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(71) Applicant *(for all designated States except US)*: **UNIVERSITY COURT OF THE UNIVERSITY OF DUNDEE** [GB/GB]; Nethergate, Perth Road, Dundee DD1 4HN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MCLEAN, William, Henry, Irwin** [GB/GB]; Human Genetics Unit, Division of Pathology & Neuroscience, Ninewells Medical School, University of Dundee, Dundee DD1 9SY (GB). **SMITH, Frances, Jane, Dorothy** [GB/GB]; Human Genetics Unit, Division of Pathology & Neuroscience, Ninewells Medical School, University of Dundee, Dundee DD1 9SY (GB).

(74) Agents: **SZCZUKA, Jan** et al.; Marks & Clerk, 19 Royal Exchange Square, Glasgow G1 3AE (GB).

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(54) Title: FILAGGRIN

(57) Abstract: The present invention relates to the identification of loss-of-function mutations in the filaggrin gene and their use in diagnosing ichthyosis vulgaris and/or susceptibility to other diseases including atopic dermatitis (eczema), asthma, psoriasis and allergies (including food allergy).

FILAGGRIN

Field of the Invention

The present invention relates to the identification of loss-of-function mutations in the filaggrin gene and their use in diagnosing ichthyosis vulgaris and/or susceptibility to other diseases including atopic dermatitis (eczema), asthma, psoriasis and allergies (including food allergy).

Background to the Invention

Ichthyosis vulgaris (IV; OMIM# 146700) is the most common inherited disorder of keratinisation and one of the most frequent single gene disorders in humans. The most widely cited incidence figure is 1 in 250 based on a survey of 6051 healthy English schoolchildren[1].

The phenotypic characteristics of IV include palmar hyperlinearity, keratosis pilaris and a fine scale most markedly seen over the lower abdomen, arms and legs[2]. Filaggrin (filament aggregating protein) is important in the formation of the stratum corneum[3-5]. Keratohyalin granules in the granular layer of interfollicular epidermis are predominantly composed of the 400 kDa protein profilaggrin. Following a short, unique N-terminal domain, most of the profilaggrin molecule consists of 10-12 repeats of the 324 amino acid filaggrin sequence[6]. Upon terminal differentiation of granular cells, profilaggrin is proteolytically cleaved into ~37 kDa filaggrin peptides and the N-terminal domain containing an S100-like calcium binding domain. Filaggrin rapidly aggregates the keratin cytoskeleton, causing collapse of the granular cells into flattened anuclear squames. This condensed cytoskeleton is cross-linked by transglutaminases during formation of the cornified cell envelope (CCE). The CCE is the outermost barrier layer of the skin which not only prevents water loss but also

impedes the entry of allergens and infectious agents[7]. Filaggrin is therefore a key protein in facilitating epidermal differentiation and maintaining barrier function.

Immunoblotting studies have shown that filaggrin protein was absent or markedly reduced in IV patients' skin and/or keratinocytes[8-10]. In addition, decreased filaggrin mRNA has been demonstrated in some individuals with IV[11]. A recessive mouse mutant, flaky tail (*ft*), bears the histological and ultrastructural hallmarks of human IV[12] and strong genetic linkage has been obtained to the murine filaggrin locus (*FLG*)[13,14]. Although biochemical analysis has shown defective profilaggrin processing in *ft/ft* homozygotes[12], any genomic mutation in the *FLG* gene has not hitherto been identified.

It is amongst the objects of the present invention to provide a method of diagnosing ichthyosis vulgaris and atopic diseases or predisposition thereto.

Summary of the Invention

The present invention is based on the identification for the first time of mutations in the human filaggrin (*FLG*) gene which lead to a loss or partial loss of protein function.

Thus, in a first aspect, the present invention provides a genetic test for ichthyosis vulgaris (IV) comprising the steps of:

a) providing a nucleic acid sample from a subject to be tested; and

b) detecting whether or not a mutation, which would lead to a loss of function or partial loss of function of the filaggrin (FLG) protein encoded by the filaggrin (*FLG*) gene, is present in the *FLG* gene of said nucleic acid.

It will be appreciated that the test may be used to diagnose IV and/or to test if a subject is predisposed to developing IV. Additionally, due to an association of IV, in severe or mild forms, with other diseases, the test may be used to also detect whether or not a subject is likely to be predisposed or suffering from atopic dermatitis (eczema), asthma, psoriasis or allergies, such as of a contact type allergy and food allergies (for example, peanut allergy). With regards to skin conditions, low levels of filaggrin expression may lead to development of mild and/or sub-clinical disease. In this manner, the present invention may also relate to the identification and/or treatment of said mild and/or sub-clinical forms of disease. Indeed, many skin conditions go undiagnosed and as such treatments may be considered more as a cosmetic treatment.

Thus, in a further aspect, the present invention provides a genetic test for atopic dermatitis (eczema), asthma, psoriasis and/or allergies comprising the steps of:

a) providing a nucleic acid sample from a subject to be tested; and

b) detecting whether or not a mutation, which would lead to a loss of function or partial loss of function of the FLG protein encoded by the *FLG* gene, is present in the *FLG* gene of said nucleic acid.

The sample to be tested may be any suitable sample from which nucleic acid may be obtained. Typically the nucleic acid is a sample of genomic DNA or mRNA. Conveniently the sample may be a sample of saliva, buccal scraping or blood sample. The sample may also be a tissue sample, such as a skin biopsy.

The subject may be any subject requiring to be tested and may suitably be a newborn or even a foetus. The subject may however be at any stage of life, and therefore includes neonates, children and adults. As mentioned above, said tests may be carried out on a subject in order to ascertain whether or not he/she is predisposed to

developing a disease. Thus, a test may be carried out, for example, in order to test a subject's suitability for a particular job, where he/she may come into contact with agents which are known to lead in some cases to the development of eczema and/or allergy. Alternatively, said test may be carried out in order to categorise a subject and predict an "at risk" status for, for example, atopic disease. In this manner subjects may be tested so as to categorise or stratify subjects for therapeutic intervention, when appropriate, based on any results obtained, so as to prevent and/or treat atopic disease.

Moreover, ascertaining a subject's *FLG* status and therefore degree of expression or lack of expression of the FLG protein may find use in determining suitable treatment for a subject suffering or predisposed to suffering from IV and/or any of the other aforementioned diseases. For example, depending on the degree of severity, or expected degree of severity, the skilled artisan can decide on an appropriate therapeutic and/or cosmetic regime and as such tailored treatments can be based on a subjects *FLG* status.

The present invention, in one embodiment, is based on the identification of previously unidentified mutations in the *FLG* gene, which lead to a loss of function of the profilaggrin and consequently filaggrin proteins. The present invention however extends to any mutation in the *FLG* gene which leads to a loss or partial loss of function of the profilaggrin and/or filaggrin proteins.

The mutation may be an addition, deletion, substitution or inversion. Typically, the mutation effects 1 – 10 nucleotides, such as a one-base substitution, or a 2 – 10 e.g. 4-base deletion. The mutation may also be due to a translocation. By partial or total loss of profilaggrin or filaggrin protein function, is understood to mean that the mutation or mutations result in incorrect processing and/or expression of the *FLG* gene such that one or more of the filaggrin peptides normally expressed, is not

functionally expressed. Typically 10 – 12 copies of the filaggrin peptide are expressed from a non-mutated *FLG* gene[6]. It is understood therefore that the mutant *FLG* genes of the present invention will result in the functional expression of less than 10-12 filaggrin peptides, typically less than 7, 5, 3 or 1 from one or both copies of the *FLG* gene, which are present in a genome.

Depending on the location and/or type of a mutation or mutations, any reduction in functional filaggrin expression can be mild, e.g. a 1 – 5 reduction in functional filaggrin peptides; significant e.g. a 7 – 13 reduction in functional filaggrin peptides; or severe, e.g. a 15 – 20 reduction in functional filaggrin peptides.

The mutation or mutations may be found in any of the exons 1, 2 and/or 3 of the *FLG* gene and may typically be found in exon 3. If the mutation or mutations is/are located in exon 3, the most detrimental mutations, with regards to functional filaggrin expression, will be found within the 5' (N-terminal) portion of the 3rd exon, such as within the first 2000 bases, e.g. mutation(s) is/are found within the unique, partial repeat, or first filaggrin repeat portion of exon 3 (see Figure 2a).

A significant number of mutations have been identified by the present inventors, which lead to a loss of function and in some cases, a total loss of function of one of the *FLG* copies. One such mutation is a 1-base substitution at position 1501 of the *FLG* gene herein (as shown in Figure 5 and SEQ ID NO.: 188). 1501C>T (numbering from initiating ATG), which results in the substitution of a cytidine by a thymidine and a corresponding amino acid change at position 501 of an arginine to a stop codon. As this mutation occurs in the first filaggrin repeat (see Figure 2) and results in the generation of a stop codon, no functional copies of the filaggrin peptide are produced.

A second mutation identified is a 4-base deletion starting at position 2282 (see Figure 5 and SEQ ID NO.: 186). The mutation has been named 2282del4 and this causes a resulting frame-shift which leads to an alternative stop codon 107 bases downstream. Again, this mutation occurs in the first filaggrin repeat and as such no functional copy of a filaggrin peptide is expressed, although a truncated mutant form of the peptide may be expressed, which possesses a unique C-terminal portion (see Figure 4 and SEQ ID NO.: 187).

A third mutation is a deletion of a G in the third filaggrin repeat. The deletion is at position 3702 and is shown in Figure 5. This mutation causes a frameshift in repeat 3, such that only 2 functional copies of filaggrin from repeats 1 and 2 are made.

Further mutations which have been identified include R2477X (repeat 7), S3247X (repeat 9), R1474X (repeat 4), Q1745X (repeat 4), Q3683X (repeat 10), 11029delCA (repeat 10), E2422X (repeat 6), 5369delG (repeat 5), 7367delCA (repeat 7), 11033del4 (repeat 100, 6867delAG (repeat 6), 3321delA (repeat 2) and S2554X (repeat 7). The most prevalent and/or recurrent mutations in the European population are R510X, 2282del4, 3702delG, R2447X and S3247X.

The nomenclature used above is to be understood as follows:
S3247X, for example means that there is a mutation found at codon position 3247 which results in a codon change from a codon which encodes a serine, to a stop codon. 5360delG is a deletion of a G at DNA base-pair position 5360 (numbering where the initiating ATG = 1), leading to a frameshift.

Detection of a mutation in the *FLG* gene may be carried out by a variety of techniques including quantitative or semi-quantitative PCR, including real-time PCR, nucleic acid sequencing, hybridisation studies and/or restriction fragment length

polymorphism (RFLP) analysis techniques, well known to the skilled addressee (see, for example, Sambrook & Russel, 2000).

Depending on where the mutation or mutations are located, it may be appropriate to amplify one or more exons or portions thereof. If the mutation(s) is/are located in exon 3, all or only a portion of exon 3 may be amplified using appropriate primers. If the mutation(s) is/are located in the first repeat, it may only be necessary to amplify the first repeat, or portion thereof comprising the mutation(s). By appropriate use of primers and optional labels, it can be possible to amplify a product and ascertain whether or not the product comprises a mutation. For example, primers may be designed which incorporate at (or very close to) the 3' terminal, a base capable of binding to the native or mutant base/sequence, such that only the native or mutant sequence will be amplified and detected. A selection of primers suitable for use in amplifying the entire exon 3, or certain specific regions of the repeated sequences of exon 3 are identified herein as SEQ ID NO.s: 1 – 182.]

SEQ ID NO.s 1 – 8 represent primers suitable for long range PCR and sequencing of the filaggrin repeats.

SEQ ID NO.s 9 – 12 represent primers suitable for generating short PCR fragments for detection of the R501X mutation.

SEQ ID NO.s 13 – 15 represent primers suitable for generating short PCR fragments for detection of mutation 2828del4.

SEQ ID NO.s 15 – 18 represent primers suitable for generating short PCR fragments for detection of mutation 3702delG.

SEQ ID NO.s 19 – 40 represent primers which are specific for repeat 0.

SEQ ID NO.s 41 – 67 represent primers which are specific for repeat 1.

SEQ ID NO.s 68 – 93 represent primers which are specific for repeat 2.

SEQ ID NO.s 94 – 136 represent primers which are specific for repeat 3.

SEQ ID NO.s 137 – 201 represent primers which are specific for repeat 4.

SEQ ID NO.s 202 – 264 represent primers which are specific for repeat 5.

SEQ ID NO.s 265 – 329 represent primers which are specific for repeat 6.

SEQ ID NO.s 330 – 377 represent primers which are specific for repeat 7.

SEQ ID NO.s 378 – 414 represent primers which are specific for repeat 8.

SEQ ID NO.s 415 – 461 represent primers which are specific for repeat 9.

SEQ ID NO.s 462 – 493 represent primers which are specific for repeat 10.

SEQ ID NO.s 494 – 497 represent primers which are specific for repeat 8.1.

SEQ ID NO.s 498 – 501 represent primers which are specific for repeat 8.2.

SEQ ID NO.s 502 – 518 represent primers which are specific for repeat 10.1.

SEQ ID NO.s 519 – 539 represent primers which are specific for repeat 10.2.

SEQ ID NO.s 540 – 544 represent primers which are specific for repeat 11.

SEQ ID NO. 545 represents a primer which is specific for the filaggrin tail.

In all cases, F at the end of a primer sequence shows that the primer is a forward primer and an R shows it is a reverse primer.

It will be appreciated that shorter or longer versions of the identified primer sequences may be used, for example, the primers may be from 12 – 50 bases in length. However, 3'-terminal base is critical for correct primer extension and so the 3'-end of any primer should be identical to the sequences as identified herein.

Labels, such as fluorescent, chemiluminescent, bioluminescent or radio-labels may be incorporated into the PCR primers so as to allow detection of the native or mutant sequence. The skilled man will appreciate that two separately labelled primers may be used in a PCR reaction, designed to facilitate amplification of a product

comprising either the native or mutant sequence and the sequence, native or mutant, detected based on the particular label being present in the product. Other labelling techniques such as the TaqMan® system of Applied Biosystems Inc., CA, USA, may be employed.

Of course, a fragment of DNA, which includes the portion of DNA which may include the mutation, may simply be amplified and sequenced, in order to determine whether or not the *FLG* gene comprises a mutation. Alternatively, such a fragment may be amplified and a hybridisation study carried out using an appropriate oligonucleotide and very stringent hybridisation conditions and washing conditions employed (see for example Sambrook et al, 2000[15]) so that only exactly matching oligonucleotides bind to the amplified fragment in the region or regions comprising the mutation(s).

It may also be appropriate to first amplify a fragment of DNA comprising the sequence which may or may not comprise a mutation(s) and thereafter detecting whether or not the fragment includes the native or mutant sequence by carrying out a further PCR reaction using primers internal to the amplified fragment, in order to detect or otherwise, a mutation(s). Such a technique is commonly known as nested PCR.

Moreover, any particular mutation may generate a new restriction site which may be detected by RFLP analysis. A fragment which would encompass a mutation which, if present, can first be amplified using appropriate primers and the fragment thereafter subjected to RFLP analysis providing the mutation or native sequence has a restriction site which is not present in the corresponding native or mutant sequence. In accordance with the present invention, the exemplary mutations identified herein result in the generation of new restriction sites which can easily be detected by first

amplifying a fragment comprising the mutation and thereafter restricting the fragment obtained using the appropriate restriction enzyme – only a fragment comprising the mutant sequence will be restricted (see Examples Section for further description).

The present invention also extends to kits which comprise one or more of the aforementioned oligonucleotides/primers. The kits may also comprise other reagents to facilitate, for example, sequencing, conducting PCR and/or RFLP analysis. Such kits may also comprise instructions for their use to detect one or more mutations in a filaggrin gene and optionally how to interpret whether or not a mutation may lead to development or predisposition to developing IV and/or any of the other aforementioned diseases/conditions.

The oligonucleotides/primers of the present invention may also be used in multiplex PCR techniques, known to the skilled addressee, see for example. Kuperstein G, Jack E and Narod SA; Genet Test. 10(1):1-7 (2006)., so as to identify mutations in the filaggrin sequence.

In addition to mutations which lead to a loss of function or partial loss of function of profilaggrin/filaggrin protein, the present inventors have now identified the specific repeat sequences which can lead to exon 3 of the filaggrin gene consisting of 11 or 12 full filaggrin repeats, as opposed to the "normal" 10 repeats. The inventors have identified that repeats 8 and/or 10 can be essentially duplicated in certain individuals, in order to generate 11 or 12 filaggrin repeats. Desirably therefore, the present invention also extends to identifying the number of filaggrin repeats in a subject as well as detecting one or more mutations. Heterozygous mutant subjects who possess one mutant allele which results in no or little filaggrin expression, but have a second wild-type allele encoding 11 or 12, filaggrin repeats, may express sufficient filaggrin to not develop disease, or only a mild form of disease.

For example, a carrier of a 12-repeat allele, will express 20% more filaggrin than a 10-repeat carrier and this difference in expression may be significant in terms of disease development.

It has been observed that the aforementioned 4-base deletion (2282del4) results in the expression of a unique peptide which comprises an N-terminal region corresponding to the N-terminal portion of the filaggrin peptide and a unique C-terminal region which has been expressed due to the frame-shift mutation. With respect to this unique peptide which is produced from the mutant sequence comprising the 4-base deletion, it is possible to detect the unique peptide using an appropriate binding agent, such as a specific antibody. It is appreciated that any such binding agent/antibody should be specific for the unique peptide and not therefore be capable of binding the native filaggrin peptide.

The skilled man will readily know how to obtain a suitable antibody, such as a monoclonal antibody, by, for example, producing the unique peptide recombinantly or using synthetic chemistry, coded for by the mutant sequence and raising antibodies thereto. Antibodies so produced can thereafter be screened to ascertain their specificity, such that only those antibodies which are specific for the unique peptide may be selected.

Such specifically reactive antibodies to the unique peptide can be optionally labelled and used in an immunoassay to detect for the presence of the unique peptide in a sample. Alternatively, the specifically reactive antibody can be used in an assay, such as an ELISA, to detect any of said unique peptide in a sample being tested.

Thus, in a further aspect there is provided a method of detecting a mutant peptide expressed from a mutant of the *FLG* gene, comprising the steps of:

a) providing a sample from a subject to be tested; and

b) detecting whether or not a mutant peptide expressed from a mutant *FLG* gene is present in the sample, by using a binding agent which is specifically reactive to said mutant peptide.

In this aspect, the sample may preferably be a skin tissue sample. Typically, the binding agent is an antibody, monoclonal antibody or fragment thereof, such as a Fab fragment. Detection may be carried out by detecting a label, such as a fluorescent, chemiluminescent, bio-luminescent or radio-label coupled to the binding agent/antibody/fragment. Alternatively, the binding agent, antibody or antibody fragment may be unlabelled and detected by way of an antibody specific for said binding agent, antibody or antibody fragment, such as in an ELISA assay.

It will be understood that the nucleic acid and mutant peptide tests described herein may be conducted individually or together.

Identification of mutants in the *FLG* gene leading to loss or partial loss of function of the FLG protein opens up the possibility of treating prophylactically or therapeutically IV and/or any of the other aforementioned diseases by gene therapy. As such a correct non-mutant copy or copies of the *FLG* gene may be used to complement for a mutant version of the *FLG* gene present in a subject.

Thus, in a further aspect there is provided use of an *FLG* gene sequence or fragment thereof, capable of encoding one or more copies of the *FLG* protein, in the manufacture of a medicament. It is understood that the medicament may be used for the prophylactic or therapeutic treatment of IV and/or diseases including atopic dermatitis (eczema), asthma, psoriasis and allergies.

The present invention therefore also provides an *FLG* gene sequence or fragment thereof, which gene sequence or fragment thereof, is capable of expressing one or more copies of the filaggrin protein, for use in therapy or prophylaxis.

It will be appreciated that the present invention also extends to methods of treating prophylactically or therapeutically any of the aforementioned diseases/conditions by administering to a patient suffering or predisposed to developing any of said aforementioned diseases a DNA construct comprising an *FLG* gene sequence or fragment thereof, which gene sequence or fragment thereof is capable of expressing one or more copies of the *FLG* protein, whereby expression of said one or more copies of the FLG protein treats or ameliorates said disease(s)/condition(s).

Typically, the *FLG* sequence or fragment thereof will be administered to a subject in the form of a recombinant molecule comprising said *FLG* sequence or fragment under appropriate transcriptional/translational controls to allow expression of said filaggrin protein when administered to a subject. It will be appreciated that the *FLG* sequence or fragment may be under control of a suitable promoter, such as a constitutive and/or controllable promoter. Convenient promoters include the native filaggrin promoter, or an appropriate late differentiation-specific keratin promoter.

The present invention also therefore provides a recombinant molecule comprising an *FLG* sequence or fragment thereof for use in therapy. The recombinant molecule may be in the form of a plasmid, phagemid or viral vector. Furthermore, recombinantly expressed, or chemically synthesised filaggrin or profilaggrin protein, or functionally important fragments thereof, may be produced and applied to the skin via a suitable ointment or other pharmaceutical vehicle, as a treatment or prophylatic measure for ichthyosis vulgaris and/or atopic diseases. Such a treatment may also be of cosmetic value as it may increase the barrier function and/or moisture-retention properties of the skin. Since filaggrin is prominently expressed in hair from early in development[16], such a treatment may also improve cosmetic qualities of the hair, such

as moisture retention, in individuals with either normal or reduced filaggrin expression.

Many different viral and non-viral vectors and methods of their delivery, for use in gene therapy, are known, such as adenovirus vectors, adeno-associated virus vectors, retrovirus vectors, lentiviral vectors, herpes virus vectors, liposomes, DNA vaccination and the like[17].

The present invention also provides a method of treating, preventing and/or ameliorating IV and/or any of the aforementioned diseases, comprising the steps of:

a) determining if expression of one or more copies of the FLG polypeptide would occur even if a subject's FLG gene comprises one or more mutations; and

b) providing a subject carries *FLG* alleles capable of expressing at least one or more copies of the FLG polypeptide, treating the subject using UV light in order to seek to increase *FLG* expression.

The intention is to increase expression of FLG polypeptides in the skin. This may most easily be achieved in heterozygote subjects, i.e. those subjects who have one mutant copy of the *FLG* gene and one native copy.

The expression of the *FLG* gene is known to be induced by UV light[18]. Thus, UV treatment of the skin of an individual carrying a heterozygous copy of a filaggrin loss-of-function mutation could increase the expression of the normal allele and thereby produce a beneficial effect.

The present invention also relates to a transgenic non-human animal which possesses one or more mutations in one or both copies of the *FLG* gene which would lead to a loss or partial loss of function of the *FLG* protein encoded by the *FLG* gene. Desirably, the *FLG* gene of the non-human animal may be replaced with a mutant

human form of the gene, in order to "humanise" the non-human animal with respect to the *FLG* gene.

The transgenic animals of the present invention can be used for the development of various treatments for IV and/or the other diseases mentioned herein including the identification of various therapeutically active agents including but not limited to other proteins, peptides, peptidomimetic drugs, small molecule drugs, chemicals and nucleic acid-based agents.

The term non-human animals is used herein to include all vertebrate animals, except humans. It also includes an individual animal in all stages of development, including embryonic and foetal stages. A transgenic animal is any animal containing one or more cells bearing genetic information altered or received, directly or indirectly, by deliberate genetic manipulation at a subcellular level, such as by targeted recombination or microinjection or infection with recombinant virus. The term transgenic animal is not intended to encompass classical cross-breading or *in vitro* fertilization, but rather is meant to encompass animals in which one or more cells are altered by, or receive, a recombinant DNA molecule.

To create a transgenic non-human animal expressing a mutant form of the *FLG* gene, mutant *FLG* nucleic acid sequences are inserted into a germ line of the animal using standard techniques of oocyte microinjection or transfection or microinjection into stem cells. Preferably, it is desired to replace the endogenous gene and homologous recombination using embryonic stem cells or foetal fibroblasts can be applied.

Mice are often used for transgenic animal models because they are easy to house, relatively inexpensive, and easy to breed. However, other non-human transgenic mammals can also be made in accordance with the present invention such

as but not limited to monkeys, sheep, rabbits, dogs and rats. Transgenic animals are those which carry a transgene, that is, a cloned gene introduced and stably incorporated which is passed on to successive generations.

For oocyte injection, for example in mice, one or more copies of the nucleic acid sequences encoding *FLG* can be inserted into the pronucleus of a just-fertilised mouse oocyte. This oocyte is then reimplanted into a pseudo-pregnant foster mother. The live born mice can then be screened for integrants using analysis of, for example, tail DNA for the presence of the mutant *FLG* sequences.

Methods of making transgenic mammals are known and described, e.g. in Wall, et al. (1992) J. Cell Biochem. 49(2): 113-20[19]; McCreath, et al. (2000) Nature 405: 1066-1069[20]; Lai, et al. (2002) Science 295: 1089-92[21]; Hogan, et al. (1986) In: Manipulating the mouse embryo. A Laboratory Manual. Cold Spring Harbour Laboratory Press, Cold Spring Harbor, N.Y.[22]; in WO 91/08216 or U.S. Pat. No. 4,736,866. The mice disclosed herein can be crossed with a hairless or nude mouse background so that skin abnormalities are visible to facilitate monitoring of disease progression and/or potential therapies.

An *in vivo* assay for identifying an agent which is useful for treating or preventing IV and/or any of the other aforementioned diseases associated with mutant *FLG* expression comprising the steps of administering a test agent to a *FLG* mutant transgenic animal; and measuring or determining whether the agent decreases or inhibits at least one sign or symptom of IV and/or any of the other aforementioned diseases which is indicative that the test agent is capable of treating or preventing IV and/or any of the other aforementioned diseases. The results of the screening assay can be compared with a control, e.g., an animal which has not been administered a test agent or an animal which has received an agent known to reduce a sign or

symptom of said diseases. The route of administration of the test agent may vary. Examples of administration routes include, but are not limited, to oral, nasal, rectal, transmucosal, intestinal, parenteral, intravenous, intraperitoneal and topical.

Examples Section

The present invention will now be further described by way of example and with reference to the Figures which show:

Figure 1 shows Pedigrees of IV families studied.

Pedigrees of IV families studied here where a family history was available. Families 1-3 are of Irish origin, Families 4-6 are Scottish and Family 7 is of US origin. In addition, 8 isolated IV cases were studied where a family history was not available (not shown). Of the latter, one case was Irish, 4 were Scottish and 3 were of US origin. All patients studied were White Caucasians. Black-filled symbols refer to the marked IV presentation; cross-hatched symbols refer to the very mild IV presentation; open symbols refer to no detectable IV phenotype. The genotypes for the two mutations R501X and 2282del4 are shown. Note that wt/wt refers only to the regions screened and does not preclude other sequence changes in the central regions of exon 3. Only two people with no detectable IV phenotype were found to have a filaggrin mutation: individual II-5 in Family 5, who carries R501X; and individual II-1 in Family 7, who is an obligate carrier of R501X. On this basis, we estimate the penetrance in heterozygotes as ~90%, although this is probably an overestimate due to ascertainment bias. Many individuals in these families, who carry one or other filaggrin mutation, either heterozygously or homozygously, have, in addition to ichthyosis vulgaris, atopic dermatitis (eczema) and/or asthma and/or allergies (see

also Figure 4). Thus, filaggrin mutations predispose individuals to these other conditions.

Figure 2 shows FLG mutation detection and confirmation.

(a) Schematic diagram of the filaggrin gene (*FLG*), annotated to show the corresponding protein structure. Exon 1 consists of a short 5'UTR sequence. Exon 2 and the 5' end of exon 3 encode the profilaggrin N-terminal domain. The remainder of exon 3 consists of 10-12 repeats of approximately 1 kb, each encoding a filaggrin peptide separated by linker sequences, followed by a short unique coding sequence and the 3'UTR. Upon terminal differentiation of the epidermis, each profilaggrin molecule is proteolytically cleaved to release 10 – 12 copies of filaggrin, which aggregate the keratin cytoskeleton and cause physical collapse of the granular cells to form squamous cells. The positions of PCR fragments used here and of the two null-mutations, R501X and 2282del4 in repeat 1 of exon 3, are shown.

(b) Long-range PCR product from genomic DNA covering exon 3 and therefore all the filaggrin repeats.

(c) Normal sequence from filaggrin repeat 1 in exon 3, corresponding to codons 499-503.

(d) The same region of the *FLG* as seen in (c), showing heterozygous transition mutation 1502C>T resulting in nonsense mutation R501X.

(e) The same region of *FLG* as in (c) showing a homozygous mutation resulting in a nonsense codon, R501X.

(f) Confirmation of mutation R501X by *Nla* III restriction digest and 2282del4 by *Dra* III restriction digest from some members of Family 3.

(g) Normal sequence from filaggrin repeat 1 in exon 3, corresponding to codons 713-717.

(h) The same region of *FLG* as in (f), showing overlapping peaks due to a heterozygous deletion mutation, 2282del4.

(i) The same region of the *FLG* as in (f), derived from a mutant clone confirming mutation 2282del4. This mutation leads to a premature stop codon 107 bp downstream and terminates translation within filaggrin repeat 1.

Figure 3 shows morphological features of filaggrin-null ichthyosis vulgaris.

(a) Skin biopsy from a normal (non-ichthyotic) control. Haematoxylin and eosin staining of formaldehyde-fixed paraffin-embedded tissue shows prominent keratohyalin granules in the granular cell layers of the superficial epidermis (arrows).

(b) Skin biopsy from the proband in Family 4, who is homozygous for nonsense mutation R501X in the *FLG* gene. In contrast with the normal control seen in (a), there is a complete absence of keratohyalin granules in the upper layers of the epidermis. The degenerating nuclei seen in the uppermost living layers (arrows), indicate that this is the area where one would normally see keratohyalin granules.

(c) Transmission electron micrograph of keratinocytes at the boundary of the granular layer and stratum corneum, from a normal individual, showing prominent keratohyalin granules (arrowheads). N = nucleus; K = keratinized material in stratum corneum. Original magnification = ~5,600x.

(d) Transmission electron micrograph of granular layer cells from the proband in Family 4, who is homozygous for nonsense mutation R501X in the *FLG* gene. There is a complete absence of keratohyalin granules (*). The stratum corneum is not fully cornified, as compared with the control (K), indicative of an epidermal barrier defect. N = nucleus. Original magnification = ~5,600x.

(e) Immunohistochemical staining of formaldehyde-fixed paraffin-embedded tissue using anti-filaggrin repeat monoclonal antibody 15C10 (Novocastra), visualized by the immunoperoxidase method. In skin biopsy material from a normal control, keratohyalin granules are strongly stained in the upper suprabasal layers of the epidermis (arrows).

(f) Immunoperoxidase staining of skin biopsy material from the proband in Family 4, shows complete absence of staining in the upper suprabasal layers (arrows) with anti-filaggrin repeat monoclonal antibody 15C10 (Novocastra). This demonstrates that no filaggrin peptides are produced in patients homozygous for R501X, consistent with a nonsense mutation within the first filaggrin repeat.

(g) Immunoperoxidase staining of skin biopsy material from a normal control individual with polyclonal antibody B1, raised against an epitope within the N-terminal domain of profilaggrin, showing prominent staining of keratohyalin granules (arrows).

(h) Immunoperoxidase staining of skin biopsy material from the proband in Family 4, with profilaggrin N-terminal antibody B1. No granular staining is seen but unlike the filaggrin repeat epitope (f), there is a diffuse pattern of residual staining. This is more pronounced in the upper suprabasal cells where profilaggrin is normally expressed (arrows) but in addition there is some patchy diffuse cytoplasmic staining throughout the epidermis (arrowheads). The epitope of this antibody is upstream of the mutation and so this shows that a truncated fragment of profilaggrin is synthesized in R501X homozygotes.

Figure 4 shows complete sequence of the filaggrin repeats and identifies the positions of the mutations identified by the inventors and positions of where the specific primers identified herein bind. These specific priming sites were identified

by analysis of alignments of the individual filaggrin repeats, including the novel additional repeats identified by the inventors.

Figure 5 shows the pedigrees of a family with IV and corresponding atopy transmission;

Figure 6 is a graph showing that filaggrin variants are associated with increased atopy;

Figure 7 is a graph showing increased number of positive allergens in carriers of filaggrin mutations;

Figure 8 is a graph showing filaggrin variants are stronger risk factors for eczema in the older asthmatics;

Figure 9 shows a) immunostaining of skin biopsy material from a normal control and an IV patient with the R510X/R2447X genotype. b) immunoblotting of skin biopsy protein extracts from a normal control and IV patients with the genotypes R501X/R2447X and R501X/R501X;

Figure 10 is a schematic diagram of profilaggrin proteins encoded by size variant alleles of *FLG*;

Figure 11 shows the DNA sequence of *FLG* size variant allele FLG^{8+};

Figure 12 shows the DNA sequence of *FLG* size variant allele FLG^{10+}; and

Figure 13 shows the sequence of a fragment from *FLG* size variant allele FLG^{8+10+}, together with annotations as follows:

Annotated Sequence – repeats in alternate plan and bold text

* = unique base pair specific to this filaggrin repeat sequence

N = base pair shared with only one other filaggrin repeat sequence, number N

N* = base pair essentially specific due to nearby differences in repeat N.

METHODS

Affected individuals and phenotypes

Blood samples were obtained from 15 families with IV and normal ethnically matched controls with informed consent that complies with all principles of the Helsinki Accord.

Long-range PCR for *FLG* exon 3

Primers FilLR2F (+ strand) 5' GTC ACT TAC CCC ATC AAA TC 3' and FilLR1R (- strand) 5' CCA CCA AAC TAA TGA AAT AC 3' were used to amplify approximately 12 kb of the filaggrin gene (including all of exon 3 and therefore all the repeat domains) from genomic DNA using the Expand Long Template PCR System (Roche Diagnostics, East Sussex, UK). A "hot start" was performed with 1U Expand Long Template enzyme mix (Roche). Reactions were amplified using the following extended PCR program: (92°C 5 min x1); (92°C 10 sec, 49°C 30 sec, 68°C 6 min) x10; (92°C 10 sec, 49°C 30 sec, 68°C 6 min plus 10 sec increment/cycle) x28; and (68°C 10 min) x1.

R501X mutation analysis

A shorter PCR fragment was designed to amplify approximately 1.5 kb for mutation analysis of R501X. Primers FilF3 (+ strand) 5' GCT GAT AAT GTG ATT CTG TCT G 3' and RPT1P6 (- strand) 5' ACC TGA GTG TCC AGA CCT ATT 3' were used in High Fidelity PCR buffer (Roche) containing 1.5 mM $MgCl_2$, 4% DMSO and 1U High Fidelity thermostable DNA polymerase mix (Roche). Reactions were amplified under the following conditions: (94°C 5 min x1); (94°C 30 sec, 57°C 1 min, 72°C 2 min) x30; and (72°C 5 min) x1. Mutation R501X creates a new *Nla* III

restriction enzyme site; this was used to confirm the mutation and screen control samples. Primers FilH1F3 (+ strand) 5' CAC GGA AAG GCT GGG CTG A 3' and RPT1P6 (above) were used to amplify 312 bp of genomic DNA using PCR buffer (Promega) containing 1.5 mM $MgCl_2$, 4% DMSO and 1U *Taq* polymerase mix (Promega). Reactions were amplified as follows: (94°C 5 min x1); (94°C 30 sec, 58°C 45 sec, 72°C 1 min) x30; and (72°C 5 min) x1. PCR products were digested with 5U *Nla* III for 4 hr at 37°C. Digests were resolved on 3% agarose gels.

2282del4 mutation analysis

A PCR fragment amplifying 811 bp of genomic DNA was amplified with primers RPT1P7 (+ strand) 5' AAT AGG TCT GGA CAC TCA GGT 3' and RPT2P1 (- strand) 5' GGG AGG ACT CAG ACT GTT T 3' using PCR buffer (Applied Biosystems) containing 1.5 mM $MgCl_2$, 4% DMSO and 1U *Taq* polymerase mix (Promega). PCR amplification conditions were: (94°C 5 min x1); (94°C 30 sec, 57°C 45 sec, 72°C 1 min 30 sec) x35; and (72°C 5 min) x1. Mutation 2282del4 creates a new *Dra* III restriction enzyme site which was used to screen samples for this mutation. PCR products were digested with 5U *Dra* III for 4 hr at 37°C. Digests were resolved on 2% agarose gels. A PCR fragment from a heterozygous individual was cloned into vector pCR2.1 (Invitrogen). Clones were screened by *Dra* III digestion and sequenced to confirm the 4 bp deletion.

Histology and electron microscopy

Routine hematoxylin and eosin (H&E) staining was performed to evaluate morphologic features of each specimen. Immunoperoxidase staining of frozen and paraffin-embedded sections utilized the Envision system (DakoCytomation,

Denmark). Antibodies used were mouse monoclonal 15C10 against an epitope in the C-terminal portion of the human filaggrin repeat unit (Novocastra, Newcastle upon Tyne, UK) and rabbit polyclonal antiserum B1 raised against the N-terminus of profilaggrin[23]. For transmission electron microscopy, skin samples from patients were fixed in half-strength Karnovsky's fixative (containing 2.5% glutaraldehyde and 2% formaldehyde) then in 1.3% osmium tetroxide and processed using standard methods, largely as described previously[24].

Lod score calculations

Lod scores were calculated with MLINK algorithm of LINKAGE version 5.1, using a semidominant model of the disease where heterozygotes were assigned a mild phenotype with 90% penetrance and homozygotes or compound heterozygotes were assigned as a severe phenotype with 100% penetrance. The combined mutant allele frequency was assumed to be 0.037 (Table 1). Recalculation with 50% penetrance in heterozygotes still yielded a highly significant maximum combined lod score of 7.08 at θ=0.

FLG consists of three exons[25,26]. Exon 1 (15 bp) consists only of 5'UTR sequences and exon 2 (159 bp) contains the initiation codon. Exon 3 is unusually large (12,753 bp) and codes for most of the N-terminal domain and all filaggrin repeats (Figure 2a). The number of filaggrin repeats varies from 10-12 in the population[6]. The homology between the repeats at the DNA level is almost 100%, making conventional PCR-based sequencing for the internal regions of this exon almost impossible. No sequence changes were found in exons 1 or 2 in five IV families. The present inventors developed long-range PCR conditions to amplify a 12 kb genomic fragment covering exon 3 and therefore all the repeat domains (Figure

2b). Full sequencing of this fragment is on-going, but initial sequencing has revealed a homozygous nonsense mutation R501X near the start of repeat 1 in three affected individuals from Family 1 (Figure 2c - e). Using a smaller PCR fragment, segregation of R501X was confirmed in Family 1 and in addition, this mutation was identified in the other 14 IV kindreds studied. The mutation creates a new *Nla* III restriction enzyme site; this was used to confirm the mutation and screen populations (Figure 2f). By this means, the mutation was found to be present at relatively high allele frequencies in Irish, Scottish and North American Caucasian populations (combined frequency, 0.027; see Table 1).

In 3 families, IV patients with a very pronounced phenotype were homozygous for R501X (Figure 1). In other families and isolated cases, individuals with the marked IV phenotype were found to be heterozygous for R501X. Further sequencing in these cases revealed a second mutation, 2282del4, in exon 3 (Figure 2g - i). This leads to a premature termination codon 107 bp downstream and, like R501X, stops protein translation within the first filaggrin repeat (Figure 2a). Mutation 2282del4 creates a *Dra* III restriction enzyme site which was used to screen IV families and control samples (Figure 2f; Table 1). This mutation segregated in 10 of the IV families studied (Figure 1). Of the 8 "sporadic" cases of clinically significant IV where family history was not available, 4 were homozygous for R501X and the remaining 4 were R501X/2282del4 compound heterozygotes. Interestingly, part of the US family previously reported to show significant linkage to the *FLG* locus[27], was studied using freshly obtained high-quality DNA required for analysis of exon 3. The severely affected individuals in Family 7 were compound heterozygous for R501X/2282del4 (Figure 1), consistent with the linkage data previously reported[27]. The semidominant mode of inheritance is best exemplified in Family 1

where there are multiple examples of IV patients with the very mild presentation as well as examples of R501X homozygotes and R501X/2282del4 compound heterozygotes with the full IV phenotype. In the studied series of families there were only two individuals who were heterozygous for a null-mutation (both R501X) and have no obvious phenotype (Families 5 & 7; Figure 1). On the basis of these small numbers, the penetrance in heterozygotes appears to be about 90%, however, this may be an overestimate due to ascertainment bias. The allele frequency for 2282del4 in US, Irish and Scottish Caucasians was found to be ~0.01 (Table 1). Using the determined allele frequencies and assuming mildly affected heterozygotes and severely affected homozygotes, the maximum combined 2-point lod score for families 1-7 (Figure 1), was 8.11 at θ=0.

Skin biopsy material from an R501X homozygote (proband, Family 4) was subjected to histological and ultrastructural analysis. The granular layer was found to be absent by conventional histology (Figure 3a & b) and electron microscopy showed complete absence of keratohyalin (Figure 3c & d). Immunohistochemistry showed that an epitope conserved in all filaggrin repeat peptides was completely absent in the R501X homozygote (Figure 3e & f). In contrast, an epitope in the N-terminal domain of profilaggrin, encoded by sequences upstream of filaggrin repeat 1, was still present, albeit in an abnormal, diffuse distribution (Figure 3g & h). Immunohistochemical analysis of an R501X/2282del4 compound heterozygote gave identical results (not shown). This confirms that either R501X or 2282del4 result in complete loss of filaggrin peptide production and so functionally, these are null-alleles.

Since profilaggrin is the major component of keratohyalin granules, this explains the absent granular layer associated with the more severe cases of IV[27] (Figure 3). The presence of a truncated profilaggrin peptide in IV epidermis (Figure

3b) is consistent with previous studies demonstrating that a peptide containing the unique N-terminal domain and a small amount of filaggrin sequence is stable *in vitro*[23]. In normal epidermis, the N-terminal Ca^{2+}-binding domain is cleaved from profilaggrin by a proprotein convertase, and subsequently localizes to different cell compartments including the nucleus[28,29]. Similar processing of the truncated peptide may occur in IV epidermis.

Here the inventors have shown that in three Caucasian populations, IV appears to be predominantly caused by two frequent null-mutations in *FLG*, leading to loss of filaggrin production and impaired epidermal barrier formation. In the IV families studied, most R501X mutations are in linkage disequilibrium with the same 156 bp allele of a microsatellite in intron 2 of *FLG* (data not shown), suggesting that, in human evolutionary terms, these are ancient mutations. Further analysis of polymorphisms near *FLG* will determine the approximate age of the mutations. Genetic drift may explain why these mutations have become so prevalent. Alternatively, a heterozygote advantage might explain the high frequencies of these alleles. One obvious hypothesis is that impaired barrier function leads to elevated exposure to bacterial or other antigens, leading to greater innate immunity. This "natural cutaneous vaccination" might allow heterozygotes to better survive when challenged by pandemic plagues or other pathogens. This should be testable using *ft* mice[12] or engineered filaggrin null-mice.

Regarding the inheritance pattern and incidence of IV; the very subtle heterozygote phenotype probably does often not come to clinical attention unless specifically sought, as was the case here. Assuming a combined null-allele frequency of ~0.037 (Table 1), and a pronounced heterozygote phenotype, then 1 in 14 people would have IV, which is clearly not the case. With this allele frequency, 1 in 730

should be homozygous or compound heterozygous and have marked IV. The subtlety of the heterozygote phenotype, combined with incomplete penetrance and seasonal variation[2], probably explains the reported incidence of 1 in 250[1]. With these high mutant allele frequencies, IV families will also frequently appear to have dominant or pseudo-dominant inheritance with reduced penetrance (Figure 1). By Southern analysis, polymorphism in the number of filaggrin repeats has been shown in humans (10-12 repeats)[6] and mice (12-20 repeats)[30]. The inventors also observed this size variation using long-range PCR and determined the sequences of the longer variant alleles (described below). It is possible that a heterozygote for a null-mutation might carry an expanded exon 3 on their other allele, lessening the overall effect of the mutation. This might explain the phenotypically normal heterozygotes seen in Families 5 and 7 (Figure 1). Due to their relatively high population frequencies, filaggrin null-mutations may themselves be modifying factors in other ichthyotic skin conditions, including congenital ichthyoses, Netherton syndrome or disorders due to defects in suprabasal keratins, where intra- and interfamilial phenotypic variation is well documented[31-34]. The association of IV with the atopic diathesis is well established; 37-50% of people with IV have atopic diseases[1,36] and conversely around 8% of atopic dermatitis patients have classical features of IV[1,35]. Thus, filaggrin may be a factor in very common skin disorders known to have a major genetic component.

In the IV families studied, many filaggrin-null or heterozygous individuals also had atopic dermatitis (AD; "eczema") and/or asthma. An example is shown in Figure 5, where 3/6 filaggrin-null heterozygotes and 5/5 homozygotes had atopic disease. The inventors therefore sought to examine the role of these variants in common atopy associated with asthma. The two filaggrin variants were genotyped in a cohort of 800 schoolchildren with unknown disease status (population cohort) and in

550 school children and adolescents with physician-diagnosed asthma from the Dundee BREATHE study. The frequency of carriers of R501X was 5.2% and the 2282del4 variant was present in 3.6% of the schoolchildren, giving a combined carrier frequency of 8.8%. Both filaggrin variants were over-represented in the asthmatic cohort, with carriers of either allele demonstrating a dominant risk (Table 2; combined genotype OR= 1.94 95%CI= 1.35-2.80, p= 0.0005). Homozygotes for both variants were observed in the asthma cohort, as were two compound heterozygotes. AD is known to be co-associated with asthma[1,36] and since filaggrin is a major epidermal structural protein, one would expect a stronger association with AD/asthma with filaggrin defects. Consistent with this, 75% of all the children in the asthma cohort carrying a filaggrin null-allele had AD, in contrast to only 46.7% of those without these filaggrin variants (Table 3; OR= 2.81 95%CI= 1.64-4.81, p=0.0001). This observation appears to be related to allergen exposure, as the risk was largely seen in individuals routinely exposed to animals (OR 5.2 95%CI= 2.36-11.50, p=0.000006).

These data suggested that a barrier function defect may lead to greater risk of allergy and this hypothesis was supported by the observation that a significantly greater number of the children with asthma had been referred to an allergy clinic for allergy testing if they carried a filaggrin null variant (OR= 1.78 95%CI=1.08-2.95, p= 0.034). Even more significantly, every individual tested that carried the null variants (n=20) was positive for at least one allergen, whereas 26 out of the 56 non-carrier individuals tested negative for allergens (p=0.00006). This striking atopic phenotype resulted in a systematic increase of the carrier frequency of the null variants as we increased the definition of the degree of atopy of the cohort (Figure 6), with 46.7% of all the individuals that had asthma, AD and immunologically-verified allergy having

the filaggrin null variants (n=75). In this group, the variant was still further associated with an increased number of positive allergens, with the mean number of allergens for a null variant carrier being substantially greater that that for the wild type individuals (Figure 7). This demonstrates that a substantial fraction of common, complex atopic disease can be accounted for by a single pair of variants in the filaggrin gene. Given the population carrier frequency of both of these variants (~9%), these observations will have a huge impact in the understanding of atopy and may lead to the development of novel treatments for asthma and allergy. Asthma and allergy can wane during adolescence and the temporal features of childhood atopy are known as the "atopic march". Here the inventors show that individuals haploinsufficient for filaggrin represent a population of persistent atopy, where the observed risk of eczema increases consistently through age in the asthmatic cohort, consistent with the atopic march (Figure 8).

Nut and food allergy

The asthma cohort was analysed for people with a recorded allergy to peanuts and/or other nuts. 23 individuals had a proven nut allergy and of these, 8 carried a filaggrin-null mutation (either 2282del4 or R501X), i.e. 35% were carriers. In a population control cohort, 60 out of 621 individuals carried a filaggrin-null mutation, i.e. 9.7%. Thus, the filaggrin mutation carrier frequency is greatly increased in people with asthma and nut allergy. Fisher's exact test gave a two-sided P value of 0.0008, which is considered extremely significant (odds ratio = 5.520 95%CI 2.248-13.554). Thus, filaggrin mutations are a highly significant risk factor for nut allergy and asthma. In addition, atopy is strongly associated with food allergy especially cow's milk, hen's egg, banana, kiwi, white fish, wheat, prawns/shrimp and strawberries[37-39].

Since nut allergy is regarded as the most reliable marker for food allergy, this strongly infers that filaggrin mutations are associated with food allergies in general.

A comprehensive mutation detection strategy for FLG.

Using primers ending on bases that had been determined by detailed sequence alignments to be absolutely specific for a given filaggrin repeat, or in a few cases, ending on bases that are shared by only two filaggrin repeats, a series of overlapping PCR fragments was generated that span exon 3 of the *FLG* gene in its entirety. These fragments were fully sequenced using the amplification primers and/or internal primers that again ended on unique bases. In some individuals, the identification of single nucleotide polymorphisms was able to show that the overlapping PCR fragments were amplifying both alleles, thus demonstrating the specificity and utility of this sequencing strategy. Using this method, individuals with a severe IV phenotype predictive of homozygous or compound heterozygous mutations were sequenced. These patients were from European populations, predominantly Irish and Scottish with some Dutch and Austrian individuals. A number of novel loss-of-function mutations were identified, all of which lead to premature termination codons, either as nonsense mutations or frameshift mutations. In many cases, these were inherited in *trans* with the more common mutations R501X or 2282del4. Specifically, these further mutations were 3702delG (repeat 3), R2447X (repeat 7), S3247X (repeat 9), R1474X (repeat 4), Q1745X (repeat 4), Q3683X (repeat 10), 11029delCA (repeat 10) in Irish and Scottish patients; E2422X (repeat 6), 5360delG (repeat 5), 7267delCA (repeat 7) and 11033del4 (repeat 10) in Dutch patients; and 6867delAG (repeat 6) in an Austrian patient. The IV phenotype of the patients carrying these more 3' mutations were essentially indistinguishable to patients carrying R501X or 2282del4

mutations in repeat 1. Thus, premature termination codon mutations essentially anywhere in the profilaggrin molecule appear to have similar or equivalent pathogenicity. The following mutations were recurrent and/or prevalent in the European population R501X, 2282del4, 3702delG, R2447X and S3247X. The Dutch and Austrian mutations were not detected in 188 Irish AD patients and may be population-specific or very rare. The remaining variants were not tested for prevalence.

Mutations in the 3' half of FLG exon 3 are essentially functional null alleles

To determine the biochemical consequences of the more 3' mutations, biopsy material was obtained from two patients with the compound heterozygote genotype R501X/R2447X. Immunostaining of skin sections with Novocastra 15C10 antibody against the filaggrin repeat domain showed that this patient has an identifiable but very restricted granular cell layer in the upper epidermis (**Figure 9A**). The more quantitative technique of immunoblotting, using protein extracts from this biopsy, revealed that only a very small quantity of a truncated profilaggrin molecule is expressed and importantly, this is not processed into mature filaggrin (**Figure 9B**). Essentially identical results were obtained for an R501X/11033del4 compound heterozygote (not shown). Thus, more 3' *FLG* mutations lead to greatly reduced expression of truncated profilaggrin and complete loss of mature filaggrin and therefore, are essentially filaggrin functional null alleles.

Mutations in more 3' repeats and repeat 1 of the FLG gene predispose to AD

A cohort of 188 Irish paediatric cases of moderate-severe AD were genotyped for 5 mutations found to be prevalent and/or recurrent in this population, R501X,

2282del4, 3702delG, R2447X and S3247X. Comparison of allele frequencies was made to an unselected Irish control population of 736 individuals genotyped for the same 5 *FLG* variants. Pearson chi-square analysis revealed that all 5 mutations are independently associated with the AD phenotype, giving individual statistically significant *P* values of <0.05 (**Table 4**). Combining the data for all 5 genotypes gave an extremely significant *P* value of 2.12×10^{-51}. About 48% of the patients in the AD cohort carried one or more of the 5 filaggrin variants. Thus, a wide range of *FLG* mutations contribute to genetic predisposition to atopy and this is a major gene in early-onset moderate-to-severe AD.

A different spectrum of FLG mutations predispose to atopy in non-European populations

The European-specific mutations R501X and 2282del4 were found to be absent from 253 Japanese individuals. We therefore sequenced the *FLG* gene in four Japanese families with IV and identified two novel mutations, 3321delA and S2554X.

We screened 143 Japanese AD patients for these null *FLG* mutations and identified them in 8 AD patients (5.6%), including S2554X in 6 patients (4.2%) and 3321delA in 2 patients (1.4%). Both null variants were absent from 156 Japanese non-atopic and non-ichthyotic controls, giving a statistically significant association between the *FLG* mutations and AD (Chi-square *P* value 0.0015).

Thus, in non-European populations, in this case Japan, there appears to be a distinct set of prevalent/recurrent *FLG* mutations that contribute to genetic predisposition to atopy. It is likely that other human populations will have their own spectrum of *FLG* mutations.

Size variants of the filaggrin gene (*FLG*)

It has been reported previously that exon 3 of the *FLG* gene is variable in size in the human population and these variant alleles were predicted, on the basis of their size, to consist of 10, 11 or 12 full filaggrin repeats in addition to the two partial repeats (Gan et al., 1990)[40]. However, the positions of these insertions within *FLG* exon 3 and the precise DNA sequences encoding these additional filaggrin repeats remained unknown.

Using specific PCR primers located in repeat 7 and repeat 11, DNA fragments were generated from unrelated individuals that, from the public sequence of the *FLG* gene (Human Genome, March 2006 Assembly, hg18), would be predicted to be ~4.2 kb in size. For convenience, this allele is designated as FLG^{N}. In some individuals, additional bands of ~5.2 and/or ~6.2 kb were observed. These larger alleles were cloned into plasmid vector pCR3.1 to allow full sequencing of these variant alleles. This revealed that some individual alleles contain a duplication of repeat 8, designated as FLG^{8+}. Another allele consisted of what was essentially a duplication of repeat 10, which was designated as FLG^{10+}. Both copies of the repeat 10 sequences on this allele showed some sequence divergence from the published genome sequence. Similarly, there were a smaller number of sequence differences between the two repeat 8 copies on the FLG^{8+} allele. In some individuals, a larger allele was present consisting of the duplicated repeat 8 and the duplicated repeat 10, which was designated as FLG^{8+10+}. The size variants are shown diagrammatically in **Figure 10**, compared to the hg18 genome database sequence, labelled FLG^{N}. The raw sequences of the duplicated regions of these alleles are shown in **Figures 11-13**. A fully annotated sequence of the FLG^{8+10+}, representing all the novel sequence data

generated here, with the positions of the previously known and novel filaggrin repeat sequences, is shown in **Figure 13.**

By alignment of these additional repeat sequences with all the existing filaggrin repeats, a number of priming sites were identified that would allow specific amplification, sequencing and mutation detection within these novel alleles. Forward and reverse primers ending on these specific bases are listed in the sequence listing as SEQ ID Nos. **494 - 539**. It is recognised that the length of these primers may be varied and still allow specific PCR amplification, sequencing, or mutation analysis, provided the 3' end of the primer ends on these specific bases or very close to them. The specific bases within the duplicated repeat regions are also annotated on **Figure 13**.

It is recognised that some individuals with ichthyosis vulgaris and/or atopic disease may carry loss-of-function mutations within the newly identified sequences that constitute these new size variant alleles. It is also recognised that size variation may modulate the phenotype of heterozygous carriers of a loss-of-function or other mutation in the *FLG* gene, i.e. a heterozygous carrier of the R501X mutation may carry a second wild-type allele encoding either 10, 11 or 12 filaggrin repeats. It is recognised that the size of the heterozygous wild-type allele may influence the phenotype observed, for example, a carrier of the 12-repeat (FLG^{8+10+}) allele will express 20% more filaggrin than a R501X carrier carrying a 10-repeat wild-type allele in *trans*. Thus, detection of these size variants may be of prognostic value in ichthyosis vulgaris and atopic disease.

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Table 1

Allele frequencies of *FLG* mutations R501X and 2282del4

Population	**Allele Frequency R501X**	**Allele Frequency 2282del4**
Irish Caucasian	0.041 (n = 97)	0.005 (n = 91)
Scottish Caucasian	0.021 (n = 145)	0.012 (n =166)
US Caucasian	0.024 (n = 124)	0.011 (n = 133)
Combined	0.027 (n = 366)	0.01 (n = 390)

Table 2: Both R501X and 2282del4 are overrepresented in a childhood asthma cohort.

R501X		2282del4		Combined	
Population	Asthma	Population	Asthma	Population	Asthma
720	484	714	494	585	390
38	46	27	35	52	69
5	2	0	2	6	6
763	532	741	531	643	465
	p=0.04		p=0.0038		p=00045

Table 3 Characteristics of asthmatic children with and without filaggrin variants

	WT n=390	NULLcarriers n=75	p
SEX (%Male)	59.2	59.0	0.522
Age	10.2(2.7-21.2)	10.3(4.1-22)	
BMI	19.1	18.8	
PEFR%	92.8	90.6	
FEV1%	98.1	96.8	
FVC%	97.1	97.0	
Eczema	46.7	73.3	0.0001
Perennial Rhinitis	29	26.7	0.784
Seasonal Rhinitis	14.8	13.3	0.861
Cold air trigger	41.0	44.4	0.596
Exercise trigger	36.1	44.4	0.213
Viral trigger	44.9	46.8	0.787
Tested for allergy	16.6	30.1	0.035

Table 4: Case control association study for 5 FLG mutations (188 Irish AD patients versus 736 Irish population controls)

Genotype	R501X Population	AD	2282del4 Population	AD	R2447X Population	AD
AA	717	137	717	152	734	18
Aa	19	51	19	35	2	
aa	0	0	0	1	0	
Totals	736	188	736	188	736	18
		$p=7.8X10^{-30}$		$p=7.8X10^{-17}$		$p=1.7X10^{-5}$

Genotype	S3247X Population	Asthma	3702delG Population	AD	Combined Population	AD
AA	720	177	735	186	680	10
Aa	16	11	1	2	55	6
aa	0	0	0	0	1	2
	736	188	736	188	736	18
		p=0.008		p=0.046		$p=2.12X10^{-5}$

CLAIMS

1. A genetic test for ichthyosis vulgaris (IV) comprising the step of:

detecting *in* vitro whether or not a mutation, which would lead to a loss of function or partial loss of function of the filaggrin (FLG) protein encoded by the filaggrin (*FLG*) gene, is present in the *FLG* gene of a sample of nucleic acid from a subject.

2. The test according to claim 1 wherein the test is used to diagnose IV and/or to test if a subject is predisposed to developing IV.

3. The test according to claims 1 or 2 wherein the test is used to also detect whether or not a subject is likely to be predisposed or suffering from atopic dermatitis (eczema), asthma, psoriasis or allergies, such as of a contact type allergy and food allergies (for example, peanut allergy).

4. The test according to claim 1 wherein the test is used to identify mild and/or sub-clinical forms of IV.

5. A genetic test for atopic dermatitis (eczema), asthma, psoriasis and/or allergies comprising the step of:

detecting *in* vitro whether or not a mutation, which would lead to a loss of function or partial loss of function of the FLG protein encoded by the *FLG* gene, is present in the *FLG* gene of a sample of nucleic acid from a subject.

6. The test according to any preceding claim wherein the nucleic acid is a sample of genomic DNA or mRNA.

7. The test according to any preceding claim wherein the subject to be tested is a newborn or a foetus.

8. The test according to any preceding claim wherein the test is carried out in order to test a subject's suitability for a particular job, where he/she may come into contact with agents which are known to lead in some cases to the development of eczema and/or allergy.

9. The test according to any one of claims 1 to 7 wherein the test is carried out in order to categorise a subject and predict an "at risk" status for disease development.

10. The test according to any preceding claim wherein the mutation effects 1 – 10 nucleotides.

11. The test according to any preceding claim wherein the mutation or mutation leads to 1 – 5, 7 – 13 or 15 – 20 reduction in functional filaggrin peptides.

12. The test according to any preceding claim wherein the mutation(s) is/are found in exon 3.

13. The test according to claim 12 wherein the mutation(s) is/are found within the unique, partial repeat, or first filaggrin repeat portion of exon 3.

14. The test according to any of claims 1 to 10 wherein the mutation(s) is selected from the group consisting of R501X, 2282del4, 3702delG, R2447X (repeat 7), S3247X (repeat 9), R1474X (repeat 4), Q3683X (repeat 10), 11029delCA (repeat 10), E2422X (repeat 6), 5360delG (repeat 5), 7267delCA (repeat 7), 11033del4 (repeat 10), 6867delAG (repeat 6), 3321delA (repeat 2) and S2554X (repeat 7).

15. The test according to any one of claims 1 to 10 wherein the mutation(s) is selected from the group consisting of R501X, 2282del4, 3702delG, R2447X and S3247X.

16. The test according to any one of claims 1 to 10 wherein the subject is of Asian origin, especially Japanese and the mutation(s) is/are 3323delA and/or S2554X.

17. The test according to any preceding claim wherein the mutation(s) is/are detected by quantitative or semi-quantitative PCR, including real-time PCR, nucleic acid sequencing, hybridisation studies and/or restriction fragment length polymorphism (RFLP) analysis techniques.

18. The test according to any preceding claim, further comprising the step of identifying the number of filaggrin repeats in the *FLG* gene from said sample.

19. Use of an oligonucleotide identified as SEQ ID. Nos. 1 - 545 in a test according to any preceding claim.

20. Use of an oligonucleotide which having at its 3' position the 3' base identified from any one of SEQ ID. Nos. 1 – 545 and which is approximately 12 – 50 nucleotides in length, in a test according to any of claims 1 – 18.

21. The use according to either of claims 19 or 20 wherein the primer further comprises a label.

22. An isolated oligonucleotide identified as SEQ ID Nos. 1 – 545 or a fragment of at least 12 nucleotides or larger oligonucleotide of up to 50 nucleotides, which fragment or larger oligonucleotide share the same 3' nucleotide as a oligonucleotide identified as SEQ ID Nos. 1 – 545, for use in detecting a mutation in a filaggrin gene of a subject.

23. The oligonucleotide according to claim 22, wherein the mutation is associated with the subject having or being pre-disposed to developing IV, atopic dermatitis, asthma, psoriasis and/or allergies.

24. The use or oligonucleotide according to any one of claims 19 – 23 wherein the oligonucleotide or oligonucleotides is selected from the SEQ ID No. 1 – 8, 9 – 12, 13 –15, etc, or a fragment or larger oligonucleotide comprising the same 3' base as said SEQ ID No.

25. A kit comprising one or more oligonucleotides according to claims 22 – 24.

26. A method of detecting a mutant peptide expressed from a mutant of the *FLG* gene, comprising the steps of:

detecting *in* vitro whether or not a mutant peptide expressed from a mutant *FLG* gene is present in a sample, by using a binding agent which is specifically reactive to said mutant peptide.

27. The method according to claim 26 wherein the binding agent is an antibody.

28. An binding agent or antibody which is capable of specifically binding to a mutant peptide generated as a result of a mutation occurring in a filaggrin sequence.

29. The binding agent or antibody according to claim 28 which is capable of specifically binding to the peptide generated as a result of the 2282del4 mutation in the filaggrin gene.

30. Use of an *FLG* gene sequence or fragment thereof, capable of encoding one or more copies of the *FLG* protein, in the manufacture of a medicament.

31. An *FLG* gene sequence or fragment thereof, which gene sequence or fragment thereof, is capable of expressing one or more copies of the FLG protein, for use in therapy or prophylaxis.

32. A method of treating prophylactically or therapeutically IV, atopic dermatitis, asthma, psoriasis and/or allergies, by administering to a patient suffering or predisposed to developing any of said aforementioned diseases/conditions, a DNA

construct comprising an *FLG* gene sequence or fragment thereof, which gene sequence or fragment thereof is capable of expressing one or more copies of the *FLG* protein, whereby expression of said one or more copies of the FLG protein treats or ameliorates said disease(s)/condition(s).

33. A recombinant molecule comprising an *FLG* sequence or fragment thereof for use in therapy.

34. The present invention also provides a method of treating, preventing and/or ameliorating IV and/or any of the aforementioned diseases, comprising the steps of:

a) determining if expression of one or more copies of the FLG polypeptide would occur even if a subject's FLG gene comprises one or more mutations; and

b) providing a subject carries *FLG* alleles capable of expressing at least one or more copies of the FLG polypeptide, treating the subject using UV light in order to seek to increase *FLG* expression.

35. A transgenic non-human animal which possesses one or more mutations in one or both copies of the *FLG* gene which would lead to a loss or partial loss of function of the *FLG* protein encoded by the *FLG* gene.

36. An *in vivo* assay for identifying an agent which is useful for treating or preventing IV, atopic dermatitis, asthma, psoriasis and/or allergies associated with mutant *FLG* expression comprising the steps of administering a test agent to a *FLG* mutant transgenic animal; and measuring or determining whether the agent decreases

or inhibits at least one sign or symptom of said disease/condition which is indicative that the test agent is capable of treating or preventing said disease/condition.

Figure 1

Pedigrees and *FLG* genotypes of of IV families studied

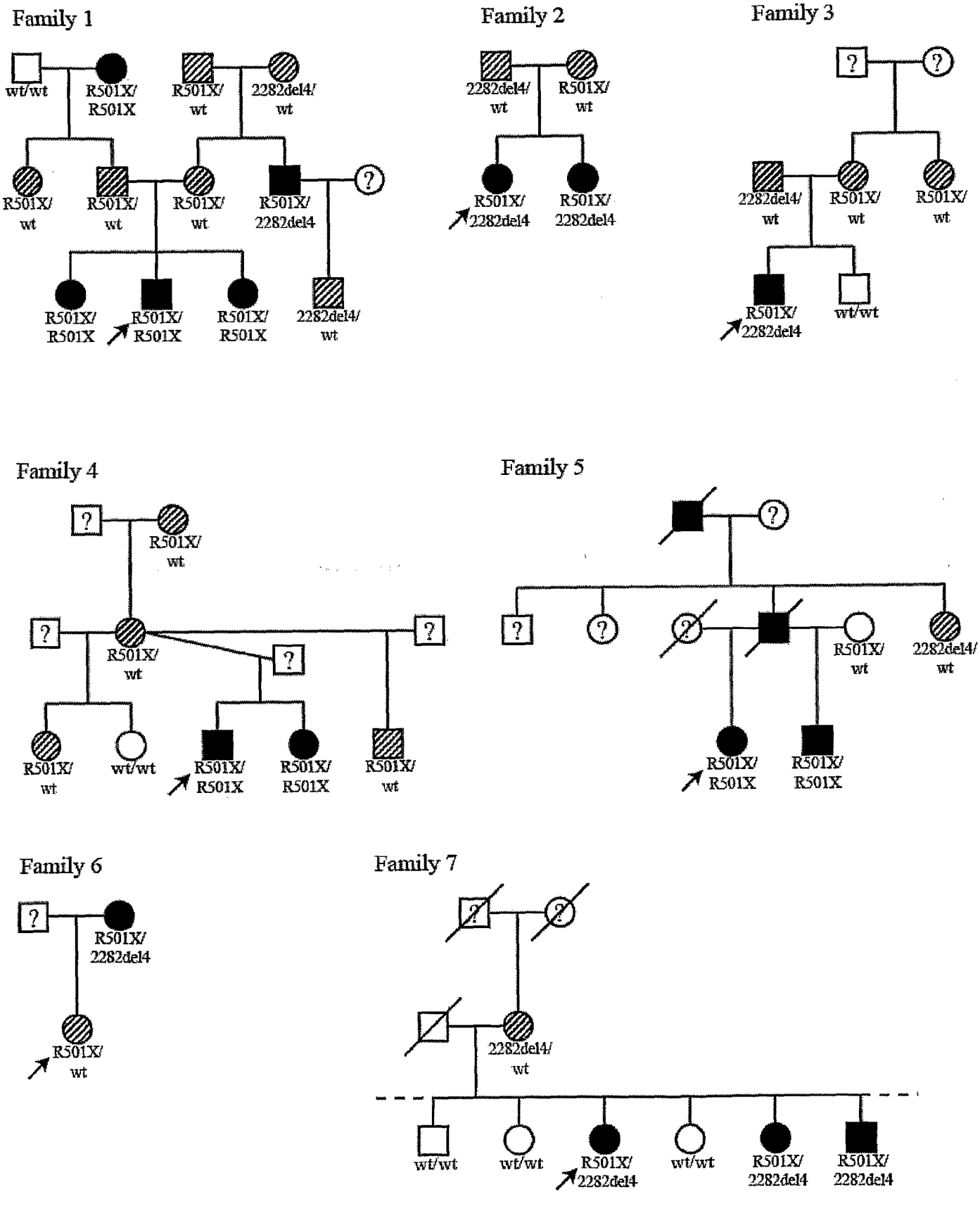

Figure 2

FLG mutation detection and confirmation

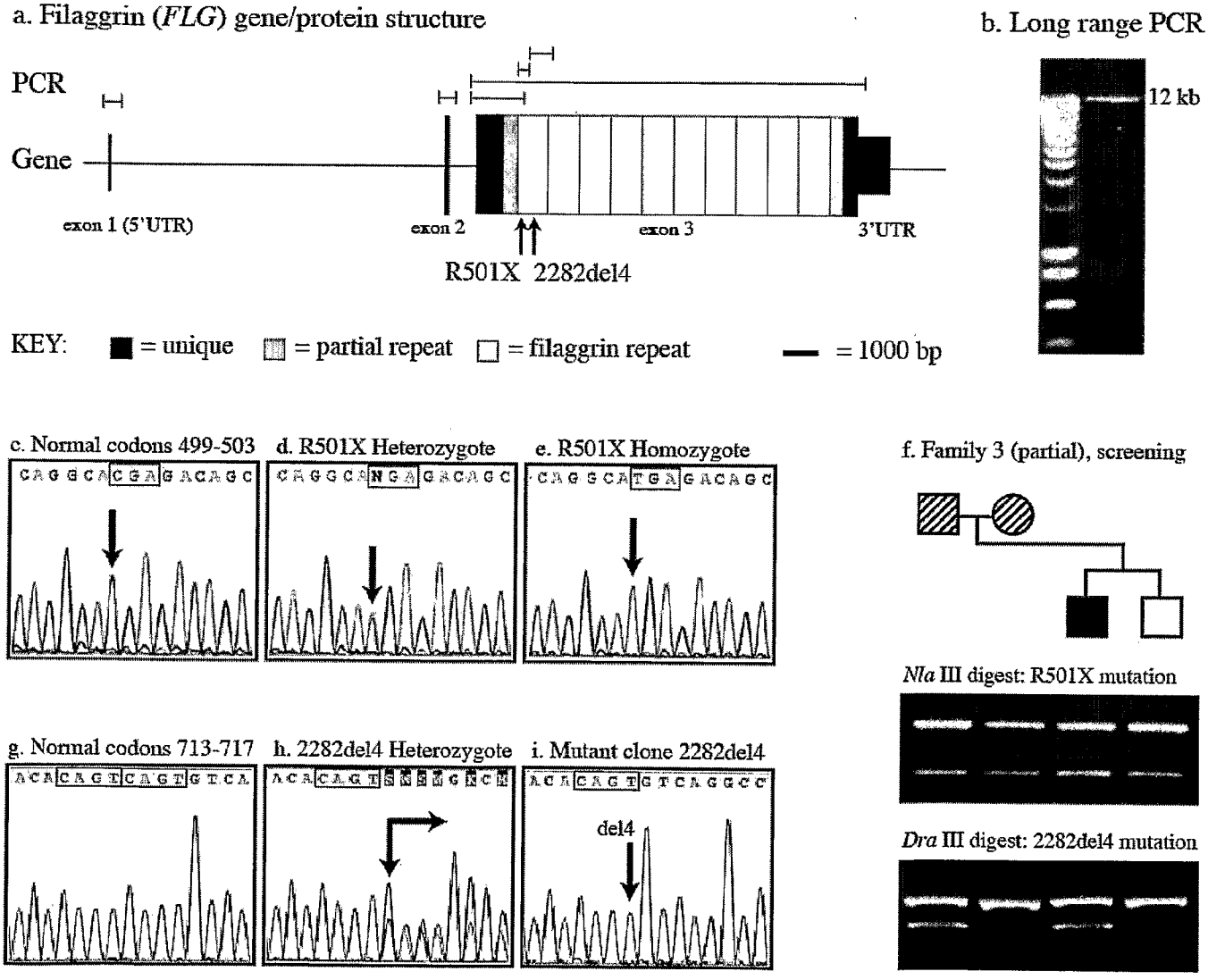

Figure 3

Histological and ultrastructural features of ichthyosis vulgaris

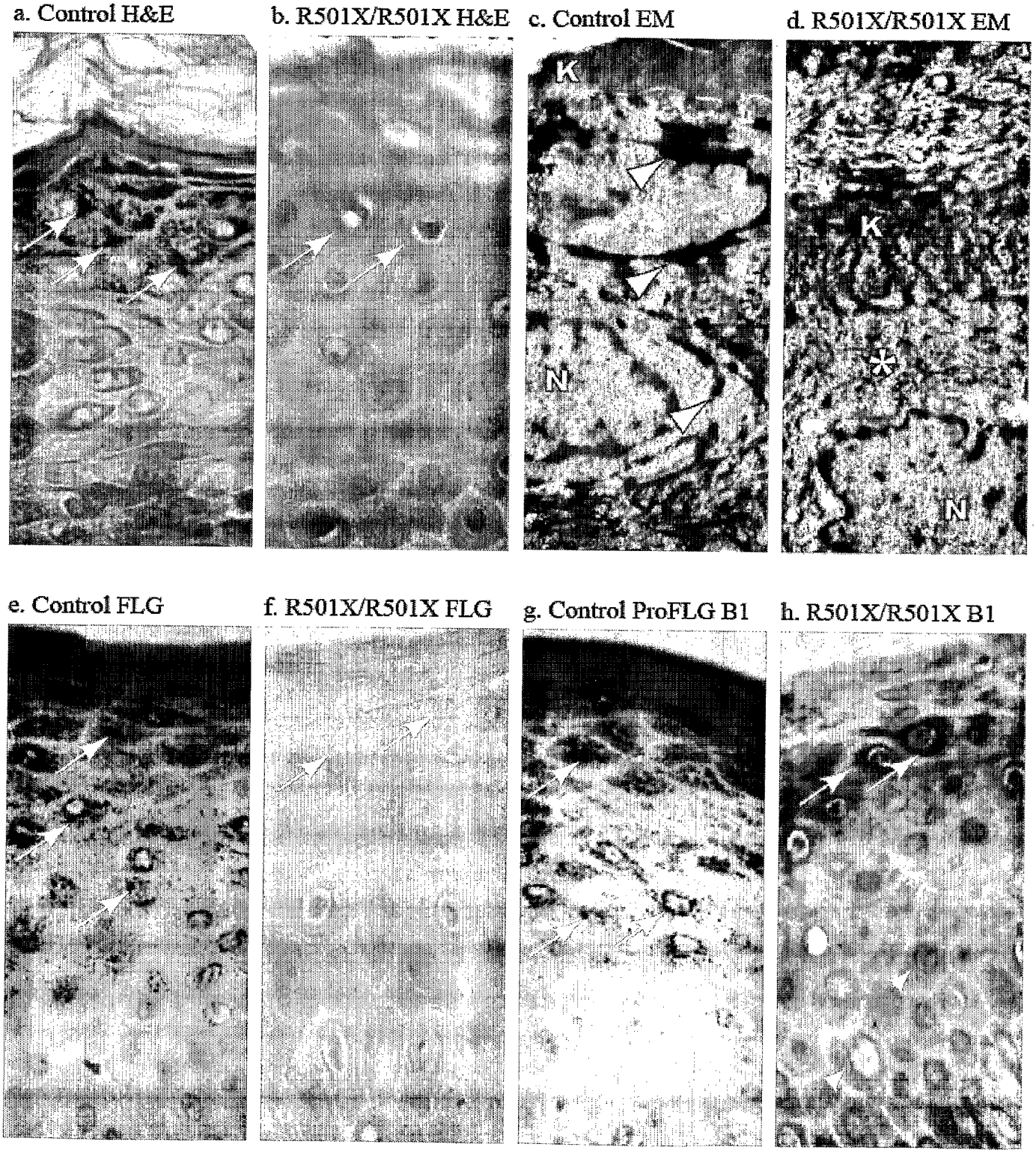

Figure 4

Profilaggrin CDS and translation

```
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domain          TACAGATGAGAGGACCTTTTGTAGAAACGGTATTAATTAGAAAAGTTCGT
                 M  S  T  L  L  E  N  I  F  A  I  I  N  L  F  K  Q

                60        70        80        90        100
                ATATTCAAAAAAAGATAAAAACACTGACACATTGAGTAAAAAAGAGCTGA
                TATAAGTTTTTTTCTATTTTTGTGACTGTGTAACTCATTTTTTCTCGACT
                  Y  S  K  K  D  K  N  T  D  T  L  S  K  K  E  L

               110       120       130       140       150
               AGGAACTTCTGGAAAAGGAATTTCGGCAAATCCTGAAGAATCCAGATGAC
               TCCTTGAAGACCTTTTCCTTAAAGCCGTTTAGGACTTCTTAGGTCTACTG
               K  E  L  L  E  K  E  F  R  Q  I  L  K  N  P  D  D

               160       170       180       190       200
               CCAGATATGGTTGATGTCTTCATGGATCACTTGGATATAGACCACAACAA
               GGTCTATACCAACTACAGAAGTACCTAGTGAACCTATATCTGGTGTTGTT
                P  D  M  V  D  V  F  M  D  H  L  D  I  D  H  N  K

               210       220       230       240       250
               GAAAATTGACTTCACTGAGTTTCTTCTGATGGTATTCAAGTTGGCTCAAG
               CTTTTAACTGAAGTGACTCAAAGAAGACTACCATAAGTTCAACCGAGTTC
                 K  I  D  F  T  E  F  L  L  M  V  F  K  L  A  Q

               260       270       280       290       300
               CATATTATGAGTCTACCAGAAAAGAGAATTTACCGATATCAGGACACAAG
               GTATAATACTCAGATGGTCTTTTCTCTTAAATGGCTATAGTCCTGTGTTC
               A  Y  Y  E  S  T  R  K  E  N  L  P  I  S  G  H  K

               310       320       330       340       350
               CACAGAAAGCACAGTCATCATGATAAACATGAAGATAATAAACAGGAAGA
               GTGTCTTTCGTGTCAGTAGTACTATTTGTACTTCTATTATTTGTCCTTCT
                H  R  K  H  S  H  H  D  K  H  E  D  N  K  Q  E  E

               360       370       380       390       400
               AAACAAAGAAAACAGAAAAAGACCCTCAAGTCTGGAAAGAAGAAACAATA
               TTTGTTTCTTTTGTCTTTTTCTGGGAGTTCAGACCTTTCTTCTTTGTTAT
                 N  K  E  N  R  K  R  P  S  S  L  E  R  R  N  N

               410       420       430       440       450
               GAAAAGGGAATAAGGGAAGATCCAAGAGCCCAAGAGAAACAGGGGGGAAA
               CTTTTCCCTTATTCCCTTCTAGGTTCTCGGGTTCTCTTTGTCCCCCCTTT
               R  K  G  N  K  G  R  S  K  S  P  R  E  T  G  G  K

               460       470       480       490       500
RPTO           AGGCATGAATCTAGTTCTGAAAAAAAAGAAAGAAAAGGATATTCACCTAC
low            TCCGTACTTAGATCAAGACTTTTTTTTCTTTCTTTTCCTATAAGTGGATG
```

```
homology      R  H  E  S  S  S  E  K  K  E  R  K  G  Y  S  P  T

                510        520        530        540        550
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AGTATCTCTTCTTCTTATACCTTTTTTGGTAGTATTGAGTTCATTTTTTC
  H  R  E  E  E  Y  G  K  N  H  H  N  S  S  K  K

                560        570        580        590        600
AGAAAAACAAGACTGAAAATACTAGATTAGGAGACAATAGGAAGAGGCTA
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E  K  N  K  T  E  N  T  R  L  G  D  N  R  K  R  L

                610        620        630        640        650
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 S  E  R  L  E  E  K  E  D  N  E  E  G  V  Y  D  Y

                660        670        680        690        700
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  E  N  T  G  R  M  T  Q  K  W  I  Q  S  G  H  I

                710        720        730        740        750
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GGTGTATAATGTGTTAGGTCCTACTTCGGATACTGTGGTGACTATCAGAT
A  T  Y  Y  T  I  Q  D  E  A  Y  D  T  T  D  S  L

                760        770        780        790        800
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 L  E  E  N  K  I  Y  E  R  S  R  S  S  D  G  K  S

                810        820        830        840        850
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  S  S  Q  V  N  R  S  R  H  E  N  T  S  Q  V  P

RPT0            860        870        880        890        900
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high      ACGTCCTCAGGTCCTGTTCTTTCGCATCCCCTAGGTCTCAATCGGTCCTG
homology    L  Q  E  S  R  T  R  K  R  R  G  S  R  V  S  Q  D

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 R  D  S  E  G  H  S  E  D  S  E  R  H  S  G  S  A

                960        970        980        990       1000
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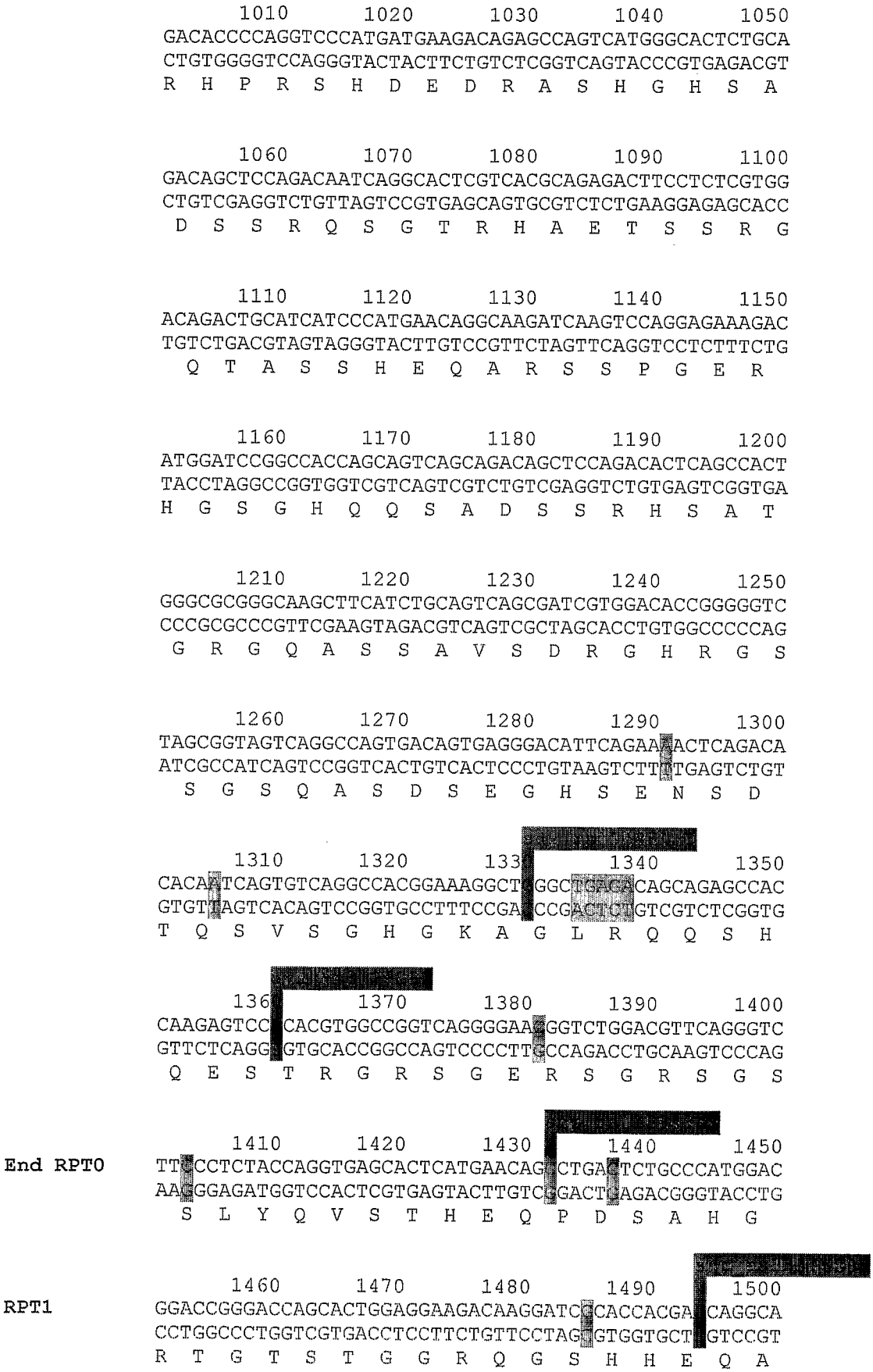
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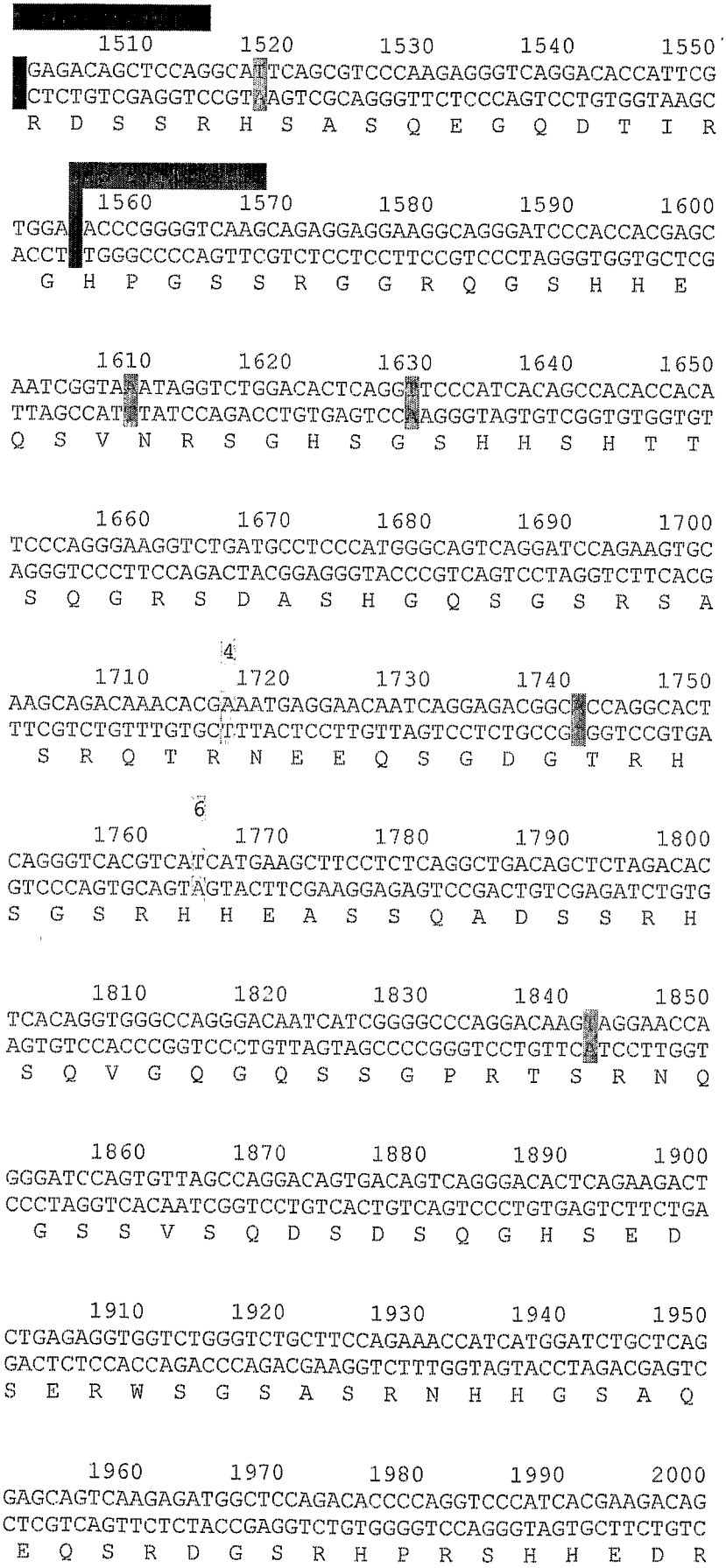
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AGGGTCCCTTCCAGACTACGGAGGGTACCCGTCAGTCCTAGGTCTTCACG
S Q G R S D A S H G Q S G S R S A
4
1710 1720 1730 1740 1750
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TTCGTCTGTTTGTGCTTTACTCCTTGTTAGTCCTCTGCCGTGGTCCGTGA
S R Q T R N E E Q S G D G T R H
6
1760 1770 1780 1790 1800
CAGGGTCACGTCATCATGAAGCTTCCTCTCAGGCTGACAGCTCTAGACAC
GTCCCAGTGCAGTAGTACTTCGAAGGAGAGTCCGACTGTCGAGATCTGTG
S G S R H H E A S S Q A D S S R H
1810 1820 1830 1840 1850
TCACAGGTGGGCCAGGGACAATCATCGGGGCCCAGGACAAGAAGGAACCA
AGTGTCCACCCGGTCCCTGTTAGTAGCCCCGGGTCCTGTTCATCCTTGGT
S Q V G Q G Q S S G P R T S R N Q
1860 1870 1880 1890 1900
GGGATCCAGTGTTAGCCAGGACAGTGACAGTCAGGGACACTCAGAAGACT
CCCTAGGTCACAATCGGTCCTGTCACTGTCAGTCCCTGTGAGTCTTCTGA
G S S V S Q D S D S Q G H S E D
1910 1920 1930 1940 1950
CTGAGAGGTGGTCTGGGTCTGCTTCCAGAAACCATCATGGATCTGCTCAG
GACTCTCCACCAGACCCAGACGAAGGTCTTTGGTAGTACCTAGACGAGTC
S E R W S G S A S R N H H G S A Q
1960 1970 1980 1990 2000
GAGCAGTCAAGAGATGGCTCCAGACACCCCAGGTCCCATCACGAAGACAG
CTCGTCAGTTCTCTACCGAGGTCTGTGGGGTCCAGGGTAGTGCTTCTGTC
E Q S R D G S R H P R S H H E D R

```
          2010       2020       2030       2040       2050
AGCTGGTCATGGGCACTCTGCAGACAGCTCCAGAAAATCAGGCACTCGTC
TCGACCAGTACCCGTGAGACGTCTGTCGAGGTCTTTTAGTCCGTGAGCAG
  A   G   H   G   H   S   A   D   S   S   R   K   S   G   T   R

          2060       2070       2080       2090       2100
ACACACAGAATTCCTCTAGTGGACAGGCTGCGTCATCCCATGAACAGGCA
TGTGTGTCTTAAGGAGATCACCTGTCCGACGCAGTAGGGTACTTGTCCGT
H   T   Q   N   S   S   S   G   Q   A   A   S   S   H   E   Q   A

                                                 555
          2110       2120       2130       2140       2150
AGATCAAGTGCAGGAGAAAGACATGGATCCCGCCACCAGCTCCAGTCAGC
TCTAGTTCACGTCCTCTTTCTGTACCTAGGGCGGTGGTCGAGGTCAGTCG
  R   S   S   A   G   E   R   H   G   S   R   H   Q   L   Q   S   A

          2160       2170       2180       2190       2200
AGACAGCTCCAGACACTCAGGCACTGGGCACGGACAAGCTTCATCTGCAG
TCTGTCGAGGTCTGTGAGTCCGTGACCCGTGCCTGTTCGAAGTAGACGTC
  D   S   S   R   H   S   G   T   G   H   G   Q   A   S   S   A

          2210       2220       2230       2240       2250
TCAGAGACAGTGGACACCGAGGGTCCAGTGGTAGTCAGGCCACTGACAGT
AGTCTCTGTCACCTGTGGCTCCCAGGTCACCATCAGTCCGGTGACTGTCA
V   R   D   S   G   H   R   G   S   S   G   S   Q   A   T   D   S

          2260       2270       2280       2290       2300
GAGGGACATTCAGAAGACTCAGACACACAGT[redacted]GTCAGGCCATGGACA
CTCCCTGTAAGTCTTCTGAGTCTGTGTGTCA[redacted]CAGTCCGGTACCTGT
  E   G   H   S   E   D   S   D   T   Q   S   V   S   G   H   G   Q

          2310       2320       2330       2340       2350
GGCTGGTCACCATCAGCAGAGCCACCAAGAGTCCGCACGTGACCGGTCAG
CCGACCAGTGGTAGTCGTCTCGGTGGTTCTCAGGCGTGCACTGGCCAGTC
  A   G   H   H   Q   Q   S   H   Q   E   S   A   R   D   R   S

          2360       2370       2380       2390       2400
GGGAAAGGTCTCGACGTTCAGGGTCTTTCCTCTACCAGGTGAGCACTCAT
CCCTTTCCAGAGCTGCAAGTCCCAGAAAGGAGATGGTCCACTCGTGAGTA
G   E   R   S   R   R   S   G   S   F   L   Y   Q   V   S   T   H

                                                     5
          2410       2420       2430       2440       2450
End RPT1  AAACAGTCTGAGTCCTCCCATGGATGGACAGGGCCCAGCACTGGAGTAAG
          TTTGTCAGACTCAGGAGGGTACCTACCTGTCCCGGGTCGTGACCTCATTC
  K   Q   S   E   S   S   H   G   W   T   G   P   S   T   G   V   R

          2460       2470       2480       2490       2500
RPT2      ACAAGGATCCCACCATGAGCAGGCACGAGACACTCCAGGCACTCAGCAT
          TGTTCCTAGGGTGGTACTCGTCCGTGCTCTGTGAGGTCCGTGAGTCGTA
  Q   G   S   H   H   E   Q   A   R   D   N   S   R   H   S   A
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                                                                    10
      2510       2520       2530       2540       2550
CCCAAGATGGTCAGGACACCATTCGTGGACACCCGGGGTCAAGCAGAAGA
GGGTTCTACCAGTCCTGTGGTAAGCACCTGTGGGCCCCAGTTCGTCTTCT
S  Q  D  G  Q  D  T  I  R  G  H  P  G  S  S  R  R

      2560       2570       2580       2590       2600
GGAAGGCAGGGGTCCCACCACGAGCAATCGGTAGATAGGTCTGGACACTC
CCTTCCGTCCCCAGGGTGGTGCTCGTTAGCCATCTATCCAGACCTGTGAG
 G  R  Q  G  S  H  H  E  Q  S  V  D  R  S  G  H  S

      2610       2620       2630       2640       2650
AGGGTCCCATCACAGCCACACCACATCCCAGGGAAGGTCTGATGCCTCCC
TCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTCCAGACTACGGAGGG
  G  S  H  H  S  H  T  T  S  Q  G  R  S  D  A  S

      2660       2670       2680       2690       2700
GTGGGCAGTCAGGATCCAGAAGTGCAAGCAGAACAACACGTAATGAGGAA
CACCCGTCAGTCCTAGGTCTTCACGTTCGTCTTGTTGTGCATTACTCCTT
R  G  Q  S  G  S  R  S  A  S  R  T  T  R  N  E  E

      2710       2720       2730       2740       2750
CAATCAAGAGACGGCTCCAGGCACTCAGGGTCACGTCACCATGAAGCTTC
GTTAGTTCTCTGCCGAGGTCCGTGAGTCCCAGTGCAGTGGTACTTCGAAG
 Q  S  R  D  G  S  R  H  S  G  S  R  H  H  E  A  S

      2760       2770       2780       2790       2800
CTCTCATGCCGACATCTCTAGACACTCACAGGCAGGCCAGGGACAATCAG
GAGAGTACGGCTGTAGAGATCTGTGAGTGTCCGTCCGGTCCCTGTTAGTC
  S  H  A  D  I  S  R  H  S  Q  A  G  Q  G  Q  S

      2810       2820       2830       2840       2850
AGGGGTCCAGGACAAGCAGGCGCCAGGGATCCAGTGTTAGCCAGGACAGT
TCCCCAGGTCCTGTTCGTCCGCGGTCCCTAGGTCACAATCGGTCCTGTCA
E  G  S  R  T  S  R  R  Q  G  S  S  V  S  Q  D  S

      2860       2870       2880       2890       2900
GACAGTGAGGGACATTCAGAAGACTCTGAGAGGTGGTCTGGGTCTGCTTC
CTGTCACTCCCTGTAAGTCTTCTGAGACTCTCCACCAGACCCAGACGAAG
 D  S  E  G  H  S  E  D  S  E  R  W  S  G  S  A  S

      2910       2920       2930       2940       2950
CAGAAACCATCGTGGATCTGCTCAGGAGCAGTCAAGACATGGCTCCAGAC
GTCTTTGGTAGCACCTAGACGAGTCCTCGTCAGTTCTGTACCGAGGTCTG
  R  N  H  R  G  S  A  Q  E  Q  S  R  H  G  S  R

      2960       2970       2980       2990       3000
ACCCCAGGTCCCATCACGAAGACAGAGCCGGTCACGGGCACTCTGCAGAC
TGGGGTCCAGGGTAGTGCTTCTGTCTCGGCCAGTGCCCGTGAGACGTCTG
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                H  P  R  S  H  H  E  D  R  A  G  H  G  H  S  A  D

                     3010       3020       3030       3040       3050
AGCTCCAGACAATCAGGAACTCTTCACGCAGAGACTTCCTCTGGTGGACA
TCGAGGTCTGTTAGTCCTTGAGAAGTGCGTCTCTGAAGGAGACCACCTGT
 S  S  R  Q  S  G  T  P  H  A  E  T  S  S  G  G  Q

                     3060       3070       3080       3090       3100
GGCTGCGTCATCCCATGAACAGGCAAGATCAAGTCCAGGAGAAAGACACG
CCGACGCAGTAGGGTACTTGTCCGTTCTAGTTCAGGTCCTCTTTCTGTGC
  A  A  S  S  H  E  Q  A  R  S  S  P  G  E  R  H

                                                      99
                     3110       3120       3130       3140       3150
GATCCCGCCACCAGCAGTCAGCAGACAGCTCCAGACACTCAGGCATTCCG
CTAGGGCGGTGGTCGTCAGTCGTCTGTCGAGGTCTGTGAGTCCGTAAGGC
G  S  R  H  Q  Q  S  A  D  S  S  R  H  S  G  I  P

                                                   9  9
                     3160       3170       3180       3190       3200
CGCAGACAAGCTTCATCTGCAGTCAGAGACAGTGGACACTGGGGGTCCAG
GCGTCTGTTCGAAGTAGACGTCAGTCTCTGTCACCTGTGACCCCCAGGTC
 R  R  Q  A  S  S  A  V  R  D  S  G  H  W  G  S  S

                           9
                     3210       3220       3230       3240       3250
TGGTAGTCAGGCCAGTGATAGTGAGGGACATTCAGAAGAGTCAGACACAC
ACCATCAGTCCGGTCACTATCACTCCCTGTAAGTCTTCTCAGTCTGTGTG
  G  S  Q  A  S  D  S  E  G  H  S  E  E  S  D  T

                     3260       3270       3280       3290       3300
AGTCAGTGTCAGGCCATGGACAGGATGGGCCCCATCAGCAGAGCCACCAA
TCAGTCACAGTCCGGTACCTGTCCTACCCGGGGTAGTCGTCTCGGTGGTT
Q  S  V  S  G  H  G  Q  D  G  P  H  Q  Q  S  H  Q

                     3310       3320       3330       3340       3350
GAGTCCGCACGTGACTGGTCAGGGGGAAGGTCTGGACGTTCAGGGTCTTT
CTCAGGCGTGCACTGACCAGTCCCCCTTCCAGACCTGCAAGTCCCAGAAA
 E  S  A  R  D  W  S  G  G  R  S  G  R  S  G  S  F

                                                      10
                     3360       3370       3380       3390       3400
End RPT2  CCTCTACCAGGTGAGCACTCATGAACAGTCTGAGTCTGCCCATGGGCGGA
          GGAGATGGTCCACTCGTGAGTACTTGTCAGACTCAGACGGGTACCCGCCT
            I  Y  Q  V  S  T  H  E  Q  S  E  S  A  H  G  R

                10                 10
                     3410       3420       3430       3440       3450
RPT3      CCAGGACCAGCACTGGACGAAGACAAGGATCCCACCACGAGCAGGCACGA
          GGTCCTGGTCGTGACCTGCTTCTGTTCCTAGGGTGGTGCTCGTCCGTGCT
          T  R  T  S  T  G  R  R  Q  G  S  H  H  E  Q  A  R

                     3460       3470       3480       3490       3500
          GACAGCTCCAGGCACTCAGCGTCCCAAGAGGGTCAGGACACCATTCGTG
          CTGTCGAGGTCCGTGAGTCGCAGGGTTCTCCCAGTCCTGTGGTAAGCAC
           D  S  S  R  H  S  A  S  Q  E  G  Q  D  T  I  R  A
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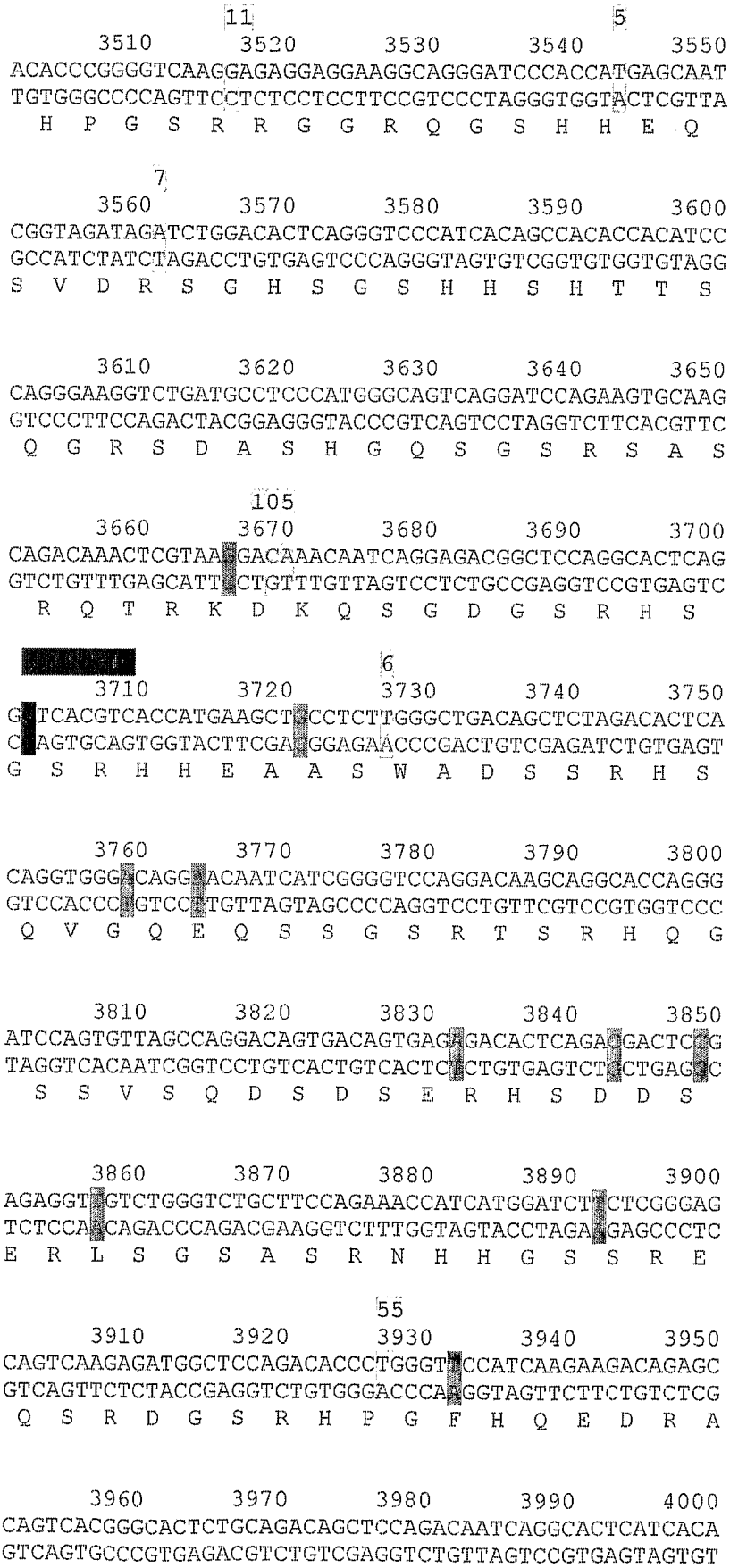
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H P G S R R G G R Q G S H H E Q
7
3560 3570 3580 3590 3600
CGGTAGATAGATCTGGACACTCAGGGTCCCATCACAGCCACACCACATCC
GCCATCTATCTAGACCTGTGAGTCCCAGGGTAGTGTCGGTGTGGTGTAGG
S V D R S G H S G S H H S H T T S
3610 3620 3630 3640 3650
CAGGGAAGGTCTGATGCCTCCCATGGGCAGTCAGGATCCAGAAGTGCAAG
GTCCCTTCCAGACTACGGAGGGTACCCGTCAGTCCTAGGTCTTCACGTTC
Q G R S D A S H G Q S G S R S A S
105
3660 3670 3680 3690 3700
CAGACAAACTCGTAAGGACAAACAATCAGGAGACGGCTCCAGGCACTCAG
GTCTGTTTGAGCATTCCTGTTTGTTAGTCCTCTGCCGAGGTCCGTGAGTC
R Q T R K D K Q S G D G S R H S
6
3710 3720 3730 3740 3750
GGTCACGTCACCATGAAGCTGCCTCTTGGGCTGACAGCTCTAGACACTCA
CCAGTGCAGTGGTACTTCGACGGAGAACCCGACTGTCGAGATCTGTGAGT
G S R H H E A A S W A D S S R H S
3760 3770 3780 3790 3800
CAGGTGGGGCAGGGACAATCATCGGGGTCCAGGACAAGCAGGCACCAGGG
GTCCACCCCGTCCCTGTTAGTAGCCCCAGGTCCTGTTCGTCCGTGGTCCC
Q V G Q E Q S S G S R T S R H Q G
3810 3820 3830 3840 3850
ATCCAGTGTTAGCCAGGACAGTGACAGTGAGAGACACTCAGACGACTCCG
TAGGTCACAATCGGTCCTGTCACTGTCACTCTCTGTGAGTCTGCTGAGGC
S S V S Q D S D S E R H S D D S
3860 3870 3880 3890 3900
AGAGGTGGTCTGGGTCTGCTTCCAGAAACCATCATGGATCTTCTCGGGAG
TCTCCACCAGACCCAGACGAAGGTCTTTGGTAGTACCTAGAAGAGCCCTC
E R L S G S A S R N H H G S S R E
55
3910 3920 3930 3940 3950
CAGTCAAGAGATGGCTCCAGACACCCTGGGTTCCATCAAGAAGACAGAGC
GTCAGTTCTCTACCGAGGTCTGTGGGACCCAAGGTAGTTCTTCTGTCTCG
Q S R D G S R H P G F H Q E D R A
3960 3970 3980 3990 4000
CAGTCACGGGCACTCTGCAGACAGCTCCAGACAATCAGGCACTCATCACA
GTCAGTGCCCGTGAGACGTCTGTCGAGGTCTGTTAGTCCGTGAGTAGTGT

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                S  H  G  H  S  A  D  S  S  R  Q  S  G  T  H  H

                     5
                4010       4020       4030       4040       4050
CAGAGTCTTCCTCTCATGGACAGGCTGTGTCATCCCATGAACAGGCAAGA
GTCTCAGAAGGAGAGTACCTGTCCGACACAGTAGGGTACTTGTCCGTTCT
T  E  S  S  S  H  G  Q  A  V  S  S  H  E  Q  A  R

                4060       4070       4080       4090       4100
TCAAGTCCAGGAGAAAGACATGGATCCCGCCACCAGCAGTCAGCAGACAG
AGTTCAGGTCCTCTTTCTGTACCTAGGGCGGTGGTCGTCAGTCGTCTGTC
 S  S  P  G  E  R  H  G  S  R  H  Q  Q  S  A  D  S

                4110       4120       4130       4140       4150
CTCCAGACACTCAGGCATTGGGCACAGACAAGCTTCATCTGCAGTCAGAG
GAGGTCTGTGAGTCCGTAACCCGTGTCTGTTCGAAGTAGACGTCAGTCTC
  S  R  H  S  G  I  G  H  R  Q  A  S  S  A  V  R

                                                1
                4160       4170       4180       4190       4200
ACAGTGGACACCGAGGGTCCAGTGGTAGTCAGGGCACTGACAGTGAGGGA
TGTCACCTGTGGCTCCCAGGTCACCATCAGTCCCGTGACTGTCACTCCCT
D  S  G  H  R  G  S  S  G  S  Q  V  T  N  S  E  G

                                                   5
                4210       4220       4230       4240       4250
CATTCAGAAGACTCAGACACACAGTCAGTGTCAGCCCACGGACAAGCTGG
GTAAGTCTTCTGAGTCTGTGTGTCAGTCACAGTCGGGTGCCTGTTCGACC
 H  S  E  D  S  D  T  Q  S  V  S  A  H  G  Q  A  G

                          5
                4260       4270       4280       4290       4300
GCCCCATCAGCAGAGCCACAAAGAGTCCGCACGTGGCCAGTCAGGGGAAA
CGGGGTAGTCGTCTCGGTGTTTCTCAGGCGTGCACCGGTCAGTCCCCTTT
  P  H  Q  Q  S  H  K  E  S  A  R  G  Q  S  G  E

                5
                4310       4320       4330       4340       4350
End RPT3        GCTCTGGACGTTCAAGGTCTTTCCTCTACCAGGTGAGCTCTCATGAACAG
                CGAGACCTGCAAGTTCCAGAAAGGAGATGGTCCACTCGAGAGTACTTGTC
                S  S  G  R  S  R  S  F  L  Y  Q  V  S  S  H  E  Q

                     6          6    6 6
                4360       4370       4380       4390       4400
RPT4            TCTGAGTCCACTCAGGACAGACTGCTCCCAGCACTGGAGGAAGACAAGG
                AGACTCAGGTGTGTCCTGTCTGACGTGGGTCGTGACCTCCTTCTGTTCC
                 S  E  S  T  H  G  Q  T  A  P  S  T  G  G  R  Q  G

                4410       4420       4430       4440       4450
ATCCCGCCATGAGCAGGCACGATACAGCTCTAGGCACTCAGCATCCCAAG
TAGGGCGGTACTCGTCCGTGCTTGTCGAGATCCGTGAGTCGTAGGGTTC
  S  R  H  E  Q  A  R  N  S  S  R  H  S  A  S  Q

                4460       4470       4480       4490       4500
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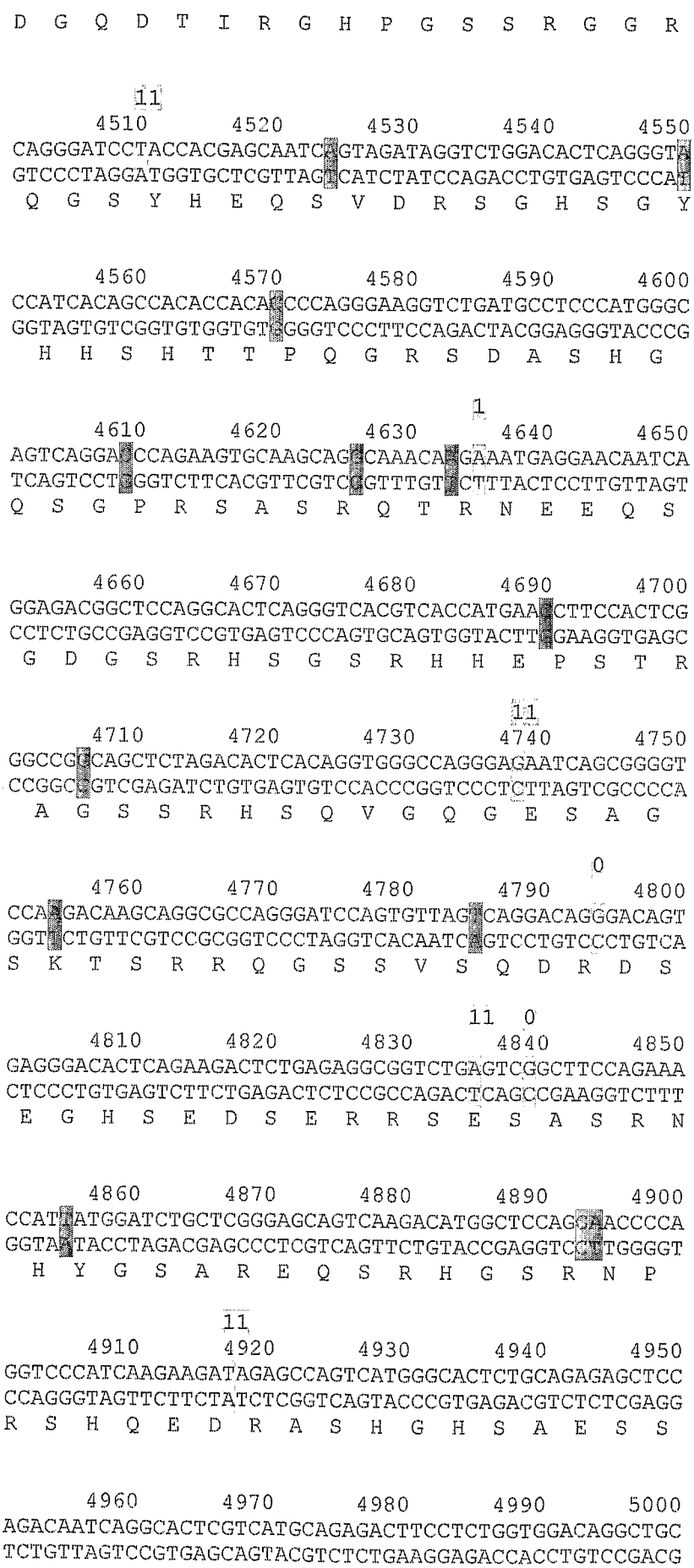
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Q G S Y H E Q S V D R S G H S G Y
4560 4570 4580 4590 4600
CCATCACAGCCACACCACACCCCAGGGAAGGTCTGATGCCTCCCATGGGC
GGTAGTGTCGGTGTGGTGTGGGGTCCCTTCCAGACTACGGAGGGTACCCG
H H S H T T P Q G R S D A S H G
1
4610 4620 4630 4640 4650
AGTCAGGACCCAGAAGTGCAAGCAGCAAACAGGAAATGAGGAACAATCA
TCAGTCCTGGGTCTTCACGTTCGTCGGTTTGTCTTTACTCCTTGTTAGT
Q S G P R S A S R Q T R N E E Q S
4660 4670 4680 4690 4700
GGAGACGGCTCCAGGCACTCAGGGTCACGTCACCATGAACTTCCACTCG
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G D G S R H S G S R H H E P S T R
11
4710 4720 4730 4740 4750
GGCCGCCAGCTCTAGACACTCACAGGTGGGCCAGGGAGAATCAGCGGGGT
CCGGCGGTCGAGATCTGTGAGTGTCCACCCGGTCCCTCTTAGTCGCCCCA
A G S S R H S Q V G Q G E S A G
0
4760 4770 4780 4790 4800
CCAAGACAAGCAGGCGCCAGGGATCCAGTGTTAGCAGGACAGGGACAGT
GGTTCTGTTCGTCCGCGGTCCCTAGGTCACAATCGTCCTGTCCCTGTCA
S K T S R R Q G S S V S Q D R D S
11 0
4810 4820 4830 4840 4850
GAGGGACACTCAGAAGACTCTGAGAGGCGGTCTGAGTCGGCTTCCAGAAA
CTCCCTGTGAGTCTTCTGAGACTCTCCGCCAGACTCAGCCGAAGGTCTTT
E G H S E D S E R R S E S A S R N
4860 4870 4880 4890 4900
CCATTATGGATCTGCTCGGGAGCAGTCAAGACATGGCTCCAGGAACCCCA
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H Y G S A R E Q S R H G S R N P
11
4910 4920 4930 4940 4950
GGTCCCATCAAGAAGATAGAGCCAGTCATGGGCACTCTGCAGAGAGCTCC
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R S H Q E D R A S H G H S A E S S
4960 4970 4980 4990 5000
AGACAATCAGGCACTCGTCATGCAGAGACTTCCTCTGGTGGACAGGCTGC
TCTGTTAGTCCGTGAGCAGTACGTCTCTGAAGGAGACCACCTGTCCGACG

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                R  Q  S  G  T  R  H  A  E  T  S  S  G  G  Q  A  A

          5010       5020       5030       5040       5050
ATCATCCCAGGAACAGGCAAGGTCAAGTCCAGGAGAAAGACATGGATCCC
TAGTAGGGTCCTTGTCCGTTCCAGTTCAGGTCCTCTTTCTGTACCTAGGG
  S  S  Q  E  Q  A  R  S  S  P  G  E  R  H  G  S

          5060       5070       5080       5090       5100
GCCACCAGCAGTCAGCAGACAGCTCCACACACTCAGGCACTGGGCGCAGA
CGGTGGTCGTCAGTCGTCTGTCGAGGTGTGTGAGTCCGTGACCCGCGTCT
R  H  Q  Q  S  A  D  S  S  T  D  S  G  T  G  R  R

          5110       5120       5130       5140       5150
CAAGTTCATCTGTAGTCCGAGACAGTGGAACCGAGGGTCCAGTGGTAG
GTTCAAGTAGACATCAGGCTCTGTCACCTTGGCTCCCAGGTCACCATC
 Q  D  S  S  V  V  G  D  S  G  N  R  G  S  S  G  S

          5160       5170       5180       5190       5200
CAGGCCAGTGACAGCGAGGGACATCAGAAGAGTCAGACACACAGTCAG
GTCCGGTCACTGTCGCTCCCTGTAGTCTTCTCAGTCTGTGTGTCAGTC
  Q  A  S  D  S  E  G  H  S  E  E  S  D  T  Q  S

          5210       5220       5230       5240       5250
TGTCAGCCCACGGACAGGCTGGGCCCCATCAGCAGAGCCACCAAGAGTCC
ACAGTCGGGTGCCTGTCCGACCCGGGGTAGTCGTCTCGGTGGTTCTCAGG
V  S  A  H  G  Q  A  G  P  H  Q  Q  S  H  Q  E  S

          5260       5270       5280       5290       5300
ACACGTGGCCAGTCAGGGGAAAGGTCTGGACGTTCAGGGTCTTTCCTCTA
TGTGCACCGGTCAGTCCCCTTTCCAGACCTGCAAGTCCCAGAAAGGAGAT
 T  R  G  Q  S  G  E  R  S  G  R  S  G  S  F  L  Y

          5310       5320       5330       5340       5350
End RPT4  CCAGGTGAGCACTCATGAACAGTCTGAGTCCGCCCATGGACGCACAGGGC
          GGTCCACTCGTGAGTACTTGTCAGACTCAGGCGGGTACCTGCGTGTCCCG
            Q  V  S  T  H  E  Q  S  E  S  A  H  G  R  T  G

          5360       5370       5380       5390       5400
RPT5      CCAGCACTGGAGGAAGACAAAGATCCCGCCACGAGCAGGCACGAGACAGC
          GGTCGTGACCTCCTTCTGTTTCTAGGGCGGTGCTCGTCCGTGCTCTGTCG
          P  S  T  G  G  R  Q  R  S  R  H  E  Q  A  R  D  S

          5410       5420       5430       5440       5450
TCCAGGCACTCAGCGTCCCAAGAGGGTCAGGACACCATTCGTGGACACCC
AGGTCCGTGAGTCGCAGGGTTCTCCCAGTCCTGTGGTAAGCACCTGTGGG
 S  R  H  S  A  S  Q  E  G  Q  D  T  I  R  G  H  P

                                              3
          5460       5470       5480       5490       5500
AGGGTCAAGCAGAGGAGGAAGGCAGGGATCCCACTATGAGCAATCGGTAG
TCCCAGTTCGTCTCCTCCTTCCGTCCCTAGGGTGATACTCGTTAGCCATC
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                G  S  S  R  G  G  R  Q  G  S  H  Y  E  Q  S  V

          (0)
       5510       5520       5530       5540       5550
ATAGTTCTGGACACTCAGGGTCTCATCACAGCCACACCACGTCCCAGGAA
TATCAAGACCTGTGAGTCCCAGAGTAGTGTCGGTGTGGTGCAGGGTCCTT
D  S  S  G  H  S  G  S  H  H  S  H  T  T  S  Q  E

       5560       5570       5580       5590       5600
AGGTCTGATGTCTCCCGTGGGCAGTCAGGATCCAGAAGTGTCAGCAGACA
TCCAGACTACAGAGGGCACCCGTCAGTCCTAGGTCTTCACAGTCGTCTGT
 R  S  D  V  S  R  G  Q  S  G  S  R  S  V  S  R  Q

             3(+0)
       5610       5620       5630       5640       5650
AACACGTAATGAGAAACAATCAGGAGACGGCTCCAGGCACTCAGGGTCGC
TTGTGCATTACTCTTTGTTAGTCCTCTGCCGAGGTCCGTGAGTCCCAGCG
  T  R  N  E  K  Q  S  G  D  G  S  R  H  S  G  S

                                                  7
       5660       5670       5680       5690       5700
GTCACCATGAAGCTTCCTCTCGGGCCGACAGCTCTAGACACTCGCAGGTG
CAGTGGTACTTCGAAGGAGAGCCCGGCTGTCGAGATCTGTGAGCGTCCAC
R  H  H  E  A  S  S  R  A  D  S  S  R  H  S  Q  V

                     6
       5710       5720       5730       5740       5750
GGCCAGGGACAATCATCAGGGCCCAGGACAAGCAGGAACCAGGGATCCAG
CCGGTCCCTGTTAGTAGTCCCGGGTCCTGTTCGTCCTTGGTCCCTAGGTC
 G  Q  G  Q  S  S  G  P  R  T  S  R  N  Q  G  S  S

       5760       5770       5780       5790       5800
TGTTAGCCAGGACAGTGACAGTCAGGGACACTCAGAAGACTCTGAGAGGT
ACAATCGGTCCTGTCACTGTCAGTCCCTGTGAGTCTTCTGAGACTCTCCA
  V  S  Q  D  S  D  S  Q  G  H  S  E  D  S  E  R

                                                  0
       5810       5820       5830       5840       5850
GGTCTGGGTCTGCTTCCAGAAACCATCTTGGATCTGCTTGGGAGCAGTCA
CCAGACCCAGACGAAGGTCTTTGGTAGAACCTAGACGAACCCTCGTCAGT
W  S  G  S  A  S  R  N  H  L  G  S  A  W  E  Q  S

                        33
       5860       5870       5880       5890       5900
AGAGATGGCTCCAGACACCCTGGGTCCCATCACGAAGACAGAGCCGGTCA
TCTCTACCGAGGTCTGTGGGACCCAGGGTAGTGCTTCTGTCTCGGCCAGT
 R  D  G  S  R  H  P  G  S  H  H  E  D  R  A  G  H

                                                  3
       5910       5920       5930       5940       5950
CGGGCACTCTGCAGACAGCTCCAGACAATCAGGCACTCGTCACACAGAGT
GCCCGTGAGACGTCTGTCGAGGTCTGTTAGTCCGTGAGCAGTGTGTCTCA
  G  H  S  A  D  S  S  R  Q  S  G  T  R  H  T  E

       5960       5970       5980       5990       6000
CTTCCTCTCGTGGACAGGCTGCGTCATCCCATGAACAGGCAAGATCAAGT
GAAGGAGAGCACCTGTCCGACGCAGTAGGGTACTTGTCCGTTCTAGTTCA
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                S  S  S  R  G  Q  A  A  S  S  H  E  Q  A  R  S  S

                                                  111
                6010       6020       6030       6040       6050
GCAGGAGAAAGACATGGATCCCACCACCAGCTCCAGTCAGCAGACAGCTC
CGTCCTCTTTCTGTACCTAGGGTGGTGGTCGAGGTCAGTCGTCTGTCGAG
 A  G  E  R  H  G  S  H  H  Q  L  Q  S  A  D  S  S

                           9
                6060       6070       6080       6090       6100
CAGACACTCAGGCATTGGGCATGGACAAGCTTCATCTGCAGTCAGAGACA
GTCTGTGAGTCCGTAACCCGTACCTGTTCGAAGTAGACGTCAGTCTCTGT
  R  H  S  G  I  G  H  G  Q  A  S  S  A  V  R  D

                6110       6120       6130       6140       6150
GTGGACACCGAGGGTACAGTGGTAGTCAGGCCAGTGACAGTGAGGGACAT
CACCTGTGGCTCCCATGTCACCATCAGTCCGGTCACTGTCACTCCCTGTA
S  G  H  R  G  Y  S  G  S  Q  A  S  D  S  E  G  H

                                                  3
                6160       6170       6180       6190       6200
TCAGAAGACTCAGACACACAGTCAGTGTCAGCTCAGGGAAAAGCTGGGCC
AGTCTTCTGAGTCTGTGTGTCAGTCACAGTCGAGTCCTTTTCGACCCGG
 S  E  D  S  D  T  Q  S  V  S  A  Q  G  K  A  G  P

                           3                       3
                6210       6220       6230       6240       6250
CCATCAGCAGAGCCACAAAGAGTCCGCACGTGGCCAGTCAGGGGAAAGCT
GGTAGTCGTCTCGGTGTTTCTCAGGCGTGCACCGGTCAGTCCCCTTTCGA
  H  Q  Q  S  H  K  E  S  A  R  G  Q  S  G  E  S

                6260       6270       6280       6290       6300
End RPT5        CTGGACGTTCAGGGTCTTTCCTCTACCAGGTGAGCACTCATGAACAGTCT
                GACCTGCAAGTCCCAGAAAGGAGATGGTCCACTCGTGAGTACTTGTCAGA
                S  G  R  S  G  S  F  L  Y  Q  V  S  T  H  E  Q  S

                     4         4    4 4
                6310       6320       6330       6340       6350
RPT6            GAGTCCACCCATGGACAGTCTGCGCCCAGCACTGGAGGAAGACAAGGATC
                CTCAGGTGGGTACCTGTCAGACGCGGGTCGTGACCTCCTTCTGTTCCTAG
                 E  S  T  H  G  Q  S  A  P  S  T  G  G  R  Q  G  S

                6360       6370       6380       6390       6400
                CCATCATGACCAGGCACAAGACAGCTCCAGGCACTCAGCATCCCAAGAGG
                GGTAGTACTGGTCCGTGTTCTGTCGAGGTCCGTGAGTCGTAGGGTTCTCC
                  H  Y  D  Q  A  Q  D  S  S  R  H  S  A  S  Q  E

                                                       11
                6410       6420       6430       6440       6450
                GTCAGGACACCATTCGTGGACACCCGGGGTCAAGCAGAGGAGGAAGACAG
                CAGTCCTGTGGTAAGCACCTGTGGGCCCCAGTTCGTCTCCTCCTTCTGTC
                G  Q  D  T  I  R  G  H  P  G  P  S  R  G  G  R  Q

                6460       6470       6480       6490       6500
                GGGTCCCACCAAGAGCAATCGGTAGATAGGTCTGGACACTCAGGGTCTCA
                CCCAGGGTGGTTCTCGTTAGCCATCTATCCAGACCTGTGAGTCCCAGAGT
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```
  G  S  H  Q  E  Q  S  V  D  R  S  G  H  S  G  S  H

      6510       6520       6530       6540       6550
TCACAGCCACACCACATCCCAGGGAAGGTCTGATGCCTCCCGTGGGCAGT
AGTGTCGGTGTGGTGTAGGGTCCCTTCCAGACTACGGAGGGCACCCGTCA
  H  S  H  T  T  S  Q  G  R  S  D  A  S  R  G  Q

                                          7
      6560       6570       6580       6590       6600
CAGGATCCAGAAGTGCAAGCAGAAAAACATATGACAAGGAACAATCAGGA
GTCCTAGGTCTTCACGTTCGTCTTTTTGTATACTGTTCCTTGTTAGTCCT
S  G  S  R  S  A  S  R  K  T  Y  D  K  E  Q  S  G

 10                    10  1              3
      6610       6620       6630       6640       6650
GATGGCTCAAGGCACTCAGGGTCGCATCATCATGAAGCTTCCTCTTGGGC
CTACCGAGATCCGTGAGTCCCAGCGTAGTAGTACTTCGAAGGAGAACCCG
 D  G  S  R  H  S  G  S  H  H  H  E  A  S  S  W  A

                                                5
      6660       6670       6680       6690       6700
CGACAGCTCTAGACACTCACAGGTGGGCCAGGGACAATCATCAGGGCCCA
GCTGTCGAGATCTGTGAGTGTCCACCCGGTCCCTGTTAGTAGTCCCGGGT
  D  S  S  R  H  S  L  V  G  Q  G  Q  S  S  G  P

                7
      6710       6720       6730       6740       6750
GGACAAGCAGGCACCGGGGATCCAGTGTTAGCCAGGACAGTGACAGTGAG
CCTGTTCGTCCGTGGCCCCTAGGTCACAATCGGTCCTGTCACTGTCACTC
R  T  S  R  P  R  G  S  S  V  S  Q  D  S  D  S  E

      6760       6770       6780       6790       6800
GGACACTCAGAAGATTCTGAGAGGCGGTCTGGGTCTGCATCCAGAAACCA
CCTGTGAGTCTTCTAAGACTCTCCGCCAGACCCAGACGTAGGTCTTTGGT
 G  H  S  E  D  S  E  R  R  S  G  S  A  S  R  N  H

      6810       6820       6830       6840       6850
TCATGGATCTGCTCAGGAGCAGTCAAGAGATGGCTCCAGACACCCCAGGT
AGTACCTAGACGAGTCCTCGTCAGTTCTCTACCGAGGTCTGTGGGGTCCA
  H  G  S  A  Q  E  Q  S  R  D  G  S  R  H  P  R

      6860       6870       6880       6890       6900
CCCATCACGAAGACAGAGCCGGTCATGGGCACTCTGCAGAGAGCTCCAGA
GGGTAGTGCTTCTGTCTCGGCCAGTACCCGTGAGACGTCTCTCGAGGTCT
S  H  H  E  D  R  A  G  H  G  H  S  A  E  S  S  R

      6910       6920       6930       6940       6950
CAATCAGGCACTCATCATGCAGAGAATTCCTCTGGTGGACAGGCTGCATC
GTTAGTCCGTGAGTAGTACGTCTCTTAAGGAGACCACCTGTCCGACGTAG
 Q  S  G  T  H  H  A  E  N  S  S  G  G  Q  A  A  S

      6960       6970       6980       6990       7000
ATCCCATGAACAGGCAAGATCAAGTGCAGGAGAGAGACACGGATCCCACC
TAGGGTACTTGTCCGTTCTAGTTCACGTCCTCTCTCTGTGCCTAGGGTGG
```

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                S  H  E  Q  A  R  S  S  A  G  E  R  H  G  S  H

                7010       7020       7030       7040       7050
ACCAGCAGTCAGCAGACAGCTCCAGACACTCAGGCATTGGGCACGGACAA
TGGTCGTCAGTCGTCTGTCGAGGTCTGTGAGTCCGTAACCCGTGCCTGTT
H  Q  Q  S  A  D  S  S  R  H  S  G  I  G  H  G  Q

                7060       7070       7080       7090       7100
GCTTCATCTGCAGTCAGAGACAGTGGACACCGAGGGTCCAGTGGTAGTCA
CGAAGTAGACGTCAGTCTCTGTCACCTGTGGCTCCCAGGTCACCATCAGT
 A  S  S  A  V  R  D  S  G  H  R  G  S  S  G  S  Q

                7110       7120       7130       7140       7150
GGCCAGTGACAGTGAGGGACATTCAGAAGACTCAGACACACAGTCAGTGT
CCGGTCACTGTCACTCCCTGTAAGTCTTCTGAGTCTGTGTGTCAGTCACA
  A  S  D  S  E  G  H  S  E  D  S  D  T  Q  S  V

                7160       7170       7180       7190       7200
CAGCCCACGGACAGGCTGGGCCCCATCAGCAGAGCCACCAAGAGTCCACA
GTCGGGTGCCTGTCCGACCCGGGGTAGTCGTCTCGGTGGTTCTCAGGTGT
S  A  H  G  Q  A  G  P  H  Q  Q  S  H  Q  E  S  T

                      10
                7210       7220       7230       7240       7250
CGTGGCCGGTCAGCAGGAAGGTCTGGACGTTCAGGGTCTTTCCTCTACCA
GCACCGGCCAGTCGTCCTTCCAGACCTGCAAGTCCCAGAAAGGAGATGGT
 R  G  R  S  A  G  R  S  G  R  S  G  S  F  L  Y  Q

                7260       7270       7280       7290       7300
End RPT6  GGTGAGCACTCATGAACAGTCTGAGTCCGCCCATGGACGGACCGGGACCA
          CCACTCGTGAGTACTTGTCAGACTCAGGCGGGTACCTGCCTGGCCCTGGT
            V  S  T  H  E  Q  S  E  S  A  H  G  R  T  G  T

                7310       7320       7330       7340       7350
RPT7      GCACTGGAGGAAGACAAGGATCCCACCACAAGCAGGCACGAGACAGCTCC
          CGTGACCTCCTTCTGTTCCTAGGGTGGTGTTCGTCCGTGCTCTGTCGAGG
          S  T  G  G  R  Q  G  S  H  H  K  Q  A  R  D  S  S

                7360       7370       7380       7390       7400
          AGGCACTCACCGTCCCAAGAGGGTCAGGACACCATTCATGGACACCCGGG
          TCCGTGAGTGGCAGGGTTCTCCCAGTCCTGTGGTAAGTACCTGTGGGCCC
           R  H  S  T  S  Q  E  G  Q  D  T  I  H  G  H  P  G

                7410       7420       7430       7440       7450
          GTCAAGCAGGGAGGAAGGCAGGGATCCCACTACGAGCAATGGTAGATA
          CAGTTCGTCCCTCCTTCCGTCCCTAGGGTGATGCTCGTTACCATCTAT
            S  S  S  G  G  R  Q  G  S  H  Y  E  Q  L  V  D

                3
                7460       7470       7480       7490       7500
          GATCTGGACACTCAGGGTCTCATCACAGCCACACCACATCCCAGGGAAGG
          CTAGACCTGTGAGTCCCAGAGTAGTGTCGGTGTGGTGTAGGGTCCCTTCC
```

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R  S  G  H  S  G  S  H  H  S  H  T  T  S  Q  G  R

      7510       7520       7530       7540       7550
TCTGATGCCTCCCATGGGCACTCAGGATCCAGAAGTGCAAGCAGACAAAC
AGACTACGGAGGGTACCCGTGAGTCCTAGGTCTTCACGTTCGTCTGTTTG
 S  D  A  S  H  G  H  S  G  S  R  S  A  S  R  Q  T

      6
      7560       7570       7580       7590       7600
TCGTAACGAAGAACAATCAGGAGACGGCTCCAGGCACTCAGGGTCGCGTC
AGCATTGCTACTTGTTAGTCCTCTGCCGAGGTCCGTGAGTCCCAGCGCAG
  R  N  D  E  Q  S  G  D  G  S  R  H  S  G  S  R

                                                5
      7610       7620       7630       7640       7650
ACCATGAAGCTTCCTCTCGGGCCGACAGCTCTGGACACTCGCAGGTGGGC
TGGTACTTCGAAGGAGAGCCCGGCTGTCGAGACCTGTGAGCGTCCACCCG
H  H  E  A  S  S  R  A  D  S  S  G  H  S  Q  V  G

                                          6
      7660       7670       7680       7690       7700
CAGGGACAATCAGAGGGGCCCAGGACAAGCAGGAACTGGGGATCCAGTCT
GTCCCTGTTAGTCTCCCCGGGTCCTGTTCGTCCTTGACCCCTAGGTCAGA
 Q  G  Q  S  E  G  P  R  T  S  R  N  W  G  S  S  F

      7710       7720       7730       7740       7750
TAGCCAGGACAGTGACAGTCAGGGACACTCAGAAGACTCTGAGAGGTGGT
ATCGGTCCTGTCACTGTCAGTCCCTGTGAGTCTTCTGAGACTCTCCACCA
  S  Q  D  S  D  S  Q  G  H  S  E  D  S  E  R  W

                                                88
      7760       7770       7780       7790       7800
CTGGGTCTGCTTCCAGAAACCATCATGGATCTGCTCAGGAGCAGCTAAGA
GACCCAGACGAAGGTCTTTGGTAGTACCTAGACGAGTCCTCGTCGATTCT
S  G  S  A  S  R  N  H  H  G  S  A  Q  E  Q  L  R

      7810       7820       7830       7840       7850
GATGGCTCCAGACACCCCAGGTCCCATCAAGAAGACAGAGCTGGTCATGG
CTACCGAGGTCTGTGGGGTCCAGGGTAGTTCTTCTGTCTCGACCAGTACC
 D  G  S  R  H  P  R  S  H  Q  E  D  R  A  G  H  G

      7860       7870       7880       7890       7900
GCACTCTGCAGACAGCTCCAGACAATCAGGCACTCGTCACACACAGACTT
CGTGAGACGTCTGTCGAGGTCTGTTAGTCCGTGAGCAGTGTGTGTCTGAA
  H  S  A  D  S  S  R  Q  S  G  T  R  H  T  Q  T

      7910       7920       7930       7940       7950
CCTCTGGTGGACAGGCTGCATCATCCCATGAACAGGCAAGATCAAGTGCA
GGAGACCACCTGTCCGACGTAGTAGGGTACTTGTCCGTTCTAGTTCACGT
S  S  G  G  Q  A  A  S  S  H  E  Q  A  R  S  S  A

      7960       7970       7980       7990       8000
GGAGAAAGACATGGATCCCACCACCAGCAGTCAGCAGACAGCTCCAGACA
CCTCTTTCTGTACCTAGGGTGGTGGTCGTCAGTCGTCTGTCGAGGTCTGT
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                G  E  R  H  G  S  H  H  Q  Q  S  A  D  S  S  R  H

                    8010       8020       8030       8040       8050
                CTCAGGCATTGGGCACGGACAAGCTTCATCTGCAGTCAGAGACAGTGGAC
                GAGTCCGTAACCCGTGCCTGTTCGAAGTAGACGTCAGTCTCTGTCACCTG
                  S  G  I  G  H  G  Q  A  S  S  A  V  R  D  S  G

                                                  8
                    8060       8070       8080       8090       8100
                ACCGAGGGTACAGTGGTAGTCAGGCCAGTGACAATGAGGGACATTCAGAA
                TGGCTCCCATGTCACCATCAGTCCGGTCACTGTTACTCCCTGTAAGTCTT
                H  R  G  Y  S  G  S  Q  A  S  D  N  E  G  H  S  E

                                                        8
                    8110       8120       8130       8140       8150
                GACTCAGACACACAGTCAGTGTCAGCCCACGGACAGGCTGGGTCCCATCA
                CTGAGTCTGTGTGTCAGTCACAGTCGGGTGCCTGTCCGACCCAGGGTAGT
                 D  S  D  T  Q  S  V  S  A  H  G  Q  A  G  S  H  Q

                                                     8
                    8160       8170       8180       8190       8200
                GCAGAGCCACCAAGAGTCCGCACGTGGCCGGTCAGGGGAAACGTCTGGAC
                CGTCTCGGTGGTTCTCAGGCGTGCACCGGCCAGTCCCCTTTGCAGACCTG
                  Q  S  H  Q  E  S  A  R  G  R  S  G  E  T  S  G

                8   8
                    8210       8220       8230       8240       8250
End RPT7        ATTCAGGATCTTTCCTCTACCAGGTGAGCACTCATGAACAGTCTGAGTCC
                TAAGTCCTAGAAAGGAGATGGTCCACTCGTGAGTACTTGTCAGACTCAGG
                H  S  G  S  F  L  Y  Q  V  S  T  H  E  Q  S  E  S

                          9          9
                    8260       8270       8280       8290       8300
RPT8            TCCCATGGATGGACGGGGCCCAGCACTAGAGGAAGACAAGGATCCCGCCA
                AGGGTACCTACCTGCCCCGGGTCGTGATCTCCTTCTGTTCCTAGGGCGGT
                 S  H  G  W  T  G  P  S  T  R  G  R  Q  G  S  R  H

                    8310       8320       8330       8340       8350
                TGAGCAGGCACAAGACAGCTCCAGGCACTCAGCATCCCAAGACGGTCAGG
                ACTCGTCCGTGTTCTGTCGAGGTCCGTGAGTCGTAGGGTTCTGCCAGTCC
                  E  Q  A  Q  D  S  S  R  H  S  A  S  Q  D  G  Q

                                                              9
                    8360       8370       8380       8390       8400
                ACACCATTCGTGGACACCCGGGGTCAAGCAGAGGAGGAAGGCAGGGGTAC
                TGTGGTAAGCACCTGTGGGCCCCAGTTCGTCTCCTCCTTCCGTCCCCATG
                D  T  I  R  G  H  P  G  S  S  R  G  G  R  Q  G  Y

                          9          9
                    8410       8420       8430       8440       8450
                CACCACGAGCATTCGGTAGATAGCTCTGGACACTCAGGGTCCCATCACAG
                GTGGTGCTCGTAAGCCATCTATCGAGACCTGTGAGTCCCAGGGTAGTGTC
                 H  H  E  H  S  V  D  S  S  G  H  S  G  S  H  H  S

                    8460       8470       8480       8490       8500
                CCACACCACATCCCAGGGAAGGTCTGATGCCTCCCGTGGGCAGTCAGGAT
                GGTGTGGTGTAGGGTCCCTTCCAGACTACGGAGGGCACCCGTCAGTCCTA
```

H T T S Q G R S D A S R G Q S G

8510 8520 8530 8540 8550
CCAGAAGTGCAAGCAGAACAACACGTAATGAGGAACAATCAGGAGACGGC
GGTCTTCACGTTCGTCTTGTTGTGCATTACTCCTTGTTAGTCCTCTGCCG
S R S A S R T T R N E E Q S G D G

8560 8570 8580 8590 8600
TCCAGGCACTCAGGGTCGCGTCACCATGAAGCTTCCACTCATGCCGACAT
AGGTCCGTGAGTCCCAGCGCAGTGGTACTTCGAAGGTGAGTACGGCTGTA
S R H S G S R H H E A S T H A D I

9 9
8610 8620 8630 8640 8650
CTCTAGACACTCACAGGCAGTCCAGGGACAATCAGAGGGGTCCAGGAGAA
GAGATCTGTGAGTGTCCGTCAGGTCCCTGTTAGTCTCCCCAGGTCCTCTT
S R H S Q A V Q G Q S E G S R R

9
8660 8670 8680 8690 8700
GCAGGCGCCAGGGATCCAGTGTGAGCCAGGACAGTGACAGTGAGGGACAT
CGTCCGCGGTCCCTAGGTCACACTCGGTCCTGTCACTGTCACTCCCTGTA
S R R Q G S S V S Q D S D S E G H

8710 8720 8730 8740 8750
TCAGAAGACTCTGAGAGGTGGTCTGGGTCTGCTTCCAGAAACCATCATGG
AGTCTTCTGAGACTCTCCACCAGACCCAGACGAAGGTCTTTGGTAGTACC
S E D S E R W S G S A S R N H H G

77
8760 8770 8780 8790 8800
ATCTGCTCAGGAGCAGCTAAGAGATGGCTCCAGACACCCCAGGTCCCATC
TAGACGAGTCCTCGTCGATTCTCTACCGAGGTCTGTGGGGTCCAGGGTAG
S A Q E Q L R D G S R H P R S H

8810 8820 8830 8840 8850
AAGAAGACAGAGCTGGTCATGGGCACTCTGCAGACAGCTCCAGACAATCA
TTCTTCTGTCTCGACCAGTACCCGTGAGACGTCTGTCGAGGTCTGTTAGT
Q E D R A G H G H S A D S S R Q S

8860 8870 8880 8890 8900
GGCACTCGTCACACACAGACTTCCTCTGGTGGACAGGCTGCATCATCCCA
CCGTGAGCAGTGTGTGTCTGAAGGAGACCACCTGTCCGACGTAGTAGGGT
G T R H T Q T S S G G Q A A S S H

8910 8920 8930 8940 8950
TGAACAGGCAAGATCAAGTGCAGGAGAAAGACATGGATCCCACCACCAGC
ACTTGTCCGTTCTAGTTCACGTCCTCTTTCTGTACCTAGGGTGGTGGTCG
E Q A R S S A G E R H G S H H Q

8960 8970 8980 8990 9000
AGTCAGCAGACAGCTCCAGACACTCAGGCATTGGGCACGGACAAGCTTCA
TCAGTCGTCTGTCGAGGTCTGTGAGTCCGTAACCCGTGCCTGTTCGAAGT

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                Q  S  A  D  S  S  R  H  S  G  I  G  H  G  Q  A  S


                    9010       9020       9030       9040       9050
                TCTGCAGTCAGAGACAGTGGACACCGAGGGTACAGTGGTAGTCAGGCCAG
                AGACGTCAGTCTCTGTCACCTGTGGCTCCCATGTCACCATCAGTCCGGTC
                 S  A  V  R  D  S  G  H  R  G  Y  S  G  S  Q  A  S

                   9
                    9060       9070       9080       9090       9100
                TGACAATGAGGGACATTCAGAAGACTCAGACACACAGTCAGTGTCAGCCC
                ACTGTTACTCCCTGTAAGTCTTCTGAGTCTGTGTGTCAGTCACAGTCGGG
                  D  N  E  G  H  S  E  D  S  D  T  Q  S  V  S  A

                            9
                    9110       9120       9130       9140       9150
                ACGGACAGGCTGGGTCCCATCAGCAGAGCCACCAAGAGTCCGCACGTGGC
                TGCCTGTCCGACCCAGGGTAGTCGTCTCGGTGGTTCTCAGGCGTGCACCG
                H  G  Q  A  G  S  H  Q  Q  S  H  Q  E  S  A  R  G

                         7          7          7
                    9160       9170       9180       9190       9200
                CGGTCAGGGGAAACGTCTGGACATTCAGGATCTTTCCTCTACCAGGTGAG
                GCCAGTCCCCTTTGCAGACCTGTAAGTCCTAGAAAGGAGATGGTCCACTC
                 R  S  G  E  T  S  G  H  S  G  S  F  L  Y  Q  V  S

                                                    8          8
                    9210       9220       9230       9240       9250
End RPT8        CACTCATGAACAGTCTGAGTCCTCCCATGGATGGACGGGGCCCAGCACTA
                GTGAGTACTTGTCAGACTCAGGAGGGTACCTACCTGCCCCGGGTCGTGAT
                  T  H  E  Q  S  E  S  S  H  G  W  T  G  P  S  T

                                                 8
                    9260       9270       9280       9290       9300
RPT9            GAGGAAGACAAGGATCCCGCCATGAGCAGGCACAAGACAGCTCCAGGCAC
                CTCCTTCTGTTCCTAGGGCGGTACTCGTCCGTGTTCTGTCGAGGTCCGTG
                R  G  R  Q  G  S  R  H  E  Q  A  Q  D  S  S  R  H

                    9310       9320       9330       9340       9350
                TCAGCATCCCAA[ ]ACGGTCAGGACACCATTCGTGGACACCCGGGGTCAAG
                AGTCGTAGGGTT[ ]TGCCAGTCCTGTGGTAAGCACCTGTGGGCCCCAGTTC
                 S  A  S  Q  Y  G  Q  D  T  I  R  G  H  P  G  S  S

                                  8          8          8
                    9360       9370       9380       9390       9400
                CAGAGGAGGAAGGCAGGGGTACCACCACGAGCATTCGGTAGATAGCTCTG
                GTCTCCTCCTTCCGTCCCCATGGTGGTGCTCGTAAGCCATCTATCGAGAC
                  R  G  G  R  Q  G  Y  H  H  E  H  S  V  D  S  S

                    9410       9420       9430       9440       9450
                GACACTCAGGGTCCCATCACAGCCACACCACATCCCAGGGAAGGTCTGAT
                CTGTGAGTCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTCCAGACTA
                G  H  S  G  S  H  H  S  H  T  T  S  Q  G  R  S  D

                    9460       9470       9480       9490       9500
                GCCTCCCGTGGGCAGTCAGGATCCAGAAGTGCAAGCAGAACAACACGTAA
                CGGAGGGCACCCGTCAGTCCTAGGTCTTCACGTTCGTCTTGTTGTGCATT
```

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  A  S  R  G  Q  S  G  S  R  S  A  S  R  T  T  R  N

      9510       9520       9530       9540       9550
TGAGGAACAATCAGGAGACAGCTCCAGGCACTCAGTGTCACGTCACCATG
ACTCCTTGTTAGTCCTCTGTCGAGGTCCGTGAGTCACAGTGCAGTGGTAC
  E  E  Q  S  G  D  S  S  R  H  S  V  S  R  H  H

                                              8  8
      9560       9570       9580       9590       9600
AAGCTTCCACTCATGCCGACATCTCTAGACACTCACAGGCAGTCCAGGGA
TTCGAAGGTGAGTACGGCTGTAGAGATCTGTGAGTGTCCGTCAGGTCCCT
E  A  S  T  H  A  D  I  S  R  H  S  Q  A  V  Q  G

                                                 8
      9610       9620       9630       9640       9650
CAATCAGAGGGGTCCAGGAGAAGCAGGCGCCAGGGATCCAGTGTGAGCCA
GTTAGTCTCCCCAGGTCCTCTTCGTCCGCGGTCCCTAGGTCACACTCGGT
 Q  S  E  G  S  R  R  S  R  R  Q  G  S  S  V  S  Q

      9660       9670       9680       9690       9700
GGACAGTGACAGTGAGGGACATTCAGAAGACTCTGAGAGGTGGTCTGGGT
CCTGTCACTGTCACTCCCTGTAAGTCTTCTGAGACTCTCCACCAGACCCA
  D  S  D  S  E  G  H  S  E  D  S  E  R  W  S  G

      9710       9720       9730       9740       9750
CTGCTTCCAGAAACCATCGTGGATCTGTTCAGGAGCAGTCAAGGCACGGC
GACGAAGGTCTTTGGTAGCACCTAGACAAGTCCTCGTCAGTTCCGTGCCG
S  A  S  R  N  H  R  G  S  V  Q  E  Q  S  R  H  G

      9760       9770       9780       9790       9800
TCCAGACACCCCAGGTCCCATCACGAAGACAGAGCCGGTCACGGGCACTC
AGGTCTGTGGGGTCCAGGGTAGTGCTTCTGTCTCGGCCAGTGCCCGTGAG
 S  R  H  P  R  S  H  H  E  D  R  A  G  H  G  H  S

      9810       9820       9830       9840       9850
TGCAGACTGCTCCAGACAATCAGGCACTCGTCACGCAGAGACTTCCTCTG
ACGTCTGACGAGGTCTGTTAGTCCGTGAGCAGTGCGTCTCTGAAGGAGAC
  A  D  R  S  R  Q  S  G  T  R  H  A  E  T  S  S

      9860       9870       9880       9890       9900
GTGGACAGGCTGCATCATCCCATGAACAGGCAAGATCAAGTCCAGGAGAG
CACCTGTCCGACGTAGTAGGGTACTTGTCCGTTCTAGTTCAGGTCCTCTC
G  G  Q  A  A  S  S  H  E  Q  A  R  S  S  P  G  E

      9910       9920       9930       9940       9950
AGACACGGATCCCGCCACCAGCAGTCAGCAGACAGCTCCAGACACTCAGG
TCTGTGCCTAGGGCGGTGGTCGTCAGTCGTCTGTCGAGGTCTGTGAGTCC
 R  H  G  S  R  H  Q  Q  S  A  D  S  S  R  H  S  G

    22   5                                         2
      9960       9970       9980       9990      10000
CATTCCGCGTGGACAAGCTTCATCTGCAGTCAGAGACAGTTGACACTGGG
GTAAGGCGCACCTGTTCGAAGTAGACGTCAGTCTCTGTCAACTGTGACCC
```

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                I  P  R  G  Q  A  S  S  A  V  R  D  S  R  H  W

                                        2
          10010      10020      10030      10040      10050
GGTCCAGTGGTAGTCAGGCCAGTGATAGTGAGGGACATTCAGAAGAGTCA
CCAGGTCACCATCAGTCCGGTCACTATCACTCCCTGTAAGTCTTCTCAGT
G  S  S  G  S  Q  A  S  D  S  E  G  H  S  E  E  S

          10060      10070      10080      10090      10100
GACACACAGTCAGTGTCAGGCCATGGACAGGCTGGGCCCCATCAGCAGAG
CTGTGTGTCAGTCACAGTCCGGTACCTGTCCGACCCGGGGTAGTCGTCTC
 D  T  Q  S  V  S  G  H  G  Q  A  G  P  H  Q  Q  S

          10110      10120      10130      10140      10150
CCACCAAGAGTCCGCACGTGACCGGTCAGGGGGAAGGTCTGGACGTTCAG
GGTGGTTCTCAGGCGTGCACTGGCCAGTCCCCCTTCCAGACCTGCAAGTC
  H  Q  E  S  A  R  D  R  S  G  G  R  S  G  R  S

          10160      10170      10180      10190      10200
End RPT9  GGTCTTTCCTCTACCAGGTGAGCACTCATGAACAGTCTGAGTCTGCCCAT
CCAGAAAGGAGATGGTCCACTCGTGAGTACTTGTCAGACTCAGACGGGTA
G  S  F  L  Y  Q  V  S  T  H  E  Q  S  E  S  A  H

          3    3          3
          10210      10220      10230      10240      10250
RPT10     GGGCGGACCAGGACCAGCACTGGACGAAGACAAGGATCCCACCACGAGCA
CCCGCCTGGTCCTGGTCGTGACCTGCTTCTGTTCCTAGGGTGGTGCTCGT
 G  R  T  R  T  S  T  G  R  R  Q  G  S  H  H  E  Q

          10260      10270      10280      10290      10300
GGCACGAGACAGCTCCAGGCACTCAGCGTCCCAAGAGGGTCAGGACACCA
CCGTGCTCTGTCGAGGTCCGTGAGTCGCAGGGTTCTCCCAGTCCTGTGGT
  A  R  D  S  S  R  H  S  A  S  Q  E  G  Q  D  T

                                        2
          10310      10320      10330      10340      10350
TTCGTGGACACCCGGGGTCAAGCAGAAGAGGAAGGCAGGGATCCCACTAC
AAGCACCTGTGGGCCCCAGTTCGTCTTCTCCTTCCGTCCCTAGGGTGATG
I  R  G  H  P  G  S  S  R  R  G  R  Q  G  S  H  Y

          10360      10370      10380      10390      10400
GAGCAATCGGTAGATAGGTCTGGACACTCAGGGTCCCATCACAGCCACAC
CTCGTTAGCCATCTATCCAGACCTGTGAGTCCCAGGGTAGTGTCGGTGTG
 E  Q  S  V  D  R  S  G  H  S  G  S  H  H  S  H  T

          10410      10420      10430      10440      10450
CACATCCCAGGGAAGGTCTGATGCCTCCCGTGGGCAGTCAGGATCCAGAA
GTGTAGGGTCCCTTCCAGACTACGGAGGGCACCCGTCAGTCCTAGGTCTT
  T  S  Q  G  R  S  D  A  S  R  G  Q  S  G  S  R

          5                  3                  6
          10460      10470      10480      10490      10500
GTGCCAGCAGACAAACTCGTAATGACGAACAATCAGGAGATGGCTCCAGG
CACGGTCGTCTGTTTGAGCATTACTGCTTGTTAGTCCTCTACCGAGGTCC
```

```
S  A  S  R  Q  T  R  N  D  E  Q  S  G  D  G  S  R

                6                          (0)
     10510      10520      10530      10540      10550
CACTCATGGTCGCATCACCATGAAGCTTCCACTCAGGCGGACAGCTCTAG
GTGAGTACCAGCGTAGTGGTACTTCGAAGGTGAGTCCGCCTGTCGAGATC
 H  S  W  S  H  H  H  E  A  S  T  Q  A  D  S  S  R

           11
     10560      10570      10580      10590      10600
ACACTCACAGTCCGGCCAGGGACAATCAGCGGGGCCCAGGACAAGCAGGA
TGTGAGTGTCAGGCCGGTCCCTGTTAGTCGCCCCGGGTCCTGTTCGTCCT
  H  S  Q  S  G  Q  G  Q  S  A  G  P  R  T  S  R

     10610      10620      10630      10640      10650
ACCAGGGATCCAGTGTTAGCCAGGACAGTGACAGTCAGGGACACTCAGAA
TGGTCCCTAGGTCACAATCGGTCCTGTCACTGTCAGTCCCTGTGAGTCTT
N  Q  G  S  S  V  S  Q  D  S  D  S  Q  G  H  S  E

     10660      10670      10680      10690      10700
GACTCTGAGAGGTGGTCTGGGTCTGCTTCCAGAAACCATCGTGGATCTGC
CTGAGACTCTCCACCAGACCCAGACGAAGGTCTTTGGTAGCACCTAGACG
 D  S  E  R  W  S  G  S  A  S  R  N  H  R  G  S  A

     10710      10720      10730      10740      10750
TCAGGAGCAGTCAAGAGATGGCTCCAGACACCCCAGGTCCCATCACGAAG
AGTCCTCGTCAGTTCTCTACCGAGGTCTGTGGGGTCCAGGGTAGTGCTTC
  Q  E  Q  S  R  D  G  S  R  H  P  T  S  H  H  E

     10760      10770      10780      10790      10800
ACAGAGCCGGTCACGGGCACTCTGCAGAGAGCTCCAGACAATCAGGCACT
TGTCTCGGCCAGTGCCCGTGAGACGTCTCTCGAGGTCTGTTAGTCCGTGA
D  R  A  G  H  G  H  S  A  E  S  S  R  Q  S  G  T

     10810      10820      10830      10840      10850
CATCATGCAGAGAATTCCTCTGGTGGACAGGCTGCATCATCCCATGAACA
GTAGTACGTCTCTTAAGGAGACCACCTGTCCGACGTAGTAGGGTACTTGT
 H  H  A  E  N  S  S  G  G  Q  A  A  S  S  H  E  Q

     10860      10870      10880      10890      10900
GGCAAGATCAAGTGCAGGAGAGAGACATGGATCCCACCACCAGCAGTCAG
CCGTTCTAGTTCACGTCCTCTCTCTGTACCTAGGGTGGTGGTCGTCAGTC
  A  R  S  S  A  G  E  R  H  G  S  H  H  Q  Q  S

     10910      10920      10930      10940      10950
CAGACAGCTCCAGACACTCAGGCATTGGGCACGGACAAGCTTCATCTGCA
GTCTGTCGAGGTCTGTGAGTCCGTAACCCGTGCCTGTTCGAAGTAGACGT
A  D  S  S  R  H  S  G  I  G  H  G  Q  A  S  S  A

     10960      10970      10980      10990      11000
GTCAGAGACAGTGGACACCGAGGGTCCAGTGGTAGTCAGGCCAGTGACAG
CAGTCTCTGTCACCTGTGGCTCCCAGGTCACCATCAGTCCGGTCACTGTC
```

```
                V  R  D  S  G  H  R  G  S  S  G  S  Q  A  S  D  S

                    11010      11020      11030      11040      11050
                TGAGGGACATTCAGAAGACTCAGACACACAGTCAGTGTCAGCCCACGGAC
                ACTCCCTGTAAGTCTTCTGAGTCTGTGTGTCAGTCACAGTCGGGTGCCTG
                  E  G  H  S  E  D  S  D  T  Q  S  V  S  A  H  G

                    11060      11070      11080      11090      11100
                AGGCTGGGCCCCATCAGCAGAGCCACCAAGAGTCCACACGTGGCCGGTCA
                TCCGACCCGGGGTAGTCGTCTCGGTGGTTCTCAGGTGTGCACCGGCCAGT
                Q  A  G  P  H  Q  Q  S  H  Q  E  S  T  R  G  R  S

                  6
                    11110      11120      11130      11140      11150
                GCAGGAAGGTCTGGACGTTCAGGGTCTTTCCTCTACCAGGTGAGCACTCA
                CGTCCTTCCAGACCTGCAAGTCCCAGAAAGGAGATGGTCCACTCGTGAGT
                 A  G  R  S  G  R  S  G  S  F  L  Y  Q  V  S  T  H

                    11160      11170      11180      11190      11200
End RPT10       TGAACAGTCTGAGTCTGCCCATGGACGGGCTGGGCCCAGTACTGGAGGAA
                ACTTGTCAGACTCAGACGGGTACCTGCCCGACCCGGGTCATGACCTCCTT
                  E  Q  S  E  S  A  H  G  R  A  G  P  S  T  G  G

                    11210      11220      11230      11240      11250
RPT11           GACAAGGATCCCGCCACGAGCAGGCACGAGACAGCTCCAGGCACTCAGCG
high            CTGTTCCTAGGGCGGTGCTCGTCCGTGCTCTGTCGAGGTCCGTGAGTCGC
homology        R  Q  G  S  R  H  E  Q  A  R  D  S  S  R  H  S  A

                    11260      11270      11280      11290      11300
                TCCCAAGAGGGTCAGGACACCATTCGTGGACACCCGGGGTCAAGGAGAGG
                AGGGTTCTCCCAGTCCTGTGGTAAGCACCTGTGGGCCCCAGTTCCTCTCC
                 S  Q  E  G  Q  D  T  I  R  G  H  P  G  S  R  R  G

                    11310      11320      11330      11340      11350
                AGGAAGACAGGGATCCTACCACGAGCAATCGGTAGATAGGTCTGGACACT
                TCCTTCTGTCCCTAGGATGGTGCTCGTTAGCCATCTATCCAGACCTGTGA
                  G  R  Q  G  S  Y  H  E  Q  S  V  D  R  S  G  H

                    11360      11370      11380      11390      11400
                CAGGGTCCCATCACAGCCACACCACATCCCAGGGAAGGTCTGATGCCTCC
                GTCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTCCAGACTACGGAGG
                S  G  S  H  H  S  H  T  T  S  Q  G  R  S  D  A  S

                    11410      11420      11430      11440      11450
                CATGGGCAGTCAGGATCCAGAAGTGCAAGCAGAGAAACACGTAATGAGGA
                GTACCCGTCAGTCCTAGGTCTTCACGTTCGTCTCTTTGTGCATTACTCCT
                 H  G  Q  S  G  S  R  S  A  S  R  E  T  R  N  E  E

                    11460      11470      11480      11490      11500
                ACAGTCAGGAGACGGCTCCAGGCACTCAGGGTCGCGTCACCATGAAGCTT
                TGTCAGTCCTCTGCCGAGGTCCGTGAGTCCCAGCGCAGTGGTACTTCGAA
```

```
                Q  S  G  D  G  S  R  H  S  G  S  R  H  H  E  A

          11510      11520      11530      11540      11550
CCACTCAGGCTGACAGCTCTAGACACTCACAGTCCGGCCAGGGTGAATCA
GGTGAGTCCGACTGTCGAGATCTGTGAGTGTCAGGCCGGTCCCACTTAGT
S  T  Q  A  D  S  S  R  H  S  Q  S  G  Q  G  E  S

          11560      11570      11580      11590      11600
GCGGGGTCCAGGAGAAGCAGGCGCCAGGGATCCAGTGTTAGCCAGGACAG
CGCCCCAGGTCCTCTTCGTCCGCGGTCCCTAGGTCACAATCGGTCCTGTC
 A  G  S  R  R  S  R  R  Q  G  S  S  V  S  Q  D  S

          11610      11620      11630      11640      11650
TGACAGTGAGGCATACCCAGAGGACTCTGAGAGGCGATCTGAGTCTGCTT
ACTGTCACTCCGTATGGGTCTCCTGAGACTCTCCGCTAGACTCAGACGAA
  D  S  E  A  Y  P  E  D  S  E  R  R  S  E  S  A

          11660      11670      11680      11690      11700
CCAGAAACCATCATGGATCTTCTCGGGAGCAGTCAAGAGATGGCTCCAGA
GGTCTTTGGTAGTACCTAGAAGAGCCCTCGTCAGTTCTCTACCGAGGTCT
S  R  N  H  H  G  S  S  R  E  Q  S  R  D  G  S  R

RPT11          11710      11720      11730      11740      11750
end       CACCCCGGATCCTCTCACCGCGATACAGCCAGTCATGTACAGTCTTCACC
high      GTGGGGCCTAGGAGAGTGGCGCTATGTCGGTCAGTACATGTCAGAAGTGG
homology   H  P  G  S  S  H  R  D  T  A  S  H  V  Q  S  S  P

          11760      11770      11780      11790      11800
TGTACAGTCAGACTCTAGTACCGCTAAGGAACATGGTCACTTTAGTAGTC
ACATGTCAGTCTGAGATCATGGCGATTCCTTGTACCAGTGAAATCATCAG
  V  Q  S  D  S  S  T  A  K  E  H  G  H  F  S  S

          11810      11820      11830      11840      11850
TTTCACAAGATTCTGCGTATCACTCAGGAATACAGTCACGTGGCAGTCCT
AAAGTGTTCTAAGACGCATAGTGAGTCCTTATGTCAGTGCACCGTCAGGA
L  S  Q  D  S  A  Y  H  S  G  I  Q  S  R  G  S  P

          11860      11870      11880      11890      11900
CACAGTTCTAGTTCTTATCATTATCAATCTGAGGGCACTGAAAGGCAAAA
GTGTCAAGATCAAGAATAGTAATAGTTAGACTCCCGTGACTTTCCGTTTT
 H  S  S  S  S  Y  H  Y  Q  S  E  G  T  E  R  Q  K

          11910      11920      11930      11940      11950
AGGTCAATCAGGTTTAGTTTGGAGACATGGCAGCTATGGTAGTGCAGATT
TCCAGTTAGTCCAAATCAAACCTCTGTACCGTCGATACCATCACGTCTAA
  G  Q  S  G  L  V  W  R  H  G  S  Y  G  S  A  D

          11960      11970      11980      11990      12000
ATGATTATGGTGAATCCGGGTTTAGACACTCTCAGCACGGAAGTGTTAGT
TACTAATACCACTTAGGCCCAAATCTGTGAGAGTCGTGCCTTCACAATCA
```

```
                Y  D  Y  G  E  S  G  F  R  H  S  Q  H  G  S  V  S


                    12010      12020      12030      12040      12050
                TACAATTCCAATCCTGTTGTTTTCAAGGAAAGATCTGATATCTGTAAAGC
                ATGTTAAGGTTAGGACAACAAAAGTTCCTTTCTAGACTATAGACATTTCG
                 Y  N  S  N  P  V  V  F  K  E  R  S  D  I  C  K  A

                    12060      12070      12080      12090      12100
                AAGTGCGTTTGGTAAAGATCATCCAAGGTATTATGCAACGTATATTAATA
                TTCACGCAAACCATTTCTAGTAGGTTCCATAATACGTTGCATATAATTAT
                  S  A  F  G  K  D  H  P  R  Y  Y  A  T  Y  I  N

End RPT11       12110      12120      12130      12140      12150
low             AGGACCCAGGTTTATGTGGCCATTCTAGTGATATATCGAAACAACTGGGA
homology        TCCTGGGTCCAAATACACCGGTAAGATCACTATATAGCTTTGTTGACCCT
                K  D  P  G  L  C  G  H  S  S  D  I  S  K  Q  L  G

                    12160      12170      12180
Tail            TTTAGTCAGTCACAGAGATACTATTACTATGAGTAA
                AAATCAGTCAGTGTCTCTATGATAATGATACTCATT
                 F  S  Q  S  Q  R  Y  Y  Y  Y  E  *
```

Figure 5.
Atopy transmitted as a dominant trait with reduced penetrance in an IV family.

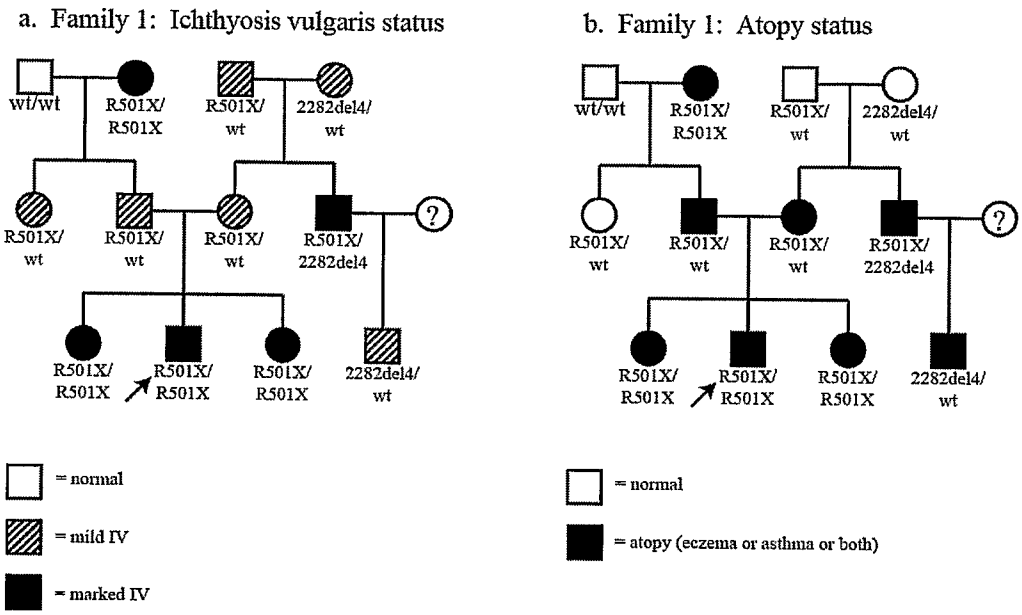

Figure 6. Filaggrin variants are associated with increased atopy

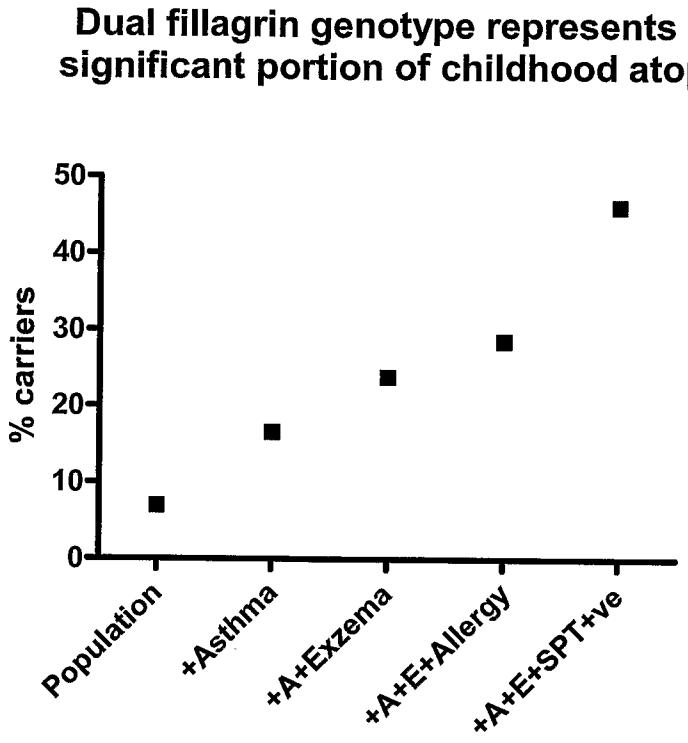

Figure 7
Increased number of positive allergens in carriers of filaggrin mutations.

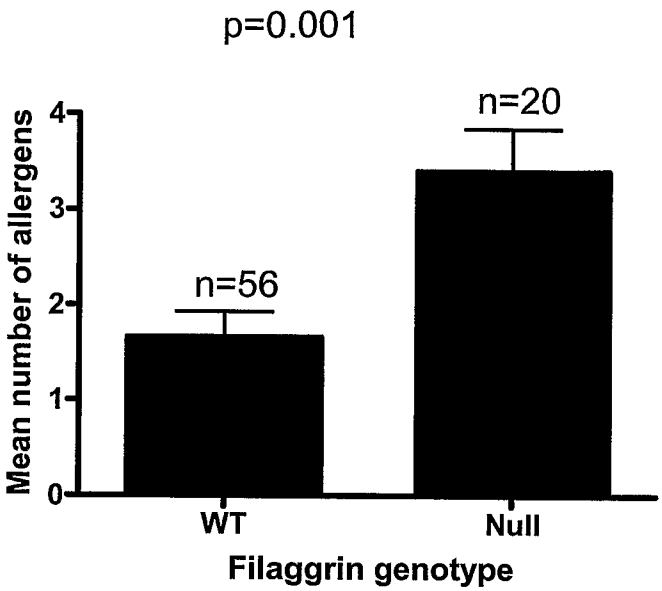

Figure 8

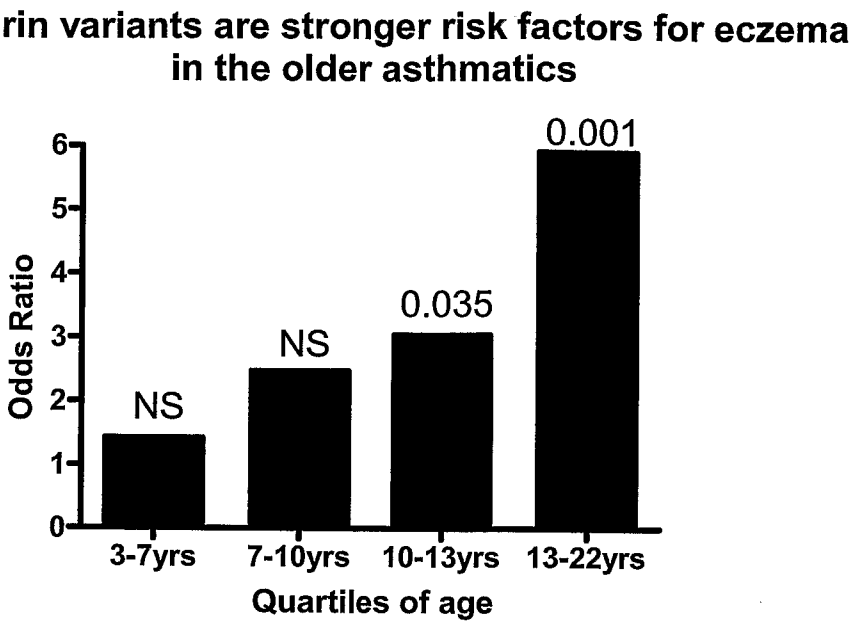
Filaggrin variants are stronger risk factors for eczema in the older asthmatics
Odds Ratio
0
1
2
3
4
5
6
NS
NS
0.035
0.001
3-7yrs
7-10yrs
10-13yrs
13-22yrs
Quartiles of age

Figure 9

Biochemical consequences of more 3' *FLG* mutations

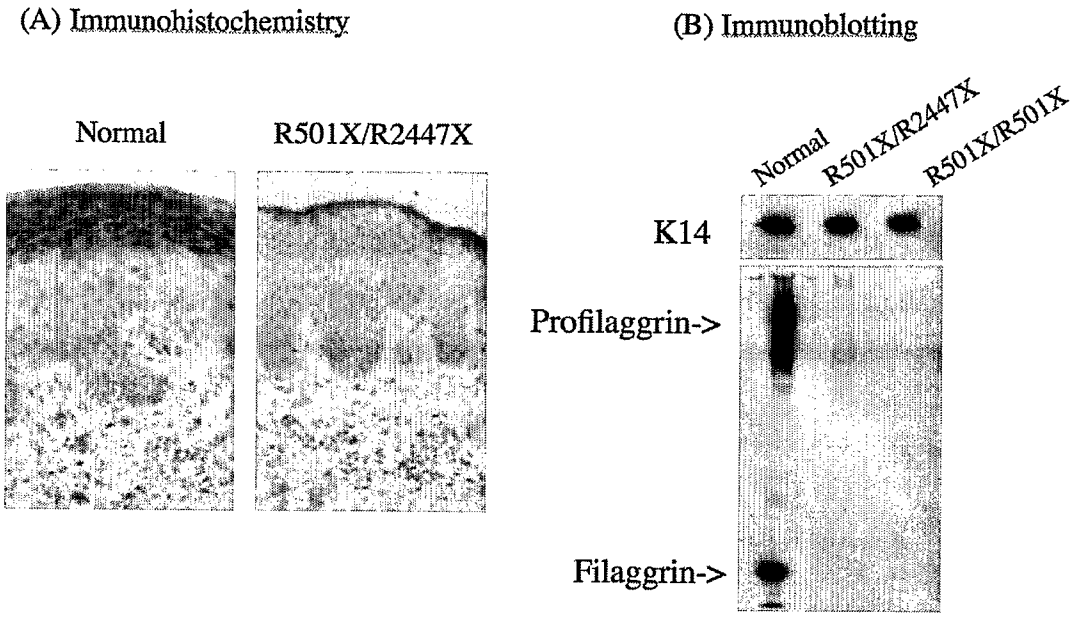

Figure 10

Schematic diagram of profilaggrin proteins encoded by size variant alleles of FLG.

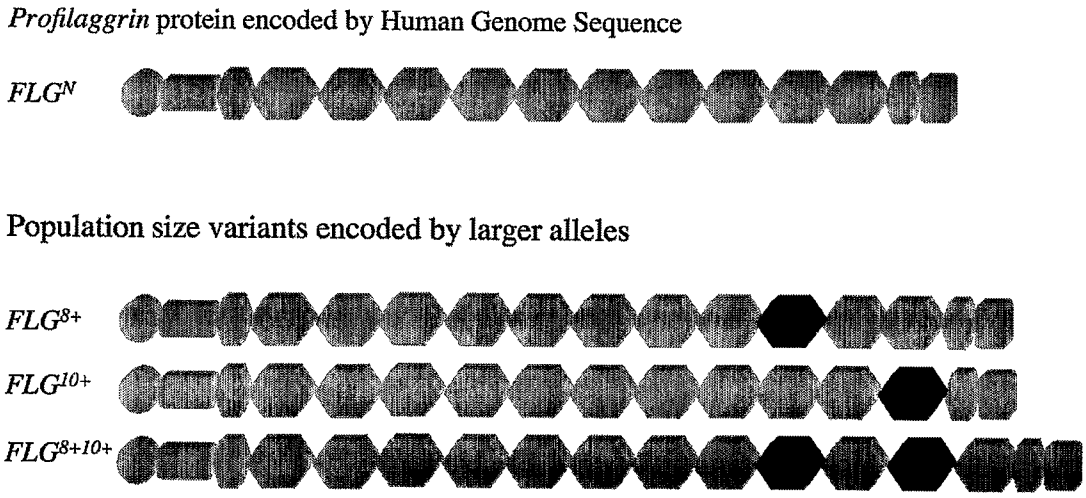

Figure 11
DNA sequence of *FLG* size variant allele FLG^{8+}

Both strands shown with amino acid translation.
Sequence Range: 1 to 5251

```
         10        20        30        40        50
AGGACAAGCAGGAACCGGGGATCCAGTTTTAGCCAGGACAGTGACAGTCA
TCCTGTTCGTCCTTGGCCCCTAGGTCAAAATCGGTCCTGTCACTGTCAGT
 R  T  S  R  N  R  G  S  S  F  S  Q  D  S  D  S  Q

         60        70        80        90       100
GGGACACTCAGAAGACTCTGAGAGGTGGTCTGGGTCTGCTTCCAGAAACC
CCCTGTGAGTCTTCTGAGACTCTCCACCAGACCCAGACGAAGGTCTTTGG
  G  H  S  E  D  S  E  R  W  S  G  S  A  S  R  N

        110       120       130       140       150
ATCATGGATCTGCTCAGGAGCAGCTAAGAGATGGCTCCAGACACCCCAGG
TAGTACCTAGACGAGTCCTCGTCGATTCTCTACCGAGGTCTGTGGGGTCC
H  H  G  S  A  Q  E  Q  L  R  D  G  S  R  H  P  R

        160       170       180       190       200
TCCCATCAAGAAGACAGAGCTGGTCATGGGCACTCTGCAGACAGCTCCAG
AGGGTAGTTCTTCTGTCTCGACCAGTACCCGTGAGACGTCTGTCGAGGTC
 S  H  Q  E  D  R  A  G  H  G  H  S  A  D  S  S  R

        210       220       230       240       250
ACAATCAGGCACTCGTCACACACAGACTTCCTCTGGTGGACAGGCTGCAT
TGTTAGTCCGTGAGCAGTGTGTGTCTGAAGGAGACCACCTGTCCGACGTA
  Q  S  G  T  R  H  T  Q  T  S  S  G  G  Q  A  A

        260       270       280       290       300
CATCCCATGAACAGGCAAGATCAAGTGCAGGAGAAAGACATGGATCCCAC
GTAGGGTACTTGTCCGTTCTAGTTCACGTCCTCTTTCTGTACCTAGGGTG
S  S  H  E  Q  A  R  S  S  A  G  E  R  H  G  S  H

        310       320       330       340       350
CACCAGCAGTCAGCAGACAGCTCCAGACACTCAGGCATTGGGCACGGACA
GTGGTCGTCAGTCGTCTGTCGAGGTCTGTGAGTCCGTAACCCGTGCCTGT
 H  Q  Q  S  A  D  S  S  R  H  S  G  I  G  H  G  Q

        360       370       380       390       400
AGCTTCATCTGCAGTCAGAGACAGTGGACACCGAGGGTACAGTGGTAGTC
TCGAAGTAGACGTCAGTCTCTGTCACCTGTGGCTCCCATGTCACCATCAG
  A  S  S  A  V  R  D  S  G  H  R  G  Y  S  G  S

        410       420       430       440       450
AGGCCAGTGACAATGAGGGACATTCAGAAGACTCAGACACACAGTCAGTG
TCCGGTCACTGTTACTCCCTGTAAGTCTTCTGAGTCTGTGTGTCAGTCAC
Q  A  S  D  N  E  G  H  S  E  D  S  D  T  Q  S  V

        460       470       480       490       500
TCAGCCCACGGACAGGCTGGGTCCCATCAGCAGAGCCACCAAGAGTCCGC
AGTCGGGTGCCTGTCCGACCCAGGGTAGTCGTCTCGGTGGTTCTCAGGCG
 S  A  H  G  Q  A  G  S  H  Q  Q  S  H  Q  E  S  A

        510       520       530       540       550
ACGTGGCCGGTCAGGGGAAACGTCTGGACATTCAGGGTCTTTCCTCTACC
TGCACCGGCCAGTCCCCTTTGCAGACCTGTAAGTCCCAGAAAGGAGATGG
  R  G  R  S  G  E  T  S  G  H  S  G  S  F  L  Y
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       560        570        580        590        600
AGGTGAGCACTCATGAACAGTCTGAGTCCTCCCATGGATGGACGGGGCCC
TCCACTCGTGAGTACTTGTCAGACTCAGGAGGGTACCTACCTGCCCCGGG
Q  V  S  T  H  E  Q  S  E  S  S  H  G  W  T  G  P

       610        620        630        640        650
AGCACTAGAGGAAGACAAGGATCCCGCCATGAGCAGGCACAAGACAGCTC
TCGTGATCTCCTTCTGTTCCTAGGGCGGTACTCGTCCGTGTTCTGTCGAG
 S  T  R  G  R  Q  G  S  R  H  E  Q  A  Q  D  S  S

       660        670        680        690        700
CAGGCACTCAGCATCCCAAGACGGTCAGGACACCATTCGTGGACACCCGG
GTCCGTGAGTCGTAGGGTTCTGCCAGTCCTGTGGTAAGCACCTGTGGGCC
  R  H  S  A  S  Q  D  G  Q  D  T  I  R  G  H  P

       710        720        730        740        750
GGTCAAGCAGAGGAGGAAGGCAGGGGTACCACCACGAGCATTCGGTAGAT
CCAGTTCGTCTCCTCCTTCCGTCCCCATGGTGGTGCTCGTAAGCCATCTA
G  S  S  R  G  G  R  Q  G  Y  H  H  E  H  S  V  D

       760        770        780        790        800
AGCTCTGGACACTCAGGGTCCCATCACAGCCACACCACATCCCAGGGAAG
TCGAGACCTGTGAGTCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTC
 S  S  G  H  S  G  S  H  H  S  H  T  T  S  Q  G  R

       810        820        830        840        850
GTCTGATGCCTCCCGTGGGCAGTCAGGATCCAGACGTGCAAGCAGAACAA
CAGACTACGGAGGGCACCCGTCAGTCCTAGGTCTGCACGTTCGTCTTGTT
  S  D  A  S  R  G  Q  S  G  S  R  R  A  S  R  T

       860        870        880        890        900
CACGTAATGAGGAACAATCAGGAGACGGCTCCAGGCACTCAGGGTCGCGT
GTGCATTACTCCTTGTTAGTCCTCTGCCGAGGTCCGTGAGTCCCAGCGCA
T  R  N  E  E  Q  S  G  D  G  S  R  H  S  G  S  R

       910        920        930        940        950
CACCATGAAGCTTCCACTCATGCCGACATCTCTAGACACTCACAGGCAGT
GTGGTACTTCGAAGGTGAGTACGGCTGTAGAGATCTGTGAGTGTCCGTCA
 H  H  E  A  S  T  H  A  D  I  S  R  H  S  Q  A  V

       960        970        980        990       1000
CCAGGGACAATCAGAGGGGTCCAGGAGAAGCAGGCGCCAGGGATCCAGTG
GGTCCCTGTTAGTCTCCCCAGGTCCTCTTCGTCCGCGGTCCCTAGGTCAC
  Q  G  Q  S  E  G  S  R  R  S  R  R  Q  G  S  S

      1010       1020       1030       1040       1050
TTAGCCAGGACAGTGACAGTGAGGGACATTCAGAAGACTCTGAGAGGTGG
AATCGGTCCTGTCACTGTCACTCCCTGTAAGTCTTCTGAGACTCTCCACC
V  S  Q  D  S  D  S  E  G  H  S  E  D  S  E  R  W

      1060       1070       1080       1090       1100
TCTGGGTCTGCTTCCAGAAACCATCATGGATCTGCTCAGGAGCAGCTAAG
AGACCCAGACGAAGGTCTTTGGTAGTACCTAGACGAGTCCTCGTCGATTC
 S  G  S  A  S  R  N  H  H  G  S  A  Q  E  Q  L  R

      1110       1120       1130       1140       1150
AGATGGCTCCAGACACCCCAGGTCCCATCAAGAAGGCAGAGCTGGTCATG
TCTACCGAGGTCTGTGGGGTCCAGGGTAGTTCTTCCGTCTCGACCAGTAC
  D  G  S  R  H  P  R  S  H  Q  E  G  R  A  G  H
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      1160       1170       1180       1190       1200
GGCACTCTGCAGACAGCTCCAGACAATCAGGCACTCGTCACACACAGACT
CCGTGAGACGTCTGTCGAGGTCTGTTAGTCCGTGAGCAGTGTGTGTCTGA
G  H  S  A  D  S  S  R  Q  S  G  T  R  H  T  Q  T

      1210       1220       1230       1240       1250
TCCTCTGGTGGACAGGCTGCATCATCYCATGAACAGGCAAGATCAAGTGC
AGGAGACCACCTGTCCGACGTAGTAGRGTACTTGTCCGTTCTAGTTCACG
 S  S  G  G  Q  A  A  S  S  H  E  Q  A  R  S  S  A

      1260       1270       1280       1290       1300
AGGAGAAAGACATGGATCCCACCACCAGCAGTCAGCAGACAGCTCCAGAC
TCCTCTTTCTGTACCTAGGGTGGTGGTCGTCAGTCGTCTGTCGAGGTCTG
  G  E  R  H  G  S  H  H  Q  Q  S  A  D  S  S  R

      1310       1320       1330       1340       1350
ACTCAGGCATTGGGCACGGACAAGCTTCATCTGCAGTCAGAGACAGTGGA
TGAGTCCGTAACCCGTGCCTGTTCGAAGTAGACGTCAGTCTCTGTCACCT
H  S  G  I  G  H  G  Q  A  S  S  A  V  R  D  S  G

      1360       1370       1380       1390       1400
CACCGAGGGTACAGTGGTAGTCAGGCCAGTGACAATGAGGGACATTCAGA
GTGGCTCCCATGTCACCATCAGTCCGGTCACTGTTACTCCCTGTAAGTCT
 H  R  G  Y  S  G  S  Q  A  S  D  N  E  G  H  S  E

      1410       1420       1430       1440       1450
AGACTCAGACACACAGTCAGTGTCAGCCCACGGACAGGCTGGGTCCCATC
TCTGAGTCTGTGTGTCAGTCACAGTCGGGTGCCTGTCCGACCCAGGGTAG
  D  S  D  T  Q  S  V  S  A  H  G  Q  A  G  S  H

      1460       1470       1480       1490       1500
AGCAGAGCCACCAAGAGTCCGCACGTGGCCGGTCAGGGGAAACGTCTGGA
TCGTCTCGGTGGTTCTCAGGCGTGCACCGGCCAGTCCCCTTTGCAGACCT
Q  Q  S  H  Q  E  S  A  R  G  R  S  G  E  T  S  G

      1510       1520       1530       1540       1550
CATTCAGGATCTTTCCTCTACCAGGTGAGCACTCATGAACAGTCTGAGTC
GTAAGTCCTAGAAAGGAGATGGTCCACTCGTGAGTACTTGTCAGACTCAG
 H  S  G  S  F  L  Y  Q  V  S  T  H  E  Q  S  E  S

      1560       1570       1580       1590       1600
CTCCCATGGATGGACGGGGCCCAGCACTAGAGGAAGACAAGGATCCCGCC
GAGGGTACCTACCTGCCCCGGGTCGTGATCTCCTTCTGTTCCTAGGGCGG
  S  H  G  W  T  G  P  S  T  R  G  R  Q  G  S  R

      1610       1620       1630       1640       1650
ATGAGCAGGCACAAGACAGCTCCAGGCACTCAGCATCCCAAGATGGTCAG
TACTCGTCCGTGTTCTGTCGAGGTCCGTGAGTCGTAGGGTTCTACCAGTC
H  E  Q  A  Q  D  S  S  R  H  S  A  S  Q  D  G  Q

      1660       1670       1680       1690       1700
GACACCATTCGTGGACACCCGGGGTCAAGCAGAGGAGGAAGGCAGGGGTA
CTGTGGTAAGCACCTGTGGGCCCCAGTTCGTCTCCTCCTTCCGTCCCCAT
 D  T  I  R  G  H  P  G  S  S  R  G  G  R  Q  G  Y

      1710       1720       1730       1740       1750
CCACCACGAGCATTCGGTAGATAGCTCTGGACACTCAGGGTCCCATCACA
GGTGGTGCTCGTAAGCCATCTATCGAGACCTGTGAGTCCCAGGGTAGTGT
  H  H  E  H  S  V  D  S  S  G  H  S  G  S  H  H
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      1760       1770       1780       1790       1800
GCCACACCACATCCCAGGGAAGGTCTGATGCCTCCCGTGGGCAGTCAGGA
CGGTGTGGTGTAGGGTCCCTTCCAGACTACGGAGGGCACCCGTCAGTCCT
S  H  T  T  S  Q  G  R  S  D  A  S  R  G  Q  S  G

      1810       1820       1830       1840       1850
TCCAGAAGTGCAAGCAGAACAACACGTAATGAGGAACAATCAGGAGACGG
AGGTCTTCACGTTCGTCTTGTTGTGCATTACTCCTTGTTAGTCCTCTGCC
 S  R  S  A  S  R  T  T  R  N  E  E  Q  S  G  D  G

      1860       1870       1880       1890       1900
CTCCAGGCACTCAGGGTCGCGTCACCATGAAGCTTCCACTCATGCCGACA
GAGGTCCGTGAGTCCCAGCGCAGTGGTACTTCGAAGGTGAGTACGGCTGT
  S  R  H  S  G  S  R  H  H  E  A  S  T  H  A  D

      1910       1920       1930       1940       1950
TCTCTAGACACTCACAGGCAGTCCAGGGACAATCAGAGGGGTCCAGGAGA
AGAGATCTGTGAGTGTCCGTCAGGTCCCTGTTAGTCTCCCCAGGTCCTCT
I  S  R  H  S  Q  A  V  Q  G  Q  S  E  G  S  R  R

      1960       1970       1980       1990       2000
AGCAGGCGCCAGGGATCCAGTGTTAGCCAGGACAGTGACAGTGAGGGACA
TCGTCCGCGGTCCCTAGGTCACAATCGGTCCTGTCACTGTCACTCCCTGT
 S  R  R  Q  G  S  S  V  S  Q  D  S  D  S  E  G  H

      2010       2020       2030       2040       2050
TTCAGAAGACTCTGAGAGGTGGTCTGGGTCTGCTTCCAGAAACCATCATG
AAGTCTTCTGAGACTCTCCACCAGACCCAGACGAAGGTCTTTGGTAGTAC
  S  E  D  S  E  R  W  S  G  S  A  S  R  N  H  H

      2060       2070       2080       2090       2100
GATCTGCTCAGGAGCAGCTAAGAGATGGCTCCAGACACCCCAGGTCCCAT
CTAGACGAGTCCTCGTCGATTCTCTACCGAGGTCTGTGGGGTCCAGGGTA
G  S  A  Q  E  Q  L  R  D  G  S  R  H  P  R  S  H

      2110       2120       2130       2140       2150
CAAGAAGACAGAGCTGGTCATGGGCACTCTGCAGACAGCTCCAGACAATC
GTTCTTCTGTCTCGACCAGTACCCGTGAGACGTCTGTCGAGGTCTGTTAG
 Q  E  D  R  A  G  H  G  H  S  A  D  S  S  R  Q  S

      2160       2170       2180       2190       2200
AGGCACTCGTCACACACAGGCTTCCTCTGGTGGACAGGCTGCATCATCCC
TCCGTGAGCAGTGTGTGTCCGAAGGAGACCACCTGTCCGACGTAGTAGGG
  G  T  R  H  T  Q  A  S  S  G  G  Q  A  A  S  S

      2210       2220       2230       2240       2250
ATGAACAGGCAAGATCAAGTGCAGGAGAAAGACATGGATCCCACCACCAG
TACTTGTCCGTTCTAGTTCACGTCCTCTTTCTGTACCTAGGGTGGTGGTC
H  E  Q  A  R  S  S  A  G  E  R  H  G  S  H  H  Q

      2260       2270       2280       2290       2300
CAGTCAGCAGACAGCTCCAGACACTCAGGCATTGGGCACGGACAAGCTTC
GTCAGTCGTCTGTCGAGGTCTGTGAGTCCGTAACCCGTGCCTGTTCGAAG
 Q  S  A  D  S  S  R  H  S  G  I  G  H  G  Q  A  S

      2310       2320       2330       2340       2350
ATCTGCAGTCAGAGACAGTGGACACCGAGGGTACAGTGGTAGTCAGGCCA
TAGACGTCAGTCTCTGTCACCTGTGGCTCCCATGTCACCATCAGTCCGGT
  S  A  V  R  D  S  G  H  R  G  Y  S  G  S  Q  A
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      2360       2370       2380       2390       2400
GTGACAATGAGGGACATTCAGAAGACTCAGACACACAGTCAGTGTCAGCC
CACTGTTACTCCCTGTAAGTCTTCTGAGTCTGTGTGTCAGTCACAGTCGG
S  D  N  E  G  H  S  E  D  S  D  T  Q  S  V  S  A

      2410       2420       2430       2440       2450
CACGGACAGGCTGGGTCCCATCAGCAGAGCCACCAAGAGTCCGCACGTGG
GTGCCTGTCCGACCCAGGGTAGTCGTCTCGGTGGTTCTCAGGCGTGCACC
 H  G  Q  A  G  S  H  Q  Q  S  H  Q  E  S  A  R  G

      2460       2470       2480       2490       2500
CCGGTCAGGGGAAACGTCTGGACATTCAGGATCTTTCCTCTACCAGGTGA
GGCCAGTCCCCTTTGCAGACCTGTAAGTCCTAGAAAGGAGATGGTCCACT
  R  S  G  E  T  S  G  H  S  G  S  F  L  Y  Q  V

      2510       2520       2530       2540       2550
GCACTCATGAACAGTCTGAGTCCTCCCATGGATGGACGGGGCCCAGCACT
CGTGAGTACTTGTCAGACTCAGGAGGGTACCTACCTGCCCCGGGTCGTGA
S  T  H  E  Q  S  E  S  S  H  G  W  T  G  P  S  T

      2560       2570       2580       2590       2600
AGAGGAAGACAAGGATCCCGCCATGAGCAGGCACAAGACAGCTCCAGGCA
TCTCCTTCTGTTCCTAGGGCGGTACTCGTCCGTGTTCTGTCGAGGTCCGT
 R  G  R  Q  G  S  R  H  E  Q  A  Q  D  S  S  R  H

      2610       2620       2630       2640       2650
CTCAGCATCCCAAGACGGTCAGGACACCATTCGTGGACACCCGGGGTCAA
GAGTCGTAGGGTTCTGCCAGTCCTGTGGTAAGCACCTGTGGGCCCCAGTT
  S  A  S  Q  D  G  Q  D  T  I  R  G  H  P  G  S

      2660       2670       2680       2690       2700
GCAGAGGAGGAAGGCAGGGGTACCACCACGAGCATTCGGTAGATAGCTCT
CGTCTCCTCCTTCCGTCCCCATGGTGGTGCTCGTAAGCCATCTATCGAGA
S  R  G  G  R  Q  G  Y  H  H  E  H  S  V  D  S  S

      2710       2720       2730       2740       2750
GGACACTCAGGGTCCCATCACAGCCACACCACATCCCAGGGAAGGTCTGA
CCTGTGAGTCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTCCAGACT
 G  H  S  G  S  H  H  S  H  T  T  S  Q  G  R  S  D

      2760       2770       2780       2790       2800
TGCCTCCCGTGGGCAGTCAGGATCCAGAAGTGCAAGCAGAACAACACGTA
ACGGAGGGCACCCGTCAGTCCTAGGTCTTCACGTTCGTCTTGTTGTGCAT
  A  S  R  G  Q  S  G  S  R  S  A  S  R  T  T  R

      2810       2820       2830       2840       2850
ATGAGGAACAATCAGGAGACAGCTCCAGGCACTCAGGGTCGCGTCACCAT
TACTCCTTGTTAGTCCTCTGTCGAGGTCCGTGAGTCCCAGCGCAGTGGTA
N  E  E  Q  S  G  D  S  S  R  H  S  G  S  R  H  H

      2860       2870       2880       2890       2900
GAAGCTTCCACTCATGCCGACATCTCTAGACACTCACAGGCAGTCCAGGG
CTTCGAAGGTGAGTACGGCTGTAGAGATCTGTGAGTGTCCGTCAGGTCCC
 E  A  S  T  H  A  D  I  S  R  H  S  Q  A  V  Q  G

      2910       2920       2930       2940       2950
ACAATCAGAGGGGTCCAGGAGAAGCAGGCGCCAGGGATCCAGTGTTAGCC
TGTTAGTCTCCCCAGGTCCTCTTCGTCCGCGGTCCCTAGGTCACAATCGG
  Q  S  E  G  S  R  R  S  R  R  Q  G  S  S  V  S
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      2960       2970       2980       2990       3000
AGGACAGTGACAGTGAGGGACATTCAGAAGACTCTGAGAGGTGGTCTGGG
TCCTGTCACTGTCACTCCCTGTAAGTCTTCTGAGACTCTCCACCAGACCC
Q  D  S  D  S  E  G  H  S  E  D  S  E  R  W  S  G

      3010       3020       3030       3040       3050
TCTGCTTCCAGAAACCATCGTGGATCTGTTCAGGAGCAGTCAAGGCACGG
AGACGAAGGTCTTTGGTAGCACCTAGACAAGTCCTCGTCAGTTCCGTGCC
 S  A  S  R  N  H  R  G  S  V  Q  E  Q  S  R  H  G

      3060       3070       3080       3090       3100
CTCCAGACACCCCAGGTCCCATCACGAAGACAGAGCCGGTCACGGGCACT
GAGGTCTGTGGGGTCCAGGGTAGTGCTTCTGTCTCGGCCAGTGCCCGTGA
  S  R  H  P  R  S  H  H  E  D  R  A  G  H  G  H

      3110       3120       3130       3140       3150
CTGCAGACCGCTCCAGACAATCAGGCACTCGTCACGCAGAGACTTCCTCT
GACGTCTGGCGAGGTCTGTTAGTCCGTGAGCAGTGCGTCTCTGAAGGAGA
S  A  D  R  S  R  Q  S  G  T  R  H  A  E  T  S  S

      3160       3170       3180       3190       3200
GGTGGACAGGCTGCATCATCCCATGAACAGGCAAGATCAAGTCCAGGAGA
CCACCTGTCCGACGTAGTAGGGTACTTGTCCGTTCTAGTTCAGGTCCTCT
 G  G  Q  A  A  S  S  H  E  Q  A  R  S  S  P  G  E

      3210       3220       3230       3240       3250
GAGACACGGATCCCGCCACCAGCAGTCAGCAGACAGCTCCAGACACTCAG
CTCTGTGCCTAGGGCGGTGGTCGTCAGTCGTCTGTCGAGGTCTGTGAGTC
  R  H  G  S  R  H  Q  Q  S  A  D  S  S  R  H  S

      3260       3270       3280       3290       3300
GCATTCCGCGTGGACAGGCTTCATCTGCAGTCAGAGACAGTAGACACTGG
CGTAAGGCGCACCTGTCCGAAGTAGACGTCAGTCTCTGTCATCTGTGACC
G  I  P  R  G  Q  A  S  S  A  V  R  D  S  R  H  W

      3310       3320       3330       3340       3350
GGGTCCAGTGGTAGTCAAGCCAGTGATAGTGAGGGACATTCAGAAGAGTC
CCCAGGTCACCATCAGTTCGGTCACTATCACTCCCTGTAAGTCTTCTCAG
 G  S  S  G  S  Q  A  S  D  S  E  G  H  S  E  E  S

      3360       3370       3380       3390       3400
AGACACACAGTCAGTGTCAGGCCATGGACAGGCTGGGCCCCATCAGCAGA
TCTGTGTGTCAGTCACAGTCCGGTACCTGTCCGACCCGGGGTAGTCGTCT
  D  T  Q  S  V  S  G  H  G  Q  A  G  P  H  Q  Q

      3410       3420       3430       3440       3450
GCCACCAAGAGTCCGCACGTGACCGGTCAGGGGGAAGGTCTGGACGTTCA
CGGTGGTTCTCAGGCGTGCACTGGCCAGTCCCCCTTCCAGACCTGCAAGT
S  H  Q  E  S  A  R  D  R  S  G  G  R  S  G  R  S

      3460       3470       3480       3490       3500
GGGTCTTTCCTCTACCAGGTGAGCACTCATGAACAGTCTGAGTCCGCCCA
CCCAGAAAGGAGATGGTCCACTCGTGAGTACTTGTCAGACTCAGGCGGGT
 G  S  F  L  Y  Q  V  S  T  H  E  Q  S  E  S  A  H

      3510       3520       3530       3540       3550
TGGGCGGACCAGGACCAGCACTGGACGAAGACAAGGATCCCACCACGAGC
ACCCGCCTGGTCCTGGTCGTGACCTGCTTCTGTTCCTAGGGTGGTGCTCG
  G  R  T  R  T  S  T  G  R  R  Q  G  S  H  H  E
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      3560       3570       3580       3590       3600
AGGCACGAGACAGCTCCAGGCACTCAGCGTCCCAAGAGGGTCAGGACACC
TCCGTGCTCTGTCGAGGTCCGTGAGTCGCAGGGTTCTCCCAGTCCTGTGG
Q  A  R  D  S  S  R  H  S  A  S  Q  E  G  Q  D  T

      3610       3620       3630       3640       3650
ATTCGTGCACACCCGGGGTCAAGCAGAAGAGGAAGGCAGGGATCCCACTA
TAAGCACGTGTGGGCCCCAGTTCGTCTTCTCCTTCCGTCCCTAGGGTGAT
 I  R  A  H  P  G  S  S  R  R  G  R  Q  G  S  H  Y

      3660       3670       3680       3690       3700
CGAGCAATCGGTAGATAGGTCTGGACACTCAGGGTCCCATCACAGCCACA
GCTCGTTAGCCATCTATCCAGACCTGTGAGTCCCAGGGTAGTGTCGGTGT
  E  Q  S  V  D  R  S  G  H  S  G  S  H  H  S  H

      3710       3720       3730       3740       3750
CCACATCCCAGGGAAGGTCTGATGCCTCCCGTGGGCAGTCAGGATCCAGA
GGTGTAGGGTCCCTTCCAGACTACGGAGGGCACCCGTCAGTCCTAGGTCT
T  T  S  Q  G  R  S  D  A  S  R  G  Q  S  G  S  R

      3760       3770       3780       3790       3800
AGTGCCAGCAGACAAACTCGTAACGACGAACAATCAGGAGACGGCTCCAG
TCACGGTCGTCTGTTTGAGCATTGCTGCTTGTTAGTCCTCTGCCGAGGTC
 S  A  S  R  Q  T  R  N  D  E  Q  S  G  D  G  S  R

      3810       3820       3830       3840       3850
GCACTCATGGTCGCATCACCATGAAGCTTCCACTCAGGCGGACAGCTCTA
CGTGAGTACCAGCGTAGTGGTACTTCGAAGGTGAGTCCGCCTGTCGAGAT
  H  S  W  S  H  H  H  E  A  S  T  Q  A  D  S  S

      3860       3870       3880       3890       3900
GACACTCACAGTCCGGCCAGGGACAATCAGCGGGGCCCAGTACAAGCAGG
CTGTGAGTGTCAGGCCGGTCCCTGTTAGTCGCCCCGGGTCATGTTCGTCC
R  H  S  Q  S  G  Q  G  Q  S  A  G  P  S  T  S  R

      3910       3920       3930       3940       3950
AACCAGGGATCCAGTGTTAGCCAGGACAGTGACAGTCAGGGACACTCAGA
TTGGTCCCTAGGTCACAATCGGTCCTGTCACTGTCAGTCCCTGTGAGTCT
 N  Q  G  S  S  V  S  Q  D  S  D  S  Q  G  H  S  E

      3960       3970       3980       3990       4000
AGACTCTGAGAGGTGGTCTGGGTCTGCTTCCAGAAACCATCATGGATCTG
TCTGAGACTCTCCACCAGACCCAGACGAAGGTCTTTGGTAGTACCTAGAC
  D  S  E  R  W  S  G  S  A  S  R  N  H  H  G  S

      4010       4020       4030       4040       4050
CTGGGGAGCAGTCAAGAGATGGCTCCAGACACCCTGGGTCCCATCAAGAA
GACCCCTCGTCAGTTCTCTACCGAGGTCTGTGGGACCCAGGGTAGTTCTT
A  G  E  Q  S  R  D  G  S  R  H  P  G  S  H  Q  E

      4060       4070       4080       4090       4100
GACAGAGCCGGTCACGGGCACTCTGCAGACAGCCCCAGACAATCAGGCAC
CTGTCTCGGCCAGTGCCCGTGAGACGTCTGTCGGGGTCTGTTAGTCCGTG
 D  R  A  G  H  G  H  S  A  D  S  P  R  Q  S  G  T

      4110       4120       4130       4140       4150
TCGTCACACAGAGTCTTCCTCTCGTGGACAGGCTGCGTCATCCCATGAAC
AGCAGTGTGTCTCAGAAGGAGAGCACCTGTCCGACGCAGTAGGGTACTTG
  R  H  T  E  S  S  S  R  G  Q  A  A  S  S  H  E
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      4160       4170       4180       4190       4200
AGGCAAGATCAAGTGCAGGAGAAAGACATGGATCCCACCACCAGCTCCAG
TCCGTTCTAGTTCACGTCCTCTTTCTGTACCTAGGGTGGTGGTCGAGGTC
Q  A  R  S  S  A  G  E  R  H  G  S  H  H  Q  L  Q

      4210       4220       4230       4240       4250
TCAGCAGACAGCTCCAGACACGCAGGCATTGGGCACGGACAAGCTTCATC
AGTCGTCTGTCGAGGTCTGTGCGTCCGTAACCCGTGCCTGTTCGAAGTAG
 S  A  D  S  S  R  H  A  G  I  G  H  G  Q  A  S  S

      4260       4270       4280       4290       4300
TGCAGTCAGAGACAGTGGACACCGAGGGTACAGTGGTAGTCAGGCCACTG
ACGTCAGTCTCTGTCACCTGTGGCTCCCATGTCACCATCAGTCCGGTGAC
  A  V  R  D  S  G  H  R  G  Y  S  G  S  Q  A  T

      4310       4320       4330       4340       4350
ACAGTGAGGGACATTCAGAAGACTCAGACACACAGTCAGTGTCAGCACAG
TGTCACTCCCTGTAAGTCTTCTGAGTCTGTGTGTCAGTCACAGTCGTGTC
D  S  E  G  H  S  E  D  S  D  T  Q  S  V  S  A  Q

      4360       4370       4380       4390       4400
GGAAAAGCTGGGCCCCATCAGCAGAGCCACAAAGAGTCCGCACGTGGCCA
CCTTTTCGACCCGGGGTAGTCGTCTCGGTGTTTCTCAGGCGTGCACCGGT
 G  K  A  G  P  H  Q  Q  S  H  K  E  S  A  R  G  Q

      4410       4420       4430       4440       4450
GTCAGGGGAAAGCTCTAGACGTTCAGGGTCTTTCCTCTACCAGGTGAGCA
CAGTCCCCTTTCGAGATCTGCAAGTCCCAGAAAGGAGATGGTCCACTCGT
  S  G  E  S  S  R  R  S  G  S  F  L  Y  Q  V  S

      4460       4470       4480       4490       4500
CTCATGAACAGTCTGAGTCTGCCCATGGACGGGCTGGGCCCAGTACTGGA
GAGTACTTGTCAGACTCAGACGGGTACCTGCCCGACCCGGGTCATGACCT
T  H  E  Q  S  E  S  A  H  G  R  A  G  P  S  T  G

      4510       4520       4530       4540       4550
GGAAGACAAGGATCCCACCACGAGCAGGCACGAGACAGCTCCAGGCACTC
CCTTCTGTTCCTAGGGTGGTGCTCGTCCGTGCTCTGTCGAGGTCCGTGAG
 G  R  Q  G  S  H  H  E  Q  A  R  D  S  S  R  H  S

      4560       4570       4580       4590       4600
AGCGTCCCAAGAGGGTCAGGACACCATTCGTGGACACCCGGGGTCAAGGA
TCGCAGGGTTCTCCCAGTCCTGTGGTAAGCACCTGTGGGCCCCAGTTCCT
  A  S  Q  E  G  Q  D  T  I  R  G  H  P  G  S  R

      4610       4620       4630       4640       4650
GAGGAGGAAGACAGGGATCCTACCACGAGCAATCGGTAGATAGGTCTGGA
CTCCTCCTTCTGTCCCTAGGATGGTGCTCGTTAGCCATCTATCCAGACCT
R  G  G  R  Q  G  S  Y  H  E  Q  S  V  D  R  S  G

      4660       4670       4680       4690       4700
CACTCAGGGTCCCATCACAGCCACACCACATCCCAGGGAAGGTCTGATGC
GTGAGTCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTCCAGACTACG
 H  S  G  S  H  H  S  H  T  T  S  Q  G  R  S  D  A

      4710       4720       4730       4740       4750
CTCCCATGGGCAGTCAGGATCCAGAAGTGCAAGCAGAGAAACACGTAATG
GAGGGTACCCGTCAGTCCTAGGTCTTCACGTTCGTCTCTTTGTGCATTAC
  S  H  G  Q  S  G  S  R  S  A  S  R  E  T  R  N
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      4760       4770       4780       4790       4800
AGGAACAGTCAGGAGACGGCTCCAGGCACTCAGGGTCGCGTCACCATGAA
TCCTTGTCAGTCCTCTGCCGAGGTCCGTGAGTCCCAGCGCAGTGGTACTT
E  E  Q  S  G  D  G  S  R  H  S  G  S  R  H  H  E

      4810       4820       4830       4840       4850
GCTTCCACTCAGGCTGACAGCTCTAGACACTCACAGTCCGGCCAGGGTGA
CGAAGGTGAGTCCGACTGTCGAGATCTGTGAGTGTCAGGCCGGTCCCACT
 A  S  T  Q  A  D  S  S  R  H  S  Q  S  G  Q  G  E

      4860       4870       4880       4890       4900
ATCAGCGGGGTCCAGGAGAAGCAGGCGCCAGGGATCCAGTGTTAGCCAGG
TAGTCGCCCCAGGTCCTCTTCGTCCGCGGTCCCTAGGTCACAATCGGTCC
  S  A  G  S  R  R  S  R  R  Q  G  S  S  V  S  Q

      4910       4920       4930       4940       4950
ACAGTGACAGTGAGGCATACCCAGAGGACTCTGAGAGGCGATCTGAGTCT
TGTCACTGTCACTCCGTATGGGTCTCCTGAGACTCTCCGCTAGACTCAGA
D  S  D  S  E  A  Y  P  E  D  S  E  R  R  S  E  S

      4960       4970       4980       4990       5000
GCTTCCAGAAACCATCATGGATCTTCTCGGGAGCAGTCAAGAGATGGCTC
CGAAGGTCTTTGGTAGTACCTAGAAGAGCCCTCGTCAGTTCTCTACCGAG
 A  S  R  N  H  H  G  S  S  R  E  Q  S  R  D  G  S

      5010       5020       5030       5040       5050
CAGACACCCCGGATCCTCTCACCGCGATACAGCCAGTCATGTACAGTCTT
GTCTGTGGGGCCTAGGAGAGTGGCGCTATGTCGGTCAGTACATGTCAGAA
  R  H  P  G  S  S  H  R  D  T  A  S  H  V  Q  S

      5060       5070       5080       5090       5100
CACCTGTACAGTCAGACTCTAGTACCGCTAAGGAACATGGTCACTTTAGT
GTGGACATGTCAGTCTGAGATCATGGCGATTCCTTGTACCAGTGAAATCA
S  P  V  Q  S  D  S  S  T  A  K  E  H  G  H  F  S

      5110       5120       5130       5140       5150
AGTCTTTCACAAGATTCTGCGTATCACTCAGGAATACAGTCACGTGGCAG
TCAGAAAGTGTTCTAAGACGCATAGTGAGTCCTTATGTCAGTGCACCGTC
 S  L  S  Q  D  S  A  Y  H  S  G  I  Q  S  R  G  S

      5160       5170       5180       5190       5200
TCCTCACAGTTCTAGTTCTTATCATTATCAATCTGAGGGCACTGAAAGGC
AGGAGTGTCAAGATCAAGAATAGTAATAGTTAGACTCCCGTGACTTTCCG
  P  H  S  S  S  S  Y  H  Y  Q  S  E  G  T  E  R

      5210       5220       5230       5240       5250
AAAAAGGTCAATCAGGTTTAGTTTGGAGACATGGCAGCTATGGTAGTGCA G
TTTTTCCAGTTAGTCCAAATCAAACCTCTGTACCGTCGATACCATCACGT C
Q  K  G  Q  S  G  L  V  W  R  H  G  S  Y  G  S  A
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Figure 12
DNA sequence of *FLG* size variant allele *FLG*$^{10+}$

Both strands shown with amino acid translation.
Sequence Range: 1 to 5251

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         10         20         30         40         50
AGGACAAGCAGGAACCGGGGATCCAGTTTTAGCCAGGACAGTGACAGTCA
TCCTGTTCGTCCTTGGCCCCTAGGTCAAAATCGGTCCTGTCACTGTCAGT
 R  T  S  R  N  R  G  S  S  F  S  Q  D  S  D  S  Q

         60         70         80         90        100
GGGACACTCAGAAGACTCTGAGAGGTGGTCTGGGTCTGCTTCCAGAAACC
CCCTGTGAGTCTTCTGAGACTCTCCACCAGACCCAGACGAAGGTCTTTGG
  G  H  S  E  D  S  E  R  W  S  G  S  A  S  R  N

        110        120        130        140        150
ATCATGGATCTGCTCAGGAGCAGCTAAGAGATGGCTCCAGACACCCCAGG
TAGTACCTAGACGAGTCCTCGTCGATTCTCTACCGAGGTCTGTGGGGTCC
H  H  G  S  A  Q  E  Q  L  R  D  G  S  R  H  P  R

        160        170        180        190        200
TCCCATCAAGAAGACAGAGCTGGTCATGGGCACTCTGCAGACAGCTCCAG
AGGGTAGTTCTTCTGTCTCGACCAGTACCCGTGAGACGTCTGTCGAGGTC
 S  H  Q  E  D  R  A  G  H  G  H  S  A  D  S  S  R

        210        220        230        240        250
ACAATCAGGCACTCGTCACACACAGACTTCCTCTGGTGGACAGGCTGCAT
TGTTAGTCCGTGAGCAGTGTGTGTCTGAAGGAGACCACCTGTCCGACGTA
  Q  S  G  T  R  H  T  Q  T  S  S  G  G  Q  A  A

        260        270        280        290        300
CATCCCATGAACAGGCAAGATCAAGTGCAGGAGAAAGACATGGATCCCAC
GTAGGGTACTTGTCCGTTCTAGTTCACGTCCTCTTTCTGTACCTAGGGTG
S  S  H  E  Q  A  R  S  S  A  G  E  R  H  G  S  H

        310        320        330        340        350
CACCAGCAGTCAGCAGACAGCTCCAGACACTCAGGCATTGGGCACGGACA
GTGGTCGTCAGTCGTCTGTCGAGGTCTGTGAGTCCGTAACCCGTGCCTGT
 H  Q  Q  S  A  D  S  S  R  H  S  G  I  G  H  G  Q

        360        370        380        390        400
AGCTTCATCTGCAGTCAGAGACAGTGGACACCGAGGGTACAGTGGTAGTC
TCGAAGTAGACGTCAGTCTCTGTCACCTGTGGCTCCCATGTCACCATCAG
  A  S  S  A  V  R  D  S  G  H  R  G  Y  S  G  S

        410        420        430        440        450
AGGCCAGTGACAATGAGGGACATTCAGAAGACTCAGACACACAGTCAGTG
TCCGGTCACTGTTACTCCCTGTAAGTCTTCTGAGTCTGTGTGTCAGTCAC
Q  A  S  D  N  E  G  H  S  E  D  S  D  T  Q  S  V

        460        470        480        490        500
TCAGCCCACGGACAGGCTGGGTCCCATCAGCAGAGCCACCAAGAGTCCGC
AGTCGGGTGCCTGTCCGACCCAGGGTAGTCGTCTCGGTGGTTCTCAGGCG
 S  A  H  G  Q  A  G  S  H  Q  Q  S  H  Q  E  S  A

        510        520        530        540        550
ACGTGGCCGGTCAGGGGAAACGTCTGGACATTCAGGGTCTTTCCTCTACC
TGCACCGGCCAGTCCCCTTTGCAGACCTGTAAGTCCCAGAAAGGAGATGG
  R  G  R  S  G  E  T  S  G  H  S  G  S  F  L  Y
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       560        570        580        590        600
AGGTGAGCACTCATGAACAGTCTGAGTCCTCCCATGGATGGACGGGGCCC
TCCACTCGTGAGTACTTGTCAGACTCAGGAGGGTACCTACCTGCCCCGGG
Q  V  S  T  H  E  Q  S  E  S  S  H  G  W  T  G  P

       610        620        630        640        650
AGCACTAGAGGAAGACAAGGATCCCGCCATGAGCAGGCACAAGACAGCTC
TCGTGATCTCCTTCTGTTCCTAGGGCGGTACTCGTCCGTGTTCTGTCGAG
 S  T  R  G  R  Q  G  S  R  H  E  Q  A  Q  D  S  S

       660        670        680        690        700
CAGGCACTCAGCATCCCAAGACGGTCAGGACACCATTCGTGGACACCCGG
GTCCGTGAGTCGTAGGGTTCTGCCAGTCCTGTGGTAAGCACCTGTGGGCC
  R  H  S  A  S  Q  D  G  Q  D  T  I  R  G  H  P

       710        720        730        740        750
GGTCAAGCAGAGGAGGAAGGCAGGGGTACCACCACGAGCATTCGGTAGAT
CCAGTTCGTCTCCTCCTTCCGTCCCCATGGTGGTGCTCGTAAGCCATCTA
G  S  S  R  G  G  R  Q  G  Y  H  H  E  H  S  V  D

       760        770        780        790        800
AGCTCTGGACACTCAGGGTCCCATCACAGCCACACCACATCCCAGGGAAG
TCGAGACCTGTGAGTCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTC
 S  S  G  H  S  G  S  H  H  S  H  T  T  S  Q  G  R

       810        820        830        840        850
GTCTGATGCCTCCCGTGGGCAGTCAGGATCCAGACGTGCAAGCAGAACAA
CAGACTACGGAGGGCACCCGTCAGTCCTAGGTCTGCACGTTCGTCTTGTT
  S  D  A  S  R  G  Q  S  G  S  R  R  A  S  R  T

       860        870        880        890        900
CACGTAATGAGGAACAATCAGGAGACGGCTCCAGGCACTCAGGGTCGCGT
GTGCATTACTCCTTGTTAGTCCTCTGCCGAGGTCCGTGAGTCCCAGCGCA
T  R  N  E  E  Q  S  G  D  G  S  R  H  S  G  S  R

       910        920        930        940        950
CACCATGAAGCTTCCACTCATGCCGACATCTCTAGACACTCACAGGCAGT
GTGGTACTTCGAAGGTGAGTACGGCTGTAGAGATCTGTGAGTGTCCGTCA
 H  H  E  A  S  T  H  A  D  I  S  R  H  S  Q  A  V

       960        970        980        990       1000
CCAGGGACAATCAGAGGGGTCCAGGAGAAGCAGGCGCCAGGGATCCAGTG
GGTCCCTGTTAGTCTCCCCAGGTCCTCTTCGTCCGCGGTCCCTAGGTCAC
  Q  G  Q  S  E  G  S  R  R  S  R  R  Q  G  S  S

      1010       1020       1030       1040       1050
TTAGCCAGGACAGTGACAGTGAGGGACATTCAGAAGACTCTGAGAGGTGG
AATCGGTCCTGTCACTGTCACTCCCTGTAAGTCTTCTGAGACTCTCCACC
V  S  Q  D  S  D  S  E  G  H  S  E  D  S  E  R  W

      1060       1070       1080       1090       1100
TCTGGGTCTGCTTCCAGAAACCATCATGGATCTGCTCAGGAGCAGCTAAG
AGACCCAGACGAAGGTCTTTGGTAGTACCTAGACGAGTCCTCGTCGATTC
 S  G  S  A  S  R  N  H  H  G  S  A  Q  E  Q  L  R

      1110       1120       1130       1140       1150
AGATGGCTCCAGACACCCCAGGTCCCATCAAGAAGGCAGAGCTGGTCATG
TCTACCGAGGTCTGTGGGGTCCAGGGTAGTTCTTCCGTCTCGACCAGTAC
  D  G  S  R  H  P  R  S  H  Q  E  G  R  A  G  H
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      1160       1170       1180       1190       1200
GGCACTCTGCAGACAGCTCCAGACAATCAGGCACTCGTCACACACAGACT
CCGTGAGACGTCTGTCGAGGTCTGTTAGTCCGTGAGCAGTGTGTGTCTGA
G  H  S  A  D  S  S  R  Q  S  G  T  R  H  T  Q  T

      1210       1220       1230       1240       1250
TCCTCTGGTGGACAGGCTGCATCATCYCATGAACAGGCAAGATCAAGTGC
AGGAGACCACCTGTCCGACGTAGTAGRGTACTTGTCCGTTCTAGTTCACG
 S  S  G  G  Q  A  A  S  S  H  E  Q  A  R  S  S  A

      1260       1270       1280       1290       1300
AGGAGAAAGACATGGATCCCACCACCAGCAGTCAGCAGACAGCTCCAGAC
TCCTCTTTCTGTACCTAGGGTGGTGGTCGTCAGTCGTCTGTCGAGGTCTG
  G  E  R  H  G  S  H  H  Q  Q  S  A  D  S  S  R

      1310       1320       1330       1340       1350
ACTCAGGCATTGGGCACGGACAAGCTTCATCTGCAGTCAGAGACAGTGGA
TGAGTCCGTAACCCGTGCCTGTTCGAAGTAGACGTCAGTCTCTGTCACCT
H  S  G  I  G  H  G  Q  A  S  S  A  V  R  D  S  G

      1360       1370       1380       1390       1400
CACCGAGGGTACAGTGGTAGTCAGGCCAGTGACAATGAGGGACATTCAGA
GTGGCTCCCATGTCACCATCAGTCCGGTCACTGTTACTCCCTGTAAGTCT
 H  R  G  Y  S  G  S  Q  A  S  D  N  E  G  H  S  E

      1410       1420       1430       1440       1450
AGACTCAGACACACAGTCAGTGTCAGCCCACGGACAGGCTGGGTCCCATC
TCTGAGTCTGTGTGTCAGTCACAGTCGGGTGCCTGTCCGACCCAGGGTAG
  D  S  D  T  Q  S  V  S  A  H  G  Q  A  G  S  H

      1460       1470       1480       1490       1500
AGCAGAGCCACCAAGAGTCCGCACGTGGCCGGTCAGGGGAAACGTCTGGA
TCGTCTCGGTGGTTCTCAGGCGTGCACCGGCCAGTCCCCTTTGCAGACCT
Q  Q  S  H  Q  E  S  A  R  G  R  S  G  E  T  S  G

      1510       1520       1530       1540       1550
CATTCAGGATCTTTCCTCTACCAGGTGAGCACTCATGAACAGTCTGAGTC
GTAAGTCCTAGAAAGGAGATGGTCCACTCGTGAGTACTTGTCAGACTCAG
 H  S  G  S  F  L  Y  Q  V  S  T  H  E  Q  S  E  S

      1560       1570       1580       1590       1600
CTCCCATGGATGGACGGGGCCCAGCACTAGAGGAAGACAAGGATCCCGCC
GAGGGTACCTACCTGCCCCGGGTCGTGATCTCCTTCTGTTCCTAGGGCGG
  S  H  G  W  T  G  P  S  T  R  G  R  Q  G  S  R

      1610       1620       1630       1640       1650
ATGAGCAGGCACAAGACAGCTCCAGGCACTCAGCATCCCAAGACGGTCAG
TACTCGTCCGTGTTCTGTCGAGGTCCGTGAGTCGTAGGGTTCTGCCAGTC
H  E  Q  A  Q  D  S  S  R  H  S  A  S  Q  D  G  Q

      1660       1670       1680       1690       1700
GACACCATTCGTGGACACCCGGGGTCAAGCAGAGGAGGAAGGCAGGGGTA
CTGTGGTAAGCACCTGTGGGCCCCAGTTCGTCTCCTCCTTCCGTCCCCAT
 D  T  I  R  G  H  P  G  S  S  R  G  G  R  Q  G  Y

      1710       1720       1730       1740       1750
CCACCACGAGCATTCGGTAGATAGCTCTGGACACTCAGGGTCCCATCACA
GGTGGTGCTCGTAAGCCATCTATCGAGACCTGTGAGTCCCAGGGTAGTGT
  H  H  E  H  S  V  D  S  S  G  H  S  G  S  H  H
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      1760       1770       1780       1790       1800
GCCACACCACATCCCAGGGAAGGTCTGATGCCTCCCGTGGGCAGTCAGGA
CGGTGTGGTGTAGGGTCCCTTCCAGACTACGGAGGGCACCCGTCAGTCCT
S  H  T  T  S  Q  G  R  S  D  A  S  R  G  Q  S  G

      1810       1820       1830       1840       1850
TCCAGAAGTGCAAGCAGAACAACACGTAATGAGGAACAATCAGGAGACAG
AGGTCTTCACGTTCGTCTTGTTGTGCATTACTCCTTGTTAGTCCTCTGTC
 S  R  S  A  S  R  T  T  R  N  E  E  Q  S  G  D  S

      1860       1870       1880       1890       1900
CTCCAGGCACTCAGGGTCGCGTCACCATGAAGCTTCCACTCATGCCGACA
GAGGTCCGTGAGTCCCAGCGCAGTGGTACTTCGAAGGTGAGTACGGCTGT
  S  R  H  S  G  S  R  H  H  E  A  S  T  H  A  D

      1910       1920       1930       1940       1950
TCTCTAGACACTCACAGGCAGTCCAGGGACAATCAGAGGGGTCCAGGAGA
AGAGATCTGTGAGTGTCCGTCAGGTCCCTGTTAGTCTCCCCAGGTCCTCT
I  S  R  H  S  Q  A  V  Q  G  Q  S  E  G  S  R  R

      1960       1970       1980       1990       2000
AGCAGGCGCCAGGGATCCAGTGTTAGCCAGGACAGTGACAGTGAGGGACA
TCGTCCGCGGTCCCTAGGTCACAATCGGTCCTGTCACTGTCACTCCCTGT
 S  R  R  Q  G  S  S  V  S  Q  D  S  D  S  E  G  H

      2010       2020       2030       2040       2050
TTCAGAAGACTCTGAGAGGTGGTCTGGGTCTGCTTCCAGAAACCATCGTG
AAGTCTTCTGAGACTCTCCACCAGACCCAGACGAAGGTCTTTGGTAGCAC
  S  E  D  S  E  R  W  S  G  S  A  S  R  N  H  R

      2060       2070       2080       2090       2100
GATCTGTTCAGGAGCAGTCAAGGCACGGCTCCAGACACCCCAGGTCCCAT
CTAGACAAGTCCTCGTCAGTTCCGTGCCGAGGTCTGTGGGGTCCAGGGTA
G  S  V  Q  E  Q  S  R  H  G  S  R  H  P  R  S  H

      2110       2120       2130       2140       2150
CACGAAGACAGAGCCGGTCACGGGCACTCTGCAGACCGCTCCAGACAATC
GTGCTTCTGTCTCGGCCAGTGCCCGTGAGACGTCTGGCGAGGTCTGTTAG
 H  E  D  R  A  G  H  G  H  S  A  D  R  S  R  Q  S

      2160       2170       2180       2190       2200
AGGCACTCGTCACGCAGAGACTTCCTCTGGTGGACAGGCTGCATCATCCC
TCCGTGAGCAGTGCGTCTCTGAAGGAGACCACCTGTCCGACGTAGTAGGG
  G  T  R  H  A  E  T  S  S  G  G  Q  A  A  S  S

      2210       2220       2230       2240       2250
ATGAACAGGCAAGATCAAGTCCAGGAGAGAGACACGGATCCCGCCACCAG
TACTTGTCCGTTCTAGTTCAGGTCCTCTCTCTGTGCCTAGGGCGGTGGTC
H  E  Q  A  R  S  S  P  G  E  R  H  G  S  R  H  Q

      2260       2270       2280       2290       2300
CAGTCAGCAGACAGCTCCAGACACTCAGGCATTCCGCGTGGACAGGCTTC
GTCAGTCGTCTGTCGAGGTCTGTGAGTCCGTAAGGCGCACCTGTCCGAAG
 Q  S  A  D  S  S  R  H  S  G  I  P  R  G  Q  A  S

      2310       2320       2330       2340       2350
ATCTGCAGTCAGAGACAGTAGACACTGGGGGTCCAGTGGTAGTCAAGCCA
TAGACGTCAGTCTCTGTCATCTGTGACCCCCAGGTCACCATCAGTTCGGT
  S  A  V  R  D  S  R  H  W  G  S  S  G  S  Q  A
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      2360       2370       2380       2390       2400
GTGATAGTGAGGGACATTCAGAAGAGTCAGACACACAGTCAGTGTCAGGC
CACTATCACTCCCTGTAAGTCTTCTCAGTCTGTGTGTCAGTCACAGTCCG
S  D  S  E  G  H  S  E  E  S  D  T  Q  S  V  S  G

      2410       2420       2430       2440       2450
CATGGACAGGCTGGGCCCCATCAGCAGAGCCACCAAGAGTCCGCACGTGA
GTACCTGTCCGACCCGGGGTAGTCGTCTCGGTGGTTCTCAGGCGTGCACT
 H  G  Q  A  G  P  H  Q  Q  S  H  Q  E  S  A  R  D

      2460       2470       2480       2490       2500
CCGGTCAGGGGGAAGGTCTGGACGTTCAGGGTCTTTCCTCTACCAGGTGA
GGCCAGTCCCCCTTCCAGACCTGCAAGTCCCAGAAAGGAGATGGTCCACT
  R  S  G  G  R  S  G  R  S  G  S  F  L  Y  Q  V

      2510       2520       2530       2540       2550
GCACTCATGAACAGTCTGAGTCCGCCCATGGGCGGACCAGGACCAGCACT
CGTGAGTACTTGTCAGACTCAGGCGGGTACCCGCCTGGTCCTGGTCGTGA
S  T  H  E  Q  S  E  S  A  H  G  R  T  R  T  S  T

      2560       2570       2580       2590       2600
GGACGAAGACAAGGATCCCACCACGAGCAGGCACGAGACAGCTCCAGGCA
CCTGCTTCTGTTCCTAGGGTGGTGCTCGTCCGTGCTCTGTCGAGGTCCGT
 G  R  R  Q  G  S  H  H  E  Q  A  R  D  S  S  R  H

      2610       2620       2630       2640       2650
CTCAGCGTCCCAAGAGGGTCAGGACACCATTCGTGCACACCCGGGGTCAA
GAGTCGCAGGGTTCTCCCAGTCCTGTGGTAAGCACGTGTGGGCCCCAGTT
  S  A  S  Q  E  G  Q  D  T  I  R  A  H  P  G  S

      2660       2670       2680       2690       2700
GCAGAAGAGGAAGGCAGGGATCCCACTACGAGCAATCGGTAGATAGGTCT
CGTCTTCTCCTTCCGTCCCTAGGGTGATGCTCGTTAGCCATCTATCCAGA
S  R  R  G  R  Q  G  S  H  Y  E  Q  S  V  D  R  S

      2710       2720       2730       2740       2750
GGACACTCAGGGTCCCATCACAGCCACACCACATCCCAGGGAAGGTCTGA
CCTGTGAGTCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTCCAGACT
 G  H  S  G  S  H  H  S  H  T  T  S  Q  G  R  S  D

      2760       2770       2780       2790       2800
TGCCTCCCGTGGGCAGTCAGGATCCAGAAGTGCCAGCAGACAAACTCGTA
ACGGAGGGCACCCGTCAGTCCTAGGTCTTCACGGTCGTCTGTTTGAGCAT
  A  S  R  G  Q  S  G  S  R  S  A  S  R  Q  T  R

      2810       2820       2830       2840       2850
ACGACGAACAATCAGGAGACGGCTCCAGGCACTCATGGTCGCATCACCAT
TGCTGCTTGTTAGTCCTCTGCCGAGGTCCGTGAGTACCAGCGTAGTGGTA
N  D  E  Q  S  G  D  G  S  R  H  S  W  S  H  H  H

      2860       2870       2880       2890       2900
GAAGCTTCCACTCAGGCGGACAGCTCTAGACACTCACAGTCCGGCCAGGG
CTTCGAAGGTGAGTCCGCCTGTCGAGATCTGTGAGTGTCAGGCCGGTCCC
 E  A  S  T  Q  A  D  S  S  R  H  S  Q  S  G  Q  G

      2910       2920       2930       2940       2950
ACAATCAGCGGGGCCCAGTACAAGCAGGAACCAGGGATCCAGTGTTAGCC
TGTTAGTCGCCCCGGGTCATGTTCGTCCTTGGTCCCTAGGTCACAATCGG
  Q  S  A  G  P  S  T  S  R  N  Q  G  S  S  V  S
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      2960       2970       2980       2990       3000
AGGACAGTGACAGTCAGGGACACTCAGAAGACTCTGAGAGGTGGTCTGGG
TCCTGTCACTGTCAGTCCCTGTGAGTCTTCTGAGACTCTCCACCAGACCC
Q  D  S  D  S  Q  G  H  S  E  D  S  E  R  W  S  G

      3010       3020       3030       3040       3050
TCTGCTTCCAGAAACCATCATGGATCTGCTGGGGAGCAGTCAAGAGATGG
AGACGAAGGTCTTTGGTAGTACCTAGACGACCCCTCGTCAGTTCTCTACC
 S  A  S  R  N  H  H  G  S  A  G  E  Q  S  R  D  G

      3060       3070       3080       3090       3100
CTCCAGACACCCTGGGTCCCATCAAGAAGACAGAGCCGGTCACGGGCACT
GAGGTCTGTGGGACCCAGGGTAGTTCTTCTGTCTCGGCCAGTGCCCGTGA
  S  R  H  P  G  S  H  Q  E  D  R  A  G  H  G  H

      3110       3120       3130       3140       3150
CTGCAGACAGCCCCAGACAATCAGGCACTCGTCACACAGAGTCTTCCTCT
GACGTCTGTCGGGGTCTGTTAGTCCGTGAGCAGTGTGTCTCAGAAGGAGA
S  A  D  S  P  R  Q  S  G  T  R  H  T  E  S  S  S

      3160       3170       3180       3190       3200
CGTGGACAGGCTGCGTCATCCCATGAACAGGCAAGATCAAGTGCAGGAGA
GCACCTGTCCGACGCAGTAGGGTACTTGTCCGTTCTAGTTCACGTCCTCT
 R  G  Q  A  A  S  S  H  E  Q  A  R  S  S  A  G  E

      3210       3220       3230       3240       3250
AAGACATGGATCCCACCACCAGCTCCAGTCAGCAGACAGCTCCAGACACG
TTCTGTACCTAGGGTGGTGGTCGAGGTCAGTCGTCTGTCGAGGTCTGTGC
  R  H  G  S  H  H  Q  L  Q  S  A  D  S  S  R  H

      3260       3270       3280       3290       3300
CAGGCATTGGGCACGGACAAGCTTCATCTGCAGTCAGAGACAGTGGACAC
GTCCGTAACCCGTGCCTGTTCGAAGTAGACGTCAGTCTCTGTCACCTGTG
A  G  I  G  H  G  Q  A  S  S  A  V  R  D  S  G  H

      3310       3320       3330       3340       3350
CGAGGGTACAGTGGTAGTCAGGCCACTGACAGTGAGGGACATTCAGAAGA
GCTCCCATGTCACCATCAGTCCGGTGACTGTCACTCCCTGTAAGTCTTCT
 R  G  Y  S  G  S  Q  A  T  D  S  E  G  H  S  E  D

      3360       3370       3380       3390       3400
CTCAGACACACAGTCAGTGTCAGCACAGGGAAAAGCTGGGCCCCATCAGC
GAGTCTGTGTGTCAGTCACAGTCGTGTCCCTTTTCGACCCGGGGTAGTCG
  S  D  T  Q  S  V  S  A  Q  G  K  A  G  P  H  Q

      3410       3420       3430       3440       3450
AGAGCCACAAAGAGTCCGCACGTGGCCAGTCAGGGGAAAGCTCTAGACGT
TCTCGGTGTTTCTCAGGCGTGCACCGGTCAGTCCCCTTTCGAGATCTGCA
Q  S  H  K  E  S  A  R  G  Q  S  G  E  S  S  R  R

      3460       3470       3480       3490       3500
TCAGGGTCTTTCCTCTACCAGGTGAGCACTCATGAACAGTCTGAGTCCAC
AGTCCCAGAAAGGAGATGGTCCACTCGTGAGTACTTGTCAGACTCAGGTG
 S  G  S  F  L  Y  Q  V  S  T  H  E  Q  S  E  S  T

      3510       3520       3530       3540       3550
CCATGGACAGTCTGTGCCCAGCACTGGAGGAAGACAAGGATCCCACCATG
GGTACCTGTCAGACACGGGTCGTGACCTCCTTCTGTTCCTAGGGTGGTAC
  H  G  Q  S  V  P  S  T  G  G  R  Q  G  S  H  H
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      3560       3570       3580       3590       3600
ATCAGGCACAAGACAGCTCCAGGCACTCAGCATCCCAAGAGGGTCAGGAC
TAGTCCGTGTTCTGTCGAGGTCCGTGAGTCGTAGGGTTCTCCCAGTCCTG
D  Q  A  Q  D  S  S  R  H  S  A  S  Q  E  G  Q  D

      3610       3620       3630       3640       3650
ACCATTCGTGGACACCCGGGGCCAAGCAGAGGAGGAAGACAGGGGTCCCA
TGGTAAGCACCTGTGGGCCCCGGTTCGTCTCCTCCTTCTGTCCCCAGGGT
 T  I  R  G  H  P  G  P  S  R  G  G  R  Q  G  S  H

      3660       3670       3680       3690       3700
CCACGAGCAATCGGTAGATAGGTCTGGACACTCAGGGTCCCATCACAGCC
GGTGCTCGTTAGCCATCTATCCAGACCTGTGAGTCCCAGGGTAGTGTCGG
  H  E  Q  S  V  D  R  S  G  H  S  G  S  H  H  S

      3710       3720       3730       3740       3750
ACACCACATCCCAGGGAAGGTCTGATGCCTCCCGTGGGCAGTCAGGACCC
TGTGGTGTAGGGTCCCTTCCAGACTACGGAGGGCACCCGTCAGTCCTGGG
H  T  T  S  Q  G  R  S  D  A  S  R  G  Q  S  G  P

      3760       3770       3780       3790       3800
AGAAGTGCAAGCAGACAAACACATGACAAGGAACAATCAGGAGACGGCTC
TCTTCACGTTCGTCTGTTTGTGTACTGTTCCTTGTTAGTCCTCTGCCGAG
 R  S  A  S  R  Q  T  H  D  K  E  Q  S  G  D  G  S

      3810       3820       3830       3840       3850
TAGGCACTCAGGGTCGCGTCATCATGAAGCTTCCTCTTGGGCCGACAGCT
ATCCGTGAGTCCCAGCGCAGTAGTACTTCGAAGGAGAACCCGGCTGTCGA
  R  H  S  G  S  R  H  H  E  A  S  S  W  A  D  S

      3860       3870       3880       3890       3900
CTAGACACTCACAGGCAGTCCAGGGACAATCAGAGGGGTCCAGGAGAAGC
GATCTGTGAGTGTCCGTCAGGTCCCTGTTAGTCTCCCCAGGTCCTCTTCG
S  R  H  S  Q  A  V  Q  G  Q  S  E  G  S  R  R  S

      3910       3920       3930       3940       3950
AGGCGCCAGGGATCCAGTGTTAGCCAGGACAGTGACAGTCAGGGACACTC
TCCGCGGTCCCTAGGTCACAATCGGTCCTGTCACTGTCAGTCCCTGTGAG
 R  R  Q  G  S  S  V  S  Q  D  S  D  S  Q  G  H  S

      3960       3970       3980       3990       4000
AGAAGACTCTGAGAGGCGGTCTGGGTCTGCTTCCAGAAACCATCGTGGAT
TCTTCTGAGACTCTCCGCCAGACCCAGACGAAGGTCTTTGGTAGCACCTA
  E  D  S  E  R  R  S  G  S  A  S  R  N  H  R  G

      4010       4020       4030       4040       4050
CTGCTCAGGAGCAGTCAAGAGATGGCTCCAGACACCCCAGGTCCCATCAC
GACGAGTCCTCGTCAGTTCTCTACCGAGGTCTGTGGGGTCCAGGGTAGTG
S  A  Q  E  Q  S  R  D  G  S  R  H  P  R  S  H  H

      4060       4070       4080       4090       4100
GAAGACAGAGCCGGTCATGGGCACTCTGCAGACAGCTCCAGACAATCAGG
CTTCTGTCTCGGCCAGTACCCGTGAGACGTCTGTCGAGGTCTGTTAGTCC
 E  D  R  A  G  H  G  H  S  A  D  S  S  R  Q  S  G

      4110       4120       4130       4140       4150
CACTCATCATGCAGAGAATTCCTCTGGTGGACAGCCTGCATCATCCCATG
GTGAGTAGTACGTCTCTTAAGGAGACCACCTGTCGGACGTAGTAGGGTAC
  T  H  H  A  E  N  S  S  G  G  Q  P  A  S  S  H
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      4160       4170       4180       4190       4200
AACAGGCAAGATCAAGTGCAGGAGAGAGACATGGATCCCACCACCAGCAG
TTGTCCGTTCTAGTTCACGTCCTCTCTCTGTACCTAGGGTGGTGGTCGTC
E  Q  A  R  S  S  A  G  E  R  H  G  S  H  H  Q  Q

      4210       4220       4230       4240       4250
TCAGCAGACAGCTCCAGACACTCAGGCATTGGGCACGGACAAGCTTCATC
AGTCGTCTGTCGAGGTCTGTGAGTCCGTAACCCGTGCCTGTTCGAAGTAG
 S  A  D  S  S  R  H  S  G  I  G  H  G  Q  A  S  S

      4260       4270       4280       4290       4300
TGCAGTCAGAGACAGTGGACACCGAGGGTCCAGTGGTAGTCAGGCCAGTG
ACGTCAGTCTCTGTCACCTGTGGCTCCCAGGTCACCATCAGTCCGGTCAC
  A  V  R  D  S  G  H  R  G  S  S  G  S  Q  A  S

      4310       4320       4330       4340       4350
ACAGTGAGGGACATTCAGAAGACTCAGACACACAGTCAGTGTCAGCCCAC
TGTCACTCCCTGTAAGTCTTCTGAGTCTGTGTGTCAGTCACAGTCGGGTG
D  S  E  G  H  S  E  D  S  D  T  Q  S  V  S  A  H

      4360       4370       4380       4390       4400
GGACAGGCTGGGCCCCATCAGCAGAGCCACCAAGAGTCCACACGTGGCCG
CCTGTCCGACCCGGGGTAGTCGTCTCGGTGGTTCTCAGGTGTGCACCGGC
 G  Q  A  G  P  H  Q  Q  S  H  Q  E  S  T  R  G  R

      4410       4420       4430       4440       4450
GTCAGCAGGAAGGTCTGGACGTTCAGGGTCTTTCCTCTACCAGGTGAGCA
CAGTCGTCCTTCCAGACCTGCAAGTCCCAGAAAGGAGATGGTCCACTCGT
  S  A  G  R  S  G  R  S  G  S  F  L  Y  Q  V  S

      4460       4470       4480       4490       4500
CTCATGAACAGTCTGAGTCTGCCCATGGACGGGCTGGGCCCAGTACTGGA
GAGTACTTGTCAGACTCAGACGGGTACCTGCCCGACCCGGGTCATGACCT
T  H  E  Q  S  E  S  A  H  G  R  A  G  P  S  T  G

      4510       4520       4530       4540       4550
GGAAGACAAGGATCCCACCACGAGCAGGCACGAGACAGCTCCAGGCACTC
CCTTCTGTTCCTAGGGTGGTGCTCGTCCGTGCTCTGTCGAGGTCCGTGAG
 G  R  Q  G  S  H  H  E  Q  A  R  D  S  S  R  H  S

      4560       4570       4580       4590       4600
AGCGTCCCAAGAGGGTCAGGACACCATTCGTGGACACCCGGGGTCAAGGA
TCGCAGGGTTCTCCCAGTCCTGTGGTAAGCACCTGTGGGCCCCAGTTCCT
  A  S  Q  E  G  Q  D  T  I  R  G  H  P  G  S  R

      4610       4620       4630       4640       4650
GAGGAGGAAGACAGGGATCCTACCACGAGCAATCGGTAGATAGGTCTGGA
CTCCTCCTTCTGTCCCTAGGATGGTGCTCGTTAGCCATCTATCCAGACCT
R  G  G  R  Q  G  S  Y  H  E  Q  S  V  D  R  S  G

      4660       4670       4680       4690       4700
CACTCAGGGTCCCATCACAGCCACACCACATCCCAGGGAAGGTCTGATGC
GTGAGTCCCAGGGTAGTGTCGGTGTGGTGTAGGGTCCCTTCCAGACTACG
 H  S  G  S  H  H  S  H  T  T  S  Q  G  R  S  D  A

      4710       4720       4730       4740       4750
CTCCCATGGGCAGTCAGGATCCAGAAGTGCAAGCAGAGAAACACGTAATG
GAGGGTACCCGTCAGTCCTAGGTCTTCACGTTCGTCTCTTTGTGCATTAC
  S  H  G  Q  S  G  S  R  S  A  S  R  E  T  R  N
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      4760       4770       4780       4790       4800
AGGAACAGTCAGGAGACGGCTCCAGGCACTCAGGGTCGCGTCACCATGAA
TCCTTGTCAGTCCTCTGCCGAGGTCCGTGAGTCCCAGCGCAGTGGTACTT
E  E  Q  S  G  D  G  S  R  H  S  G  S  R  H  H  E

      4810       4820       4830       4840       4850
GCTTCCACTCAGGCTGACAGCTCTAGACACTCACAGTCCGGCCAGGGTGA
CGAAGGTGAGTCCGACTGTCGAGATCTGTGAGTGTCAGGCCGGTCCCACT
 A  S  T  Q  A  D  S  S  R  H  S  Q  S  G  Q  G  E

      4860       4870       4880       4890       4900
ATCAGCGGGGTCCAGGAGAAGCAGGCGCCAGGGATCCAGTGTTAGCCAGG
TAGTCGCCCCAGGTCCTCTTCGTCCGCGGTCCCTAGGTCACAATCGGTCC
  S  A  G  S  R  R  S  R  R  Q  G  S  S  V  S  Q

      4910       4920       4930       4940       4950
ACAGTGACAGTGAGGCATACCCAGAGGACTCTGAGAGGCGATCTGAGTCT
TGTCACTGTCACTCCGTATGGGTCTCCTGAGACTCTCCGCTAGACTCAGA
D  S  D  S  E  A  Y  P  E  D  S  E  R  R  S  E  S

      4960       4970       4980       4990       5000
GCTTCCAGAAACCATCATGGATCTTCTCGGGAGCAGTCAAGAGATGGCTC
CGAAGGTCTTTGGTAGTACCTAGAAGAGCCCTCGTCAGTTCTCTACCGAG
 A  S  R  N  H  H  G  S  S  R  E  Q  S  R  D  G  S

      5010       5020       5030       5040       5050
CAGACACCCCGGATCCTCTCACCGCGATACAGCCAGTCATGTACAGTCTT
GTCTGTGGGGCCTAGGAGAGTGGCGCTATGTCGGTCAGTACATGTCAGAA
  R  H  P  G  S  S  H  R  D  T  A  S  H  V  Q  S

      5060       5070       5080       5090       5100
CACCTGTACAGTCAGACTCTAGTACCGCTAAGGAACATGGTCACTTTAGT
GTGGACATGTCAGTCTGAGATCATGGCGATTCCTTGTACCAGTGAAATCA
S  P  V  Q  S  D  S  S  T  A  K  E  H  G  H  F  S

      5110       5120       5130       5140       5150
AGTCTTTCACAAGATTCTGCGTATCACTCAGGAATACAGTCACGTGGCAG
TCAGAAAGTGTTCTAAGACGCATAGTGAGTCCTTATGTCAGTGCACCGTC
 S  L  S  Q  D  S  A  Y  H  S  G  I  Q  S  R  G  S

      5160       5170       5180       5190       5200
TCCTCACAGTTCTAGTTCTTATCATTATCAATCTGAGGGCACTGAAAGGC
AGGAGTGTCAAGATCAAGAATAGTAATAGTTAGACTCCCGTGACTTTCCG
  P  H  S  S  S  S  Y  H  Y  Q  S  E  G  T  E  R

      5210       5220       5230       5240       5250
AAAAAGGTCAATCAGGTTTAGTTTGGAGACATGGCAGCTATGGTAGTGCA G
TTTTTCCAGTTAGTCCAAATCAAACCTCTGTACCGTCGATACCATCACGT C
Q  K  G  Q  S  G  L  V  W  R  H  G  S  Y  G  S  A
```

Figure 13
Specific fragment from *FLG* size variant allele "*FLG*$^{8+10+}$"

Sequence Range: 1 to 6223

Repeat 7 (partial)

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                                                                    50
AGGACAAGCA GGAACCGGGG ATCCAGTTTT AGCCAGGACA GTGACAGTCA
TCCTGTTCGT CCTTGGCCCC TAGGTCAAAA TCGGTCCTGT CACTGTCAGT
 R  T  S   R  N  R  G   S  S  F   S  Q  D   S  D  S  Q

                                                                   100
GGGACACTCA GAAGACTCTG AGAGGTGGTC TGGGTCTGCT TCCAGAAACC
CCCTGTGAGT CTTCTGAGAC TCTCCACCAG ACCCAGACGA AGGTCTTTGG
  G  H  S   E  D  S   E  R  W  S   G  S  A   S  R  N

                                                                   150
ATCATGGATC TGCTCAGGAG CAGCTAAGAG ATGGCTCCAG ACACCCCAGG
TAGTACCTAG ACGAGTCCTC GTCGATTCTC TACCGAGGTC TGTGGGGTCC
H  H  G  S   A  Q  E   Q  L  R   D  G  S  R   H  P  R

                                                                   200
TCCCATCAAG AAGACAGAGC TGGTCATGGG CACTCTGCAG ACAGCTCCAG
AGGGTAGTTC TTCTGTCTCG ACCAGTACCC GTGAGACGTC TGTCGAGGTC
 S  H  Q   E  D  R  A   G  H  G   H  S  A   D  S  S  R

                                                                   250
ACAATCAGGC ACTCGTCACA CACAGACTTC CTCTGGTGGA CAGGCTGCAT
TGTTAGTCCG TGAGCAGTGT GTGTCTGAAG GAGACCACCT GTCCGACGTA
  Q  S  G   T  R  H   T  Q  T  S   S  G  G   Q  A  A

                                                                   300
CATCCCATGA ACAGGCAAGA TCAAGTGCAG GAGAAAGACA TGGATCCCAC
GTAGGGTACT TGTCCGTTCT AGTTCACGTC CTCTTTCTGT ACCTAGGGTG
S  S  H  E   Q  A  R   S  S  A   G  E  R  H   G  S  H

                                                                   350
CACCAGCAGT CAGCAGACAG CTCCAGACAC TCAGGCATTG GGCACGGACA
GTGGTCGTCA GTCGTCTGTC GAGGTCTGTG AGTCCGTAAC CCGTGCCTGT
 H  Q  Q   S  A  D  S   S  R  H   S  G  I   G  H  G  Q

                                                                   400
AGCTTCATCT GCAGTCAGAG ACAGTGGACA CCGAGGGTAC AGTGGTAGTC
TCGAAGTAGA CGTCAGTCTC TGTCACCTGT GGCTCCCATG TCACCATCAG
  A  S  S   A  V  R   D  S  G  H   R  G  Y   S  G  S

                                                                   450
AGGCCAGTGA CAATGAGGGA CATTCAGAAG ACTCAGACAC ACAGTCAGTG
TCCGGTCACT GTTACTCCCT GTAAGTCTTC TGAGTCTGTG TGTCAGTCAC
Q  A  S  D   N  E  G   H  S  E   D  S  D  T   Q  S  V

                                                                   500
TCAGCCCACG GACAGGCTGG GTCCCATCAG CAGAGCCACC AAGAGTCCGC
AGTCGGGTGC CTGTCCGACC CAGGGTAGTC GTCTCGGTGG TTCTCAGGCG
 S  A  H   G  Q  A  G   S  H  Q   Q  S  H   Q  E  S  A
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                                                                    550
ACGTGGCCGG TCAGGGGAAA CGTCTGGACA TTCAGGGTCT TTCCTCTACC
TGCACCGGCC AGTCCCCTTT GCAGACCTGT AAGTCCCAGA AAGGAGATGG
  R  G  R   S  G  E   T  S  G  H   S  G  S   F  L  Y

                          Repeat 8.1                            600
AGGTGAGCAC TCATGAACAG TCTGAGTCCT CCCATGGATG GACGGGGCCC
TCCACTCGTG AGTACTTGTC AGACTCAGGA GGGTACCTAC CTGCCCCGGG
Q  V  S  T   H  E  Q   S  E  S   S  H  G  W   T  G  P
Repeat 8.1

                                                                    650
AGCACTAGAG GAAGACAAGG ATCCCGCCAT GAGCAGGCAC AAGACAGCTC
TCGTGATCTC CTTCTGTTCC TAGGGCGGTA CTCGTCCGTG TTCTGTCGAG
 S  T  R   G  R  Q  G   S  R  H   E  Q  A   Q  D  S  S

                                                                    700
CAGGCACTCA GCATCCCAAG ACGGTCAGGA CACCATTCGT GGACACCCGG
GTCCGTGAGT CGTAGGGTTC TGCCAGTCCT GTGGTAAGCA CCTGTGGGCC
  R  H  S   A  S  Q   D  G  Q  D   T  I  R   G  H  P

                                                                    750
GGTCAAGCAG AGGAGGAAGG CAGGGGTACC ACCACGAGCA TTCGGTAGAT
CCAGTTCGTC TCCTCCTTCC GTCCCCATGG TGGTGCTCGT AAGCCATCTA
G  S  S  R   G  G  R   Q  G  Y   H  H  E  H   S  V  D

                                                                    800
AGCTCTGGAC ACTCAGGGTC CCATCACAGC CACACCACAT CCCAGGGAAG
TCGAGACCTG TGAGTCCCAG GGTAGTGTCG GTGTGGTGTA GGGTCCCTTC
 S  S  G   H  S  G  S   H  H  S   H  T  T   S  Q  G  R

                                                                    850
GTCTGATGCC TCCCGTGGGC AGTCAGGATC CAGACGTGCA AGCAGAACAA
CAGACTACGG AGGGCACCCG TCAGTCCTAG GTCTGCACGT TCGTCTTGTT
  S  D  A   S  R  G   Q  S  G  S   R  R  A   S  R  T

                                                                    900
CACGTAATGA GGAACAATCA GGAGACGGCT CCAGGCACTC AGGGTCGCGT
GTGCATTACT CCTTGTTAGT CCTCTGCCGA GGTCCGTGAG TCCCAGCGCA
T  R  N  E   E  Q  S   G  D  G   S  R  H  S   G  S  R

                                                                    950
CACCATGAAG CTTCCACTCA TGCCGACATC TCTAGACACT CACAGGCAGT
GTGGTACTTC GAAGGTGAGT ACGGCTGTAG AGATCTGTGA GTGTCCGTCA
 H  H  E   A  S  T  H   A  D  I   S  R  H   S  Q  A  V

                                                                   1000
CCAGGGACAA TCAGAGGGGT CCAGGAGAAG CAGGCGCCAG GGATCCAGTG
GGTCCCTGTT AGTCTCCCCA GGTCCTCTTC GTCCGCGGTC CCTAGGTCAC
  Q  G  Q   S  E  G   S  R  R  S   R  R  Q   G  S  S

                                                                   1050
TTAGCCAGGA CAGTGACAGT GAGGGACATT CAGAAGACTC TGAGAGGTGG
AATCGGTCCT GTCACTGTCA CTCCCTGTAA GTCTTCTGAG ACTCTCCACC
V  S  Q  D   S  D  S   E  G  H   S  E  D  S   E  R  W

                                                                   1100
TCTGGGTCTG CTTCCAGAAA CCATCATGGA TCTGCTCAGG AGCAGCTAAG
AGACCCAGAC GAAGGTCTTT GGTAGTACCT AGACGAGTCC TCGTCGATTC
 S  G  S   A  S  R  N   H  H  G   S  A  Q   E  Q  L  R
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                                                                    *                1150
AGATGGCTCC AGACACCCCA GGTCCCATCA AGAAGGCAGA GCTGGTCATG
TCTACCGAGG TCTGTGGGGT CCAGGGTAGT TCTTCCGTCT CGACCAGTAC
  D  G  S   R  H  P   R  S  H  Q   E  G  R   A  G  H

                                                                              1200
GGCACTCTGC AGACAGCTCC AGACAATCAG GCACTCGTCA CACACAGACT
CCGTGAGACG TCTGTCGAGG TCTGTTAGTC CGTGAGCAGT GTGTGTCTGA
G  H  S  A   D  S  S   R  Q  S   G  T  R  H   T  Q  T

                                                                              1250
TCCTCTGGTG GACAGGCTGC ATCATCCCAT GAACAGGCAA GATCAAGTGC
AGGAGACCAC CTGTCCGACG TAGTAGRGTA CTTGTCCGTT CTAGTTCACG
 S  S  G   G  Q  A  A   S  S  H   E  Q  A   R  S  S  A

                                                                              1300
AGGAGAAAGA CATGGATCCC ACCACCAGCA GTCAGCAGAC AGCTCCAGAC
TCCTCTTTCT GTACCTAGGG TGGTGGTCGT CAGTCGTCTG TCGAGGTCTG
  G  E  R   H  G  S   H  H  Q  Q   S  A  D   S  S  R

                                                                              1350
ACTCAGGCAT TGGGCACGGA CAAGCTTCAT CTGCAGTCAG AGACAGTGGA
TGAGTCCGTA ACCCGTGCCT GTTCGAAGTA GACGTCAGTC TCTGTCACCT
H  S  G  I   G  H  G   Q  A  S   S  A  V  R   D  S  G

                                                                              1400
CACCGAGGGT ACAGTGGTAG TCAGGCCAGT GACAATGAGG GACATTCAGA
GTGGCTCCCA TGTCACCATC AGTCCGGTCA CTGTTACTCC CTGTAAGTCT
 H  R  G   Y  S  G  S   Q  A  S   D  N  E   G  H  S  E

                                                                              1450
AGACTCAGAC ACACAGTCAG TGTCAGCCCA CGGACAGGCT GGGTCCCATC
TCTGAGTCTG TGTGTCAGTC ACAGTCGGGT GCCTGTCCGA CCCAGGGTAG
  D  S  D   T  Q  S   V  S  A  H   G  Q  A   G  S  H

                                                                              1500
AGCAGAGCCA CCAAGAGTCC GCACGTGGCC GGTCAGGGGA AACGTCTGGA
TCGTCTCGGT GGTTCTCAGG CGTGCACCGG CCAGTCCCCT TTGCAGACCT
Q  Q  S  H   Q  E  S   A  R  G   R  S  G  E   T  S  G

                                                                    Repeat 8.2 1550
CATTCAGGAT CTTTCCTCTA CCAGGTGAGC ACTCATGAAC AGTCTGAGTC
GTAAGTCCTA GAAAGGAGAT GGTCCACTCG TGAGTACTTG TCAGACTCAG
 H  S  G   S  F  L  Y   Q  V  S   T  H  E   Q  S  E  S
Repeat 8.2

                                                                              1600
CTCCCATGGA TGGACGGGGC CCAGCACTAG AGGAAGACAA GGATCCCGCC
GAGGGTACCT ACCTGCCCCG GGTCGTGATC TCCTTCTGTT CCTAGGGCGG
  S  H  G   W  T  G   P  S  T  R   G  R  Q   G  S  R

                                                                    *         1650
ATGAGCAGGC ACAAGACAGC TCCAGGCACT CAGCATCCCA AGATGGTCAG
TACTCGTCCG TGTTCTGTCG AGGTCCGTGA GTCGTAGGGT TCTACCAGTC
H  E  Q  A   Q  D  S   S  R  H   S  A  S  Q   D  G  Q

                                                                              1700
GACACCATTC GTGGACACCC GGGGTCAAGC AGAGGAGGAA GGCAGGGGTA
CTGTGGTAAG CACCTGTGGG CCCCAGTTCG TCTCCTCCTT CCGTCCCCAT
 D  T  I   R  G  H  P   G  S  S   R  G  G   R  Q  G  Y
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                                                                    1750
CCACCACGAG CATTCGGTAG ATAGCTCTGG ACACTCAGGG TCCCATCACA
GGTGGTGCTC GTAAGCCATC TATCGAGACC TGTGAGTCCC AGGGTAGTGT
  H  H  E   H  S  V   D  S  S  G   H  S  G   S  H  H

                                                                    1800
GCCACACCAC ATCCCAGGGA AGGTCTGATG CCTCCCGTGG GCAGTCAGGA
CGGTGTGGTG TAGGGTCCCT TCCAGACTAC GGAGGGCACC CGTCAGTCCT
S  H  T  T   S  Q  G   R  S  D   A  S  R  G   Q  S  G

                                                                    1850
TCCAGAAGTG CAAGCAGAAC AACACGTAAT GAGGAACAAT CAGGAGACGG
AGGTCTTCAC GTTCGTCTTG TTGTGCATTA CTCCTTGTTA GTCCTCTGCC
 S  R  S   A  S  R  T   T  R  N   E  E  Q   S  G  D  G

                                                                    1900
CTCCAGGCAC TCAGGGTCGC GTCACCATGA AGCTTCCACT CATGCCGACA
GAGGTCCGTG AGTCCCAGCG CAGTGGTACT TCGAAGGTGA GTACGGCTGT
  S  R  H   S  G  S   R  H  H  E   A  S  T   H  A  D

                                                                    1950
TCTCTAGACA CTCACAGGCA GTCCAGGGAC AATCAGAGGG GTCCAGGAGA
AGAGATCTGT GAGTGTCCGT CAGGTCCCTG TTAGTCTCCC CAGGTCCTCT
I  S  R  H   S  Q  A   V  Q  G   Q  S  E  G   S  R  R

                                                                    2000
AGCAGGCGCC AGGGATCCAG TGTTAGCCAG GACAGTGACA GTGAGGGACA
TCGTCCGCGG TCCCTAGGTC ACAATCGGTC CTGTCACTGT CACTCCCTGT
 S  R  R   Q  G  S  S   V  S  Q   D  S  D   S  E  G  H

                                                                    2050
TTCAGAAGAC TCTGAGAGGT GGTCTGGGTC TGCTTCCAGA AACCATCATG
AAGTCTTCTG AGACTCTCCA CCAGACCCAG ACGAAGGTCT TTGGTAGTAC
  S  E  D   S  E  R   W  S  G  S   A  S  R   N  H  H

                                                                    2100
GATCTGCTCA GGAGCAGCTA AGAGATGGCT CCAGACACCC CAGGTCCCAT
CTAGACGAGT CCTCGTCGAT TCTCTACCGA GGTCTGTGGG GTCCAGGGTA
G  S  A  Q   E  Q  L   R  D  G   S  R  H  P   R  S  H

                                                                    2150
CAAGAAGACA GAGCTGGTCA TGGGCACTCT GCAGACAGCT CCAGACAATC
GTTCTTCTGT CTCGACCAGT ACCCGTGAGA CGTCTGTCGA GGTCTGTTAG
 Q  E  D   R  A  G  H   G  H  S   A  D  S   S  R  Q  S

                                                                    2200
AGGCACTCGT CACACACAGG CTTCCTCTGG TGGACAGGCT GCATCATCCC
TCCGTGAGCA GTGTGTGTCC GAAGGAGACC ACCTGTCCGA CGTAGTAGGG
  G  T  R   H  T  Q   A  S  S  G   G  Q  A   A  S  S

                                                                    2250
ATGAACAGGC AAGATCAAGT GCAGGAGAAA GACATGGATC CCACCACCAG
TACTTGTCCG TTCTAGTTCA CGTCCTCTTT CTGTACCTAG GGTGGTGGTC
H  E  Q  A   R  S  S   A  G  E   R  H  G  S   H  H  Q

                                                                    2300
CAGTCAGCAG ACAGCTCCAG ACACTCAGGC ATTGGGCACG GACAAGCTTC
GTCAGTCGTC TGTCGAGGTC TGTGAGTCCG TAACCCGTGC CTGTTCGAAG
 Q  S  A   D  S  S  R   H  S  G   I  G  H   G  Q  A  S
```

```
                                                                    2350
ATCTGCAGTC AGAGACAGTG GACACCGAGG GTACAGTGGT AGTCAGGCCA
TAGACGTCAG TCTCTGTCAC CTGTGGCTCC CATGTCACCA TCAGTCCGGT
  S  A  V   R  D  S   G  H  R  G   Y  S  G   S  Q  A

                                                                    2400
GTGACAATGA GGGACATTCA GAAGACTCAG ACACACAGTC AGTGTCAGCC
CACTGTTACT CCCTGTAAGT CTTCTGAGTC TGTGTGTCAG TCACAGTCGG
S  D  N  E   G  H  S   E  D  S   D  T  Q  S   V  S  A

                                                                    2450
CACGGACAGG CTGGGTCCCA TCAGCAGAGC CACCAAGAGT CCGCACGTGG
GTGCCTGTCC GACCCAGGGT AGTCGTCTCG GTGGTTCTCA GGCGTGCACC
 H  G  Q   A  G  S  H   Q  Q  S   H  Q  E   S  A  R  G

                                                                    2500
CCGGTCAGGG GAAACGTCTG GACATTCAGG ATCTTTCCTC TACCAGGTGA
GGCCAGTCCC CTTTGCAGAC CTGTAAGTCC TAGAAAGGAG ATGGTCCACT
  R  S  G   E  T  S   G  H  S  G   S  F  L   Y  Q  V

                        Repeat 9                                    2550
GCACTCATGA ACAGTCTGAG TCCTCCCATG GATGGACGGG GCCCAGCACT
CGTGAGTACT TGTCAGACTC AGGAGGGTAC CTACCTGCCC CGGGTCGTGA
S  T  H  E   Q  S  E   S  S  H   G  W  T  G   P  S  T
Repeat 9

                                                                    2600
AGAGGAAGAC AAGGATCCCG CCATGAGCAG GCACAAGACA GCTCCAGGCA
TCTCCTTCTG TTCCTAGGGC GGTACTCGTC CGTGTTCTGT CGAGGTCCGT
 R  G  R   Q  G  S  R   H  E  Q   A  Q  D   S  S  R  H

                                                                    2650
CTCAGCATCC CAAGACGGTC AGGACACCAT TCGTGGACAC CCGGGGTCAA
GAGTCGTAGG GTTCTGCCAG TCCTGTGGTA AGCACCTGTG GGCCCCAGTT
  S  A  S   Q  D  G   Q  D  T  I   R  G  H   P  G  S

                                                                    2700
GCAGAGGAGG AAGGCAGGGG TACCACCACG AGCATTCGGT AGATAGCTCT
CGTCTCCTCC TTCCGTCCCC ATGGTGGTGC TCGTAAGCCA TCTATCGAGA
S  R  G  G   R  Q  G   Y  H  H   E  H  S  V   D  S  S

                                                                    2750
GGACACTCAG GGTCCCATCA CAGCCACACC ACATCCCAGG GAAGGTCTGA
CCTGTGAGTC CCAGGGTAGT GTCGGTGTGG TGTAGGGTCC CTTCCAGACT
 G  H  S   G  S  H  H   S  H  T   T  S  Q   G  R  S  D

                                                                    2800
TGCCTCCCGT GGGCAGTCAG GATCCAGAAG TGCAAGCAGA ACAACACGTA
ACGGAGGGCA CCCGTCAGTC CTAGGTCTTC ACGTTCGTCT TGTTGTGCAT
  A  S  R   G  Q  S   G  S  R  S   A  S  R   T  T  R

                                                                    2850
ATGAGGAACA ATCAGGAGAC AGCTCCAGGC ACTCAGGGTC GCGTCACCAT
TACTCCTTGT TAGTCCTCTG TCGAGGTCCG TGAGTCCCAG CGCAGTGGTA
N  E  E  Q   S  G  D   S  S  R   H  S  G  S   R  H  H

                                                                    2900
GAAGCTTCCA CTCATGCCGA CATCTCTAGA CACTCACAGG CAGTCCAGGG
CTTCGAAGGT GAGTACGGCT GTAGAGATCT GTGAGTGTCC GTCAGGTCCC
 E  A  S   T  H  A  D   I  S  R   H  S  Q   A  V  Q  G
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                                                                    2950
ACAATCAGAG GGGTCCAGGA GAAGCAGGCG CCAGGGATCC AGTGTTAGCC
TGTTAGTCTC CCCAGGTCCT CTTCGTCCGC GGTCCCTAGG TCACAATCGG
  Q  S  E   G  S  R   R  S  R  R   Q  G  S   S  V  S

                                                                    3000
AGGACAGTGA CAGTGAGGGA CATTCAGAAG ACTCTGAGAG GTGGTCTGGG
TCCTGTCACT GTCACTCCCT GTAAGTCTTC TGAGACTCTC CACCAGACCC
Q  D  S  D   S  E  G   H  S  E   D  S  E  R   W  S  G

                                                                    3050
TCTGCTTCCA GAAACCATCG TGGATCTGTT CAGGAGCAGT CAAGGCACGG
AGACGAAGGT CTTTGGTAGC ACCTAGACAA GTCCTCGTCA GTTCCGTGCC
 S  A  S   R  N  H  R   G  S  V   Q  E  Q   S  R  H  G

                                                                    3100
CTCCAGACAC CCCAGGTCCC ATCACGAAGA CAGAGCCGGT CACGGGCACT
GAGGTCTGTG GGGTCCAGGG TAGTGCTTCT GTCTCGGCCA GTGCCCGTGA
  S  R  H   P  R  S   H  H  E  D   R  A  G   H  G  H

                                                                    3150
CTGCAGACCG CTCCAGACAA TCAGGCACTC GTCACGCAGA GACTTCCTCT
GACGTCTGGC GAGGTCTGTT AGTCCGTGAG CAGTGCGTCT CTGAAGGAGA
S  A  D  R   S  R  Q   S  G  T   R  H  A  E   T  S  S

                                                                    3200
GGTGGACAGG CTGCATCATC CCATGAACAG GCAAGATCAA GTCCAGGAGA
CCACCTGTCC GACGTAGTAG GGTACTTGTC CGTTCTAGTT CAGGTCCTCT
 G  G  Q   A  A  S  S   H  E  Q   A  R  S   S  P  G  E

                                                                    3250
GAGACACGGA TCCCGCCACC AGCAGTCAGC AGACAGCTCC AGACACTCAG
CTCTGTGCCT AGGGCGGTGG TCGTCAGTCG TCTGTCGAGG TCTGTGAGTC
  R  H  G   S  R  H   Q  Q  S  A   D  S  S   R  H  S

                                                                    3300
GCATTCCGCG TGGACAGGCT TCATCTGCAG TCAGAGACAG TAGACACTGG
CGTAAGGCGC ACCTGTCCGA AGTAGACGTC AGTCTCTGTC ATCTGTGACC
G  I  P  R   G  Q  A   S  S  A   V  R  D  S   R  H  W

                                                                    3350
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CCCAGGTCAC CATCAGTTCG GTCACTATCA CTCCCTGTAA GTCTTCTCAG
 G  S  S   G  S  Q  A   S  D  S   E  G  H   S  E  E  S

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TCTGTGTGTC AGTCACAGTC CGGTACCTGT CCGACCCGGG GTAGTCGTCT
  D  T  Q   S  V  S   G  H  G  Q   A  G  P   H  Q  Q

                                                                    3450
GCCACCAAGA GTCCGCACGT GACCGGTCAG GGGGAAGGTC TGGACGTTCA
CGGTGGTTCT CAGGCGTGCA CTGGCCAGTC CCCCTTCCAG ACCTGCAAGT
S  H  Q  E   S  A  R   D  R  S   G  G  R  S   G  R  S

                                                                    3500
GGGTCTTTCC TCTACCAGGT GAGCACTCAT GAACAGTCTG AGTCCGCCCA
CCCAGAAAGG AGATGGTCCA CTCGTGAGTA CTTGTCAGAC TCAGGCGGGT
 G  S  F   L  Y  Q  V   S  T  H   E  Q  S   E  S  A  H
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Repeat 10.1

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ACCCGCCTGG TCCTGGTCGT GACCTGCTTC TGTTCCTAGG GTGGTGCTCG
  G  R  T   R  T  S   T  G  R  R   Q  G  S   H  H  E

                                                                    3600
AGGCACGAGA CAGCTCCAGG CACTCAGCGT CCCAAGAGGG TCAGGACACC
TCCGTGCTCT GTCGAGGTCC GTGAGTCGCA GGGTTCTCCC AGTCCTGTGG
Q  A  R  D   S  S  R   H  S  A   S  Q  E  G   Q  D  T

                                                                    3650
ATTCGTGCAC ACCCGGGGTC AAGCAGAAGA GGAAGGCAGG GATCCCACTA
TAAGCACGTG TGGGCCCCAG TTCGTCTTCT CCTTCCGTCC CTAGGGTGAT
 I  R  A   H  P  G  S   S  R  R   G  R  Q   G  S  H  Y

                                                                    3700
CGAGCAATCG GTAGATAGGT CTGGACACTC AGGGTCCCAT CACAGCCACA
GCTCGTTAGC CATCTATCCA GACCTGTGAG TCCCAGGGTA GTGTCGGTGT
  E  Q  S   V  D  R   S  G  H  S   G  S  H   H  S  H

                                                                    3750
CCACATCCCA GGGAAGGTCT GATGCCTCCC GTGGGCAGTC AGGATCCAGA
GGTGTAGGGT CCCTTCCAGA CTACGGAGGG CACCCGTCAG TCCTAGGTCT
T  T  S  Q   G  R  S   D  A  S   R  G  Q  S   G  S  R

                                                                    3800
AGTGCCAGCA GACAAACTCG TAACGACGAA CAATCAGGAG ACGGCTCCAG
TCACGGTCGT CTGTTTGAGC ATTGCTGCTT GTTAGTCCTC TGCCGAGGTC
 S  A  S   R  Q  T  R   N  D  E   Q  S  G   D  G  S  R.

       0                                          0*
                                                                    3850
GCACTCATGG TCGCATCACC ATGAAGCTTC CACTCAGGCG GACAGCTCTA
CGTGAGTACC AGCGTAGTGG TACTTCGAAG GTGAGTCCGC CTGTCGAGAT
  H  S  W   S  H  H   H  E  A  S   T  Q  A   D  S  S

          11                                          *
                                                                    3900
GACACTCACA GTCCGGCCAG GGACAATCAG CGGGGCCCAG TACAAGCAGG
CTGTGAGTGT CAGGCCGGTC CCTGTTAGTC GCCCCGGGTC ATGTTCGTCC
R  H  S  Q   S  G  Q   G  Q  S   A  G  P  S   T  S  R

                                                                    3950
AACCAGGGAT CCAGTGTTAG CCAGGACAGT GACAGTCAGG GACACTCAGA
TTGGTCCCTA GGTCACAATC GGTCCTGTCA CTGTCAGTCC CTGTGAGTCT
 N  Q  G   S  S  V  S   Q  D  S   D  S  Q   G  H  S  E

                                                                    4000
AGACTCTGAG AGGTGGTCTG GGTCTGCTTC CAGAAACCAT CATGGATCTG
TCTGAGACTC TCCACCAGAC CCAGACGAAG GTCTTTGGTA GTACCTAGAC
  D  S  E   R  W  S   G  S  A  S   R  N  H   H  G  S

                                                                    4050
CTGGGGAGCA GTCAAGAGAT GGCTCCAGAC ACCCTGGGTC CCATCAAGAA
GACCCCTCGT CAGTTCTCTA CCGAGGTCTG TGGGACCCAG GGTAGTTCTT
A  G  E  Q   S  R  D   G  S  R   H  P  G  S   H  Q  E

                                                  11*
                                                                    4100
GACAGAGCCG GTCACGGGCA CTCTGCAGAC AGCCCCAGAC AATCAGGCAC
CTGTCTCGGC CAGTGCCCGT GAGACGTCTG TCGGGGTCTG TTAGTCCGTG
 D  R  A   G  H  G  H   S  A  D   S  P  R   Q  S  G  T
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                                                                    4150
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AGCAGTGTGT CTCAGAAGGA GAGCACCTGT CCGACGCAGT AGGGTACTTG
  R  H  T   E  S  S   S  R  G  Q   A  A  S   S  H  E

                                                                    4200
AGGCAAGATC AAGTGCAGGA GAAAGACATG GATCCCACCA CCAGCTCCAG
TCCGTTCTAG TTCACGTCCT CTTTCTGTAC CTAGGGTGGT GGTCGAGGTC
Q  A  R  S   S  A  G   E  R  H   G  S  H  H   Q  L  Q

                                                                    4250
TCAGCAGACA GCTCCAGACA CGCAGGCATT GGGCACGGAC AAGCTTCATC
AGTCGTCTGT CGAGGTCTGT GCGTCCGTAA CCCGTGCCTG TTCGAAGTAG
 S  A  D   S  S  R  H   A  G  I   G  H  G   Q  A  S  S

                                                                    4300
TGCAGTCAGA GACAGTGGAC ACCGAGGGTA CAGTGGTAGT CAGGCCACTG
ACGTCAGTCT CTGTCACCTG TGGCTCCCAT GTCACCATCA GTCCGGTGAC
  A  V  R   D  S  G   H  R  G  Y   S  G  S   Q  A  T

                                                                    4350
ACAGTGAGGG ACATTCAGAA GACTCAGACA CACAGTCAGT GTCAGCACAG
TGTCACTCCC TGTAAGTCTT CTGAGTCTGT GTGTCAGTCA CAGTCGTGTC
D  S  E  G   H  S  E   D  S  D   T  Q  S  V   S  A  Q

                                                                    4400
GGAAAAGCTG GGCCCCATCA GCAGAGCCAC AAAGAGTCCG CACGTGGCCA
CCTTTTCGAC CCGGGGTAGT CGTCTCGGTG TTTCTCAGGC GTGCACCGGT
 G  K  A   G  P  H  Q   Q  S  H   K  E  S   A  R  G  Q

                                                                    4450
GTCAGGGGAA AGCTCTAGAC GTTCAGGGTC TTTCCTCTAC CAGGTGAGCA
CAGTCCCCTT TCGAGATCTG CAAGTCCCAG AAAGGAGATG GTCCACTCGT
  S  G  E   S  S  R   R  S  G  S   F  L  Y   Q  V  S

                Repeat 10.2                                         4500
CTCATGAACA GTCTGAGTCC ACCCATGGAC AGTCTGTGCC CAGCACTGGA
GAGTACTTGT CAGACTCAGG TGGGTACCTG TCAGACACGG GTCGTGACCT
T  H  E  Q   S  E  S   T  H  G   Q  S  V  P   S  T  G
Repeat 10.2

                                                                    4550
GGAAGACAAG GATCCCACCA TGATCAGGCA CAAGACAGCT CCAGGCACTC
CCTTCTGTTC CTAGGGTGGT ACTAGTCCGT GTTCTGTCGA GGTCCGTGAG
 G  R  Q   G  S  H  H   D  Q  A   Q  D  S   S  R  H  S

                                                                    4600
AGCATCCCAA GAGGGTCAGG ACACCATTCG TGGACACCCG GGGCCAAGCA
TCGTAGGGTT CTCCCAGTCC TGTGGTAAGC ACCTGTGGGC CCCGGTTCGT
  A  S  Q   E  G  Q   D  T  I  R   G  H  P   G  P  S

                                                                    4650
GAGGAGGAAG ACAGGGGTCC CACCACGAGC AATCGGTAGA TAGGTCTGGA
CTCCTCCTTC TGTCCCCAGG GTGGTGCTCG TTAGCCATCT ATCCAGACCT
R  G  G  R   Q  G  S   H  H  E   Q  S  V  D   R  S  G

                                                                    4700
CACTCAGGGT CCCATCACAG CCACACCACA TCCCAGGGAA GGTCTGATGC
GTGAGTCCCA GGGTAGTGTC GGTGTGGTGT AGGGTCCCTT CCAGACTACG
 H  S  G   S  H  H  S   H  T  T   S  Q  G   R  S  D  A
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CTCCCGTGGG CAGTCAGGAC CCAGAAGTGC AAGCAGACAA ACACATGACA
GAGGGCACCC GTCAGTCCTG GGTCTTCACG TTCGTCTGTT TGTGTACTGT
  S  R  G   Q  S  G   P  R  S  A   S  R  Q   T  H  D

6                         6                              4800
AGGAACAATC AGGAGACGGC TCTAGGCACT CAGGGTCGCG TCATCATGAA
TCCTTGTTAG TCCTCTGCCG AGATCCGTGA GTCCCAGCGC AGTAGTACTT
K  E  Q  S   G  D  G   S  R  H   S  G  S  R   H  H  E

                                                         4850
GCTTCCTCTT GGGCCGACAG CTCTAGACAC TCACAGGCAG TCCAGGGACA
CGAAGGAGAA CCCGGCTGTC GAGATCTGTG AGTGTCCGTC AGGTCCCTGT
 A  S  S   W  A  D  S   S  R  H   S  Q  A   V  Q  G  Q

                                                         4900
ATCAGAGGGG TCCAGGAGAA GCAGGCGCCA GGGATCCAGT GTTAGCCAGG
TAGTCTCCCC AGGTCCTCTT CGTCCGCGGT CCCTAGGTCA CAATCGGTCC
  S  E  G   S  R  R   S  R  R  Q   G  S  S   V  S  Q

                                                         4950
ACAGTGACAG TCAGGGACAC TCAGAAGACT CTGAGAGGCG GTCTGGGTCT
TGTCACTGTC AGTCCCTGTG AGTCTTCTGA GACTCTCCGC CAGACCCAGA
D  S  D  S   Q  G  H   S  E  D   S  E  R  R   S  G  S

                                                         5000
GCTTCCAGAA ACCATCGTGG ATCTGCTCAG GAGCAGTCAA GAGATGGCTC
CGAAGGTCTT TGGTAGCACC TAGACGAGTC CTCGTCAGTT CTCTACCGAG
 A  S  R   N  H  R  G   S  A  Q   E  Q  S   R  D  G  S

                                                         5050
CAGACACCCC AGGTCCCATC ACGAAGACAG AGCCGGTCAT GGGCACTCTG
GTCTGTGGGG TCCAGGGTAG TGCTTCTGTC TCGGCCAGTA CCCGTGAGAC
  R  H  P   R  S  H   H  E  D  R   A  G  H   G  H  S

                                                         5100
CAGACAGCTC CAGACAATCA GGCACTCATC ATGCAGAGAA TTCCTCTGGT
GTCTGTCGAG GTCTGTTAGT CCGTGAGTAG TACGTCTCTT AAGGAGACCA
A  D  S  S   R  Q  S   G  T  H   H  A  E  N   S  S  G

          *                                              5150
GGACAGCCTG CATCATCCCA TGAACAGGCA AGATCAAGTG CAGGAGAGAG
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 G  Q  P   A  S  S  H   E  Q  A   R  S  S   A  G  E  R

                                                         5200
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  H  G  S   H  H  Q   Q  S  A  D   S  S  R   H  S  G

                                                         5250
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I  G  H  G   Q  A  S   S  A  V   R  D  S  G   H  R  G

                                                         5300
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 S  S  G   S  Q  A  S   D  S  E   G  H  S   E  D  S  D
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  T  Q  S   V  S  A   H  G  Q  A   G  P  H   Q  Q  S

                                                                    5400
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H  Q  E  S   T  R  G   R  S  A   G  R  S  G   R  S  G

                                                Repeat 11           5450
TCTTTCCTCT ACCAGGTGAG CACTCATGAA CAGTCTGAGT CTGCCCATGG
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 S  F  L   Y  Q  V  S   T  H  E   Q  S  E   S  A  H  G
Repeat 11 (partial)
                                                                    5500
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TGCCCGACCC GGGTCATGAC CTCCTTCTGT TCCTAGGGTG GTGCTCGTCC
  R  A  G   P  S  T   G  G  R  Q   G  S  H   H  E  Q

                                                                    5550
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A  R  D  S   S  R  H   S  A  S   Q  E  G  Q   D  T  I

                                                                    5600
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 R  G  H   P  G  S  R   R  G  G   R  Q  G   S  Y  H  E

                                                                    5650
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                                                                    5700
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T  S  Q  G   R  S  D   A  S  H   G  Q  S  G   S  R  S

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                                                                    5800
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  S  G  S   R  H  H   E  A  S  T   Q  A  D   S  S  R

                                                                    5850
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H  S  Q  S   G  Q  G   E  S  A   G  S  R  R   S  R  R


                                                                    5900
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 Q  G  S   S  V  S  Q   D  S  D   S  E  A   Y  P  E  D
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  S  E  R   R  S  E   S  A  S  R   N  H  H   G  S  S

                                                                  6000
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R  E  Q  S   R  D  G   S  R  H   P  G  S  S   H  R  D

                                                                  6050
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                                                                  6100
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                                                                  6150
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S  G  I  Q   S  R  G   S  P  H   S  S  S  S   Y  H  Y

                                                                  6200
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 Q  S  E   G  T  E  R   Q  K  G   Q  S  G   L  V  W  R

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McLean , Irwin
smith, Frances J D

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filaggrin Sequence listing.ST25

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filaggrin Sequence listing.ST25

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filaggrin Sequence listing.ST25

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<210> 547
<211> 975
<212> DNA
<213> Human Profilaggrin Repeat 1

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<210> 548
<211> 325

filaggrin Sequence listing.ST25

<212> PRT

<213> Human Profilaggrin Repeat 1

<400> 548

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Gly Ser His His Glu Gln Ala Arg Asp Ser Ser Arg His Ser Ala Ser
            20                  25                  30

Gln Glu Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser Arg Gly
        35                  40                  45

Gly Arg Gln Gly Ser His His Glu Gln Ser Val Asn Arg Ser Gly His
    50                  55                  60

Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp Ala
65                  70                  75                  80

Ser His Gly Gln Ser Gly Ser Arg Ser Ala Ser Arg Gln Thr Arg Asn
                85                  90                  95

Glu Glu Gln Ser Gly Asp Gly Thr Arg His Ser Gly Ser Arg His His
            100                 105                 110

Glu Ala Ser Ser Gln Ala Asp Ser Ser Arg His Ser Gln Val Gly Gln
        115                 120                 125

Gly Gln Ser Ser Gly Pro Arg Thr Ser Arg Asn Gln Gly Ser Ser Val
    130                 135                 140

Ser Gln Asp Ser Asp Ser Gln Gly His Ser Glu Asp Ser Glu Arg Trp
145                 150                 155                 160

Ser Gly Ser Ala Ser Arg Asn His His Gly Ser Ala Gln Glu Gln Ser
                165                 170                 175

Arg Asp Gly Ser Arg His Pro Arg Ser His His Glu Asp Arg Ala Gly
            180                 185                 190

His Gly His Ser Ala Asp Ser Ser Arg Lys Ser Gly Thr Arg His Thr
        195                 200                 205

Gln Asn Ser Ser Ser Gly Gln Ala Ala Ser Ser His Glu Gln Ala Arg
    210                 215                 220

Ser Ser Ala Gly Glu Arg His Gly Ser Arg His Gln Leu Gln Ser Ala
225                 230                 235                 240
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Asp Ser Ser Arg His Ser Gly Thr Gly His Gly Gln Ala Ser Ser Ala
245 250 255

Val Arg Asp Ser Gly His Arg Gly Ser Ser Gly Ser Gln Ala Thr Asp
260 265 270

Ser Glu Gly His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Gly His
275 280 285

Gly Gln Ala Gly His His Gln Gln Ser His Gln Glu Ser Ala Arg Asp
290 295 300

Arg Ser Gly Glu Arg Ser Arg Arg Ser Gly Ser Phe Leu Tyr Gln Val
305 310 315 320

Ser Thr His Lys Gln
325

<210> 549

<211> 971

<212> DNA

<213> Human Profilaggrin Repeat 1 - 2282del4

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ggacacccgg ggtcaagcag aggaggaagg cagggatccc accacgagca atcggtaaat 180

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tcccatgggc agtcaggatc cagaagtgca agcagacaaa cacgaaatga ggaacaatca 300

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agaaaatcag gcactcgtca cacacagaat tcctctagtg gacaggctgc gtcatcccat 660

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gacacacagt gtcaggccat ggacaggctg gtcaccatca gcagagccac caagagtccg 900

cacgtgaccg gtcaggggaa aggtctcgac gttcagggtc tttcctctac caggtgagca 960

ctcataaaca g 971

filaggrin Sequence listing.ST25

<210> 550

<211> 323

<212> PRT

<213> Human Profilaggrin Repeat 1 - 2282del4

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<222> (319)..()

<223> X = STOP

<220>

<221> MISC_FEATURE

<222> (1)..(323)

<223> X = STOP

<400> 550

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1               5                  10                  15

Gly Ser His His Glu Gln Ala Arg Asp Ser Ser Arg His Ser Ala Ser
            20                  25                  30

Gln Glu Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser Arg Gly
        35                  40                  45

Gly Arg Gln Gly Ser His His Glu Gln Ser Val Asn Arg Ser Gly His
    50                  55                  60

Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp Ala
65                  70                  75                  80

Ser His Gly Gln Ser Gly Ser Arg Ser Ala Ser Arg Gln Thr Arg Asn
                85                  90                  95

Glu Glu Gln Ser Gly Asp Gly Thr Arg His Ser Gly Ser Arg His His
            100                 105                 110

Glu Ala Ser Ser Gln Ala Asp Ser Ser Arg His Ser Gln Val Gly Gln
        115                 120                 125

Gly Gln Ser Ser Gly Pro Arg Thr Ser Arg Asn Gln Gly Ser Ser Val
    130                 135                 140
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Ser Gln Asp Ser Asp Ser Gln Gly His Ser Glu Asp Ser Glu Arg Trp
145 150 155 160

Ser Gly Ser Ala Ser Arg Asn His His Gly Ser Ala Gln Glu Gln Ser
165 170 175

Arg Asp Gly Ser Arg His Pro Arg Ser His His Glu Asp Arg Ala Gly
180 185 190

His Gly His Ser Ala Asp Ser Ser Arg Lys Ser Gly Thr Arg His Thr
195 200 205

Gln Asn Ser Ser Ser Gly Gln Ala Ala Ser Ser His Glu Gln Ala Arg
210 215 220

Ser Ser Ala Gly Glu Arg His Gly Ser Arg His Gln Leu Gln Ser Ala
225 230 235 240

Asp Ser Ser Arg His Ser Gly Thr Gly His Gly Gln Ala Ser Ser Ala
245 250 255

Val Arg Asp Ser Gly His Arg Gly Ser Ser Gly Ser Gln Ala Thr Asp
260 265 270

Ser Glu Gly His Ser Glu Asp Ser Asp Thr Gln Cys Gln Ala Met Asp
275 280 285

Arg Leu Val Thr Ile Ser Arg Ala Thr Lys Ser Pro His Val Thr Gly
290 295 300

Gln Gly Lys Gly Leu Asp Val Gln Gly Leu Ser Ser Thr Arg Xaa Ala
305 310 315 320

Leu Ile Asn

<210> 551

<211> 975

<212> DNA

<213> Human Profilaggrin repeat 1 - R501X C>T

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ggacacccgg ggtcaagcag aggaggaagg cagggatccc accacgagca atcggtaaat 180

aggtctggac actcaggttc ccatcacagc cacaccacat cccagggaag gtctgatgcc 240

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agacacccca ggtcccatca cgaagacaga gctggtcatg ggcactctgc agacagctcc 600

agaaaatcag gcactcgtca cacacagaat tcctctagtg gacaggctgc gtcatcccat 660

gaacaggcaa gatcaagtgc aggagaaaga catggatccc gccaccagct ccagtcagca 720

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tccgcacgtg accggtcagg ggaaaggtct cgacgttcag ggtctttcct ctaccaggtg 960

agcactcata aacag 975

<210> 552

<211> 325

<212> PRT

<213> Human Profilaggrin Repeat 1 R501X C>T

<220>

<221> MISC_FEATURE

<222> (1)..(325)

<223> X = STOP

<400> 552

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Gly Ser His His Glu Gln Ala Xaa Asp Ser Ser Arg His Ser Ala Ser
20 25 30

Gln Glu Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser Arg Gly
35 40 45

Gly Arg Gln Gly Ser His His Glu Gln Ser Val Asn Arg Ser Gly His
50 55 60

Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp Ala
65 70 75 80

Ser His Gly Gln Ser Gly Ser Arg Ser Ala Ser Arg Gln Thr Arg Asn
85 90 95

Glu Glu Gln Ser Gly Asp Gly Thr Arg His Ser Gly Ser Arg His His
100 105 110

Glu Ala Ser Ser Gln Ala Asp Ser Ser Arg His Ser Gln Val Gly Gln
115 120 125

Gly Gln Ser Ser Gly Pro Arg Thr Ser Arg Asn Gln Gly Ser Ser Val
130 135 140

Ser Gln Asp Ser Asp Ser Gln Gly His Ser Glu Asp Ser Glu Arg Trp
145 150 155 160

Ser Gly Ser Ala Ser Arg Asn His His Gly Ser Ala Gln Glu Gln Ser
165 170 175

Arg Asp Gly Ser Arg His Pro Arg Ser His His Glu Asp Arg Ala Gly
180 185 190

His Gly His Ser Ala Asp Ser Ser Arg Lys Ser Gly Thr Arg His Thr
195 200 205

Gln Asn Ser Ser Ser Gly Gln Ala Ala Ser Ser His Glu Gln Ala Arg
210 215 220

Ser Ser Ala Gly Glu Arg His Gly Ser Arg His Gln Leu Gln Ser Ala
225 230 235 240

Asp Ser Ser Arg His Ser Gly Thr Gly His Gly Gln Ala Ser Ser Ala
245 250 255

Val Arg Asp Ser Gly His Arg Gly Ser Ser Gly Ser Gln Ala Thr Asp
260 265 270

Ser Glu Gly His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Gly His
275 280 285

Gly Gln Ala Gly His His Gln Gln Ser His Gln Glu Ser Ala Arg Asp
290 295 300

Arg Ser Gly Glu Arg Ser Arg Arg Ser Gly Ser Phe Leu Tyr Gln Val
305 310 315 320

Ser Thr His Lys Gln
325

<210> 553

filaggrin Sequence listing.ST25

<211> 5251

<212> DNA

<213> Homo sapiens

<400> 553

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cagctaagag atggctccag acaccccagg tcccatcaag aagacagagc tggtcatggg 180

cactctgcag acagctccag acaatcaggc actcgtcaca cacagacttc ctctggtgga 240

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gcagtcagag acagtggaca ccgagggtac agtggtagtc aggccagtga caatgaggga 420

cattcagaag actcagacac acagtcagtg tcagcccacg gacaggctgg gtcccatcag 480

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<400> 554

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Asn His His Gly Ser Ala Gln Glu Gln Leu Arg Asp Gly Ser Arg His
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Pro Arg Ser His Gln Glu Asp Arg Ala Gly His Gly His Ser Ala Asp
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Ser Ser Arg Gln Ser Gly Thr Arg His Thr Gln Thr Ser Ser Gly Gly
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Gln Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser Ala Gly Glu Arg
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His Gly Ser His His Gln Gln Ser Ala Asp Ser Ser Arg His Ser Gly
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Ile Gly His Gly Gln Ala Ser Ser Ala Val Arg Asp Ser Gly His Arg
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Gly Tyr Ser Gly Ser Gln Ala Ser Asp Asn Glu Gly His Ser Glu Asp
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Ser Asp Thr Gln Ser Val Ser Ala His Gly Gln Ala Gly Ser His Gln
145 150 155 160

Gln Ser His Gln Glu Ser Ala Arg Gly Arg Ser Gly Glu Thr Ser Gly
165 170 175

His Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His Glu Gln Ser Glu
180 185 190

Ser Ser His Gly Trp Thr Gly Pro Ser Thr Arg Gly Arg Gln Gly Ser
195 200 205

Arg His Glu Gln Ala Gln Asp Ser Ser Arg His Ser Ala Ser Gln Asp
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Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser Arg Gly Gly Arg
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Gln Gly Tyr His His Glu His Ser Val Asp Ser Ser Gly His Ser Gly
245 250 255

Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp Ala Ser Arg
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Gly Gln Ser Gly Ser Arg Arg Ala Ser Arg Thr Thr Arg Asn Glu Glu
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Gln Ser Gly Asp Gly Ser Arg His Ser Gly Ser Arg His His Glu Ala
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Ser Thr His Ala Asp Ile Ser Arg His Ser Gln Ala Val Gln Gly Gln
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Ser Glu Gly Ser Arg Arg Ser Arg Arg Gln Gly Ser Ser Val Ser Gln
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Asp Ser Asp Ser Glu Gly His Ser Glu Asp Ser Glu Arg Trp Ser Gly
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Ser Ala Ser Arg Asn His His Gly Ser Ala Gln Glu Gln Leu Arg Asp
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Gly Ser Arg His Pro Arg Ser His Gln Glu Gly Arg Ala Gly His Gly
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His Ser Ala Asp Ser Ser Arg Gln Ser Gly Thr Arg His Thr Gln Thr
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Ser Ser Gly Gly Gln Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser
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Ala Gly Glu Arg His Gly Ser His His Gln Gln Ser Ala Asp Ser Ser
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Arg His Ser Gly Ile Gly His Gly Gln Ala Ser Ser Ala Val Arg Asp
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Ser Gly His Arg Gly Tyr Ser Gly Ser Gln Ala Ser Asp Asn Glu Gly
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His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Ala His Gly Gln Ala
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Gly Ser His Gln Gln Ser His Gln Glu Ser Ala Arg Gly Arg Ser Gly
485 490 495

Glu Thr Ser Gly His Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His
500 505 510

Glu Gln Ser Glu Ser Ser His Gly Trp Thr Gly Pro Ser Thr Arg Gly
515 520 525

Arg Gln Gly Ser Arg His Glu Gln Ala Gln Asp Ser Ser Arg His Ser
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Ala Ser Gln Asp Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser
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Arg Gly Gly Arg Gln Gly Tyr His His Glu His Ser Val Asp Ser Ser
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Asp Ala Ser Arg Gly Gln Ser Gly Ser Arg Ser Ala Ser Arg Thr Thr
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Arg Asn Glu Glu Gln Ser Gly Asp Gly Ser Arg His Ser Gly Ser Arg
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His His Glu Ala Ser Thr His Ala Asp Ile Ser Arg His Ser Gln Ala
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Val Gln Gly Gln Ser Glu Gly Ser Arg Arg Ser Arg Arg Gln Gly Ser
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Ser Val Ser Gln Asp Ser Asp Ser Glu Gly His Ser Glu Asp Ser Glu
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Arg Trp Ser Gly Ser Ala Ser Arg Asn His His Gly Ser Ala Gln Glu
675 680 685

Gln Leu Arg Asp Gly Ser Arg His Pro Arg Ser His Gln Glu Asp Arg
690 695 700

Ala Gly His Gly His Ser Ala Asp Ser Ser Arg Gln Ser Gly Thr Arg
705 710 715 720

His Thr Gln Ala Ser Ser Gly Gly Gln Ala Ala Ser Ser His Glu Gln
725 730 735

Ala Arg Ser Ser Ala Gly Glu Arg His Gly Ser His His Gln Gln Ser
740 745 750

Ala Asp Ser Ser Arg His Ser Gly Ile Gly His Gly Gln Ala Ser Ser
755 760 765

Ala Val Arg Asp Ser Gly His Arg Gly Tyr Ser Gly Ser Gln Ala Ser
770 775 780

Asp Asn Glu Gly His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Ala
785 790 795 800

His Gly Gln Ala Gly Ser His Gln Gln Ser His Gln Glu Ser Ala Arg
805 810 815

Gly Arg Ser Gly Glu Thr Ser Gly His Ser Gly Ser Phe Leu Tyr Gln
820 825 830

Val Ser Thr His Glu Gln Ser Glu Ser Ser His Gly Trp Thr Gly Pro
835 840 845

Ser Thr Arg Gly Arg Gln Gly Ser Arg His Glu Gln Ala Gln Asp Ser
850 855 860

Ser Arg His Ser Ala Ser Gln Asp Gly Gln Asp Thr Ile Arg Gly His
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Pro Gly Ser Ser Arg Gly Gly Arg Gln Gly Tyr His His Glu His Ser
885 890 895

Val Asp Ser Ser Gly His Ser Gly Ser His His Ser His Thr Thr Ser
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Gln Gly Arg Ser Asp Ala Ser Arg Gly Gln Ser Gly Ser Arg Ser Ala
915 920 925

Ser Arg Thr Thr Arg Asn Glu Glu Gln Ser Gly Asp Ser Ser Arg His
930 935 940

Ser Gly Ser Arg His His Glu Ala Ser Thr His Ala Asp Ile Ser Arg
945 950 955 960

His Ser Gln Ala Val Gln Gly Gln Ser Glu Gly Ser Arg Arg Ser Arg
965 970 975

Arg Gln Gly Ser Ser Val Ser Gln Asp Ser Asp Ser Glu Gly His Ser
980 985 990

Glu Asp Ser Glu Arg Trp Ser Gly Ser Ala Ser Arg Asn His Arg Gly
995 1000 1005

Ser Val Gln Glu Gln Ser Arg His Gly Ser Arg His Pro Arg Ser
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His His Glu Asp Arg Ala Gly His Gly His Ser Ala Asp Arg Ser
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Arg Gln Ser Gly Thr Arg His Ala Glu Thr Ser Ser Gly Gly Gln
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Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser Pro Gly Glu Arg
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His Gly Ser Arg His Gln Gln Ser Ala Asp Ser Ser Arg His Ser
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Gly Ile Pro Arg Gly Gln Ala Ser Ser Ala Val Arg Asp Ser Arg
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His Trp Gly Ser Ser Gly Ser Gln Ala Ser Asp Ser Glu Gly His
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Ser Glu Glu Ser Asp Thr Gln Ser Val Ser Gly His Gly Gln Ala
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Gly Pro His Gln Gln Ser His Gln Glu Ser Ala Arg Asp Arg Ser
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Gly Gly Arg Ser Gly Arg Ser Gly Ser Phe Leu Tyr Gln Val Ser
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Thr His Glu Gln Ser Glu Ser Ala His Gly Arg Thr Arg Thr Ser
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Thr Gly Arg Arg Gln Gly Ser His His Glu Gln Ala Arg Asp Ser
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Ser Arg His Ser Ala Ser Gln Glu Gly Gln Asp Thr Ile Arg Ala
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His Pro Gly Ser Ser Arg Arg Gly Arg Gln Gly Ser His Tyr Glu
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Gln Ser Val Asp Arg Ser Gly His Ser Gly Ser His His Ser His
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Thr Thr Ser Gln Gly Arg Ser Asp Ala Ser Arg Gly Gln Ser Gly
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Ser Arg Ser Ala Ser Arg Gln Thr Arg Asn Asp Glu Gln Ser Gly
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Asp Gly Ser Arg His Ser Trp Ser His His His Glu Ala Ser Thr
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Gln Ala Asp Ser Ser Arg His Ser Gln Ser Gly Gln Gly Gln Ser
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Ala Gly Pro Ser Thr Ser Arg Asn Gln Gly Ser Ser Val Ser Gln
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Asp Ser Asp Ser Gln Gly His Ser Glu Asp Ser Glu Arg Trp Ser
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Gly Ser Ala Ser Arg Asn His His Gly Ser Ala Gly Glu Gln Ser
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Arg Asp Gly Ser Arg His Pro Gly Ser His Gln Glu Asp Arg Ala
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His Thr Glu Ser Ser Ser Arg Gly Gln Ala Ala Ser Ser His Glu
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Leu Gln Ser Ala Asp Ser Ser Arg His Ala Gly Ile Gly His Gly
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Gln Ala Ser Ser Ala Val Arg Asp Ser Gly His Arg Gly Tyr Ser
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Gly Ser Gln Ala Thr Asp Ser Glu Gly His Ser Glu Asp Ser Asp
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Thr Gln Ser Val Ser Ala Gln Gly Lys Ala Gly Pro His Gln Gln
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Ser His Lys Glu Ser Ala Arg Gly Gln Ser Gly Glu Ser Ser Arg
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Arg Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His Glu Gln Ser
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Glu Ser Ala His Gly Arg Ala Gly Pro Ser Thr Gly Gly Arg Gln
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Gly Ser His His Glu Gln Ala Arg Asp Ser Ser Arg His Ser Ala
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Ser Gln Glu Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Arg
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Arg Gly Gly Arg Gln Gly Ser Tyr His Glu Gln Ser Val Asp Arg
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Ser Gly His Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly
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Arg Ser Asp Ala Ser His Gly Gln Ser Gly Ser Arg Ser Ala Ser
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Arg Glu Thr Arg Asn Glu Glu Gln Ser Gly Asp Gly Ser Arg His
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Ser Gly Ser Arg His His Glu Ala Ser Thr Gln Ala Asp Ser Ser
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Arg His Ser Gln Ser Gly Gln Gly Glu Ser Ala Gly Ser Arg Arg
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Ser Arg Arg Gln Gly Ser Ser Val Ser Gln Asp Ser Asp Ser Glu
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Ala Tyr Pro Glu Asp Ser Glu Arg Arg Ser Glu Ser Ala Ser Arg
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Asn His His Gly Ser Ser Arg Glu Gln Ser Arg Asp Gly Ser Arg
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His Pro Gly Ser Ser His Arg Asp Thr Ala Ser His Val Gln Ser
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Ser Pro Val Gln Ser Asp Ser Ser Thr Ala Lys Glu His Gly His
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Phe Ser Ser Leu Ser Gln Asp Ser Ala Tyr His Ser Gly Ile Gln
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Ser Arg Gly Ser Pro His Ser Ser Ser Ser Tyr His Tyr Gln Ser
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<213> Homo sapiens

<400> 556

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Asn His His Gly Ser Ala Gln Glu Gln Leu Arg Asp Gly Ser Arg His
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Pro Arg Ser His Gln Glu Asp Arg Ala Gly His Gly His Ser Ala Asp
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Ser Ser Arg Gln Ser Gly Thr Arg His Thr Gln Thr Ser Ser Gly Gly
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Gln Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser Ala Gly Glu Arg
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His Gly Ser His His Gln Gln Ser Ala Asp Ser Ser Arg His Ser Gly
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Ile Gly His Gly Gln Ala Ser Ser Ala Val Arg Asp Ser Gly His Arg
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Gly Tyr Ser Gly Ser Gln Ala Ser Asp Asn Glu Gly His Ser Glu Asp
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Ser Asp Thr Gln Ser Val Ser Ala His Gly Gln Ala Gly Ser His Gln
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Gln Ser His Gln Glu Ser Ala Arg Gly Arg Ser Gly Glu Thr Ser Gly
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His Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His Glu Gln Ser Glu
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Ser Ser His Gly Trp Thr Gly Pro Ser Thr Arg Gly Arg Gln Gly Ser
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Arg His Glu Gln Ala Gln Asp Ser Ser Arg His Ser Ala Ser Gln Asp
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Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser Arg Gly Gly Arg
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Gln Gly Tyr His His Glu His Ser Val Asp Ser Ser Gly His Ser Gly
245 250 255

Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp Ala Ser Arg
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Gly Gln Ser Gly Ser Arg Arg Ala Ser Arg Thr Thr Arg Asn Glu Glu
275 280 285

Gln Ser Gly Asp Gly Ser Arg His Ser Gly Ser Arg His His Glu Ala
290 295 300

Ser Thr His Ala Asp Ile Ser Arg His Ser Gln Ala Val Gln Gly Gln
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Ser Glu Gly Ser Arg Arg Ser Arg Arg Gln Gly Ser Ser Val Ser Gln
325 330 335

Asp Ser Asp Ser Glu Gly His Ser Glu Asp Ser Glu Arg Trp Ser Gly
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Ser Ala Ser Arg Asn His His Gly Ser Ala Gln Glu Gln Leu Arg Asp
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Gly Ser Arg His Pro Arg Ser His Gln Glu Gly Arg Ala Gly His Gly
370 375 380

His Ser Ala Asp Ser Ser Arg Gln Ser Gly Thr Arg His Thr Gln Thr
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Ser Ser Gly Gly Gln Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser
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Ala Gly Glu Arg His Gly Ser His His Gln Gln Ser Ala Asp Ser Ser
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Arg His Ser Gly Ile Gly His Gly Gln Ala Ser Ser Ala Val Arg Asp
435 440 445

Ser Gly His Arg Gly Tyr Ser Gly Ser Gln Ala Ser Asp Asn Glu Gly
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His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Ala His Gly Gln Ala
465 470 475 480

Gly Ser His Gln Gln Ser His Gln Glu Ser Ala Arg Gly Arg Ser Gly
485 490 495

Glu Thr Ser Gly His Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His
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Glu Gln Ser Glu Ser Ser His Gly Trp Thr Gly Pro Ser Thr Arg Gly
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Arg Gln Gly Ser Arg His Glu Gln Ala Gln Asp Ser Ser Arg His Ser
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Ala Ser Gln Asp Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser
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Arg Gly Gly Arg Gln Gly Tyr His His Glu His Ser Val Asp Ser Ser
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Gly His Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser
580 585 590

Asp Ala Ser Arg Gly Gln Ser Gly Ser Arg Ser Ala Ser Arg Thr Thr
595 600 605

Arg Asn Glu Glu Gln Ser Gly Asp Ser Ser Arg His Ser Gly Ser Arg
610 615 620

His His Glu Ala Ser Thr His Ala Asp Ile Ser Arg His Ser Gln Ala
625 630 635 640

Val Gln Gly Gln Ser Glu Gly Ser Arg Arg Ser Arg Arg Gln Gly Ser
645 650 655

Ser Val Ser Gln Asp Ser Asp Ser Glu Gly His Ser Glu Asp Ser Glu
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Arg Trp Ser Gly Ser Ala Ser Arg Asn His Arg Gly Ser Val Gln Glu
675 680 685

Gln Ser Arg His Gly Ser Arg His Pro Arg Ser His His Glu Asp Arg
690 695 700

Ala Gly His Gly His Ser Ala Asp Arg Ser Arg Gln Ser Gly Thr Arg
705 710 715 720

His Ala Glu Thr Ser Ser Gly Gly Gln Ala Ala Ser Ser His Glu Gln
725 730 735

Ala Arg Ser Ser Pro Gly Glu Arg His Gly Ser Arg His Gln Gln Ser
740 745 750

Ala Asp Ser Ser Arg His Ser Gly Ile Pro Arg Gly Gln Ala Ser Ser
755 760 765

Ala Val Arg Asp Ser Arg His Trp Gly Ser Ser Gly Ser Gln Ala Ser
770 775 780

Asp Ser Glu Gly His Ser Glu Glu Ser Asp Thr Gln Ser Val Ser Gly
785 790 795 800

His Gly Gln Ala Gly Pro His Gln Gln Ser His Gln Glu Ser Ala Arg
805 810 815

Asp Arg Ser Gly Gly Arg Ser Gly Arg Ser Gly Ser Phe Leu Tyr Gln
820 825 830

Val Ser Thr His Glu Gln Ser Glu Ser Ala His Gly Arg Thr Arg Thr
835 840 845

Ser Thr Gly Arg Arg Gln Gly Ser His His Glu Gln Ala Arg Asp Ser
850 855 860

Ser Arg His Ser Ala Ser Gln Glu Gly Gln Asp Thr Ile Arg Ala His
865 870 875 880

Pro Gly Ser Ser Arg Arg Gly Arg Gln Gly Ser His Tyr Glu Gln Ser
885 890 895

Val Asp Arg Ser Gly His Ser Gly Ser His His Ser His Thr Thr Ser
900 905 910

Gln Gly Arg Ser Asp Ala Ser Arg Gly Gln Ser Gly Ser Arg Ser Ala
915 920 925

Ser Arg Gln Thr Arg Asn Asp Glu Gln Ser Gly Asp Gly Ser Arg His
930 935 940

Ser Trp Ser His His His Glu Ala Ser Thr Gln Ala Asp Ser Ser Arg
945 950 955 960

His Ser Gln Ser Gly Gln Gly Gln Ser Ala Gly Pro Ser Thr Ser Arg
965 970 975

Asn Gln Gly Ser Ser Val Ser Gln Asp Ser Asp Ser Gln Gly His Ser
980 985 990

Glu Asp Ser Glu Arg Trp Ser Gly Ser Ala Ser Arg Asn His His Gly
995 1000 1005

Ser Ala Gly Glu Gln Ser Arg Asp Gly Ser Arg His Pro Gly Ser
1010 1015 1020

His Gln Glu Asp Arg Ala Gly His Gly His Ser Ala Asp Ser Pro
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Arg Gln Ser Gly Thr Arg His Thr Glu Ser Ser Ser Arg Gly Gln
1040 1045 1050

Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser Ala Gly Glu Arg
1055 1060 1065

His Gly Ser His His Gln Leu Gln Ser Ala Asp Ser Ser Arg His
1070 1075 1080

Ala Gly Ile Gly His Gly Gln Ala Ser Ser Ala Val Arg Asp Ser
1085 1090 1095

Gly His Arg Gly Tyr Ser Gly Ser Gln Ala Thr Asp Ser Glu Gly
1100 1105 1110

His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Ala Gln Gly Lys
1115 1120 1125

Ala Gly Pro His Gln Gln Ser His Lys Glu Ser Ala Arg Gly Gln
1130 1135 1140

Ser Gly Glu Ser Ser Arg Arg Ser Gly Ser Phe Leu Tyr Gln Val
1145 1150 1155

Ser Thr His Glu Gln Ser Glu Ser Thr His Gly Gln Ser Val Pro
1160 1165 1170

Ser Thr Gly Gly Arg Gln Gly Ser His His Asp Gln Ala Gln Asp
1175 1180 1185

Ser Ser Arg His Ser Ala Ser Gln Glu Gly Gln Asp Thr Ile Arg
1190 1195 1200

Gly His Pro Gly Pro Ser Arg Gly Gly Arg Gln Gly Ser His His
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Glu Gln Ser Val Asp Arg Ser Gly His Ser Gly Ser His His Ser
1220 1225 1230

His Thr Thr Ser Gln Gly Arg Ser Asp Ala Ser Arg Gly Gln Ser
1235 1240 1245

Gly Pro Arg Ser Ala Ser Arg Gln Thr His Asp Lys Glu Gln Ser
1250 1255 1260

Gly Asp Gly Ser Arg His Ser Gly Ser Arg His His Glu Ala Ser
1265 1270 1275

Ser Trp Ala Asp Ser Ser Arg His Ser Gln Ala Val Gln Gly Gln
1280 1285 1290

Ser Glu Gly Ser Arg Arg Ser Arg Arg Gln Gly Ser Ser Val Ser
1295 1300 1305

Gln Asp Ser Asp Ser Gln Gly His Ser Glu Asp Ser Glu Arg Arg
1310 1315 1320

Ser Gly Ser Ala Ser Arg Asn His Arg Gly Ser Ala Gln Glu Gln
1325 1330 1335

Ser Arg Asp Gly Ser Arg His Pro Arg Ser His His Glu Asp Arg
1340 1345 1350

Ala Gly His Gly His Ser Ala Asp Ser Ser Arg Gln Ser Gly Thr
1355 1360 1365

His His Ala Glu Asn Ser Ser Gly Gly Gln Pro Ala Ser Ser His
1370 1375 1380

Glu Gln Ala Arg Ser Ser Ala Gly Glu Arg His Gly Ser His His
1385 1390 1395

Gln Gln Ser Ala Asp Ser Ser Arg His Ser Gly Ile Gly His Gly
1400 1405 1410

Gln Ala Ser Ser Ala Val Arg Asp Ser Gly His Arg Gly Ser Ser
1415 1420 1425

Gly Ser Gln Ala Ser Asp Ser Glu Gly His Ser Glu Asp Ser Asp
1430 1435 1440

Thr Gln Ser Val Ser Ala His Gly Gln Ala Gly Pro His Gln Gln
1445 1450 1455

Ser His Gln Glu Ser Thr Arg Gly Arg Ser Ala Gly Arg Ser Gly
1460 1465 1470

Arg Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His Glu Gln Ser
1475 1480 1485

Glu Ser Ala His Gly Arg Ala Gly Pro Ser Thr Gly Gly Arg Gln
1490 1495 1500

Gly Ser His His Glu Gln Ala Arg Asp Ser Ser Arg His Ser Ala
1505 1510 1515

Ser Gln Glu Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Arg
1520 1525 1530

Arg Gly Gly Arg Gln Gly Ser Tyr His Glu Gln Ser Val Asp Arg
1535 1540 1545

Ser Gly His Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly
1550 1555 1560

Arg Ser Asp Ala Ser His Gly Gln Ser Gly Ser Arg Ser Ala Ser
1565 1570 1575

Arg Glu Thr Arg Asn Glu Glu Gln Ser Gly Asp Gly Ser Arg His
1580 1585 1590

Ser Gly Ser Arg His His Glu Ala Ser Thr Gln Ala Asp Ser Ser
1595 1600 1605

Arg His Ser Gln Ser Gly Gln Gly Glu Ser Ala Gly Ser Arg Arg
1610 1615 1620

Ser Arg Arg Gln Gly Ser Ser Val Ser Gln Asp Ser Asp Ser Glu
1625 1630 1635

Ala Tyr Pro Glu Asp Ser Glu Arg Arg Ser Glu Ser Ala Ser Arg
1640 1645 1650

Asn His His Gly Ser Ser Arg Glu Gln Ser Arg Asp Gly Ser Arg
1655 1660 1665

His Pro Gly Ser Ser His Arg Asp Thr Ala Ser His Val Gln Ser
1670 1675 1680

Ser Pro Val Gln Ser Asp Ser Ser Thr Ala Lys Glu His Gly His
1685 1690 1695

Phe Ser Ser Leu Ser Gln Asp Ser Ala Tyr His Ser Gly Ile Gln
1700 1705 1710

Ser Arg Gly Ser Pro His Ser Ser Ser Ser Tyr His Tyr Gln Ser
1715 1720 1725

filaggrin Sequence listing.ST25

Glu Gly Thr Glu Arg Gln Lys Gly Gln Ser Gly Leu Val Trp Arg
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His Gly Ser Tyr Gly Ser Ala
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<211> 6173

<212> DNA

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gcagtcagag acagtggaca ccgagggtac agtggtagtc aggccagtga caatgaggga 420

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<211> 2074

<212> PRT

<213> Homo sapiens

<400> 558

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Asn His His Gly Ser Ala Gln Glu Gln Leu Arg Asp Gly Ser Arg His
35 40 45

Pro Arg Ser His Gln Glu Asp Arg Ala Gly His Gly His Ser Ala Asp
50 55 60

Ser Ser Arg Gln Ser Gly Thr Arg His Thr Gln Thr Ser Ser Gly Gly
65 70 75 80

Gln Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser Ala Gly Glu Arg
85 90 95

His Gly Ser His His Gln Gln Ser Ala Asp Ser Ser Arg His Ser Gly
100 105 110

Ile Gly His Gly Gln Ala Ser Ser Ala Val Arg Asp Ser Gly His Arg
115 120 125

Gly Tyr Ser Gly Ser Gln Ala Ser Asp Asn Glu Gly His Ser Glu Asp
130 135 140

Ser Asp Thr Gln Ser Val Ser Ala His Gly Gln Ala Gly Ser His Gln
145 150 155 160

Gln Ser His Gln Glu Ser Ala Arg Gly Arg Ser Gly Glu Thr Ser Gly
165 170 175

His Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His Glu Gln Ser Glu
180 185 190

Ser Ser His Gly Trp Thr Gly Pro Ser Thr Arg Gly Arg Gln Gly Ser
195 200 205

Arg His Glu Gln Ala Gln Asp Ser Ser Arg His Ser Ala Ser Gln Asp
210 215 220

Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser Arg Gly Gly Arg
225 230 235 240

Gln Gly Tyr His His Glu His Ser Val Asp Ser Ser Gly His Ser Gly
245 250 255

Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp Ala Ser Arg
260 265 270

Gly Gln Ser Gly Ser Arg Arg Ala Ser Arg Thr Thr Arg Asn Glu Glu
275 280 285

Gln Ser Gly Asp Gly Ser Arg His Ser Gly Ser Arg His His Glu Ala
290 295 300

Ser Thr His Ala Asp Ile Ser Arg His Ser Gln Ala Val Gln Gly Gln
305 310 315 320

Ser Glu Gly Ser Arg Arg Ser Arg Arg Gln Gly Ser Ser Val Ser Gln
325 330 335

Asp Ser Asp Ser Glu Gly His Ser Glu Asp Ser Glu Arg Trp Ser Gly
340 345 350

Ser Ala Ser Arg Asn His His Gly Ser Ala Gln Glu Gln Leu Arg Asp
355 360 365

Gly Ser Arg His Pro Arg Ser His Gln Glu Gly Arg Ala Gly His Gly
370 375 380

His Ser Ala Asp Ser Ser Arg Gln Ser Gly Thr Arg His Thr Gln Thr
385 390 395 400

Ser Ser Gly Gly Gln Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser
405 410 415

Ala Gly Glu Arg His Gly Ser His His Gln Gln Ser Ala Asp Ser Ser
420 425 430

Arg His Ser Gly Ile Gly His Gly Gln Ala Ser Ser Ala Val Arg Asp
435 440 445

Ser Gly His Arg Gly Tyr Ser Gly Ser Gln Ala Ser Asp Asn Glu Gly
450 455 460

His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Ala His Gly Gln Ala
465 470 475 480

Gly Ser His Gln Gln Ser His Gln Glu Ser Ala Arg Gly Arg Ser Gly
485 490 495

Glu Thr Ser Gly His Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His
500 505 510

Glu Gln Ser Glu Ser Ser His Gly Trp Thr Gly Pro Ser Thr Arg Gly
515 520 525

Arg Gln Gly Ser Arg His Glu Gln Ala Gln Asp Ser Ser Arg His Ser
530 535 540

Ala Ser Gln Asp Gly Gln Asp Thr Ile Arg Gly His Pro Gly Ser Ser
545 550 555 560

Arg Gly Gly Arg Gln Gly Tyr His His Glu His Ser Val Asp Ser Ser
565 570 575

Gly His Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly Arg Ser
580 585 590

Asp Ala Ser Arg Gly Gln Ser Gly Ser Arg Ser Ala Ser Arg Thr Thr
595 600 605

Arg Asn Glu Glu Gln Ser Gly Asp Gly Ser Arg His Ser Gly Ser Arg
610 615 620

His His Glu Ala Ser Thr His Ala Asp Ile Ser Arg His Ser Gln Ala
625 630 635 640

Val Gln Gly Gln Ser Glu Gly Ser Arg Arg Ser Arg Arg Gln Gly Ser
645 650 655

Ser Val Ser Gln Asp Ser Asp Ser Glu Gly His Ser Glu Asp Ser Glu
660 665 670

Arg Trp Ser Gly Ser Ala Ser Arg Asn His His Gly Ser Ala Gln Glu
675 680 685

Gln Leu Arg Asp Gly Ser Arg His Pro Arg Ser His Gln Glu Asp Arg
690 695 700

Ala Gly His Gly His Ser Ala Asp Ser Ser Arg Gln Ser Gly Thr Arg
705 710 715 720

His Thr Gln Ala Ser Ser Gly Gly Gln Ala Ala Ser Ser His Glu Gln
725 730 735

Ala Arg Ser Ser Ala Gly Glu Arg His Gly Ser His His Gln Gln Ser
740 745 750

Ala Asp Ser Ser Arg His Ser Gly Ile Gly His Gly Gln Ala Ser Ser
755 760 765

Ala Val Arg Asp Ser Gly His Arg Gly Tyr Ser Gly Ser Gln Ala Ser
770 775 780

Asp Asn Glu Gly His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Ala
785 790 795 800

His Gly Gln Ala Gly Ser His Gln Gln Ser His Gln Glu Ser Ala Arg
805 810 815

Gly Arg Ser Gly Glu Thr Ser Gly His Ser Gly Ser Phe Leu Tyr Gln
820 825 830

Val Ser Thr His Glu Gln Ser Glu Ser Ser His Gly Trp Thr Gly Pro
835 840 845

Ser Thr Arg Gly Arg Gln Gly Ser Arg His Glu Gln Ala Gln Asp Ser
850 855 860

Ser Arg His Ser Ala Ser Gln Asp Gly Gln Asp Thr Ile Arg Gly His
865 870 875 880

Pro Gly Ser Ser Arg Gly Gly Arg Gln Gly Tyr His His Glu His Ser
885 890 895

Val Asp Ser Ser Gly His Ser Gly Ser His His Ser His Thr Thr Ser
900 905 910

Gln Gly Arg Ser Asp Ala Ser Arg Gly Gln Ser Gly Ser Arg Ser Ala
915 920 925

Ser Arg Thr Thr Arg Asn Glu Glu Gln Ser Gly Asp Ser Ser Arg His
930 935 940

Ser Gly Ser Arg His His Glu Ala Ser Thr His Ala Asp Ile Ser Arg
945 950 955 960

His Ser Gln Ala Val Gln Gly Gln Ser Glu Gly Ser Arg Arg Ser Arg
965 970 975

Arg Gln Gly Ser Ser Val Ser Gln Asp Ser Asp Ser Glu Gly His Ser
980 985 990

Glu Asp Ser Glu Arg Trp Ser Gly Ser Ala Ser Arg Asn His Arg Gly
995 1000 1005

Ser Val Gln Glu Gln Ser Arg His Gly Ser Arg His Pro Arg Ser
1010 1015 1020

His His Glu Asp Arg Ala Gly His Gly His Ser Ala Asp Arg Ser
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Arg Gln Ser Gly Thr Arg His Ala Glu Thr Ser Ser Gly Gly Gln
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Ala Ala Ser Ser His Glu Gln Ala Arg Ser Ser Pro Gly Glu Arg
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His Gly Ser Arg His Gln Gln Ser Ala Asp Ser Ser Arg His Ser
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Gly Ile Pro Arg Gly Gln Ala Ser Ser Ala Val Arg Asp Ser Arg
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His Trp Gly Ser Ser Gly Ser Gln Ala Ser Asp Ser Glu Gly His
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Gly Pro His Gln Gln Ser His Gln Glu Ser Ala Arg Asp Arg Ser
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Gly Gly Arg Ser Gly Arg Ser Gly Ser Phe Leu Tyr Gln Val Ser
1145 1150 1155

Thr His Glu Gln Ser Glu Ser Ala His Gly Arg Thr Arg Thr Ser
1160 1165 1170

Thr Gly Arg Arg Gln Gly Ser His His Glu Gln Ala Arg Asp Ser
1175 1180 1185

Ser Arg His Ser Ala Ser Gln Glu Gly Gln Asp Thr Ile Arg Ala
1190 1195 1200

His Pro Gly Ser Ser Arg Arg Gly Arg Gln Gly Ser His Tyr Glu
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Gln Ser Val Asp Arg Ser Gly His Ser Gly Ser His His Ser His
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Thr Thr Ser Gln Gly Arg Ser Asp Ala Ser Arg Gly Gln Ser Gly
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Ser Arg Ser Ala Ser Arg Gln Thr Arg Asn Asp Glu Gln Ser Gly
1250 1255 1260

Asp Gly Ser Arg His Ser Trp Ser His His His Glu Ala Ser Thr
1265 1270 1275

Gln Ala Asp Ser Ser Arg His Ser Gln Ser Gly Gln Gly Gln Ser
1280 1285 1290

Ala Gly Pro Ser Thr Ser Arg Asn Gln Gly Ser Ser Val Ser Gln
1295 1300 1305

Asp Ser Asp Ser Gln Gly His Ser Glu Asp Ser Glu Arg Trp Ser
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Gly Ser Ala Ser Arg Asn His His Gly Ser Ala Gly Glu Gln Ser
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Arg Asp Gly Ser Arg His Pro Gly Ser His Gln Glu Asp Arg Ala
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His Thr Glu Ser Ser Ser Arg Gly Gln Ala Ala Ser Ser His Glu
1370 1375 1380

Gln Ala Arg Ser Ser Ala Gly Glu Arg His Gly Ser His His Gln
1385 1390 1395

Leu Gln Ser Ala Asp Ser Ser Arg His Ala Gly Ile Gly His Gly
1400 1405 1410

Gln Ala Ser Ser Ala Val Arg Asp Ser Gly His Arg Gly Tyr Ser
1415 1420 1425

Gly Ser Gln Ala Thr Asp Ser Glu Gly His Ser Glu Asp Ser Asp
1430 1435 1440

Thr Gln Ser Val Ser Ala Gln Gly Lys Ala Gly Pro His Gln Gln
1445 1450 1455

Ser His Lys Glu Ser Ala Arg Gly Gln Ser Gly Glu Ser Ser Arg
1460 1465 1470

Arg Ser Gly Ser Phe Leu Tyr Gln Val Ser Thr His Glu Gln Ser
1475 1480 1485

Glu Ser Thr His Gly Gln Ser Val Pro Ser Thr Gly Gly Arg Gln
1490 1495 1500

Gly Ser His His Asp Gln Ala Gln Asp Ser Ser Arg His Ser Ala
1505 1510 1515

Ser Gln Glu Gly Gln Asp Thr Ile Arg Gly His Pro Gly Pro Ser
1520 1525 1530

Arg Gly Gly Arg Gln Gly Ser His His Glu Gln Ser Val Asp Arg
1535 1540 1545

Ser Gly His Ser Gly Ser His His Ser His Thr Thr Ser Gln Gly
1550 1555 1560

Arg Ser Asp Ala Ser Arg Gly Gln Ser Gly Pro Arg Ser Ala Ser
1565 1570 1575

Arg Gln Thr His Asp Lys Glu Gln Ser Gly Asp Gly Ser Arg His
1580 1585 1590

Ser Gly Ser Arg His His Glu Ala Ser Ser Trp Ala Asp Ser Ser
1595 1600 1605

Arg His Ser Gln Ala Val Gln Gly Gln Ser Glu Gly Ser Arg Arg
1610 1615 1620

Ser Arg Arg Gln Gly Ser Ser Val Ser Gln Asp Ser Asp Ser Gln
1625 1630 1635

Gly His Ser Glu Asp Ser Glu Arg Arg Ser Gly Ser Ala Ser Arg
1640 1645 1650

Asn His Arg Gly Ser Ala Gln Glu Gln Ser Arg Asp Gly Ser Arg
1655 1660 1665

His Pro Arg Ser His His Glu Asp Arg Ala Gly His Gly His Ser
1670 1675 1680

Ala Asp Ser Ser Arg Gln Ser Gly Thr His His Ala Glu Asn Ser
1685 1690 1695

Ser Gly Gly Gln Pro Ala Ser Ser His Glu Gln Ala Arg Ser Ser
1700 1705 1710

Ala Gly Glu Arg His Gly Ser His His Gln Gln Ser Ala Asp Ser
1715 1720 1725

Ser Arg His Ser Gly Ile Gly His Gly Gln Ala Ser Ser Ala Val
1730 1735 1740

Arg Asp Ser Gly His Arg Gly Ser Ser Gly Ser Gln Ala Ser Asp
1745 1750 1755

Ser Glu Gly His Ser Glu Asp Ser Asp Thr Gln Ser Val Ser Ala
1760 1765 1770

His Gly Gln Ala Gly Pro His Gln Gln Ser His Gln Glu Ser Thr
1775 1780 1785

Arg Gly Arg Ser Ala Gly Arg Ser Gly Arg Ser Gly Ser Phe Leu
1790 1795 1800

Tyr Gln Val Ser Thr His Glu Gln Ser Glu Ser Ala His Gly Arg
1805 1810 1815

Ala Gly Pro Ser Thr Gly Gly Arg Gln Gly Ser His His Glu Gln
1820 1825 1830

Ala Arg Asp Ser Ser Arg His Ser Ala Ser Gln Glu Gly Gln Asp
1835 1840 1845

Thr Ile Arg Gly His Pro Gly Ser Arg Arg Gly Gly Arg Gln Gly
1850 1855 1860

Ser Tyr His Glu Gln Ser Val Asp Arg Ser Gly His Ser Gly Ser
1865 1870 1875

His His Ser His Thr Thr Ser Gln Gly Arg Ser Asp Ala Ser His
1880 1885 1890

Gly Gln Ser Gly Ser Arg Ser Ala Ser Arg Glu Thr Arg Asn Glu
1895 1900 1905

Glu Gln Ser Gly Asp Gly Ser Arg His Ser Gly Ser Arg His His
1910 1915 1920

Glu Ala Ser Thr Gln Ala Asp Ser Ser Arg His Ser Gln Ser Gly
1925 1930 1935

Gln Gly Glu Ser Ala Gly Ser Arg Arg Ser Arg Arg Gln Gly Ser
1940 1945 1950

Ser Val Ser Gln Asp Ser Asp Ser Glu Ala Tyr Pro Glu Asp Ser
1955 1960 1965

Glu Arg Arg Ser Glu Ser Ala Ser Arg Asn His His Gly Ser Ser
1970 1975 1980

Arg Glu Gln Ser Arg Asp Gly Ser Arg His Pro Gly Ser Ser His
1985 1990 1995

Arg Asp Thr Ala Ser His Val Gln Ser Ser Pro Val Gln Ser Asp
2000 2005 2010

Ser Ser Thr Ala Lys Glu His Gly His Phe Ser Ser Leu Ser Gln
2015 2020 2025

Asp Ser Ala Tyr His Ser Gly Ile Gln Ser Arg Gly Ser Pro His
2030 2035 2040

Ser Ser Ser Ser Tyr His Tyr Gln Ser Glu Gly Thr Glu Arg Gln
2045 2050 2055

Lys Gly Gln Ser Gly Leu Val Trp Arg His Gly Ser Tyr Gly Ser
2060 2065 2070

Ala