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(54) **INTERFERON-ALPHA INDUCED GENE**

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(57) **ABSTRACT**

The present invention relates to identification of a gene upregulated by interferon-α administration corresponding to the cDNA sequence set forth in SEQ. ID. No. 1 and SEQ. ID. No. 3. Determination of expression products of this gene is proposed ahaigutility in predicting responsiveness to treatment with interferon-at and othe interferons which act at the Type 1 interferon receptor. Therapeutic use of the protein encoded by the same gene is also envisaged.

INTERFERON-ALPHA INDUCED GENE

FIELD OF THE INVENTION

[0001] The present invention relates to identification of a human gene upregulated by interferon-α (IFN-α) administration, the coding sequence of which is believed to be previously unknown. Detection of expression products of this gene may find use in predicting responsiveness to IFN-α and other interferons which act at the Type 1 interferon receptor. Therapeutic use of the isolated novel protein encoded by the same gene is also envisaged.

BACKGROUND OF THE INVENTION

[0002] IFN-α is widely used for the treatment of a number of disorders. Disorders which may be treated using IFN-α include neoplastic diseases such as leukemia, lymphomas, and solid tumours, AIDS-related Kaposi's sarcoma and viral infections such as chronic hepatitis. IFN-α has also been proposed for administration via the oromucosal route for the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic and viral disease. In particular, IFN-α has been proposed, for example, for the treatment of multiple sclerosis, leprosy, tuberculosis, encephalitis, malaria, cervical cancer, genital herpes, hepatitis B and C, HIV, HPV and HSV-1 and 2. It has also been suggested for the treatment of arthritis, lupus and diabetes. Neoplastic diseases such as multiple myeloma, hairy cell leulkemia, chronic myelogenous leukemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma and brain tumours are also suggested as being treatable by administration of IFN-α via the oromucosal route, i.e. the oral route or the nasal route.

[0003] IFN-α is a member of the Type 1 interferon family, which exert their characteristic biological activities through interaction with the Type 1 interferon receptor. Other Type 1 interferons include IFN-β, IFN-ω and IFN-τ.

[0004] Unfortunately, not all potential patients for treatment with a Type 1 interferon such as interferon-α, particularly, for example, patients suffering from chronic viral hepatitis, neoplastic disease and relapsing remitting multiple sclerosis, respond favourably to Type 1 interferon therapy and only a fraction of those who do respond exhibit long-term benefit. The inability of the physician to confidently predict the therapeutic outcome of Type 1 interferon treatment raises serious concerns as to the cost-benefit ratio of such treatment, not only in terms of wastage of an expensive biopharmaceutical and lost time in therapy, but also in terms of the serious side effects to which the patient is exposed. Furthermore, abnormal production of IFN-α has been shown to be associated with a number of autoimmune diseases. For these reasons, there is much interest in identifying Type 1 interferon responsive genes since Type 1 interferons exert their therapeutic action by modulating the expression of a number of genes. Indeed, it is the specific pattern of gene expression induced by Type 1 interferon treatment that determines whether a patient will respond favourably or not to the treatment.

SUMMARY OF THE INVENTION

[0005] A human gene cDNA has now been identified as corresponding to a mouse gene upregulated by administration of IFN-α by an oromucosal route or intraperitoneally and is believed to represent a novel DNA. The corresponding human gene is thus now also designated an IFN-α upregulated gene.

[0006] The protein encoded by the same gene is referred to below as HuIFRG 68.1 protein. This protein, and functional variants thereof, are now envisaged as therapeutic agents, in particular for use as an anti-viral, anti-tumour or immunomodulatory agent. For example, they may be used in the treatment of autoimmune, mycobacterial, neurodegenerative, parasitic or viral disease, arthritis, diabetes, lupus, multiple sclerosis, leprosy, tuberculosis, encephalitis, malaria, cervical cancer, genital herpes, hepatitis B or C, HIV, HPV, HSV-1 or 2, or neoplastic disease such as multiple myeloma, hairy cell leukemia, chronic myelogenous leulkemia, low grade lymphoma, cutaneous T-cell lymphoma, carcinoid tumours, cervical cancer, sarcomas including Kaposi's sarcoma, kidney tumours, carcinomas including renal cell carcinoma, hepatic cellular carcinoma, nasopharyngeal carcinoma, haematological malignancies, colorectal cancer, glioblastoma, laryngeal papillomas, lung cancer, colon cancer, malignant melanoma or brain tumours. In other words, such a protein may find use in treating any Type 1 interferon treatable disease.

[0007] Determination of the level of HuIFRG 68.1 protein or a naturally-occurring variant thereof, or the corresponding mRNA, in cell samples of Type 1 interferon-treated patients, e.g. patients treated with IFN-α, e.g. such as by the oromucosal route or intravenously, may also be used to predict responsiveness to such treatment. It has additionally been found that alternatively, and more preferably, such responsiveness may be judged, for example, by treating a sample of human peripheral blood mononuclear cells in vitro with a Type 1 interferon and looking for upregulation or downregulation of an expression product, preferably mRNA, corresponding to the HuIFRG 68.1 gene.

[0008] According to a first aspect of the invention, there is thus provided an isolated polypeptide comprising;

[0009] (i) the amino acid sequence of SEQ ID NO: 2;

[0010] (ii) a variant thereof having substantially similar function, e.g. an immunomodulatory activity and/or an anti-viral activity and/or an anti-tumour activity; or

[0011] (iii) a fragment of (i) or (ii) which retains substantially similar function, e.g. an immunomodulatory activity and/or an anti-viral activity and/or an anti-tumour activity.

[0012] In a preferred embodiment of the first aspect of the invention, such an isolated polypeptide may comprise:

[0013] (i) the amino acid sequence of SEQ ID NO: 4;

[0014] (ii) a variant thereof having substantially similar function; or

[0015] (iii) a fragment of (i) or (ii) which retains substantially similar function.

[0016] The invention also provides such a protein for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent. As indicated above, such use may extend to any Type 1 interferon treatable disease.

[0017] According to another aspect of the invention, there is provided an isolated polynucleotide encoding a polypeptide of the invention as defined above or a complement thereof. Such a polynucleotide will typically include a sequence comprising:

[0018] (a) the nucleic acid of SEQ. ID. No. 1 or the coding sequence thereof and/or a sequence complementary thereto;

[0019] (b) a sequence which hybridises, e.g. under stringent conditions, to a sequence complementary to a sequence as defined in (a);

[0020] (c) a sequence which is degenerate as a result of the genetic code to a sequence as defined in (a) or (b);

[0021] (d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c).

[0022] In a preferred embodiment, such a polynucleotide will include a sequence comprising:

[0023] (a) the nucleic acid of SEQ ID No: 3 or the coding sequence thereof and/or a sequence complementary thereto;

[0024] (b) a sequence which hybridises, e.g. under stringent conditions, to a sequence complementary to a sequence complementary to a sequence as defined in (a);

[0025] (c) a sequence which is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or

[0026] (d) a sequence having at least 60% identity to a sequence as defined on (a), (b) or (c).

[0027] The invention also provides;

[0028] an expression vector which comprises a polynucleotide of the invention and which is capable of expressing a polypeptide of the invention;

[0029] a host cell containing an expression vector of the invention;

[0030] an antibody specific for a polypeptide of the invention;

[0031] a method of treating a subject having a Type 1 interferon treatable disease, which method comprises administering to the said patient an effective amount of HuIFRG 68.1 protein or a functional variant thereof

[0032] use of such a polypeptide in the manufacture of a medicament for use in therapy as an anti-viral or anti-tumour or immunomodulatory agent, more particularly for use in treatment of a Type 1 interferon treatable disease;

[0033] a pharmaceutical composition comprising a polypeptide of the invention and a pharmaceutically acceptable carrier or diluent;

[0034] a method of producing a polypeptide of the invention, which method comprises maintaining host cells of the invention under conditions suitable for obtaining expression of the polypeptide and isolating the said polypeptide;

[0035] a polynucleotide of the invention, e.g. in the form of an expression vector, which directs expression in vivo of a polypeptide as defined above for use in therapeutic treatment of a human or non-human animal, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent;

[0036] a pharmaceutical composition comprising such a polynucleotide and a pharmaceutically acceptable carrier or diluent;

[0037] a method of treating a subject having a Type 1 interferon treatable disease, which method comprises administering to said patient an effective amount of such a polynucleotide;

[0038] use of such a polynucleotide in the manufacture of a medicament, e.g. a vector preparation, for use in therapy as an anti-viral, anti-tumour or immunomodulatory agent, more particularly for use in treating a Type 1 interferon treatable disease; and

[0039] a method of identifying a compound having immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity comprising providing a cell capable of expressing HuIFRG 68.1 protein or a naturally occurring variant thereof, incubating said cell with a compound under test and monitoring for upregulation of HuIFRG 68.1 gene expression.

[0040] In a still further aspect, the invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN-α treatment (such as IFN-α treatment by the oromucosal route or a parenteral route, for example, intravenously, subcutaneously, or intramuscularly), which comprises determining the level of HuIFRG 68.1 protein or a naturally-occurring variant thereof, e.g. an allelic variant, or the corresponding mRNA, in a cell sample from said patient, e.g. a blood sample, wherein said sample is obtained from said patient following administration of a Type 1 interferon, e.g. IFN-α by an oromucosal route or intravenously, or is treated prior to said determining with a Type 1 interferon such as IFN-α in vitro. The invention also extends to kits for carrying out such testing.

BRIEF DESCRIPTION OF THE SEQUENCES

[0041] SEQ. ID. No. 1 is the amino acid sequence of human protein HuIFRG 68.1 and its encoding cDNA.

[0042] SEQ. ID. No.2 is the amino acid sequence alone of HuIFRG 68.1 protein.

[0043] SEQ. ID. No. 3 is the amino acid sequence of a variant of HuIFRG 68.1 which is extended at the amino terminus, and its coding sequence.

[0044] SEQ. ID. No. 4 is the amino acid sequence alone of a variant of HuIFRG 68.1 protein which is extended at the amino terminus.

DETAILED DESCRIPTION OF THE INVENTION

[0045] As indicated above, human protein HuIFRG 68.1 and functional variants thereof are now envisaged as thera-

peutically useful agents, more particularly for use as an anti-viral, anti-tumour or immunomodulatory agent.

[0046] A variant of HuIFRG 68.1 protein for this purpose may be a naturally occurring variant, either an allelic variant or species variant, which has substantially the same functional activity as HuIFRG 68.1 protein and is also upregulated in response to administration of IFN-α. Alternatively, a variant of HuIFRG 68.1 protein for therapeutic use may comprise a sequence which varies from SEQ. ID. No. 2 or from SEQ. ID. No. 4 but which is a non-natural mutant.

[0047] The term "functional variant" refers to a polypeptide which has the same essential character or basic function of HuIFRG 68.1 protein. The essential character of HuIFRG 68.1 protein may be deemed to be as an immunomodulatory peptide. A functional variant polypeptide may show additionally or alternatively anti-viral activity and/or anti-tumour activity.

[0048] Desired anti-viral activity may, for example, be tested or monitored as follows. A sequence encoding a variant to be tested is cloned into a retroviral vector such as a retroviral vector derived from the Moloney murine leulkemia virus (MoMuLV) containing the viral packaging signal ψ, and a drug-resistance marker. A pantropic packaging cell line containing the viral gag, and pol, genes is then co-transfected with the recombinant retroviral vector and a plasmid, pVSV-G, containing the vesicular stomatitis virus envelope glycoprotein in order to produce high-titre infectious replication incompetent virus (Burns et al., Proc. Natl. Acad. Sci. USA 84, 5232-5236). The infectious recombinant virus is then used to transfect interferon sensitive fibroblasts or lymphoblastoid cells and cell lines that stably express the variant protein are then selected and tested for resistance to virus infection in a standard interferon bio-assay (Tovey et al., Nature, 271, 622-625, 1978). Growth inhibition using a standard proliferation assay (Mosmann, T., J. Immunol. Methods, 65, 55-63, 1983) and expression of MHC class I and class II antigens using standard techniques may also be determined.

[0049] A desired functional variant of HuIFRG 68.1 may consist essentially of the sequence of SEQ. ID. No. 2 or of SEQ. ID. No. 4. A functional variant of SEQ. ID. No.2 or of SEQ. ID. No. 4 may be a polypeptide which has a least 60% to 70% identity, preferably at least 80% or at least 90% and particularly preferably at least 95%, at least 97% or at least 99% identity with the amino acid sequence of SEQ. ID. No. 2 or of SEQ. ID. No. 4 over a region of at least 20, preferably at least 30, for instance at least 100 contiguous amino acids or over the full length of SEQ. ID. No. 2 or of SEQ. D. No. 4. Methods of measuring protein identity are well known in the art.

[0050] Amino acid substitutions may be made, for example from 1, 2 or 3 to 10, 20 or 30 substitutions. Conservative substitutions may be made, for example according to the following Table. Amino acids in the same block in the second column and preferably in the same line in the third column may be substituted for each other.

ALIPHATIC	Non-polar	GAP
		ILV
	Polar-uncharged	CSTM
		NQ
	Polar-charged	DE
		KR
AROMATIC		HFWY

[0051] Variant polypeptide sequences for therapeutic use in accordance with the invention may be shorter polypeptide sequences, for example, a peptide of at least 20 amino acids or up to 50, 60, 70, 80, 100, 150 or 200 amino acids in length is considered to fall within the scope of the invention provided it retains appropriate biological activity of HuIFRG 68.1 protein. In particular, but not exclusively, this aspect-of the invention encompasses the situation when the variant is a fragment of a complete natural naturally-occurring protein sequence.

[0052] Also encompassed by the invention are modified forms of HuIFRG 68.1 protein and fragments thereof which can be used to raise anti-HuIFRG 68.1 protein antibodies. Such variants will comprise an epitope of the HuIFRG 68.1 protein.

[0053] Polypeptides of the invention may be chemically modified, e.g. post-translationally modified. For example, they may be glycosylated and/or comprise modified amino acid residues. They may also be modified by the addition of a sequence at the N-terminus and/or C-terminus, for example by provision of histidine residues or a T7 tag to assist their purification or by the addition of a signal sequence to promote insertion into the cell membrane. Such modified polypeptides fall within the scope of the term "polypeptide" of the invention.

[0054] A polypeptide of the invention may be labelled with a revealing label. The revealing label may be any suitable label which allows the polypeptide to be detected. Suitable labels include radioisotopes such as ^{125}I, ^{35}S or enzymes, antibodies, polynucleotides and linkers such as biotin. Labelled polypeptides of the invention may be used in assays. In such assays it may be preferred to provide the polypeptide attached to a solid support. The present invention also relates to such labelled and/or immobilised polypeptides packaged in the form of a kit in a container. The kit may optionally contain other suitable reagent(s), control(s) or instructions and the like.

[0055] The polypeptides of the invention may be made synthetically or by recombinant means. Such polypeptides of the invention may be modified to include non-naturally occurring amino acids, e.g. D amino acids. Variant polypeptides of the invention may have modifications to increase stability in vitro and/or in vivo. When the polypeptides are produced by synthetic means, such modifications may be introduced during production. The polypeptides may also be modified following either synthetic or recombinant production.

[0056] A number of side chain modifications are known in the protein modification art and may be present in polypeptides of the invention. Such modifications include, for example, modifications of amino acids by reductive alkyla-

tion by reaction with an aldehyde followed by reduction with $NaBH_4$, amidination with methylacetimidate or acylation with acetic anhydride.

[0057] Polypeptides of the invention will be in substantially isolated form. It will be understood that the polypeptides may be mixed with carriers or diluents which will not interfere with the intended purpose of the polypeptide and still be regarded as substantially isolated. A polypeptide of the invention may also be in substantially purified form, in which case it will generally comprise the polypeptide in a preparation in which more than 90%, for example more than 95%, 98% or 99%, by weight of polypeptide in the preparation is a polypeptide of the invention.

[0058] Polynucleotides

[0059] The invention also includes isolated nucleotide sequences that encode HuIFRG 68.1 protein or a variant thereof as well as isolated nucleotide sequences which are complementary thereto. The nucleotide sequence may be DNA or RNA, single or double stranded, including genomic DNA, synthetic DNA or cDNA. Preferably the nucleotide sequence is a DNA sequence and most preferably, a cDNA sequence.

[0060] As indicated above, such a polynucleotide will typically include a sequence comprising:

[0061] (a) the nucleic acid of SEQ. ID. No. 1 or SEQ. ID. No. 3 or the coding sequence thereof and/or a sequence complementary thereto;

[0062] (b) a sequence which hybridises, e.g. under stringent conditions, to a sequence complementary to a sequence as defined in (a);

[0063] (c) a sequence which is degenerate as a result of the genetic code to a sequence as defined in (a) or (b);

[0064] (d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c).

[0065] Polynucleotides comprising an appropriate coding sequence can be isolated from human cells or synthesised according to methods well known in the art, as described by way of example in Sambrook et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory Press.

[0066] Polynucleotides of the invention may include within them synthetic or modified nucleotides. A number of different types of modification to polynucleotides are known in the art. These include methylphosphonate and phosphothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. Such modifications may be carried out in order to enhance the in vivo activity or lifespan of polynucleotides of the invention.

[0067] Typically a polynucleotide of the invention will include a sequence of nucleotides, which may preferably be a contiguous sequence of nucleotides, which is capable of hybridising under selective conditions to the coding sequence or the complement of the coding sequence of SEQ. ID. No. 1 or SEQ. ID. No. 3. Such hybridisation will occur at a level significantly above background. Background hybridisation may occur, for example, because of other cDNAs present in a cDNA library. The signal level generated by the interaction between a polynucleotide of the invention and the coding sequence or complement of the coding sequence of SEQ. ID. No. 1 or SEQ. ID. No. 3 will typically be at least 10 fold, preferably at least 100 fold, as intense as interactions between other polynucleotides and the coding sequence of SEQ. ID. No. 1 or SEQ. ID. No. 3. The intensity of interaction may be measured, for example, by radiolabelling the probe, e.g. with ^{32}P. Selective hybridisation may typically be achieved using conditions of low stringency (0.3 M sodium chloride and 0.03 M sodium citrate at about 40° C.), medium stringency (for example, 0.3 M sodium chloride and 0.03 M sodium citrate at about 50° C.) or high stringency (for example, 0.03 M sodium chloride and 0.03 M sodium citrate at about 60° C.).

[0068] The coding sequence of SEQ ID No: 1 or SEQ ID No: 3 may be modified by nucleotide substitutions, for example from 1, 2 or 3 to 10, 25, 50 or 100 substitutions. Degenerate substitutions may be made and/or substitutions may be made which would result in a conservative amino acid substitution when the modified sequence is translated, for example as shown in the table above. The coding sequence of SEQ ID NO: 1 or SEQ ID No: 3 may alternatively or additionally be modified by one or more insertions and/or deletions and/or by an extension at either or both ends.

[0069] A polynucleotide of the invention capable of selectively hybridising to a DNA sequence selected from SEQ. ID No.1 or 3, the coding sequence thereof and DNA sequences complementary thereto will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% or 97%, homologous to the target sequence. This homology may typically be over a region of at least 20, preferably at least 30, for instance at least 40, 60 or 100 or more contiguous nucleotides.

[0070] Any combination of the above mentioned degrees of homology and minimum sized may be used to define polynucleotides of the invention, with the more stringent combinations (i.e. higher homology over longer lengths) being preferred. Thus for example a polynucleotide which is at least 80% homologous over 25, preferably over 30 nucleotides forms may be found suitable, as may be a polynucleotide which is at least 90% homologous over 40 nucleotides.

[0071] Homologues of polynucleotide or protein sequences as referred to herein may be determined in accordance with well-known means of homology calculation, e.g. protein homology may be calculated on the basis of amino acid identity (sometimes referred to as "hard homology"). For example the UWGCG Package provides the BESTFIT program which can be used to calculate homology, for example used on its default settings, (Devereux et al. (1984) Nucleic Acids Research 12, 387-395). The PILEUP and BLAST algorithms can be used to calculate homology or line up sequences or to identify equivalent or corresponding sequences, typically used on their default settings, for example as described in Altschul S. F. (1993) J. Mol. Evol. 36,290-300; Altschul, S. F. et al. (1990) J. Mol. Biol. 215,403-10.

[0072] Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (http://www.ncbi.nhn.nih.gov/). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query

sequence that either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighbourhood word score threshold (Altschul et al., supra). These initial neighbourhood word hits act as seeds for initiating searches to find HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extensions for the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLAST program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henilkoff and Henikoff(1992) Proc. Natl. Acad. Sci. USA 89,10915-10919) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

[**0073**] The BLAST algorithm performs a statistical analysis of the similarity between two sequences; see e.g., Karlin and Altschul (1993) Proc. Natl. Acad. Sci. USA 90: 5873-5787. One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a sequence is considered similar to another sequence if the smallest sum probability in comparison of the first sequence to the second sequence is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

[**0074**] Polynucleotides according to the invention have utility in production of the proteins according to the invention, which may take place in vitro, in vivo or ex vivo. In such a polynucteotide, the coding sequence for the desired protein of the invention will be operably-linked to a promoter sequence which is capable of directing expression of the desired protein in the chosen host cell. Such a polynucleotide will generally be in the form of an expression vector. Polynucleotides of the invention, e.g. in the form of an expression vector, which direct expression in vivo of a polypeptide of the invention having immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity may also be used as a therapeutic agent.

[**0075**] Expression vectors for such purposes may be constructed in accordance with conventional practices in the art of recombinant DNA technology. They may, for example, involve the use of plasmid DNA. They may be provided with an origin of replication. Such a vector may contain one or more selectable marker genes, for example an ampicillin resistance gene in the case of a bacterial plasmid. Other features of vectors of the invention may include appropriate initiators, enhancers and other elements, such as for example polyadenylation signals which may be desirable, and which are positioned in the correct orientation, in order to allow for protein expression. Other suitable non-plasmid vectors would be apparent to persons skilled in the art. By way of further example in this regard reference is made again to Sambrook et al., 1989 (supra). Such vectors additionally include, for example, viral vectors. Examples of suitable viral vectors include herpes simplex viral vectors, replication-defective retroviruses, including lentiviruses, adenoviruses, adeno-associated virus, HPV viruses (such as HPV-16 and HPV-18) and attenuated influenza virus vectors.

[**0076**] Promoters and other expression regulation signals may be selected to be compatible with the host cell for which expression is designed. For example, yeast promoters include *S. cerevisiae* GAL4 and ADH promoters, *S. pombe* nmt1 and adh promoter. Mammalian promoters include the metallothionein promoter which can be induced in response to heavy metals such as cadmium and P-actin promoters. Viral promoters such as the SV40 large T antigen promoter or adenovirus promoters may also be used. Other examples of viral promoters which may be employed include the Moloney murine leukemia virus long terminal repeat (LV LTR), the rous sarcoma virus (RSV) LTR promoter, the human cytomegalovirus (CMV) IE promoter, and HPV promoters, particularly the HPV.upstream regulatory region (URR). Other suitable promoters will be well-known to those skilled in the recombinant DNA art.

[**0077**] An expression vector of the invention may further include sequences flanking the coding sequence for the desired polypeptide of the invention providing sequences homologous to eukaryotic genomic sequences, preferably mammalian genomic sequences, or viral genomic sequences. This will allow the introduction of such polynucleotides of the invention into the genome of eulcaryotic cells or viruses by homologous recombination. In particular, a plasmid vector comprising the expression cassette flanlked by viral sequences can be used to prepare a viral vector suitable for delivering the polynucleotides of the invention to a mammalian cell.

[**0078**] The invention also includes cells in vitro, for example prokaryotic or eukaryotic cells, which have been modified to express the HuIFRG 68.1 protein or a variant thereof. Such cells include stable, e.g. eulkaryotic, cell lines wherein a polynucleotide encoding HuIFRG 68.1 protein or a variant thereof is incorporated into the host genome. Host cells of the invention may be mammalian cells or insect cells, lower eukaryotic cells, such as yeast or prokaryotic cells such as bacterial cells. Particular examples of cells which may be modified by insertion of vectors encoding for a polypeptide according to the invention include mammalian HEK293T, CHO, HeLa and COS cells. Preferably a cell line may be chosen which is not only stable, but also allows for mature glycosylation of a polypeptide. Expression may, for example, be achieved in transformed oocytes.

[**0079**] A polypeptide of the invention may be expressed in cells of a transgenic non-human animal, preferably a mouse. A transgenic non-human animal capable of expressing a polypeptide of the invention is included within the scope of the invention.

[**0080**] Polynucleotides according to the invention may also be inserted into vectors as described above in an antisense orientation in order to provide for the production of antisense sequences. Antisense RNA or other antisense polynucleotides may also be produced by synthetic means.

[**0081**] A polynucleotide, e.g. in the form of an expression vector, capable of expressing in vivo an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ. ID. No. 2, or a naturally-occurring variant thereof, for example that defined by SEQ ID No. 4, for use in therapeutic

treatment of a human or non-human animal is also envisaged as constituting an additional aspect of the invention. Such a polynucleotide will find use in treatment of diseases associated with upregulation of HuIFRG 68.1 protein.

[0082] Polynucleotides of the invention extend to sets of primers for nucleic acid amplification which target sequences within the cDNA for a polypeptide of the invention, e.g. pairs of primers for PCR amplification. The invention also provides probes suitable for targeting a sequence within a cDNA or RNA for a polypeptide of the invention which may be labelled with a revealing label, e.g. a radioactive label or a non-radioactive label such as an enzyme or biotin. Such probes may be attached to a solid support. Such a solid support may be a micro-array (also commonly referred to as nucleic acid, probe or DNA chip) carrying probes for further nucleic acids, e.g. mRNAs or amplification products thereof corresponding to other Type 1 interferon upregulated genes, e.g. such genes identified as upregulated in response to oromucosal or intravenous administration of IFN-α. Methods for constructing such micro-arrays are well-known (see, for example, EP-B 0476014 and 0619321 of Affymax Technologies N.V. and Nature Genetics Supplement January 1999 entitled "The Chipping Forecast").

[0083] The nucleic acid sequence of such a primer or probe will preferably be at least 10, preferably at least 15 or at least 20, for example at least 25, at least 30 or at least 40 nucleotides in length. It may, however, be up to 40, 50, 60, 70, 100 or 150 nucleotides in length or even longer.

[0084] Another aspect of the invention is the use of probes or primers of the invention to identify mutations in HuIFRG 68.1 genes, for example single nucleotide polymorphisms (SNPs).

[0085] As indicated above, in a still further aspect the present invention provides a method of identifying a compound having immunomodulatory activity and/or antiviral activity and/or anti-tumour activity comprising providing a cell capable of expressing HuIFRG 68.1 protein or a naturally-occurring variant thereof, incubating said cell with a compound under test and monitoring for upregulation of HuIFRG 68.1 gene expression. Such monitoring may be by probing for mRNA encoding HuIFRG 68.1 protein or a naturally-occurring variant thereof. Alternatively antibodies or antibody fragments capable of specifically binding one or more of HuIFRG 68.1 and naturally-occurring variants thereof may be employed.

[0086] Antibodies

[0087] According to another aspect, the present invention also relates to antibodies (for example polyclonal or preferably monoclonal antibodies, chimeric antibodies, humanised antibodies and fragments thereof which retain antigen-binding capability) which have been obtained by conventional techniques and are specific for a polypeptide of the invention. Such antibodies could, for example, be useful in purification, isolation or screening methods involving immunoprecipitation and may be used as tools to further elucidate the function of HuIFRG 68.1 protein or a variant thereof. They may be therapeutic agents in their own right. Such antibodies may be raised against specific epitopes of proteins according to the invention. An antibody specifically binds to a protein when it binds with high affinity to the protein for which it is specific but does not bind or binds with only low affinity to other proteins. A variety of protocols for competitive binding or immunoradiometric assays to determine the specific binding capability of an antibody are well-known.

[0088] Pharmaceutical Compositions

[0089] A polypeptide of the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. The pharmaceutical carrier or diluent may be, for example, an isotonic solution. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methyl cellulose, carboxymethylcellulose or polyvinyl pyrrolidone; desegregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film coating processes.

[0090] Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

[0091] Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methyl cellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspensions or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

[0092] Solutions for intravenous administration or infusions may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

[0093] A suitable dose of HuIFRG 68.1 protein or a functional analogue thereof for use in accordance with the invention may be determined according to various parameters, especially according to the substance used; the age, weight and condition of the patient to be treated; the route of administration; and the required regimen. Again, a physician will be able to determine the required route of administration and dosage for any particular patient. A typical daily dose may be from about 0.1 to 50 mg per kg, preferably from about 0.1 mg/kg to 10 mg/kg of body weight, according to the activity of the specific inhibitor, the age, weight and condition of the subject to be treated, and the frequency and route of administration. Preferably, daily dosage levels may be from 5 mg to 2 g.

[0094] A polynucleotide of the invention suitable for therapeutic use will also typically be formulated for administration with a pharmaceutically acceptable carrier or diluent. Such a polynucleotide may be administered by any known technique whereby expression of the desired polypeptide can be attained in vivo. For example, the

polynucleotide may be introduced by injection, preferably intradermally, subcutaneously or intramuscularly. Alternatively, the nucleic acid may be delivered directly across the skin using a particle-mediated delivery device. A polynucleotide of the invention suitable for therapeutic nucleic acid may alternatively be administered to the oromucosal surface for example by intranasal or oral administration.

[0095] A non-viral vector of the invention suitable for therapeutic use may, for example, be packaged into liposomes or into surfactant containing vector delivery particles. Uptake of nucleic acid constructs of the invention may be enhanced by several known transfection techniques, for example those including the use of transfection agents. Examples of these agents include cationic agents, for example calcium phosphate and DEAE dextran and lipofectants, for example lipophectam and transfectam. The dosage of the nucleic acid to be administered can be varied. Typically, the nucleic acid will be administered in the range of from 1 pg to 1 mg, preferably from 1 pg to 10 μg nucleic acid for particle-mediated gene delivery and from 10 μg to 1 mg for other routes.

[0096] Prediction of Type 1 Interferon Responsiveness

[0097] As also indicated above, in a still further aspect the present invention provides a method of predicting responsiveness of a patient to treatment with a Type 1 interferon, e.g. IFN-α treatment such as IFN-α treatment by an oromucosal route or intravenously, which comprises determining the level of HuIFRG 68.1 protein or a naturally-occurring variant thereof, for example a protein having the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, or the corresponding mRNA, in a cell sample from said patient, wherein said sample is taken from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon in vitro.

[0098] Preferably, the Type 1 interferon for testing responsiveness will be the Type 1 interferon selected for treatment. It may be administered by the proposed treatment route and at the proposed treatment dose. Preferably, the subsequent sample analysed may be, for example, a blood sample or a sample of peripheral blood mononuclear cells (PBMCs) isolated from a blood sample.

[0099] More conveniently and preferably, a sample obtained from the patient comprising PBMCs isolated from blood may be treated in vitro with a Type 1 interferon, e.g. at a dosage range of about 1 to 10,000 IU/ml. Such treatment may be for a period of hours, e.g. about 7 to 8 hours. Preferred treatment conditions for such in vitro testing may be determined by testing PBMCs taken from normal donors with the same interferon and looking for upregulation of an appropriate expression product. Again, the Type 1 interferon employed will preferably be the Type 1 interferon proposed for treatment of the patient, e.g. recombinant IFN-α. PBMCs for such testing may be isolated in conventional manner from a blood sample using Ficoll-Hypaque density gradients. An example of a suitable protocol for such in vitro testing of Type 1 interferon responsiveness is provided in Example 3 below.

[0100] The sample, if appropriate after in vitro treatment with a Type 1 interferon, may be analysed for the level of HuIFRG 68.1 protein or a naturally-occurring variant thereof. This may be done using an antibody or antibodies capable of specifically binding one or more of HuIFRG 68.1 protein and naturally-occurring variants thereof, e.g. allelic variants thereof. Preferably, however, the sample will be analysed for mRNA encoding HuIFRG 68.1 protein or a naturally-occurring variant thereof. Such mRNA analysis may employ any of the techniques known for detection of mRNAs, e.g. Northern blot detection or mRNA differential display. A variety of known nucleic acid amplification protocols may be employed to amplify any mRNA of interest present in the sample, or a portion thereof, prior to detection. The mRNA of interest, or a corresponding amplified nucleic acid, may be probed for using a nucleic acid probe attached to a solid support. Such a solid support may be a micro-array as previously discussed above carrying probes to determine the level of further mRNAs or amplification products thereof corresponding to Type 1 interferon upregulated genes, e.g. such genes identified as upregulated in response to oromucosal or intravenous administration of IFN-α.

[0101] The following examples illustrate the invention:

EXAMPLES

Example 1

[0102] Previous experiments had shown that the application of 5 μl of crystal violet to each nostril of a normal adult mouse using a P20 Eppendorf micropipette resulted in an almost immediate distribution of the dye over the whole surface of the oropharyngeal cavity. Staining of the oropharyngeal cavity was still apparent some 30 minutes after application of the dye. These results were confirmed by using ^{125}I-labelled recombinant human IFN-α1-8 applied in the same manner. The same method of administration was employed to effect oromucosal administration in the studies which are described below.

[0103] Six week old, male DBA/2 mice were treated with either 100,000 IU of recombinant murine interferon α (IFN α) purchased from Life Technologies Inc, in phosphate buffered saline (PBS), 10 μg of recombinant human interleukin 15 (IL-15) purchased from Protein Institute Inc, PBS containing 100 μg/ml of bovine serum albumin (BSA), or left untreated. Eight hours later, the mice were sacrificed by cervical dislocation and the lymphoid tissue was removed surgically from the oropharyngeal cavity and snap frozen in liquid nitrogen and stored at −80° C. RNA was extracted from the lymphoid tissue by the method of Chomczynski and Sacchi 1987, (Anal. Biochem. 162, 156-159) and subjected to mRNA Differential Display Analysis (Lang, P. and Pardee, A. B., Science, 257, 967-971).

[0104] Differential Display Analysis

[0105] Differential display analysis was carried out using the "Message Clean" and "RNA image" kits of the GenHunter Corporation essentially as described by the manufacturer. Briefly, RNA was treated with RNase-free DNase, and 1 μg was reverse-transcribed in 100 μl of reaction buffer using either one or the other of the three one-base anchored

oligo-(dT) primers A, C, or G. RNA was also reverse-transcribed using one or the other of the 9 two-base anchored oligo-(dT) primers AA, CC, GG, AC, CA, GA, AG, CG, GC. All the samples to be compared were reverse transcribed in the same experiment, separated into aliquots and frozen. The amplification was performed with only 1 μl of the reverse transcription sample in 10 μl of amplification mixture containing Taq DNA polymerase and α- ^{33}P dATP (3,000 Ci/mmole). Eighty 5' end (HAP) random sequence primers were used in combination with each of the (HT1 1) A, C, G, AA, CC, GG, AC, CA, GA, AG, CG or GC primers. Samples were then run on 7% denaturing polyacrylamide gels and exposed to authoradiography. Putative differentially expressed bands were cut out, reamplified according to the instructions of the supplier, and further used as probes to hybridize Northern blots of RNA extracted from the oropharyngeal cavity of IFN treated, IL-15 treated, and excipient treated animals.

[0106] Cloning and Sequencing

[0107] Re-amplified bands from the differential display screen were cloned in the Sfr 1 site of the pPCR-Script SK(+) plasmid (Stratagene) and cDNAs amplified from the rapid amplification of cDNA ends were isolated by TA cloning in the pCR3 plasmid (Invitrogen). DNA was sequenced using an automatic di-deoxy sequencer (Perkin Elmer ABI PRISM 377).

[0108] Isolation of Human cDNA

[0109] Differentially expressed murine 3' sequences identified from the differential display screen were compared with random human expressed sequence tags (EST) present in the dbEST database of GenBank™ of the United States National Center for Biotechnology Information (NCBI). The sequences potentially related to the murine EST isolated from the differential display screen were combined in a contig and used to construct a human consensus sequence corresponding to a putative cDNA. One such cDNA was found to be 2175 nucleotides in length. This corresponded to a mouse gene whose expression was found to be enhanced approximately 8-fold in the lymphoid tissue of the oral cavity of mice following oromucosal administration of IFN-α.

[0110] In order to establish that this putative cDNA corresponded to an authentic human gene, primers derived from the 5' and 3' ends of the consensus sequence were used to synthesise cDNA from mRNA extracted from human peripheral blood leukocytes (PBL) by specific reverse transcription and PCR amplification. A unique cDNA fragment of the predicted size was obtained, cloned and sequenced (SEQ. ID. No.1). This human cDNA contains an open reading frame (ORF) of 1818 bp in length at positions 42-1859 encoding a protein of 605 amino acids with a deduced molecular weight of 68.45 kDa (SEQ. ID. No. 2).

[0111] A second cDNA was found to be 3411 nucleotides in length. As described above, a unique cDNA fragment of the predicted size was obtained, cloned and sequenced (SEQ ID No: 3). This human cDNA contains an open reading frame (ORF) of 3297 bp in length at positions 95 to 3391 encoding a protein of 1098 amino acids with deduced molecular weight of 124 kDa (SEQ ID No: 4). The nucleotide sequence of SEQ ID No: 3 is a longer form of the nucleotide sequence of SEQ ID No: 1 and encodes a variant of the HuIFRG 68.1 protein of SEQ ID No: 2 which is extended at the amino terminus.

Example 2

[0112] Intravenous Administration of IFN-α

[0113] Male DBA/2 mice were injected intraperitoneally with 100,000 IU of recombinant murine IFN-α purchased from Life Technologies Inc. in 200 μl of PBS or treated with an equal volume of PBS alone. Eight hours later, the animals were sacrificed by cervical dislocation and the spleen was removed using conventional procedures. Total RNA was extracted by the method of Chomczynski and Sacchi (Anal. Biochem. (1987) 162,156-159) and 10.0 μg of total RNA per sample was subjected to Northern blotting in the presence of glyoxal and hybridised with a cDNA probe for HuIFRG 68.1 mRNA as described by Dandoy-Dron et al.(J. Biol. Chem. (1998) 273, 7691-7697). The blots were first exposed to autoradiography and then quantified using a Phospholmager according to the manufacturer's instructions. Enhanced levels of mRNA for HuIFRG 68.1 protein (approximately 10 fold) were detected in samples of RNA extracted from spleens of IFN-α treated animals relative to animals treated with excipient alone.

Example 3

[0114] Testing Type 1 Interferon Responsiveness in vitro

[0115] Human Daudi, Jurkat or HeLa cells were treated in vitro with 10,000 IU of recombinant human IFN-α2 (Intron A from Schering-Plough) in PBS or with an equal volume of PBS alone. Eight hours later the cells were centrifuged (800×g for 10 minutes) and the cell pellet recovered. Total RNA was extracted from the cell pellet by the method of Chomczynski and Sacchi and 10.0 μg of total RNA per sample was subjected to Northern blotting in the presence of glyoxal and hybridised with a cDNA probe for HuIFRG 68.1 mRNA as previously described in Example 2 above and an equivalent cDNA probe for the HuIFRG 68.1 variant described in Example 1. Enhanced levels of mRNA for HuIFRG 68.1 protein (approximately 5-fold) were detected in samples of RNA extracted from IFN-α treated Daudi or HeLa cells compared to samples treated with PBS alone. Enhanced levels of mRNA for HuIFRG 68.1 variant protein (approximately 5-fold) were detected in samples of RNA extracted from IFN-α treated Daudi or Jurkat cells compared to samples treated with PBS alone.

[0116] The same procedure may be used to predict Type 1 interferon responsiveness using PBMCs taken from a patient proposed to be treated with a Type 1 interferon.

Example 4

[0117] Expression of HuIFRG 68.1 Variant mRNA

[0118] The HuIFRG 68.1 variant coding sequence was amplified and used as a probe to determine the tissue distribution of HuIFRG 68.1 variant mRNA. HuIFRG 68.1 variant expression was assessed in a wide variety of tissues and was found to be widely expressed.

SEQUENCE LISTING

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Lys Glu Tyr Tyr Ser Lys Asn Pro Lys Ile Thr Pro Val Gln Ala Val
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aat gtt ggg cag ttg ctg gcc gta aat gcc gag gag gac gcc tgg tta      152
Asn Val Gly Gln Leu Leu Ala Val Asn Ala Glu Glu Asp Ala Trp Leu
            25                  30                  35

cgg gca cag gtc atc tca aca gaa gag aac aaa ata aag gta tgc tat      200
Arg Ala Gln Val Ile Ser Thr Glu Glu Asn Lys Ile Lys Val Cys Tyr
        40                  45                  50

gtt gac tat ggt ttt agt gaa aat gtt gaa aaa agc aaa gca tac aaa      248
Val Asp Tyr Gly Phe Ser Glu Asn Val Glu Lys Ser Lys Ala Tyr Lys
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tta aac ccg aag ttt tgt tca ctc tca ttt caa gct aca aaa tgt aag      296
Leu Asn Pro Lys Phe Cys Ser Leu Ser Phe Gln Ala Thr Lys Cys Lys
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ctt gca ggc ttg gaa gtc cta agc gat gac cct gat cta gtg aag gtg      344
Leu Ala Gly Leu Glu Val Leu Ser Asp Asp Pro Asp Leu Val Lys Val
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gtt gaa tct tta act tgt gga aag atc ttt gca gtg gaa ata ctt gac      392
Val Glu Ser Leu Thr Cys Gly Lys Ile Phe Ala Val Glu Ile Leu Asp
            105                 110                 115

aaa gct gac att cca ctt gtt gtt ctg tac gat acc tca gga gaa gat      440
Lys Ala Asp Ile Pro Leu Val Val Leu Tyr Asp Thr Ser Gly Glu Asp
        120                 125                 130

gat atc aat atc aat gcc acc tgc ttg aag gct ata tgt gac aag tca      488
Asp Ile Asn Ile Asn Ala Thr Cys Leu Lys Ala Ile Cys Asp Lys Ser
    135                 140                 145

cta gag gtt cac ctg cag gtt gac gcc atg tac aca aat gtc aaa gta      536
Leu Glu Val His Leu Gln Val Asp Ala Met Tyr Thr Asn Val Lys Val
150                 155                 160                 165

act aat att tgc tct gat ggg aca ctc tac tgc cag gtg cct tgt aag      584
Thr Asn Ile Cys Ser Asp Gly Thr Leu Tyr Cys Gln Val Pro Cys Lys
                170                 175                 180

ggt ctg aac aag ctc agt gac ctt cta cgt aag ata gag gac tac ttc      632
Gly Leu Asn Lys Leu Ser Asp Leu Leu Arg Lys Ile Glu Asp Tyr Phe
            185                 190                 195

cat tgc aag cac atg acc tct gag tgc ttt gtt tca tta ccc ttc tgt      680
His Cys Lys His Met Thr Ser Glu Cys Phe Val Ser Leu Pro Phe Cys
        200                 205                 210

ggg aaa atc tgc ctc ttc cat tgc aaa gga aaa tgg tta cga gta gag      728
Gly Lys Ile Cys Leu Phe His Cys Lys Gly Lys Trp Leu Arg Val Glu
    215                 220                 225

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Ser Gly Thr Val Thr Ser Val Lys Val Ser Glu Leu Arg Glu Ile Pro
                250                 255                 260

cct cgg ttt cta caa gaa atg att gca ata cca cct cag gcc att aag      872
Pro Arg Phe Leu Gln Glu Met Ile Ala Ile Pro Pro Gln Ala Ile Lys
            265                 270                 275

tgc tgt tta gca gat ctt cca caa tct att ggc atg tgg aca cca gat      920
Cys Cys Leu Ala Asp Leu Pro Gln Ser Ile Gly Met Trp Thr Pro Asp
        280                 285                 290

gca gtg ctg tgg tta aga gat tct gtt ttg aat tgc tcg gac tgt agc      968
Ala Val Leu Trp Leu Arg Asp Ser Val Leu Asn Cys Ser Asp Cys Ser
    295                 300                 305

att aag gtt aca aaa gtg gat gaa acc aga ggg atc gca cat gtt tat     1016
Ile Lys Val Thr Lys Val Asp Glu Thr Arg Gly Ile Ala His Val Tyr
310                 315                 320                 325

tta ttt acc cct aag aac ttc cct gac cct cat cgc agt att aat cgc     1064
Leu Phe Thr Pro Lys Asn Phe Pro Asp Pro His Arg Ser Ile Asn Arg
                330                 335                 340

cag att aca aat gca gac ttg tgg aag cat cag aag gat gtg ttt ttg     1112
Gln Ile Thr Asn Ala Asp Leu Trp Lys His Gln Lys Asp Val Phe Leu
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agt gcc ata tcc agt gga gct gac tct ccc aac agc aaa aat ggc aac     1160
Ser Ala Ile Ser Ser Gly Ala Asp Ser Pro Asn Ser Lys Asn Gly Asn
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atg ccc atg tcg ggc aac act gga gag aat ttc aga aag aac ctc aca     1208
Met Pro Met Ser Gly Asn Thr Gly Glu Asn Phe Arg Lys Asn Leu Thr
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gat gtc atc aaa aag tcc atg gtg gac cat acg agc gct ttc tcc aca     1256
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gag gaa ctg cca cct cct gtc cac tta tca aag cca ggg gaa cac atg     1304
Glu Glu Leu Pro Pro Pro Val His Leu Ser Lys Pro Gly Glu His Met
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gat gtg tat gtg cct gtg gcc tgt cac cca ggc tac ttc gtc atc cag     1352
Asp Val Tyr Val Pro Val Ala Cys His Pro Gly Tyr Phe Val Ile Gln
            425                 430                 435

cct tgg cag gag ata cat aag ttg gaa gtt ctg atg gaa gag atg att     1400
Pro Trp Gln Glu Ile His Lys Leu Glu Val Leu Met Glu Glu Met Ile
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cta tat tac agc gtg tct gaa gag cgc cac ata gca gtg gag aaa gac     1448
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    455                 460                 465

caa gtg tat gct gca aaa gtg gaa aat aag tgg cac agg gtg ctt tta     1496
Gln Val Tyr Ala Ala Lys Val Glu Asn Lys Trp His Arg Val Leu Leu
470                 475                 480                 485

aaa gga atc ctg acc aat gga ctg gta tct gtg tat gag ctg gat tat     1544
Lys Gly Ile Leu Thr Asn Gly Leu Val Ser Val Tyr Glu Leu Asp Tyr
                490                 495                 500

ggc aaa cac gaa tta gtc aac ata aga aaa gta cag ccc cta gtg gac     1592
Gly Lys His Glu Leu Val Asn Ile Arg Lys Val Gln Pro Leu Val Asp
            505                 510                 515

atg ttc cga aag ctg ccc ttc caa gca gtc aca gct caa ctt gca gga     1640
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tcg ttg cca gac acc gat acc tgg att cat gat ttt atg tca gag tat     1832
Ser Leu Pro Asp Thr Asp Thr Trp Ile His Asp Phe Met Ser Glu Tyr
            585                 590                 595

ctg ata gag ctt tca aaa gtt aat taa tgactgcctc tgaaaccttg           1879
Leu Ile Glu Leu Ser Lys Val Asn  *
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acaactaatt cagatttttt agcaataaca aaatgtagta ggcttaaaaa aaatcttaac   1939

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Ser Lys Ala Tyr Lys Leu Asn Pro Lys Phe Cys Ser Leu Ser Phe Gln
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Ala Thr Lys Cys Lys Leu Ala Gly Leu Glu Val Leu Ser Asp Asp Pro
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Val Glu Ile Leu Asp Lys Ala Asp Ile Pro Leu Val Val Leu Tyr Asp
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25 30 35

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gtg cca gca gtg gtc agg ata gag act rgt aga tct gga gag att acc 307
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Cys Tyr Ala Met Ala Cys Thr Glu Thr Ala Arg Ile Ala Gln Leu Val
75 80 85

gct cgt caa agg agt tct aaa agg aaa acc ggg cgt caa gtt aat tgt 403
Ala Arg Gln Arg Ser Ser Lys Arg Lys Thr Gly Arg Gln Val Asn Cys
90 95 100

cag atg aga gtg aag aaa acc atg cca ttt ttt cta gaa gga aaa cca 451
Gln Met Arg Val Lys Lys Thr Met Pro Phe Phe Leu Glu Gly Lys Pro
105 110 115

aaa gca acc ctc aga caa cca gga ttt gct tca aat ttt tct gtt ggc 499
Lys Ala Thr Leu Arg Gln Pro Gly Phe Ala Ser Asn Phe Ser Val Gly
120 125 130 135

aaa aaa cct aat cca gca ccg tta aga gac aaa gga aac tct gtt gga 547
Lys Lys Pro Asn Pro Ala Pro Leu Arg Asp Lys Gly Asn Ser Val Gly
140 145 150

gtt aag cct gat gct gaa atg tct cct tat atg cta cac aca act ctt 595
Val Lys Pro Asp Ala Glu Met Ser Pro Tyr Met Leu His Thr Thr Leu
155 160 165

gga aat gaa gca ttc aaa gac att cca gtg caa agg cat gtg acc atg 643
Gly Asn Glu Ala Phe Lys Asp Ile Pro Val Gln Arg His Val Thr Met
170 175 180

tcc acc aac aac agg ttt agc cca aag gcg tcc ctt caa cca cct ttg 691
Ser Thr Asn Asn Arg Phe Ser Pro Lys Ala Ser Leu Gln Pro Pro Leu
185 190 195

cag atg cat ctc tca aga acc tct act aag gaa atg agt gat aat tta 739
Gln Met His Leu Ser Arg Thr Ser Thr Lys Glu Met Ser Asp Asn Leu
200 205 210 215

aat cag act gtt gaa aaa ccc aat gtc aag cct cct gcc tct tac act 787
Asn Gln Thr Val Glu Lys Pro Asn Val Lys Pro Pro Ala Ser Tyr Thr
220 225 230

tat aaa atg gat gag gtt caa aat cgc ata aag gaa ata cta aac aag 835
Tyr Lys Met Asp Glu Val Gln Asn Arg Ile Lys Glu Ile Leu Asn Lys
235 240 245

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cat aac aat ggc att tgg ata tct aag ctt cca cat ttt tac aaa gag      883
His Asn Asn Gly Ile Trp Ile Ser Lys Leu Pro His Phe Tyr Lys Glu
        250                 255                 260

tta tat aaa gaa gac ctt aat caa gga att tta caa cag ttt gaa cac      931
Leu Tyr Lys Glu Asp Leu Asn Gln Gly Ile Leu Gln Gln Phe Glu His
    265                 270                 275

tgg cct cat att tgc acg gtg gag aaa cct tgc agt ggt ggc caa gat      979
Trp Pro His Ile Cys Thr Val Glu Lys Pro Cys Ser Gly Gly Gln Asp
280                 285                 290                 295

tta ctt ctt tat cca gct aag aga aag cag ctt ttg aga agt gaa ctg     1027
Leu Leu Leu Tyr Pro Ala Lys Arg Lys Gln Leu Leu Arg Ser Glu Leu
                300                 305                 310

gat act gag aaa gta cct cta tcc cca cta cct ggt ccc aaa caa aca     1075
Asp Thr Glu Lys Val Pro Leu Ser Pro Leu Pro Gly Pro Lys Gln Thr
            315                 320                 325

cca ccg ttg aaa ggg tgt cca aca gtt atg gca gga gac ttt aaa gaa     1123
Pro Pro Leu Lys Gly Cys Pro Thr Val Met Ala Gly Asp Phe Lys Glu
        330                 335                 340

aaa gtg gca gac ctg ctg gtg aaa tac aca agt ggc ctt tgg gcc agt     1171
Lys Val Ala Asp Leu Leu Val Lys Tyr Thr Ser Gly Leu Trp Ala Ser
    345                 350                 355

gca ctt ccg aaa gca ttt gag gaa atg tac aaa gtg aaa ttc cct gag     1219
Ala Leu Pro Lys Ala Phe Glu Glu Met Tyr Lys Val Lys Phe Pro Glu
360                 365                 370                 375

gat gcc tta aaa aat ctt gcc tca ctt tct gat gta tgc agc ata gac     1267
Asp Ala Leu Lys Asn Leu Ala Ser Leu Ser Asp Val Cys Ser Ile Asp
                380                 385                 390

tac att tct gga aat ccc cag aag gcc att ctc tat gct aaa ctt cca     1315
Tyr Ile Ser Gly Asn Pro Gln Lys Ala Ile Leu Tyr Ala Lys Leu Pro
            395                 400                 405

ttg ccc act gac aaa atc caa aag gat gca ggg caa gca cat ggt gat     1363
Leu Pro Thr Asp Lys Ile Gln Lys Asp Ala Gly Gln Ala His Gly Asp
        410                 415                 420

aat gat atc aag gct atg gtt gaa caa gag tat ttg cag gta gaa gaa     1411
Asn Asp Ile Lys Ala Met Val Glu Gln Glu Tyr Leu Gln Val Glu Glu
    425                 430                 435

agc att gct gaa agt gct aat acc ttt atg gag gac ata aca gtt cct     1459
Ser Ile Ala Glu Ser Ala Asn Thr Phe Met Glu Asp Ile Thr Val Pro
440                 445                 450                 455

cct tta atg att cca act gaa gca tca cca tct gta ttg gtg gtt gaa     1507
Pro Leu Met Ile Pro Thr Glu Ala Ser Pro Ser Val Leu Val Val Glu
                460                 465                 470

ctg agc aac aca aat gaa gtg gtt atc agg tat gtg ggc aaa gac tat     1555
Leu Ser Asn Thr Asn Glu Val Val Ile Arg Tyr Val Gly Lys Asp Tyr
            475                 480                 485

tct gct gct cag gaa tta atg gaa gat gag atg aag gaa tat tac agt     1603
Ser Ala Ala Gln Glu Leu Met Glu Asp Glu Met Lys Glu Tyr Tyr Ser
        490                 495                 500

aag aat cct aag atc aca cca gtc cag gct gtg aat gtt ggg cag ttg     1651
Lys Asn Pro Lys Ile Thr Pro Val Gln Ala Val Asn Val Gly Gln Leu
    505                 510                 515

ctg gcc gta aat gcc gag gag gac gcc tgg tta cgg gca cag gtc atc     1699
Leu Ala Val Asn Ala Glu Glu Asp Ala Trp Leu Arg Ala Gln Val Ile
520                 525                 530                 535

tca aca gaa gag aac aaa ata aag gta tgc tat gtt gac tat ggt ttt     1747
Ser Thr Glu Glu Asn Lys Ile Lys Val Cys Tyr Val Asp Tyr Gly Phe
                540                 545                 550
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agt gaa aat gtt gaa aaa agc aaa gca tac aaa tta aac ccg aag ttt     1795
Ser Glu Asn Val Glu Lys Ser Lys Ala Tyr Lys Leu Asn Pro Lys Phe
            555                 560                 565

tgt tca ctc tca ttt caa gct aca aaa tgt aag ctt gca ggc ttg gaa     1843
Cys Ser Leu Ser Phe Gln Ala Thr Lys Cys Lys Leu Ala Gly Leu Glu
        570                 575                 580

gtc cta agc gat gac cct gat cta gtg aag gtg gtt gaa tct tta act     1891
Val Leu Ser Asp Asp Pro Asp Leu Val Lys Val Val Glu Ser Leu Thr
    585                 590                 595

tgt gga aag atc ttt gca gtg gaa ata ctt gac aaa gct gac att cca     1939
Cys Gly Lys Ile Phe Ala Val Glu Ile Leu Asp Lys Ala Asp Ile Pro
600                 605                 610                 615

ctt gtt gtt ctg tac gat acc tcr gga gaa gat gat atc aat atc aat     1987
Leu Val Val Leu Tyr Asp Thr Xaa Gly Glu Asp Asp Ile Asn Ile Asn
                620                 625                 630

gcc acc tgc ttg aag gct ata tgt gac aag tca cta gag gtt cac ctg     2035
Ala Thr Cys Leu Lys Ala Ile Cys Asp Lys Ser Leu Glu Val His Leu
            635                 640                 645

cag gtt gac gcc atg tac aca aat gtc aaa gta act aat att tgc tct     2083
Gln Val Asp Ala Met Tyr Thr Asn Val Lys Val Thr Asn Ile Cys Ser
        650                 655                 660

gat ggg aca ctc tac tgc cag gtg cct tgt aag ggt ctg aac aag ctc     2131
Asp Gly Thr Leu Tyr Cys Gln Val Pro Cys Lys Gly Leu Asn Lys Leu
    665                 670                 675

agt gac ctt cta cgt aag ata gag gac tac ttc cat tgc aag cac atg     2179
Ser Asp Leu Leu Arg Lys Ile Glu Asp Tyr Phe His Cys Lys His Met
680                 685                 690                 695

acc tct gag tgc ttt gtt tca tta ccc ttc tgt ggg aaa atc tgc ctc     2227
Thr Ser Glu Cys Phe Val Ser Leu Pro Phe Cys Gly Lys Ile Cys Leu
                700                 705                 710

ttc cat tgc aaa gga aaa tgg tta cga gta gag atc aca aat gtt cac     2275
Phe His Cys Lys Gly Lys Trp Leu Arg Val Glu Ile Thr Asn Val His
            715                 720                 725

agc agc cgg gct ctt gat gtt cag ttc ctg gac tct ggc act gtg aca     2323
Ser Ser Arg Ala Leu Asp Val Gln Phe Leu Asp Ser Gly Thr Val Thr
        730                 735                 740

tct gta aaa gtg tca gag ctc agg gaa att cca cct cgg ttt cta caa     2371
Ser Val Lys Val Ser Glu Leu Arg Glu Ile Pro Pro Arg Phe Leu Gln
    745                 750                 755

gaa atg att gca ata cca cct cag gcc att aag tgc tgt tta gca gat     2419
Glu Met Ile Ala Ile Pro Pro Gln Ala Ile Lys Cys Cys Leu Ala Asp
760                 765                 770                 775

ctt cca caa tct att ggc atg tgg aca cca gat gca gtg ctg tgg tta     2467
Leu Pro Gln Ser Ile Gly Met Trp Thr Pro Asp Ala Val Leu Trp Leu
                780                 785                 790

aga gat tct gtt ttg aat tgc tcg gac tgt agc att aag gtt aca aaa     2515
Arg Asp Ser Val Leu Asn Cys Ser Asp Cys Ser Ile Lys Val Thr Lys
            795                 800                 805

gtg gat gaa acc aga ggg atc gca cat gtt tat tta ttt acc cct aag     2563
Val Asp Glu Thr Arg Gly Ile Ala His Val Tyr Leu Phe Thr Pro Lys
        810                 815                 820

aac ttc cct gac cct cat cgc agt att aat cgc cag att aca aat gca     2611
Asn Phe Pro Asp Pro His Arg Ser Ile Asn Arg Gln Ile Thr Asn Ala
    825                 830                 835

gac ttg tgg aag cat cag aag gat gtg ttt ttg agt gcc ata tcc agt     2659
Asp Leu Trp Lys His Gln Lys Asp Val Phe Leu Ser Ala Ile Ser Ser
840                 845                 850                 855
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gga gct gac tct ccc aac agc aaa aat ggc aac atg ccc atg tcg ggc     2707
Gly Ala Asp Ser Pro Asn Ser Lys Asn Gly Asn Met Pro Met Ser Gly
                860                 865                 870

aac act gga gag aat ttc aga aag aac ctc aca gat gtc atc aaa aag     2755
Asn Thr Gly Glu Asn Phe Arg Lys Asn Leu Thr Asp Val Ile Lys Lys
            875                 880                 885

tcc atg gtg gac cat acg agc gct ttc tcc aca gag gaa ctg cca cct     2803
Ser Met Val Asp His Thr Ser Ala Phe Ser Thr Glu Glu Leu Pro Pro
        890                 895                 900

cct gtc cac tta tca aag cca ggg gaa cac atg gat gtg tat gtg cct     2851
Pro Val His Leu Ser Lys Pro Gly Glu His Met Asp Val Tyr Val Pro
    905                 910                 915

gtg gcc tgt cac cca ggc tac ttc gtc atc cag cct tgg cag gag ata     2899
Val Ala Cys His Pro Gly Tyr Phe Val Ile Gln Pro Trp Gln Glu Ile
920                 925                 930                 935

cat aag ttg gaa gtt ctg atg gaa gag atg att cta tat tac agc gtg     2947
His Lys Leu Glu Val Leu Met Glu Glu Met Ile Leu Tyr Tyr Ser Val
                940                 945                 950

tct gaa gag cgc cac ata gca gtg gag aaa gac caa gtg tat gct gca     2995
Ser Glu Glu Arg His Ile Ala Val Glu Lys Asp Gln Val Tyr Ala Ala
            955                 960                 965

aaa gtg gaa aat aag tgg cac agg gtg ctt tta aaa gga atc ctg acc     3043
Lys Val Glu Asn Lys Trp His Arg Val Leu Leu Lys Gly Ile Leu Thr
        970                 975                 980

aat gga ctg gta tct gtg tat gag ctg gat tat ggc aaa cac gaa tta     3091
Asn Gly Leu Val Ser Val Tyr Glu Leu Asp Tyr Gly Lys His Glu Leu
     985                 990                 995

gtc aac ata aga aaa gta cag ccc cta gtg gac atg ttc cga aag ctg     3139
Val Asn Ile Arg Lys Val Gln Pro Leu Val Asp Met Phe Arg Lys Leu
1000                1005                1010                1015

ccc ttc caa gca gtc aca gct caa ctt gca gga gtg aag tgc aac cag     3187
Pro Phe Gln Ala Val Thr Ala Gln Leu Ala Gly Val Lys Cys Asn Gln
                1020                1025                1030

tgg tct gag gag gct tct atg gtg ttt cga aat cat gtg gag aag aaa     3235
Trp Ser Glu Glu Ala Ser Met Val Phe Arg Asn His Val Glu Lys Lys
            1035                1040                1045

cct ctg gtg gca ctg gtg cag aca gtc att gaa aat gct aac cct tgg     3283
Pro Leu Val Ala Leu Val Gln Thr Val Ile Glu Asn Ala Asn Pro Trp
        1050                1055                1060

gac cgg aaa gta gtg gtc tac tta gtg gac aca tcg ttg cca gac acc     3331
Asp Arg Lys Val Val Val Tyr Leu Val Asp Thr Ser Leu Pro Asp Thr
    1065                1070                1075

gat acc tgg att cat gat ttt atg tca gag tat ctg ata gag ctt tca     3379
Asp Thr Trp Ile His Asp Phe Met Ser Glu Tyr Leu Ile Glu Leu Ser
1080                1085                1090                1095

aaa gtt aat taa tgactgcctc tgaaaccttg                               3411
Lys Val Asn  *
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<210> SEQ ID NO 4
<211> LENGTH: 1098
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 65
<223> OTHER INFORMATION: 'Xaa' at location 65 stands for Gly, or Ser
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: 623
<223> OTHER INFORMATION: 'Xaa' at location 623 stands for Ser

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<400> SEQUENCE: 4

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Met Leu Glu Gly Asp Leu Val Ser Lys Met Leu Arg Ala Val Leu Gln
 1               5                  10                  15

Ser His Lys Asn Gly Val Ala Leu Pro Arg Leu Gln Gly Glu Tyr Arg
            20                  25                  30

Ser Leu Thr Gly Asp Trp Ile Pro Phe Lys Gln Leu Gly Phe Pro Thr
        35                  40                  45

Leu Glu Ala Tyr Leu Arg Ser Val Pro Ala Val Val Arg Ile Glu Thr
    50                  55                  60

Xaa Arg Ser Gly Glu Ile Thr Cys Tyr Ala Met Ala Cys Thr Glu Thr
65                  70                  75                  80

Ala Arg Ile Ala Gln Leu Val Ala Arg Gln Arg Ser Ser Lys Arg Lys
                85                  90                  95

Thr Gly Arg Gln Val Asn Cys Gln Met Arg Val Lys Lys Thr Met Pro
            100                 105                 110

Phe Phe Leu Glu Gly Lys Pro Lys Ala Thr Leu Arg Gln Pro Gly Phe
        115                 120                 125

Ala Ser Asn Phe Ser Val Gly Lys Lys Pro Asn Pro Ala Pro Leu Arg
    130                 135                 140

Asp Lys Gly Asn Ser Val Gly Val Lys Pro Asp Ala Glu Met Ser Pro
145                 150                 155                 160

Tyr Met Leu His Thr Thr Leu Gly Asn Glu Ala Phe Lys Asp Ile Pro
                165                 170                 175

Val Gln Arg His Val Thr Met Ser Thr Asn Asn Arg Phe Ser Pro Lys
            180                 185                 190

Ala Ser Leu Gln Pro Pro Leu Gln Met His Leu Ser Arg Thr Ser Thr
        195                 200                 205

Lys Glu Met Ser Asp Asn Leu Asn Gln Thr Val Glu Lys Pro Asn Val
    210                 215                 220

Lys Pro Pro Ala Ser Tyr Thr Tyr Lys Met Asp Glu Val Gln Asn Arg
225                 230                 235                 240

Ile Lys Glu Ile Leu Asn Lys His Asn Asn Gly Ile Trp Ile Ser Lys
                245                 250                 255

Leu Pro His Phe Tyr Lys Glu Leu Tyr Lys Glu Asp Leu Asn Gln Gly
            260                 265                 270

Ile Leu Gln Gln Phe Glu His Trp Pro His Ile Cys Thr Val Glu Lys
        275                 280                 285

Pro Cys Ser Gly Gly Gln Asp Leu Leu Leu Tyr Pro Ala Lys Arg Lys
    290                 295                 300

Gln Leu Leu Arg Ser Glu Leu Asp Thr Glu Lys Val Pro Leu Ser Pro
305                 310                 315                 320

Leu Pro Gly Pro Lys Gln Thr Pro Pro Leu Lys Gly Cys Pro Thr Val
                325                 330                 335

Met Ala Gly Asp Phe Lys Glu Lys Val Ala Asp Leu Leu Val Lys Tyr
            340                 345                 350

Thr Ser Gly Leu Trp Ala Ser Ala Leu Pro Lys Ala Phe Glu Glu Met
        355                 360                 365

Tyr Lys Val Lys Phe Pro Glu Asp Ala Leu Lys Asn Leu Ala Ser Leu
    370                 375                 380

Ser Asp Val Cys Ser Ile Asp Tyr Ile Ser Gly Asn Pro Gln Lys Ala
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385                 390                 395                 400

Ile Leu Tyr Ala Lys Leu Pro Leu Pro Thr Asp Lys Ile Gln Lys Asp
                405                 410                 415

Ala Gly Gln Ala His Gly Asp Asn Asp Ile Lys Ala Met Val Glu Gln
            420                 425                 430

Glu Tyr Leu Gln Val Glu Glu Ser Ile Ala Glu Ser Ala Asn Thr Phe
        435                 440                 445

Met Glu Asp Ile Thr Val Pro Pro Leu Met Ile Pro Thr Glu Ala Ser
    450                 455                 460

Pro Ser Val Leu Val Val Glu Leu Ser Asn Thr Asn Glu Val Val Ile
465                 470                 475                 480

Arg Tyr Val Gly Lys Asp Tyr Ser Ala Ala Gln Glu Leu Met Glu Asp
                485                 490                 495

Glu Met Lys Glu Tyr Tyr Ser Lys Asn Pro Lys Ile Thr Pro Val Gln
            500                 505                 510

Ala Val Asn Val Gly Gln Leu Leu Ala Val Asn Ala Glu Glu Asp Ala
        515                 520                 525

Trp Leu Arg Ala Gln Val Ile Ser Thr Glu Glu Asn Lys Ile Lys Val
    530                 535                 540

Cys Tyr Val Asp Tyr Gly Phe Ser Glu Asn Val Glu Lys Ser Lys Ala
545                 550                 555                 560

Tyr Lys Leu Asn Pro Lys Phe Cys Ser Leu Ser Phe Gln Ala Thr Lys
                565                 570                 575

Cys Lys Leu Ala Gly Leu Glu Val Leu Ser Asp Asp Pro Asp Leu Val
            580                 585                 590

Lys Val Val Glu Ser Leu Thr Cys Gly Lys Ile Phe Ala Val Glu Ile
        595                 600                 605

Leu Asp Lys Ala Asp Ile Pro Leu Val Val Leu Tyr Asp Thr Xaa Gly
    610                 615                 620

Glu Asp Asp Ile Asn Ile Asn Ala Thr Cys Leu Lys Ala Ile Cys Asp
625                 630                 635                 640

Lys Ser Leu Glu Val His Leu Gln Val Asp Ala Met Tyr Thr Asn Val
                645                 650                 655

Lys Val Thr Asn Ile Cys Ser Asp Gly Thr Leu Tyr Cys Gln Val Pro
            660                 665                 670

Cys Lys Gly Leu Asn Lys Leu Ser Asp Leu Leu Arg Lys Ile Glu Asp
        675                 680                 685

Tyr Phe His Cys Lys His Met Thr Ser Glu Cys Phe Val Ser Leu Pro
    690                 695                 700

Phe Cys Gly Lys Ile Cys Leu Phe His Cys Lys Gly Lys Trp Leu Arg
705                 710                 715                 720

Val Glu Ile Thr Asn Val His Ser Ser Arg Ala Leu Asp Val Gln Phe
                725                 730                 735

Leu Asp Ser Gly Thr Val Thr Ser Val Lys Val Ser Glu Leu Arg Glu
            740                 745                 750

Ile Pro Pro Arg Phe Leu Gln Glu Met Ile Ala Ile Pro Pro Gln Ala
        755                 760                 765

Ile Lys Cys Cys Leu Ala Asp Leu Pro Gln Ser Ile Gly Met Trp Thr
    770                 775                 780

Pro Asp Ala Val Leu Trp Leu Arg Asp Ser Val Leu Asn Cys Ser Asp
785                 790                 795                 800
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Cys Ser Ile Lys Val Thr Lys Val Asp Glu Thr Arg Gly Ile Ala His
                805                 810                 815

Val Tyr Leu Phe Thr Pro Lys Asn Phe Pro Asp Pro His Arg Ser Ile
            820                 825                 830

Asn Arg Gln Ile Thr Asn Ala Asp Leu Trp Lys His Gln Lys Asp Val
        835                 840                 845

Phe Leu Ser Ala Ile Ser Ser Gly Ala Asp Ser Pro Asn Ser Lys Asn
    850                 855                 860

Gly Asn Met Pro Met Ser Gly Asn Thr Gly Glu Asn Phe Arg Lys Asn
865                 870                 875                 880

Leu Thr Asp Val Ile Lys Lys Ser Met Val Asp His Thr Ser Ala Phe
                885                 890                 895

Ser Thr Glu Glu Leu Pro Pro Pro Val His Leu Ser Lys Pro Gly Glu
            900                 905                 910

His Met Asp Val Tyr Val Pro Val Ala Cys His Pro Gly Tyr Phe Val
        915                 920                 925

Ile Gln Pro Trp Gln Glu Ile His Lys Leu Glu Val Leu Met Glu Glu
    930                 935                 940

Met Ile Leu Tyr Tyr Ser Val Ser Glu Glu Arg His Ile Ala Val Glu
945                 950                 955                 960

Lys Asp Gln Val Tyr Ala Ala Lys Val Glu Asn Lys Trp His Arg Val
                965                 970                 975

Leu Leu Lys Gly Ile Leu Thr Asn Gly Leu Val Ser Val Tyr Glu Leu
            980                 985                 990

Asp Tyr Gly Lys His Glu Leu Val Asn Ile Arg Lys Val Gln Pro Leu
        995                 1000                1005

Val Asp Met Phe Arg Lys Leu Pro Phe Gln Ala Val Thr Ala Gln Leu
    1010                1015                1020

Ala Gly Val Lys Cys Asn Gln Trp Ser Glu Glu Ala Ser Met Val Phe
1025                1030                1035                1040

Arg Asn His Val Glu Lys Lys Pro Leu Val Ala Leu Val Gln Thr Val
                1045                1050                1055

Ile Glu Asn Ala Asn Pro Trp Asp Arg Lys Val Val Val Tyr Leu Val
            1060                1065                1070

Asp Thr Ser Leu Pro Asp Thr Asp Thr Trp Ile His Asp Phe Met Ser
        1075                1080                1085

Glu Tyr Leu Ile Glu Leu Ser Lys Val Asn
    1090                1095
```

1. An isolated polypeptide comprising

(i) the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4;

(ii) a variant thereof having substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity; or

(iii) a fragment of (i) or (ii) which retains substantially similar function selected from immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity.

2. A variant or fragment of the polypeptide defined by the amino acid sequence set forth in SEQ. ID. No. 2 or SEQ ID No: 4 suitable for raising specific antibodies for said polypeptide and/or a naturally-occurring variant thereof.

3. A polynucleotide encoding a polypeptide as claimed in claim 1 or **2**.

4. A polynucleotide as claimed in claim 3 which is a cDNA.

5. A polynucleotide encoding a polypeptide as claimed in claim 1, which polynucleotide comprises:

(a) the nucleic acid sequence of SEQ ID NO: 1 or SEQ ID NO. 3 or the coding sequence thereof and/or a sequence complementary thereto;

(b) a sequence which hybridises to a sequence as defined in (a);

(c) a sequence that is degenerate as a result of the genetic code to a sequence as defined in (a) or (b); or

(d) a sequence having at least 60% identity to a sequence as defined in (a), (b) or (c).

6. An expression vector comprising a polynucleotide sequence as claimed in any one of claims 3 to 5, which is capable of expressing a polypeptide according to claim 1 or **2**.

7. A host cell containing an expression vector according to claim 6.

8. An antibody specific for a polypeptide as claimed in claim 1 or claim 2.

9. An isolated polynucleotide which directs expression in vivo of a polypeptide as claimed in claim 1.

10. A polypeptide as claimed in claim 1 or a polynucleotide as claimed in claim 9 for use in therapeutic treatment of a human or non-human animal.

11. A pharmaceutical composition comprising a polypeptide as claimed in claim 1 or a polynucleotide as claimed in claim 9 and a pharmaceutically acceptable carrier or diluent.

12. Use of a polypeptide as claimed in claim 1 or a polynucleotide as claimed in claim 9 in the preparation of medicament for use in therapy as an anti-viral, anti-tumour or immunomodulatory agent.

13. A method of treating a patient having a Type 1 interferon treatable disease, which comprises administering to said patient an effective amount of a polypeptide as claimed in claim 1 or a polynucleotide as claimed in claim 9.

14. A method of producing a polypeptide according to claim 1 or **2**, which method comprises culturing host cells as claimed in claim 7 under conditions suitable for obtaining expression of the polypeptide and isolating the said polypeptide.

15. A method of identifying a compound having immunomodulatory activity and/or anti-viral activity and/or anti-tumour activity comprising providing a cell capable of expressing the polypeptide of SEQ. ID. No. 2 or SEQ. ID. No: 4 or a naturally-occurring variant thereof, incubating said cell with a compound under test and monitoring for upregulation of the gene encoding said polypeptide or variant.

16. A polynucleotide capable of expressing in vivo an antisense sequence to a coding sequence for the amino acid sequence defined by SEQ. ID. No.2 or SEQ. ID. No. 4 or a naturally-occurring variant of said coding sequence for use in therapeutic treatment of a human or non-human animal.

17. An antibody as claimed in claim 8 for use in therapeutic treatment.

18. A set of primers for nucleic acid amplification which target sequences within a cDNA as claimed in claim 4.

19. A nucleic acid probe derived from a polynucleotide as claimed in any one of claims 3 to 5.

20. A probe as claimed in claim 19 which is attached to a solid support.

21. A method of predicting responsiveness of a patient to treatment with a Type 1 interferon, which comprises determining the level of the protein defined by the amino acid sequence set forth in SEQ. ID. No. 2 or SEQ. ID. No. 4 or a naturally-occurring variant thereof, or the corresponding mRNA, in a cell sample from said patient, wherein said sample is obtained from said patient following administration of a Type 1 interferon or is treated prior to said determining with a Type 1 interferon in vitro.

22. A method as claimed in claim 21 wherein the interferon administered prior to obtaining said sample or used to treat said sample in vitro is the interferon proposed for treatment of said patient.

23. A method as claimed in claim 21 or claim 22 wherein a sample comprising peripheral blood mononuclear cells isolated from a blood sample of the patient is treated with a Type 1 interferon in vitro.

24. A method as claimed in any one of claims 21 to 23 wherein said determining comprises determining the level of mRNA encoding the protein defined by the sequence set forth in SEQ. ID. No. 2 or SEQ. ID. No. 4 or a naturally-occurring variant of said protein.

25. A non-human transgenic animal capable of expressing a polypeptide that is claimed in claim 1.

* * * * *

专利名称(译)	干扰素-α诱导的基因		
公开(公告)号	US20040175803A1	公开(公告)日	2004-09-09
申请号	US10/469189	申请日	2002-02-26
[标]申请(专利权)人(译)	MERITET让弗朗索瓦 DRON MICHEL 托维MICHAEL GERARD		
申请(专利权)人(译)	MERITET JEAN-FRANCOIS DRON MICHEL 托维MICHAEL GERARD		
当前申请(专利权)人(译)	MERITET JEAN-FRANCOIS DRON MICHEL 托维MICHAEL GERARD		
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摘要(译)

本发明涉及鉴定通过干扰素-α给药而上调的基因，该基因对应于SEQ.ID. NO.1所示的cDNA序列。 ID。 No.1和SEQ。 ID。该基因的表达产物的确定被提议用于预测对干扰素-α和其它干扰素治疗的反应性的敏感性，所述干扰素作用于1型干扰素受体。还设想了由相同基因编码的蛋白质的治疗用途。

ALIPHATIC	Non-polar	GAP
		ILV
	Polar-uncharged	CSTM
		NQ
	Polar-charged	DE
		KR
AROMATIC		HFWY