1.32	1.81	1.12	1.55	2.08	1.92	1.17	1.23	1.16		
PRKCL2	0.78	0.96	0.90	0.65	0.82	0.91	0.68	1.05	0.81	1.14	0.90	1.26	0.65	1.06	0.67	0.87	1.17	1.21	1.21	1.29	2.09	1.40	1.24	0.85	1.21	1.26	1.06	0.99	1.61	1.10	1.23	0.89	1.08	
INCL	1.13	1.19	1.00	1.02	0.58	0.91	0.68	1.05	1.01	0.81	0.88	0.86	1.11	0.92	0.85	0.77	1.17	1.21	1.21	1.29	2.09	1.40	1.24	0.85	1.21	1.26	1.06	0.99	1.61	1.10	1.23	0.89	1.08	
GNFR1	1.18	0.74	0.88	0.82	0.74	0.78	1.53	0.83	1.14	0.90	1.26	0.65	1.06	0.67	0.87	1.17	1.21	1.21	1.29	2.09	1.40	1.24	0.85	1.21	1.26	1.06	0.99	1.61	1.10	1.23	0.89	1.08		
GNFR2	0.68	1.20	1.03	0.80	0.92	0.91	1.13	1.17	0.81	1.05	1.18	0.96	1.14	1.61	1.24	0.83	0.85	0.94	0.70	0.59	0.60	0.50	0.98	0.85	0.72	0.72	0.50	0.49	0.70	0.52	0.63	0.67	0.56	1.02
GNFR2	0.75	1.61	0.90	0.93	0.96	0.75	1.11	1.03	1.28	1.03	0.97	0.97	1.22	1.77	1.23	1.04	0.75	0.94	0.81	0.81	0.81	0.81	0.81	0.81	0.81	0.81	0.81	0.81	0.81	0.81	0.81	0.81	0.81	
GNFR2	0.81	1.31	1.00	1.07	0.97	0.89	1.12	1.40	1.17	1.09	1.18	0.96	1.11	1.09	1.38	1.15	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	0.90	
GNFR2	1.01	1.82	0.97	1.44	0.90	1.13	0.93	0.65	1.35	1.04	1.02	0.98	1.16	1.55	1.26	2.20	1.55	1.00	0.76	0.88	0.93	0.06	1.22	0.70	0.70	0.50	0.49	0.70	0.52	0.63	0.67	0.56	1.02	
GNFR2	0.94	1.79	1.47	1.89	0.91	1.04	1.01	0.91	1.09	0.81	1.04	1.22	0.98	1.18	1.46	0.88	0.83	1.00	0.76	0.88	0.93	0.06	1.22	0.70	0.70	0.50	0.49	0.70	0.52	0.63	0.67	0.56	1.02	
GNFR2	1.24	2.73	1.20	1.87	1.68	1.15	1.21	1.10	1.04	1.11	0.98	0.98	1.26	1.59	1.53	0.86	0.83	1.00	0.76	0.88	0.93	0.06	1.22	0.70	0.70	0.50	0.49	0.70	0.52	0.63	0.67	0.56	1.02	
GNFR2	0.95	0.99	0.83	1.19	1.79	0.89	1.38	0.85	0.84	0.75	0.92	0.92	1.08	1.31	1.40	0.85	0.83	1.00	0.76	0.88	0.93	0.06	1.22	0.70	0.70	0.50	0.49	0.70	0.52	0.63	0.67			

Fig 3

Sample	#02		#07		#14		#16		#29		#31		#33	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
POLR2B	0.71	2.30	0.69	1.29	1.00	1.04	0.49	1.90	1.08	1.27	0.38	3.00	1.22	1.36
PAP	0.89	2.07	0.88	1.16	1.43	0.98	0.57	1.32	1.06	1.07	0.39	4.25	0.80	1.96
TOP2B	0.78	1.97	0.88	0.76	1.11	1.03	0.35	1.45	0.89	1.40	0.32	3.03	1.17	1.32
ADAM17	0.85	1.76	0.79	0.79	1.41	0.98	0.39	1.57	0.98	1.25	0.40	2.06	1.22	1.42
P2Y5	1.09	2.88	1.11	1.39	1.40	0.80	0.32	4.02	0.87	2.03	0.33	7.35	1.25	2.11
TAF2F	0.68	4.16	0.93	1.51	2.16	0.91	0.37	2.80	0.95	3.03	0.20	8.46	1.22	2.66
ADH5	1.01	4.61	1.58	0.97	1.90	0.75	0.28	2.12	1.22	2.40	0.39	4.42	0.98	2.59
TCB1L	0.99	2.07	1.08	1.00	1.22	1.02	0.39	1.90	1.17	2.01	0.49	2.67	1.07	1.90
RBBP7	1.06	3.35	1.08	1.15	1.13	1.02	0.54	1.79	1.30	1.32	0.39	2.37	1.30	1.45
HSPA4	0.92	3.09	1.23	1.45	1.03	1.03	0.44	1.39	0.96	1.18	0.39	1.83	1.02	1.52
HSPD1	0.98	5.19	1.12	1.04	1.43	1.01	0.43	1.32	0.94	1.92	0.36	2.38	1.30	1.58
COX7A2L	1.00	2.58	0.91	0.97	0.86	0.69	0.31	2.21	0.99	1.35	0.41	2.08	0.89	1.58
FCER1A	1.35	4.04	0.50	0.54	1.79	0.94	0.50	5.98	0.84	2.34	0.47	5.60	1.51	2.07
TAF2G	0.80	3.78	0.97	0.71	1.28	0.66	0.37	3.76	1.07	1.63	0.44	1.55	1.47	1.37
API1	1.05	1.88	0.55	1.66	1.70	0.99	0.62	1.40	0.98	1.46	0.45	3.70	0.94	1.38
ATP2G1	1.01	1.72	0.63	1.60	1.29	1.03	0.71	1.51	0.96	1.11	0.49	2.36	0.95	1.06
COX6C	1.07	4.95	1.71	0.66	0.90	0.69	0.35	1.87	0.90	2.54	1.17	3.06	1.41	5.04
HSP1E1	0.89	7.35	2.33	0.75	1.65	0.72	0.42	1.20	0.87	2.48	0.96	2.38	1.48	2.91
ESD	1.28	2.90	1.45	0.66	1.50	0.87	0.54	1.36	1.61	2.18	0.87	2.36	1.38	2.40
HSBP1	0.94	3.52	1.25	0.90	1.42	0.87	0.63	1.73	0.95	1.66	0.67	2.15	1.03	2.06
ATP6J	1.15	2.94	2.20	0.67	2.01	0.90	0.36	2.50	0.83	2.76	0.74	3.63	1.16	3.40
THFSF10	0.72	4.28	2.19	1.44	2.73	1.24	0.73	1.95	0.97	3.74	0.65	3.29	0.95	3.49
NRF	1.03	2.58	0.96	1.06	1.22	1.55	0.55	1.36	1.12	1.31	0.63	2.31	1.22	1.47
PGK1	0.80	3.64	1.37	1.08	1.27	1.40	0.52	1.85	1.02	1.68	0.82	1.54	1.10	1.45
GZMA	0.88	7.84	1.23	0.82	0.86	0.73	0.30	4.67	1.31	1.79	0.45	7.88	0.97	5.41
COX7B	0.86	2.04	0.92	0.79	0.73	0.97	0.67	1.73	1.14	1.88	0.85	1.83	1.14	2.31
PIK3C3	0.74	2.97	1.31	1.24	1.79	1.00	0.54	1.32	1.02	1.89	0.51	2.55	1.13	1.57
FGF2	0.89	4.18	1.49	1.15	3.19	0.69	0.35	1.49	1.43	2.06	0.29	8.05	1.18	2.78
HSPA10	0.90	3.97	1.35	0.96	1.58	0.90	0.61	1.22	1.34	1.23	0.40	3.24	1.19	1.89
CASP5	0.83	2.03	1.06	1.04	1.55	0.87	0.65	1.25	1.28	1.50	0.59	1.67	1.01	1.75
HSPCA	0.52	11.19	3.04	0.94	3.14	0.71	0.27	0.87	0.80	5.63	0.48	10.91	1.14	5.31
CASP1	0.74	4.88	1.75	1.49	2.18	0.80	1.05	1.23	1.17	1.64	0.50	4.41	0.72	2.91
DAP3	1.00	2.21	1.20	1.16	1.22	0.92	0.84	1.05	1.22	1.06	0.81	2.83	1.07	1.51
TCB1	0.69	3.27	1.27	1.02	0.98	1.03	0.68	1.18	0.95	1.17	0.74	1.90	1.09	1.73
POLE	1.13	4.59	1.03	1.13	1.66	0.98	0.94	1.53	0.89	1.02	0.53	1.39	1.04	1.76
RAB4	1.00	2.10	1.00	0.99	0.88	0.82	0.73	1.29	0.91	1.70	0.78	2.06	1.22	1.74
HDAC1	0.98	1.57	1.07	1.04	1.08	1.05	0.99	1.27	1.03	1.12	0.72	1.47	1.08	0.99
RBBP6	0.98	2.15	1.69	0.99	1.46	1.09	1.48	1.62	1.01	2.23	0.48	2.49	1.03	2.18
RAB7L1	0.70	1.28	0.86	0.78	0.53	1.27	0.65	1.93	0.74	1.64	0.79	3.25	1.12	2.16
PPP3CC	0.91	0.98	0.81	1.22	0.95	0.45	2.32	0.96	1.98	1.29	1.98	1.29	1.17	1.64
SLC35A1	0.87	1.47	1.15	0.53	0.78	0.96	0.75	1.88	0.91	0.92	0.72	1.55	1.00	1.36
AP1S2	0.98	1.26	1.14	0.93	0.70	0.89	0.39	2.87	1.19	1.21	0.60	3.52	1.33	1.55
IL10RA	0.77	1.08	1.11	0.96	0.84	1.03	0.84	1.93	1.22	1.01	0.51	1.80	1.05	1.16
MSH6	0.89	1.92	0.74	0.84	0.63	1.23	0.73	1.61	0.94	0.80	0.43	1.62	1.12	0.87
PTPN7	0.98	1.45	0.86	1.01	0.75	1.00	0.66	1.35	1.20	1.04	0.77	1.14	1.22	1.05
CDC10	0.81	2.57	1.07	1.62	1.31	1.11	0.81	1.52	0.98	1.96	0.73	4.27	0.90	2.18
RBBP4	1.12	1.41	0.71	1.76	0.78	1.30	0.82	1.29	1.00	1.07	0.37	2.68	1.25	1.07
TOPBP1	0.90	1.43	0.61	1.32	0.60	1.36	0.89	1.83	0.90	1.27	0.30	3.70	1.04	1.24
ITGB1	0.88	2.16	0.47	2.32	1.09	1.06	1.09	1.00	0.72	1.08	0.24	4.66	0.93	1.12
RAP1A	1.20	2.74	0.84	1.79	1.23	1.17	0.64	1.87	0.95	1.18	0.31	3.42	0.86	1.26
CLK1	1.40	2.16	0.29	1.90	1.36	0.60	0.63	2.36	0.79	1.48	0.11	6.18	0.99	1.11
IFNGR1	0.82	1.55	0.78	2.31	1.66	0.84	0.88	1.80	0.89	1.51	0.29	6.91	1.06	1.46
TNFRSF6	0.71	2.60	0.99	1.70	1.84	1.03	1.04	2.02	0.66	1.42	0.38	4.86	0.80	1.18
ALDH10	1.00	2.06	0.78	1.20	0.70	1.27	0.83	1.82	0.63	1.12	0.38	2.39	1.06	1.24
ARNTL	0.69	1.79	0.53	1.25	0.82	0.98	1.04	2.13	0.75	1.22	0.36	2.15	0.86	1.19
IRS4	0.77	1.77	0.63	1.58	1.20	1.10	1.13	1.80	0.69	1.43	0.33	3.57	0.85	1.11
GNG10	0.58	2.31	0.51	1.61	0.98	1.16	1.07	5.34	0.84	1.32	0.37	5.06	0.75	1.59
RPC39	1.38	1.24	0.82	1.01	1.02	1.09	0.74	1.51	1.18	1.43	0.46	2.19	1.06	1.57
PIK3CA	0.97	1.75	0.66	1.46	1.04	1.27	0.67	1.39	1.00	1.10	0.61	2.20	0.94	0.79
CTNNB1	0.74	1.50	0.62	1.76	0.78	1.63	0.83	1.63	1.06	1.11	0.61	2.14	0.97	1.18
KRAS2	1.03	1.35	0.57	1.15	0.87	1.28	0.45	1.97	0.76	0.87	0.32	2.71	0.85	0.83
MAP3K7	1.12	1.49	0.53	1.08	0.74	1.08	0.49	1.91	0.84	0.98	0.20	2.78	0.99	0.89
PRKCH	1.02	1.22	0.72	1.38	0.60	1.09	0.53	1.37	1.00	0.73	0.42	2.10	0.96	0.97
NR3C1	0.78	0.99	0.43	1.66	0.92	1.24	0.60	2.10	0.74	0.89	0.28	2.52	0.84	0.80
ING1	1.19	0.67	1.02	1.28	0.83	1.02	1.01	1.39	0.92	1.28	0.59	1.73	1.00	1.11
RBBP1	1.04	1.54	0.95	1.88	1.16	1.24	1.42	1.80	0.92	1.22	1.62	3.91	0.99	1.28
INS	0.80	0.56	0.73	0.74	0.83	1.15	1.02	0.88	0.96	0.83	1.61	0.54	1.35	0.75
CD163	0.88	0.45	0.64	0.89	0.81	1.09	1.24	0.93	1.49	0.57	1.04	0.68	0.97	0.53
SKK2	1.16	0.33	1.17	1.09	0.79	1.03	1.71	0.79	1.20	0.64	1.74	0.61	1.02	0.66
HTE	1.61	0.62	0.93	0.77	0.75	0.91	1.03	0.66	1.22	0.90	1.77	0.47	1.04	0.76
KARPI	1.48	1.05	1.35	0.77	0.93	1.02	1.43	0.84	1.13	0.91	1.82	0.55	1.18	0.91



Fig 5

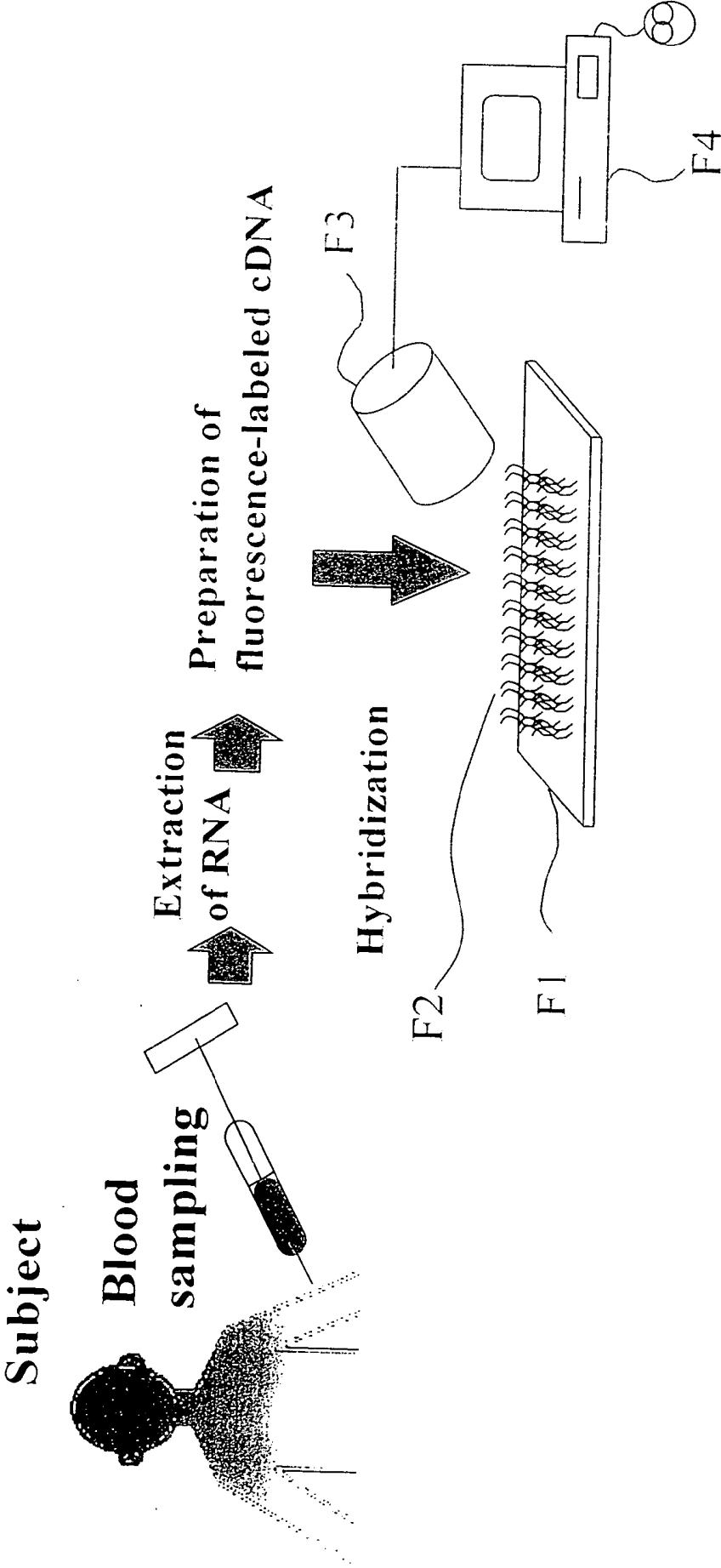


Fig 6

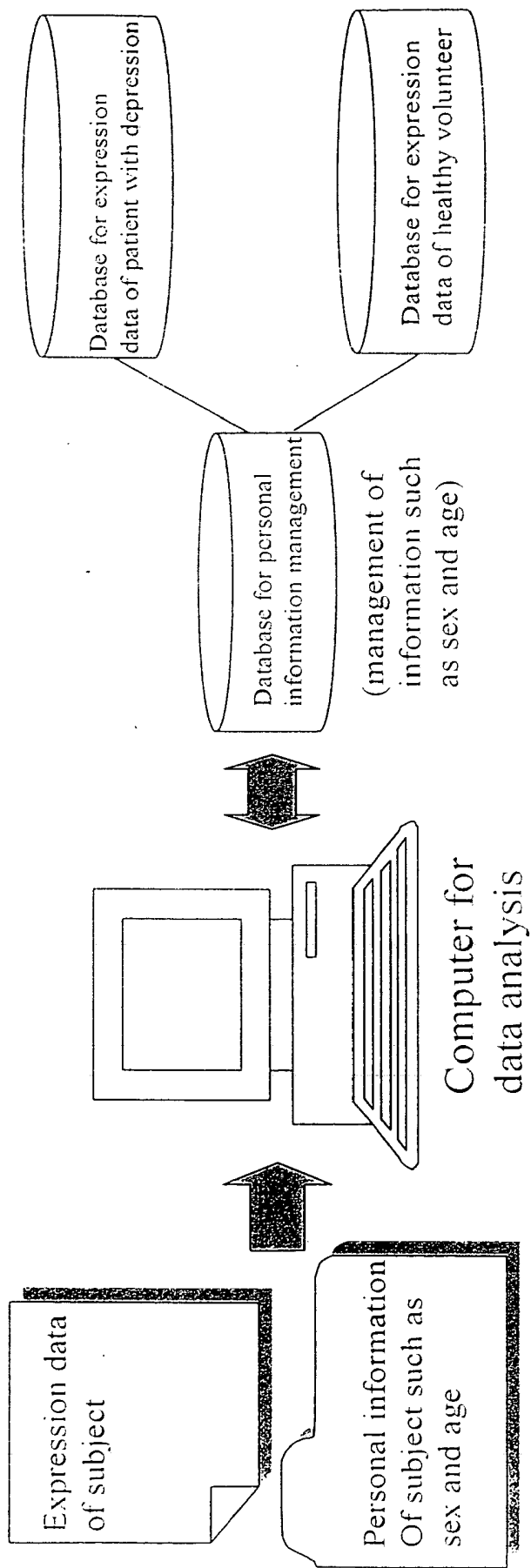


Fig 7

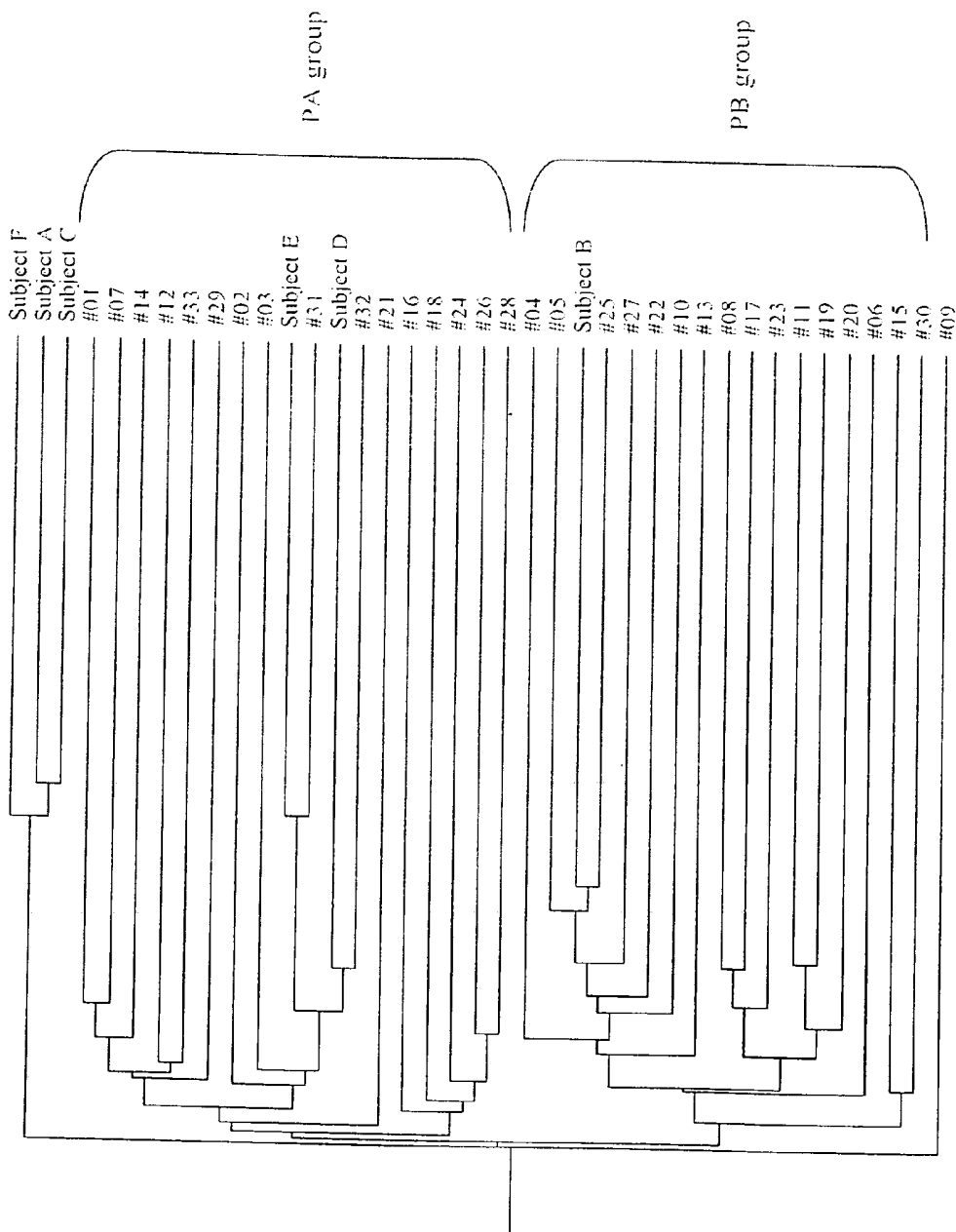


Fig 8

Gene	#02		#07		#14		#18		#25		#31		#33		#35		#36	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
	POLR2B	0.71	2.30	0.69	1.29	1.00	1.04	0.49	1.90	1.08	1.27	0.38	3.00	1.22	1.36	0.38	2.13	0.58
PAP	0.89	7.07	0.88	1.16	1.43	0.58	0.57	1.22	1.06	1.07	0.39	4.25	0.80	1.96	0.39	2.60	0.42	1.43
TOP2B	0.78	1.97	0.76	1.11	1.03	0.35	1.45	0.89	1.40	0.32	3.03	1.17	1.32	0.39	1.99	0.46	1.90	2.14
ADAM17	0.85	1.76	0.79	1.41	0.98	0.39	1.57	0.98	1.25	0.40	2.06	1.22	1.42	0.42	1.36	0.42	1.36	2.14
P2Y5	1.08	2.88	1.11	1.39	1.40	0.80	0.32	4.02	0.87	2.03	0.33	7.35	1.25	2.11	0.41	4.89	0.53	1.85
TAF2	0.66	4.16	0.93	1.51	2.16	0.91	0.37	2.80	0.95	3.03	0.20	8.45	1.22	2.36	0.20	3.05	0.38	2.71
ADMS	1.01	4.61	1.58	1.97	1.90	0.79	0.35	2.12	1.22	2.40	0.39	4.42	0.98	2.59	0.48	2.95	0.61	1.84
TGEBL	0.89	2.07	1.08	1.22	1.02	0.39	1.90	1.17	2.01	0.49	2.67	1.07	1.90	0.54	1.96	0.99	1.43	1.84
RBPP1	1.06	3.35	1.08	1.15	1.10	0.2	0.54	1.78	1.30	3.7	0.39	2.37	1.30	1.45	0.48	1.99	0.88	1.11
HSP44	0.92	3.09	1.23	1.45	1.03	0.44	1.38	0.96	1.18	0.59	1.63	1.07	1.52	0.55	1.62	0.79	1.14	1.14
HSPD1	0.98	5.19	1.12	1.04	1.43	1.01	0.43	1.32	0.94	1.92	0.36	2.38	1.30	1.58	0.28	2.67	0.54	1.35
COX12L	1.00	2.58	0.77	0.97	0.86	0.31	2.21	0.99	1.35	0.89	1.20	2.06	0.89	1.58	0.42	2.11	0.68	1.16
FCERIA	1.35	4.04	0.50	0.54	1.79	0.94	0.50	5.98	0.84	2.34	0.47	5.60	1.51	2.07	0.37	1.64	0.66	1.66
TAF2G	0.80	3.78	0.97	0.71	1.28	0.65	0.37	3.76	1.07	1.63	0.44	1.55	1.47	1.32	0.59	2.10	0.50	1.46
API1	1.05	1.88	0.55	1.66	1.70	0.89	0.62	1.40	0.98	1.48	0.45	3.70	0.84	1.38	0.42	0.98	0.39	1.63
ATP2D1	1.01	1.72	0.63	1.60	1.29	1.03	0.71	1.51	0.96	1.11	0.49	2.36	0.55	1.06	0.45	1.13	0.67	1.12
COX6C	1.07	4.85	1.71	0.86	0.90	0.69	0.35	1.87	0.90	2.54	1.17	3.06	1.41	5.04	1.04	1.86	0.92	2.26
HSP1	0.89	7.35	2.33	0.75	1.65	0.72	0.42	1.20	0.87	2.48	0.96	2.38	1.48	2.91	0.76	1.37	0.68	2.02
ESD	1.28	2.80	1.45	0.66	1.90	0.87	0.54	1.36	1.61	2.18	0.87	2.36	1.38	2.40	1.11	1.39	1.04	1.55
HSPB1	0.94	3.52	1.25	0.90	1.42	0.87	0.63	1.73	0.95	1.66	0.67	2.15	1.03	2.05	0.95	1.72	0.71	1.31
ATP6J	1.15	2.94	2.20	0.67	2.01	0.90	0.36	2.90	0.83	2.76	0.74	3.63	1.16	3.40	1.04	2.08	0.63	2.95
TNFSF10	0.72	4.28	2.19	1.44	2.73	1.24	0.73	1.95	0.97	3.74	0.65	3.29	1.95	3.48	1.27	5.11	0.63	1.41
NRF	1.03	2.58	0.96	1.06	1.22	1.55	0.55	1.38	1.12	1.31	0.63	2.31	1.22	1.47	1.06	1.17	0.83	1.41
PKK1	0.80	3.64	1.37	1.08	1.27	1.40	0.52	1.85	1.02	1.68	0.99	1.84	1.10	1.45	1.18	1.40	1.15	1.15
CD3A	0.58	7.84	1.23	0.92	0.88	0.73	0.30	4.67	1.31	1.79	0.45	7.88	0.97	5.41	0.42	2.11	0.55	2.54
COX7B	0.86	2.04	0.92	0.78	0.73	0.97	0.67	1.73	1.14	1.88	0.85	1.83	1.14	2.31	0.86	1.38	0.91	1.07
TAF3C	0.94	2.97	1.31	1.24	1.78	0.90	0.54	1.32	1.02	1.89	0.51	2.55	1.13	1.57	0.58	2.04	0.53	1.85
FOF2	0.89	4.18	1.49	1.15	3.19	0.68	0.35	1.49	1.43	2.06	0.29	6.05	1.18	2.78	0.36	2.52	0.48	2.91
HSPA10	0.90	3.97	1.35	0.96	1.58	0.90	0.61	1.22	1.34	1.23	0.40	3.24	1.19	1.89	0.42	2.03	0.47	2.08
CASP5	0.83	2.03	1.06	1.04	1.55	0.87	0.65	1.25	1.28	1.50	0.59	1.67	1.01	1.75	0.61	1.52	0.65	1.23
HSPCA	0.52	11.19	3.04	0.94	3.14	0.71	0.27	0.87	0.80	5.63	0.48	10.91	1.14	5.31	0.17	11.03	0.24	4.94
CASP1	0.74	4.88	1.75	1.49	2.18	0.80	1.05	1.23	1.17	1.64	0.50	4.41	0.72	2.91	0.61	3.42	0.68	1.57
DAP3	1.00	2.21	1.20	1.16	1.22	0.92	0.84	1.05	1.22	1.06	0.61	2.83	1.07	1.51	0.76	1.29	0.72	1.40
TEEB1	0.69	3.27	1.27	1.02	0.99	1.03	0.68	1.18	0.95	1.17	0.74	1.90	1.09	1.73	0.70	1.63	0.97	1.26
POLB	1.13	4.59	1.03	1.13	1.66	0.98	0.94	1.53	0.85	1.02	0.53	1.39	1.04	1.96	0.54	1.56	0.47	1.56
RAB4	0.90	2.10	1.00	0.99	1.08	0.82	0.73	1.29	0.81	1.70	0.78	2.06	1.22	1.74	0.91	3.63	1.02	1.31
HDAC1	0.98	1.57	1.07	1.04	1.08	1.05	0.99	1.27	1.03	1.12	0.72	1.47	1.08	0.99	0.85	1.44	1.13	1.16
RBPP1	0.58	2.15	1.69	0.99	1.46	1.09	1.48	1.62	1.01	2.23	0.48	2.49	1.03	2.18	0.43	3.04	0.95	0.75
RAB7L1	0.70	1.28	0.86	0.78	0.53	1.27	0.65	1.93	0.74	1.64	0.79	3.25	1.12	2.16	0.52	2.91	1.47	1.01
PPP3C	0.91	0.98	0.81	0.81	1.77	0.95	0.45	2.32	0.96	1.98	1.29	1.98	1.17	1.64	0.45	3.08	1.32	1.28
SLC35A1	0.87	1.47	1.15	0.53	0.78	0.96	0.75	1.88	0.91	0.92	0.72	1.55	1.80	1.36	0.91	2.61	0.87	1.39
ADPS2	0.88	1.26	1.14	0.93	0.70	0.89	0.99	2.87	1.18	1.21	0.60	3.52	1.33	1.55	0.76	2.25	0.87	1.33
IL10RA	0.77	1.08	1.11	0.96	0.84	1.03	0.84	1.93	1.27	1.01	0.51	1.89	1.05	1.16	0.59	1.58	1.13	1.20
MSH6	0.89	1.92	0.74	0.84	0.63	1.23	0.73	1.61	0.94	0.80	0.43	1.62	1.12	0.87	0.49	1.73	0.97	0.86
PTPN7	0.98	1.45	0.88	1.01	0.75	1.00	0.66	1.35	1.20	1.04	0.77	1.14	1.22	1.05	0.68	1.39	0.97	1.12
CDC10	0.81	2.57	1.07	1.62	1.31	1.11	0.61	1.52	0.98	1.86	0.73	4.27	0.90	2.18	0.59	5.56	0.43	1.62
RBPP1	1.12	1.41	0.71	1.76	0.78	1.30	0.82	1.29	1.00	1.07	0.37	2.68	1.25	1.07	0.27	4.44	0.59	1.24
TOPBP1	0.90	1.43	0.61	1.32	0.60	1.36	0.89	1.83	0.90	1.27	0.30	3.70	1.04	1.24	0.21	6.19	0.77	1.00
ITGB1	0.98	2.16	0.47	2.32	1.05	1.06	1.09	1.00	0.72	1.08	0.24	4.66	0.93	1.12	0.19	6.25	0.42	1.08
RAP1A	1.20	2.74	0.84	1.79	1.23	1.17	0.64	1.87	0.95	1.18	0.31	3.42	0.86	1.26	0.15	6.26	0.60	1.10
CLK1	1.40	2.16	0.28	1.90	1.36	0.60	0.63	2.36	0.78	1.48	0.11	6.18	0.89	1.11	0.14	15.05	0.22	2.01
IFNGR1	0.82	1.55	0.78	2.31	1.66	0.84	0.88	1.80	0.89	1.51	0.28	6.91	1.06	1.46	0.34	5.49	0.35	1.66
TNFRSF6	0.71	2.60	0.99	1.70	1.84	1.03	1.04	2.02	0.66	1.42	0.38	4.86	0.80	1.18	0.39	6.95	0.27	1.62
ALDH10	1.00	2.06	0.78	1.20	0.70	1.27	0.83	1.82	0.63	1.12	0.36	2.39	1.06	1.24	0.31	3.31	1.07	1.01
ARNTL	0.69	1.79	0.53	1.25	0.82	0.98	1.04	2.13	0.75	1.27	0.36	2.15	0.88	1.19	0.25	4.30	0.73	1.03
IRS4	0.77	1.71	0.63	1.58	1.20	1.10	1.13	1.80	0.89	1.43	0.33	3.57	0.85	1.11	0.27	4.89	1.15	1.19
GNGL10	0.58	2.31	0.51	1.61	0.88	1.16	1.07	5.34	0.84	1.32	0.37	5.06	0.75	1.39	0.29	7.65	0.89	1.27
RPC29	1.38	1.24	0.82	1.01	1.02	1.09	0.74	1.51	1.18	1.43	0.46	2.19	1.08	1.57	0.48	3.41	0.89	1.01
PKJCA	0.97	1.75	0.66	1.46	1.04	1.27	0.67	1.39	1.00	1.10	0.61	2.79	1.08	1.57	0.46	3.41	0.89	1.01
CTNNA1	0.74	1.50	0.82	1.76	0.78	1.63	0.83	1.63	1.06	1.11	0.61	2.14	0.87	1.18	0.35	2.98	0.71	0.92
KRAS3	1.03	1.35	0.57	1.15	0.87	1.28	0.45	1.97	0.76	0.87	0.32	2.71	0.85	0.83	0.35	2.98		



Fig 10

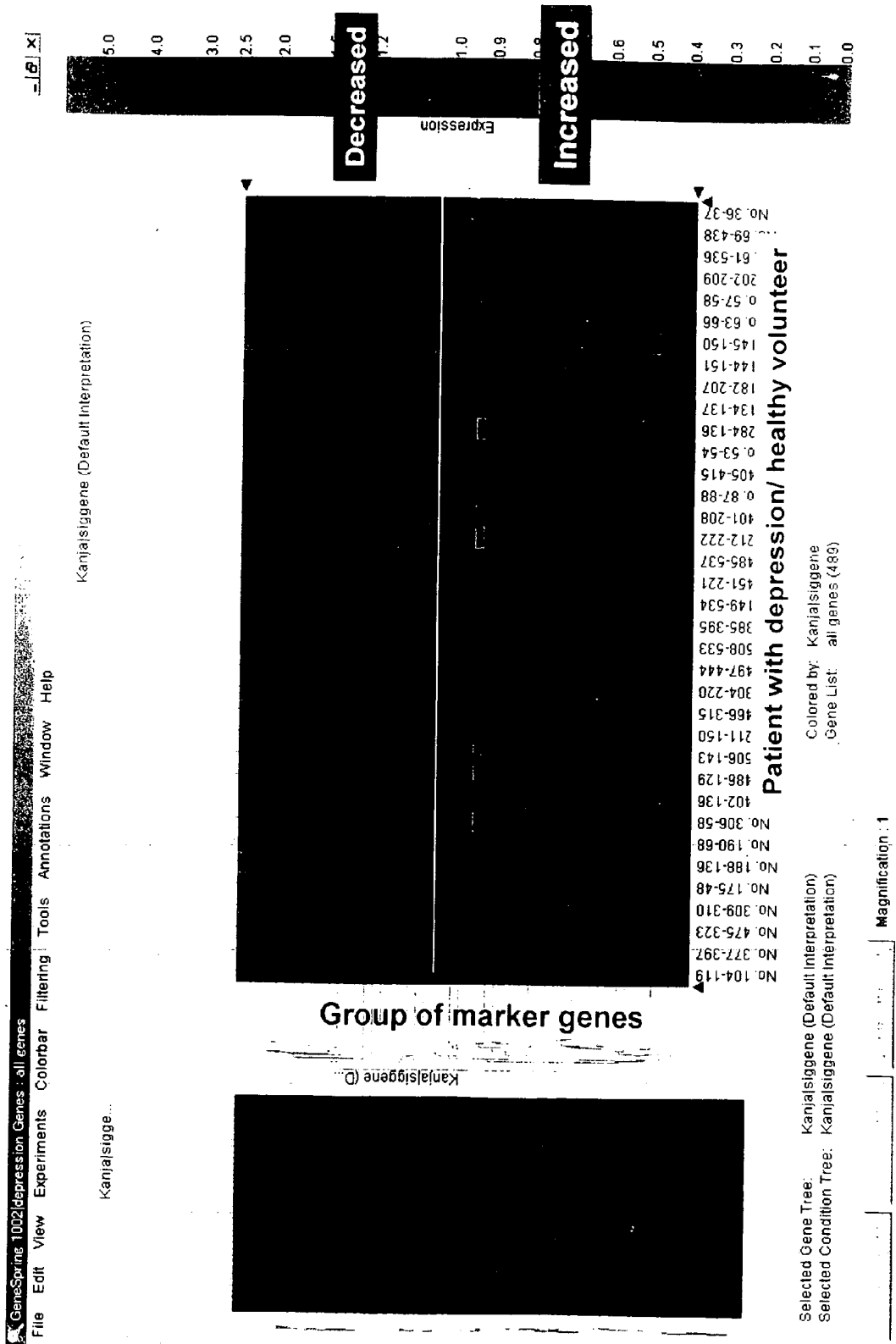




Fig 12

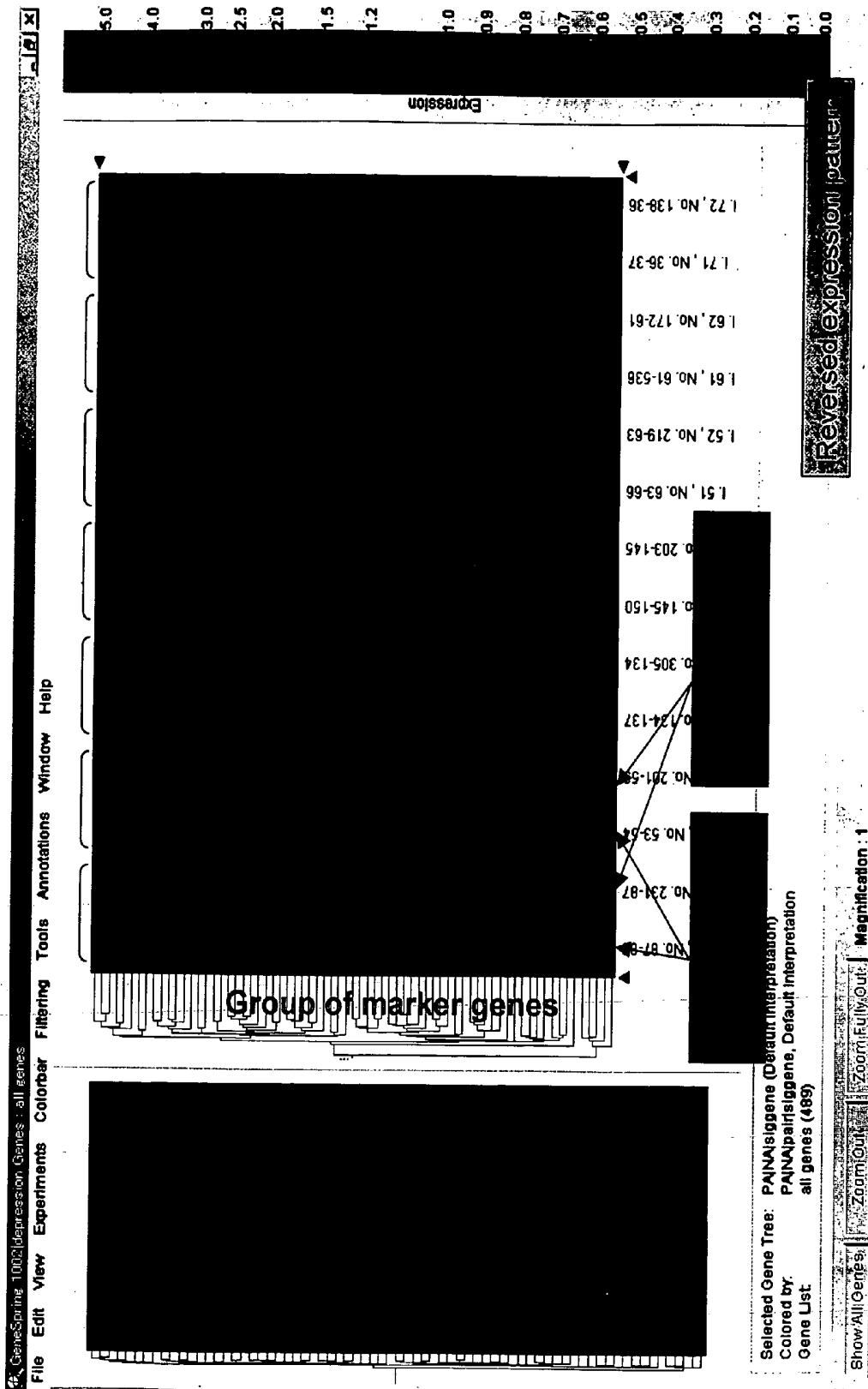


Fig 13

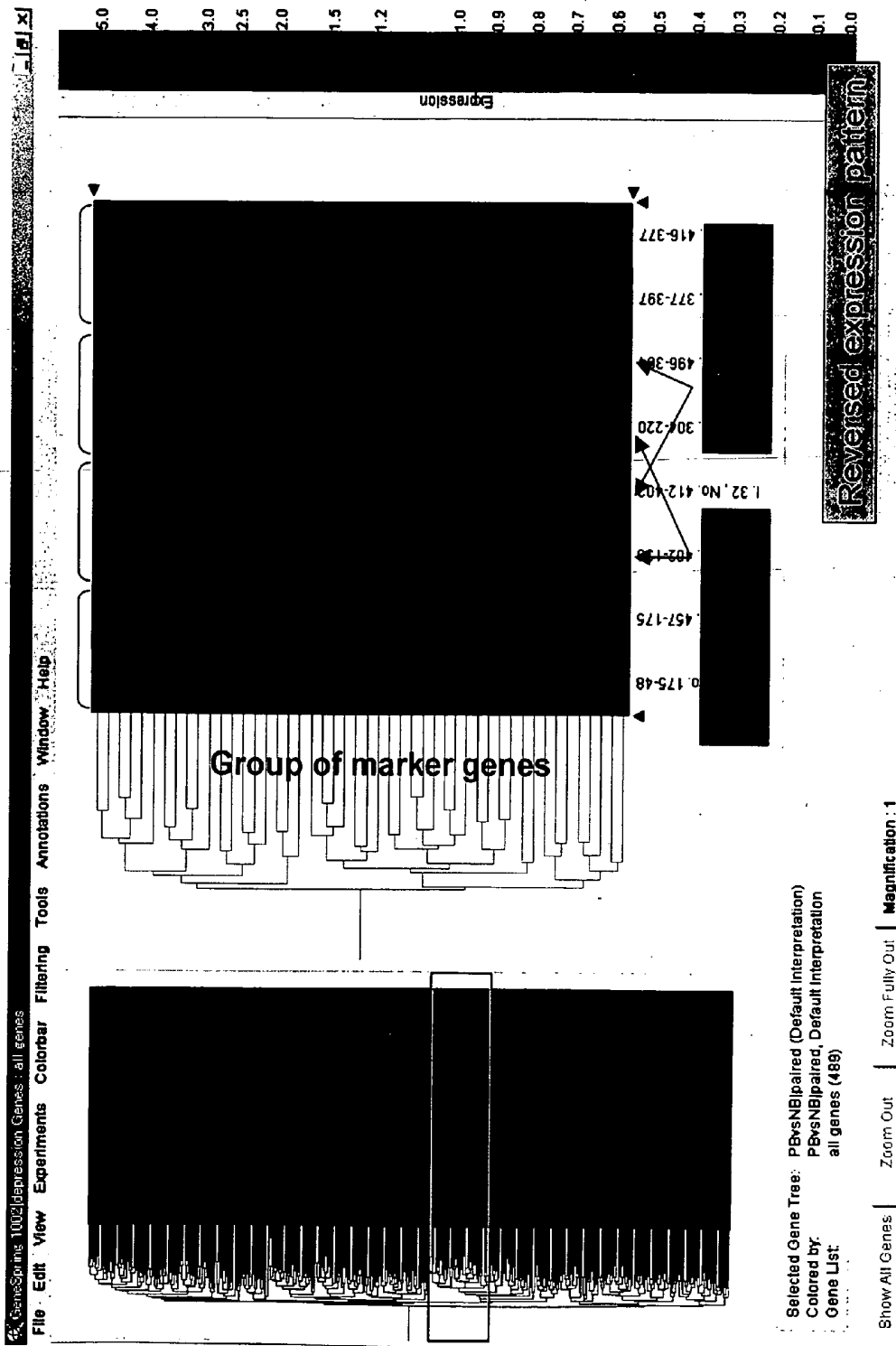


Fig 14

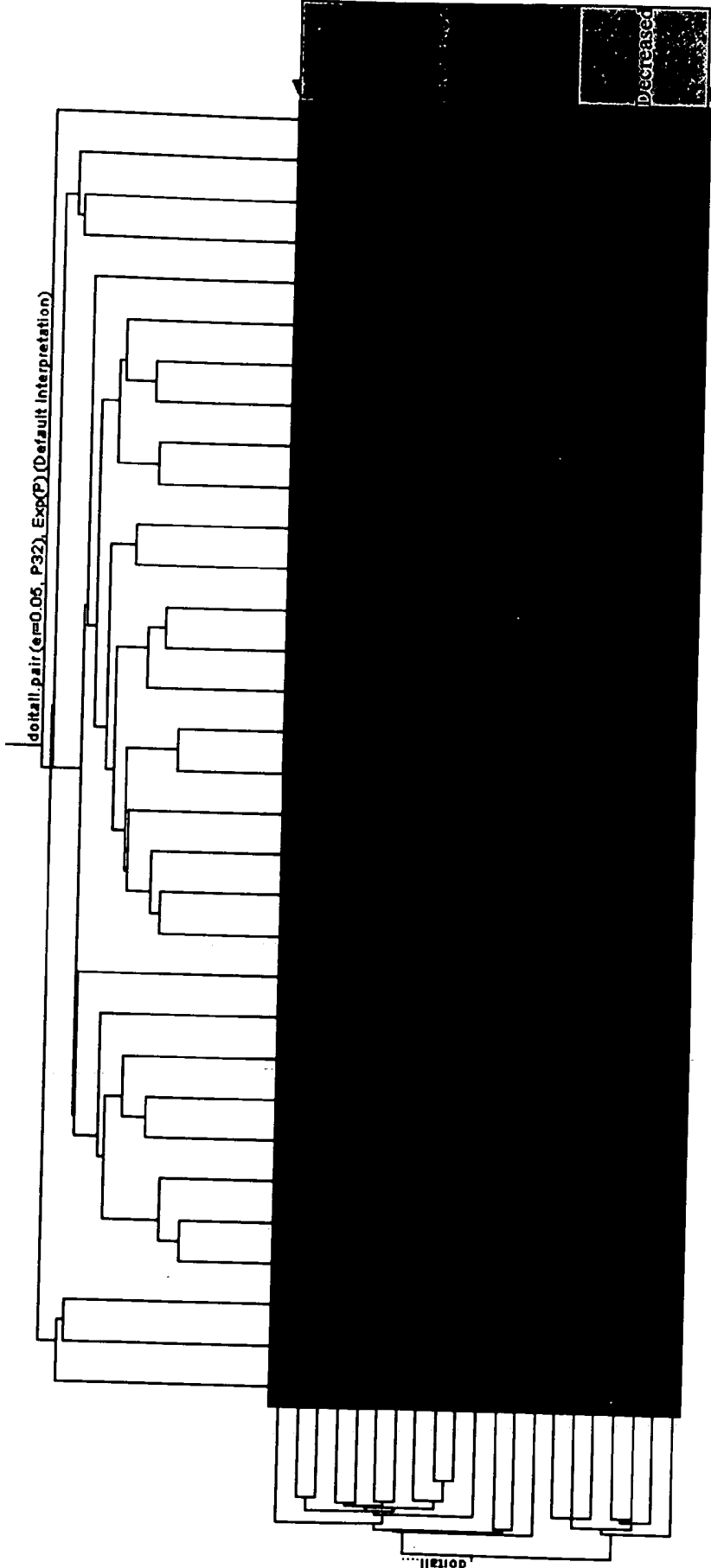


Fig 15

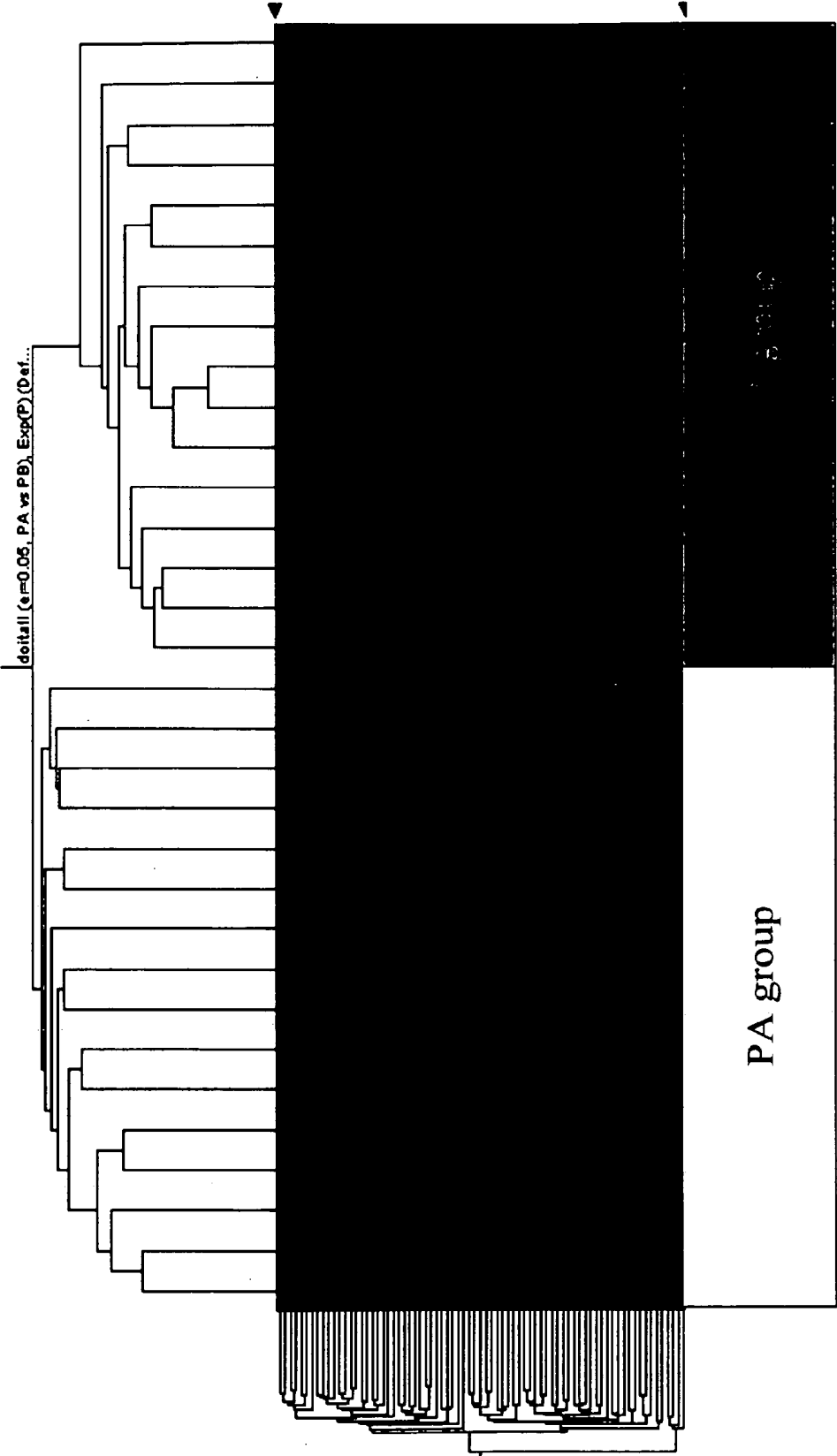


Fig 16

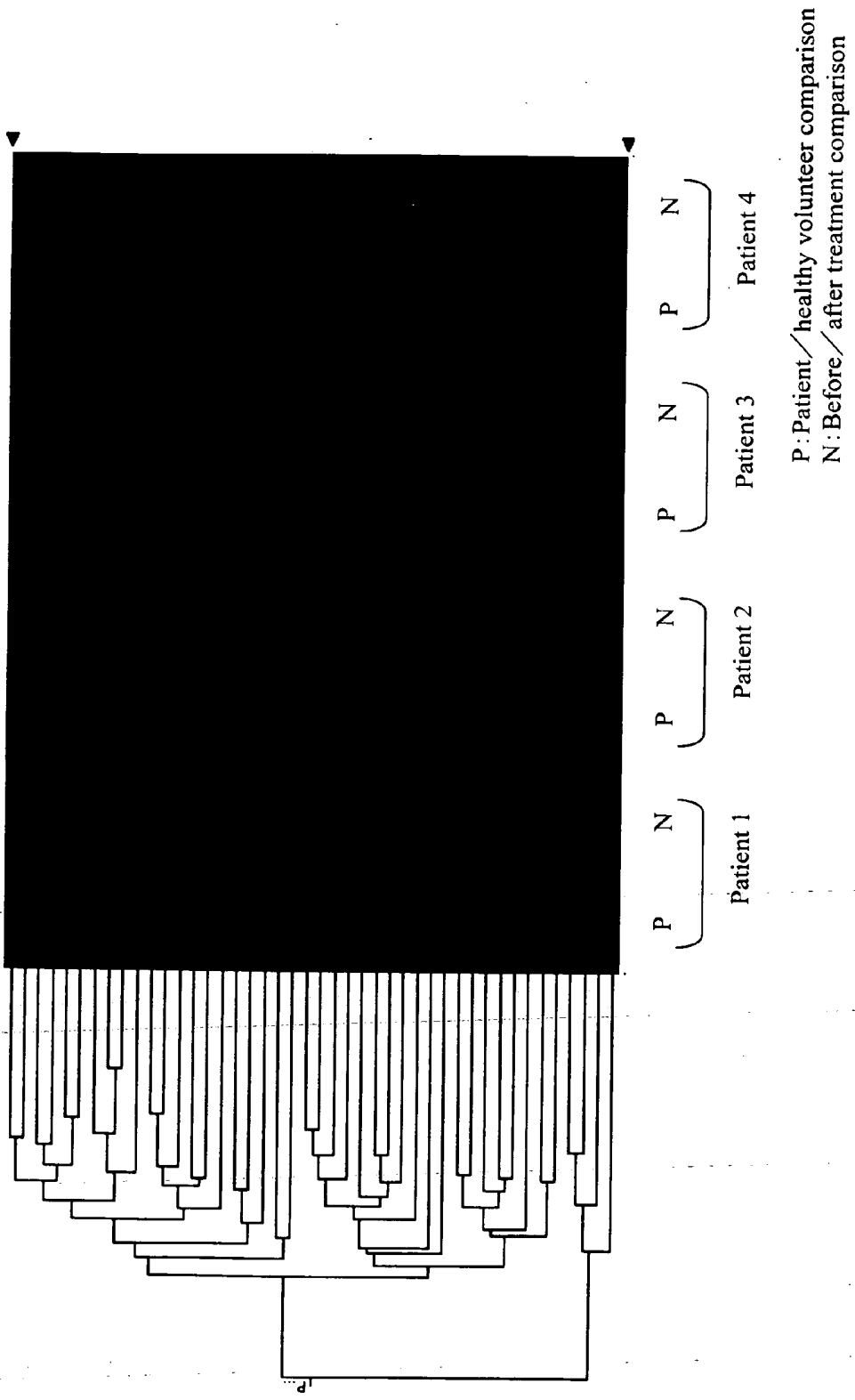
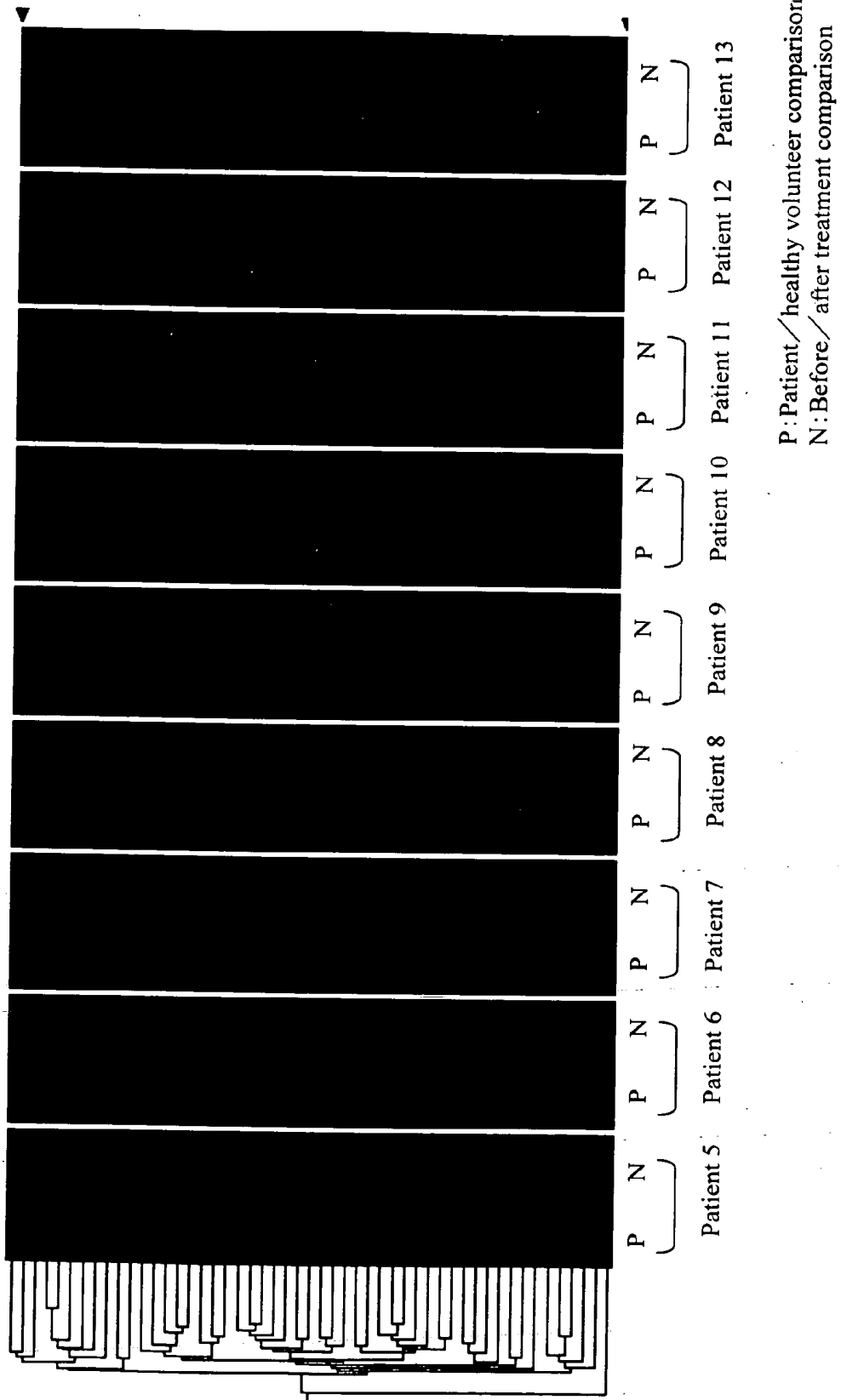


Fig 17



## METHOD OF DIAGNOSING DEPRESSION

[0001] The present application claims priority from Japanese applications JP 2004-096068 filed on Mar. 29, 2004 and JP 2005-042534 filed on Feb. 18, 2005, the contents of which are hereby incorporated by reference into this application.

### TECHNICAL FIELD

[0002] The present invention relates to a method of diagnosing depression. More particularly, the present invention relates to a method of diagnosing depression, wherein gene expression is analyzed using mRNA of patients' peripheral bloods to cluster patients afflicted with depression, and conditions thereof are then diagnosed.

### BACKGROUND ART

[0003] Depression is a disease with high lifetime morbidity of approximately up to 10%, and this rate is predicted to further increase in the future due to stress in contemporary society. This disease seriously afflicts patients mentally and physically and imposes enormous damage upon their social lives. In addition, it is a serious disease that often leads to suicide. It is deduced that many of the people who commit suicide (as many as 30,000 or more per year in Japan) are afflicted with depression. This disease is also deeply associated with societal problems such as truancy, unemployment, and social withdrawal or medical problems such as alcohol-related disorders. Establishment of methods of precisely diagnosing and promptly treating this disease is indispensable for improving the quality of life, and thus is an urgent need of society as a whole.

[0004] Diagnosis of depression is, however, far from simple. Cardinal symptoms of depression are, for example, depressive mood, hypobulia, loss of interest and pleasure, disrupted concentration and attention, lowered self-esteem and self-confidence, feelings of guilt and worthlessness, pessimism about the future, thoughts of suicide, sleep disorders, and loss of appetite. These symptoms have features peculiar to depression, which differ from depressed feelings experienced by anyone, and also differ from the lowered mental activity and sense of exhaustion experienced by people afflicted with physical diseases. The symptoms of depression are mainly comprehended by taking a precise medical history, questioning when and how the symptoms in terms of mental activity were developed and what types of damages have been imposed upon their social and domestic lives, and confirming various symptoms based on a patient's attitude or the contents of conversations during consultation. For example, family medical history, anamnesis, physical conditions, early developmental history, life history, personality inclination, premorbid social adaptation, and the occurrence of any episode(s) that had triggered the disease can be important references. In order to accurately comprehend these factors, an interview needs to be conducted by a highly skilled specialist in psychiatric medicine for approximately 1 hour. Further, it should be confirmed that a patient does not have any major abnormalities in terms of general physical or neurological conditions. If necessary, the possibility of the existence of organic brain disorders is to be eliminated by electroencephalography or brain imaging tests. The patient is then subjected to diagnosis. The findings are compared with the diagnostic standards issued by the World Health

Organization (WHO) or the American Psychiatric Association, and the diagnosis can be generally confirmed.

[0005] As a major drawback, conventional diagnostic methods require skilled techniques. Needless to say, thorough knowledge and practice concerning depression are required. However, there are numerous psychological, mental, and physical states that result in the exhibition of depressive conditions even though they are not forms of depression. Differential diagnosis also becomes essential. Accordingly, diagnosis must be conducted by a thoroughly trained specialist in psychiatric medicine. Depression, which is a common disease with lifetime morbidity of approximately 10%, however, is often the subject of consultation with primary care doctors. Diagnosis of depression without objective medical findings is not always easy for general doctors who may not be acquainted with psychiatric consultation. Depression is a medical disease that requires treatment of the body (brain), including medication. Accordingly, it is difficult for specialists in clinical psychology, such as clinical psychotherapists, or mental health workers, such as public health nurses, to independently diagnose depression.

[0006] Technical skill is required for diagnosis mainly because of a lack of simple and objective methods of diagnosis regarding symptoms. Although there is a screening method utilizing a self-administered questionnaire, people tend to fill in the questionnaire based on their subjective viewpoints. Thus, genuine depression cannot be distinguished from depressed feelings caused by personality-based factors, environmental factors, or poor physical conditions. Symptom rating scales employed by doctors are often used in determination of severity, although adequate questioning is required to evaluate each item. Thus, such methods cannot be alternatives to diagnosis.

[0007] Many testing methods have been heretofore attempted, with the aim of utilizing them as objective indicators. Depression causes functional alteration in brain monoamine systems. This alteration is known to have a considerable influence upon the neuroendocrine system, the neuroimmune system, and the autonomic nervous system via psychosomatic correlation. In particular, the application of the results of a dexamethasone suppression test that allows accurate comprehension of neuroendocrine abnormalities, i.e., a minor level of adrenal cortical hormone hypersecretion, to diagnosis of depression has been extensively examined from the 1980s onwards. Clinical application thereof was, however, not realized due to the necessity for complicated procedures such as the administration of test drugs and limitations in terms of sensitivity or specificity. At the study phase, other abnormalities in the neuroendocrine system, the neuroimmune system, the autonomic nervous system, circadian rhythms, sleep architecture, and the like had been reported. Recently, changes regarding conditions of brain blood flow or brain monoamine receptors are also pointed out as objective indicators, although they are still disadvantageous in terms of sensitivity and reproducibility. Given the aforementioned factors, diagnosis of a complicated psychiatric disease, i.e., depression, is difficult by a method of testing limited factors. Enormous amounts of time and labor are required to perform conventional testing methods and to diagnose the disease. From the viewpoint of simplicity, conventional techniques cannot be applied to routine medical care at present.

[0008] In the past, the catecholamine hypothesis, the indoleamine hypothesis, the GABA hypothesis, the glutamine hypothesis, the dopamine hypothesis, the neurogenesis hypothesis, and the like have been proposed as causes of depression. Many discrepancies of these hypotheses have been pointed out, and they have not yet resulted in conclusions. Linkage studies and association studies based on molecular genetic engineering and the search for sensitive domains of chromosomes by linkage analysis have been carried out. In the case of a disease such as depression, the diathesis (biological feature) of which is generated through interactions among multiple genes and environmental factors such as stress, therefore analysis of the pathogenic gene is extremely difficult. Based on past gene analysis, genes such as those related to serotonin transporter, serotonin 1A/2C receptor, dopamine D2/D3 receptor, dopamine transporter, tyrosine hydroxylase, tryptophan hydroxylase, monoamine oxidase, and ATPase have been reported as candidate functional genes associated with depression. For example, the correlation between Na/K-ATPase and psychiatric diseases, such as depression (*Depress Anxiety* 1997, 5, pp. 53-65) or dysthymia (*J. Basic Clin. Physiol. Pharmacol.* 2000, 11 (4), pp. 375-94), has been pointed out. Improvement of symptoms caused by an antidepressant, i.e., carbamazepine, is reported to be correlated with elevation of erythrocyte Na/K-ATPase activity (*Neuropsychobiology* 1999, 40 (3), pp. 134-9). Some researchers are, however, skeptical about the aforementioned reports, and additional tests have been conducted thereon.

#### SUMMARY OF THE INVENTION

[0009] An object of the present invention is to provide a novel method of diagnosing the conditions of depression of a subject in a simple, objective, and accurate manner.

[0010] The present inventors have focused on peripheral leukocytes that can be easily obtained as specimens and allow many receptors of factors associated with stress responses to be expressed therein in order to objectively diagnose the conditions of depression, in the development of which stress plays an important role. They have extensively analyzed the expression patterns of mRNAs of approximately 1,500 genes associated with stress responses and then developed certain patterns. Thus, they have found a method that is capable of classification patients afflicted with depression and diagnosing the conditions thereof. This has led to the completion of the present invention.

[0011] More specifically, the present invention relates to a method of diagnosing depression, wherein gene expression is analyzed using mRNA of a subject's peripheral blood to evaluate whether or not the subject is afflicted with depression, the type of depression of a subject who had been evaluated as being afflicted with depression is identified, and the conditions of depression are then diagnosed in accordance with the type of depression.

[0012] According to this method, the expression profiles of the marker gene for depression (an indicator for evaluating whether or not a subject has been afflicted with depression) selected from among the genes listed in Table 1 can be employed to evaluate whether or not a subject is afflicted with depression. When a subject was evaluated as being afflicted with depression, the expression profiles of the marker gene for classification (an indicator for classifying a

patient afflicted with depression) selected from among the genes listed in Table 2 can be employed to identify the type of depression in the subject to be type PA or PB.

[0013] ATP2A2, SCYA5, STIP1, EEF1A1, GRB10, CASP6, TSSC1, RAB9, NFATC3, and TPR are particularly useful marker genes for depression. GNG10, CLK1, P2Y5, IFNGR1, TAF2F, PIM1, MAP2K3, HDGF, INSR, and COX6C are particularly useful marker genes for classification.

[0014] When a subject was evaluated to have type PA depression, the expression profile of the marker gene for diagnosing type PA depression (an indicator for the conditions or a course of treatment of a patient with type PA depression) selected from among the genes listed in Table 3 can be employed to more precisely diagnose the conditions thereof. When a subject was evaluated to have type PB depression, the expression profile of the marker gene for diagnosing type PB depression (an indicator for the conditions or a course of treatment of a patient with type PB depression) selected from among the genes listed in Table 4 can be employed to more precisely diagnose the conditions thereof.

[0015] CDC10, GZMA, TNFRSF6, HSPCA, NR3C1, TOPBP1, ARNTL, RAP1A, POLR2B, and ITGB1 are particularly useful marker genes for depression. POU2F2, BCL2L1, DAXX, COX4, CD3G, FCER1G, NME2, CPT1B, HSPE1, and COX7A2 are particularly useful marker genes for classification.

[0016] According to another embodiment of the present invention, the expression profiles of the marker gene for depression selected from among the genes listed in Table 7 can be employed to evaluate whether or not a subject is afflicted with depression. When a subject was evaluated to be afflicted with depression, the expression profiles of the marker gene for classification selected from among the genes listed in Table 8 can be employed to identify the type of depression to be type PA or PB.

[0017] HLA-G, HRH4, PSMB9, ATP2A2, SCYA5, SLC6A4, CASP6, CSF2, HSD3B1, and RAB9 are particularly useful marker genes for depression. HSPE1, PSMA4, ADH5, PSMA6, COX17, HMG1, GPR24, COX6C, FGF2, and COX7C are particularly useful marker genes for classification.

[0018] When a subject was evaluated to have type PA depression, the expression profile of the marker gene for diagnosing type PA depression selected from among the genes listed in Table 9 can be employed to more precisely diagnose the conditions thereof. When a subject was evaluated to have type PB depression, the expression profile of the marker gene for diagnosing type PB depression selected from among the genes listed in Table 10 can be employed to more precisely diagnose the conditions thereof.

[0019] CLK1, PSMC6, TAF2F, P2Y5, CASP3, HSPCA, MSH2, SLC38A2, B2M, and AKAP11 are particularly useful marker genes for diagnosing type PA depression. CCNA2, HGF, GPR24, PTGER3, COX7A2, BDKRB2, UFD1L, HMG1, PSMA4, and ATP6J are particularly useful marker genes for diagnosing type PB depression.

[0020] According to the method of diagnosing depression of the present invention, the course of treating a single

subject who had been diagnosed to be afflicted with depression can be accurately evaluated by comparing and analyzing the gene expression profiles before and after the treatment of the subject.

[0021] The methods of analyzing gene expression that are employed in the present invention are not particularly limited. DNA-immobilized solid substrates, such as chips, arrays, membrane filters, and capillaries, are preferable.

[0022] The present invention also provides a solid substrate for diagnosing depression having immobilized thereon probes that each independently specifically hybridize to any one of the genes listed in Tables 1 to 4 for detecting the target gene. Preferably, the target genes at least include ATP2A2, SCYA5, STIP1, EEF1A1, GRB10, CASP6, TSSC1, RAB9, NFATC3, and TPR listed in Table 1, GNG10, CLK1, P2Y5, IFNGR1, TAF2F, PIM1, MAP2K3, HDGF, INSR, and COX6C listed in Table 2, CDC10, GZMA, TNFRSF6, HSPCA, NR3C1, TOPBP1, ARNTL, RAP1A, POLR2B, and ITGB1 listed in Table 3, and POU2F2, BCL2L1, DAXX, COX4, CD3G, FCER1G, NME2, CPT1B, HSPE1, and COX7A2 listed in Table 4.

[0023] According to another embodiment of the present invention, the present invention provides a solid substrate for diagnosing depression having immobilized thereon probes that each independently specifically hybridize to any one of the genes listed in Tables 7 to 10 for detecting the target gene. Preferably, the target genes at least include HLA-G, HRH4, PSMB9, ATP2A2, SCYA5, SLC6A4, CASP6, CSF2, HSD3B1, and RAB9 listed in Table 7, HSPE1, PSMA4, ADH5, PSMA6, COX17, HMG1, GPR24, COX6C, FGF2, and COX7C listed in Table 8, CLK1, PSMC6, TAF2F, P2Y5, CASP3, HSPCA, MSH2, SLC38A2, B2M, and AKAP11 listed in Table 9, and CCNA2, HGF, GPR24, PTGER3, COX7A2, BDKRB2, UFD1L, HMG1, PSMA4, and ATP6J listed in Table 10.

[0024] The present invention further provides a system for diagnosing depression for performing the method of diagnosing depression of the present invention. This system comprises a means for comparing and analyzing the gene expression data of a subject with that of a healthy volunteer and of a patient afflicted with depression, which had been previously obtained, and can diagnose the conditions of depression of the subject in accordance with the type of depression.

[0025] Preferably, the aforementioned system further comprises a means of comparing and analyzing the gene expression data of a subject, of a healthy volunteer, and of a patient afflicted with depression in combination with the data concerning their age and sex.

[0026] In the present invention, gene expression is analyzed using patients' peripheral bloods to cluster patients afflicted with depression, and conditions thereof or the course of treatment are then diagnosed. Thus, depression can be diagnosed in a non-invasive, simple, and accurate manner.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0027] FIG. 1 shows the groups of genes exhibiting significant differences between patients and healthy volunteers. Shading indicates the difference in expression levels of 10 or lower.

[0028] FIG. 2 shows the groups of genes exhibiting significant differences between the PA group and the PB group. Shading indicates the difference in expression levels of 10 or lower.

[0029] FIG. 3 shows the groups of genes exhibiting significant differences before/after treatment in the PA group. Shading indicates the difference in expression levels of 10 or lower.

[0030] FIG. 4 shows the groups of genes exhibiting significant differences before/after treatment in the PB group. Shading indicates the difference in expression levels of 10 or lower.

[0031] FIG. 5 schematically shows the method of diagnosing depression according to the present invention; wherein F1 indicates a DNA chip, F2 indicates probe DNA corresponding to the gene selected in the present invention, F3 indicates an excitation light source and a fluorescence detector, and F4 indicates a computer for regulating a fluorescence detector.

[0032] FIG. 6 schematically shows the system of diagnosing depression according to the present invention; wherein a database of personal information stores information such as sex and age.

[0033] FIG. 7 shows clustering of patient/healthy volunteer comparison.

[0034] FIG. 8 shows the gene expression data of subjects of the PA group. Shading indicates the difference in expression levels of 10 or lower.

[0035] FIG. 9 shows the gene expression data of subjects of the PB group. Shading indicates the difference in expression levels of 10 or lower.

[0036] FIG. 10 is a colored chart showing the results of cluster analysis for the group of genes with varying expression levels common in the patient group.

[0037] FIG. 11 is a colored chart showing the results of cluster analysis for the patients/healthy volunteers.

[0038] FIG. 12 is a colored chart showing the results of cluster analysis between a patient and a healthy volunteer and before/after treatment in the PA group.

[0039] FIG. 13 is a colored chart showing the results of cluster analysis between a patient and a healthy volunteer and before/after treatment in the PB group.

[0040] FIG. 14 is a colored chart showing the results of cluster analysis for the group of genes with varying expression levels common in the patient group.

[0041] FIG. 15 is a colored chart showing the results of cluster analysis for the patients/healthy volunteers.

[0042] FIG. 16 is a colored chart showing the results of cluster analysis between a patient and a healthy volunteer (P) and before/after treatment (N) in the PA group.

[0043] FIG. 17 is a colored chart showing the results of cluster analysis between a patient and a healthy volunteer (P) and before/after treatment (N) in the PB group.

#### DETAILED DESCRIPTION OF THE INVENTION

##### [0044] 1. Marker Genes for Diagnosing Depression

[0045] The present inventors extracted RNA from the whole blood collected from patients and healthy volunteers as described below, and gene expression of patients was then analyzed using DNA chips, along with that of healthy volunteers. The marker genes were determined based on the results. A DNA chip comprises DNA fragments having

nucleotide sequences corresponding to numerous genes immobilized on a substrate such as a glass substrate, and it is used for detecting RNA in a sample by hybridization. Instead of the aforementioned DNA chip, other DNA-immobilized solid substrates (such as DNA arrays, capillaries, or membrane filters) or quantitative assay techniques may be employed, as long as extensive analysis of gene expression is feasible.

[0046] Target patients were those who had agreed with the written description for participating in the research for developing the present diagnostic method selected from among untreated patients afflicted with depression. Patients with serious physical complications or those taking therapeutic agents for physical diseases were excluded. Diagnosis was made in accordance with a depressive episode specified in the International Classification of Diseases, 10th revision (ICD-10). Healthy volunteers with the same sex and age conditions were selected for each of the patients for comparison.

[0047] Differences in gene expression levels between samples obtained from patients and samples obtained from healthy volunteers or those between samples obtained from a single patient before and after treatment were determined. A group of genes having fluorescence intensities of 300 or higher in both of the data on patient/healthy volunteer comparison and the data on before/after treatment comparison was selected as the target genes.

[0048] Among the data on patient/healthy volunteer comparison, the gene with a significantly higher or lower expression level was selected via a significant difference test. The gene of the patient with significantly higher or lower expression level compared to that of the healthy volunteer was then selected as an indicator for evaluating whether or not the patient has been afflicted with depression, i.e., as the "marker gene for depression."

[0049] Subsequently, the data on patient/healthy volunteer comparison was subjected to cluster analysis employing all the target genes (hierarchical clustering based on the cosine coefficient distance without a weight between clusters). As a result, the present inventors found that the patient/healthy volunteer comparison samples were roughly divided into two groups, i.e., the PA group and the PB group. The tests were carried out between groups, and the gene that was peculiar to each group was selected as an indicator for classifying a patient afflicted with depression, i.e., as the "marker gene for classification" of the patient afflicted with depression.

[0050] Based on the above results, the data on before/after treatment comparison was grouped. The data on patient/healthy volunteer comparison and the data on before/after treatment comparison were aligned for each patient in each group, and the data were compared and analyzed. The group of genes with reversed expression patterns between the data on patient/healthy volunteer comparison and the data on before/after treatment comparison was extracted. The reversed expression patterns between the data on patient/healthy volunteer comparison and the data on before/after treatment comparison indicate a change in gene expression that is observed characteristically when the patient afflicted with depression received treatment involving the use of an antidepressant. Specifically, the extracted group of genes is useful as an indicator for the conditions or the course of

treatment of the patients afflicted with depression in each group. This group of genes was selected as the "marker genes for diagnosing each group (e.g., the marker genes for diagnosing type PA depression and the marker genes for diagnosing type PB depression)."

[0051] Expression levels of the marker gene was employed as an indicator to evaluate whether or not the subject had been afflicted with depression and the course of treatment by classification. This result was very consistent with the results of clinical finding. Thus, the marker genes according to the present invention were found to be effective.

[0052] 2. Association Between Marker Gene and Depression

[0053] At present, mechanisms of depression are indefinite, although the following is known as a correlation between the group of genes selected as marker genes and depression or other psychiatric diseases.

[0054] The genes, the expression levels of which had been significantly varied in the patient/healthy volunteer comparison samples, contained a large number of cytokine-associated genes, such as SCYA5 encoding a T-cell-specific protein, TNFRSF9 or TNFSF10 belonging to the TNF superfamily, or IL1R2 or IL2RB (an interleukin receptor). The association between cytokine and depression has been pointed out. Inflammatory cytokines such as interleukins (IL)-1, 6, and 8 are associated with stress responses, and affect the central nervous system, thereby causing drowsiness, loss of appetite, and other symptoms. As a major side effect of interferon  $\alpha$  used for treating hepatitis C, development of depression is well known. Based on the results attained via the present invention, significant changes in the expression level of cytokine-associated genes were observed in patients afflicted with depression, in the development of which stress may be involved, as anticipated. In particular, the expression level of interferon-associated genes was significantly changed. Thus, development of depression is considered to be associated with interferon therapy. Therefore, analysis of mRNA expression patterns of factors regulating functions of immune system cells was considered to be very useful for diagnosing depression.

[0055] It has been pointed out that ATRX is associated with X-chromosome-linked mental retardation (e.g., ATR-X syndrome, Carpenter syndrome, Juberg-Marsidi syndrome, or Smith-Fineman-Myers syndrome).

[0056] The expression level of the genes associated with the renin-angiotensin system, such as NR3C1 and SGK2, was found to vary in the case of patients afflicted with depression before and after treatment. Association of the renin-angiotensin system and sporadic Alzheimer's disease has been pointed out (Eur J Hum Genet. 2001; 9(6): 437-444). Also, association of the angiotensin-converting enzyme (ACE) gene polymorphism with schizophrenia has also been analyzed (Neuropsychobiology 2001; 44(1): 31-35).

[0057] Recently, the concept of perceiving clinical conditions involved with ion channel dysfunctions as "channel diseases" has been proposed. An ion channel serves as the most important function for neuron cell activity, and its association with epilepsy, ataxia, migraine, schizophrenia, Alzheimer's disease, and other neurodegenerative diseases

has been pointed out (CNS Drug Rev 2001; 7(2): 214-240). Concerning Na/K-ATPase and psychiatric diseases, association of the ion channel with depression (Depress Anxiety 1997, 5, pp. 53-65) or dysthymia (J. Basic Clin. Physiol. Pharmacol. 2000, 11 (4), pp. 375-94) has been particularly noted. For example, the association between the Na/K-ATPase  $\alpha$  subunit ATP1A3 (Biol Psychiatry 1998; 44: 47-51) or subunit ATP1B3 (Biol Psychiatry 1995; 37: 235-244) and bipolar disorders has been reported. Further, improvement of symptoms caused by an antidepressant, carbamazepine, is known to be correlated with elevation of erythrocyte Na/K-ATPase activity (Neuropsychobiology 1999, 40 (3), pp. 134-9). ATP1B3P1 is a pseudogene of ATP1B3 and is transcribed from the same genome. In the present invention, changes in the mRNA expression patterns of the gene encoding ATPase, such as ATP2A2, ATP2C1, ATP5JD, or ATP6H, reflect the state of depression. Accordingly, it was suggested that these genes were associated with depression in one way or another.

[0058] The expression level of the heat shock protein (HSP) family that is induced by a variety of forms of environmental stress and that contributes to the acquisition of stress responsiveness and stress resistance of cells also showed relatively major variation in leukocytes of patients afflicted with depression. mRNA expression levels were varied in HSPCB, HSPD1, HSPA10, or HSPA4. These HSP families are considered to be a group of genes important for the diagnosis of depression.

[0059] At present, mRNA expression levels of RNA polymerase II subunits or binding protein genes were both found to have been lowered, and their expression levels were found to have been restored as the disease state reached a state of remission, although association thereof with depression has not yet been clarified. Expression levels of a group of polymerase-associated genes, such as 140 kDa RNA polymerase II subunit protein gene (POLR2B), RNA polymerase II transcription elongation factor B (SIII) polypeptide 1 (TCEB1), RNA polymerase II transcription elongation factor B (SIII) polypeptide 1 homolog (TCEB1L), poly(A) polymerase, RNA polymerase  $\beta$  subunit, RNA polymerase III, and UDP-galactose transporter novel isozyme (SLC35A1), reflected conditions of depression.

[0060] Recently, research into the causes of depression in relation to receptor signalings and transcription factors mediating distinct gene expressions has drawn attention, in addition to the search for association of metabolism of neurotransmitters including monoamine or receptors themselves with depression. A monoamine receptor is a 7-transmembrane G-protein-coupled receptor that activates inositol phosphate cycles and protein kinase C (PKC). This receptor also activates the elevation of cyclic AMP and the protein kinase A (PKA) pathway. Further, transcription factors activated by these signal transducing molecules and their gene products are focused, and it is expected that associations of these pathways with functional disorders will be discovered. Lithium derivatives, the effects of which as mood stabilizers for patients afflicted with bipolar disorders have been verified, are actually reported to act on signal-transducing pathways such as G-proteins, inositol phosphate cycles, PKC, PKA, glycogen synthase kinase 3- $\beta$ , or Akt cascade, thereby exhibiting pharmacological actions (Br J Psychiatry 2001; 41: suppl 128-133).

[0061] Evidence that would support such reports was found in a group of genes associated with conditions of depression. Lowered mRNA expression levels of signal-transducing factors, such as PKC $\eta$  (PRKCH), PKC $\beta$ 1 isozyme, and phosphoinositide 3'-kinase  $\alpha$  subunit (PIK3CA), were observed. Lithium inactivates glycogen synthase kinase 3 and intensifies Wnt signals. In the case of patients afflicted with depression, expression levels of connective tissue growth factor-associated protein WISP-3,  $\beta$ -catenin (CTNNB1), and transcription factor E2A (TCF3) were lowered, and their expression levels were restored as the symptoms reached a state of remission. Lowered mRNA expression levels of GTP-binding proteins, i.e., RAB4 and RAB7L1, were observed, and their restoration through treatment was observed.

[0062] Concerning growth factor-associated proteins, mRNA expression levels of TGF- $\beta$  receptor, TGF- $\beta$ -induced clone 22 homolog (TSC22), and the insulin signal transducing molecule IRS4, reflected the symptoms of depression. In addition, mRNA expression levels of anti-oncogenes, i.e., Rb-associated protein RBBP7 and growth inhibitory factors ING1 and PTEN, were all lowered in patients afflicted with depression, and these expression levels were restored as the disease condition reached a state of remission. In a reflection of the expression patterns of these growth-associated genes, mRNA expression levels of CDKN2C, CDK7, CCNB2, and CCNG1 associated with a cell cycle were all lowered, and lowered mRNA expression levels of topoisomerase II $\beta$  and topoisomerase II-binding protein (TOPBP1) associated with DNA replication were observed. The evidence that suggests lowered general mitogen activity was observed in leukocytes of patients afflicted with depression. Expression levels of these genes were also restored as the symptoms reached a state of remission. Lowered mRNA expression levels of the DNA repair enzyme MSH6, an apoptosis signal molecule DAP3 or API1, and caspase 10 were associated with symptoms of patients afflicted with depression. When variations in growth-associated genes were examined altogether, a cell cycle was deduced to be generally lowered in leukocytes of patients afflicted with depression.

[0063] 3. Method for Diagnosing Depression and System for Diagnosing Depression

[0064] The present invention has been completed based on the results of above experimentation. In the present invention, mRNA is extracted from a subject's peripheral blood, and its expression profile is examined, thereby resulting in diagnosis of depression in the subject in accordance with the type of depression. FIG. 5 schematically shows the method of diagnosing depression of the present invention, and FIG. 6 schematically shows the system of diagnosing depression of the present invention.

[0065] Techniques for examining the gene expression levels employed in the present invention are not limited to the DNA chips shown in FIG. 5. Any conventional techniques for analysis in the art can be employed. For example, nucleic acid hybridization utilizing other DNA-immobilized solid substrates such as DNA arrays or membrane filters, quantitative PCR such as RT-PCR or real-time PCR, Northern blotting, subtraction, differential display, differential hybridization, and cross-hybridization, can be employed. DNA-immobilized solid substrates, such as DNA chips, DNA arrays, membrane filters, and capillaries, are particularly

preferable since a large number of genes can be extensively analyzed at a single operation.

[0066] The solid substrate that is employed in the present invention is prepared by immobilizing probes that each independently specifically hybridize to any one of the genes listed in Tables 1 to 4 to detect the target gene on a solid substrate, such as a glass or nylon membrane. Preferably, the target genes to be immobilized on the substrate at least include ATP2A2, SCYA5, STIP1, EEF1A1, GRB10, CASP6, TSSC1, RAB9, NFATC3, and TPR listed in Table 1, GNG10, CLK1, P2Y5, IFNGR1, TAF2F, PIM1, MAP2K3, HDGF, INSR, and COX6C listed in Table 2, CDC10, GZMA, TNFRSF6, HSPCA, NR3C1, TOPBP1, ARNTL, RAP1A, POLR2B, and ITGB1 listed in Table 3, and POU2F2, BCL2L1, DAXX, COX4, CD3G, FCER1Q, NME2, CPT1B, HSPE1, and COX7A2 listed in Table 4. Alternatively, the solid substrate of the present invention is prepared by immobilizing probes that each independently specifically hybridize to any one of the genes listed in Tables 7 to 10 to detect the target gene on a solid substrate, such as a glass or nylon membrane. Preferably, the target genes to be immobilized on the substrate at least include HLA-G, HRH4, PSMB9, ATP2A2, SCYA5, SLC6A4, CASP6, CSF2, HSD3B1, and RAB9 listed in Table 7, HSPE1, PSMA4, ADH5, PSMA6, COX17, HMG1, GPR24, COX6C, FGF2, and COX7C listed in Table 8, CLK1, PSMC6, TAF2F, P2Y5, CASP3, HSPCA, MSH2, SLC38A2, B2M, and AKAP11 listed in Table 9, and CCNA2, HGF, GPR24, PTGER3, COX7A2, BDKRB2, UFD1L, HMG1, PSMA4, and ATP6J listed in Table 10. A probe that is employed to detect genes can be designed as a sequence that is complementary to a region with high specificity of the marker gene (e.g., 3' UTR) in accordance with a conventional technique. A synthetic oligo probe with a 25-100 base length or a PCR product with a 300-1,000 base length can be employed. A method of immobilizing a probe on a solid substrate is not particularly limited. In accordance with a conventional technique, a synthesized probe may be spotted on a solid substrate or a probe may be synthesized on a solid substrate.

[0067] For example, the RNA sample collected from a subject and the RNA sample collected from a healthy volunteer are respectively labeled with fluorescent dyes having different emission wavelengths, and they are applied to the same DNA chip for diagnosing depression to conduct competitive hybridization. The fluorescence intensity of each probe on the chip represents the differences in the gene expression intensities between the subject and the healthy volunteer. The expression profiles thereof can be then examined to diagnose the conditions of depression in the subject.

[0068] Alternatively, a certain RNA sample, for example, a commercialized universal RNA sample, is used as a standard sample, and comparison and analysis of expression levels of the subject's sample and the standard sample are conducted separately from those of the healthy volunteer's sample and the standard sample in the aforementioned manner to analyze expression data for both groups in comparison with each other. Thus, the conditions of depression in the subject can be diagnosed.

[0069] In any case, a subject and a healthy volunteer to be compared therewith preferably have the same age and sex conditions. For example, an acceptable age gap between them is up to 5 years.

[0070] If the expression data for healthy volunteers are classified in accordance with their age and sex and stored in a database, the subject and a healthy volunteer can be compared and analyzed by simply retrieving the data that match the conditions of the subject in terms of age and sex from the database. Also, the expression data for patients afflicted with depression and those for healthy volunteers are previously stored in the computer, and the computer is allowed to determine which of the expression patterns for patients or healthy volunteers are more similar to the subject's expression data, thereby diagnosing the conditions of depression in the subject (see FIG. 6).

[0071] Further, if the expression data for patients afflicted with depression is stored in the computer in accordance with the group (the PA group and the PB group), more accurate diagnosis in accordance with the type of depression in the subject can be realized. In accordance with the expression data of each group stored in the computer, for example, the computer is allowed to determine which of the expression patterns are more similar to those of the subject who had been diagnosed as afflicted with depression, and the evaluated data is then clustered. The clustered data of the subject is further evaluated by the computer in terms of the conditions or the course of treatment based on the expression profile of a diagnostic marker specific for each group.

[0072] A method for data analysis is not limited to clustering. Any conventional analytical techniques in the art, for example, a machine learning algorithm such as the one utilizing a support vector machine can be employed.

[0073] The method of the present invention can conduct the analysis with the use of 5 ml of blood obtained by conventional blood sampling without special cooperation provided by a patient. This diagnostic method can be carried out in a non-invasive, simple, and routine manner. This method of multidimensionally comprehending biological functions based on numerous mRNA expression levels is more adequate as a method of diagnosing complicated psychiatric diseases involving both mental and physical conditions such as depression in terms of its principle compared with the conventional method that assays only limited factors.

[0074] The results attained by the method of the present invention can be simply and clearly evaluated, they can be easily employed by primary care doctors as objective indicators for depression, and they are extremely useful for the establishment of diagnosis and introduction of therapy. A high-risk group can be accurately selected from among the groups of people through medical checkups or complete physical examinations provided by workplaces, schools, and communities. This enables early detection of depression in a simple and cost-effective manner. Accordingly, the method of the present invention significantly contributes to the improvement of peoples' mental health from the viewpoint of preventive care.

[0075] The usefulness of the method according to the present invention is not limited to primary care and medical checkups. Specialists in psychiatric medicine can apply this technique to the search for psychological, social, and environmental factors associated with the development of depression, evaluation of clinical conditions, diagnosis, evaluation of treatment, and determination of prognosis. Thus, this technique can be a revolutionary test technique in

the field of psychiatric medicine, which dramatically improves a technique of diagnosing depression.

[0076] The present invention is hereafter described in greater detail with reference to the following examples, although it is not limited to these examples.

#### EXAMPLE 1

##### Selection of Marker Gene

###### [0077] 1. Patients and Healthy Volunteers

[0078] Target patients were those who had agreed with the written description for participating in the research for developing the present diagnostic method selected from among untreated patients afflicted with depression who had visited the Department of Psychiatry and Neurology of the Tokushima University Hospital between November 2001 and June 2002. This research was approved by the ethics committee of Tokushima University Hospital. Diagnosis was made in accordance with a depressive episode specified in the International Classification of Diseases, 10th revision (ICD-10). Patients with serious physical complications or those taking therapeutic agents for physical diseases were excluded. Healthy volunteers with the same sex and age conditions were selected for each patient for comparison.

[0079] Thirty three patients whose samples before treatment had been obtained were 25 males and 8 females aged 23 to 74 (45.7 years old on average), and their Hamilton scores were between 10 and 38 points (23.2 points on average).

[0080] Samples were obtained from 15 patients after the treatment. They were 13 males and 2 females aged 27 to 68 (48.1 years old on average), and their Hamilton scores were between 2 and 25 (6.9 points on average). Treatment was mainly carried out by medication using antidepressants. The remission of symptoms was determined based on general clinical diagnosis. Samples satisfied the standard of having scores of 7 or less on the Hamilton Rating Scale, which are generally regarded as representing remission of symptoms, except for 5 samples. Samples after treatment were collected 68 to 211 days after the collection of samples before treatment (121 days on average). The mRNA expression level after treatment was compared with that of a sample taken from the same subject before treatment.

###### [0081] 2. Analysis of Gene Expression

[0082] Blood (5 ml) was collected from the patients, and total RNA was extracted using a PAXgene Blood RNA System (Qiagen). Blood was collected by a doctor or nurse between 10:00 am and 1:00 pm from the patients under fasting conditions through cubitus veins under resting conditions. The yield of total RNA was 5  $\mu$ g to 15  $\mu$ g.

[0083] Subsequently, 5  $\mu$ g of total RNA extracted from each patient was separated, annealed with an oligo (dT) 24 primer comprising a T7 promoter sequence added thereto, and first-strand DNA was synthesized. Thereafter, this first-strand DNA was used as a template to synthesize second-strand DNA having a T7 promoter sequence. Finally, the second-strand DNA was used as a template to synthesize RNA with the aid of T7 RNA polymerase. A random hexamer was annealed to 6  $\mu$ g of the synthesized RNA to conduct a reverse transcriptase reaction, and Cy5-dCTP was incorporated into the strand. Thus, fluorescence-labeled cDNA was synthesized.

[0084] In a manner similar to the case of the patients, 5 ml of blood was collected from each of 33 healthy volunteers with the same sex and age conditions, and total RNA was then extracted. cDNA was similarly synthesized except for the use of Cy3 as a fluorescent label.

[0085] When comparing samples of a single subject before and after treatment, cDNA labeled with Cy3 and cDNA labeled with Cy5 were synthesized from the samples before and after treatment, respectively.

[0086] Equivalent amounts of two types of cDNAs for comparison and analysis were mixed, the resultant was applied to a DNA chip (a DNA chip for analyzing drug response, Hitachi Co., Ltd.), and hybridization was carried out at 62° C. for 12 hours. After washing, fluorescence intensity at each spot was assayed using a scanner (ScanArray 5000, GSI-Lumonics). Differences in gene expression levels between samples obtained from patients and samples obtained from healthy volunteers or those between samples obtained from a single patient before and after treatment were determined.

###### [0087] 3. Data Analysis

###### [0088] (1) Selection of Marker Gene for Depression

[0089] A group of genes (489 genes) having fluorescence intensities of 300 or higher in all 48 groups of data was selected as the object of analysis. Among the data on patient/healthy volunteer comparison, the gene with a significantly higher or lower expression level was selected via a significant difference test. There were 30 genes of the patient with a significantly higher expression level compared to that of the healthy volunteer and 22 genes thereof with a significantly lower expression level (FIG. 1, FIG. 10, Table 1). These 52 genes are useful for evaluating whether or not the subject has been afflicted with depression, i.e., they are useful as marker genes for depression. Among them, the expression levels of ATP2A2, SCYA5, STIP1, EEF1A1, GRB10, CASP6, TSSC1, RAB9, NEATC3, and TPR were significantly varied, and thus, they were considered to be particularly useful marker genes for depression.

TABLE 1

Group of genes exhibiting significant differences between patient/healthy volunteer			
Symbol	Name	Category	GenBank ID
AGTR1B	<i>H. sapiens</i> mRNA for angiotensin II receptor	angiotensin	X65699
AKAP6	<i>Homo sapiens</i> A kinase (PRKA) anchor protein 6 (AKAP6)	Signal	NM_004274
ALDH8	Human aldehyde dehydrogenase (ALDH8) mRNA	ALDH	U37519
ATP2A2	ATPase, Ca <sup>++</sup> transporting, cardiac muscle, slow twitch 2	ATPase	M23114

TABLE 1-continued

Group of genes exhibiting significant differences between patient/healthy volunteer			
Symbol	Name	Category	GenBank ID
ATP5J2	ATP synthase, H <sup>+</sup> transporting, mitochondrial F0 complex, subunit f, isoform 2	ATPase	AF047436
ATP6J	ATPase, H <sup>+</sup> transporting, lysosomal (vacuolar proton pump), member J	ATPase	AF038954
ATRX	Alpha thalassemia/mental retardation syndrome X-linked	ATPase	U72938
CASP4	Human cysteine protease (ICErel-II) mRNA, complete cds	Apoptosis	U28014
CASP6	Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds	Apoptosis, Signal	U20536
CCNA2	Human mRNA for cyclin A; Cyclin A2	CellCycle	X51688
CD3D	<i>Homo sapiens</i> CD3D antigen, delta polypeptide (TIT3 complex) (CD3D), mRNA	Signal	NM_000732
CD3E	Human mRNA for T3 epsilon chain (20K) of T-cell receptor (from peripheral blood lymphocytes).	Signal	X03884
CHST1	<i>Homo sapiens</i> mRNA for keratan sulfate Gal-6-sulfotransferase	sulfotransferase	AB003791
CHST2	<i>Homo sapiens</i> carbohydrate (N-acetylglucosamine-6-O) sulfotransferase 2 (CHST2)	sulfotransferase	NM_004267
COX7A2	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_001865
COX7C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIc	mitochondria & stress	NM_001867
CPT2	<i>Homo sapiens</i> camitine palmitoyltransferase II (CPT2), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_000098
CYP8B1	<i>Homo sapiens</i> sterol 12-alpha hydroxylase CYP8B1 (Cyp8b1) mRNA, partial cds	P450	AF090318
EEF1A1	<i>Homo sapiens</i> eukaryotic translation elongation factor 1 alpha 1 (EEF1A1)	glucocorticoids (Cortisol)	NM_001402
GNB2L1	Human MHC protein homologous to chicken B complex protein mRNA; Guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1	Signal	M24194
GNG5	<i>Homo sapiens</i> G protein gamma 5 subunit mRNA; Guanine nucleotide binding protein (G protein), gamma 5	Signal	AF038955
GRB10	<i>Homo sapiens</i> growth factor receptor-bound protein 10 (GRB10), mRNA	Insulin	NM_005311
HLA-DRA	Human HLA-DR alpha-chain mRNA; Class II MHC alpha	Signal	K01171
HSPCB	Human 90-kDa heat-shock protein gene, cDNA; Heat shock 90 kD protein 1, beta	hsp	M16660
IL1R2	<i>H. sapiens</i> IL-1R2 mRNA for type II interleukin-1 receptor, (cell line CB23).	Cytokine	X59770
IL2RB	Human interleukin 2 receptor beta chain (p70-75) mRNA, complete cds	Cytokine, Signal	M26062
IPF1	<i>Homo sapiens</i> insulin promoter factor 1, homeodomain transcription facto (IPF1)	Insulin	NM_000209
ISG20	Human HEM45 mRNA, complete cds	Cytokine	U88964
KARP1	Ku86 autoantigen related protein 1	Signal	AF039597
LBC	Human P47 LBC oncogene mRNA, complete cds	oncogene	U03634
NFATC3	<i>Homo sapiens</i> NF-AT4c mRNA, complete cds	Signal, TF	L41067
NFKBIA	<i>Homo sapiens</i> MAD-3 mRNA encoding Ikb-like activity, complete cds. IkbAlpha	Signal	M69043
NPR2L	<i>Homo sapiens</i> candidate tumor suppressor gene 21 protein mRNA, complete cds	Supressor	AF040708
PGK1	phosphoglycerate kinase 1	polymerase	V00572
PPARA	Human peroxisome proliferator activated receptor mRNA, complete cds	PPAR	L02932
PRKCH	Human protein kinase C-L (PRKCL) mRNA: Protein kinase C, eta	Signal	M55284
PSMC5	Proteasome (prosome, macropain) 26S subunit. ATPase, 5	ATPase	AF035309
RAB9	Human small GTP binding protein Rab9 mRNA, complete cds.	oncogene	U44103
RBBP5	<i>H. sapiens</i> RBQ-3 mRNA	Signal	X85134
RPA1	Replication protein A1 (70 kD)	Signal	M63488
SCYA5	Human T cell-specific protein (RANTES) mRNA. Small inducible cytokine A5	Cytokine	M21121
SP100	Human nuclear autoantigen (SP-100) mRNA	Signal	M60618
STAT3	<i>Homo sapiens</i> DNA-binding protein (APRF) mRNA, complete cds	Signal, TF	L29277
STIP1	<i>Homo sapiens</i> stress-induced-phosphoprotein 1 (Hsp70/Hsp90-organizing protein)	stress	NM_006819
SULT1C1	Human sulfotransferase mRNA family 1C, member 1 (SULT1C1)	sulfotransferase	U66036
TNFRSF9	Human activation dependent T cell mRNA, complete cds	Cytokine	L12964
TNFSF10	Human TNF-related apoptosis inducing ligand TRAIL mRNA, complete cds	Cytokine	U37518
TPR	<i>H. sapiens</i> tpr mRNA: Translocated promoter region (to activated MET oncogene)	oncogene	X66397
TSC22	Human putative regulatory protein TGF-beta-stimulated clone 22 homolog	GF	U35048
TSSC1	<i>Homo sapiens</i> tumor suppressing STF cDNA 1 (TSSC1) mRNA, complete cds	Supressor	AF019952
UGT1A6	<i>Homo sapiens</i> phenol UDP-glucuronosyltransferas (UDPGT) mRNA	UGT	J04093
WNT1	<i>Homo sapiens</i> wingless-type MMTV integration site family, member 1 (WNT1), mRNA	oncogene, Signal	NM_005430

[0090] (2) Selection of Marker Gene for Classification

[0091] Thirty three pairs of subjects for patient/healthy volunteer comparison were subjected to cluster analysis utilizing all the genes (489 genes). Analysis was carried out by hierarchical clustering based on the cosine coefficient

distance without a weight between clusters. This cluster analysis demonstrated that the patient/healthy volunteer comparison samples were roughly divided into 2 groups. Such 2 groups were designated as the PA group and the PB group. The 33 pairs of subjects for patient/healthy volunteer

comparison were divided into the PA group (16 pairs), the PB group (16 pairs), and a pair that did not belong to either group. In order to extract the genes that were peculiar to the PA group and to the PB group, these groups were compared to each other. There were 56 genes that exhibited significant differences between the PA group and the PB group (FIG. 2, FIG. 11, Table 2). These 56 genes are useful for assigning

patients afflicted with depression to the PA or PB group, i.e., they are useful as marker genes for classification the patients afflicted with depression. Among them, the expression levels of GNG10, CLK1, P2Y5, IFNGR1, TAF2F, PIM1, MAP2K3, HDGF, INSR, and COX6C were significantly varied, and thus, they were considered to be particularly useful marker genes for classification (Table 4).

TABLE 2

Genes exhibiting significant differences between PA group and PB group			
Symbol	Name	Category	GenBank ID
AFG3L2	AFG3 (ATPase family gene 3, yeast)-like 2	ATPase	NM_006796
AP11	Human inhibitor of apoptosis protein 2 mRNA; Apoptosis inhibitor 1	Apoptosis, Signal	U45879
ARHGAP8	<i>Homo sapiens</i> Rho GTPase activating protein 8 (ARHGAP8), mRNA	Signal	NM_015366
ARNTL	<i>Homo sapiens</i> mRNA for BMAL1a: aryl hydrocarbon receptor nuclear translocator-like	Ah receptor	D89722
ATP2C1	ATPase, Ca <sup>++</sup> -sequestering	ATPase	AF225981
CCNG1	Human cyclin G1 mRNA, complete cds	CellCycle	U47413
CD163	<i>Homo sapiens</i> CD163 antigen (CD163)	expressed exclusively on human monocyte; glucocorticoid-inducible	NM_004244
CDC10	hCDC10 = CDC10 homolog [human, fetal lung, mRNA, 2314 nt].	CellCycle	S72008
CDK8	<i>Homo sapiens</i> mRNA for CDK8 protein kinase.	CellCycle	X85753
CLK1	<i>Homo sapiens</i> clk1 mRNA; CDC-like kinase 1	CellCycle	L29222
COX6C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIc (COX6C), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_004374
COX7B	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIb	mitochondria & stress	NM_301866
CRYBB1	Human beta B1-crystallin mRNA	sulfotransferase	U35340
CTNNB1	<i>H. sapiens</i> mRNA for beta-catenin	Signal	X87838
DAXX	<i>Homo sapiens</i> Fas-binding protein Daxx mRNA, complete cds	Signal	AF015956
E2F4	<i>Homo sapiens</i> E2F transcription factor 4, p107/p130-binding (E2F4)	TF	NM_001950
FCER1A	Human mRNA for high affinity IgE receptor alpha-subunit (FcER1); Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide	Signal	X06948
GNG10	Human G protein gamma-10 subunit mRNA; Guanine nucleotide binding protein 10	Signal	U31383
GSTM3	Human glutathione transferase M3 (GSTM3) mRNA	GSTM	J05459
HDGF	Human mRNA for hepatoma-derived growth factor, complete cds	GF	D16431
HIF1A	<i>Homo sapiens</i> hypoxia-inducible factor 1, alpha subunit (basic helix-loop-helix transcription factor)	hypoxia, TF	NM_001530
HSBP1	<i>Homo sapiens</i> heat shock factor binding protein 1 HSBP1 mRNA; Heat shock factor binding protein 1	hsp	AF068754
HSPD1	Heat shock 60 kD protein 1 (chaperonin)	hsp	M34664
IFNAR1	Human interferon-alpha receptor (HuIFN-alpha-Rec) mRNA, complete cds	Cytokine, Signal	J03171
IFNGR1	Human interferon-gamma receptor mRNA, complete cds	Cytokine, Signal	J03143
ING1	<i>Homo sapiens</i> growth inhibitor p33ING1 (ING1) mRNA, complete cds	Signal, Suppressor	AF001954
INSR	<i>Homo sapiens</i> insulin receptor (INSR), mRNA,	Insulin	NM_000208
IRS4	<i>Homo sapiens</i> insulin receptor substrate 4 (IRS4)	Insulin	NM_003604
ITGB1	Integrin beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12);	Signal	X07979
KRAS2	Human K-ras oncogene protein mRNA (KRAS2)	oncogene	M54968
MAP2K3	Human mRNA for MAP kinase kinase 3b, complete cds, MEK3	Signal	D87116
NCOR2	Human silencing mediator of retinoid and thyroid hormone action (SMRT) mRNA, Nuclear receptor co-repressor 2	NR	U37146
NR1H4	Human farnesol receptor HRR-1 (HRR-1) mRNA, complete cds	NR1(FXR)	U68233
NR3C1	Human glucocorticoid receptor alpha mRNA, complete cds	glucocorticoids (Cortisol)	M10901
NTE	<i>Homo sapiens</i> mRNA for neuropathy target esterase	esterase	AJ004832
P2Y5	<i>Homo sapiens</i> purinergic receptor P2Y5 mRNA	Signal	AF000546
PAP	poly(A) polymerase	polymerase	X76770
PIK3C3	<i>H. sapiens</i> mRNA for phosphatidylinositol 3-kinase, Phosphoinositide-3-kinase, class 3	Signal	Z46973
PIK3CA	Human phosphoinositide 3'-hydroxykinase p110-alpha subunit mRNA, Phosphoinositide-3-kinase, catalytic, alpha polypeptide	Signal	U79143
PIM1	Human h-pim-1 protein (h-pim-1) mRNA, complete cds	oncogene	M54915
PLG	Human mRNA for plasminogen	Signal	X05199
POLB	polymerase (DNA directed), beta	polymerase	D29013
POLQ	polymerase (DNA-directed), theta	polymerase	AF043628
POLR2B	polymerase (RNA) II (DNA directed) polypeptide B (140 kD)	polymerase	X63563
PPAR	Human peroxisome proliferator activated receptor mRNA, complete cds	PPAR	L07592
PRKCL2	Human lipid-activated, protein kinase PRK2 mRNA; Protein kinase C-like 2	Signal	U33052
PTEN	Human mutated in multiple advanced cancers protein (MMAC1) mRNA; putative protein-tyrosine phosphatase PTEN	Suppressor	U92436
PTPRC	Human mRNA for T200 leukocyte common antigen (CD45, LC-A).	Signal	Y00062

TABLE 2-continued

<u>Genes exhibiting significant differences between PA group and PB group</u>			
Symbol	Name	Category	GenBank ID
RAP1A	Human ras-related protein (Krev-1) mRNA, complete cds	Suppressor	M22995
RBBP1	<i>Homo sapiens</i> retinoblastoma-binding protein 1 (RBBP1) mRNA	Signal	NM_002892
TAF2F	TATA box binding protein (TBP)-associated factor, RNA polymerase II, F, 55 kD	polymerase, TF	U18062
TANK	Human TRAF family member-associated NF-kB activator TANK mRNA, I-TRAF	Signal	U63830
TCEB1	transcription elongation factor B (SIII), polypeptide 1 (15 kD, elongin C)	polymerase, TF	L34587
TCF4	<i>Homo sapiens</i> transcription factor 4 (TCF4)	Signal, TF	NM_003199
TLR1	<i>Homo sapiens</i> Toll-like receptor 1 (TLR1) mRNA, complete cds	Signal	U88540
TNFRSF6	<i>H. sapiens</i> mRNA for APO-1 cell surface antigen, FAS	Apoptosis, Cytokine, Signal	X63717

**[0092]** (3) Selection of Diagnostic Marker Gene for Each Group

**[0093]** Based on the results attained above, 15 subjects for before/after treatment comparison were divided into the PA group (7 subjects) and the PB group (8 subjects). The data on patient/healthy volunteer comparison and the data on before/after treatment comparison were aligned for each patient in each group, and the data were compared and analyzed. The group of genes with reversed expression patterns between the patient/healthy volunteer comparison sample and the before/after treatment comparison sample was extracted (PA group: **FIG. 3**, **FIG. 12**, Table 3; PB group: **FIG. 4**, **FIG. 13**, Table 4). Concerning the PA group, variations in expression levels of CDC10, GZMA, TNFRSF6, HSPCA, NR3C1, TOPBP1, ARNTL, RAP1A, POLR2B, and ITGB1 were particularly significant among

the genes listed in Table 3. Concerning the PB group, variations in expression levels of POU2F2, BCL2L1, DAXX, COX4, CD3G, FCER1G, NME2, CPT1B, HSPE1, and COX7A2 were particularly significant among the genes listed in Table 4.

**[0094]** Changes in the Hamilton scores before and after the treatment are shown in Table 5. The reversed expression patterns between the data on patient/healthy volunteer comparison and the data on before/after treatment comparison indicate a change in gene expression that is observed characteristically when the patient afflicted with depression received treatment involving the use of an antidepressant. The group of genes is useful as an indicator for the conditions or the course of treatment of the patients afflicted with depression in each group. Specifically, they are useful diagnostic marker genes that are specific for each group.

TABLE 3

<u>Genes exhibiting significant differences before and after treatment in PA group</u>			
Symbol	Name	Category	GenBank ID
ADAM17	<i>Homo sapiens</i> snake venom-like protease (cSVP) mRNA. A disintegrin and metalloproteinase domain 17 (tumor necrosis factor, alpha, converting enzyme)	Cytokine	U92649
ADH5	Human alcohol dehydrogenase class III (ADH5) mRNA	ADH	M29872
ALDH10	Human microsomal aldehyde dehydrogenase (ALDH10) mRNA	ALDH	U46689
AP1S2	<i>Homo sapiens</i> adaptor-related protein complex 1, sigma 2 subunit (AP1S2)	AP-1	NM_003916
API1	Human inhibitor of apoptosis protein 2 mRNA; Apoptosis inhibitor 1	Apoptosis, Signal	U45879
ARNTL	<i>Homo sapiens</i> mRNA for BMAL1a; aryl hydrocarbon receptor nuclear translocator-like	Ah receptor	D89722
ATP2C1	ATPase, Ca <sup>++</sup> -sequestering	ATPase	AF225981
ATP6J	ATPase, H <sup>+</sup> transporting, lysosomal (vacuolar proton pump), member J	ATPase	AF038954
CASP1	Human interleukin 1-beta converting enzyme isoform delta (IL1BCE) mRNA, complete cds	Apoptosis, Signal	U13699
CASP5	Human cysteine protease (ICErel-III) mRNA, complete cds	Apoptosis	U28015
CD163	<i>Homo sapiens</i> CD163 antigen (CD163)	expressed exclusively on human monocyte;	NM_004244
CDC10	hCDC10 = CDC10 homolog [human, fetal lung, mRNA, 2314 nt].	glucocorticoid-inducible CellCycle	S72008
CLK1	<i>Homo sapiens</i> clk1 mRNA; CDC-like kinase 1	CellCycle	L29222
COX6C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIc (COX6C), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_004374
COX7A2L	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIa polypeptide 2 like	mitochondria & stress	NM_004718
COX7B	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIb	mitochondria & stress	NM_001866
CTNNB1	<i>H. sapiens</i> mRNA for beta-catenin	Signal	X87838
DAP3	Human ionizing radiation resistance conferring protein mRNA; Death associated protein 3	Apoptosis	U18321

TABLE 3-continued

<u>Genes exhibiting significant differences before and after treatment in PA group</u>			
Symbol	Name	Category	GenBank ID
ESD	<i>Homo sapiens</i> esterase D mRNA	esterase	AF112219
FCER1A	Human mRNA for high affinity IgE receptor alpha-subunit (FcERI); Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide	Signal	X06948
FGF2	Human basic fibroblast growth factor (FGF) mRNA (BFGP; FGF2)	GF	M27968
GNG10	Human C protein gamma-10 subunit mRNA; Guanine nucleotide binding protein 10	Signal	U31383
GZMA	Human Hanukah factor serine protease (HuHF) mRNA (cytotoxic T-lymphocyte-associated serine esterase 3)	esterase	M18737
HDAC1	Human mRNA for RPD3 protein, Histone deacetylase 1	Signal, TF	D50405
HSBP1	<i>Homo sapiens</i> heat shock factor binding protein 1 HSBP1 mRNA; Heat shock factor binding protein 1	hsp	AF068754
HSPA10	<i>Homo sapiens</i> heat shock 70 kD protein 10 (HSC71) (HSPA10), mRNA	hsp	NM_006597
HSPA4	Human heat shock protein 70 (hsp70) mRNA; Heat shock 70 kD protein 4	hsp	L12723
HSPCA	<i>Homo sapiens</i> Hsp89-alpha-delta-N mRNA; Heat shock 90 kD protein 1, alpha	hsp	AF028832
HSPD1	Heat shock 60 kD protein 1 (chaperonin)	hsp	M34664
HSPE1	Human chaperonin 10 mRNA; Heat shock 10 kD protein 1	hsp	U07550
IFNGR1	Human interferon-gamma receptor mRNA, complete cds	Cytokine, Signal	J03143
IL10RA	Human interleukin-10 receptor mRNA, complete cds	Cytokine	U00672
ING1	<i>Homo sapiens</i> growth inhibitor p33ING1 (ING1) mRNA, complete cds	Signal, Suppressor	AF001954
INS	<i>Homo sapiens</i> insulin (INS), mRNA	Tyrosine Hydroxylase, insulin	NM_000207
IRS4	<i>Homo sapiens</i> insulin receptor substrate 4 (IRS4)	Insulin	NM_003604
ITGB1	Integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12);	Signal	X07979
KARP1	Ku86 autoantigen related protein 1	Signal	AF039597
KRAS2	Human K-ras oncogene protein mRNA (KRAS2)	oncogene	M54968
MAP3K7	<i>Homo sapiens</i> mitogen-activated protein kinase kinase kinase 7 (MAP3K7), mRNA, TAK1	Signal	NM_003188
MSH6	Human DNA mismatch repair protein MSH6; mutS alpha 160-kDa subunit; G/T mismatch binding protein (GTMBP; GTBP)	DNArepair	U54777
NR3C1	Human glucocorticoid receptor alpha mRNA, complete cds	glucocorticoids (Cortisol)	M10901
NRF	<i>Homo sapiens</i> transcription factor NRF	mitochondria & stress	NM_017544
NTE	<i>Homo sapiens</i> mRNA for neuropathy target esterase	esterase	AJ004832
P2Y5	<i>Homo sapiens</i> purinergic receptor P2Y5 mRNA	Signal	AF000546
PAP	poly(A) polymerase	polymerase	X76770
PGK1	phosphoglycerate kinase 1	polymerase	V00572
PIK3C3	<i>H. sapiens</i> mRNA for phosphatidylinositol 3-kinase, Phosphoinositide-3-kinase, class 3	Signal	Z46973
PIK3CA	Human phosphoinositide 3'-hydroxykinase p110-alpha subunit mRNA, Phosphoinositide-3-kinase, catalytic, alpha polypeptide	Signal	U79143
POLB	polymerase (DNA directed), beta	polymerase	D29013
POLR2B	polymerase (RNA) II (DNA directed) polypeptide B (140 kD)	polymerase	X63563
PPP3CC	calcineurin A catalytic subunit [human, testis, mRNA, 2134 nt]; Protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)	Signal	S46622
PRKCH	Human protein kinase C-L (PRKCL) mRNA; Protein kinase C, eta	Signal	M55284
PTPN7	Human mRNA for protein-tyrosine phosphatase; Protein tyrosine phosphatase, non-receptor type 7, HePTP	Signal	D11327
RAB4	<i>Homo sapiens</i> GTP-binding protein (RAB4) mRNA, complete cds.	oncogene	M28211
RAB7L1	<i>Homo sapiens</i> mRNA for small GTP-binding protein, complete cds	oncogene	D84488
RAP1A	Human ras-related protein (Krev-1) mRNA, complete cds	Suppressor	M22995
RBBP1	<i>Homo sapiens</i> retinoblastoma-binding protein 1 (RBBP1) mRNA	Signal	NM_002892
RBBP4	Human chromatin assembly factor 1 p48 subunit (CAF1 p48 subunit); retinoblastoma-binding protein 4	Signal	X74262
RBBP6	<i>H. sapiens</i> RBQ-1 mRNA	Signal	X85133
RBBP7	Human retinoblastoma-binding protein (RbAp46) mRNA, complete cds	Signal	U35143
RPC39	polymerase (RNA) III (DNA directed) (39 kD)	polymerase	U93869
SGK2	<i>Homo sapiens</i> serum/glucocorticoid regulated kinase 2	hyperosmotic stress	NM_016276
SLC35A1	solute carrier family 35 (CMP-sialic acid transporter), member 1	polymerase	D87969
TAF2F	TATA box binding protein (TBP)-associated factor, RNA polymerase II, F, 55 kD	polymerase, TF	U18062
TAF2G	TATA box binding protein (TBP)-associated factor, RNA polymerase II, G, 32 kD	polymerase, TF	U21858
TCEB1	transcription elongation factor B (SIII), polypeptide 1 (15 kD, elongin C)	polymerase, TF	L34587
TCEB1L	transcription elongation factor B (SIII), polypeptide 1-like	polymerase, TF	Z47087
TNFRSF6	<i>H. sapiens</i> mRNA for APO-1 cell surface antigen, FAS	Apoptosis, Cytokine, Signal	X63717
TNFSF10	Human TNF-related apoptosis inducing ligand TRAIL mRNA, complete cds	Cytokine	U37518

TABLE 3-continued

<u>Genes exhibiting significant differences before and after treatment in PA group</u>			
Symbol	Name	Category	GenBank ID
TOP2B	<i>H. sapiens</i> TOP2 mRNA for DNA topoisomerase II (partial); Topoisomerase (DNA) II beta (180 kD)	topoisomerase	Z15115
TOPBP1	<i>Homo sapiens</i> mRNA for DNA topoisomerase II binding protein, complete cds	topoisomerase	AB019397

[0095]

TABLE 4

<u>Genes exhibiting significant differences before and after treatment in PB group</u>			
Symbol	Name	Category	GenBank ID
5T4	<i>H. sapiens</i> 5T4 gene for 5T4 Oncofetal antigen	oncogene	Z29083
AANAT	Human serotonin N-acetyltransferase mRNA, complete cds	NAT	U40347
ADCY9	<i>Homo sapiens</i> adenylate cyclase 9 (ADCY9)	Signal	NM_001116
ADH5	Human alcohol dehydrogenase class III (ADH5) mRNA	ADH	M29872
ADPRTL1	ADP-ribosyltransferase (NAD <sup>+</sup> ; poly (ADP-ribose) polymerase)-like 1	polymerase	AF057160
AKAP6	<i>Homo sapiens</i> A kinase (PRKA) anchor protein 6 (AKAP6)	Signal	NM_004274
AKR1B1	<i>Homo sapiens</i> aldo-keto reductase family 1, member B1 (aldose reductase)	hyperosmotic stress	NM_001628
ALDH10	Human microsomal aldehyde dehydrogenase (ALD10) mRNA	ALDH	U46689
APG-1	<i>Homo sapiens</i> mRNA for heat shock protein apg-1; Heat shock protein (hsp110 family)	hsp	AB023421
ARNTL	<i>Homo sapiens</i> mRNA for BMAL1a: aryl hydrocarbon receptor nuclear translocator-like	Ah receptor	D89722
ATP2A2	ATPase, Ca <sup>++</sup> transporting, cardiac muscle, slow twitch 2	ATPase	M23114
ATP5J2	ATP synthase, H <sup>+</sup> transporting, mitochondrial F0 complex, subunit f, isoform 2	ATPase	AF047436
ATP5JD	ATP synthase, H <sup>+</sup> transporting, mitochondrial F1F0, subunit d	ATPase	AF087135
AIP6DV	Vacuolar proton-ATPase, subunit D; V-ATPase, subunit D	ATPase	X71490
ATP6E	ATPase, H <sup>+</sup> transporting, lysosomal (vacuolar proton pump) 31 kD; Vacuolar proton-ATPase, subunit E; V-ATPase, subunit E	ATPase	X76228
ATP6H	ATPase, H <sup>+</sup> transporting, lysosomal (vacuolar proton pump) 9 kD	ATPase	Y15286
ATP6S14	ATPase, vacuolar, 14 kD	ATPase	D49400
BAK1	Human bcl2 homologous antagonist/killer (BAK)	Apoptosis	U23765
BCL2L1	<i>H. sapiens</i> bcl-xL mRNA; BCL2-like 1	Signal	Z23115
CASP10	Human apoptotic cysteine protease Mch4 (Mch4) mRNA, complete cds	Apoptosis, Signal	U60519
CCNB2	Human cyclin B2 mRNA, complete cds	CellCycle	AF002822
CD3E	Human mRNA for T3 epsilon chain (20K) of T-cell receptor (from peripheral blood lymphocytes),	Signal	X03884
CD3G	Human mRNA for T-cell receptor T3 gamma polypeptide, RON alpha	Signal	X04145
CD86	Human CD86 antigen mRNA, complete cds	Signal	U04343
CDC25C	Human cdc25Bs mRNA, complete cds	CellCycle	M34065
CDC2L5	Human cdc2-related protein kinase (CHED) mRNA; Cell division cycle 2-like 5 (cholinesterase-related cell division controller)	CellCycle	M80629
CDC37	Human CDC37 homolog mRNA, complete cds	CellCycle	U63131
CDK7	<i>H. sapiens</i> CDK activating kinase mRNA	CellCycle	X77743
CDKN2C	<i>Homo sapiens</i> cyclin-dependent kinase inhibitor (CDKN2C) mRNA, complete cds;; p18	CellCycle	AF041248
CHST1	<i>Homo sapiens</i> mRNA for keratan sulfate Gal-6-sulfotransferase	sulfotransferase	AB003791
COX4	<i>Homo sapiens</i> cytochrome c oxidase subunit IV (COX4), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_001861
COX5A	<i>Homo sapiens</i> cytochrome c oxidase subunit Va	mitochondria & stress	NM_304255
COX6C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIc (COX6C), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_004374
COX7A2	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_001865
COX7A2L	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIa polypeptide 2 like	mitochondria & stress	NM_004718
COX7B	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIb	mitochondria & stress	NM_001866
COX7C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIc	mitochondria & stress	NM_001867
CPT1B	<i>Homo sapiens</i> carnitine palmitoyltransferase I, muscle (CPT1B)	mitochondria & stress	NM_104377
CSF1R	Human macrophage colony stimulating factor I receptor precursor (CSF1R); a proto-oncogene (c-fms)	oncogene	X03663
CSF2RB	Human GM-CSF receptor beta chain mRNA; IL3R-beta	Cytokine, Signal	M59941

TABLE 4-continued

Genes exhibiting significant differences before and after treatment in PB group			
Symbol	Name	Category	GenBank ID
CSNK1A1	<i>Homo sapiens</i> casein kinase I alpha isoform (CSNK1A1) mRNA	Signal	L37042
CYP2A7	Human cytochrome P450 (CYP2A7) mRNA, complete cds	P450	U22029
CYP2C19	Human cytochrome P450C19 (CYP2C19) mRNA, clone 11a	P450	M61854
CYP3A5P1	Human cytochrome P450 pseudogene mRNA	P450	L26985
DAXX	<i>Homo sapiens</i> Fas-binding protein Daxx mRNA, complete cds	Signal	AF015956
DCC	Human tumor suppressor protein DCC precursor; colorectal cancer suppressor	Suppressor	X76132
DDOST	Human mRNA for KIAA0115 gene; Dolichyl-diphosphooligosaccharide-protein glycosyltransferase	UGT	D29643
DOK1	Docking protein 1, 62 kD (downstream of tyrosine kinase 1)	Gap-junciton	J70987
DUSP1	<i>H. sapiens</i> CL 100 mRNA for protein tyrosine phosphatase. Dual specificity phosphatase 1, MKP1	Signal	X68277
E2F2	<i>Homo sapiens</i> transcription factor E2F-2 mRNA, complete cds (clone 9).	TF	L22846
E2F3	<i>Homo sapiens</i> E2F transcription factor 3(E2F3)	TF	Y10479
EEF1A1	<i>Homo sapiens</i> eukaryotic translation elongation factor 1 alpha 1 (EEF1A1)	glucocorticoids (Cortisol)	NM_001402
ESD	<i>Homo sapiens</i> esterase D mRNA	esterase	AF112219
FCER1G	Human Fc-epsilon-receptor gamma-chain mRNA; Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	Signal	M33195
FOS	<i>Homo sapiens</i> v-fos FBJ murine osteosarcoma viral oncogene homolog (FOS), mRNA.	oncogene, Signal, TF	NM_005252
FRAT1	<i>Homo sapiens</i> frequently rearranged in advanced T-cell lymphomas (FRAT1) mRNA	Signal	NM_005479
G22P1	Human Ku protein subunit mRNA; Thyroid autoantigen 70 kD (Ku antigen)	Signal	M32865
GJA5	gap junction protein, alpha 5, 40 kD (connexin 40)	Gap-junciton	L34954
GNA15	Human G-alpha 16 protein mRNA, complete cds; Guanine nucleotide binding protein (G protein), alpha 15 (Gq class)	Signal	M63904
GNB3	Human guanine nucleotide-binding protein beta-3 subunit mRNA; Guanine nucleotide binding protein (G protein), beta polypeptide 3	Signal	M31328
HLA-DRA	Human HLA-DR alpha-chain mRNA; Class II MHC alpha	Signal	K01171
HLA-DRB1	Human mRNA for HLA class II DR-beta 1 (Dw14); Class II MHC beta	Signal	X02902
HMG1	Human mRNA for high mobility group-1 protein (HMG-1).	sulfotransferase	X12597
HSBP1	<i>Homo sapiens</i> heat shock factor binding protein 1 HSBP1 mRNA; Heat shock factor binding protein 1	hsp	AF068754
HSPA4	Human heat shock protein 70 (hsp70) mRNA; Heat shock 70 kD protein 4	hsp	L12723
HSPCB	Human 90-kDa heat-shock protein gene, cDNA; Heat shock 90 kD protein 1, beta	hsp	M16660
HSPD1	Heat shock 60 kD protein 1 (chaperonin)	hsp	M34664
HSPE1	Human chaperonin 10 mRNA; Heat shock 10 kD protein 1	hsp	U07550
IGF1R	Human mRNA for insulin-like growth factor I receptor	GF, Signal	X04434
IGFBP7	prolactin-stimulating factor [human, cultured diploid fibroblastcells, mRNA, 1124 nt].	GF	S75725
IL1R2	<i>H. sapiens</i> IL-1R2 mRNA for type II interleukin-1 receptor, (cell line CB23).	Cytokine	X59770
IL2RG	Human mRNA for interleukin 2 receptor gamma chain	Cytokine, Signal	D11086
ITGB2	Human leukocyte adhesion protein (LFA-1/Mac-1/p150.95 family) beta subunit mRNA, CD18	Signal	M15395
LOC51189	ATPase inhibitor precursor	ATPase	AB029042
MADD	<i>Homo sapiens</i> MAP kinase-activating death domain protein (MADD) mRNA	Signal	U77352
MAFG	<i>Homo sapiens</i> basic-leucine zipper transcription factor MafG (MAFG), mRNA, complete cds	oncogene, TF	AF059195
MAX	<i>H. sapiens</i> max mRNA	Signal	X60287
NFATC1	Human NF-ATc mRNA, complete cds	Signal, TF	U08015
NFATC3	<i>Homo sapiens</i> NF-AT4c mRNA, complete cds	Signal, TF	L41067
NME2	Human putative NDP kinase (nm23-H2S) mRNA, complete cds; c-myc purine-binding transcription factor puf	TF	M36981
NR1H4	Human farnesol receptor HRR-1 (HRR-1) mRNA, complete cds	NR1(FXR)	U68233
NRF	<i>Homo sapiens</i> transcription factor NRF	mitochondria & stress	NM_017544
NTRK1	Human mRNA of transforming tyrosine kinase protein trk oncogene; high-affinity nerve growth factor receptor precursor;	oncogene	X03541
PDAP1	Human PDGF associated protein mRNA (PAP)	GF	U41745
PDCD8	<i>Homo sapiens</i> apoptosis-inducing factor AIF mRNA, nuclear gene encoding mitochondrial protein; Programmed cell death 8	Signal	AF100928
PGK1	phosphoglycerate kinase 1	polymerase	V00572
PIK3C3	<i>H. sapiens</i> mRNA for phosphatidylinositol 3-kinase, Phosphoinositide-3-kinase, class 3	Signal	Z46973
PLCB4	<i>Homo sapiens</i> phospholipase C beta 4 (PLCB4) mRNA; Phospholipase C, beta 4	Signal	L41349
POLR2B	polymerase (RNA) II (DNA directed) polypeptide B (140 kD)	polymerase	X63563
POLRMT	polymerase (RNA) mitochondrial (DNA directed)	polymerase	U75370
POU2F1	Human mRNA for octamer-binding protein Oct-1; POU domain, class 2, transcription factor 1	TF	X13403

TABLE 4-continued

<u>Genes exhibiting significant differences before and after treatment in PB group</u>			
Symbol	Name	Category	GenBank ID
POU2F2	Human lymphoid-specific transcription factor mRNA; POU domain, class 2, transcription factor 2	TF	M36542
PPARA	Human peroxisome proliferator activated receptor mRNA, complete cds	PPAR	L02932
PPARD	Human peroxisome proliferator activated receptor mRNA, complete cds	PPAR	L07592
PRKCBP1	<i>Homo sapiens</i> protein kinase C-binding protein RACK7 mRNA, partial cds; Protein kinase C binding protein 1	Signal	U48251
PRKCH	Human protein kinase C-L (PRKCL) mRNA; Protein kinase C, eta	Signal	M55284
PRKCQ	Human protein kinase C theta (PKC) mRNA; Protein kinase C, theta	Signal	L07032
PSMC1	Proteasome (prosome, macropain) 26S subunit, ATPase, 1	ATPase	L02426
PTPN11	<i>Homo sapiens</i> SH-PTP3 mRNA for protein-tyrosine phosphatase: Protein tyrosine phosphatase, non-receptor type 11; Shp2	Signal	D13540
PTPN6	<i>H. sapiens</i> PTP1C mRNA for protein-tyrosine phosphatase 1C.; Protein tyrosine phosphatase, non-receptor type 6; SHP-1	Signal	X62055
PTPN7	Human mRNA for protein-tyrosine phosphatase; Protein tyrosine phosphatase, non-receptor type 7, HePTP	Signal	D11327
RAB7L1	<i>Homo sapiens</i> mRNA for small GTP-binding protein, complete cds	oncogene	D84488
RASSF1	<i>Homo sapiens</i> putative tumor suppressor protein (RDA32) mRNA, complete cds	Suppressor	AF061836
RBBP2	RBP2 = retinoblastoma binding protein 2 [human, Nalm-6 pre-B cell leukemia, mRNA, 6455 nt].	Signal	S66431
RDS	Retinal degeneration, slow (retinitis pigmentosa 7)	ATPase	M73531
RPA40	RNA polymerase I subunit	polymerase	AF008442
RXRG	Human retinoid X receptor-gamma mRNA, complete cds	RXR	U38480
SGK2	<i>Homo sapiens</i> serum/glucocorticoid regulated kinase 2	hyperosmotic stress	NM_016276
SLC35A1	solute carrier family 35 (CMP-sialic acid transporter), member 1	polymerase	D87969
SLC7A2	<i>Homo sapiens</i> solute carrier family 7 (cationic amino acid transporter, y <sup>+</sup> system) member 2	hyperosmotic stress	NM_003046
ST14	Human SNC19 mRNA sequence Suppression of tumorigenicity 14 (colon carcinoma, matriptase, epithin)	Suppressor	U20428
STAT3	<i>Homo sapiens</i> DNA-binding protein (APRF) mRNA, complete cds	Signal, TF	L29277
STAT5	<i>Homo sapiens</i> signal transducer and activator of transcription (STAT5) mRNA	Signal, TF	L41142
STAT5B	Human signal transducer and activator of transcription Stat5B mRNA, complete cds	TF	U47686
STAT6	Human transcription factor IL-4 Stat mRNA, complete cds	Signal, TF	U16031
STIP1	<i>Homo sapiens</i> stress-induced-phosphoprotein 1 (Hsp70/Hsp90-organizing protein)	stress	NM_006819
TAF2F	TATA box binding protein (TBP)-associated factor, RNA polymerase II, F, 55 kD	polymerase, TF	U18062
TCEB1	transcription elongation factor B (SIII), polypeptide 1 (15 kD, elongin C)	polymerase, TF	L34587
TCEB1L	transcription elongation factor B (SIII), polypeptide 1-like	polymerase, TF	Z47087
TCF15	Human basic helix-loop-helix transcription factor mRNA, complete cds	Signal, TF	U08336
TCF3	Human transcription factor (E2A) mRNA, complete cds	Signal, TF	M31523
TCF7L2	<i>Homo sapiens</i> mRNA for hTCF-4	Signal, TF	Y11306
TCFL1	Human YL-1 mRNA for YL-1 protein (nuclear protein with DNA-binding ability), complete cds	Signal, TF	D43642
TFDP2	Human DP2 (Humdp2) mRNA; Transcription factor Dp-2 (E2F dimerization partner 2)	TF	U18422
TGFB1	Human transforming growth factor-beta (TGF-beta; TGFB)	GF, Signal	X02812
TPST2	<i>Homo sapiens</i> tyrosylprotein sulfotransferase-2 mRNA	sulfotransferase	AF049891
TRA@	Human mRNA for T-cell receptor alpha chain (TCR-alpha),	Signal	X02592
TSSC1	<i>Homo sapiens</i> tumor suppressing STF cDNA 1 (TSSC1) mRNA, complete cds	Suppressor	AF019952
VAV1	Human mRNA for vav oncogene	oncogene, Signal	X16316
WISP2	<i>Homo sapiens</i> connective tissue growth factor related protein WISP-2 (WISP2) mRNA, complete cds.	Signal	AF100780

[0096]

TABLE 5

<u>Changes in Hamilton scores before and after treatment</u>		
	Before treatment	After treatment
#02	20	4
#04	26	25
#05	25	9
#06	19	10

TABLE 5-continued

<u>Changes in Hamilton scores before and after treatment</u>		
	Before treatment	After treatment
#07	12	2
#10	16	3
#13	29	7
#14	19	5
#15	31	9

TABLE 5-continued

<u>Changes in Hamilton scores before and after treatment</u>		
	Before treatment	After treatment
#16	27	—
#17	19	3
#29	28	8
#30	34	7
#31	15	3
#33	23	2

—: no data

## EXAMPLE 2

## Diagnosis of Depression Using Diagnostic Marker

[0097] The samples obtained from patients afflicted with depression and the samples obtained from healthy volunteers were employed to cluster the patients afflicted with depression and the healthy volunteers and to evaluate the course of treatment for the patients afflicted with depression.

## [0098] 1. Subjects

[0099] Three patients afflicted with depression and three healthy volunteers were employed as the subjects. Diagnosis was made in accordance with a depressive episode specified in the International Classification of Diseases, 10th revision (ICD-10). Patients with serious physical complications or those taking therapeutic agents for physical diseases were excluded. The samples obtained from 6 subjects were concealed whether they were patients afflicted with depression or healthy volunteers. Those samples were designated as Subjects A, B, C, D, E, and F.

## [0100] 2. Analysis of Gene Expression

[0101] Blood (5 ml) was collected from the subjects, and total RNA was extracted using a PAXgene Blood RNA System (Qiagen). The yield of total RNA was 5  $\mu$ g to 15  $\mu$ g. Subsequently, 5  $\mu$ g of total RNA extracted from each subject was separated, annealed with an oligo (dT) 24 primer comprising a T7 promoter sequence added thereto, and first-strand DNA was synthesized. Thereafter, this first-strand DNA was used as a template to synthesize second-strand DNA having a T7 promoter sequence. Finally, the second-strand DNA was used as a template to synthesize RNA with the aid of T7 RNA polymerase. A random hexamer was annealed to 6  $\mu$ g of RNA to conduct a reverse transcriptase reaction, and Cy5-dCTP was incorporated into the strand. Thus, fluorescence-labeled cDNA was synthesized.

[0102] For comparison, blood was collected from healthy volunteers having the same age and sex conditions with the subjects, and Cy3-cDNA was synthesized in the same manner as in the case of the patients' samples. Cy5-cDNA prepared from each subject's sample (6  $\mu$ g) was mixed with the equivalent amount of Cy3-cDNA as a standard sample, the resultant was applied to a DNA chip (a DNA chip for analyzing drug response, Hitachi Co., Ltd.), and hybridization was carried out at 62° C. for 12 hours. After washing, fluorescence intensity at each spot was assayed using a scanner (ScanArray 5000, GSI-Lumonics), and the differences in the expression intensities of each gene between the

standard sample and the sample obtained from the subject were determined using quantifying software (QuantArray, GSI-Lumonics).

## [0103] 3. Classification of Subjects

[0104] In accordance with the method described in Example 1, these 6 subjects were subjected to hierarchical clustering based on the cosine coefficient distance without a weight between clusters with the 33 subjects for patient/healthy volunteer comparison who had been already analyzed. This analysis demonstrated that Subjects D and E belonged to the PA group, Subject B belonged to the PB group, and Subjects A, C, and F did not belong to either group (FIG. 7). The concealed sample names were examined in relation to the results of clustering. This demonstrated that Subjects B, D, and E were patients afflicted with depression, and Subjects A, C, and F were healthy volunteers, which were completely consistent with the results of clustering.

## [0105] 4. Evaluation of Course of Treatment in Accordance with Type

[0106] Subsequently, the samples obtained from Subjects B, D, and E after treatment involving the use of antidepressants and the samples thereof before treatment were similarly subjected to analysis via DNA chips. The groups of genes listed in Table 3 were employed to observe changes in the gene expression patterns before and after treatment for Subjects D and E of the PA group. Similarly, the groups of genes listed in Table 4 were employed for Subject B of the PB group. After treatment, the gene expression patterns of all the patients were reversed from those before treatment. This indicates that the clinical conditions are in recovery trends (FIG. 8, FIG. 9).

## [0107] 5. Examination (Comparison with Hamilton Scaling)

[0108] The Hamilton scores of 3 patients afflicted with depression were as follows: Subject B: 22 points before treatment and 6 points after treatment; Subject D: 15 points before treatment and 1 point after treatment; and Subject E: 30 points before treatment and 2 points after treatment. Thus, the Hamilton scores were extremely consistent with the recovery trends of the clinical conditions indicated by the expression patterns of the groups of genes. Changes in the Hamilton scores before and after treatment are shown in Table 6.

TABLE 6

<u>Changes in Hamilton scores before and after treatment</u>		
	Before treatment	After treatment
Subject B	30	2
Subject D	22	6
Subject E	15	1

## 6. Conclusion

[0109] As is apparent from the foregoing, diagnosis of depression via analysis of expression levels of a specific group of genes was extremely consistent with the results attained by clinical finding in terms of classification and

evaluation of the course of treatment of patients afflicted with depression. This indicates that the present invention is very effective.

### EXAMPLE 3

#### Selection of Diagnostic Marker

##### [0110] 1. Patients and Healthy Volunteers

[0111] Target patients were those who had agreed with the written description for participating in the research for developing the present diagnostic method selected from among untreated patients afflicted with depression who had visited the Department of Psychiatry and Neurology of the Tokushima University Hospital between November 2001 and February 2004. This research was approved by the ethics committee of Tokushima University Hospital. Diagnosis was made in accordance with a depressive episode specified in the International Classification of Diseases, 10th revision (ICD-10). Patients with serious physical complications or those taking therapeutic agents for physical diseases were excluded. Healthy volunteers with the same sex and age conditions with each patient were selected for comparison.

[0112] Thirty two patients whose samples before treatment had been obtained were 20 males and 12 females aged 23 to 74 (45.1 years old on average), and their Hamilton scores were between 10 and 35 points (21.3 points on average).

[0113] Samples were obtained from 16 patients after the treatment. They were 9 males and 7 females aged 23 to 70 (47.5 years old on average), and their Hamilton scores were between 1 and 10 (4.3 points on average). Treatment was mainly carried out by medication using antidepressants. The remission of symptoms was determined based on general clinical diagnosis. After treatment, all the samples satisfied the standard of having scores of 7 or less on the Hamilton Rating Scale, which are generally regarded as representing remission of symptoms, or the standard such that the Hamilton scores were reduced to half or less those before treatment. Thus, all the samples were determined to have reached the state of remission after treatment.

##### [0114] 2. Analysis of Gene Expression

[0115] Blood (5 ml) was collected from the patients, and total RNA was extracted using a PAXgene Blood RNA System (Qiagen). Blood was collected by a doctor or nurse between 10:00 am and 1:00 pm from the patients under fasting conditions through cubitus veins under resting conditions. The yield of total RNA was 5  $\mu$ g to 15  $\mu$ g.

[0116] Subsequently, 5  $\mu$ g of total RNA extracted from each patient was separated, annealed with an oligo (dT) 24 primer comprising a T7 promoter sequence added thereto, and first-strand DNA was synthesized. Thereafter, this first-strand DNA was used as a template to synthesize second-strand DNA having a T7 promoter sequence. Finally, the second-strand DNA was used as a template to synthesize RNA with the aid of T7 RNA polymerase. A random hexamer was annealed to 6  $\mu$ g of the synthesized RNA to conduct a reverse transcriptase reaction, and Cy5-dCTP was incorporated into the strand. Thus, fluorescence-labeled cDNA was synthesized.

[0117] In a manner similar to the case of the patients, 5 ml of blood was collected from each of 32 healthy volunteers having the same sex and age conditions with the patients, and total RNA was then extracted. cDNA was similarly synthesized except for the use of Cy3 as a fluorescent label.

[0118] When comparing samples of a single subject before and after treatment, cDNA labeled with Cy3 and cDNA labeled with Cy5 were synthesized from the samples before and after treatment, respectively.

[0119] Equivalent amounts of two types of cDNAs for comparison and analysis were mixed, the resultant was applied to a DNA chip (Stress Chip, Hitachi Co., Ltd.), and hybridization was carried out at 62° C. for 12 hours. After washing, fluorescence intensity at each spot was assayed using a scanner (ScanArray 5000, GSI-Lumonics). Differences in gene expression levels between samples obtained from patients and samples obtained from healthy volunteers or those between samples obtained from a single patient before and after treatment were determined.

##### [0120] 3. Data Analysis

###### [0121] (1) Selection of Marker Gene for Depression

[0122] A group of genes (801 genes) having fluorescence intensities of 300 or higher for Cy5 or Cy3 in all 48 groups of data was selected as the object of analysis. Among the data on patient/healthy volunteer comparison, the gene with a significantly higher or lower expression level was selected via a significant difference test. There were 14 genes of the patient with a significantly higher expression level compared to that of the healthy volunteer and 7 genes thereof with a significantly lower expression level (FIG. 14, Table 7). These 21 genes are useful for evaluating whether or not the subject has been afflicted with depression, i.e., they are useful as marker genes for depression. Among them, the expression levels of HLA-G, HRH4, PSMB9, ATP2A2, SCYA5, SLC6A4, CASP6, CSF2, HSD3B1, and RAB9 were significantly varied, and thus, they were considered to be particularly useful marker genes for depression.

TABLE 7

Group of genes exhibiting significant differences between patient and healthy volunteer			
Symbol	Name	Category	GenBank ID
HLA-G	HLA-G histocompatibility antigen, class I, G	—	M32800
HRH4	histamine H4 receptor	—	NM_021624
PSMB9	proteasome (prosome, macropain) subunit, beta type, g (large multifunctional protease 2)	—	BC008795
ATP2A2	ATPase, Ca <sup>++</sup> transporting, cardiac muscle, slow twitch 2	ATPase	M23114
SCYA5	Human T cell-specific protein (RANTES) mRNA. Small inducible cytokine A5	Cytokine	M21121

TABLE 7-continued

Group of genes exhibiting significant differences between patient and healthy volunteer			
Symbol	Name	Category	GenBank ID
SLC6A4	solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	—	NM_001045
CASP6	Human cysteine protease Mch2 isoform alpha (Mch2) mRNA, complete cds	Apoptosis, Signal	U20536
CSF2	Human T-cell granulocyte-macrophage colony stimulating factor (GM-CSF) mRNA	Cytokine, Signal	M10663
HSD3B1	<i>Homo sapiens</i> hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 (HSD3B1)	glucocorticoids (Cortisol)	NM_000862
RAB9	Human small GTP binding protein Rab9 mRNA, complete cds,	oncogene	U44103
TPR	<i>H. sapiens</i> tpr mRNA; Translocated promoter region (to activated MET oncogene)	oncogene	X66397
ABCF1	<i>Homo sapiens</i> TNF-alpha stimulated ABC protein (ABC50) mRNA, complete cds	ABC transporter	AF027302
AKAP6	<i>Homo sapiens</i> A kinase (PRKA) anchor protein 6 (AKAP6)	Signal	NM_004274
PSMC5	Proteasome (prosome, macropain) 26S subunit, ATPase, 5	ATPase	AF035309
Hs.14438	<i>Homo sapiens</i> . Similar to histamine N-methyltransferase, clone MGC: 14500 IMAGE: 4249496, mRNA, complete cds	—	BC005907
KLK6	kallikrein 6 (neurosin, zyme)	—	AF013988
STIP1	<i>Homo sapiens</i> stress-induced-phosphoprotein 1 (Hsp70/Hsp90-organizing protein)	stress	NM_006819
PGK1	phosphoglycerate kinase 1	polymerase	V00572
PSMD5	proteasome (prosome, macropain) 26S subunit, non-ATPase,5	—	D31889
TGFBR3	Human transforming growth factor-beta type III receptor (TGF-beta) mRNA, complete cds	GF	L07594
TSSC1	<i>Homo sapiens</i> tumor suppressing STF cDNA 1 (TSSC1) mRNA, complete cds	Suppressor	AF019952

## [0123] (2) Selection of Marker Gene for Classification

[0124] Thirty two pairs of subjects for patient/healthy volunteer comparison were subjected to cluster analysis utilizing all the genes (801 genes). Analysis was carried out by hierarchical clustering based on the cosine coefficient distance without a weight between clusters. This cluster analysis demonstrated that the patient/healthy volunteer comparison samples were roughly divided into 2 groups. Such 2 groups were designated as the PA group and the PB group. The 32 pairs of subjects for patient/healthy volunteer comparison were divided into the PA group (16 pairs) and the PB group (16 pairs). In order to extract the genes that

were peculiar to the PA group and to the PB group, these groups were compared to each other. There were 75 genes that exhibited significant differences between the PA group and the PB group (FIG. 15, Table 8). These 75 genes are useful for assigning patients afflicted with depression to the PA or PB group, i.e., they are useful as marker genes for classification the patients afflicted with depression. Among them, the expression levels of HSPE1, PSMA4, ADH5, PSMA6, COX17, HMG1, GPR24, COX6C, FGF2, and COX7C were significantly varied, and thus, they were considered to be particularly useful marker genes for classification.

TABLE 8

Group of genes exhibiting significant differences between PA group and PB group			
Symbol	Name	Category	GenBank ID
HSPE1	Human chaperonin 10 mRNA; Heat shock 10 kD protein 1	hsp	U07550
PSMA4	proteasome (prosome, macropain) subunit, alpha type, 4	—	BC005361
ADH5	Human alcohol dehydrogenase class III (ADH5) mRNA	ADH	M29872
PSMA6	proteasome (prosome, macropain) subunit, alpha type 6	—	X59417
COX17	<i>Homo sapiens</i> COX17 (yeast) homolog, cytochrome c oxidase assembly protein	mitochondria & stress	NM_005694
HMG1	Human mRNA for high mobility group-1 protein (HMG-1).	sulfotransferase	X12597
GPR24	G protein-coupled receptor 24	—	BC001736
COX6C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIc (COX6C), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_004374
FGF2	Human basic fibroblast growth factor (FGF) mRNA (BFGF; FGFB; FGF2)	GF	M27968
COX7C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIc	mitochondria & stress	NM_001867
CCNA2	Human mRNA for cyclin A; Cyclin A2	CellCycle	X51688
PTGER3	prostaglandin E receptor 3 (subtype EP3)	—	X83860
APG-1	<i>Homo sapiens</i> mRNA for heat shock protein apg-1; Heat shock protein (hsp110 family)	hsp	AB023421
HSPCA	<i>Homo sapiens</i> Hsp89-alpha-delta-N mRNA; Heat shock 90 kD protein 1, alpha	hsp	AF028832
UBL1	ubiquitin-like 1 (sentrin)	Gap-juncton	U61397

TABLE 8-continued

Group of genes exhibiting significant differences between PA group and PB group			
Symbol	Name	Category	GenBank ID
UCHL3	Human ubiquitin carboxyl-terminal hydrolase (PGP 9.5, UCH-L3) isozyme L3 mRNA	esterase	M30496
HINT	<i>Homo sapiens</i> protein kinase C inhibitor (PKCI-1) mRNA, Histidine triad nucleotide-binding protein	Signal	U51004
BDKRB2	<i>Homo sapiens</i> bradykinin receptor B2	heart stress	NM_000623
SOD1	<i>Homo sapiens</i> superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult)) (SOD1); Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))	SOD	NM_000454
IL13RA2	Human interleukin-13 receptor mRNA, complete cds	Cytokine	U70981
HSBP1	<i>Homo sapiens</i> heat shock factor binding protein 1 HSBP1 mRNA; Heat shock factor binding protein 1	hsp	AF068754
EEF1A1	<i>Homo sapiens</i> eukaryotic translation elongation factor 1 alpha 1 (EEF1A1)	glucocorticoids (Cortisol)	NM_001402
PSMA7	proteasome (prosome, macropain) subunit, alpha type, 7	—	BC004427
PSMA3	proteasome (prosome, macropain) subunit, alpha type, 3	—	BC005265
UFD1L	Ubiquitin fusion degradation 1-like	—	BC005087
CCNH	Human cyclin H mRNA, complete cds	CellCycle	U11791
ATP6J	ATPase, H <sup>+</sup> transporting, lysosomal (vacuolar proton pump), member J	ATPase	AF038954
HGF	Human hepatocyte growth factor mRNA (HGF); scatter factor (SF); hepatopocitin A	GF	M60718
PRDX4	peroxiredoxin 4	—	BC003609
GZMA	Human Hanukah factor serine protease (HuHF) mRNA (cytotoxic/T-lymphocyte-associated serine esterase 3)	esterase	M18737
PSMD10	proteasome (prosome, macropain) 26S subunit, non-ATPase, 10	—	NM_002814
COX7A2	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIa polypeptide 2 (liver) (COX7A2), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_001865
HSJ2	Human heat shock protein, <i>E. coli</i> DnaJ homologue mRNA, complete cds; Heat shock protein, DnaJ-like 2	hsp	L08069
B2M	beta-2-microglobulin	—	AY007153
TCEB1	transcription elongation factor B (SIIE), polypeptide 1 (15 kD, elongin C)	polymerase, TF	L34587
HTR6	5-hydroxytryptamine (serotonin) receptor 6	—	NM_000871
TXN	thioredoxin	—	X77584
HSPD1	Heat shock 60 kD protein 1 (chaperonin)	hsp	M34664
PSMC6	Proteasome (prosome, macropain) 26S subunit, ATPase, 6	ATPase	AF006305
POLR2A	polymerase (RNA) II (DNA directed) polypeptide A (220 kD); <i>H. sapiens</i> mRNA for RNA polymerase II largest subunit	polymerase	X63564
HSPA4	Human heat shock protein 70 (hsp70) mRNA; Heat shock 70 kD protein 4	hsp	L12723
DAP3	Human ionizing radiation resistance conferring protein mRNA; Death associated protein 3	Apoptosis	U18321
NME2	Human putative NDP kinase (nm23-H2S) mRNA, complete cds; c-myc purine-binding transcription factor puf	TF	M36981
CD86	Human CD86 antigen mRNA, complete cds	Signal	U04343
IGBP1	Immunoglobulin (CD79A) binding protein 1	Signal	Y08915
WISP3	<i>Homo sapiens</i> connective tissue growth factor related protein WISP-3 (WISP3) mRNA, complete cds.	Signal	AF100781
COP55	Human Jun activation domain binding protein mRNA, complete cds	oncogene	U65928
DBI	diazepam binding inhibitor (GABA receptor modulator, acyl-Coenzyme A binding protein)	—	BC006466
SCYA7	<i>Homo sapiens</i> mRNA for monocyte chemotactic protein-3 (MCP-3). Small inducible cytokine A7 (monocyte chemotactic protein 3)	Cytokine	X72308
NCOR2	Human silencing mediator of retinoid and thyroid hormone action (SMRT) mRNA. Nuclear receptor co-repressor 2	NR	U37146
PSMB1	proteasome (prosome, macropain) subunit, beta type, 1	—	BC000508
DMBT1	<i>Homo sapiens</i> mRNA for DMBT1 6 kb transcript variant 1 (DMBT1/6 kb.1). Suppressor	—	AJ000342
POLR2H	Human RNA polymerase II subunit (hsRPB8) mRNA; polymerase (RNA) II (DNA directed) polypeptide H	polymerase	U37689
PSMA1	proteasome (prosome, macropain) subunit, alpha type, 1	—	BC002577
PAP	poly(A) polymerase	polymerase	X76770
HSPA10	<i>Homo sapiens</i> heat shock 70 kD protein 10 (HSC71) (HSPA10), mRNA	hsp	NM_006597
PSMA5	proteasome (prosome, macropain) subunit, alpha type, 5	—	X61970
P2Y5	<i>Homo sapiens</i> purinergic receptor P2Y5 mRNA	Signal	AF000546
SLC35A1	solute carrier family 35 (CMP-sialic acid transporter), member 1	polymerase	D87969
COX7B	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIb	mitochondria & stress	NM_001866
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A	—	X57830
KLK12	<i>Homo sapiens</i> kallikrein 12 (KLK12), mRNA	—	NM_019598
Hs.351290	<i>Homo sapiens</i> cDNA FLJ30648 fis, clone CTONG2006449, moderately similar to <i>Drosophila melanogaster</i> 26S proteasome regulatory complex subunit p42A mRNA	—	AK055210
ACE	<i>Homo sapiens</i> dipeptidyl carboxypeptidase 1 (angiotensin I converting enzyme) (ACE)	angiotensin	NM_000789
NR1H4	Human farnesol receptor HRR-1 (HRR-1) mRNA, complete cds	NR1(FXR)	U68233
KIAA0107	KIAA0107 gene product	—	BC000904

TABLE 8-continued

Group of genes exhibiting significant differences between PA group and PB group			
Symbol	Name	Category	GenBank ID
COX7A2L	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIa polypeptide 2 like	mitochondria & stress	NM_004718
VCP	valosin-containing protein	—	BC007562
RPA40	RNA polymerase I subunit	polymerase	AF008442
TXNL	thioredoxin-like, 32 kD	—	BC001156
TAF2G	TATA box binding protein (TBP)-associated factor, RNA polymerase II, G, 32 kD	polymerase, TF	U21858
TGFBR1	Human activin receptor-like kinase (ALK-5) mRNA, complete cds	GF, Signal	L11695
DIA4	Human, NAD(P)H: menadione oxidoreductase mRNA	NQO	J03934
MAP2K3	Human mRNA for MAP kinase kinase 3b complete cds, MEK3	Signal	D87116
ATP5JD	ATP synthase, H <sup>+</sup> transporting, mitochondrial F1F0, subunit d	ATPase	AF087135

**[0125]** (3) Selection of Diagnostic Marker Gene for Each Group

**[0126]** Based on the results attained above, 16 subjects for before/after treatment comparison were divided into the PA group (7 subjects) and the PB group (9 subjects). The data on patient/healthy volunteer comparison and the data on before/after treatment comparison were aligned for each patient in each group, and the data were compared and analyzed. The group of genes with reversed expression patterns between the data on patient/healthy volunteer com-

parison and the data on before/after treatment comparison was extracted (PA group: **FIG. 16** (reversed patterns were clearly observed in 4 individuals), Table 9; PB group: **FIG. 17**, Table 10). Concerning the PA group, variation in expression levels of CLK1, PSMC6, TAF2F, P2Y5, CASP3, HSPCA, MSH2, SLC38A2, B2M, and AKAP11 were particularly significant among the genes listed in Table 9. Concerning the PB group, variation in expression levels of CCNA2, HGF, GPR24, PTGER3, COX7A2, BDKRB2, UFD1L, HMG1, PSMA4, and ATP6J were particularly significant among the genes listed in Table 10.

TABLE 9

Group of genes exhibiting significant differences before and after treatment in PA group			
Symbol	Name	Category	GenBank ID
CLK1	<i>Homo sapiens</i> clk1 mRNA; CDC-like kinase 1	CellCycle	L29222
PSMC6	Proteasome (prosome, macropain) 26S subunit, ATPase, 6	ATPase	AF006305
TAF2F	TATA box binding protein (TBP)-associated factor, RNA polymerase II, F, 55 kD	polymerase, TF	U18062
P2Y5	<i>Homo sapiens</i> purinergic receptor P2Y5 mRNA	Signal	AF000546
CASP3	Human cysteine protease CPP32 isoform alpha mRNA, complete cds	Apoptosis, Signal	U13737
HSPCA	<i>Homo sapiens</i> Hsp89-alpha-delta-N mRNA; Heat shock 90 kD protein 1, alpha	hsp	AF028832
MSH2	Human DNA mismatch repair protein MSH2	DNAREPAIR	U04045
SLC38A2	amino acid transporter 2	—	AF259799
B2M	beta-2-microglobulin	—	AY007153
AKAP11	A kinase (PRKA) anchor protein 11 (AKAP11); <i>Homo sapiens</i> mRNA for KIAA0629 protein, partial cds	Signal	AB014529
PSMA4	proteasome (prosome, macropain) subunit, alpha type, 4	—	BC005361
EEF1A1	<i>Homo sapiens</i> eukaryotic translation elongation factor 1 alpha 1 (EEF1A1)	glucocorticoids (Cortisol)	NM_001402
MAP2K6	Human MAP kinase kinase 6 mRNA, complete cds; MEK6	Signal	U39064
BMI1	Human prot-oncogene (BMI-1) mRNA, complete cds	oncogene	L13689
GABPB1	<i>Homo sapiens</i> GA-binding protein transcription factor, beta subunit 1 (53 kD); nuclear respiratory factor-2	mitochondria & stress	NM_005254
PTPRC	Human mRNA for T200 leukocyte common antigen (CD45, LC-A).	Signal	Y00062
TNFRSF6	<i>H. sapiens</i> mRNA for APO-1 cell surface antigen, FAS	Apoptosis, Cytokine, Signal	X63717
FGF2	Human basic fibroblast growth factor (FGF) mRNA (BFGF; FGFB; FGF2)	GF	M27968
GJA4	gap junction protein, alpha 4, 37 kD (connexin 37)	Gap-junciton	M96789
BCL2	Human bcl-2 mRNA; apoptosis regulator bcl2	oncogene, Signal	M14745
SMARCA3	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 3	ATPase	Z46606
IFIT1	Human mRNA for 56-KDa protein induced by interferon	Cytokine	X03557
IFNGR1	Human interferon-gamma receptor mRNA, complete cds	Cytokine, Signal	J03143
FCER1A	Human mRNA for high affinity IgE receptor alpha-subunit (FcER1); Pe fragment of IgE, high affinity I, receptor for; alpha polypeptide	Signal	X06948
GNG2	<i>Homo sapiens</i> clone FLB4307 PRO1107 mRNA	Signal	AF130106
E2F3	<i>Homo sapiens</i> E2F transcription factor 3(E2F3)	TF	Y10479
IL8	Human beta-thromboglobulin-like protein mRNA, complete cds	Cytokine, Signal	M17017
FRAT1	<i>Homo sapiens</i> frequently rearranged in advanced T-cell lymphomas (FRAT1) mRNA	Signal	NM_005479

TABLE 9-continued

Group of genes exhibiting significant differences before and after treatment in PA group			
Symbol	Name	Category	GenBank ID
COX17	<i>Homo sapiens</i> COX17 (yeast) homolog, cytochrome c oxidase assembly protein	mitochondria & stress	NM_005694
GZMA	Human Hanukah factor serine protease (HuHF) mRNA (cytotoxic T-lymphocyte-associated serine esterase 3)	esterase	M18737
CDC10	hCDC10 = CDC10 homolog [human, fetal lung, mRNA, 2314 nt].	CellCycle	S72008
ADH5	Human alcohol dehydrogenase class II (ADH5) mRNA	ADH	M29872
API1	Human inhibitor of apoptosis protein 2 mRNA; Apoptosis inhibitor 1	Appoptosis, Signal	U45879
PPP3CB	Human calcineurin A2 mRNA;	Signal	M29551
GNG10	Human G protein gamma-10 subunit mRNA; Guanine nucleotide binding protein 10	Signal	U31383
MAP3K7	<i>Homo sapiens</i> mitogen-activated protein kinase kinase kinase 7 (MAP3K7), mRNA, TAK1	Signal	NM_003188
POLB	polymerase (DNA directed), beta	polymerase	D29013
NR3C1	Human glucocorticoid receptor alpha mRNA, complete cds	glucocorticoids (Cortisol)	M10901
ITGB1	Integrin, beta 1 (fibronectin receptor, beta polypeptide, antigen CD29 includes MDF2, MSK12);	Signal	X07979
COX6C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIc (COX6C), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_004374
HSJ2	Human heat shock protein, <i>E. coli</i> DnaJ homologue mRNA, complete cds; Heat shock protein, DNAJ-like 2	hsp	L08069
AHR	Human AH-receptor mRNA, complete cds	Ah receptor	L19872
TAF2G	TATA box binding protein (TBP)-associated factor, RNA polymerase II, G, 32 kD	polymerase, TF	U21858
IL1R2	<i>H. sapiens</i> IL-1R2 mRNA for type II interleukin-1 receptor, (cell line CB23).	Cytokine	X59770

[0127]

TABLE 10

Group of genes exhibiting significant differences before and after treatment in PB group			
Symbol	Name	Category	GenBank ID
CCNA2	Human mRNA for cyclin A; Cyclin A2	CellCycle	X51688
HGF	Human hepatocyte growth factor mRNA (HGF); scatter factor (SF); hepatopoeitin A	GF	M60718
GPR24	G protein-coupled receptor 24	—	BC001736
PTGER3	prostaglandin E receptor 3 (subtype EP3)	—	X83860
COX7A2	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIa polypeptide 2 (liver) COX7A2), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_001865
BDKRB2	<i>Homo sapiens</i> bradykinin receptor B2	heart stress	NM_000623
UFD1L	Ubiquitin fusion degradation 1-like	—	BC005087
HMG1	Human mRNA for high mobility group-1 protein (HMG-1).	sulfotransferase	X12597
PSMA4	proteasome (prosome, macropain) subunit, alpha type, 4	—	BC005361
ATP6J	ATPase, H <sup>+</sup> transporting, lysosomal (vacuolar proton pump), member J	ATPase	AF038954
HSPE1	Human chaperonin 10 mRNA; Heat shock 10 kD protein 1	hsp	U07550
IL13RA2	Human interleukin-13 receptor mRNA, complete cds	Cytokine	U70981
COX17	<i>Homo sapiens</i> COX17 (yeast) homolog, cytochrome c oxidase assembly protein	mitochondria & stress	NM_005694
TSSC1	<i>Homo sapiens</i> tumor suppressing STF cDNA 1 (TSSC1) mRNA, complete cds	Supressor	AF019952
PSMA7	proteasome (prosome, macropain) subunit, alpha type, 7	—	BC004427
ATP5J2	ATP synthase, H <sup>+</sup> transporting, mitochondrial F0 complex, subunit f, isoform 2	ATPase	AF047436
POLE	polymerase (DNA directed), epsilon	polymerase	L09561
HTR6	5-hydroxytryptamine (serotonin) receptor 6	—	NM_000871
APG-1	<i>Homo sapiens</i> mRNA for heat shock protein apg-1; Heat shock protein (hsp110 family)	hsp	AB023421
CASP4	Human cysteine protease (ICErel-II) mRNA, complete cds	Appoptosis	U28014
HSPCA	<i>Homo sapiens</i> Hsp89-alpha-delta-N mRNA; Heat shock 90 kD protein 1, alpha	hsp	AF028832
FGF2	Human basic fibroblast growth factor (FGF) mRNA (BFGF; FGFb; FGF2)	GF	M27968
ADH5	Human alcohol dehydrogenase class III (ADH5) mRNA	ADH	M29872
PSMA6	proteasome (prosome, macropain) subunit, alpha type 6	—	X59417
CCNH	Human cyclin H mRNA, complete cds	CellCycle	U11791
COX7C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIIc	mitochondria & stress	NM_001867
SOD1	<i>Homo sapiens</i> superoxide dismutase 1, soluble (amyotrophic lateral	SOD	NM_000454

TABLE 10-continued

Group of genes exhibiting significant differences before and after treatment in PB group			
Symbol	Name	Category	GenBank ID
	sclerosis 1 (adult) (SOD1); Superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult))		
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A	—	X57830
HSJ2	Human heat shock protein, <i>E. coli</i> DnaJ homologue mRNA, complete cds; Heat shock protein, DnaJ-like 2	hsp	L08069
DAP3	Human ionizing radiation resistance conferring protein mRNA; Death associated protein 3	Apoptosis	U18321
UCHL3	Human ubiquitin carboxyl-terminal hydrolase (PGP 9.5, UCH-L3) isozyme L3 mRNA	esterase	M30496
CREBBP	Human CREB-binding protein (CBP) mRNA, complete cds	ATF/CREB	U47741
GSTTLp28	glutathione-S-transferase like; glutathione transferase omega	—	BC000127
PSMA3	proteasome (prosome, macropain) subunit, alpha type, 3	—	BC005265
UBL1	ubiquitin-like 1 (sentrin)	Gap-junciton	U61397
HSBP1	<i>Homo sapiens</i> heat shock factor binding protein 1 HSBP1 mRNA; Heat shock factor binding protein 1	hsp	AF068754
NME2	Human putative NDP kinase (nm23-H2S) mRNA, complete cds; c-myc purine-binding transcription factor puf	TF	M36981
PRDX4	peroxiredoxin 4	—	BC003609
COX4	<i>Homo sapiens</i> cytochrome c oxidase subunit IV (COX4), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_001861
TGFB1	Human activin receptor-like kinase (ALK-5) mRNA, complete cds	GF, Signal	L11695
PSMB7	proteasome (prosome, macropain) subunit, beta type, 7	—	BC000509
COX6C	<i>Homo sapiens</i> cytochrome c oxidase subunit VIc (COX6C), nuclear gene encoding mitochondrial protein	mitochondria & stress	NM_004374
GABRR2	gamma-aminobutyric acid (GABA) receptor, rho 2	—	NM_002043
CASP5	Human cysteine protease (ICErel-III) mRNA, complete cds	Apoptosis	U28015
POLR2H	Human RNA polymerase II subunit (hsRPB8) mRNA; polymerase (RNA) II (DNA directed) polypeptide H	polymerase	U37689
PSMB4	proteasome (prosome, macropain) subunit, beta type, 4	—	S71381
PSMB1	proteasome (prosome, macropain) subunit, beta type, 1	—	BC000508
HSPD1	Heat shock 60 kD protein 1 (chaperonin)	hsp	M34664
ESD	<i>Homo sapiens</i> esterase D mRNA	esterase	AF112219
WISP3	<i>Homo sapiens</i> connective tissue growth factor related protein WISP-3 (WISP3) mRNA, complete cds,	Signal	AF100781
ATP5JD	ATP synthase, H <sup>+</sup> transporting, mitochondrial F1F0, subunit d	ATPase	AF087135

## INDUSTRIAL APPLICABILITY

[0128] The method according to the present invention is a useful method for objectively diagnosing depression or evaluating the course of treatment for patients afflicted with depression in clinical settings.

1. A method of diagnosing depression, wherein gene expression is analyzed using mRNA of a subject's peripheral blood to evaluate whether or not the subject is afflicted with depression, the type of depression of a subject who had been evaluated as being afflicted with depression is identified, and the conditions of depression are then diagnosed in accordance with the type of depression.

2. The method of diagnosing depression according to claim 1, wherein the expression profiles of the marker gene for depression selected from among the genes listed in Table 1 are employed to evaluate whether or not a subject is afflicted with depression and the expression profiles of the marker gene for classification selected from among the genes listed in Table 2 are employed to identify the type of depression to be type PA or PB.

3. The method of diagnosing depression according to claim 2, wherein the marker gene for depression includes at least ATP2A2, SCYA5, STIP1, EEF1A1, GRB10, CASP6, TSSC1, RAB9, NFATC3, and TPR listed in Table 1 and the marker gene for classification includes at least GNG10,

CLK1, P2Y5, IFNGR1, TAF2F, PIM1, MAP2K3, HDGF, INSR, and COX6C listed in Table 2.

4. The method of diagnosing depression according to claim 2, wherein the expression profiles of the marker gene for diagnosing type PA depression selected from among the genes listed in Table 3 are employed to diagnose the conditions of the type PA depression and the expression profiles of the marker gene for diagnosing type PB depression selected from among the genes listed in Table 4 are employed to diagnose the conditions of the type PB depression.

5. The method of diagnosing depression according to claim 4, wherein the marker gene for diagnosing type PA depression includes at least CDC10, GZMA, TNFRSF6, HSPCA, NR3C1, TOPBP1, ARNTL, RAP1A, POLR2B, and ITGB1 listed in Table 3 and the marker gene for diagnosing type PB depression includes at least POU2F2, BCL2L1, DAXX, COX4, CD3GG, FCERIG, NME2, CPT1B, HSPE1, and COX7A2 listed in Table 4.

6. The method of diagnosing depression according to claim 1, wherein the course of treating a single subject is evaluated by comparing and analyzing the gene expression profiles of the subject before and after the treatment.

7. The method of diagnosing depression according to claim 1, wherein the gene expression analysis is carried out using DNA-immobilized solid substrates including chips, arrays, membrane filters, and capillaries.

8. The method of diagnosing depression according to claim 1, wherein the expression profiles of the marker gene for depression selected from among the genes listed in Table 7 are employed to evaluate whether or not a subject is afflicted with depression and the expression profiles of the marker gene for classification selected from among the genes listed in Table 8 are employed to identify the type of depression to be type PA or PB.

9. The method of diagnosing depression according to claim 8, wherein the marker gene for depression includes at least HLA-G, HRH4, PSMB9, ATP2A2, SCYA5, SLC6A4, CASP6, CSF2, HSD3B1, and RAB9 and the marker gene for classification includes at least HSPE1, PSMA4, ADH5, PSMA6, COX17, HMG1, GPR24, COX6C, FGF2, and COX7C.

10. The method of diagnosing depression according to claim 9, wherein the expression profile of the marker gene for diagnosing type PA depression selected from among the genes listed in Table 9 are employed to diagnose the conditions of the type PA depression and the expression profile of the marker gene for diagnosing type PB depression selected from among the genes listed in Table 10 are employed to diagnose the conditions of the type PB depression.

11. The method of diagnosing depression according to claim 10, wherein the marker gene for diagnosing type PA depression includes at least CLK1, PSMC6, TAF2F, P2Y5, CASP3, HSPCA, MSH2, SLC38A2, B2M, and AKAP11 and the marker gene for diagnosing type PB depression includes at least CCNA2, HGF, GPR24, PTGER3, COX7A2, BDKRB2, UFD1L, HMG1, PSMA4, and ATP6J.

12. A solid substrate for diagnosing depression having immobilized thereon probes each independently specifically hybridize to any one of the genes listed in Tables 1 to 4 or the genes listed in Tables 7 to 10 for detecting the target gene.

13. A solid substrate for diagnosing depression according to claim 12 having immobilized thereon probes each inde-

pendently specifically hybridize to any one of the genes listed in Tables 1 to 4 for detecting the target gene, wherein the genes at least include ATP2A2, SCYA5, STIP1, EEF1A1, GRB10, CASP6, TSSC1, RAB9, NFATC3, and TPR listed in Table 1, GNG10, CLK1, P2Y5, IFNGR1, TAF2F, PIM1, MAP2K3, HDGF, INSR, and COX6C listed in Table 2, CDC10, GZMA, TNFRSF6, HSPCA, NR3C1, TOPBP1, ARNTL, RAP1A, POLR2B, and ITGB1 listed in Table 3, and POU2F2, BCL2L1, DAXX, COX4, CD3Q FCER1, NME2, CPT1B, HSPE1, and COX7A2 listed in Table 4.

14. A solid substrate for diagnosing depression according to claim 12 having immobilized thereon probes each independently specifically hybridize to any one of the genes listed in Tables 7 to 10 for detecting the target gene, wherein the genes at least include HLA-G, HRH4, PSMB9, ATP2A2, SCYA5, SLC6A4, CASP6, CSF2, HSD3B1, and RAB9 listed in Table 7, HSPE1, PSMA4, ADH5, PSMA6, COX17, HMG1, GPR24, COX6C, FGF2, and COX7C listed in Table 8, CLK1, PSMC6, TAF2F, P2Y5, CASP3, HSPCA, MSH2, SLC38A2, B2M, and AKAP11 listed in Table 9, and CCNA2, HGF, GPR24, PTGER3, COX7A2, BDKRB2, UFD1L, HMG1, PSMA4, and ATP6J listed in Table 10.

15. A system for diagnosing depression for performing the method of diagnosing depression according to claim 1, which comprises a means for comparing and analyzing the gene expression data of a subject with that of a healthy volunteer and of a patient afflicted with depression, which had been previously obtained, and diagnoses the conditions of depression of the subject in accordance with the type of depression.

16. The system for diagnosing depression according to claim 15, which further comprises a means of comparing and analyzing the gene expression data of a subject, of a healthy volunteer, and of a patient afflicted with depression in combination with the data concerning their age and sex.

\* \* \* \* \*

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摘要(译)

本发明提供了一种以简单, 客观和准确的方式诊断患者抑郁症状的新方法。在该方法中, 使用受试者外周血的mRNA分析基因表达, 以评估受试者是否患有抑郁症, 识别被评估为患有抑郁症的受试者的抑郁类型, 以及然后根据抑郁症的类型诊断抑郁症。

Fig 1

