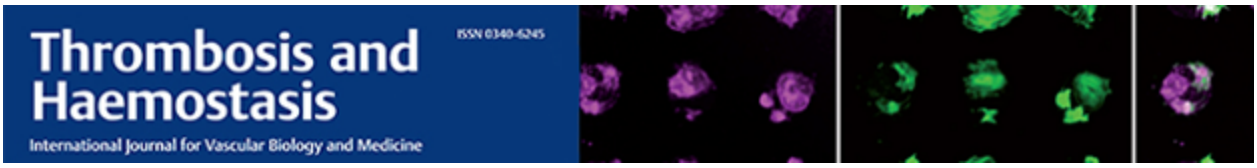

Analysis of 272 genetic variants in the upgraded interactive FXI web database reveals new insights on FXI deficiency

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Abstract:	Coagulation Factor XI (FXI) is a plasma glycoprotein composed of four apple (Ap) domains and a serine protease (SP) domain. FXI circulates as a dimer and activates Factor IX (FIX), promoting thrombin production and preventing excess blood loss. Genetic variants that degrade FXI structure and function often lead to bleeding diatheses, commonly termed FXI deficiency. The first interactive FXI variant database underwent initial development in 2003 at https://www.factorxi.org. Here, based on a much improved FXI crystal structure, the upgraded FXI database contains information regarding 272 FXI variants (including 154 missense variants) found in 657 patients, this being a significant increase from the 183 variants identified in the 2009 update. Type I variants involve the simultaneous reduction of FXI coagulant activity (FXI:C) and FXI antigen levels (FXI:Ag), whereas Type II variants result in decreased FXI:C yet normal FXI:Ag. The database updates now highlight the predominance of Type I variants in FXI. Analysis in terms of a consensus Ap domain revealed the near-uniform distribution of 81 missense variants across the Ap domains. A further 66 missense variants were identified in the SP domain, showing that all regions of the FXI protein were important for function. The variants clarified the critical importance of changes in surface solvent accessibility, as well as those of cysteine residues and the dimer interface. The updated database provides an easy-to-use web resource on FXI deficiency for clinicians that facilitates future diagnoses and treatments.

REGULAR ARTICLE (Category - Coagulation and Fibrinolysis)

Analysis of 272 genetic variants in the upgraded interactive FXI web database reveals new insights into FXI deficiency

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Correspondence: Professor Stephen J. Perkins, Department of Structural and Molecular Biology, Darwin Building, University College London, Gower Street, London WC1E 6BT, U.K. Tel.: +44 20 7679 7048; fax: +44 20 7679 7193; e-mail: s.perkins@ucl.ac.uk This manuscript contains 25 pages, including 8 Figures.

ABSTRACT

Coagulation Factor XI (FXI) is a plasma glycoprotein composed of four apple (Ap) domains and a serine protease (SP) domain. FXI circulates as a dimer and activates Factor IX (FIX), promoting thrombin production and preventing excess blood loss. Genetic variants that degrade FXI structure and function often lead to bleeding diatheses, commonly termed FXI deficiency. The first interactive FXI variant database underwent initial development in 2003 at https://www.factorxi.org. Here, based on a much improved FXI crystal structure, the upgraded FXI database contains information regarding 272 FXI variants (including 154 missense variants) found in 657 patients, this being a significant increase from the 183 variants identified in the 2009 update. Type I variants involve the simultaneous reduction of FXI coagulant activity (FXI:C) and FXI antigen levels (FXI:Ag), whereas Type II variants result in decreased FXI:C yet normal FXI:Ag. The database updates now highlight the

predominance of Type I variants in FXI. Analysis in terms of a consensus Ap domain revealed the near-uniform distribution of 81 missense variants across the Ap domains. A further 66 missense variants were identified in the SP domain, showing that all regions of the FXI protein were important for function. The variants clarified the critical importance of changes in surface solvent accessibility, as well as those of cysteine residues and the dimer interface. The updated database provides an easy-to-use web resource on FXI deficiency for clinicians that facilitates future diagnoses and treatments.

Key words: Coagulation factors, haemostasis, protein structure/folding, inherited coagulation disorders, gene mutations

SUMMARY TABLE

What is known on this topic:

(1) Many more FXI variants have been published in the literature since we last updated our interactive web database at https://www.factorxi.org in 2005 and 2009.

(2) The crystal structure of the FXI zymogen dimer enables an assessment of the damaging effects of FXI missense variants, and these need updating in the light of the significantly improved FXI crystal structure from 2019.

What this paper adds:

(1) Of the 272 unique variants from 657 case reports that are now in our interactive database from literature searches, 227 are disease-causing, the majority of which are phenotypically classified as Type I, and 45 are non-disease-associated.

(2) We explain the molecular basis of many Type I variants in FXI in terms of the altered surface accessibility of the affected residues, the importance of affected Cys residues in disulphide bridges, and perturbations of the Ap4-Ap4 contacts that form the FXI dimer.

(3) Our interactive FXI website was upgraded for improved clarity and ease of use in order to enable the better utility of sequences and structural modelling to analyse FXI genetic variants and predict their effects.

Introduction

Factor XI (FXI), a coagulation serine protease, is encoded by the *F11* gene located on the long arm of human chromosome 4 (4q35). The 23 kb gene comprises 15 exons that translate into a signal peptide, four apple (Ap) domains (Ap1-Ap4) and the catalytic serine protease (SP) domain (Figure 1).[1-2] The Ap domains in FXI are structurally homologous to each other and to those in human prekallikrein (PK), a zymogen protease involved in the kallikrein-kinin-system (KKS). Together such Ap domains form part of the plasminogen-apple-nematode (PAN) domain superfamily.[3] Specifically, FXI appeared to arise from the duplication of the PK gene, *Klkb1,* making FXI and PK paralogs of each other. The four Ap domains in each of FXI and PK form disk-like structures that are comprised of an antiparallel β-sheet attached to an α-helix through disulphide bridges.[4-5] FXI is synthesized as a 607 amino acid zymogen, which circulates in plasma in a dimeric form prior to activation. The dimer comprises two identical 80 kDa subunits, which are held together through non-covalent interactions between the two single Ap4 domains. The dimer is further stabilised by a Cys339-Cys339 interchain disulphide bridge between the Ap4 domains. The non-covalent interactions that stabilise dimer formation include hydrophobic ones as well as two Glu305-Lys349 and Asp307-Arg363 salt bridges. The activation of each FXI subunit involves the cleavage of the Arg387-Ile388 bond and can be driven by Factor XII (FXIIa), thrombin or by FXIa itself in a process known as autoactivation.[1,5-6] Once activated, FXIa cleaves zymogenic Factor IX (FIX) into FIXa. Subsequently, FIXa feeds into the coagulation cascade to promote thrombin production, aiding fibrin assembly and preventing excess blood loss.[1,7]

Owing to the importance of FXI in coagulation, genetic variants that disrupt the native FXI structure and function lead to bleeding diatheses. Such disorders are most commonly referred to as FXI deficiency, but have been termed Haemophilia C, Rosenthal syndrome or Plasma Thromboplastin Antecedent deficiency in the past.[8-9] FXI deficiency occurs at a frequency of one in a million in the general population with higher incidence amongst the Ashkenazi Jewish population (one in 450 individuals).[10-12] Specifically, the heterozygous and homozygous frequencies within the Ashkenazi population are believed to be 9% and 0.22% respectively. In 1953, Rosenthal identified the first case of FXI deficiency in a Jewish family in the USA.[8] Many subsequent cases were identified in individuals of similar descent, with the nonsense mutation Glu135* and the missense variant Phe301Leu emerging as the

founding causative variants. The most prominent mutations associated with FXI deficiency in Jewish populations are classified as being one of Type I-IV. The above point mutations are classified as Type II (Glu135*) and Type III (Phe301Leu) and remain as some of the most common FXI variants found today. Type I and IV mutations occur more sporadically and interfere with standard pre-mRNA splicing. Type I is a substitution and Type IV a deletion, both within intron N.[10-11,13-14] Despite the prevalence of FXI deficiency amongst the Jewish population, founding FXI variants have also been identified in other populations. Gln106* is a founding variant in French Nantes families, Cys56Arg in French Basques families, and Cys146* in English families.[14-16] The original nomenclature refers to FXI variants as having a cross-reacting material negative (CRM^-) or cross-reacting material positive (CRM^+) phenotype. CRM^- (presently known as Type I) variants result in the simultaneous reduction of FXI coagulant activity (FXI:C) and FXI antigen (FXI:Ag) levels, most likely a result of the degradation of mutant FXI protein within cells. CRM^+ (presently known as Type II) variants result in a reduction of the FXI:C level but do not impact the FXI:Ag level. Such variants are most likely to be dysfunctional variants that go undetected by normal cellular quality control systems. FXI:C levels typically range from 70–150 IU/dL in unaffected individuals, while moderately deficient individuals have FXI:C levels ranging between 15-70 IU/dL and severely deficient individuals have levels <15 IU/dL.[2]

What has been unclear is the lack of correlation between FXI activity, FXI deficiency and disease severity. To understand this relationship better, we created the first interactive web database for the coagulation proteins (https://www.factorxi.org/) in 2003 as an easy-to-use facility for users, which was published in 2005, and updated in 2009 to report all 183 FXI variants identified at the time.[17,18] To date, over 18,000 visits have been recorded on this website. We have extended this interactive database and upgraded it to other coagulation proteins such as FIX and others.[19] These interactive variant databases bring key advantages of easy-to-use search and genetic and structural analysis tools for clinicians and scientists. In the present study, we now update and upgrade our FXI database for which we summarise information for a total of 272 variants in the *F11* gene (Figure 1) and include the improved crystal structure from 2019.[20] The increased number of known and novel FXI variants clarifies the molecular basis of FXI deficiency. In particular, by comparisons with other coagulation proteases, we correlate the predominance of Type I (CRM^-) mutations within FXI with changes in surface solvent accessibilities of the affected residues, and with the occurrence of variants in cysteine residues. The amino acid accessibilities in the closely-

packed domain structure of the FXI dimer with the extended ones in other coagulation proteases now explain the notable imbalance between Type I and Type II variants in FXI. The availability of the upgraded website for users significantly clarifies the molecular basis of FXI deficiency.

Methods

Source of the FXI database

The interactive FXI web database at https://www.factorxi.org currently holds 272 genetic alterations in *F11* that are associated with FXI deficiency. The database was created at University College London, the website copyright is retained by S. J. Perkins and University College London, and database copying is not permitted without explicit permission from the author. The FXI database was initially populated in 2003 starting from a non-interactive website of the *F11* gene with 65 variants, together with literature searches of PubMed at https://pubmed.ncbi.nlm.nih.gov/.[17] Further *F11* genetic variants were obtained from 32 patient records at the Haemophilia Centre and Thrombosis Unit at the Royal Free Hospital in London, as well as additional literature searches, making a total of 183 variants in 2009.[18] For the current database, the literature cut-off date was April 2021, giving an overall total of 272 unique variants found in 657 patients. These data were compiled into a spreadsheet and used to update the existing FXI MySQL database, using phpMyAdmin software (https://www.phpmyadmin.net/) as an intermediary platform to the MySQL database. As a quality control, the original literature sources used for the 2005 and 2009 projects were re-consulted in order to re-validate and correct the entries if required. If required for personal or private research use, a list of the variants and their associated fields can be downloaded from the Variants menu on our website.

Analysis of FXI variants

The interactive database records DNA changes in HGVS format, where +1 refers to the A of the ATG initiation codon, at the start of the 18-residue signal peptide. Protein changes are recorded in HGVS format, with codon +1 referring to the ATG initiation codon (Figures 1 and 2). To enable comparison with older FXI publications, legacy numbering was included for protein changes on the web database, with codon +1 referring to the first codon of the mature FXI protein.

The original full-length FXI zymogen crystal structure at 0.287 nm structural resolution (PDB ID: 2F83) representing Cys-20 to Thr-622 (HGVS numbering) was recently superseded by an improved FXI zymogen crystal structure at 0.260 nm resolution (PDB ID: 6I58).[20,21] The latter was used here as the three-dimensional protein structural model on which the FXI variant analyses were based. The FXI dimer was created from the 6I58 structure using the Proteins, Interfaces, Structures and Assemblies (PDBePISA) server (https://www.ebi.ac.uk/pdbe/pisa/).[22] Whilst all structural analyses were carried out using the 6I58 model, 95 additional FXI structures have become available in the protein database (PDB) since 2009 and are listed in our updated database. Of these, 92 crystal structures correspond to truncated FXI structures with only the serine protease domain present, and three are full-length FXI proteins in complexes with ligands. These structures do not show the full FXI zymogen in its native conformation and thus were not used.

The 6I58 crystal structure of unliganded FXI was analysed using the Definition of Secondary Structure of Proteins (DSSP) tool at https://www3.cmbi.umcn.nl/xssp/ to determine the secondary structure of each FXI residue (Figure 2).[23-24] DSSP was applied both to the intact 6I58 structure as well as to the separated 6I58 domains. Residues were individually assigned secondary structures to be one of H (α-helix), B (β-bridge), E (extended β-strand), G (3_{10} helix), I (π-helix), T (hydrogen-bonded turn), S (bend) or C (undefined coil region). In addition, DSSP was used to determine the relative surface accessibility of each residue in the FXI crystal structure in $Å^2$ (Figure 2). The accessibilities were converted into % accessibility by dividing the DSSP output by the theoretical solvent accessible surface area of the amino acid sidechain in question.[23-25] The results were simplified as follows. Percentage accessibilities of 0-9% were given the value 0, 10-19% the value 1, 20-29% the value 2, and so on. Residues with accessibilities of 0 or 1 were classified as buried and those with accessibilities of 2-9 were classified as solvent-exposed.

The Ap domain secondary structure was comprised of a five-stranded antiparallel β-sheet with the β-strand topology C-E-D-G-A, a two-stranded B-F β-sheet and a centrally located α-helix (A1). The seven β-strands were labelled alphabetically (A-G) in the order in which they occurred in the sequence. The α-helix A1 and 3_{10}-helices G1-G3 were similarly labelled in sequential order.[17] The six conserved cysteine residues of the Ap domains were numbered from C1 to C6 in the order they occurred in each Ap sequence. The three disulphide bridges between the α-helix and β-strands were denoted C1-C6, C2-C5 and C3-C4

and stabilised the folded Ap structure.[26] The SP domain was comprised of β-strands A-O, α-helices A1-A2 and 3_{10}-helices G1-G5. As detailed previously, the Ap2 structure was used to represent the consensus Ap domain, owing to its low average root mean square deviation relative to the other three Ap domains after superimposition using the online secondary structure alignment program SSAP at http://www.cathdb.info/cgi-bin/cath/SsapServer.pl.[18,27] The interactions at the FXI dimer interface and between the Ap1-Ap4 and SP domains also utilised the PDBePISA tool.[22]

Results

Classification of FXI variants and polymorphisms in the updated interactive web database

The interactive FXI web database (https://www.factorxi.org) currently presents information regarding 272 genetic variants (Figure 1) from 657 patient records, this being an almost 50% increase of 89 variants compared to the 2009 update, and an increase of 207 variants from the initial 2005 publication.[17-18] The 89 newer variants were sourced from 34 new research articles, increasing the literature pool by 30% from that in 2009. As well as the increased number of rare variants, the database has also been updated in terms of its interactive features, to follow our FIX website (https://www.factorix.org), where a site map facilitates user navigation.[19] The home page features two movies of the dimeric FXI and monomeric FXI structures with its variants, facilitating a three-dimensional visualisation of the variant distribution. Allelic frequencies (AF) are also provided for variants when possible using the data supplied by the genome aggregation database (gnomAD) version 2.1.1 at https://gnomad.broadinstitute.org/.[28] The gnomAD v2.1.1 data set spanned 125,748 exome sequences and 15,708 whole-genome sequences and 117 (43%) of the 272 identified FXI variants were found in this. The AF was used as an indication of the relative frequency of a given variant at a specific genetic locus. The AF cut-off was taken as 0.01, thus an AF > 0.01 indicated a commonly-occurring variant. Of the 117 variants available in the gnomAD dataset, only 9 had AF > 0.01, all of which corresponded to known polymorphisms. The remaining 108 variants had AF < 0.01, highlighting that most FXI variants are rare. Using a more stringent AF cut-off of 0.001, only four additional variants occurred more frequently, leaving 104 rare FXI variants within the gnomAD data set. Additional database features include a multiple sequence alignment of human FXI with other FXI species, to help users understand the phylogenetic history of the *F11* gene and the extent of residue conservation in

related sequences. An interactive FXI structure is presented onto which missense variants can be mapped and analysed for clearer structural and functional analysis of their consequence. Lastly, additional FXI structures and literature references provide a more up to date knowledge of FXI research.

Of the 272 variants identified, 227 are disease-causing and 45 are non-disease associated polymorphisms. The 272 variants can be classified by genetic event, of which point variants make up 73.53%, polymorphisms 16.54%, deletions 6.99%, duplications 1.47% and insertions 1.47% (Figure 3(a)). The point variants can be further subdivided into missense (77.00%), nonsense (13.50%) and silent (1.00%) variants, with the remaining 8.50% of point variants being undefined (Figure 3(b)). The variants are uniformly distributed throughout the FXI sequence, with variants found in all five domains and linker regions (Figure 3(c)). Of the disease-causing variants, 96 (42.3%) are phenotypically classified as Type I, 12 (5.3%) as Type II and 119 (52.4 %) as unknown. Here, Type II variants are characterised by a FXI:C to FXI:Ag ratio < 0.7. The Type I variants are scattered evenly across all domains whereas the Type II variants predominantly cluster in the SP domain (66.7%) (Figure 2). The two most common variants are Glu135* and Cys56Arg, both of which are phenotypically classified as Type I. A total of 61 Glu135* and 36 Cys56Arg cases have been recorded in the web database. These are increases of five Glu135* and 24 Cys56Arg variants compared to the 2009 update. Other commonly occurring variants include Phe301Leu, Cys146* and Gln281* of which there are 22 cases of each.

Crystal structure analysis of secondary structures and accessibilities

The FXI protein structure rationalises the three-dimensional distribution of the variants. The previously used FXI zymogen crystal structure (PDB ID: 2F83) has now been superseded by a much improved one (PDB ID: 6I58). The 6I58 structure showed an improved structural resolution of 0.260 nm compared to that of 0.287 nm for 2F83 and this enabled better visualisation and analysis of the distribution of variants in FXI.[20-21] When subjected to Ramachandran plot quality analysis (http://www.ebi.ac.uk/pdbsum), the 6I58 model gave an observed goodness-of-fit R-value of 0.216 when compared to the experimental X-ray data, compared to a larger R-value of 0.235 in the 2F83 crystal structure. In the 6I58 structure, 87% of amino acids were categorised in the “most favoured” conformational regions, 13% were in the “additional allowed” regions, and there were no conformational outliers. This outcome was improved compared to the 2F83 structure for

which the corresponding figures were 74%, 20% and nine Ramachandran outliers respectively.[20-21,29] In Figure 2, 96 out of the 625 residues showed a different secondary structure assignment in the improved 6I58 structure compared to that in the 2F83 structure, even though the overall secondary structure was unaffected, and the changes affected mostly the loop conformations at the surface of the protein. From Figure 2 likewise, 209 out of the 625 residues showed changes in surface accessibilities of at least 10% when comparing the 6I58 structure to 2F83, and 49 residues showed changes of more than 20%. The improved quality of the newer protein structure thus had clear effects on the analyses of the variants below.

The 6I58 structure was used to display 142 missense variants and 14 polymorphisms found in the FXI zymogen (Figure 4(a)). The four Ap domains in each monomer were each composed of seven β-strands and an α-helix, which came together to form a five-stranded antiparallel β-sheet C-E-D-G-A, a two stranded B-F β-sheet and a central α-helix. This is most clearly seen for the Ap2 domain of Monomer 2 in Figure 4(a). Ap2, Ap3 and Ap4 also contained short C-terminal 3_{10}-helices (Figure 2). The SP domain contained 15 β-strands, two α-helices and five short 3_{10}-helices, all arranged as two subdomains, each of which flanked a substrate binding cleft between them (Figure 2). The catalytic triad of His431-Asp480-Ser575 is shown for Monomer 2 in Figure 4(a). In the full 6I58 structure, 322 residues out of 625 had percentage surface accessibilities of 0 or 1 (assigned as buried), 263 residues had accessibilities over 2 (assigned as surface exposed), and 40 residues were absent from the crystal structure and therefore not classified. The 6I58 structure revealed 98 variants with percentage surface accessibilities of 0 or 1, indicating sidechain burial, and 50 variants with accessibilities of 2 or more, indicating surface exposure (Figure 2). Note that the accessibilities of three variants in the SP domain were undeterminable due to structural limitations. Variant changes in buried positions are likely to interfere with intradomain interactions and overall protein conformation, accounting for the predominance of Type I variants in FXI, due to the high proportion of affected buried residues and the compact domain structure (Figure 4). In contrast, variants found at surface exposed locations are more likely to interfere with protein function without disturbing the overall structure. The low number of Type II variants in the Ap domains highlights their importance in maintaining the compact FXI structure, whereas the clustering of Type II variants in the catalytic SP domain indicates its significance in protein function rather than structure.

A consensus Ap domain represents an average of the four Ap domains in FXI. The consensus enables all the Ap1-Ap4 variants to be shown in one view in order to determine features common to all four domains (Figure 5(a)). The predominance of Type I variants (red) in the Ap domains is highlighted in Figure 5(b), where Type II variants (green) are almost absent. In this representation, Thr33 (in a buried location at the end of the Ap α-helix) and Gly80 (in a buried location at the end of the Ap β-sheet G) represent hotspots that disrupt the Ap domains.

Analysis of disulphide bridges and Cys variants in FXI

Further analyses focussed on specific details of the FXI structure. The covalent links formed by 17 disulphide bridges in a FXI monomer are key to the structure and function of FXI. Each Ap domain possesses three intrachain disulphide bridges C1-C6, C2-C5 and C3-C4 (black highlights in Figure 5(a)), the first of which stabilises the link between the N-terminus and C-terminus of each Ap domain. These occur at Ap1 (Cys20-Cys103, Cys46-Cys76, Cys50-Cys56), Ap2 (Cys110-Cys193, Cys136-Cys165, Cys140-Cys146), Ap3 (Cys200-Cys283, Cys226-Cys255, Cys230-Cys236) and Ap4 (Cys291-Cys374, Cys317-Cys346, Cys321-Cys327). There is a free Cys29 residue in Ap1. The SP domain has five bridges (Cys380-Cys500, Cys416-Cys432, Cys514-Cys,581, Cys545-Cys560, Cys571-Cys599). The Ap4 domains form an additional interchain disulphide bridge at Cys339-Cys339 to stabilise dimer formation.[1,26,30-31] Type I Cys variants disrupt disulphide bridge formation, destabilising the protein structure and leading to a FXI deficient state. A total of 28 distinct Cys variants have been identified within FXI, 20 of which are in the Ap domains and eight are in the SP domain. Of the 28 variants, 12 have Type I phenotypes (Cys46Phe, Cys56Arg/Trp, Cys76Tyr, Cys110Gly, Cys136*, Cys140Tyr, Cys146*, Cys255Tyr, Cys327*, Cys416Tyr, Cys545Tyr), one has a Type II phenotype (Cys599*) and one is a non-disease associated polymorphism (Cys339Phe). The remaining 14 variants do not have defined phenotypes (Cys56*, Cys76Arg/Phe, Cys136Arg, Cys200Ser/Tyr, Cys230Arg/Ser, Cys374Arg, Cys500Arg/Trp, Cys581Arg/Phe, Cys599Tyr) (Figure 2). The 13 substitution variants that introduce new Cys residues into FXI predominantly possess Type I phenotypes (Trp246Cys, Arg326Cys, Trp425Cys, Arg443Cys, Tyr445Cys, Trp515Cys, Trp519Cys, Gly596Cys), with only one possessing a Type II phenotype (Arg396Cys in the SP domain) and four with unknown phenotypes (Tyr151Cys, Arg162Cys, Arg268Cys, Tyr521Cys). All individuals with such variants in a homozygous or compound heterozygous form exhibit a severe FXI deficiency. In addition to the Cys residues being Type I mutational hotspots,

variants that neighbour Cys residues are also able to perturb the disulphide bridge packing within the protein fold (Figure 5(c)).

Analysis of variants at the FXI dimer interface

The PDBePISA tool was used to identify the 17 Ap4 contact residues involved in FXI dimerization with buried surface area changes of over 5 Å^2 (Leu302 to Val309, Thr333, Cys339, Asn340, Lys345, Tyr347, Lys349, Thr357, Leu360, Arg363) (green in Figure 5(a)).[22] Specifically, Cys339 forms an interchain disulphide bond, which is important for stabilisation but is not essential for dimer formation or functionality.[30] There are 36 Ap4 variants in total, yet only three are found at the dimer interface (Ile308Phe/Thr, Cys339Phe), highlighting the importance of the conservation of residues at the dimer interface (Figures 5(a) and 5(d)). Ile308Phe/Thr and Cys339Phe are non-disease associated polymorphisms. Given that Ile, Phe, Thr, and Cys have neutral side chains, the Ile308Phe/Thr and Cys339Phe substitutions are unlikely to have a large impact on the non-covalent dimerization interactions.

Comparison of variant phenotypes with residue accessibilities

The high proportion of Type I variants was investigated further by calculating the surface accessibilities of 142 FXI missense variants and 14 polymorphisms using the PDBePISA tool for (a) the intact FXI protein and (b) the individually separated FXI domains (Figure 6). Notably a high 67% of Type I variants (42 of 63) showed accessibilities of 0 or 1, highlighting their predisposition to be buried within the FXI protein structure (Figure 6(a)). In contrast, Type II variants and polymorphisms appeared at both exposed and buried regions of the FXI structure, with no clear preference for either location. Many variant residues were of unknown phenotype, however interestingly the majority of these showed low accessibilities. Following domain separation, the resulting changes in accessibility compared to the intact protein enabled identification of residues that made interdomain contacts. An even higher proportion of 91% of Type I variants (57 of 63) were located to residues that showed small accessibility changes after domain separation (Figure 6(b)). The same outcome was also seen for Type II variants, polymorphisms and unassigned phenotypes. The predominance of Type I variants (and others) at such sites illustrates that small perturbations in the FXI structure, through the introduction of variants that lead to slight changes in surface accessibility, are sufficient to inactivate the protein and lead to disease states.

For further insight into the above outcome, four individual variant residues were visually highlighted. The FXI Ap domains were tightly packed together to form a compact structure with intricate interdomain interactions. Four distinct residues associated with Type I variants were identified, namely (a) Val38Ala, (b) Pro41Leu, (c) Cys110Gly and (d) Arg326Cys (Figure 7). Following domain separation, the accessibilities of these four residues increased significantly, corresponding to a transition from burial to exposure. These accessibility changes indicated the extent to which the residues interact with and are packed together against surrounding domains. Missense variants at such locations will perturb these interdomain interactions, disrupting the native FXI structure and resulting in premature protein degradation. Thus, we have provided a molecular explanation for the relative abundance of Type I variants in FXI in terms of small but significant disruptions to the tightly packed domain structure.

Discussion

The new data sets for FXI in this study have significantly improved the quality of the analyses of variants compared to our previous study,[18] and lead to further insights into the occurrence of FXI disease states. Most notably, we show that these variants are found across the FXI protein structure, and that accessibility changes in the packing arrangement of amino acid residues in the folded FXI structure by residue substitution is a major cause of FXI deficiency. Accessibility changes may be a good predictor for the changes associated with a variant. This upgraded analysis of the FXI variants has resulted from three main advances: (a) the availability of an additional 50% of reported rare variants from literature sources to make a total of 272 variants (Figure 1); (b) the significantly improved crystal structure for the FXI zymogen;[20] (c) upgrade of the previous UCL FXI website user interface into that similar to the UCL coagulation Factor IX website.[19]

In the coagulation proteases, FXI presents unique features by virtue of its compact protein domain structure. There are other proteins that likewise possess compact domain structures, such as the serine protease Factor I of the complement cascade of immune defence that contains five domains in contact with each other (complement proteins are evolutionarily related to coagulation proteins). Like FXI, Factor I shows that variants are distributed throughout the protein structures, implying that any of these will perturb the correctly folded protein structure. However, Factor I is monomeric and not dimeric as is FXI.[32] In contrast,

three-dimensional structures for Factors VII, IX and X (FVII, FIX and FX) present extended domain arrangements based on the four domains termed Gla-EGF1-EGF2-SP. Where the phenotypes are known, FVII, FIX and FX variants show a higher proportion of Type II phenotypes and are associated with functional defects, rather than Type I.[33-34] This outcome is as expected given that these three proteins have extended domain arrangements. For proteins that are dominantly affected by functional defects, such as Factor H and C3 of complement, these show tendencies to reveal "hot-spots" where genetic variants accumulate in small but functionally important regions of the protein structure. Certain types of variants do not exist in FXI. There are no variants reported that affect the catalytic residues His431-Asp480-Ser575 that make up the peptide cleavage site in FXI; presumably these would be incompatible with life. Likewise, there are no variants reported that prevent FXI from forming dimers and these too would appear to be incompatible with life. Very few of the contact residues at the dimer interface are associated with variants, and those that do only show minor perturbations to the protein structure. In support of this outcome, FXI-deficient mice exhibit increased bleeding, akin to the bleeding in FXI-deficient patients that is reported as the result of traumatic or surgical injuries.[35]

Specific residue types are becoming more abundant as the number of observed genetic variants increase. In this study, Cys residues were flagged up as being a frequent source of disease-causing variants in FXI (Figure 5(c)). Cys residues are important for the stability and functionality of FXI, and there are 18 disulphide bridges in a FXI monomer. Unsurprisingly the breakage of a Cys-Cys disulphide bridge is expected to impact severely on the FXI protein. The higher frequency of variants at Cys32 and Cys58 was already evident in the consensus Ap domain in 2009 where all six Cys residues were associated with variants.[18] In the present study, the involvement of all six Cys residues in variants in the consensus Ap domain was verified (Figure 5(a)). A similar outcome was also recently noted with the consensus short complement regulator domain in the complement proteins, which possesses two conserved disulphide bridges. Initially the Cys residues were not prominent as variant hotspots, but the most recent update of the web database showed that these were prominent with 5-13 occurrences.[36-37]

Our interactive FXI database serves as a useful resource for clinicians and scientists to diagnose FXI deficiency and provide insight into suitable therapeutic approaches. Database technology becomes required given the large increases in the known genetic variants in FXI,

when a simple flat list is no longer adequate to monitor these. The website layout is designed to present genetic and structural information on FXI as two distinct but parallel themes, similar to that for our original FXI database[17,18] and the FIX database.[19] This is illustrated using genetic and structural outputs for the established Phe301Leu variant (the Jewish Type III variant with legacy numbering Phe283Leu), for which 22 patient records exist (Figure 8). On the left, further insight on the conservation of Phe301 is obtained from the AA Alignments tab which shows Phe301 aligned with six other mammalian species to show that this residue is fully conserved and therefore essential for FXI function. On the right, the structural analysis shows that Phe301 is a buried residue on a β-strand, and the JMol viewer shows that this is located inside the Apple 4 domain. Further research into FXI will be key to understanding the relationship between FXI deficiency and disease severity, including experimental studies. While the improved 2019 crystal structure for the FXI zymogen has greatly facilitated variant analysis, a crystal structure for activated FXIa will further help explain the molecular basis of FXI deficiency. There may be a large conformational difference in FXIa compared to FXI, by analogy with the structure of activated plasma kallikrein compared to the FXI zymogen; kallikrein is homologous to FXI.[20]

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Figure Legends

Figure 1: Distribution of the 272 variants identified within the *F11* gene.

The Ap1-Ap4 and serine protease domains are drawn to scale. The number of variants in each of the respective domains and UTR regions is shown in large font above or below the variant lists. Intronic variants are included in their respective domains according to sequence numbering. The residue numbering in HGVS format (starting with 1 at the signal peptide) denotes the amino acids that start and end each domain. N and C represent the N- and C-termini of FXI respectively. Note that the two variants in the 3'UTR do not follow HGVS numbering.

Figure 2: Secondary structure and accessibility analysis of variants in the FXI crystal structure.

The FXI sequence is shown with the secondary structure assignments highlighted in grey boxes. Residues are denoted either H (α-helix), B (β-bridge), E (extended β-strand), G (3_{10} helix), I (π-helix), T (hydrogen-bonded turn), S (bend) or C (undefined coil region). β-strands are labelled alphabetically in the order in which they occur. The β-strands in the Ap and SP domains are denoted A-G and A-O respectively. 3_{10}-helices are denoted G1-G5 and α–helices are denoted A1-A2. The SP catalytic triad His431-Asp480-Ser575 residues are highlighted in black. The 24 conserved cysteine residues within the four Ap domains are shown in yellow text. Putative N-glycosylated residues are highlighted in yellow boxes. The positions of 198 point variants found in the *F11* gene are highlighted, where 75 red highlights denote Type I mutations, 11 green highlights denote Type II mutations, and 56 orange highlights denote mutations with unknown phenotype. The 13 purple highlights denote non-disease associated polymorphisms and the blue highlight denotes a residue (G368) associated with both Type I and Type II phenotypes. Note that several highlights correspond to multiple variants at one residue position. All numbering is in HGVS format.

Figure 3: Distribution of the 272 variants found in the *F11* gene.

The panels (a-c) indicate breakdowns of the 272 FXI variants into variant type, effect and location within the *F11* gene sequence. The charts illustrated here distinguish the non-disease associated polymorphisms from the disease-causing genetic variants.

(a) The relative frequency of five different types of unique variants in the F11 gene.

(b) Effect of the 200 point variants found in the F11 gene sequence.

(c) Distribution of the 272 FXI variants across the *F11* gene sequence and FXI protein domains. Note, the variant in the undefined category is a 31.5 kb deletion that cannot be assigned to a single domain/region.

Figure 4: Structural and schematic view of variants within FXI

The dimer was created using its crystallographic symmetry, with the two Ap4 domains in contact with each other about an axis depicted as a dashed vertical line.

(a) Distribution of 142 missense variants and 14 polymorphisms within dimeric FXI. The crystal structure of the FXI dimer is shown in ribbon format, with the Cα positions of variants and polymorphisms highlighted as spheres. Variant locations are illustrated in Monomer 1 and are coloured according to phenotype. Type I (CRM-) variants are in red, Type II (CRM+) variants in green, and those with unknown phenotype in yellow. The non-disease associated polymorphisms are depicted in purple. The catalytic triad His431-Asp480-Ser575 is shown in the SP domain of Monomer 2 as black spheres. The ribbon colours correspond to those used on our website https://www.factorxi.org.

(b) Schematic representation of the five domains in monomeric FXI. The five domains are aligned and depicted in the same orientation and colours as in the ribbons in (a) above. The four variants highlighted, Val38Ala, Pro41Leu, Cys110Gly and Arg326Cys are Type I variants found at interdomain contact points (see below).

Figure 5: Mutational residue frequency in terms of a consensus Ap domain.

A consensus Ap domain of length 87 residues shows the distribution of 90 Ap variants (missense and polymorphisms) in the four Ap1-Ap4 domains merged together.

(a) The four Ap domain sequences are aligned to form a consensus, with the averaged secondary structure (Sec) and accessibility (Acc) of each residue listed directly below. The 'Tot' row illustrates the total number of variants found at each residue in the consensus. The six conserved Cys residues in each domain are highlighted in black and numbered 1-6 underneath the alignment. Type I variants are circled in red, Type II in green and those of unknown phenotype in orange. Non-disease associated polymorphisms are circled in purple. The green residues in Ap4 mark those present at the FXI dimer interface. The 'Sec' rows highlight the α-helix region (H) and the five β-strand regions (E) in the consensus Ap domain. The β-strand regions are denoted AB, C, D, E and FG. The 'Acc' row denotes the

relative accessibility of each consensus residue, where accessibilities of 0 or 1 indicate buried sidechains and accessibilities > 1 indicate sidechain exposure to solvent.

(b) Variants are coloured according to phenotype. Type I variants are coloured in red, Type II in green and those of unknown phenotype in yellow. Polymorphisms are shown in purple. The sphere colour represents the most commonly occurring phenotype at that position according to the sequence alignment in (a). The size of the spheres indicates the number of variants found at that position, and ranges from one to five. N and C refer to the N- and C-termini respectively.

(c) Cys variants and their neighbouring residues are shown as dark and light pink spheres respectively. All other variants are depicted in blue. The size of the spheres is again indicative of the number of variants found at that position. The six Cys residues are labelled C1-C6.

(d) The FXI dimer interface is highlighted in green and the β-strands present at the interface are labelled. Variants found within Ap4 are shown as spheres, coloured according to their phenotype as in (b)

Figure 6: Graphical illustration of 142 missense variants and 14 polymorphisms in the *F11* gene.

(a) FXI variants are grouped by phenotypic classification (CLASS). The variants are further subdivided according to the native residue accessibility (ACC) of the intact protein. Accessibility was determined using DSSP and is explained in detail in the methods section. Accessibilities of 0 or 1 indicate sidechain burial and values >1 indicate exposure.

(b) FXI variants are again grouped by phenotypic classification (CLASS) and accessibility (ACC). Here, accessibility refers to the change in residue accessibility when the intact FXI protein is chopped into five distinct domains, Apple1, Apple2, Apple3, Apple4 and the SP domain.

Figure 7: Molecular graphic representation of residues within the FXI protein structure.

The left-hand panel highlights the residue of interest and its calculated solvent accessibility in the native FXI protein. The right-hand side panel shows the same residue in its respective isolated domain, with its corresponding accessibility. Panels (a), (b), (c) and (d) highlight the residues Val38, Pro41, Cys110 and Arg326 respectively. Accessibility calculations are

detailed in the Methods section. The domain colouring corresponds to that in Figure 3. All residue numbering is given in HGVS format.

Figure 8: Screenshots of the upgraded FXI web site to illustrate the analysis made for the Phe301Leu variant.

The upper panel displays the output when residue 301 is inputted on the home page. By clicking "Show" on the patient information, the lower left panel lists genetic information for the 22 patients reported with Phe301Leu variant, of which the first five records are visible, together with the source of the patient record. The sequence alignment is shown underneath with Phe301 highlighted. Clicking "HERE" on the structural interpretation gives the image shown on the bottom right panel. This assesses the buried or exposed accessibility of the variant and its location in the FXI protein structure. A JMol view of the FXI structure is displayed that can be rotated and zoomed into as desired.

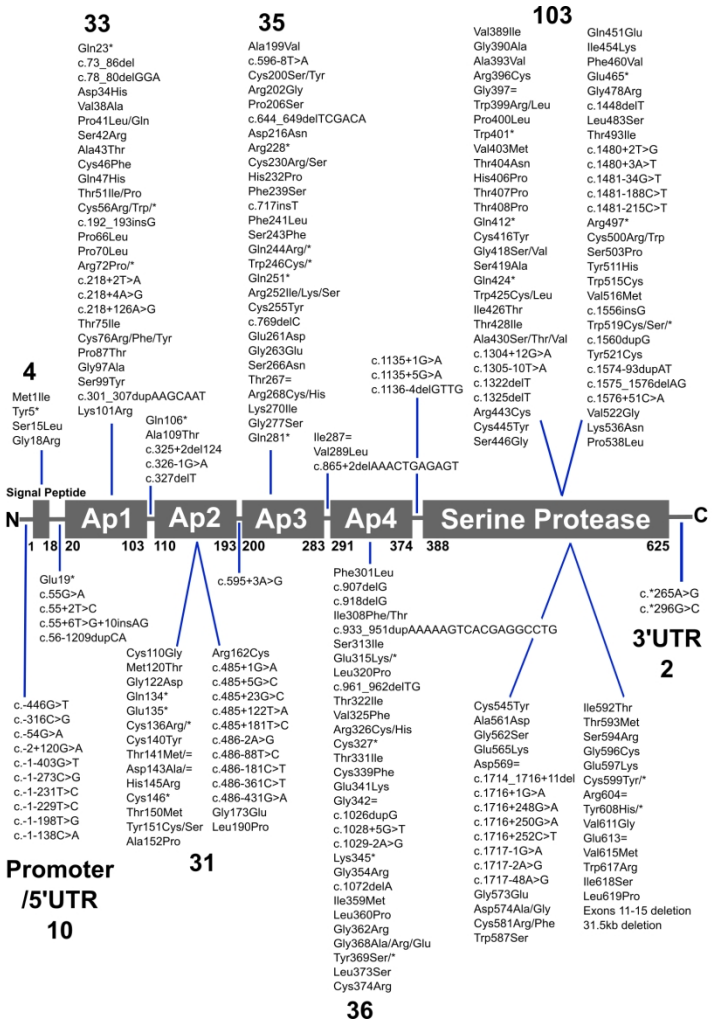

Figure 1. Variants.

289x292mm (200 x 200 DPI)

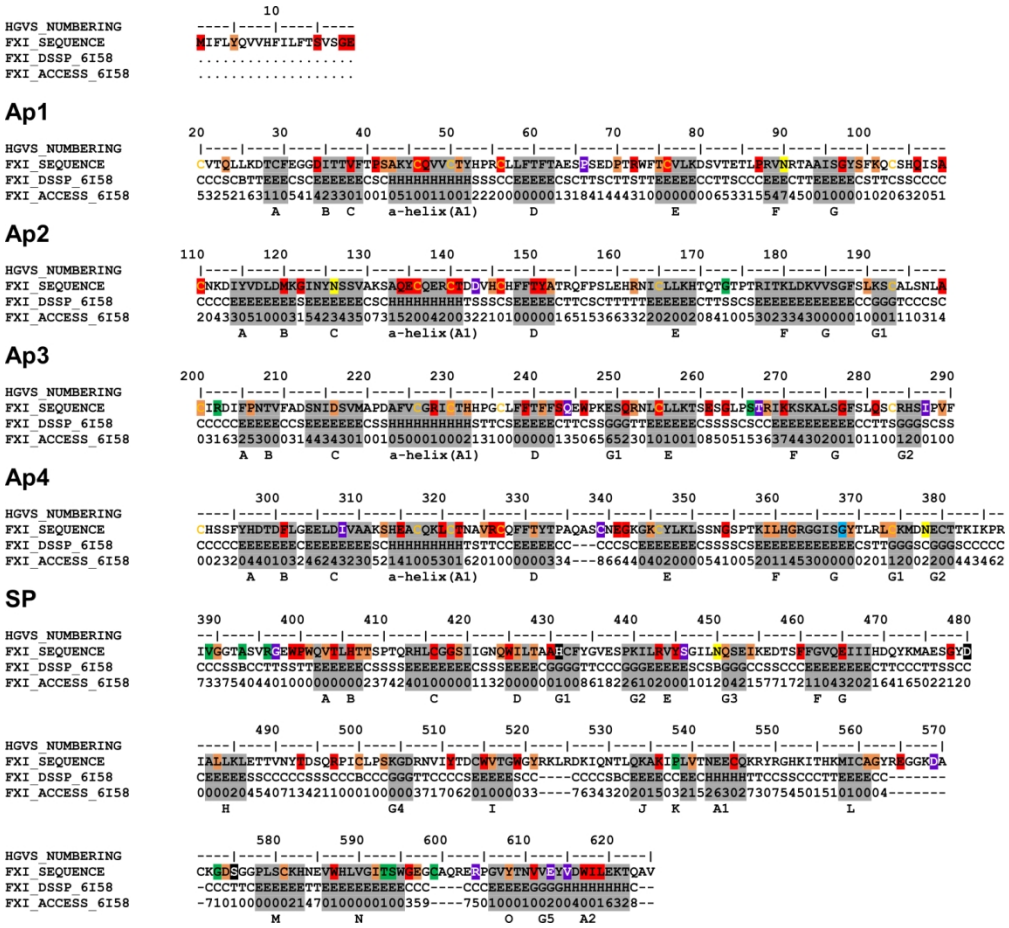

Figure 2. Sequence.

201x185mm (200 x 200 DPI)

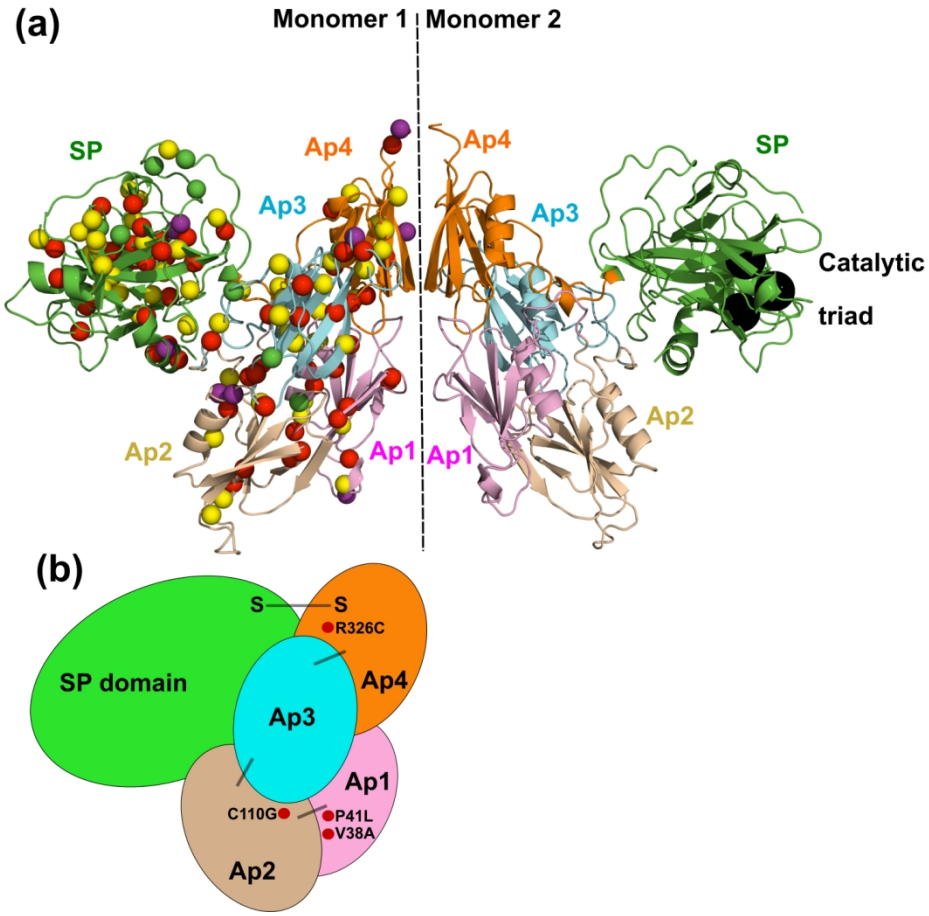

Figure 3. Dimer

204x189mm (200 x 200 DPI)

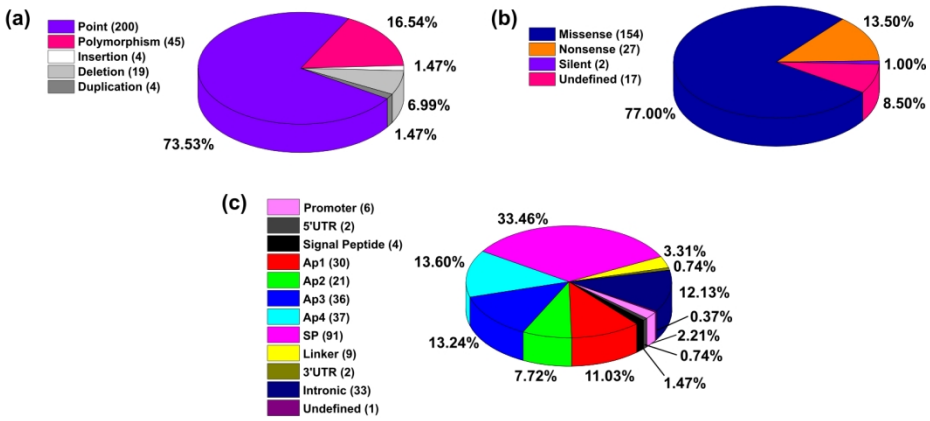

Figure 4. Pie chart.

233x141mm (200 x 200 DPI)

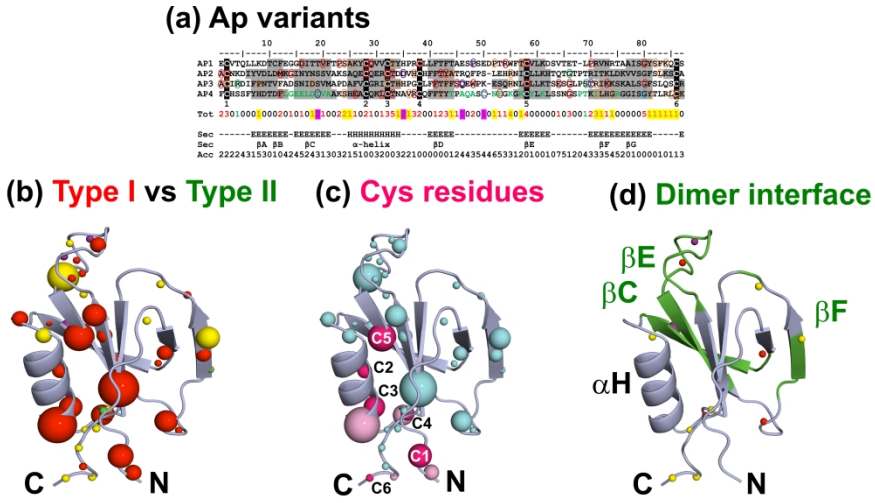

Figure 5. Consensus

355x175mm (300 x 300 DPI)

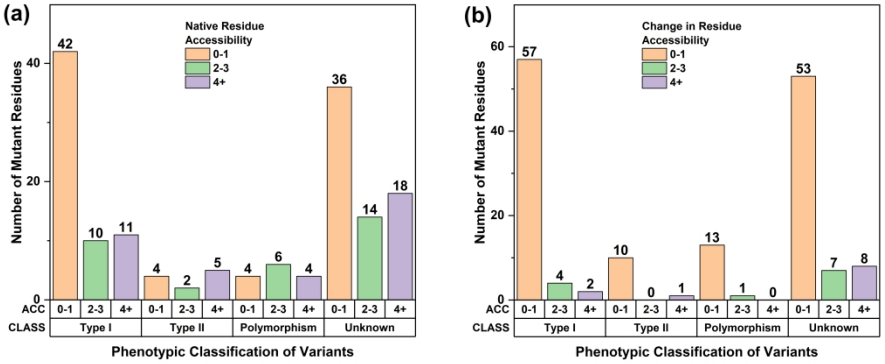

Figure 6. Accessibility

508x208mm (300 x 300 DPI)

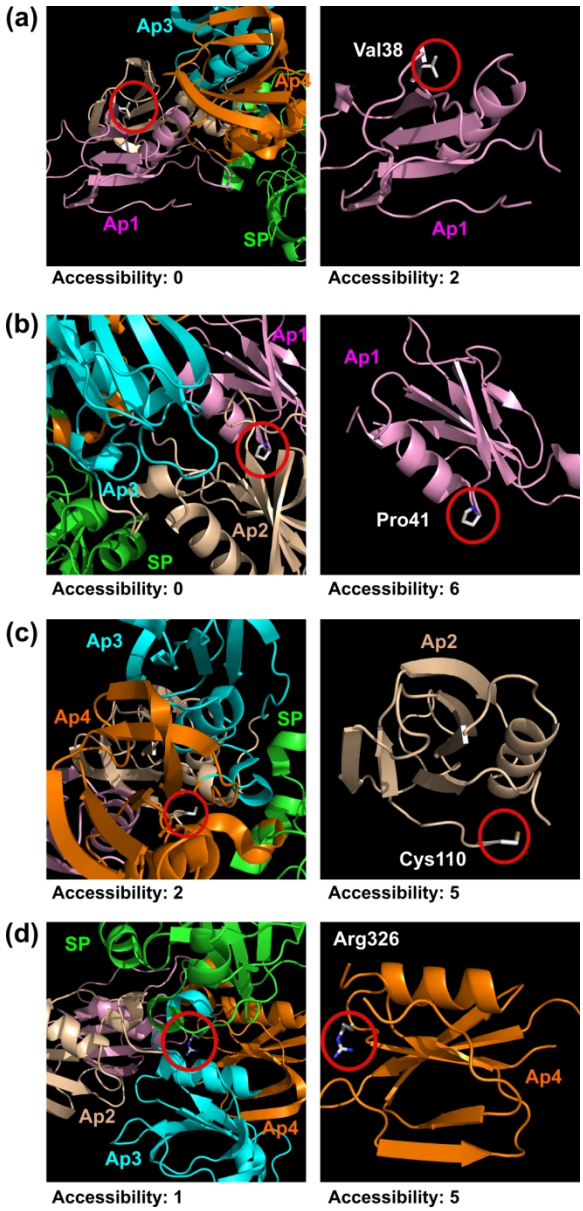

Figure 7. Views

134x281mm (200 x 200 DPI)

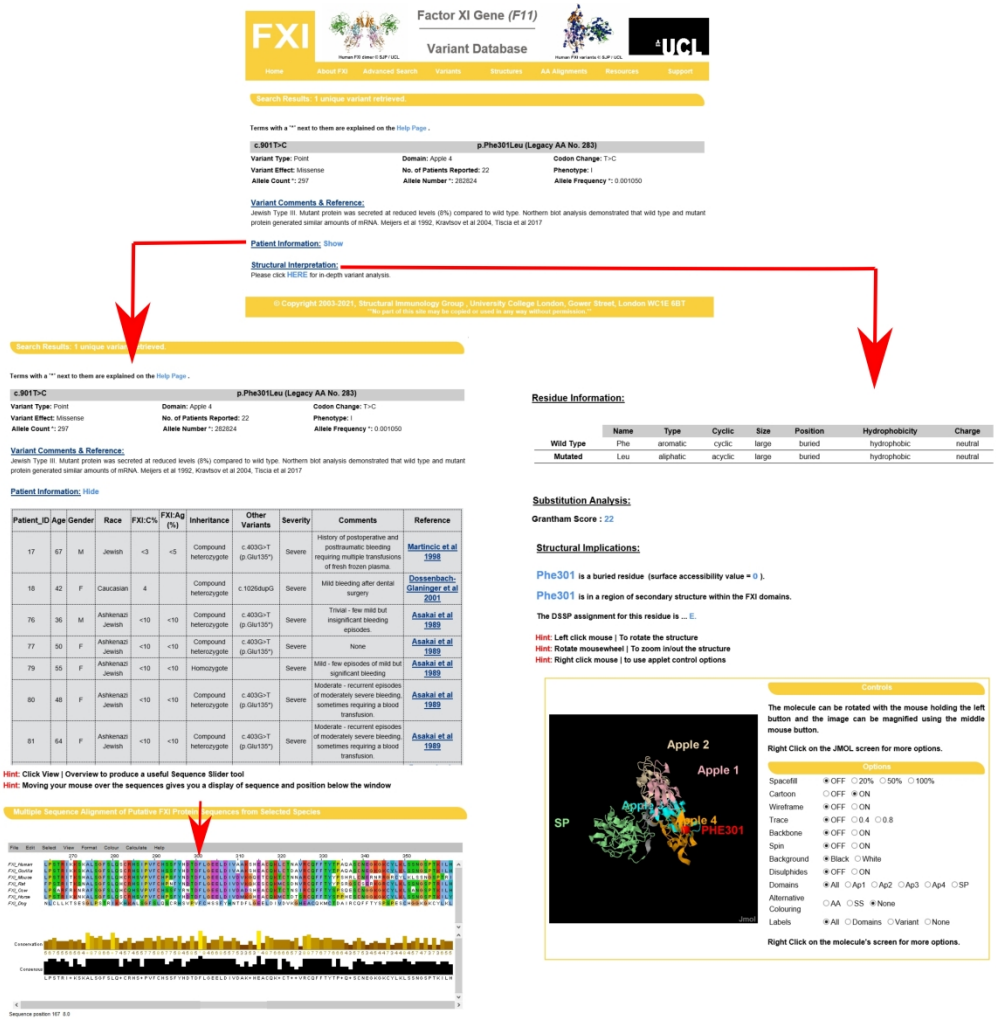

Figure 8. Website

570x579mm (200 x 200 DPI)

Patient ID	Age	Gender	Race	Variant ID	Type	Effect	cDNA	Mutation(c
212			UK populat	130	Point		-54	c.-54G>A
438				130	Point		-54	c.-54G>A
505		M	Tunisian	184	Deletion		0	Exons 11-1
154				109	Deletion		0	31.5KbDele
215			UK populat	132	Point	Missense	3	c.3G>T
373				132	Point	Missense	3	c.3G>T
190	36	F	Morrocan	120	Point	Missense	44	c.44C>T
401	26	F	Czech	227	Insertion	Frameshift	55	c.55+6T>G+
213			Uk Populati	131	Point	Nonsense	55	c.55G>T
290	2	F	Non-Ashke	160	Deletion	Frameshift	73	c.73_86del
510			Italian	258	Deletion	Inframe	78	c.78_80del
280	34	F	French	152	Point	Missense	113	c.113T>C
216			UK Populat	133	Point	Missense	122	c.122C>A
199	34	F	French	125	Point	Missense	122	c.122C>T
402				228	Point	Missense	126	c.126C>G
616	44	F	Chinese	228	Point	Missense	126	c.126C>G
165	15	F		113	Point	Missense	137	c.137G>T
166	10	F		113	Point	Missense	137	c.137G>T
167	45	M		113	Point	Missense	137	c.137G>T
617	32	F	Chinese	113	Point	Missense	137	c.137G>T
217			UK Populat	24	Point	Missense	141	c.141G>C
518	7	M	Turkish	159	Point	Missense	151	c.151A>C
524	10	F	Turkish	159	Point	Missense	151	c.151A>C
563	52	M	Spanish	68	Point	Missense	166	c.166T>C
564	45	F	Spanish	68	Point	Missense	166	c.166T>C
1	50	F	French Bas	68	Point	Missense	166	c.166T>C
571	51	M	Spanish	68	Point	Missense	166	c.166T>C
572	40	F	Spanish	68	Point	Missense	166	c.166T>C
573	57	M	Spanish	68	Point	Missense	166	c.166T>C
574	53	F	Spanish	68	Point	Missense	166	c.166T>C
575	44	F	Spanish	68	Point	Missense	166	c.166T>C
576	47	M	Spanish	68	Point	Missense	166	c.166T>C
577	32	F	Spanish	68	Point	Missense	166	c.166T>C
578	79	M	Spanish	68	Point	Missense	166	c.166T>C
579	58	F	Spanish	68	Point	Missense	166	c.166T>C
580	42	M	Spanish	68	Point	Missense	166	c.166T>C
581	68	M	Spanish	68	Point	Missense	166	c.166T>C
582	49	M	Spanish	68	Point	Missense	166	c.166T>C
583	52	M	Spanish	68	Point	Missense	166	c.166T>C
584	59	F	Spanish	68	Point	Missense	166	c.166T>C
585	49	M	Spanish	68	Point	Missense	166	c.166T>C
565	53	F	Spanish	68	Point	Missense	166	c.166T>C
566	41	M	Spanish	68	Point	Missense	166	c.166T>C
567	52	M	Spanish	68	Point	Missense	166	c.166T>C
568	47	M	Spanish	68	Point	Missense	166	c.166T>C
569	43	M	Spanish	68	Point	Missense	166	c.166T>C
570	63	F	Spanish	68	Point	Missense	166	c.166T>C
7	34	F	French Bas	68	Point	Missense	166	c.166T>C
3	35	F	French Bas	68	Point	Missense	166	c.166T>C

6	40	M	French Bas(	68	Point	Missense	166	c.166T>C
98	22	M	French Bas(	68	Point	Missense	166	c.166T>C
99	28	M		68	Point	Missense	166	c.166T>C
100	53	F		68	Point	Missense	166	c.166T>C
101	61	M	French Bas(	68	Point	Missense	166	c.166T>C
102	51	F	French Bas(	68	Point	Missense	166	c.166T>C
586	71	F	Spanish	68	Point	Missense	166	c.166T>C
209	58	M	French	68	Point	Missense	166	c.166T>C
511			Italian	219	Point	Missense	168	c.168T>G
512		F	Czech	259	Point	Missense	215	c.215G>C
631	66	F	Indian	352	Point		218	c.218+4A>C
632	8	M	Indian	352	Point		218	c.218+4A>C
633	63	M	Indian	352	Point		218	c.218+4A>C
219			UK Populat	134	Point	Missense	227	c.227G>T
147			Jewish	102	Point	Missense	227	c.227G>A
403				230	Point	Missense	296	c.296C>A
439				230	Point	Missense	296	c.296C>A
56			Portuguese	36	Duplication	Frameshift	301	c.301_307d
57			Portuguese	36	Duplication	Frameshift	301	c.301_307d
168	38	M		114	Point	Missense	302	c.302A>G
24	41	M	Nantes	8	Point	Nonsense	316	c.316C>T
26	46	F	Nantes	8	Point	Nonsense	316	c.316C>T
23	64	F	Nantes	8	Point	Nonsense	316	c.316C>T
25	36	F	Nantes	8	Point	Nonsense	316	c.316C>T
28	9	M	Nantes	8	Point	Nonsense	316	c.316C>T
522	4	M	Turkish	135	Point	Missense	325	c.325G>A
523	42	M	Turkish	135	Point	Missense	325	c.325G>A
604	60	M	Spanish	135	Point	Missense	325	c.325G>A
284		F	Italian	135	Point	Missense	325	c.325G>A
221			UK Populat	135	Point	Missense	325	c.325G>A
529	37	M	Italian	135	Point	Missense	325	c.325G>A
530	31	F	Italian	135	Point	Missense	325	c.325G>A
528	12	F	Italian	135	Point	Missense	325	c.325G>A
650	32	F	Taiwanese	341	Point		326	c.326-1G>A
200	43	M	French	126	Point	Missense	328	c.328T>G
201	14	M	French	126	Point	Missense	328	c.328T>G
405				231	Point	Missense	359	c.359T>C
406				231	Point	Missense	359	c.359T>C
12				60	Point	Missense	365	c.365G>A
8				60	Point	Missense	365	c.365G>A
117				60	Point	Missense	365	c.365G>A
224			UK Populat	60	Point	Missense	365	c.365G>A
225			UK Populat	60	Point	Missense	365	c.365G>A
440				60	Point	Missense	365	c.365G>A
404	42	M		60	Point	Missense	365	c.365G>A
186			Austrian	104	Point	Nonsense	400	c.400C>T
407	61	M	Italian	104	Point	Nonsense	400	c.400C>T
149			Austrian	104	Point	Nonsense	400	c.400C>T
466	24	M	Iranian	58	Point	Nonsense	403	c.403G>T
634	54	M	Indian	58	Point	Nonsense	403	c.403G>T

441				58	Point	Nonsense	403	c.403G>T
442				58	Point	Nonsense	403	c.403G>T
443				58	Point	Nonsense	403	c.403G>T
51		M	Portuguese	58	Point	Nonsense	403	c.403G>T
52		M	Portuguese	58	Point	Nonsense	403	c.403G>T
53		F	Portuguese	58	Point	Nonsense	403	c.403G>T
92		F	Portuguese	58	Point	Nonsense	403	c.403G>T
93		M	Portuguese	58	Point	Nonsense	403	c.403G>T
526	6	M	Turkish	58	Point	Nonsense	403	c.403G>T
527	60	M	Turkish	58	Point	Nonsense	403	c.403G>T
189	41	F	Jewish	58	Point	Nonsense	403	c.403G>T
445				58	Point	Nonsense	403	c.403G>T
446				58	Point	Nonsense	403	c.403G>T
183	12	M	Italian	58	Point	Nonsense	403	c.403G>T
184	34	M	Italian	58	Point	Nonsense	403	c.403G>T
531	30	F	Italian	58	Point	Nonsense	403	c.403G>T
532	80	M	Italian	58	Point	Nonsense	403	c.403G>T
533	40	F	Italian	58	Point	Nonsense	403	c.403G>T
94		F	Portuguese	58	Point	Nonsense	403	c.403G>T
76	36	M	Ashkenazi J	58	Point	Nonsense	403	c.403G>T
77	50	F	Ashkenazi J	58	Point	Nonsense	403	c.403G>T
80	48	F	Ashkenazi J	58	Point	Nonsense	403	c.403G>T
81	64	F	Ashkenazi J	58	Point	Nonsense	403	c.403G>T
335			Non-Jewish	58	Point	Nonsense	403	c.403G>T
336			Czech	58	Point	Nonsense	403	c.403G>T
457	61	M	Italian	58	Point	Nonsense	403	c.403G>T
17	67	M	Jewish	58	Point	Nonsense	403	c.403G>T
235			UK Populat	58	Point	Nonsense	403	c.403G>T
400				58	Point	Nonsense	403	c.403G>T
351	18	F	Jewish	58	Point	Nonsense	403	c.403G>T
383		F		58	Point	Nonsense	403	c.403G>T
384		F		58	Point	Nonsense	403	c.403G>T
388		M		58	Point	Nonsense	403	c.403G>T
419		F	French	58	Point	Nonsense	403	c.403G>T
420		F		58	Point	Nonsense	403	c.403G>T
461		M		58	Point	Nonsense	403	c.403G>T
447				58	Point	Nonsense	403	c.403G>T
444				58	Point	Nonsense	403	c.403G>T
534	58	F	Italian	58	Point	Nonsense	403	c.403G>T
163	32	M	Italian	58	Point	Nonsense	403	c.403G>T
398	32	M	Italian	58	Point	Nonsense	403	c.403G>T
418	32	M	Italian	58	Point	Nonsense	403	c.403G>T
272			French Bas	58	Point	Nonsense	403	c.403G>T
148			Jewish	58	Point	Nonsense	403	c.403G>T
483	44	F	Ashkenazi J	58	Point	Nonsense	403	c.403G>T
279	2	F	Non-Ashke	58	Point	Nonsense	403	c.403G>T
67	22	F	Bedouin	58	Point	Nonsense	403	c.403G>T
105	48	F	Bedouin	58	Point	Nonsense	403	c.403G>T
106	11	M	Bedouin	58	Point	Nonsense	403	c.403G>T
107	9	M	Bedouin	58	Point	Nonsense	403	c.403G>T

108	13	F	Bedouin	58	Point	Nonsense	403	c.403G>T
109	16	F	Bedouin	58	Point	Nonsense	403	c.403G>T
110	18	F	Bedouin	58	Point	Nonsense	403	c.403G>T
158	56	F	Italian	58	Point	Nonsense	403	c.403G>T
159	61	M	Italian	58	Point	Nonsense	403	c.403G>T
160	29	M	Italian	58	Point	Nonsense	403	c.403G>T
151			European	105	Point	Nonsense	408	c.408C>A
226			UK Populat	105	Point	Nonsense	408	c.408C>A
161	36	M	Italian	105	Point	Nonsense	408	c.408C>A
162	15	F	Italian	105	Point	Nonsense	408	c.408C>A
513		M	Italian	121	Point	Missense	419	c.419G>A
191	68	M		121	Point	Missense	419	c.419G>A
192	42	M		121	Point	Missense	419	c.419G>A
193	31	M		121	Point	Missense	419	c.419G>A
295			Non-Jewish	121	Point	Missense	419	c.419G>A
289	61	M	Italian	161	Point	Missense	422	c.422C>T
637		F	Croatian	353	Point	Missense	428	c.428A>C
638		F	Croatian	353	Point	Missense	428	c.428A>C
639		M	Croatian	353	Point	Missense	428	c.428A>C
611	45	F	Indonesian	232	Point	Missense	434	c.434A>G
612	14	M	Indonesian	232	Point	Missense	434	c.434A>G
613	12	M	Indonesian	232	Point	Missense	434	c.434A>G
655	13	M	Taiwanese	232	Point	Missense	434	c.434A>G
75	63	F		20	Point	Nonsense	438	c.438C>A
70	59	F	English/Irisl	20	Point	Nonsense	438	c.438C>A
72	35	M	Scottish	20	Point	Nonsense	438	c.438C>A
74	18	M	Irish	20	Point	Nonsense	438	c.438C>A
88	63	M		20	Point	Nonsense	438	c.438C>A
89	32	F	Scottish/En	20	Point	Nonsense	438	c.438C>A
90	54	F	English	20	Point	Nonsense	438	c.438C>A
91	50	F	English	20	Point	Nonsense	438	c.438C>A
39	50	M	Non-Jewish	20	Point	Nonsense	438	c.438C>A
448				20	Point	Nonsense	438	c.438C>A
71	86	M	English	20	Point	Nonsense	438	c.438C>A
73	50	M	English	20	Point	Nonsense	438	c.438C>A
60			North Euro	20	Point	Nonsense	438	c.438C>A
504	65	M	Australian	20	Point	Nonsense	438	c.438C>A
240			UK Populat	20	Point	Nonsense	438	c.438C>A
214			UK Populat	20	Point	Nonsense	438	c.438C>A
222			UK Populat	20	Point	Nonsense	438	c.438C>A
227			UK Populat	20	Point	Nonsense	438	c.438C>A
374		F		20	Point	Nonsense	438	c.438C>A
169	29	F		20	Point	Nonsense	438	c.438C>A
170	33	F		20	Point	Nonsense	438	c.438C>A
171	55	F		20	Point	Nonsense	438	c.438C>A
409				138	Point	Missense	449	c.449C>T
535	27	M	Italian	138	Point	Missense	449	c.449C>T
536	49	M	Italian	138	Point	Missense	449	c.449C>T
537	12	M	Italian	138	Point	Missense	449	c.449C>T
538	43	M	Italian	138	Point	Missense	449	c.449C>T

228			UK Populat	139	Point	Missense	452	c.452A>G
43		F		29	Point	Missense	452	c.452A>C
229			UK Populat	29	Point	Missense	452	c.452A>C
410				29	Point	Missense	452	c.452A>C
172	28	F		29	Point	Missense	452	c.452A>C
40				21	Point	Missense	454	c.454G>C
230			UK Populat	21	Point	Missense	454	c.454G>C
131			Austrian	94	Point	Missense	484	c.484C>T
118				71	Point		486	c.486-2A>G
231			UK Populat	71	Point		486	c.486-2A>G
197	36	F	Italian	71	Point		486	c.486-2A>G
451				238	Point	Missense	518	c.518G>A
450				238	Point	Missense	518	c.518G>A
452				238	Point	Missense	518	c.518G>A
135			Chinese	97	Point	Missense	569	c.569T>C
188			Austrian	69	Point		595	c.595+3A>C
232			UK Populat	69	Point		595	c.595+3A>C
546	55	F	Italian	69	Point		595	c.595+3A>C
104	5	M	French Bas	69	Point		595	c.595+3A>C
417	24	F	Italian	69	Point		595	c.595+3A>C
621	51	F	Chinese	343	Point		596	c.596-8T>A
476	23	F	French	163	Point	Missense	596	c.596C>T
415	29	F		22	Point	Missense	599	c.599G>A
233			UK Populat	22	Point	Missense	599	c.599G>A
648	60	F	Taiwanese	336	Point	Missense	599	c.599G>C
416			Italian	165	Point	Missense	604	c.604A>G
196	36	M	French	123	Point	Missense	616	c.616T>C
187			Austrian	119	Deletion	Inframe	644	c.644_649d
29	28	M	Lebanese	11	Point	Nonsense	682	c.682C>T
421		F	French	222	Point	Missense	688	c.688T>A
422		F	French	222	Point	Missense	688	c.688T>A
234			UK Populat	23	Point	Missense	688	c.688T>C
41			Japanese	23	Point	Missense	688	c.688T>C
542	25	M	Italian	23	Point	Missense	688	c.688T>C
543	55	F	Italian	23	Point	Missense	688	c.688T>C
627	4	M	Indian	349	Point	Missense	695	c.695A>C
423	43	M	Japanese	32	Point	Missense	716	c.716T>C
424			Japanese	32	Point	Missense	716	c.716T>C
47			Japanese	32	Point	Missense	716	c.716T>C
425	9	F	Australian	209	Insertion	Frameshift	717	c.717insT
144	34	M		101	Point	Missense	728	c.728C>T
145				101	Point	Missense	728	c.728C>T
426	39	F	Japanese	155	Point	Nonsense	730	c.730C>T
642		F	Chinese	95	Point	Nonsense	738	c.738G>A
644		F	Chinese	95	Point	Nonsense	738	c.738G>A
645		F	Chinese	95	Point	Nonsense	738	c.738G>A
133			Chinese	95	Point	Nonsense	738	c.738G>A
652	58	M	Taiwanese	95	Point	Nonsense	738	c.738G>A
624	5	F	Chinese	95	Point	Nonsense	738	c.738G>A
132		F	Chinese	95	Point	Nonsense	738	c.738G>A

61	68	F	Italian	41	Point	Missense	738	c.738G>C
128		F	Italian	41	Point	Missense	738	c.738G>C
129		F	Italian	41	Point	Missense	738	c.738G>C
124		M	Italian	41	Point	Missense	738	c.738G>C
125		M	Italian	41	Point	Missense	738	c.738G>C
126		F	Italian	41	Point	Missense	738	c.738G>C
127		F	Italian	41	Point	Missense	738	c.738G>C
130		F	Italian	41	Point	Missense	738	c.738G>C
428	26	F		235	Point	Missense	755	c.755G>A
236			UK Populat	141	Point	Missense	756	c.756A>T
237			UK Populat	141	Point	Missense	756	c.756A>T
4	13	M	French Bas	52	Point	Missense	764	c.764G>A
103	10	M		52	Point	Missense	764	c.764G>A
506	53	M		253	Deletion	Frameshift	769	c.769delC
204	20	M	French	128	Point	Missense	783	c.783G>C
173	27	F		115	Point	Missense	788	c.788G>A
174	52	F		115	Point	Missense	788	c.788G>A
16		F	African Am	63	Point	Missense	797	c.797G>A
15	9	M	African Am	63	Point	Missense	797	c.797G>A
45				30	Point	Missense	802	c.802C>T
238			UK Populat	30	Point	Missense	802	c.802C>T
44				30	Point	Missense	802	c.802C>T
603	69	F	Spanish	30	Point	Missense	802	c.802C>T
239			UK Populat	30	Point	Missense	802	c.802C>T
356	9	F		210	Point	Missense	803	c.803G>A
435	46	F	Czech	40	Point	Missense	809	c.809A>T
507				255	Point	Missense	829	c.829G>A
651	43	F	Taiwanese	42	Point	Nonsense	841	c.841C>T
656	38	F	Taiwanese	42	Point	Nonsense	841	c.841C>T
615	30	F		42	Point	Nonsense	841	c.841C>T
65	42	F	Japanese	42	Point	Nonsense	841	c.841C>T
122		M	Japanese	42	Point	Nonsense	841	c.841C>T
62	17	F	Chinese	42	Point	Nonsense	841	c.841C>T
115	20	F	Chinese	42	Point	Nonsense	841	c.841C>T
119		F	Japanese	42	Point	Nonsense	841	c.841C>T
120		M	Japanese	42	Point	Nonsense	841	c.841C>T
121		F	Japanese	42	Point	Nonsense	841	c.841C>T
123		M	Japanese	42	Point	Nonsense	841	c.841C>T
64	56	F	Chinese	42	Point	Nonsense	841	c.841C>T
150	29	M	Japanese	42	Point	Nonsense	841	c.841C>T
618	26	F	Chinese	42	Point	Nonsense	841	c.841C>T
619	41	F	Chinese	42	Point	Nonsense	841	c.841C>T
625	22	F	Chinese	42	Point	Nonsense	841	c.841C>T
626	33	M	Chinese	42	Point	Nonsense	841	c.841C>T
399	25	F	Chinese	42	Point	Nonsense	841	c.841C>T
79	55	F	Ashkenazi J	65	Point	Missense	901	c.901T>C
454				65	Point	Missense	901	c.901T>C
112		F	Caucasian	65	Point	Missense	901	c.901T>C
113		M	Caucasian	65	Point	Missense	901	c.901T>C
453				65	Point	Missense	901	c.901T>C

455				65	Point	Missense	901	c.901T>C	
545	54	M	Italian	65	Point	Missense	901	c.901T>C	
549	36	F	Italian	65	Point	Missense	901	c.901T>C	
283	53	F	Italian	65	Point	Missense	901	c.901T>C	
477	40	F	Czech	65	Point	Missense	901	c.901T>C	
18	42	F	Caucasian	65	Point	Missense	901	c.901T>C	
490		F		65	Point	Missense	901	c.901T>C	
544	19	F	Italian	65	Point	Missense	901	c.901T>C	
547	12	F	Italian	65	Point	Missense	901	c.901T>C	
5	17	M	French Bas	59	Deletion	Frameshift	907	c.907delG	
175	57	F		116	Deletion	Frameshift	918	c.918delG	
429				166	Duplication	Frameshift	933	c.933_951d	
641		M	Chinese	354	Point	Missense	938	c.938G>T	
643		F	Chinese	354	Point	Missense	938	c.938G>T	
646		M	Chinese	354	Point	Missense	938	c.938G>T	
640	32	F	Chinese	354	Point	Missense	938	c.938G>T	
152				122	Point	Missense	943	c.943G>A	
210	31	M	French	122	Point	Missense	943	c.943G>A	
194	57	M	French	122	Point	Missense	943	c.943G>A	
195	25	F	French	122	Point	Missense	943	c.943G>A	
553	53	F	Italian	122	Point	Missense	943	c.943G>A	
554	29	F	Italian	122	Point	Missense	943	c.943G>A	
430				122	Point	Missense	943	c.943G>A	
551	31	F	Italian	122	Point	Missense	943	c.943G>A	
561	3	F	Italian	122	Point	Missense	943	c.943G>A	
562	30	F	Italian	122	Point	Missense	943	c.943G>A	
495	24	F	Belgic	122	Point	Missense	943	c.943G>A	
431	47	M	French	142	Deletion	Frameshift	961	c.961_962d	
241			UK Populat	142	Deletion	Frameshift	961	c.961_962d	
211	36	F	French	3	Point	Missense	965	c.965C>T	
602	42	M	Spanish	3	Point	Missense	965	c.965C>T	
242			UK Populat	3	Point	Missense	965	c.965C>T	
434				194	Point	Missense	973	c.973G>T	
432				194	Point	Missense	973	c.973G>T	
433				194	Point	Missense	973	c.973G>T	
19				5	Point	Missense	976	c.976C>T	
243			UK Populat	5	Point	Missense	976	c.976C>T	
437				5	Point	Missense	976	c.976C>T	
436	85	F	Australian	5	Point	Missense	976	c.976C>T	
458	45	M	Iranian	169	Point	Missense	992	c.992C>T	
134			Chinese	4	Point	Missense	1021	c.1021G>A	
220			UK Populat	4	Point	Missense	1021	c.1021G>A	
459	33	F	Ashkenazi J	4	Point	Missense	1021	c.1021G>A	
111		M	Caucasian	67	Duplication	Frameshift	1026	c.1026dupC	
54		F	Portuguese	34	Point	Silent	1026	c.1026G>T	
55		F	Portuguese	34	Point	Silent	1026	c.1026G>T	
470	50	F	Portugese	34	Point	Silent	1026	c.1026G>T	
456				239	Point		1028	c.1028+5G>	
658	64	M		361	Point	Nonsense	1033	c.1033A>T	
381			Non-Jewish	12	Point	Missense	1060	c.1060G>A	

58			Portuguese	37	Deletion	Frameshift	1072	c.1072delA
471	58	F	Portgugese	37	Deletion	Frameshift	1072	c.1072delA
244			UK Populat	143	Point	Missense	1077	c.1077A>G
460	17	M	Iranian	170	Point	Missense	1079	c.1079T>C
246			UK Populat	144	Point	Missense	1084	c.1084G>A
620	6	F	Chinese	18	Point	Missense	1103	c.1103G>A
143	6	F	Indian	100	Point	Missense	1106	c.1106A>C
653	69	F	Taiwanese	43	Point	Nonsense	1107	c.1107C>A
63	10	F	Chinese	43	Point	Nonsense	1107	c.1107C>A
116	18	F	Chinese	43	Point	Nonsense	1107	c.1107C>A
649	29	M	Taiwanese	43	Point	Nonsense	1107	c.1107C>A
657	61	M		43	Point	Nonsense	1107	c.1107C>A
659	7	M		43	Point	Nonsense	1107	c.1107C>A
247			UK Populat	145	Point	Missense	1118	c.1118T>C
248			UK Populat	146	Point	Missense	1120	c.1120T>C
153				108	Point		1135	c.1135+1G>
463	29	F	Japanese	108	Point		1135	c.1135+1G>
249			UK Populat	147	Point	Missense	1135	c.1135+5G>
155		F	Chinese	110	Deletion	Frameshift	1136	c.1136-4de
156		M	Chinese	110	Deletion	Frameshift	1136	c.1136-4de
268		F	Chinese	110	Deletion	Frameshift	1136	c.1136-4de
622	12	F	Chinese	110	Deletion	Frameshift	1136	c.1136-4de
464	26	M	Italian	171	Point	Missense	1165	c.1165G>A
467				241	Point	Missense	1178	c.1178C>T
245			UK Populat	98	Point	Missense	1186	c.1186C>T
468		F		98	Point	Missense	1186	c.1186C>T
389		F		224	Point	Missense	1196	C.1196G>T
32	8	F	Arab	15	Point	Missense	1211	c.1211C>A
33		M	Arab	15	Point	Missense	1211	c.1211C>A
34		F	Arab	15	Point	Missense	1211	c.1211C>A
469	32	F	French	173	Point	Missense	1217	c.1217A>C
250			UK Populat	26	Point	Missense	1219	c.1219A>C
508				256	Point	Missense	1222	c.1222A>C
628	14	M	Indian	363	Point	Nonsense	1234	c.1234C>T
84		F	English	51	Point	Missense	1247	c.1247G>A
251			UK Populat	51	Point	Missense	1247	c.1247G>A
525	28	F	Turkish	51	Point	Missense	1247	c.1247G>A
587	25	M	Spanish	51	Point	Missense	1247	c.1247G>A
588	50	F	Spanish	51	Point	Missense	1247	c.1247G>A
589	43	M	Spanish	51	Point	Missense	1247	c.1247G>A
590	32	F	Spanish	51	Point	Missense	1247	c.1247G>A
591	80	F	Spanish	51	Point	Missense	1247	c.1247G>A
592	38	M	Spanish	51	Point	Missense	1247	c.1247G>A
85			English	51	Point	Missense	1247	c.1247G>A
114			Hispanic	51	Point	Missense	1247	c.1247G>A
146	38	F		51	Point	Missense	1247	c.1247G>A
252			UK Populat	51	Point	Missense	1247	c.1247G>A
472				51	Point	Missense	1247	c.1247G>A
36		F	Chinese	16	Point	Missense	1253	c.1253G>T
516	8	F	Turkish	16	Point	Missense	1253	c.1253G>T

86			US	16	Point	Missense	1253	c.1253G>T
35	53	M	Italian and	16	Point	Missense	1253	c.1253G>T
557	53	F	Italian	16	Point	Missense	1253	c.1253G>T
305	19	F	Italian	16	Point	Missense	1253	c.1253G>T
427	62	M	Japanese	16	Point	Missense	1253	c.1253G>T
623	50	M	Chinese	16	Point	Missense	1253	c.1253G>T
473				243	Point	Missense	1255	c.1255T>G
614	49	F	Chinese	148	Point	Nonsense	1270	c.1270C>T
253			UK Populat	148	Point	Nonsense	1270	c.1270C>T
474	7		African	174	Point	Missense	1275	c.1275G>C
605	25	M	Spanish	300	Point	Missense	1277	c.1277T>C
636	28	F	Indian	175	Point	Missense	1283	c.1283C>T
475				175	Point	Missense	1283	c.1283C>T
479				244	Point	Missense	1288	c.1288G>T
20		F		6	Point	Missense	1289	c.1289C>T
478	31	F		6	Point	Missense	1289	c.1289C>T
480				176	Point		1304	c.1304+12G
59			Portuguese	38	Point		1305	c.1305-10T
654	52	M	Taiwanese	357	Deletion	Frameshift	1322	c.1322delT
647	54	F	Taiwanese	357	Deletion	Frameshift	1322	c.1322delT
481				156	Point	Missense	1327	c.1327C>T
482				156	Point	Missense	1327	c.1327C>T
38	37	F	Non-Jewish	19	Point	Missense	1378	c.1378T>G
69	25	M	Japanese	46	Point	Nonsense	1393	c.1393G>T
486	6	F	Japanese	177	Point	Missense	1394	c.1394C>G
487		M	Japanese	177	Point	Missense	1394	c.1394C>G
42				62	Point	Missense	1432	c.1432G>A
142	11	M	Indian	62	Point	Missense	1432	c.1432G>A
635	14	M	Indian	62	Point	Missense	1432	c.1432G>A
254			UK Populat	62	Point	Missense	1432	c.1432G>A
206	40	F	French	62	Point	Missense	1432	c.1432G>A
13				62	Point	Missense	1432	c.1432G>A
10				62	Point	Missense	1432	c.1432G>A
207	4	M	French	62	Point	Missense	1432	c.1432G>A
141	9	M	Indian	62	Point	Missense	1432	c.1432G>A
208	2	M	French	62	Point	Missense	1432	c.1432G>A
408				62	Point	Missense	1432	c.1432G>A
630	42	M	Indian	351	Point	Missense	1448	c.1448T>C
46				31	Point	Missense	1478	c.1478C>T
164		M	Non-Jewish	31	Point	Missense	1478	c.1478C>T
255			UK Populat	31	Point	Missense	1478	c.1478C>T
489	29	F	Ashkenazi J	178	Point	Missense	1480	c.1480+2T>
258			UK Populat	149	Point	Nonsense	1489	c.1489C>T
491				246	Point	Missense	1498	c.1498T>C
259			UK Populat	150	Point	Missense	1500	c.1500C>G
492	12	M	Iranian	180	Point	Missense	1507	c.1507T>C
2	22	F	French Bas	53	Point	Missense	1531	c.1531T>C
97	22	F	French Bas	53	Point	Missense	1531	c.1531T>C
202	29	F	French	127	Point	Missense	1545	c.1545G>T
558	25	F	Italian	127	Point	Missense	1545	c.1545G>T

559		52	M	Italian	127	Point	Missense	1545	c.1545G>T
560		49	F	Italian	127	Point	Missense	1545	c.1545G>T
493					214	Point	Missense	1546	c.1546G>A
303			F	Iranian	47	Insertion	Frameshift	1556	c.1556insG
488			F	Japanese	47	Insertion	Frameshift	1556	c.1556insG
484		2	M	Japanese	47	Insertion	Frameshift	1556	c.1556insG
485		4	M	Japanese	47	Insertion	Frameshift	1556	c.1556insG
66		65	M	Japanese	44	Point	Nonsense	1556	c.1556G>A
517		11	F	Turkish	44	Point	Nonsense	1556	c.1556G>A
521		45	F	Turkish	44	Point	Nonsense	1556	c.1556G>A
548		45	M	Italian	44	Point	Nonsense	1556	c.1556G>A
550		7	M	Italian	44	Point	Nonsense	1556	c.1556G>A
552		54	M	Italian	44	Point	Nonsense	1556	c.1556G>A
48		38	F	Lebanese	33	Point	Missense	1557	c.1557G>C
49			F	Lebanese	33	Point	Missense	1557	c.1557G>C
50			M	Lebanese	33	Point	Missense	1557	c.1557G>C
509					33	Point	Missense	1557	c.1557G>C
607		64	F	Chinese	331	Point	Missense	1562	c.1562A>G
608			F	Chinese	331	Point	Missense	1562	c.1562A>G
609			F	Chinese	331	Point	Missense	1562	c.1562A>G
610			M	Chinese	331	Point	Missense	1562	c.1562A>G
95			M	Portuguese	35	Point	Missense	1608	c.1608G>C
601		47	F	Spanish	35	Point	Missense	1608	c.1608G>C
599		71	M	Spanish	50	Point	Missense	1613	c.1613C>T
600		88	F	Spanish	50	Point	Missense	1613	c.1613C>T
83	8on		M		50	Point	Missense	1613	c.1613C>T
179		65	F		50	Point	Missense	1613	c.1613C>T
180		47	F		50	Point	Missense	1613	c.1613C>T
256				UK Populat	50	Point	Missense	1613	c.1613C>T
257				UK Populat	50	Point	Missense	1613	c.1613C>T
494			F		50	Point	Missense	1613	c.1613C>T
205			M	French	50	Point	Missense	1613	c.1613C>T
515		26	F	Turkish	262	Point	Missense	1619	c.1619T>G
496					247	Point	Missense	1684	c.1684G>A
497					247	Point	Missense	1684	c.1684G>A
593		26	F	Spanish	117	Point	Missense	1693	c.1693G>A
594		44	F	Spanish	117	Point	Missense	1693	c.1693G>A
595		49	F	Spanish	117	Point	Missense	1693	c.1693G>A
596		32	M	Spanish	117	Point	Missense	1693	c.1693G>A
597		55	F	Spanish	117	Point	Missense	1693	c.1693G>A
598		72	F	Spanish	117	Point	Missense	1693	c.1693G>A
177		54	F		117	Point	Missense	1693	c.1693G>A
178		32	F		117	Point	Missense	1693	c.1693G>A
203		33	F	French	117	Point	Missense	1693	c.1693G>A
465		9	F	Iranian	117	Point	Missense	1693	c.1693G>A
68		30	M	Jewish	45	Deletion		1714	c.1714_171
555		7	F	Italian	326	Point		1716	c.1716+248
556		48	F	Italian	326	Point		1716	c.1716+248
260				UK Populat	48	Point		1716	c.1716+1G>
78		44	M	Ashkenazi J	48	Point		1716	c.1716+1G>

82			Bucharian-J	49	Point	Missense	1718	c.1718G>A
261			UK Populat	49	Point	Missense	1718	c.1718G>A
629	15	F	Indian	350	Point	Missense	1721	c.1721A>C
519	3.5	M	Turkish	263	Point	Missense	1741	c.1741T>C
520	32	F	Turkish	263	Point	Missense	1741	c.1741T>C
263			UK Populat	151	Point	Missense	1742	c.1742G>T
87			US	17	Point	Missense	1760	c.1760G>C
37	49	M	German	17	Point	Missense	1760	c.1760G>C
606	53	M	Spanish	301	Point	Missense	1775	c.1775T>C
136	22	F	Lebanese	9	Point	Missense	1778	c.1778C>T
137		F	Lebanese	9	Point	Missense	1778	c.1778C>T
138		M	Lebanese	9	Point	Missense	1778	c.1778C>T
139		F	Lebanese	9	Point	Missense	1778	c.1778C>T
140		F	Lebanese	9	Point	Missense	1778	c.1778C>T
262			UK Populat	9	Point	Missense	1778	c.1778C>T
498		F		9	Point	Missense	1778	c.1778C>T
499		F		249	Point	Missense	1782	c.1782C>A
501				249	Point	Missense	1782	c.1782C>A
500				249	Point	Missense	1782	c.1782C>A
502	28	F		181	Point	Missense	1789	c.1789G>A
31	85	F	Nantes	13	Point	Nonsense	1797	c.1797T>A
30	71	M	Nantes	13	Point	Nonsense	1797	c.1797T>A
503	44	M	Iranian	250	Point	Missense	1822	c.1822T>C
265			UK Populat	27	Point	Nonsense	1824	c.1824C>A
181	32	F		27	Point	Nonsense	1824	c.1824C>A
157	72	F	Japanese	111	Point	Missense	1849	c.1849T>G
266			UK Populat	28	Point	Missense	1853	c.1853T>C
182	62	F		28	Point	Missense	1853	c.1853T>C
267			UK Populat	28	Point	Missense	1853	c.1853T>C
514		F	Italian	260	Point	Missense	1856	c.1856T>C

HGVS Amin	Legacy Ami	Protein Cha	Domain	Other Varia	FXI:C%	FXI:Ag%	Inheritance	Clinical Sev
0	0		Promoter R	0	67		Heterozygo	Not Report
0	0		Promoter R	0	29		Heterozygo	Not Report
0	0		Serine Prot	0	<1		Homozygot	Severe
0	0			0	32		Heterozygo	Mild
1	-18	p.Met1Ile	Signal Pepti	0			Heterozygo	Not Report
1	-18	p.Met1Ile	Signal Pepti	0	43		Heterozygo	Not Report
15	-4	p.Ser15Leu	Signal Pepti	0	3	3	Homozygot	Not Report
0	0		Linker	0	1	3	Homozygot	Not Report
19	1	p.Glu19*	Linker	0	43		Heterozygo	Not Report
0	0		Apple 1	0	<1	<1	Compound	Severe
0	0		Apple 1	0	20	32	Heterozygo	Not Report
38	20	p.Val38Ala	Apple 1	0		32	Heterozygo	Not Report
41	23	p.Pro41Gln	Apple 1	0	56		Heterozygo	Not Report
41	23	p.Pro41Leu	Apple 1	0	30	39	Heterozygo	Not Report
42	24	p.Ser42Arg	Apple 1	0	29		Heterozygo	Not Report
42	24	p.Ser42Arg	Apple 1	1	2		Compound	Not Report
46	28	p.Cys46Phe	Apple 1	0	24	35	Heterozygo	Mild
46	28	p.Cys46Phe	Apple 1	0	31	41	Heterozygo	Mild
46	28	p.Cys46Phe	Apple 1	0	26		Heterozygo	Mild
46	28	p.Cys46Phe	Apple 1	1	1		Compound	Not Report
47	29	p.Gln47His	Apple 1	0			Heterozygo	Not Report
51	33	p.Thr51Pro	Apple 1	0			Heterozygo	Not Report
51	33	p.Thr51Pro	Apple 1	0			Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	1		Homozygot	Not Report
56	38	p.Cys56Arg	Apple 1	0	3		Homozygot	Not Report
56	38	p.Cys56Arg	Apple 1	0	<1		Homozygot	Severe
56	38	p.Cys56Arg	Apple 1	0	40		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	44		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	44		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	41		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	37		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	37		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	34		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	28		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	42		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	49		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	40		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	68		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	58		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	42		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	25		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	41		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	36		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	30		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	38		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	41		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	42		Heterozygo	Not Report
56	38	p.Cys56Arg	Apple 1	0	18		Heterozygo	Mild
56	38	p.Cys56Arg	Apple 1	0	30		Heterozygo	Mild

56	38	p.Cys56Arg	Apple 1	0		36		Heterozygo	Mild	
56	38	p.Cys56Arg	Apple 1	0		40		Heterozygo	Mild	
56	38	p.Cys56Arg	Apple 1	0		40		Heterozygo	Mild	
56	38	p.Cys56Arg	Apple 1	0		45		Heterozygo	Mild	
56	38	p.Cys56Arg	Apple 1	0		34		Heterozygo	Mild	
56	38	p.Cys56Arg	Apple 1	0		40		Heterozygo	Mild	
56	38	p.Cys56Arg	Apple 1	1		2		Compound	Not Report	
56	38	p.Cys56Arg	Apple 1	1	<1		<1	Compound	Severe	
56	38	p.Cys56Trp	Apple 1	0		20	46	Heterozygo	Not Report	
72	54	p.Arg72Pro	Apple 1	0		63	77	Heterozygo	Not Report	
0	0		Intronic	0	<1			Homozygot	Not Report	
0	0		Intronic	0	<1			Homozygot	Not Report	
0	0		Intronic	0	<1			Heterozygo	Not Report	
76	58	p.Cys76Phe	Apple 1	0	<1			Homozygot	Severe	
76	58	p.Cys76Tyr	Apple 1	0		26		Heterozygo	Not Report	
99	81	p.Ser99Tyr	Apple 1	0		57		Heterozygo	Not Report	
99	81	p.Ser99Tyr	Apple 1	0		57		Heterozygo	Not Report	
0	0		Apple 1	0		15		Heterozygo	Severe	
0	0		Apple 1	0		4	48	Heterozygo	Severe	
101	83	p.Lys101Ar	Apple 1	0		38		Heterozygo	Mild	
106	88	p.Gln106*	Linker	0	<1		0	Homozygot	Severe	
106	88	p.Gln106*	Linker	0	<1		0	Homozygot	Severe	
106	88	p.Gln106*	Linker	0		60	51	Heterozygo	Mild	
106	88	p.Gln106*	Linker	0		46	41	Heterozygo	Mild	
106	88	p.Gln106*	Linker	1	<1		1	Compound	Severe	
109	91	p.Ala109Th	Linker	0				Heterozygo	Not Report	
109	91	p.Ala109Th	Linker	0				Heterozygo	Not Report	
109	91	p.Ala109Th	Linker	0		37		Heterozygo	Not Report	
109	91	p.Ala109Th	Linker	0		26	39	Heterozygo	Not Report	
109	91	p.Ala109Th	Linker	0		45		Heterozygo	Not Report	
109	91	p.Ala109Th	Linker	0		32		Heterozygo	Not Report	
109	91	p.Ala109Th	Linker	0		35		Heterozygo	Not Report	
109	91	p.Ala109Th	Linker	0	<1			Compound	Not Report	
0	0		Intronic	1	<1			Compound	Not Report	
110	92	p.Cys110Gl	Apple 2	0		47	40	Heterozygo	Not Report	
110	92	p.Cys110Gl	Apple 2	0		21	44	Heterozygo	Not Report	
120	102	p.Met120T	Apple 2	0				Heterozygo	Not Report	
120	102	p.Met120T	Apple 2	0		40		Heterozygo	Not Report	
122	104	p.Gly122As	Apple 2	0		42		Heterozygo	Not Report	
122	104	p.Gly122As	Apple 2	0		35		Heterozygo	Mild	
122	104	p.Gly122As	Apple 2	0		33		Heterozygo	Mild	
122	104	p.Gly122As	Apple 2	0		58	61	Heterozygo	Not Report	
122	104	p.Gly122As	Apple 2	0		44		Heterozygo	Not Report	
122	104	p.Gly122As	Apple 2	0		45		Heterozygo	Not Report	
122	104	p.Gly122As	Apple 2	1		2		Compound	Not Report	
134	116	p.Gln134*	Apple 2	0		52	43	Heterozygo	Not Report	
134	116	p.Gln134*	Apple 2	1		1	4	Compound	Severe	
134	116	p.Gln134*	Apple 2	0		10			Not Report	
135	117	p.Glu135*	Apple 2	0		16		Homozygot	Not Report	
135	117	p.Glu135*	Apple 2	0	<1			Homozygot	Not Report	

135	117	p.Glu135*	Apple 2	0	<1		<1		Homozygot	Severe
135	117	p.Glu135*	Apple 2	0	<1			4	Homozygot	Severe
135	117	p.Glu135*	Apple 2	0	<1				Homozygot	Severe
135	117	p.Glu135*	Apple 2	0		1		7	Homozygot	Severe
135	117	p.Glu135*	Apple 2	0		1		14	Homozygot	Severe
135	117	p.Glu135*	Apple 2	0		4			Homozygot	Severe
135	117	p.Glu135*	Apple 2	0		1			Homozygot	Severe
135	117	p.Glu135*	Apple 2	0		2			Homozygot	Severe
135	117	p.Glu135*	Apple 2	0					Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0					Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		18			Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		44			heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		62			Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		35		33	Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		32		39	Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		38			Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		42			Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		34			Heterozygo	Not Report
135	117	p.Glu135*	Apple 2	0		47		88	Heterozygo	Mild
135	117	p.Glu135*	Apple 2	1	<10		<10		Compound	Severe
135	117	p.Glu135*	Apple 2	1	<10		<10		Compound	Severe
135	117	p.Glu135*	Apple 2	1	<10		<10		Compound	Severe
135	117	p.Glu135*	Apple 2	1	<10		<10		Compound	Severe
135	117	p.Glu135*	Apple 2	0					Compound	Not Report
135	117	p.Glu135*	Apple 2	1		1		3	Compound	Not Report
135	117	p.Glu135*	Apple 2	1	<0.5			4	Compound	Severe
135	117	p.Glu135*	Apple 2	1	<3		<5		Compound	Severe
135	117	p.Glu135*	Apple 2	1	<1		<3		Compound	Severe
135	117	p.Glu135*	Apple 2	1		0.02			Compound	Severe
135	117	p.Glu135*	Apple 2	0		0.02			Compound	Severe
135	117	p.Glu135*	Apple 2	0	<1				Compound	Severe
135	117	p.Glu135*	Apple 2	0	<1				Compound	Severe
135	117	p.Glu135*	Apple 2	0	<1		<1		Compound	Severe
135	117	p.Glu135*	Apple 2	1	<1				Compound	Severe
135	117	p.Glu135*	Apple 2	1	<1				Compound	Severe
135	117	p.Glu135*	Apple 2	1	<1		<1		Compound	Severe
135	117	p.Glu135*	Apple 2	1				3	Compound	Not Report
135	117	p.Glu135*	Apple 2	1		6			Compound	Not Report
135	117	p.Glu135*	Apple 2	1	<1				Compound	Not Report
135	117	p.Glu135*	Apple 2	0	<1			5	Compound	Severe
135	117	p.Glu135*	Apple 2	0	<1			5	Compound	Severe
135	117	p.Glu135*	Apple 2	1	<1			5	Compound	Severe
135	117	p.Glu135*	Apple 2	0					Compound	Not Report
135	117	p.Glu135*	Apple 2	1		2			Compound	Not Report
135	117	p.Glu135*	Apple 2	1	<1		<1		Compound	Severe
135	117	p.Glu135*	Apple 2	0	<1		<1		Compound	Severe
135	117	p.Glu135*	Apple 2	0		0				Severe
135	117	p.Glu135*	Apple 2	0		42				Mild
135	117	p.Glu135*	Apple 2	0		30				Mild
135	117	p.Glu135*	Apple 2	0		1				Severe

135	117	p.Glu135*	Apple 2	0		59				Mild
135	117	p.Glu135*	Apple 2	0		22				Mild
135	117	p.Glu135*	Apple 2	0		43				Mild
135	117	p.Glu135*	Apple 2	0	<1			0		Mild
135	117	p.Glu135*	Apple 2	0	<1			0		Severe
135	117	p.Glu135*	Apple 2	0	<1			1		Severe
136	118	p.Cys136*	Apple 2	1	<1				Compound	Severe
136	118	p.Cys136*	Apple 2	1	<1				Compound	Severe
136	118	p.Cys136*	Apple 2	0	<1			0		Mild
136	118	p.Cys136*	Apple 2	0	<1			0		Mild
140	122	p.Cys140Ty	Apple 2	0		4		3	Homozygot	Not Report
140	122	p.Cys140Ty	Apple 2	0		25			Heterozygo	Not Report
140	122	p.Cys140Ty	Apple 2	0		24			Heterozygo	Not Report
140	122	p.Cys140Ty	Apple 2	0		31			Heterozygo	Not Report
140	122	p.Cys140Ty	Apple 2	0					Compound	Not Report
141	123	p.Thr141M	Apple 2	0		1		4	Compound	Severe
143	125	p.Asp143Al	Apple 2	0		49			Heterozygo	Not Report
143	125	p.Asp143Al	Apple 2	0		47			Heterozygo	Not Report
143	125	p.Asp143Al	Apple 2	0					Heterozygo	Not Report
145	127	p.His145Ar	Apple 2	0		27		125	Heterozygo	Not Report
145	127	p.His145Ar	Apple 2	0		52		118	Heterozygo	Not Report
145	127	p.His145Ar	Apple 2	0		56		157	Heterozygo	Not Report
145	127	p.His145Ar	Apple 2	1		7			Compound	Not Report
146	128	p.Cys146*	Apple 2	0	<1				Homozygot	Severe
146	128	p.Cys146*	Apple 2	0	<1				Homozygot	Severe
146	128	p.Cys146*	Apple 2	0		65		64	Heterozygo	Mild
146	128	p.Cys146*	Apple 2	0		34		27	Heterozygo	Mild
146	128	p.Cys146*	Apple 2	0		38			Heterozygo	Not Report
146	128	p.Cys146*	Apple 2	0		45			Heterozygo	Not Report
146	128	p.Cys146*	Apple 2	0		46			Heterozygo	Not Report
146	128	p.Cys146*	Apple 2	0		16			Heterozygo	Not Report
146	128	p.Cys146*	Apple 2	0		49		41	Heterozygo	Mild
146	128	p.Cys146*	Apple 2	0		61			Heterozygo	Not Report
146	128	p.Cys146*	Apple 2	0	<2				Compound	Severe
146	128	p.Cys146*	Apple 2	0	<1		<1		Compound	Severe
146	128	p.Cys146*	Apple 2	1		4			Compound	Severe
146	128	p.Cys146*	Apple 2	1	<2				Compound	Severe
146	128	p.Cys146*	Apple 2	1		4			Compound	Not Report
146	128	p.Cys146*	Apple 2	1	<1		<3		Compound	Severe
146	128	p.Cys146*	Apple 2	1		2			Compound	Not Report
146	128	p.Cys146*	Apple 2	1	<1				Compound	Severe
146	128	p.Cys146*	Apple 2	0	<1				Compound	Severe
146	128	p.Cys146*	Apple 2	0		29		29		Not Report
146	128	p.Cys146*	Apple 2	0		44		38		Not Report
146	128	p.Cys146*	Apple 2	0		41				Not Report
150	132	p.Thr150M	Apple 2	0		23			Heterozygo	Not Report
150	132	p.Thr150M	Apple 2	0		34			Heterozygo	Not Report
150	132	p.Thr150M	Apple 2	0		52			Heterozygo	Not Report
150	132	p.Thr150M	Apple 2	0		37			Heterozygo	Not Report
150	132	p.Thr150M	Apple 2	0		43			Heterozygo	Not Report

151	133	p.Tyr151Cy	Apple 2	0		47		Heterozygo	Not Report	
151	133	p.Tyr151Se	Apple 2	0		38		Homozygot	Mild	
151	133	p.Tyr151Se	Apple 2	0		50		Heterozygo	Not Report	
151	133	p.Tyr151Se	Apple 2	0		36		Heterozygo	Not Report	
151	133	p.Tyr151Se	Apple 2	0		38			Not Report	
152	134	p.Ala152Pr	Apple 2	0				Homozygot	Not Report	
152	134	p.Ala152Pr	Apple 2	0	<1			Homozygot	Severe	
162	144	p.Arg162Cy	Apple 2	0		35		Heterozygo	Not Report	
0	0		Intronic	0		3		Homozygot	Severe	
0	0		Intronic	0		56		Heterozygo	Not Report	
0	0		Intronic	0		36	25	Heterozygo	Not Report	
173	155	p.Gly173Gl	Apple 2	0		41		Heterozygo	Not Report	
173	155	p.Gly173Gl	Apple 2	0		43	64	Heterozygo	Not Report	
173	155	p.Gly173Gl	Apple 2	0		30		Heterozygo	Not Report	
190	172	p.Leu190Pr	Apple 2	0				Heterozygo	Not Report	
0	0		Intronic	0		33		Heterozygo	Not Report	
0	0		Intronic	0		51		Heterozygo	Not Report	
0	0		Intronic	0		85		Heterozygo	Not Report	
0	0		Intronic	0		35		Heterozygo	Mild	
0	0		Intronic	1		46	10	Compound	Not Report	
0	0		Apple 3	1		5		Compound	Not Report	
199	181	p.Ala199Va	Apple 3	1		0.07	0.07	Compound	Severe	
200	182	p.Cys200Ty	Apple 3	0		47		Heterozygo	Not Report	
200	182	p.Cys200Ty	Apple 3	0		34		Heterozygo	Not Report	
200	182	p.Cys200Se	Apple 3	0		34		Heterozygo	Not Report	
202	184	p.Arg202Gl	Apple 3	0		69	121	Heterozygo	Not Report	
206	188	p.Pro206Se	Apple 3	0		30		Heterozygo	Not Report	
0	0	p.Ile215_As	Apple 3	0		39	34	Heterozygo	Not Report	
228	210	p.Arg228*	Apple 3	1	<1		3	Compound	Severe	
230	212	p.Cys230Se	Apple 3	0		38		Heterozygo	Not Report	
230	212	p.Cys230Se	Apple 3	0		35		Heterozygo	Not Report	
230	212	p.Cys230Ar	Apple 3	0		1		Homozygot	Not Report	
230	212	p.Cys230Ar	Apple 3	0				Homozygot	Severe	
230	212	p.Cys230Ar	Apple 3	0		34		Heterozygo	Not Report	
230	212	p.Cys230Ar	Apple 3	0		34		Heterozygo	Not Report	
232	214	p.His232Pr	Apple 3	0	<1			Homozygot	Not Report	
239	221	p.Phe239Se	Apple 3	0	<3		7	Homozygot	Severe	
239	221	p.Phe239Se	Apple 3	1				Compound	Not Report	
239	221	p.Phe239Se	Apple 3	1				Compound	Severe	
0	0		Apple 3	1		24		Compound	Not Report	
243	225	p.Ser243Ph	Apple 3	0		22	22	Heterozygo	Not Report	
243	225	p.Ser243Ph	Apple 3	0		25	25	Heterozygo	Not Report	
244	226	p.Gln244*	Apple 3	0	<3			Heterozygo	Severe	
246	228	p.Trp246*	Apple 3	0		62	64.1	Heterozygo	Not Report	
246	228	p.Trp246*	Apple 3	0		40	48.3	Heterozygo	Not Report	
246	228	p.Trp246*	Apple 3	0		38	44.8	Heterozygo	Not Report	
246	228	p.Trp246*	Apple 3	0				Heterozygo	Not Report	
246	228	p.Trp246*	Apple 3	1	<1			Compound	Not Report	
246	228	p.Trp246*	Apple 3	0	<1			Compound	Not Report	
246	228	p.Trp246*	Apple 3	1				Compound	Not Report	

246	228	p.Trp246Cy	Apple 3	0		2	Undetectat	Homozygot	Severe	
246	228	p.Trp246Cy	Apple 3	0		3		Homozygot	Severe	
246	228	p.Trp246Cy	Apple 3	0		6		Homozygot	Severe	
246	228	p.Trp246Cy	Apple 3	0		40		Heterozygo	Mild	
246	228	p.Trp246Cy	Apple 3	0		36		Heterozygo	Mild	
246	228	p.Trp246Cy	Apple 3	0		50		Heterozygo	Mild	
246	228	p.Trp246Cy	Apple 3	0		31		Heterozygo	Mild	
246	228	p.Trp246Cy	Apple 3	0		53		Heterozygo	Mild	
252	234	p.Arg252Ly	Apple 3	0		41		Heterozygo	Not Report	
252	234	p.Arg252Se	Apple 3	0		42		Heterozygo	Not Report	
252	234	p.Arg252Se	Apple 3	0		38		Heterozygo	Not Report	
255	237	p.Cys255Ty	Apple 3	0	<1			Compound	Severe	
255	237	p.Cys255Ty	Apple 3	1	<1				Severe	
0	0		Apple 3	0		3		Compound	Not Report	
261	243	p.Glu261As	Apple 3	0		30	28	Heterozygo	Not Report	
263	245	p.Gly263Gl	Apple 3	0		31	26	Heterozygo	Mild	
263	245	p.Gly263Gl	Apple 3	0		61		Heterozygo	Mild	
266	248	p.Ser266As	Apple 3	0		67	80	Heterozygo	Not Report	
266	248	p.Ser266As	Apple 3	0		42	70	Compound	Mild	
268	250	p.Arg268Cy	Apple 3	0				Homozygot	Severe	
268	250	p.Arg268Cy	Apple 3	0		8		Homozygot	Not Report	
268	250	p.Arg268Cy	Apple 3	0				Heterozygo	Not Report	
268	250	p.Arg268Cy	Apple 3	0		35		Heterozygo	Not Report	
268	250	p.Arg268Cy	Apple 3	0		53		Heterozygo	Not Report	
268	250	p.Arg268Hi	Apple 3	0		24		Compound	Not Report	
270	252	p.Lys270Ile	Apple 3	1		4	2	Compound	Not Report	
277	259	p.Gly277Se	Apple 3	0		44	34	Heterozygo	Not Report	
281	263	p.Gln281*	Apple 3	0		1		Homozygot	Not Report	
281	263	p.Gln281*	Apple 3	0	<1			Homozygot	Not Report	
281	263	p.Gln281*	Apple 3	0		1	<1	Homozygot	Not Report	
281	263	p.Gln281*	Apple 3	0	<1		Undetectat	Homozygot	Severe	
281	263	p.Gln281*	Apple 3	0	<1			Homozygot	Severe	
281	263	p.Gln281*	Apple 3	0		45		Heterozygo	Mild	
281	263	p.Gln281*	Apple 3	0		49		Heterozygo	Mild	
281	263	p.Gln281*	Apple 3	0		55		Heterozygo	Mild	
281	263	p.Gln281*	Apple 3	0		40		Heterozygo	Mild	
281	263	p.Gln281*	Apple 3	0		61		Heterozygo	Mild	
281	263	p.Gln281*	Apple 3	0		40		Heterozygo	Mild	
281	263	p.Gln281*	Apple 3	1		1		Compound	Severe	
281	263	p.Gln281*	Apple 3	0	<1		<1	Compound	Severe	
281	263	p.Gln281*	Apple 3	1		3		Compound	Not Report	
281	263	p.Gln281*	Apple 3	1		4		Compound	Not Report	
281	263	p.Gln281*	Apple 3	1	<1			Compound	Not Report	
281	263	p.Gln281*	Apple 3	1		2		Compound	Not Report	
281	263	p.Gln281*	Apple 3	0		260	3	Compound	Not Report	
301	283	p.Phe301Le	Apple 4	0	<10		<10	Homozygot	Severe	
301	283	p.Phe301Le	Apple 4	0		7		Homozygot	Not Report	
301	283	p.Phe301Le	Apple 4	0		76		Heterozygo	Mild	
301	283	p.Phe301Le	Apple 4	0		87		Heterozygo	Mild	
301	283	p.Phe301Le	Apple 4	0		35		Heterozygo	Not Report	

301	283	p.Phe301Le	Apple 4	0	48		Heterozygo	Not Report	
301	283	p.Phe301Le	Apple 4	0	51		Heterozygo	Not Report	
301	283	p.Phe301Le	Apple 4	0	85		Heterozygo	Not Report	
301	283	p.Phe301Le	Apple 4	0	2	6	Compound	Not Report	
301	283	p.Phe301Le	Apple 4	1	2	2	Compound	Not Report	
301	283	p.Phe301Le	Apple 4	1	4		Compound	Severe	
301	283	p.Phe301Le	Apple 4	1	1	<1	Compound	Not Report	
301	283	p.Phe301Le	Apple 4	1	4		Compound	Not Report	
301	283	p.Phe301Le	Apple 4	1	6		Compound	Not Report	
0	0		Apple 4	0	48		Heterozygo	Mild	
0	0		Apple 4	0	36			Not Report	
0	0		Apple 4	0	66		Heterozygo	Not Report	
313	295	p.Ser313Ile	Apple 4	0	41	47.4	Heterozygo	Not Report	
313	295	p.Ser313Ile	Apple 4	0	58	63.1	Heterozygo	Not Report	
313	295	p.Ser313Ile	Apple 4	0	57	59.8	Heterozygo	Not Report	
313	295	p.Ser313Ile	Apple 4	1	2	5.4	Compound	Not Report	
315	297	p.Glu315Ly	Apple 4	0	40		Heterozygo	Not Report	
315	297	p.Glu315Ly	Apple 4	0	40	52	Heterozygo	Not Report	
315	297	p.Glu315Ly	Apple 4	0	38	39	Heterozygo	Not Report	
315	297	p.Glu315Ly	Apple 4	0	40		Heterozygo	Not Report	
315	297	p.Glu315Ly	Apple 4	0	39		Heterozygo	Not Report	
315	297	p.Glu315Ly	Apple 4	0	29		Heterozygo	Not Report	
315	297	p.Glu315Ly	Apple 4	1	4		Compound	Not Report	
315	297	p.Glu315Ly	Apple 4	1	7		Compound	Not Report	
315	297	p.Glu315Ly	Apple 4	1	34		Compound	Not Report	
315	297	p.Glu315Ly	Apple 4	1	36		Compound	Not Report	
315	297	p.Glu315Ly	Apple 4	1	<2	<5	Compound	Severe	
0	0	p.Cys321Hi	Apple 4	0	<1	<1	Homozygot	Severe	
0	0	p.Cys321Hi	Apple 4	0	57		Heterozygo	Not Report	
322	304	p.Thr322Ile	Apple 4	0	11	26	Homozygot	Not Report	
322	304	p.Thr322Ile	Apple 4	0	47		Heterozygo	Not Report	
322	304	p.Thr322Ile	Apple 4	0	51		Heterozygo	Not Report	
325	307	p.Val325Ph	Apple 4	0	50		Heterozygo	Not Report	
325	307	p.Val325Ph	Apple 4	0	55		Heterozygo	Not Report	
325	307	p.Val325Ph	Apple 4	0	52		Heterozygo	Not Report	
326	308	p.Arg326Cy	Apple 4	0	41	33	Heterozygo	Mild	
326	308	p.Arg326Cy	Apple 4	0	43	33	Heterozygo	Not Report	
326	308	p.Arg326Cy	Apple 4	0	36		Heterozygo	Not Report	
326	308	p.Arg326Cy	Apple 4	1	52		Compound	Not Report	
331	313	p.Thr331Ile	Apple 4	0	<1		Homozygot	Severe	
341	323	p.Glu341Ly	Apple 4	0			Heterozygo	Not Report	
341	323	p.Glu341Ly	Apple 4	1	9		Compound	Not Report	
341	323	p.Glu341Ly	Apple 4	1	9	9	Compound	Not Report	
0	0		Apple 4	0	56		Heterozygo	Mild	
342	324	p.Gly342=	Apple 4	1	1	5	Compound	Severe	
342	324	p.Gly342=	Apple 4	1	1	12	Compound	Severe	
342	324	p.Gly342=	Apple 4	1	2		Compound	Not Report	
0	0		Apple 4	0	45		Heterozygo	Not Report	
345	327	p.Lys345*	Apple 4	0	1	<1	Compound	Not Report	
354	336	p.Gly354Ar	Apple 4	0			Compound	Not Report	

0	0		Apple 4	0		1		15	Homozygot Severe
0	0		Apple 4	1		2			Compound Not Report
359	341	p.Ile359Me	Apple 4	0					Heterozygo Not Report
360	342	p.Leu360Pr	Apple 4	0	<1				Homozygot Severe
362	344	p.Gly362Ar	Apple 4	0		38			Heterozygo Not Report
368	350	p.Gly368Gl	Apple 4	1		1			Compound Not Report
369	351	p.Tyr369Se	Apple 4	0	<1				Homozygot Severe
369	351	p.Tyr369*	Apple 4	0	<1				Homozygot Not Report
369	351	p.Tyr369*	Apple 4	0		53			Heterozygo Mild
369	351	p.Tyr369*	Apple 4	0		59			Heterozygo Mild
369	351	p.Tyr369*	Apple 4	1	<1				Compound Not Report
369	351	p.Tyr369*	Apple 4	1		2	<1		Compound Not Report
369	351	p.Tyr369*	Apple 4	1		1	<1		Compound Not Report
373	355	p.Leu373Se	Apple 4	0		67			Heterozygo Not Report
374	356	p.Cys374Ar	Apple 4	0		40			Heterozygo Not Report
0	0		Intronic	0	<1				Heterozygo Severe
0	0		Intronic	0		50			Heterozygo Not Report
378	360		Intronic	0		73			Heterozygo Not Report
0	0		Intronic	0	<10		<50		Homozygot Severe
0	0		Intronic	0	<10		<50		Homozygot Severe
0	0		Intronic	0	<10		<50		Homozygot Severe
0	0		Intronic	0		3			Compound Not Report
389	371	p.Val389Ile	Serine Prot	0		34		102	Heterozygo Not Report
393	375	p.Ala393Va	Serine Prot	0		35		69	Heterozygo Not Report
396	378	p.Arg396Cy	Serine Prot	0		61		83	Heterozygo Not Report
396	378	p.Arg396Cy	Serine Prot	0		44			Heterozygo Not Report
399	381	p.Trp399Le	Serine Prot	0		35		40	Heterozygo Not Report
404	386	p.Thr404As	Serine Prot	0		2	Decreased		Homozygot Severe
404	386	p.Thr404As	Serine Prot	0		2	Decreased		Homozygot Severe
404	386	p.Thr404As	Serine Prot	0		108	Normal		Heterozygo Mild
406	388	p.His406Pr	Serine Prot	0		0.36		0.37	Heterozygo Severe
407	389	p.Thr407Pr	Serine Prot	0		35			Heterozygo Not Report
408	390	p.Thr408Pr	Serine Prot	0					Heterozygo Not Report
412	394	p.Gln412*	Serine Prot	0	<1				Homozygot Not Report
416	398	p.Cys416Ty	Serine Prot	0	<1				Homozygot Severe
416	398	p.Cys416Ty	Serine Prot	0	<1				Homozygot Severe
416	398	p.Cys416Ty	Serine Prot	0					Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		28			Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		22			Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		34			Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		26			Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		37			Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		33			Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		40			Heterozygo Mild
416	398	p.Cys416Ty	Serine Prot	0		40			Heterozygo Mild
416	398	p.Cys416Ty	Serine Prot	0		25		25	Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		58			Heterozygo Not Report
416	398	p.Cys416Ty	Serine Prot	0		43			Heterozygo Not Report
418	400	p.Gly418Va	Serine Prot	0	<2				Homozygot Severe
418	400	p.Gly418Va	Serine Prot	0					Heterozygo Not Report

418	400	p.Gly418Va	Serine Prot	0	15		Heterozygo	Not Report	
418	400	p.Gly418Va	Serine Prot	0	15	Decreased	Heterozygo	Not Report	
418	400	p.Gly418Va	Serine Prot	0	45		Heterozygo	Not Report	
418	400	p.Gly418Va	Serine Prot	0	<3	10	Compound	Severe	
418	400	p.Gly418Va	Serine Prot	1	<3		Compound	Severe	
418	400	p.Gly418Va	Serine Prot	1	3		Compound	Not Report	
419	401	p.Ser419Al	Serine Prot	0	30			Not Report	
424	406	p.Gln424*	Serine Prot	0	<1		Homozygot	Not Report	
424	406	p.Gln424*	Serine Prot	0	46		Heterozygo	Not Report	
425	407	p.Trp425Cy	Serine Prot	0	0.22	0.27	Heterozygo	Severe	
426	408	p.Ile426Thr	Serine Prot	0	28		Heterozygo	Not Report	
428	410	p.Thr428Ile	Serine Prot	0	25		Heterozygo	Not Report	
428	410	p.Thr428Ile	Serine Prot	0	38		Heterozygo	Not Report	
430	412	p.Ala430Se	Serine Prot	0	35	35	Heterozygo	Not Report	
430	412	p.Ala430Va	Serine Prot	0	45	39	Heterozygo	Mild	
430	412	p.Ala430Va	Serine Prot	1	<1	1	Compound	Severe	
0	0		Intronic	0	50		Heterozygo	Not Report	
0	0		Intronic	0	1		Homozygot	Severe	
0	0		Serine Prot	0	<1		Homozygot	Not Report	
0	0		Serine Prot	1	1	4.1	Compound	Not Report	
443	425	p.Arg443Cy	Serine Prot	0	46		Heterozygo	Not Report	
443	425	p.Arg443Cy	Serine Prot	0	31	39	Heterozygo	Not Report	
460	442	p.Phe460V	Serine Prot	0	47	50	Heterozygo	Mild	
465	447	p.Glu465*	Serine Prot	1	Undetectat	Undetectat	Compound	Severe	
451	433	p.Gln451Gl	Serine Prot	0	64		Heterozygo	Not Report	
451	433	p.Gln451Gl	Serine Prot	0	58		Heterozygo	Not Report	
478	460	p.Gly478Ar	Serine Prot	0			Homozygot	Severe	
478	460	p.Gly478Ar	Serine Prot	0	<1		Homozygot	Severe	
478	460	p.Gly478Ar	Serine Prot	0	<1		Homozygot	Not Report	
478	460	p.Gly478Ar	Serine Prot	0	<1		Homozygot	Severe	
478	460	p.Gly478Ar	Serine Prot	0	5		Homozygot	Not Report	
478	460	p.Gly478Ar	Serine Prot	0	51		Heterozygo	Not Report	
478	460	p.Gly478Ar	Serine Prot	0	42		Heterozygo	Mild	
478	460	p.Gly478Ar	Serine Prot	0	32		Heterozygo	Not Report	
478	460	p.Gly478Ar	Serine Prot	1	2		Compound	Not Report	
478	460	p.Gly478Ar	Serine Prot	1	18	13	Compound	Not Report	
478	460	p.Gly478Ar	Serine Prot	1	2	2	Compound	Not Report	
483	465	p.Leu483Se	Serine Prot	0	34		Heterozygo	Not Report	
493	475	p.Thr493Ile	Serine Prot	0			Heterozygo	Mild	
493	475	p.Thr493Ile	Serine Prot	0	39	27	Heterozygo	Mild	
493	475	p.Thr493Ile	Serine Prot	0	46		Heterozygo	Not Report	
494	476		Serine Prot	0	38	20	Heterozygo	Not Report	
497	479	p.Arg497*	Serine Prot	0	55		Heterozygo	Not Report	
500	482	p.Cys500Ar	Serine Prot	0	9		Heterozygo	Not Report	
500	482	p.Cys500Tr	Serine Prot	0	37		Heterozygo	Not Report	
503	485	p.Ser503Pr	Serine Prot	0	<1		Homozygot	Severe	
511	493	p.Tyr511Hi	Serine Prot	1	2		Compound	Severe	
511	493	p.Tyr511Hi	Serine Prot	1	1		Compound	Severe	
515	497	p.Trp515Cy	Serine Prot	0	22	25	Heterozygo	Not Report	
515	497	p.Trp515Cy	Serine Prot	0	36		Heterozygo	Not Report	

515	497	p.Trp515Cy	Serine Prot	0		36		Heterozygo	Not Report	
515	497	p.Trp515Cy	Serine Prot	0		40		Heterozygo	Not Report	
516	498	p.Val516M	Serine Prot	1		1		Compound	Not Report	
0	0		Serine Prot	0		35		Heterozygo	Not Report	
0	0		Serine Prot	0		54		Heterozygo	Not Report	
0	0		Serine Prot	1	<1			Compound	Severe	
0	0		Serine Prot	1		4		Compound	Not Report	
519	501	p.Trp519*	Serine Prot	0	<5		Undetectat	Homozygot	Severe	
519	501	p.Trp519*	Serine Prot	0				Heterozygo	Not Report	
519	501	p.Trp519*	Serine Prot	0				Heterozygo	Not Report	
519	501	p.Trp519*	Serine Prot	0		114		Heterozygo	Not Report	
519	501	p.Trp519*	Serine Prot	0		47		Heterozygo	Not Report	
519	501	p.Trp519*	Serine Prot	0		36		Heterozygo	Not Report	
519	501	p.Trp519Cy	Serine Prot	0		2	<1	Homozygot	Severe	
519	501	p.Trp519Cy	Serine Prot	0		36	36	Heterozygo	Mild	
519	501	p.Trp519Cy	Serine Prot	0		40	32	Heterozygo	Mild	
519	501	p.Trp519Cy	Serine Prot	1		2	<1	Compound	Not Report	
521	503	p.Tyr521Cy	Serine Prot	0		13	76	Homozygot	Not Report	
521	503	p.Tyr521Cy	Serine Prot	0		38	93	Heterozygo	Not Report	
521	503	p.Tyr521Cy	Serine Prot	0		42	102	Heterozygo	Not Report	
521	503	p.Tyr521Cy	Serine Prot	0		37	98	Heterozygo	Not Report	
536	518	p.Lys536As	Serine Prot	0				Heterozygo	Mild	
536	518	p.Lys536As	Serine Prot	1		3		Compound	Not Report	
538	520	p.Pro538Le	Serine Prot	0		20		Homozygot	Not Report	
538	520	p.Pro538Le	Serine Prot	0		59		Heterozygo	Not Report	
538	520	p.Pro538Le	Serine Prot	0		34		Heterozygo	Not Report	
538	520	p.Pro538Le	Serine Prot	0		43	90	Heterozygo	Not Report	
538	520	p.Pro538Le	Serine Prot	0		48		Heterozygo	Not Report	
538	520	p.Pro538Le	Serine Prot	0		48	80	Heterozygo	Not Report	
538	520	p.Pro538Le	Serine Prot	0		53		Heterozygo	Not Report	
538	520	p.Pro538Le	Serine Prot	0		50	74	Heterozygo	Not Report	
538	520	p.Pro538Le	Serine Prot	1		30		Compound	Not Report	
540	522	p.Val540Gl	Serine Prot	0				Heterozygo	Not Report	
562	544	p.Gly562Se	Serine Prot	0		62		Heterozygo	Not Report	
562	544	p.Gly562Se	Serine Prot	0		105		Heterozygo	Not Report	
565	547	p.Glu565Ly	Serine Prot	0		30		Heterozygo	Not Report	
565	547	p.Glu565Ly	Serine Prot	0		41		Heterozygo	Not Report	
565	547	p.Glu565Ly	Serine Prot	0		36		Heterozygo	Not Report	
565	547	p.Glu565Ly	Serine Prot	0		45		Heterozygo	Not Report	
565	547	p.Glu565Ly	Serine Prot	0		32		Heterozygo	Not Report	
565	547	p.Glu565Ly	Serine Prot	0		63		Heterozygo	Not Report	
565	547	p.Glu565Ly	Serine Prot	0		49	37	Heterozygo	Mild	
565	547	p.Glu565Ly	Serine Prot	0		25	18	Heterozygo	Mild	
565	547	p.Glu565Ly	Serine Prot	0		23	32	Heterozygo	Not Report	
565	547	p.Glu565Ly	Serine Prot	1		35		Compound	Not Report	
0	0		Serine Prot	1	<1		<10	Compound	Severe	
0	0		Intronic	0		37		Heterozygo	Not Report	
0	0		Intronic	0		60		Heterozygo	Not Report	
0	0		Serine Prot	0		71		Heterozygo	Not Report	
0	0		Serine Prot	1	<10		<10	Compound	Severe	

573	555	p.Gly573Gl	Serine Prot	0	<1			100	Homozygot	Severe
573	555	p.Gly573Gl	Serine Prot	0		51			Heterozygo	Not Report
574	556	p.Asp574Al	Serine Prot	0	<1				Homozygot	Not Report
581	563	p.Cys581Ar	Serine Prot	0					Homozygot	Not Report
581	563	p.Cys581Ar	Serine Prot	0					Heterozygo	Not Report
581	563	p.Cys581Ph	Serine Prot	0		45			Heterozygo	Not Report
587	569	p.Trp587Se	Serine Prot	0		15			Heterozygo	Not Report
587	569	p.Trp587Se	Serine Prot	0					Heterozygo	Not Report
592	574	p.Ile592Thr	Serine Prot	0		43			Heterozygo	Not Report
593	575	p.Thr593M	Serine Prot	0		2		105	Homozygot	Not Report
593	575	p.Thr593M	Serine Prot	0		38		83	Heterozygo	Not Report
593	575	p.Thr593M	Serine Prot	0		67		25	Heterozygo	Not Report
593	575	p.Thr593M	Serine Prot	0		43		106	Heterozygo	Not Report
593	575	p.Thr593M	Serine Prot	0		43		112	Heterozygo	Not Report
593	575	p.Thr593M	Serine Prot	0		51		85	Heterozygo	Not Report
593	575	p.Thr593M	Serine Prot	0		39			Heterozygo	Not Report
594	576	p.Ser594Ar	Serine Prot	0		27		23	Heterozygo	Mild
594	576	p.Ser594Ar	Serine Prot	0		27		23	Heterozygo	Not Report
594	576	p.Ser594Ar	Serine Prot	0		46		71	Heterozygo	Not Report
597	579	p.Glu597Ly	Serine Prot	0		15			Heterozygo	Not Report
599	581	p.Cys599*	Serine Prot	1		1		20	Homozygot	Severe
599	581	p.Cys599*	Serine Prot	0		1		44	Compound	Severe
608	590	p.Tyr608Hi	Serine Prot	0	<1				Homozygot	Severe
608	590	p.Tyr608*	Serine Prot	0		41			Heterozygo	Not Report
608	590	p.Tyr608*	Serine Prot	0		30				Not Report
617	599	p.Trp617Ar	Serine Prot	0	<1		<1		Homozygot	Severe
618	600	p.Ile618Ser	Serine Prot	0	<2				Homozygot	Severe
618	600	p.Ile618Ser	Serine Prot	0		42		35	Heterozygo	Not Report
618	600	p.Ile618Ser	Serine Prot	0		23			Heterozygo	Not Report
619	601	p.Leu619Pr	Serine Prot	0	<1		<1		Homozygot	Severe

Comments	Reference
ed	Mitchell et al 2006
ed	Saunders et al 2009
Patient's bl	Zucker et al 2007
Mild bleedi	Mitchell et al 2004
ed	Mitchell et al 2006
ed	Mitchell et al 2007
ed	Quelin et al 2006
No bleedin	Castaman et al 2008
ed	Mitchell et al 2006
Gingival	Zucker et al 2007
FXI:C/FXI:A	Spena et al 2009
Asymptom	Zucker et al 2007
ed	Mitchell et al 2006
ed	Quelin et al 2005
ed	Saunders et al 2009
Bleeding fo	Shao et al 2016
Menorrhag	Hill et al 2005
Easy bruisir	Hill et al 2005
Bleeding pc	Hill et al 2005
Easy bruisir	Shao et al 2016
ed	Mitchell et al 2006
Epistaxis	Colakoglu et al 2018
Epistaxis	Colakoglu et al 2018
	Esteban et al 2017
	Esteban et al 2017
No bleedin	Zivelin et al 2002
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
Mild bleedi	Zivelin et al 2002
	Zivelin et al 2002

Hematoma	Zivelin et al 2002
No bleedin	Zivelin et al 2002
	Zivelin et al 2002
	Zivelin et al 2002
	Zivelin et al 2002
	Zivelin et al 2002
	Esteban et al 2017
	Quelin et al 2005
FXI:C/FXI:A	Spena et al 2009
FXI:C/FXI:A	Spena et al 2009
Excessive b	Kawankar et al 2016
No bleedin	Kawankar et al 2016
Spontaneo	Kawankar et al 2016
	Mitchell et al 2006
No bleedin	Zivelin et al 1999 (Abstract)
ed	Saunders et al 2009
ed	Saunders et al 2009
Non-bleede	Ventura et al 2000
Non-bleede	Ventura et al 2000
Asymptom	Hill et al 2005
No excessiv	Quelin et al 2004
Patient tre	Quelin et al 2004
No excessiv	Quelin et al 2004
No excessiv	Quelin et al 2004
	Quelin et al 2004
Asymptom	Colakoglu et al 2018
Asymptom	Colakoglu et al 2018
	Esteban et al 2017
Haemorrha	Guella et al 2008
ed	Mitchell et al 2006
Epistaxis	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Bleeding af	Lin et al 2020
ed	Quelin et al 2005
Epistaxis	Quelin et al 2005
ed	Mitchell et al 2006
bleeding pc	Mitchell et al 2007
Suffered fr	Alhaq et al 2000
	Mitchell et al 2003
	Mitchell et al 2003
ed	Mitchell et al 2006
ed	Mitchell et al 2006
ed	Saunders et al 2009
APTT: 106 s	Duncan et al 2008
ed	Dossenbach-Glaninger & Hopmeier 2006
Bleeding af	Castaman et al 2008
Bleeding at	Dossenbach-Glaninger et al 2002
Bleeding af	Karimi et al 2009
Bleeding du	Kawankar et al 2016

	Saunders et al 2009
	Saunders et al 2009
	Saunders et al 2009
Excessive b	Ventura et al 2000
Moderate E	Ventura et al 2000
Non-bleede	Ventura et al 2000
Non-bleede	Ventura et al 2000
Non-bleede	Ventura et al 2000
Epistaxis	Colakoglu et al 2018
Asymptom	Colakoglu et al 2018
Bleeding af	Quelin et al 2006
ed	Saunders et al 2009
ed	Saunders et al 2009
Recurrent e	Solda et al 2005
Recurrent e	Solda et al 2005
Asymptom	Tiscia et al 2017
Superficial	Tiscia et al 2017
Asymptom	Tiscia et al 2017
	Ventura et al 2000
Trivial - few	Asakai et al 1989
None	Asakai et al 1989
Moderate -	Asakai et al 1989
Moderate -	Asakai et al 1989
ed	Castaman et al 2007 (ISTH Abstract)
ed	Castaman et al 2008
	Castaman et al 2008
History of p	Martincic et al 1998
	Mitchell et al 2006
	Neerman-Arbez et al 2007
Gastroente	Neerman-Arbez M et al 2007
transfusion	Quelin et al 2009
Post-operat	Quelin et al 2009
Post traum	Quelin et al 2009
Transfusion	Quelin et al 2009
Patient suff	Quelin et al 2009
Post traum	Quelin et al 2009
ed	Saunders et al 2009
ed	Saunders et al 2009
Asymptom	Tiscia et al 2017
Ecchymose	Zadra et al 2004
Ecchymose	Zadra et al 2004
Ecchymose	Zadra et al 2004
ed	Zivelin et al 1999 (Abstract 2)
ed	Zivelin et al 1999 (Abstract)
Menorrhag	Zucker et al 2007
Gingival ble	Zucker et al 2007
Patient was	Hatskelzon et al 1996
	Hatskelzon et al 1996
	Hatskelzon et al 1996
	Hatskelzon et al 1996

	Hatskelzon et al 1996
	Hatskelzon et al 1996
	Hatskelzon et al 1996
Patient had	Zadra et al 2004
Frequently	Zadra et al 2004
Patient has	Zadra et al 2004
	Bolton-Maggs et al 1999 Abstract
	Mitchell et al 2006
At the age (	Zadra et al 2004
Prolonged I	Zadra et al 2004
FXI:C/FXI:A	Spena et al 2009
No bleedin	Quelin et al 2006
Bleeding af	Quelin et al 2006
Easy bruisir	Quelin et al 2006
ed	Castaman et al 2007 (ISTH Abstract)
Bleeding af	Castaman et al 2008
Menorrhag	JerÄ iÄ‡ et al 2020
Menorrhag	JerÄ iÄ‡ et al 2020
Asymptom	JerÄ iÄ‡ et al 2020
Asymptom	Cataman et al 2013
Asymptom	Cataman et al 2013
Asymptom	Cataman et al 2013
Easy bruisir	Lin et al 2020
Long APTT	Bolton-Maggs et al 2004
Fall resultin	Zacharski & French 1978
Bleed after	Bolton-Maggs et al 2004
Bled after c	Bolton-Maggs et al 2004
Cerebal her	Bolton-Maggs et al 2004
Easy bruisir	Bolton-Maggs et al 2004
Extensive b	Bolton-Maggs et al 2004
Menorrhag	Bolton-Maggs et al 2004
History of e	Imanaka et al 1995
ed	Saunders et al 2009
Patient alsc	Bolton-Maggs et al 2004
Misdiagnos	Bolton-Maggs et al 2004
No active b	Dai et al 2004
Patient has	Duncan et al 2008
ed	Mitchell et al 2006
	Mitchell et al 2006
ed	Mitchell et al 2006
	Mitchell et al 2006
Menorrhag	Mitchell et al 2007
Post-Partur	Hill et al 2005
Asymtomat	Hill et al 2005
Post Partun	Hill et al 2005
ed	Mitchell et al 2006
Epistaxis	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017

ed	Mitchell et al 2006
	Bolton-Maggs et al 2003 Abstract
ed	Mitchell et al 2006
No relevant	Mitchell et al 2007
Menorrhag	Hill et al 2005
ed	Bolton-Maggs et al 2003 Abstract
	Mitchell et al 2006
Patient atte	Dossenbach-Glaninger and Hopmeier 2
	Mitchell et al 2003
ed	Mitchell et al 2006
ed	Quelin et al 2006
ed	Alhaq et al 2000
ed	O'Connell et al 2005
ed	Saunders et al 2009
ed	Wu et al 2004 (Abstract)
None	Dossenbach-Glaninger & Hopmeier 2006
ed	Mitchell et al 2006
Asymptom	Tiscia et al 2017
No bleedin	Zivelin et al 2002
No Hx of bl	Guella et al 2008
Easy brusin	Shao et al 2016
Menorrhag	de Raucourt et al 2008
Patient has	Duncan et al 2008
ed	Mitchell et al 2006
	Lin et al 2020
Asymptom	Guella et al 2008
ed	Quelin et al 2006
ed	Dossenbach-Glaninger & Hopmeier 2006
No excessiv	Quelin et al 2004
Bleeding fo	Quelin et al 2009
Easy bruisir	Quelin et al 2009
ed	Mitchell et al 2006
	Morishita et al 2003 (Abstract)
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
No bleedin	Kawankar et al 2016
	Okumura et al 2006
ed	Kuroda et al 2005 (Abstract)
	Morishita et al 2003 (Abstract)
Patient has	Duncan et al 2008
History of k	Kravtsov et al 2005
ed	Kravtsov et al 2005
	Okumura et al 2006
No bleedin	Wang et al 2019
No bleedin	Wang et al 2019
No bleedin	Wang et al 2019
ed	Wu et al 2004 (Abstract)
Gastrointes	Lin et al 2020
Epistaxis - a	Shao et al 2016
ed	Wu et al 2003 (Abstract)

Presented v	Alhaq et al 1999
No history (	Alhaq et al 1999
No history (	Alhaq et al 1999
No history (	Alhaq et al 1999
No history (	Alhaq et al 1999
No history (	Alhaq et al 1999
No history (	Alhaq et al 1999
No history (	Alhaq et al 1999
aPTT media	Papagrigoriou et al 2006
ed	Mitchell et al 2006
ed	Mitchell et al 2006
No bleedin	Zivelin et al 2002
No bleedin	Zivelin et al 2002
Second mu	Vasileiadis et al 2009
Easy Bruisir	Quelin et al 2005
Easy bruisir	Hill et al 2005
Asymptom	Hill et al 2005
History of a	Martincic et al 1998
History of e	Martincic et al 1998
	Bolton-Maggs et al 2003 Abstract
ed	Mitchell et al 2006
ed	Bolton-Maggs et al 2003 Abstract
	Esteban et al 2017
ed	Mitchell et al 2006
Patient has	Duncan et al 2008
ed	Castaman et al 2008
ed	Unpublished Data
Easy bruisir	Lin et al 2020
Bleeding af	Lin et al 2020
Peptic ulce	Lin et al 2020
No history (	Sato et al 2000
	Sato et al 2000
No history (	Au et al 2003
	Au et al 2003
	Sato et al 2000
	Sato et al 2000
	Sato et al 2000
	Sato et al 2000
Patient initi	Au et al 2003
Spontaneo	Kawaguchi et al 2000
Bleeding up	Shao et al 2016
Bleeding fo	Shao et al 2016
Epistaxis an	Shao et al 2016
Bleeding fo	Shao et al 2016
ed	Wang et al 2009
Mild - few e	Asakai et al 1989
ed	Saunders et al 2009
Mild bleedi	Dossenbach-Glaninger et al 2001
No evidenc	Dossenbach-Glaninger et al 2001
ed	Saunders et al 2009

ed	Saunders et al 2009
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Menorrhag	Castaman et al 2008
Epistaxis, p	Castaman et al 2008
Mild bleedi	Dossenbach-Glaninger et al 2001
No bleedin	Quelin et al 2009
Asymptom	Tiscia et al 2017
Surgery-rel	Tiscia et al 2017
No bleedin	Zivelin et al 2002
Menorrhag	Hill et al 2005
ed	Saunders et al 2009
No bleedin	Wang et al 2019
No bleedin	Wang et al 2019
No bleedin	Wang et al 2019
Heavy men	Wang et al 2019
No bleedin	Mathonet et al 1999 (Abstract)
ed	Quelin et al 2005
Epistaxis	Quelin et al 2006
ed	Quelin et al 2006
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
No bleedin	Hopmeier et al 2004
Vaginal ble	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Bleeding af	Zucker et al 2007
	Quelin et al 2006
ed	Mitchell et al 2006
Epistaxis, M	Quelin et al 2005
	Esteban et al 2017
ed	Mitchell et al 2006
ed	Saunders et al 2009
ed	Saunders et al 2009
ed	Saunders et al 2009
History of e	Mitchell et al 1999
ed	Mitchell et al 2006
ed	Saunders et al 2009
Median aPT	Duncan et al 2008
Moderate h	Fard-Esfahani et al 2008
ed	Wu et al 2004 (Abstract)
ed	Mitchell et al 2006
Epistaxis	Zucker et al 2007
No evidenc	Dossenbach-Glaninger et al 2001
Excessive b	Ventura et al 2000
Non-bleede	Ventura et al 2000
No bleedin	Zucker et al 2007
ed	Saunders et al 2009
No bleedin	Lin et al 2020
ed	Castaman et al 2005

Non-bleede	Ventura et al 2000
No Bleedin	Zucker et al 2007
ed	Mitchell et al 2006
Moderate h	Fard-Esfahani et al 2008
ed	Mitchell et al 2006
Epistaxis	Shao et al 2016
None	Jayandharan et al 2005
Asymptom	Lin et al 2020
No history	Au et al 2003
	Au et al 2003
Bleeding af	Lin et al 2020
No bleedin	Lin et al 2020
Epistaxis	Lin et al 2020
ed	Mitchell et al 2006
ed	Mitchell et al 2006
Bleeding at	Hayashi et al 1997 Abstract
ed	Okumura et al 2006
ed	Mitchell et al 2006
	Xie et al 2005
	Xie et al 2005
	Xie et al 2005
Bleeding fo	Shao et al 2016
Asymptom	Bozzao et al 2007
ed	Saunders et al 2009
ed	Mitchell et al 2006
Patient ble	Mitchell et al 2007
Pt presente	Quelin et al 2009
No history	Wistinghausen et al 1997
Minor blee	Wistinghausen et al 1997
	Wistinghausen et al 1997
No persona	de Raucourt et al 2008
ed	Mitchell et al 2006
ed	Unpublished Data
No bleedin	Kawankar et al 2016
Menorrhag	Gailani et al 2001 Abstract B
	Mitchell et al 2006
Asymptom	Colakoglu et al 2018
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
No bleedin	Gailani et al 2001 Abstract B
No bleedin	Gailani et al 2001 Abstract B
Heavy post	Kravtsov et al 2005
ed	Mitchell et al 2006
ed	Saunders et al 2009
Frequent gi	Kravtsov et al 2004
Asymptom	Colakoglu et al 2018

Bleeding af	Gailani et al 2001 Abstract B
History of e	Kravtsov et al 2004
Easy bruisir	Tiscia et al 2017
Bleeding af	Castaman et al 2008
	Okumura et al 2006
Easy bruisir	Shao et al 2016
No bleedin	Hopmeier et al 2004
Easy bruisir	Shao et al 2016
ed	Mitchell et al 2006
No persona	de Raucourt et al 2008
	Esteban et al 2017
No bleedin	Kawankar et al 2016
ed	Saunders et al 2009
ed	Saunders et al 2009
Dental wor	Mitchell et al 1999
Patient alsc	Hill et al 2005
ed	Saunders et al 2009
Excessive b	Ventura et al 2000
Asymptom	Lin et al 2020
Easy bruisir	Lin et al 2020
ed	Mitchell et al 2006
ed	Saunders et al 2009
History of e	Imanaka et al 1995
Asymptom	Tsukahara et al 2003
ed	Ishikawa et al 2007
Father of p	Ishikawa et al 2007
	Bolton-Maggs et al 2003 Abstract
Severe blee	Jayandharan et al 2005
Epistaxis	Kawankar et al 2016
	Mitchell et al 2006
ed	Quelin et al 2005
Long histor	Alhaq et al 2000
	Mitchell et al 2003
ed	Quelin et al 2005
Post op ble	Jayandharan et al 2005
ed	Quelin et al 2005
ed	Saunders et al 2009
Post traum	Kawankar et al 2016
	Bolton-Maggs et al 2003 Abstract
Asymptom	McVey et al 2005
ed	Mitchell et al 2006
Patient has	no bleeding Hx.
ed	Mitchell et al 2006
ed	Saunders et al 2009
ed	Mitchell et al 2006
Off-spring c	Fard-Esfahani et al 2008
No bleedin	Zivelin et al 2002
No bleedin	Zivelin et al 2002
ed	Quelin et al 2005
Asymptom	Tiscia et al 2017

Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Clinically, th	Kwon et al 2008
Prolonged I	Fard-Esfahani et al 2008
Patient's hu	Ishikawa et al 2007
No history o	Ishikawa et al 2007
Frequent ep	Ishikawa et al 2007
No apparer	Iijima et al 2000
Bruising, bl	Colakoglu et al 2018
Asymptom	Colakoglu et al 2018
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
Patient exp	de Moerloose et al 2004
	de Moerloose et al 2004
	de Moerloose et al 2004
ed	Unpublished Data
	Su et al 2018
	Su et al 2018
	Su et al 2018
	Su et al 2018
	Ventura et al 2000
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
Prolonged I	Gailani et al 2001 Abstract B
Patient alsc	Hill et al 2005
Easy bruisir	Hill et al 2005
ed	Mitchell et al 2006
ed	Mitchell et al 2006
No bleedin	Quelin et al 2009
ed	Quelin et al 2005
Asymptom	Colakoglu et al 2018
ed	Saunders et al 2009
Mother of p	Saunders et al 2009
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
	Esteban et al 2017
Post Partun	Hill et al 2005
2 Post-part	Hill et al 2005
Epistaxis	Quelin et al 2005
Haematuria	Karimi et al 2009
	Peretz et al 1996
Asymptom	Tiscia et al 2017
Asymptom	Tiscia et al 2017
ed	Mitchell et al 2006
Mild - few e	Asakai et al 1989

Injury-relat	Zivelin et al 2001 (Abstract)
ed	Mitchell et al 2006
Epistaxis	Kawankar et al 2016
Bruising an	Colakoglu et al 2018
Asymptom	Colakoglu et al 2018
ed	Mitchell et al 2006
Bleeding af	Gailani et al 2001 Abstract B
History of n	Kravtsov et al 2004
	Esteban et al 2017
No persona	Germanos-Haddad et al 2005
ed	Germanos-Haddad et al 2005
ed	Germanos-Haddad et al 2005
ed	Germanos-Haddad et al 2005
ed	Germanos-Haddad et al 2005
ed	Mitchell et al 2006
Menorrhag	Mitchell et al 2007
Patient suff	Mitchell et al 1999
ed	Mitchell et al 2006
ed	O'Connell et al 2005
No spontan	Quelin et al 2006
Patient suff	Quelin et al 2004
Patient rec	Quelin et al 2004
Moderate h	Fard-Esfahani et al 2008
ed	Mitchell et al 2006
Menorrhag	Hill et al 2005
Asymptom	Takamiya et al 2005
	Mitchell et al 2006
Mild bleedi	Hill et al 2005
ed	Mitchell et al 2006
Menorrhag	Spena et al 2009

Variant ID	No. of Case	Type	Effect	cDNA	Mutation (c	Amino Acid	Amino Acid	Protein Cha
313	0	Point		-446	c.-446G>T	0	0	
312	0	Point		-316	c.-316C>G	0	0	
130	2	Point		-54	c.-54G>A	0	0	
314	0	Point		-2	c.-2+120G>	0	0	
74	0	Point		-1	c.-1-231T>C	0	0	
75	0	Point		-1	c.-1-198T>C	0	0	
76	0	Point		-1	c.-1-138C>A	0	0	
92	0	Point		-1	c.-1-403G>T	0	0	
315	0	Point		-1	c.-1-229T>C	0	0	
93	0	Point		-1	c.-1-273C>G	0	0	
109	3	Deletion		0	31.5KbDele	0	0	
184	1	Deletion		0	Exons 11-15	0	0	
284	1	Point	Missense	0	Unspecified	136	118	p.Cys136Ar
337	0	Point	Missense	0	Unspecified	326	308	p.Arg326Hi
273	0	Point	Missense	0	Unspecified	403	385	p.Val403Me
338	0	Point	Missense	0	Unspecified	425	407	p.Trp425Le
339	0	Point	Missense	0	Unspecified	519	501	p.Trp519Se
132	3	Point	Missense	3	c.3G>T	1	-18	p.Met1Ile
226	1	Point	Nonsense	15	c.15T>A	5	-14	p.Tyr5*
120	1	Point	Missense	44	c.44C>T	15	-4	p.Ser15Leu
225	0	Point	Missense	52	c.52G>C	18	-1	p.Gly18Arg
340	0	Point		55	c.55+2T>C	0	0	
227	1	Insertion	Frameshift	55	c.55+6T>G+	0	0	
131	1	Point	Nonsense	55	c.55G>T	19	1	p.Glu19*
77	0	Duplication	Frameshift	56	c.56-1209d	0	0	
185	0	Point	Nonsense	67	c.67C>T	23	5	p.Gln23*
160	1	Deletion	Frameshift	73	c.73_86del	0	0	
258	1	Deletion	Inframe	78	c.78_80del	0	0	
1	0	Point	Missense	100	c.100G>C	34	16	p.Asp34His
152	1	Point	Missense	113	c.113T>C	38	20	p.Val38Ala
125	1	Point	Missense	122	c.122C>T	41	23	p.Pro41Leu
133	1	Point	Missense	122	c.122C>A	41	23	p.Pro41Gln
228	2	Point	Missense	126	c.126C>G	42	24	p.Ser42Arg
271	0	Point	Missense	127	c.127G>A	43	25	p.Ala43Thr
113	4	Point	Missense	137	c.137G>T	46	28	p.Cys46Phe
24	1	Point	Missense	141	c.141G>C	47	29	p.Gln47His
159	2	Point	Missense	151	c.151A>C	51	33	p.Thr51Pro
158	0	Point	Missense	152	c.152C>T	51	33	p.Thr51Ile
68	36	Point	Missense	166	c.166T>C	56	38	p.Cys56Arg
153	0	Point	Nonsense	168	c.168T>A	56	38	p.Cys56*
219	1	Point	Missense	168	c.168T>G	56	38	p.Cys56Trp
10	1	Insertion	Frameshift	192	c.192_193i	0	0	
78	0	Point	Missense	197	c.197C>T	66	48	p.Pro66Leu
229	0	Point	Missense	209	c.209C>T	70	52	p.Pro70Leu
218	0	Point	Nonsense	214	c.214C>T	72	54	p.Arg72*
259	1	Point	Missense	215	c.215G>C	72	54	p.Arg72Pro
352	3	Point		218	c.218+4A>C	0	0	
79	0	Point		218	c.218+126A	0	0	
205	1	Point		218	c.218+2T>A	0	0	

221	0	Point	Missense	224	c.224C>T	75	57	p.Thr75Ile
154	0	Point	Missense	226	c.226G>C	76	58	p.Cys76Arg
102	1	Point	Missense	227	c.227G>A	76	58	p.Cys76Tyr
134	1	Point	Missense	227	c.227G>T	76	58	p.Cys76Phe
327	0	Point		250	c.1716+25(	0	0	
328	0	Point		252	c.1716+252	0	0	
129	1	Point	Missense	259	c.259C>A	87	69	p.Pro87Thr
329	0	Point		265	c.*265A>G	0	0	
187	1	Point	Missense	290	c.290G>C	97	79	p.Gly97Ala
330	0	Point		296	c.*296G>C	0	0	
230	2	Point	Missense	296	c.296C>A	99	81	p.Ser99Tyr
36	2	Duplication	Frameshift	301	c.301_307(	0	0	
114	1	Point	Missense	302	c.302A>G	101	83	p.Lys101Ar
8	5	Point	Nonsense	316	c.316C>T	106	88	p.Gln106*
364	1	Deletion		325	c.325+2del	0	0	
135	11	Point	Missense	325	c.325G>A	109	91	p.Ala109Th
341	4	Point		326	c.326-1G>A	0	0	
346	0	Deletion	Frameshift	327	c.327delT	0	0	
126	2	Point	Missense	328	c.328T>G	110	92	p.Cys110Gl
231	2	Point	Missense	359	c.359T>C	120	102	p.Met120Tl
60	7	Point	Missense	365	c.365G>A	122	104	p.Gly122As
104	3	Point	Nonsense	400	c.400C>T	134	116	p.Gln134*
58	61	Point	Nonsense	403	c.403G>T	135	117	p.Glu135*
105	4	Point	Nonsense	408	c.408C>A	136	118	p.Cys136*
121	5	Point	Missense	419	c.419G>A	140	122	p.Cys140Ty
161	2	Point	Missense	422	c.422C>T	141	123	p.Thr141M
304	0	Point	Silent	423	c.423G>A	141	123	p.Thr141=
353	3	Point	Missense	428	c.428A>C	143	125	p.Asp143Al
39	0	Point	Silent	429	c.429C>T	143	125	p.Asp143=
232	4	Point	Missense	434	c.434A>G	145	127	p.His145Ar
20	22	Point	Nonsense	438	c.438C>A	146	128	p.Cys146*
138	6	Point	Missense	449	c.449C>T	150	132	p.Thr150M
29	4	Point	Missense	452	c.452A>C	151	133	p.Tyr151Se
139	2	Point	Missense	452	c.452A>G	151	133	p.Tyr151Cy
21	2	Point	Missense	454	c.454G>C	152	134	p.Ala152Pr
94	1	Point	Missense	484	c.484C>T	162	144	p.Arg162Cy
86	0	Point		485	c.485+23G>	0	0	
342	0	Point		485	c.485+1G>A	0	0	
70	0	Point		485	c.485+5G>(	0	0	
317	0	Point		485	c.485+122T	0	0	
318	0	Point		485	c.485+181T	0	0	
80	0	Point		486	c.486-431G	0	0	
319	0	Point		486	c.486-88T>(	0	0	
320	0	Point		486	c.486-181C	0	0	
87	0	Point		486	c.486-361C	0	0	
71	3	Point		486	c.486-2A>G	0	0	
238	3	Point	Missense	518	c.518G>A	173	155	p.Gly173Gl
97	1	Point	Missense	569	c.569T>C	190	172	p.Leu190Pr
69	6	Point		595	c.595+3A>(	0	0	
343	1	Point		596	c.596-8T>A	0	0	

163	1	Point	Missense	596	c.596C>T	199	181	p.Ala199Va
22	2	Point	Missense	599	c.599G>A	200	182	p.Cys200Ty
336	1	Point	Missense	599	c.599G>C	200	182	p.Cys200Se
165	2	Point	Missense	604	c.604A>G	202	184	p.Arg202Gl
123	1	Point	Missense	616	c.616T>C	206	188	p.Pro206Se
119	2	Deletion	Inframe	644	c.644_649d	0	0	p.Ile215_As
234	0	Point	Missense	646	c.646G>A	216	198	p.Asp216As
11	1	Point	Nonsense	682	c.682C>T	228	210	p.Arg228*
23	4	Point	Missense	688	c.688T>C	230	212	p.Cys230Ar
222	4	Point	Missense	688	c.688T>A	230	212	p.Cys230Se
349	1	Point	Missense	695	c.695A>C	232	214	p.His232Pr
32	3	Point	Missense	716	c.716T>C	239	221	p.Phe239Se
209	1	Insertion	Frameshift	717	c.717insT	0	0	
275	0	Point	Missense	723	c.723C>G	241	223	p.Phe241Le
101	2	Point	Missense	728	c.728C>T	243	225	p.Ser243Ph
155	3	Point	Nonsense	730	c.730C>T	244	226	p.Gln244*
64	0	Point	Missense	731	c.731A>G	244	226	p.Gln244Ar
41	8	Point	Missense	738	c.738G>C	246	228	p.Trp246Cy
95	9	Point	Nonsense	738	c.738G>A	246	228	p.Trp246*
140	1	Point	Nonsense	751	c.751C>T	251	233	p.Gln251*
25	0	Point	Missense	755	c.755G>T	252	234	p.Arg252Ile
235	1	Point	Missense	755	c.755G>A	252	234	p.Arg252Ly
141	2	Point	Missense	756	c.756A>T	252	234	p.Arg252Se
52	2	Point	Missense	764	c.764G>A	255	237	p.Cys255Ty
253	1	Deletion	Frameshift	769	c.769delC	0	0	
128	2	Point	Missense	783	c.783G>C	261	243	p.Glu261As
115	2	Point	Missense	788	c.788G>A	263	245	p.Gly263Gl
63	2	Point	Missense	797	c.797G>A	266	248	p.Ser266As
55	0	Point	Silent	801	c.801A>G	267	249	p.Thr267=
30	5	Point	Missense	802	c.802C>T	268	250	p.Arg268Cy
210	2	Point	Missense	803	c.803G>A	268	250	p.Arg268Hi
40	4	Point	Missense	809	c.809A>T	270	252	p.Lys270Ile
255	1	Point	Missense	829	c.829G>A	277	259	p.Gly277Se
42	20	Point	Nonsense	841	c.841C>T	281	263	p.Gln281*
81	0	Point	Silent	861	c.861C>T	287	269	p.Ile287=
220	0	Deletion	Frameshift	865	c.865+2del	0	0	
99	1	Point	Missense	865	c.865G>C	289	271	p.Val289Le
65	22	Point	Missense	901	c.901T>C	301	283	p.Phe301Le
59	1	Deletion	Frameshift	907	c.907delG	0	0	
116	1	Deletion	Frameshift	918	c.918delG	0	0	
82	0	Point	Missense	922	c.922A>T	308	290	p.Ile308Phe
118	0	Point	Missense	923	c.923T>C	308	290	p.Ile308Thr
166	1	Duplication	Frameshift	933	c.933_951d	0	0	
354	4	Point	Missense	938	c.938G>T	313	295	p.Ser313Ile
236	1	Point	Nonsense	943	c.943G>T	315	297	p.Glu315*
122	11	Point	Missense	943	c.943G>A	315	297	p.Glu315Ly
2	0	Point	Missense	959	c.959T>C	320	302	p.Leu320Pr
142	2	Deletion	Frameshift	961	c.961_962d	0	0	p.Cys321Hi
3	3	Point	Missense	965	c.965C>T	322	304	p.Thr322Ile
194	3	Point	Missense	973	c.973G>T	325	307	p.Val325Ph

5	4	Point	Missense	976	c.976C>T	326	308	p.Arg326Cy
240	1	Point	Nonsense	981	c.981C>A	327	309	p.Cys327*
169	1	Point	Missense	992	c.992C>T	331	313	p.Thr331Ile
54	0	Point	Missense	1016	c.1016G>T	339	321	p.Cys339Ph
4	4	Point	Missense	1021	c.1021G>A	341	323	p.Glu341Ly
67	2	Duplication	Frameshift	1026	c.1026dupC	0	0	
34	3	Point	Silent	1026	c.1026G>T	342	324	p.Gly342=
239	1	Point		1028	c.1028+5G>	0	0	
72	0	Point		1029	c.1029-2A>	0	0	
361	1	Point	Nonsense	1033	c.1033A>T	345	327	p.Lys345*
12	2	Point	Missense	1060	c.1060G>A	354	336	p.Gly354Ar
37	2	Deletion	Frameshift	1072	c.1072delA	0	0	
143	1	Point	Missense	1077	c.1077A>G	359	341	p.Ile359Me
170	1	Point	Missense	1079	c.1079T>C	360	342	p.Leu360Pr
144	1	Point	Missense	1084	c.1084G>A	362	344	p.Gly362Ar
223	1	Point	Missense	1102	c.1102G>A	368	350	p.Gly368Ar
14	1	Point	Missense	1103	c.1103G>C	368	350	p.Gly368Ala
18	1	Point	Missense	1103	c.1103G>A	368	350	p.Gly368Gl
100	1	Point	Missense	1106	c.1106A>C	369	351	p.Tyr369Se
360	3	Point	Silent	1107	c.1107C>T	369	351	p.Tyr369=
43	8	Point	Nonsense	1107	c.1107C>A	369	351	p.Tyr369*
145	1	Point	Missense	1118	c.1118T>C	373	355	p.Leu373Se
146	1	Point	Missense	1120	c.1120T>C	374	356	p.Cys374Ar
108	2	Point		1135	c.1135+1G>	0	0	
147	1	Point	Missense	1135	c.1135+5G>	378	360	
110	6	Deletion	Frameshift	1136	c.1136-4de	0	0	
171	1	Point	Missense	1165	c.1165G>A	389	371	p.Val389Ile
196	1	Point	Missense	1169	c.1169G>C	390	372	p.Gly390Ala
241	1	Point	Missense	1178	c.1178C>T	393	375	p.Ala393Va
98	2	Point	Missense	1186	c.1186C>T	396	378	p.Arg396Cy
66	0	Point	Silent	1191	c.1191T>C	397	379	p.Gly397=
252	0	Point	Missense	1195	c.1195T>C	399	381	p.Trp399Ar
224	1	Point	Missense	1196	C.1196G>T	399	381	p.Trp399Le
106	3	Point	Missense	1199	c.1199C>T	400	382	p.Pro400Le
96	1	Point	Nonsense	1202	c.1202G>A	401	383	p.Trp401*
15	3	Point	Missense	1211	c.1211C>A	404	386	p.Thr404As
173	1	Point	Missense	1217	c.1217A>C	406	388	p.His406Pr
26	1	Point	Missense	1219	c.1219A>C	407	389	p.Thr407Pr
256	1	Point	Missense	1222	c.1222A>C	408	390	p.Thr408Pr
363	1	Point	Nonsense	1234	c.1234C>T	412	394	p.Gln412*
51	17	Point	Missense	1247	c.1247G>A	416	398	p.Cys416Ty
242	0	Point	Missense	1252	c.1252G>A	418	400	p.Gly418Se
16	8	Point	Missense	1253	c.1253G>T	418	400	p.Gly418Va
243	1	Point	Missense	1255	c.1255T>G	419	401	p.Ser419Ala
148	2	Point	Nonsense	1270	c.1270C>T	424	406	p.Gln424*
174	1	Point	Missense	1275	c.1275G>C	425	407	p.Trp425Cy
300	1	Point	Missense	1277	c.1277T>C	426	408	p.Ile426Thr
175	2	Point	Missense	1283	c.1283C>T	428	410	p.Thr428Ile
164	3	Point	Missense	1288	c.1288G>A	430	412	p.Ala430Th
244	1	Point	Missense	1288	c.1288G>T	430	412	p.Ala430Se

6	2	Point	Missense	1289	c.1289C>T	430	412	p.Ala430Va
176	1	Point		1304	c.1304+12G	0	0	
38	1	Point		1305	c.1305-10T	0	0	
357	2	Deletion	Frameshift	1322	c.1322delT	0	0	
347	0	Deletion	Frameshift	1325	c.1325delT	0	0	p.Leu442Cy
156	2	Point	Missense	1327	c.1327C>T	443	425	p.Arg443Cy
103	2	Point	Missense	1334	c.1334A>G	445	427	p.Tyr445Cy
217	0	Point	Missense	1336	c.1336A>G	446	428	p.Ser446Gl
19	1	Point	Missense	1378	c.1378T>G	460	442	p.Phe460Va
46	1	Point	Nonsense	1393	c.1393G>T	465	447	p.Glu465*
177	4	Point	Missense	1394	c.1394C>G	451	433	p.Gln451Gl
62	11	Point	Missense	1432	c.1432G>A	478	460	p.Gly478Ar
348	0	Deletion	Frameshift	1448	c.1448delT	0	0	
351	1	Point	Missense	1448	c.1448T>C	483	465	p.Leu483Se
31	3	Point	Missense	1478	c.1478C>T	493	475	p.Thr493Ile
344	0	Point	Missense	1480	c.1480+3A>	0	0	
178	1	Point	Missense	1480	c.1480+2T>	494	476	
322	0	Point		1481	c.1481-215	0	0	
324	0	Point		1481	c.1481-34G	0	0	
303	0	Point		1481	c.1481-188	0	0	
149	2	Point	Nonsense	1489	c.1489C>T	497	479	p.Arg497*
246	1	Point	Missense	1498	c.1498T>C	500	482	p.Cys500Ar
150	1	Point	Missense	1500	c.1500C>G	500	482	p.Cys500Tr
180	1	Point	Missense	1507	c.1507T>C	503	485	p.Ser503Pr
53	2	Point	Missense	1531	c.1531T>C	511	493	p.Tyr511His
127	4	Point	Missense	1545	c.1545G>T	515	497	p.Trp515Cy
214	1	Point	Missense	1546	c.1546G>A	516	498	p.Val516Me
47	7	Insertion	Frameshift	1556	c.1556insG	0	0	
44	8	Point	Nonsense	1556	c.1556G>A	519	501	p.Trp519*
33	4	Point	Missense	1557	c.1557G>C	519	501	p.Trp519Cy
215	1	Duplication	Frameshift	1560	c.1560dupC	0	0	
331	4	Point	Missense	1562	c.1562A>G	521	503	p.Tyr521Cy
84	0	Duplication	Frameshift	1574	c.1574-93d	0	0	
325	0	Point		1576	c.1576+51C	0	0	
35	4	Point	Missense	1608	c.1608G>C	536	518	p.Lys536As
50	9	Point	Missense	1613	c.1613C>T	538	520	p.Pro538Le
262	1	Point	Missense	1619	c.1619T>G	540	522	p.Val540Gl
167	1	Point	Missense	1634	c.1634G>A	545	527	p.Cys545Ty
280	2	Point	Missense	1682	c.1682G>A	561	543	p.Ala561As
247	2	Point	Missense	1684	c.1684G>A	562	544	p.Gly562Se
117	10	Point	Missense	1693	c.1693G>A	565	547	p.Glu565Ly
332	0	Point	Missense	1694	c.1694T>A	454	436	p.Ile454Lys
85	0	Point	Silent	1707	c.1707C>T	569	551	p.Asp569=
45	1	Deletion		1714	c.1714_171	0	0	
48	2	Point		1716	c.1716+1G>	0	0	
326	2	Point		1716	c.1716+248	0	0	
83	0	Point		1717	c.1717-48A	0	0	
206	0	Point		1717	c.1717-2A>	573	555	
49	2	Point	Missense	1718	c.1718G>A	573	555	p.Gly573Gl
350	1	Point	Missense	1721	c.1721A>C	574	556	p.Asp574Al

248	0	Point	Missense	1721	c.1721A>G	574	556 p.Asp574Gl
263	2	Point	Missense	1741	c.1741T>C	581	563 p.Cys581Ar
151	1	Point	Missense	1742	c.1742G>T	581	563 p.Cys581Ph
17	2	Point	Missense	1760	c.1760G>C	587	569 p.Trp587Se
301	1	Point	Missense	1775	c.1775T>C	592	574 p.Ile592Thr
9	8	Point	Missense	1778	c.1778C>T	593	575 p.Thr593M
249	3	Point	Missense	1782	c.1782C>A	594	576 p.Ser594Ar
168	1	Point	Missense	1786	c.1786G>A	596	578 p.Gly596Cy
181	1	Point	Missense	1789	c.1789G>A	597	579 p.Glu597Ly
299	1	Point	Missense	1796	c.1796G>A	599	581 p.Cys599Ty
13	2	Point	Nonsense	1797	c.1797T>A	599	581 p.Cys599*
56	0	Point	Silent	1812	c.1812G>T	604	586 p.Arg604=
250	1	Point	Missense	1822	c.1822T>C	608	590 p.Tyr608Hi
27	2	Point	Nonsense	1824	c.1824C>A	608	590 p.Tyr608*
257	1	Point	Missense	1832	c.1832T>G	611	593 p.Val611Gl
57	0	Point	Silent	1839	c.1839G>A	613	595 p.Glu613=
311	0	Point	Missense	1843	c.1843G>A	615	597 p.Val615M
111	1	Point	Missense	1849	c.1849T>G	617	599 p.Trp617Ar
28	3	Point	Missense	1853	c.1853T>C	618	600 p.Ile618Ser
260	1	Point	Missense	1856	c.1856T>C	619	601 p.Leu619Pr

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