



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

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Abstract:	<p>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 <a href="https://www.factorxi.org">https://www.factorxi.org</a>. 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.</p>

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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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**Running title:** Analysis of variants in 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

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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

For Peer Review

## 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).<sup>1-2</sup> 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.<sup>3</sup> Specifically, FXI appeared to arise from the duplication of the PK gene, *Klkbl*, 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  $\beta$ -sheet attached to an  $\alpha$ -helix through disulphide bridges.<sup>4-5</sup> 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.<sup>1,5-6</sup> 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.<sup>1,7</sup>

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.<sup>8-9</sup> 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).<sup>10-12</sup> 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.<sup>8</sup> Many subsequent cases were identified in individuals of similar descent, with the nonsense mutation Glu135\* and the missense variant Phe301Leu emerging as the

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

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36 What has been unclear is the lack of correlation between FXI activity, FXI deficiency  
37 and disease severity. To understand this relationship better, we created the first interactive  
38 web database for the coagulation proteins (<https://www.factorxi.org/>) in 2003 as an easy-to-  
39 use facility for users, which was published in 2005, and updated in 2009 to report all 183 FXI  
40 variants identified at the time.<sup>17,18</sup> To date, over 18,000 visits have been recorded on this  
41 website. We have extended this interactive database and upgraded it to other coagulation  
42 proteins such as FIX and others.<sup>19</sup> These interactive variant databases bring key advantages of  
43 easy-to-use search and genetic and structural analysis tools for clinicians and scientists. In the  
44 present study, we now update and upgrade our FXI database for which we summarise  
45 information for a total of 272 variants in the *F11* gene (Figure 1) and include the improved  
46 crystal structure from 2019.<sup>20</sup> The increased number of known and novel FXI variants  
47 clarifies the molecular basis of FXI deficiency. In particular, by comparisons with other  
48 coagulation proteases, we correlate the predominance of Type I (CRM<sup>-</sup>) mutations within  
49 FXI with changes in surface solvent accessibilities of the affected residues, and with the  
50 occurrence of variants in cysteine residues. The amino acid accessibilities in the closely-  
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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/>.<sup>17</sup> 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.<sup>18</sup> 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).<sup>20,21</sup> 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/>).<sup>22</sup> 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).<sup>23-24</sup> 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 ( $\alpha$ -helix), B ( $\beta$ -bridge), E (extended  $\beta$ -strand), G ( $3_{10}$  helix), I ( $\pi$ -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  $\text{\AA}^2$  (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.<sup>23-25</sup> 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  $\beta$ -sheet with the  $\beta$ -strand topology C-E-D-G-A, a two-stranded B-F  $\beta$ -sheet and a centrally located  $\alpha$ -helix (A1). The seven  $\beta$ -strands were labelled alphabetically (A-G) in the order in which they occurred in the sequence. The  $\alpha$ -helix A1 and  $3_{10}$ -helices G1-G3 were similarly labelled in sequential order.<sup>17</sup> 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  $\alpha$ -helix and  $\beta$ -strands were denoted C1-C6, C2-C5 and C3-C4

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and stabilised the folded Ap structure.<sup>26</sup> The SP domain was comprised of  $\beta$ -strands A-O,  $\alpha$ -helices A1-A2 and 3<sub>10</sub>-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>.<sup>18,27</sup> The interactions at the FXI dimer interface and between the Ap1-Ap4 and SP domains also utilised the PDBePISA tool.<sup>22</sup>

## Results

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

The interactive FXI web database (<https://www.factorix.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.<sup>17-18</sup> 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.<sup>19</sup> 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/>.<sup>28</sup> 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 *FII* 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.<sup>20-21</sup> 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.<sup>20-21,29</sup> 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  $\beta$ -strands and an  $\alpha$ -helix, which came together to form a five-stranded antiparallel  $\beta$ -sheet C-E-D-G-A, a two stranded B-F  $\beta$ -sheet and a central  $\alpha$ -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  $\beta$ -strands, two  $\alpha$ -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  $\alpha$ -helix) and Gly80 (in a buried location at the end of the Ap  $\beta$ -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-Cys581, Cys545-Cys560, Cys571-Cys599). The Ap4 domains form an additional interchain disulphide bridge at Cys339-Cys339 to stabilise dimer formation.<sup>1,26,30-31</sup> 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,

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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<sup>2</sup> (Leu302 to Val309, Thr333, Cys339, Asn340, Lys345, Tyr347, Lys349, Thr357, Leu360, Arg363) (green in Figure 5(a)).<sup>22</sup> Specifically, Cys339 forms an interchain disulphide bond, which is important for stabilisation but is not essential for dimer formation or functionality.<sup>30</sup> 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,<sup>18</sup> 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;<sup>20</sup> (c) upgrade of the previous UCL FXI website user interface into that similar to the UCL coagulation Factor IX website.<sup>19</sup>

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.<sup>32</sup> 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.<sup>33-34</sup> 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.<sup>35</sup>

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.<sup>18</sup> 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.<sup>36-37</sup>

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<sup>17,18</sup> and the FIX database.<sup>19</sup> 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  $\beta$ -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.<sup>20</sup>

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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 ( $\alpha$ -helix), B ( $\beta$ -bridge), E (extended  $\beta$ -strand), G ( $3_{10}$  helix), I ( $\pi$ -helix), T (hydrogen-bonded turn), S (bend) or C (undefined coil region).  $\beta$ -strands are labelled alphabetically in the order in which they occur. The  $\beta$ -strands in the Ap and SP domains are denoted A-G and A-O respectively.  $3_{10}$ -helices are denoted G1-G5 and  $\alpha$ -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 C $\alpha$  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  $\alpha$ -helix region (H) and the five  $\beta$ -strand regions (E) in the consensus Ap domain. The  $\beta$ -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  $\beta$ -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.**

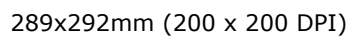
The left-hand panel highlights the residue of interest and its calculated solvent accessibility in the native FXI protein. The right-hand side panel shows the same residue in its respective isolated domain, with its corresponding accessibility. Panels (a), (b), (c) and (d) highlight the residues Val38,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

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3 detailed in the Methods section. The domain colouring corresponds to that in Figure 3. All  
4 residue numbering is given in HGVS format.  
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9 **Figure 8: Screenshots of the upgraded FXI web site to illustrate the analysis made for**  
10 **the Phe301Leu variant.**

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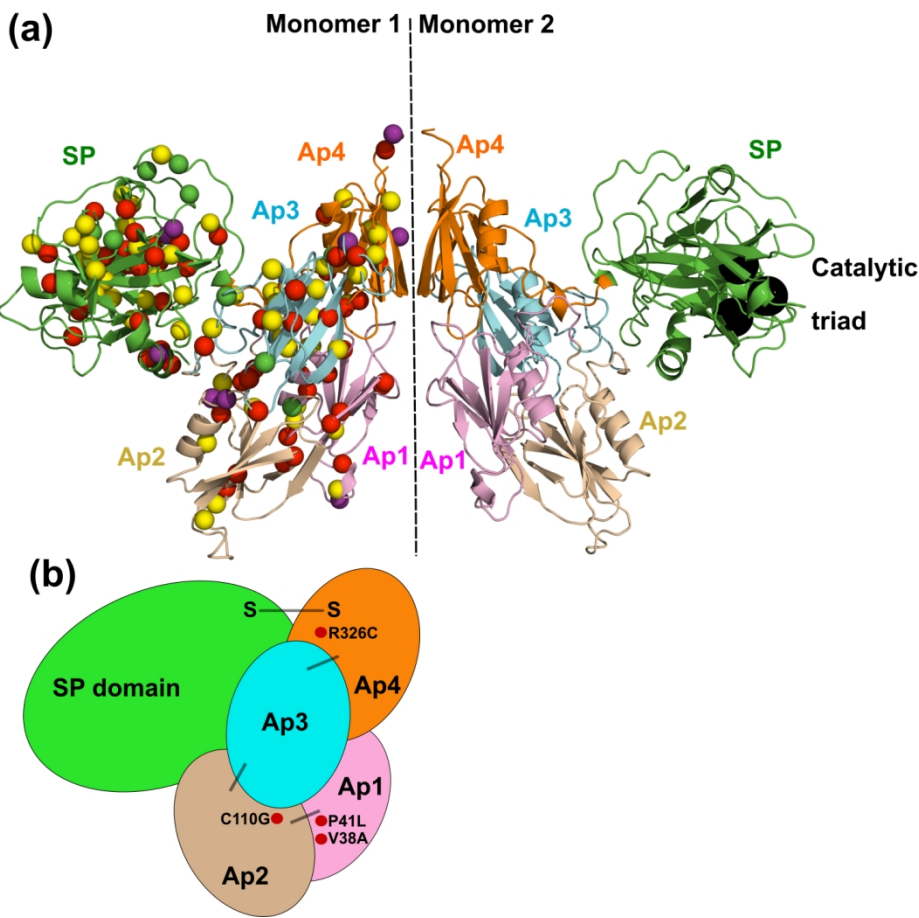


Figure 3. Dimer

204x189mm (200 x 200 DPI)

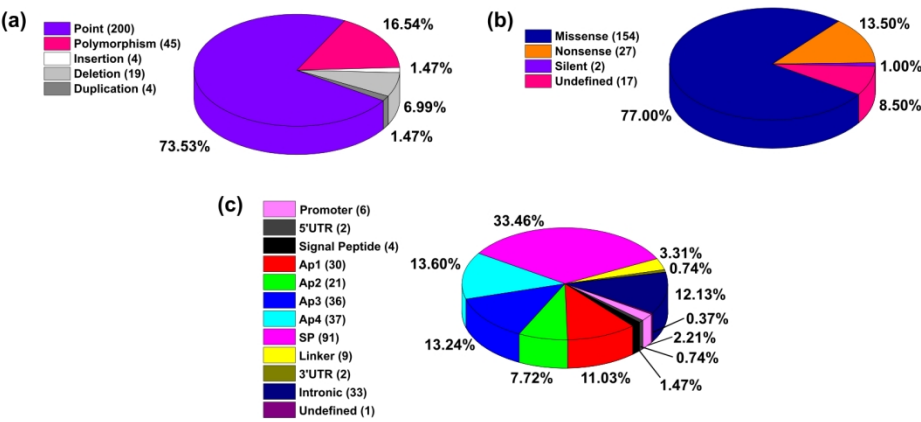


Figure 4. Pie chart.

233x141mm (200 x 200 DPI)

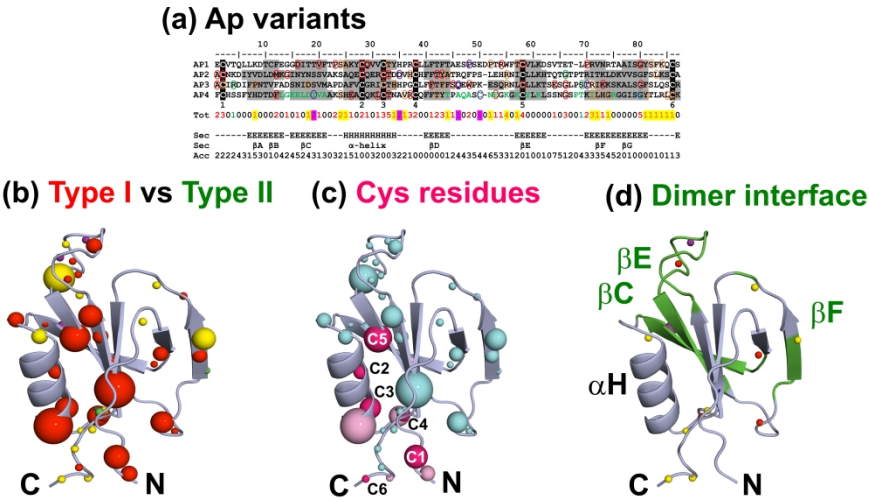


Figure 5. Consensus

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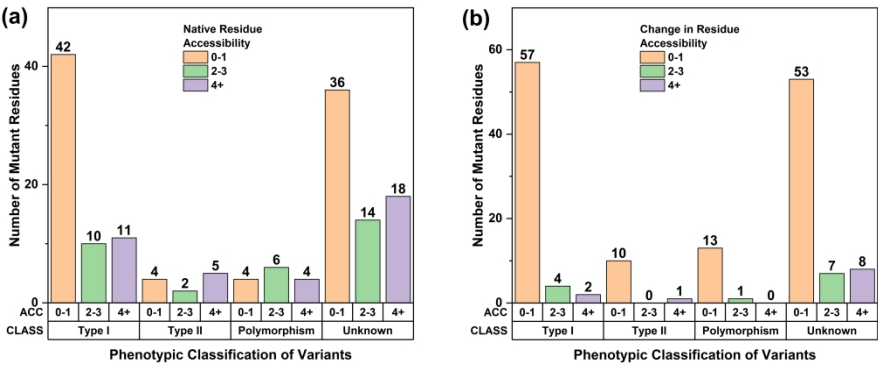


Figure 6. Accessibility

508x208mm (300 x 300 DPI)

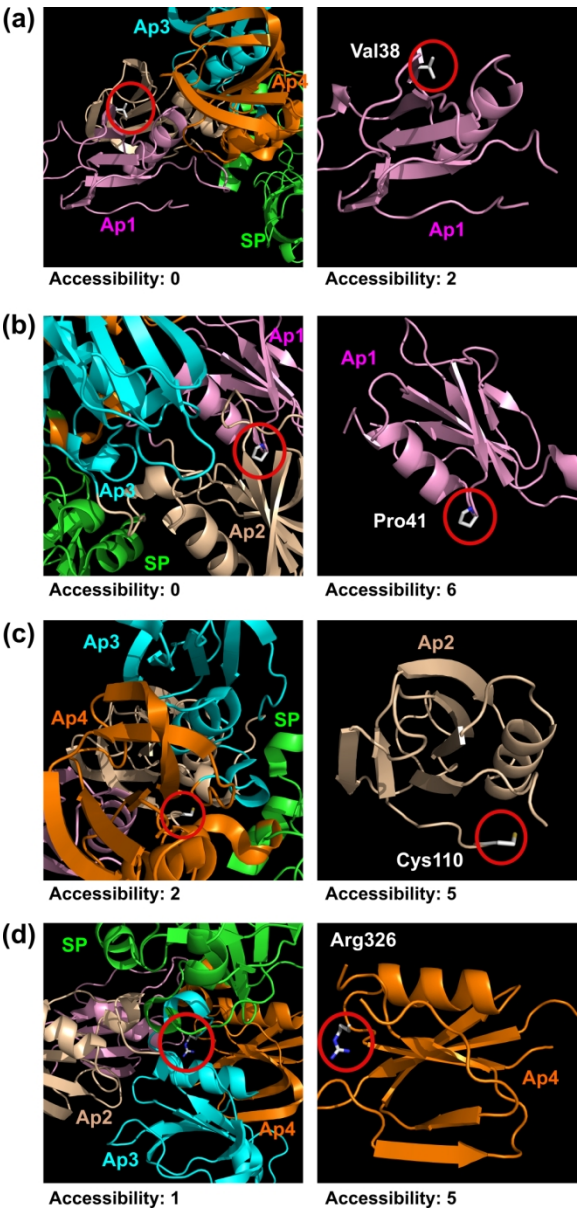


Figure 7. Views

134x281mm (200 x 200 DPI)

**FXI** Factor XI Gene (*F11*) Variant Database

Home About F11 Advanced Search Variants Structure AA Information Resources Support

Search Results: 1 unique variant retrieved.

Terms with a "\*" next to them are explained on the Help Page.

**c.801T>C** **p.Phe301Leu (Legacy AA No. 283)**

Variant Type: Point Domain: Apple 4 Codon Change: T>C  
 Variant Effect: Missense No. of Patients Reported: 22 Phenotype: 1  
 Allele Count\*: 297 Allele Number\*: 28324 Allele Frequency\*: 0.001000

**Variant Comments & Reference:**  
 Jewish Type II. Mutant protein was secreted at reduced levels (8%) compared to wild type. Northern blot analysis demonstrated that wild type and mutant protein generated similar amounts of mRNA. Meijers et al 1992, Krawbow et al 2004, Tzsch et al 2017

**Patient Information:** [Show](#)

**Structural Interpretation:**  
 Please click [HERE](#) for in-depth variant analysis.

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 "No part of this site may be copied or used in any way without permission."

Search Results: 1 unique variant retrieved.

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**Patient Information:** [Hide](#)

Patient_ID	Age	Gender	Race	FXI:C (%)	FXI:A (%)	Inheritance	Other Variants	Severity	Comments	Reference
17	67	M	Jewish	<3	<3	Compound heterozygote	c.403G>T (p.Glu135*)	Severe	History of postoperative and posttraumatic bleeding requiring multiple transfusions of fresh frozen plasma	<a href="#">Martincic et al 1998</a>
18	42	F	Caucasian	4		Compound heterozygote	c.1025dupG	Severe	Mild bleeding after dental surgery	<a href="#">Dosenbach-Glaner et al 2011</a>
76	36	M	Ashkenazi Jewish	<10	<10	Compound heterozygote	c.403G>T (p.Glu135*)	Severe	Trivial - few mild but insignificant bleeding episodes	<a href="#">Asakhi et al 1989</a>
77	50	F	Ashkenazi Jewish	<10	<10	Compound heterozygote	c.403G>T (p.Glu135*)	Severe	None	<a href="#">Asakhi et al 1989</a>
79	55	F	Ashkenazi Jewish	<10	<10	Compound heterozygote	c.403G>T (p.Glu135*)	Severe	Mild - few episodes of mild but significant bleeding	<a href="#">Asakhi et al 1989</a>
80	48	F	Ashkenazi Jewish	<10	<10	Compound heterozygote	c.403G>T (p.Glu135*)	Severe	Moderate - recurrent episodes of moderately severe bleeding sometimes requiring a blood transfusion	<a href="#">Asakhi et al 1989</a>
81	64	F	Ashkenazi Jewish	<10	<10	Compound heterozygote	c.403G>T (p.Glu135*)	Severe	Moderate - recurrent episodes of moderately severe bleeding sometimes requiring a blood transfusion	<a href="#">Asakhi et al 1989</a>

**Hint:** Click View | Overview to produce a useful Sequence Slider tool  
**Hint:** Moving your mouse over the sequences gives you a display of sequence and position below the window

Multiple Sequence Alignment of Putative F11 Protein Sequences from Selected Species

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	Patient ID	Age	Gender	Race	Variant ID	Type	Effect	cDNA	Mutation(c
1									
2									
3		212		UK populat	130	Point		-54	c.-54G>A
4		438			130	Point		-54	c.-54G>A
5		505	M	Tunisian	184	Deletion		0	Exons 11-1!
6		154			109	Deletion		0	31.5KbDele
7		215		UK populat	132	Point	Missense	3	c.3G>T
8		373			132	Point	Missense	3	c.3G>T
10		190	36 F	Morrocan	120	Point	Missense	44	c.44C>T
11		401	26 F	Czech	227	Insertion	Frameshift	55	c.55+6T>G+
12		213		Uk Populati	131	Point	Nonsense	55	c.55G>T
13		290	2 F	Non-Ashkei	160	Deletion	Frameshift	73	c.73_86del
14		510		Italian	258	Deletion	Inframe	78	c.78_80del
15		280	34 F	French	152	Point	Missense	113	c.113T>C
16		216		UK Populat	133	Point	Missense	122	c.122C>A
17		199	34 F	French	125	Point	Missense	122	c.122C>T
18		402			228	Point	Missense	126	c.126C>G
19		616	44 F	Chinese	228	Point	Missense	126	c.126C>G
20		165	15 F		113	Point	Missense	137	c.137G>T
21		166	10 F		113	Point	Missense	137	c.137G>T
22		167	45 M		113	Point	Missense	137	c.137G>T
23		617	32 F	Chinese	113	Point	Missense	137	c.137G>T
24		217		UK Populat	24	Point	Missense	141	c.141G>C
25		518	7 M	Turkish	159	Point	Missense	151	c.151A>C
26		524	10 F	Turkish	159	Point	Missense	151	c.151A>C
27		563	52 M	Spanish	68	Point	Missense	166	c.166T>C
28		564	45 F	Spanish	68	Point	Missense	166	c.166T>C
29		1	50 F	French Bas	68	Point	Missense	166	c.166T>C
30		571	51 M	Spanish	68	Point	Missense	166	c.166T>C
31		572	40 F	Spanish	68	Point	Missense	166	c.166T>C
32		573	57 M	Spanish	68	Point	Missense	166	c.166T>C
33		574	53 F	Spanish	68	Point	Missense	166	c.166T>C
34		575	44 F	Spanish	68	Point	Missense	166	c.166T>C
35		576	47 M	Spanish	68	Point	Missense	166	c.166T>C
36		577	32 F	Spanish	68	Point	Missense	166	c.166T>C
37		578	79 M	Spanish	68	Point	Missense	166	c.166T>C
38		579	58 F	Spanish	68	Point	Missense	166	c.166T>C
39		580	42 M	Spanish	68	Point	Missense	166	c.166T>C
40		581	68 M	Spanish	68	Point	Missense	166	c.166T>C
41		582	49 M	Spanish	68	Point	Missense	166	c.166T>C
42		583	52 M	Spanish	68	Point	Missense	166	c.166T>C
43		584	59 F	Spanish	68	Point	Missense	166	c.166T>C
44		585	49 M	Spanish	68	Point	Missense	166	c.166T>C
45		565	53 F	Spanish	68	Point	Missense	166	c.166T>C
46		566	41 M	Spanish	68	Point	Missense	166	c.166T>C
47		567	52 M	Spanish	68	Point	Missense	166	c.166T>C
48		568	47 M	Spanish	68	Point	Missense	166	c.166T>C
49		569	43 M	Spanish	68	Point	Missense	166	c.166T>C
50		570	63 F	Spanish	68	Point	Missense	166	c.166T>C
51		7	34 F	French Bas	68	Point	Missense	166	c.166T>C
52		3	35 F	French Bas	68	Point	Missense	166	c.166T>C



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2	6	40 M	French Basque	68 Point	Missense	166 c.166T>C
3	98	22 M	French Basque	68 Point	Missense	166 c.166T>C
4	99	28 M		68 Point	Missense	166 c.166T>C
5	100	53 F		68 Point	Missense	166 c.166T>C
6	101	61 M	French Basque	68 Point	Missense	166 c.166T>C
7	102	51 F	French Basque	68 Point	Missense	166 c.166T>C
8	586	71 F	Spanish	68 Point	Missense	166 c.166T>C
9	209	58 M	French	68 Point	Missense	166 c.166T>C
10	511		Italian	219 Point	Missense	168 c.168T>G
11	512	F	Czech	259 Point	Missense	215 c.215G>C
12	631	66 F	Indian	352 Point		218 c.218+4A>C
13	632	8 M	Indian	352 Point		218 c.218+4A>C
14	633	63 M	Indian	352 Point		218 c.218+4A>C
15	219		UK Populatio	134 Point	Missense	227 c.227G>T
16	147		Jewish	102 Point	Missense	227 c.227G>A
17	403			230 Point	Missense	296 c.296C>A
18	439			230 Point	Missense	296 c.296C>A
19	56		Portuguese	36 Duplication	Frameshift	301 c.301_307c
20	57		Portuguese	36 Duplication	Frameshift	301 c.301_307c
21	168	38 M		114 Point	Missense	302 c.302A>G
22	24	41 M	Nantes	8 Point	Nonsense	316 c.316C>T
23	26	46 F	Nantes	8 Point	Nonsense	316 c.316C>T
24	23	64 F	Nantes	8 Point	Nonsense	316 c.316C>T
25	25	36 F	Nantes	8 Point	Nonsense	316 c.316C>T
26	28	9 M	Nantes	8 Point	Nonsense	316 c.316C>T
27	522	4 M	Turkish	135 Point	Missense	325 c.325G>A
28	523	42 M	Turkish	135 Point	Missense	325 c.325G>A
29	604	60 M	Spanish	135 Point	Missense	325 c.325G>A
30	284	F	Italian	135 Point	Missense	325 c.325G>A
31	221		UK Populatio	135 Point	Missense	325 c.325G>A
32	529	37 M	Italian	135 Point	Missense	325 c.325G>A
33	530	31 F	Italian	135 Point	Missense	325 c.325G>A
34	528	12 F	Italian	135 Point	Missense	325 c.325G>A
35	650	32 F	Taiwanese	341 Point		326 c.326-1G>A
36	200	43 M	French	126 Point	Missense	328 c.328T>G
37	201	14 M	French	126 Point	Missense	328 c.328T>G
38	405			231 Point	Missense	359 c.359T>C
39	406			231 Point	Missense	359 c.359T>C
40	12			60 Point	Missense	365 c.365G>A
41	8			60 Point	Missense	365 c.365G>A
42	117			60 Point	Missense	365 c.365G>A
43	224		UK Populatio	60 Point	Missense	365 c.365G>A
44	225		UK Populatio	60 Point	Missense	365 c.365G>A
45	440			60 Point	Missense	365 c.365G>A
46	404	42 M		60 Point	Missense	365 c.365G>A
47	186		Austrian	104 Point	Nonsense	400 c.400C>T
48	407	61 M	Italian	104 Point	Nonsense	400 c.400C>T
49	149		Austrian	104 Point	Nonsense	400 c.400C>T
50	466	24 M	Iranian	58 Point	Nonsense	403 c.403G>T
51	634	54 M	Indian	58 Point	Nonsense	403 c.403G>T

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2	441			58 Point	Nonsense	403 c.403G>T
3	442			58 Point	Nonsense	403 c.403G>T
4	443			58 Point	Nonsense	403 c.403G>T
5	51	M	Portuguese	58 Point	Nonsense	403 c.403G>T
6	52	M	Portuguese	58 Point	Nonsense	403 c.403G>T
7	53	F	Portuguese	58 Point	Nonsense	403 c.403G>T
8	92	F	Portuguese	58 Point	Nonsense	403 c.403G>T
9	93	M	Portuguese	58 Point	Nonsense	403 c.403G>T
10	526	6 M	Turkish	58 Point	Nonsense	403 c.403G>T
11	527	60 M	Turkish	58 Point	Nonsense	403 c.403G>T
12	189	41 F	Jewish	58 Point	Nonsense	403 c.403G>T
13	445			58 Point	Nonsense	403 c.403G>T
14	446			58 Point	Nonsense	403 c.403G>T
15	183	12 M	Italian	58 Point	Nonsense	403 c.403G>T
16	184	34 M	Italian	58 Point	Nonsense	403 c.403G>T
17	531	30 F	Italian	58 Point	Nonsense	403 c.403G>T
18	532	80 M	Italian	58 Point	Nonsense	403 c.403G>T
19	533	40 F	Italian	58 Point	Nonsense	403 c.403G>T
20	94	F	Portuguese	58 Point	Nonsense	403 c.403G>T
21	76	36 M	Ashkenazi J	58 Point	Nonsense	403 c.403G>T
22	77	50 F	Ashkenazi J	58 Point	Nonsense	403 c.403G>T
23	80	48 F	Ashkenazi J	58 Point	Nonsense	403 c.403G>T
24	81	64 F	Ashkenazi J	58 Point	Nonsense	403 c.403G>T
25	335		Non-Jewish	58 Point	Nonsense	403 c.403G>T
26	336		Czech	58 Point	Nonsense	403 c.403G>T
27	457	61 M	Italian	58 Point	Nonsense	403 c.403G>T
28	17	67 M	Jewish	58 Point	Nonsense	403 c.403G>T
29	235		UK Populat	58 Point	Nonsense	403 c.403G>T
30	400			58 Point	Nonsense	403 c.403G>T
31	351	18 F	Jewish	58 Point	Nonsense	403 c.403G>T
32	383	F		58 Point	Nonsense	403 c.403G>T
33	384	F		58 Point	Nonsense	403 c.403G>T
34	388	M		58 Point	Nonsense	403 c.403G>T
35	419	F	French	58 Point	Nonsense	403 c.403G>T
36	420	F		58 Point	Nonsense	403 c.403G>T
37	461	M		58 Point	Nonsense	403 c.403G>T
38	447			58 Point	Nonsense	403 c.403G>T
39	444			58 Point	Nonsense	403 c.403G>T
40	534	58 F	Italian	58 Point	Nonsense	403 c.403G>T
41	163	32 M	Italian	58 Point	Nonsense	403 c.403G>T
42	398	32 M	Italian	58 Point	Nonsense	403 c.403G>T
43	418	32 M	Italian	58 Point	Nonsense	403 c.403G>T
44	272		French Bas	58 Point	Nonsense	403 c.403G>T
45	148		Jewish	58 Point	Nonsense	403 c.403G>T
46	483	44 F	Ashkenazi J	58 Point	Nonsense	403 c.403G>T
47	279	2 F	Non-Ashke	58 Point	Nonsense	403 c.403G>T
48	67	22 F	Bedouin	58 Point	Nonsense	403 c.403G>T
49	105	48 F	Bedouin	58 Point	Nonsense	403 c.403G>T
50	106	11 M	Bedouin	58 Point	Nonsense	403 c.403G>T
51	107	9 M	Bedouin	58 Point	Nonsense	403 c.403G>T

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2	108	13 F	Bedouin	58 Point	Nonsense	403 c.403G>T
3	109	16 F	Bedouin	58 Point	Nonsense	403 c.403G>T
4	110	18 F	Bedouin	58 Point	Nonsense	403 c.403G>T
5	158	56 F	Italian	58 Point	Nonsense	403 c.403G>T
6	159	61 M	Italian	58 Point	Nonsense	403 c.403G>T
7	160	29 M	Italian	58 Point	Nonsense	403 c.403G>T
8	151		European	105 Point	Nonsense	408 c.408C>A
9	226		UK Populat	105 Point	Nonsense	408 c.408C>A
10	161	36 M	Italian	105 Point	Nonsense	408 c.408C>A
11	162	15 F	Italian	105 Point	Nonsense	408 c.408C>A
12	513	M	Italian	121 Point	Missense	419 c.419G>A
13	191	68 M		121 Point	Missense	419 c.419G>A
14	192	42 M		121 Point	Missense	419 c.419G>A
15	193	31 M		121 Point	Missense	419 c.419G>A
16	295		Non-Jewish	121 Point	Missense	419 c.419G>A
17	289	61 M	Italian	161 Point	Missense	422 c.422C>T
18	637	F	Croatian	353 Point	Missense	428 c.428A>C
19	638	F	Croatian	353 Point	Missense	428 c.428A>C
20	639	M	Croatian	353 Point	Missense	428 c.428A>C
21	611	45 F	Indonesian	232 Point	Missense	434 c.434A>G
22	612	14 M	Indonesian	232 Point	Missense	434 c.434A>G
23	613	12 M	Indonesian	232 Point	Missense	434 c.434A>G
24	655	13 M	Taiwanese	232 Point	Missense	434 c.434A>G
25	75	63 F		20 Point	Nonsense	438 c.438C>A
26	70	59 F	English/Irisl	20 Point	Nonsense	438 c.438C>A
27	72	35 M	Scottish	20 Point	Nonsense	438 c.438C>A
28	74	18 M	Irish	20 Point	Nonsense	438 c.438C>A
29	88	63 M		20 Point	Nonsense	438 c.438C>A
30	89	32 F	Scottish/En	20 Point	Nonsense	438 c.438C>A
31	90	54 F	English	20 Point	Nonsense	438 c.438C>A
32	91	50 F	English	20 Point	Nonsense	438 c.438C>A
33	39	50 M	Non-Jewish	20 Point	Nonsense	438 c.438C>A
34	448			20 Point	Nonsense	438 c.438C>A
35	71	86 M	English	20 Point	Nonsense	438 c.438C>A
36	73	50 M	English	20 Point	Nonsense	438 c.438C>A
37	60		North Euro	20 Point	Nonsense	438 c.438C>A
38	504	65 M	Australian	20 Point	Nonsense	438 c.438C>A
39	240		UK Populat	20 Point	Nonsense	438 c.438C>A
40	214		UK Populat	20 Point	Nonsense	438 c.438C>A
41	222		UK Populat	20 Point	Nonsense	438 c.438C>A
42	227		UK Populat	20 Point	Nonsense	438 c.438C>A
43	374	F		20 Point	Nonsense	438 c.438C>A
44	169	29 F		20 Point	Nonsense	438 c.438C>A
45	170	33 F		20 Point	Nonsense	438 c.438C>A
46	171	55 F		20 Point	Nonsense	438 c.438C>A
47	409			138 Point	Missense	449 c.449C>T
48	535	27 M	Italian	138 Point	Missense	449 c.449C>T
49	536	49 M	Italian	138 Point	Missense	449 c.449C>T
50	537	12 M	Italian	138 Point	Missense	449 c.449C>T
51	538	43 M	Italian	138 Point	Missense	449 c.449C>T

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2	228		UK Populat	139 Point	Missense	452 c.452A>G
3	43	F		29 Point	Missense	452 c.452A>C
4	229		UK Populat	29 Point	Missense	452 c.452A>C
5	410			29 Point	Missense	452 c.452A>C
6	172	28 F		29 Point	Missense	452 c.452A>C
7	40			21 Point	Missense	454 c.454G>C
8	230		UK Populat	21 Point	Missense	454 c.454G>C
9	131		Austrian	94 Point	Missense	484 c.484C>T
10	118			71 Point		486 c.486-2A>G
11	231		UK Populat	71 Point		486 c.486-2A>G
12	197	36 F	Italian	71 Point		486 c.486-2A>G
13	451			238 Point	Missense	518 c.518G>A
14	450			238 Point	Missense	518 c.518G>A
15	452			238 Point	Missense	518 c.518G>A
16	135		Chinese	97 Point	Missense	569 c.569T>C
17	188		Austrian	69 Point		595 c.595+3A>C
18	232		UK Populat	69 Point		595 c.595+3A>C
19	546	55 F	Italian	69 Point		595 c.595+3A>C
20	104	5 M	French Bas	69 Point		595 c.595+3A>C
21	417	24 F	Italian	69 Point		595 c.595+3A>C
22	621	51 F	Chinese	343 Point		596 c.596-8T>A
23	476	23 F	French	163 Point	Missense	596 c.596C>T
24	415	29 F		22 Point	Missense	599 c.599G>A
25	233		UK Populat	22 Point	Missense	599 c.599G>A
26	648	60 F	Taiwanese	336 Point	Missense	599 c.599G>C
27	416		Italian	165 Point	Missense	604 c.604A>G
28	196	36 M	French	123 Point	Missense	616 c.616T>C
29	187		Austrian	119 Deletion	Inframe	644 c.644_649c
30	29	28 M	Lebanese	11 Point	Nonsense	682 c.682C>T
31	421	F	French	222 Point	Missense	688 c.688T>A
32	422	F	French	222 Point	Missense	688 c.688T>A
33	234		UK Populat	23 Point	Missense	688 c.688T>C
34	41		Japanese	23 Point	Missense	688 c.688T>C
35	542	25 M	Italian	23 Point	Missense	688 c.688T>C
36	543	55 F	Italian	23 Point	Missense	688 c.688T>C
37	627	4 M	Indian	349 Point	Missense	695 c.695A>C
38	423	43 M	Japanese	32 Point	Missense	716 c.716T>C
39	424		Japanese	32 Point	Missense	716 c.716T>C
40	47		Japanese	32 Point	Missense	716 c.716T>C
41	425	9 F	Australian	209 Insertion	Frameshift	717 c.717insT
42	144	34 M		101 Point	Missense	728 c.728C>T
43	145			101 Point	Missense	728 c.728C>T
44	426	39 F	Japanese	155 Point	Nonsense	730 c.730C>T
45	642	F	Chinese	95 Point	Nonsense	738 c.738G>A
46	644	F	Chinese	95 Point	Nonsense	738 c.738G>A
47	645	F	Chinese	95 Point	Nonsense	738 c.738G>A
48	133		Chinese	95 Point	Nonsense	738 c.738G>A
49	652	58 M	Taiwanese	95 Point	Nonsense	738 c.738G>A
50	624	5 F	Chinese	95 Point	Nonsense	738 c.738G>A
51	132	F	Chinese	95 Point	Nonsense	738 c.738G>A

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2	61	68 F	Italian	41 Point	Missense	738 c.738G>C
3	128	F	Italian	41 Point	Missense	738 c.738G>C
4	129	F	Italian	41 Point	Missense	738 c.738G>C
5	124	M	Italian	41 Point	Missense	738 c.738G>C
6	125	M	Italian	41 Point	Missense	738 c.738G>C
7	126	F	Italian	41 Point	Missense	738 c.738G>C
8	127	F	Italian	41 Point	Missense	738 c.738G>C
9	130	F	Italian	41 Point	Missense	738 c.738G>C
10	130	F	Italian	41 Point	Missense	738 c.738G>C
11	428	26 F		235 Point	Missense	755 c.755G>A
12	236		UK Populat	141 Point	Missense	756 c.756A>T
13	237		UK Populat	141 Point	Missense	756 c.756A>T
14	237		UK Populat	141 Point	Missense	756 c.756A>T
15	4	13 M	French Bas	52 Point	Missense	764 c.764G>A
16	103	10 M		52 Point	Missense	764 c.764G>A
17	506	53 M		253 Deletion	Frameshift	769 c.769delC
18	204	20 M	French	128 Point	Missense	783 c.783G>C
19	173	27 F		115 Point	Missense	788 c.788G>A
20	173	27 F		115 Point	Missense	788 c.788G>A
21	174	52 F		115 Point	Missense	788 c.788G>A
22	16	F	African Am	63 Point	Missense	797 c.797G>A
23	15	9 M	African Am	63 Point	Missense	797 c.797G>A
24	15	9 M	African Am	63 Point	Missense	797 c.797G>A
25	45			30 Point	Missense	802 c.802C>T
26	238		UK Populat	30 Point	Missense	802 c.802C>T
27	44			30 Point	Missense	802 c.802C>T
28	603	69 F	Spanish	30 Point	Missense	802 c.802C>T
29	239		UK Populat	30 Point	Missense	802 c.802C>T
30	239		UK Populat	30 Point	Missense	802 c.802C>T
31	356	9 F		210 Point	Missense	803 c.803G>A
32	435	46 F	Czech	40 Point	Missense	809 c.809A>T
33	507			255 Point	Missense	829 c.829G>A
34	651	43 F	Taiwanese	42 Point	Nonsense	841 c.841C>T
35	656	38 F	Taiwanese	42 Point	Nonsense	841 c.841C>T
36	656	38 F	Taiwanese	42 Point	Nonsense	841 c.841C>T
37	615	30 F		42 Point	Nonsense	841 c.841C>T
38	65	42 F	Japanese	42 Point	Nonsense	841 c.841C>T
39	122	M	Japanese	42 Point	Nonsense	841 c.841C>T
40	62	17 F	Chinese	42 Point	Nonsense	841 c.841C>T
41	115	20 F	Chinese	42 Point	Nonsense	841 c.841C>T
42	115	20 F	Chinese	42 Point	Nonsense	841 c.841C>T
43	119	F	Japanese	42 Point	Nonsense	841 c.841C>T
44	120	M	Japanese	42 Point	Nonsense	841 c.841C>T
45	121	F	Japanese	42 Point	Nonsense	841 c.841C>T
46	123	M	Japanese	42 Point	Nonsense	841 c.841C>T
47	123	M	Japanese	42 Point	Nonsense	841 c.841C>T
48	64	56 F	Chinese	42 Point	Nonsense	841 c.841C>T
49	150	29 M	Japanese	42 Point	Nonsense	841 c.841C>T
50	618	26 F	Chinese	42 Point	Nonsense	841 c.841C>T
51	619	41 F	Chinese	42 Point	Nonsense	841 c.841C>T
52	625	22 F	Chinese	42 Point	Nonsense	841 c.841C>T
53	625	22 F	Chinese	42 Point	Nonsense	841 c.841C>T
54	626	33 M	Chinese	42 Point	Nonsense	841 c.841C>T
55	399	25 F	Chinese	42 Point	Nonsense	841 c.841C>T
56	79	55 F	Ashkenazi J	65 Point	Missense	901 c.901T>C
57	454			65 Point	Missense	901 c.901T>C
58	112	F	Caucasian	65 Point	Missense	901 c.901T>C
59	113	M	Caucasian	65 Point	Missense	901 c.901T>C
60	113	M	Caucasian	65 Point	Missense	901 c.901T>C
	453			65 Point	Missense	901 c.901T>C



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2	455			65 Point	Missense	901 c.901T>C
3	545	54 M	Italian	65 Point	Missense	901 c.901T>C
4	549	36 F	Italian	65 Point	Missense	901 c.901T>C
5	283	53 F	Italian	65 Point	Missense	901 c.901T>C
6	477	40 F	Czech	65 Point	Missense	901 c.901T>C
7	18	42 F	Caucasian	65 Point	Missense	901 c.901T>C
8	490	F		65 Point	Missense	901 c.901T>C
9	544	19 F	Italian	65 Point	Missense	901 c.901T>C
10	547	12 F	Italian	65 Point	Missense	901 c.901T>C
11	5	17 M	French Bas	59 Deletion	Frameshift	907 c.907delG
12	175	57 F		116 Deletion	Frameshift	918 c.918delG
13	429			166 Duplication	Frameshift	933 c.933_951c
14	641	M	Chinese	354 Point	Missense	938 c.938G>T
15	643	F	Chinese	354 Point	Missense	938 c.938G>T
16	646	M	Chinese	354 Point	Missense	938 c.938G>T
17	640	32 F	Chinese	354 Point	Missense	938 c.938G>T
18	152			122 Point	Missense	943 c.943G>A
19	210	31 M	French	122 Point	Missense	943 c.943G>A
20	194	57 M	French	122 Point	Missense	943 c.943G>A
21	195	25 F	French	122 Point	Missense	943 c.943G>A
22	553	53 F	Italian	122 Point	Missense	943 c.943G>A
23	554	29 F	Italian	122 Point	Missense	943 c.943G>A
24	430			122 Point	Missense	943 c.943G>A
25	551	31 F	Italian	122 Point	Missense	943 c.943G>A
26	561	3 F	Italian	122 Point	Missense	943 c.943G>A
27	562	30 F	Italian	122 Point	Missense	943 c.943G>A
28	495	24 F	Belgic	122 Point	Missense	943 c.943G>A
29	431	47 M	French	142 Deletion	Frameshift	961 c.961_962c
30	241		UK Populat	142 Deletion	Frameshift	961 c.961_962c
31	211	36 F	French	3 Point	Missense	965 c.965C>T
32	602	42 M	Spanish	3 Point	Missense	965 c.965C>T
33	242		UK Populat	3 Point	Missense	965 c.965C>T
34	434			194 Point	Missense	973 c.973G>T
35	432			194 Point	Missense	973 c.973G>T
36	433			194 Point	Missense	973 c.973G>T
37	19			5 Point	Missense	976 c.976C>T
38	243		UK Populat	5 Point	Missense	976 c.976C>T
39	437			5 Point	Missense	976 c.976C>T
40	436	85 F	Australian	5 Point	Missense	976 c.976C>T
41	458	45 M	Iranian	169 Point	Missense	992 c.992C>T
42	134		Chinese	4 Point	Missense	1021 c.1021G>A
43	220		UK Populat	4 Point	Missense	1021 c.1021G>A
44	459	33 F	Ashkenazi J	4 Point	Missense	1021 c.1021G>A
45	111	M	Caucasian	67 Duplication	Frameshift	1026 c.1026dupC
46	54	F	Portuguese	34 Point	Silent	1026 c.1026G>T
47	55	F	Portuguese	34 Point	Silent	1026 c.1026G>T
48	470	50 F	Portugese	34 Point	Silent	1026 c.1026G>T
49	456			239 Point		1028 c.1028+5G>
50	658	64 M		361 Point	Nonsense	1033 c.1033A>T
51	381		Non-Jewish	12 Point	Missense	1060 c.1060G>A

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2	58		Portuguese	37 Deletion	Frameshift	1072 c.1072delA
3	471	58 F	Portuguese	37 Deletion	Frameshift	1072 c.1072delA
4	244		UK Populat	143 Point	Missense	1077 c.1077A>G
5	460	17 M	Iranian	170 Point	Missense	1079 c.1079T>C
6	246		UK Populat	144 Point	Missense	1084 c.1084G>A
7						
8	620	6 F	Chinese	18 Point	Missense	1103 c.1103G>A
9	143	6 F	Indian	100 Point	Missense	1106 c.1106A>C
10	653	69 F	Taiwanese	43 Point	Nonsense	1107 c.1107C>A
11	63	10 F	Chinese	43 Point	Nonsense	1107 c.1107C>A
12						
13	116	18 F	Chinese	43 Point	Nonsense	1107 c.1107C>A
14	649	29 M	Taiwanese	43 Point	Nonsense	1107 c.1107C>A
15	657	61 M		43 Point	Nonsense	1107 c.1107C>A
16	659	7 M		43 Point	Nonsense	1107 c.1107C>A
17	247		UK Populat	145 Point	Missense	1118 c.1118T>C
18	248		UK Populat	146 Point	Missense	1120 c.1120T>C
19						
20	153			108 Point		1135 c.1135+1G>
21	463	29 F	Japanese	108 Point		1135 c.1135+1G>
22	249		UK Populat	147 Point	Missense	1135 c.1135+5G>
23	155	F	Chinese	110 Deletion	Frameshift	1136 c.1136-4de
24	156	M	Chinese	110 Deletion	Frameshift	1136 c.1136-4de
25						
26	268	F	Chinese	110 Deletion	Frameshift	1136 c.1136-4de
27	622	12 F	Chinese	110 Deletion	Frameshift	1136 c.1136-4de
28	464	26 M	Italian	171 Point	Missense	1165 c.1165G>A
29	467			241 Point	Missense	1178 c.1178C>T
30						
31	245		UK Populat	98 Point	Missense	1186 c.1186C>T
32	468	F		98 Point	Missense	1186 c.1186C>T
33	389	F		224 Point	Missense	1196 C.1196G>T
34	32	8 F	Arab	15 Point	Missense	1211 c.1211C>A
35	33	M	Arab	15 Point	Missense	1211 c.1211C>A
36						
37	34	F	Arab	15 Point	Missense	1211 c.1211C>A
38	469	32 F	French	173 Point	Missense	1217 c.1217A>C
39	250		UK Populat	26 Point	Missense	1219 c.1219A>C
40	508			256 Point	Missense	1222 c.1222A>C
41	628	14 M	Indian	363 Point	Nonsense	1234 c.1234C>T
42	84	F	English	51 Point	Missense	1247 c.1247G>A
43						
44	251		UK Populat	51 Point	Missense	1247 c.1247G>A
45	525	28 F	Turkish	51 Point	Missense	1247 c.1247G>A
46	587	25 M	Spanish	51 Point	Missense	1247 c.1247G>A
47						
48	588	50 F	Spanish	51 Point	Missense	1247 c.1247G>A
49	589	43 M	Spanish	51 Point	Missense	1247 c.1247G>A
50	590	32 F	Spanish	51 Point	Missense	1247 c.1247G>A
51	591	80 F	Spanish	51 Point	Missense	1247 c.1247G>A
52	592	38 M	Spanish	51 Point	Missense	1247 c.1247G>A
53						
54	85		English	51 Point	Missense	1247 c.1247G>A
55	114		Hispanic	51 Point	Missense	1247 c.1247G>A
56	146	38 F		51 Point	Missense	1247 c.1247G>A
57	252		UK Populat	51 Point	Missense	1247 c.1247G>A
58	472			51 Point	Missense	1247 c.1247G>A
59						
60	36	F	Chinese	16 Point	Missense	1253 c.1253G>T
	516	8 F	Turkish	16 Point	Missense	1253 c.1253G>T

1						
2	86		US	16 Point	Missense	1253 c.1253G>T
3	35	53 M	Italian and	16 Point	Missense	1253 c.1253G>T
4	557	53 F	Italian	16 Point	Missense	1253 c.1253G>T
5	305	19 F	Italian	16 Point	Missense	1253 c.1253G>T
6	427	62 M	Japanese	16 Point	Missense	1253 c.1253G>T
7	623	50 M	Chinese	16 Point	Missense	1253 c.1253G>T
8	473			243 Point	Missense	1255 c.1255T>G
9	614	49 F	Chinese	148 Point	Nonsense	1270 c.1270C>T
10	253		UK Populat	148 Point	Nonsense	1270 c.1270C>T
11	474	7	African	174 Point	Missense	1275 c.1275G>C
12	605	25 M	Spanish	300 Point	Missense	1277 c.1277T>C
13	636	28 F	Indian	175 Point	Missense	1283 c.1283C>T
14	475			175 Point	Missense	1283 c.1283C>T
15	479			244 Point	Missense	1288 c.1288G>T
16	20	F		6 Point	Missense	1289 c.1289C>T
17	478	31 F		6 Point	Missense	1289 c.1289C>T
18	480			176 Point		1304 c.1304+12C
19	59		Portuguese	38 Point		1305 c.1305-10T
20	654	52 M	Taiwanese	357 Deletion	Frameshift	1322 c.1322delT
21	647	54 F	Taiwanese	357 Deletion	Frameshift	1322 c.1322delT
22	481			156 Point	Missense	1327 c.1327C>T
23	482			156 Point	Missense	1327 c.1327C>T
24	38	37 F	Non-Jewish	19 Point	Missense	1378 c.1378T>G
25	69	25 M	Japanese	46 Point	Nonsense	1393 c.1393G>T
26	486	6 F	Japanese	177 Point	Missense	1394 c.1394C>G
27	487	M	Japanese	177 Point	Missense	1394 c.1394C>G
28	42			62 Point	Missense	1432 c.1432G>A
29	142	11 M	Indian	62 Point	Missense	1432 c.1432G>A
30	635	14 M	Indian	62 Point	Missense	1432 c.1432G>A
31	254		UK Populat	62 Point	Missense	1432 c.1432G>A
32	206	40 F	French	62 Point	Missense	1432 c.1432G>A
33	13			62 Point	Missense	1432 c.1432G>A
34	10			62 Point	Missense	1432 c.1432G>A
35	207	4 M	French	62 Point	Missense	1432 c.1432G>A
36	141	9 M	Indian	62 Point	Missense	1432 c.1432G>A
37	208	2 M	French	62 Point	Missense	1432 c.1432G>A
38	408			62 Point	Missense	1432 c.1432G>A
39	630	42 M	Indian	351 Point	Missense	1448 c.1448T>C
40	46			31 Point	Missense	1478 c.1478C>T
41	164	M	Non-Jewish	31 Point	Missense	1478 c.1478C>T
42	255		UK Populat	31 Point	Missense	1478 c.1478C>T
43	489	29 F	Ashkenazi J	178 Point	Missense	1480 c.1480+2T>
44	258		UK Populat	149 Point	Nonsense	1489 c.1489C>T
45	491			246 Point	Missense	1498 c.1498T>C
46	259		UK Populat	150 Point	Missense	1500 c.1500C>G
47	492	12 M	Iranian	180 Point	Missense	1507 c.1507T>C
48	2	22 F	French Bas	53 Point	Missense	1531 c.1531T>C
49	97	22 F	French Bas	53 Point	Missense	1531 c.1531T>C
50	202	29 F	French	127 Point	Missense	1545 c.1545G>T
51	558	25 F	Italian	127 Point	Missense	1545 c.1545G>T



1						
2	559	52 M	Italian	127 Point	Missense	1545 c.1545G>T
3	560	49 F	Italian	127 Point	Missense	1545 c.1545G>T
4	493			214 Point	Missense	1546 c.1546G>A
5	303	F	Iranian	47 Insertion	Frameshift	1556 c.1556insG
6	488	F	Japanese	47 Insertion	Frameshift	1556 c.1556insG
7						
8	484	2 M	Japanese	47 Insertion	Frameshift	1556 c.1556insG
9	485	4 M	Japanese	47 Insertion	Frameshift	1556 c.1556insG
10	66	65 M	Japanese	44 Point	Nonsense	1556 c.1556G>A
11	517	11 F	Turkish	44 Point	Nonsense	1556 c.1556G>A
12						
13	521	45 F	Turkish	44 Point	Nonsense	1556 c.1556G>A
14	548	45 M	Italian	44 Point	Nonsense	1556 c.1556G>A
15	550	7 M	Italian	44 Point	Nonsense	1556 c.1556G>A
16	552	54 M	Italian	44 Point	Nonsense	1556 c.1556G>A
17	48	38 F	Lebanese	33 Point	Missense	1557 c.1557G>C
18	49	F	Lebanese	33 Point	Missense	1557 c.1557G>C
19						
20	50	M	Lebanese	33 Point	Missense	1557 c.1557G>C
21	509			33 Point	Missense	1557 c.1557G>C
22	607	64 F	Chinese	331 Point	Missense	1562 c.1562A>G
23	608	F	Chinese	331 Point	Missense	1562 c.1562A>G
24						
25	609	F	Chinese	331 Point	Missense	1562 c.1562A>G
26	610	M	Chinese	331 Point	Missense	1562 c.1562A>G
27	95	M	Portuguese	35 Point	Missense	1608 c.1608G>C
28	601	47 F	Spanish	35 Point	Missense	1608 c.1608G>C
29	599	71 M	Spanish	50 Point	Missense	1613 c.1613C>T
30	600	88 F	Spanish	50 Point	Missense	1613 c.1613C>T
31						
32	83 8on	M		50 Point	Missense	1613 c.1613C>T
33	179	65 F		50 Point	Missense	1613 c.1613C>T
34	180	47 F		50 Point	Missense	1613 c.1613C>T
35						
36	256		UK Populat	50 Point	Missense	1613 c.1613C>T
37	257		UK Populat	50 Point	Missense	1613 c.1613C>T
38	494	F		50 Point	Missense	1613 c.1613C>T
39	205	M	French	50 Point	Missense	1613 c.1613C>T
40	515	26 F	Turkish	262 Point	Missense	1619 c.1619T>G
41	496			247 Point	Missense	1684 c.1684G>A
42						
43	497			247 Point	Missense	1684 c.1684G>A
44	593	26 F	Spanish	117 Point	Missense	1693 c.1693G>A
45	594	44 F	Spanish	117 Point	Missense	1693 c.1693G>A
46	595	49 F	Spanish	117 Point	Missense	1693 c.1693G>A
47						
48	596	32 M	Spanish	117 Point	Missense	1693 c.1693G>A
49	597	55 F	Spanish	117 Point	Missense	1693 c.1693G>A
50	598	72 F	Spanish	117 Point	Missense	1693 c.1693G>A
51	177	54 F		117 Point	Missense	1693 c.1693G>A
52	178	32 F		117 Point	Missense	1693 c.1693G>A
53						
54	203	33 F	French	117 Point	Missense	1693 c.1693G>A
55	465	9 F	Iranian	117 Point	Missense	1693 c.1693G>A
56	68	30 M	Jewish	45 Deletion		1714 c.1714_171
57	555	7 F	Italian	326 Point		1716 c.1716+248
58	556	48 F	Italian	326 Point		1716 c.1716+248
59	260		UK Populat	48 Point		1716 c.1716+1G>
60	78	44 M	Ashkenazi J	48 Point		1716 c.1716+1G>

1						
2	82		Bucharian-J	49 Point	Missense	1718 c.1718G>A
3	261		UK Populat	49 Point	Missense	1718 c.1718G>A
4	629	15 F	Indian	350 Point	Missense	1721 c.1721A>C
5	519	3.5 M	Turkish	263 Point	Missense	1741 c.1741T>C
6	520	32 F	Turkish	263 Point	Missense	1741 c.1741T>C
7						
8	263		UK Populat	151 Point	Missense	1742 c.1742G>T
9	87		US	17 Point	Missense	1760 c.1760G>C
10	37	49 M	German	17 Point	Missense	1760 c.1760G>C
11	606	53 M	Spanish	301 Point	Missense	1775 c.1775T>C
12						
13	136	22 F	Lebanese	9 Point	Missense	1778 c.1778C>T
14	137	F	Lebanese	9 Point	Missense	1778 c.1778C>T
15	138	M	Lebanese	9 Point	Missense	1778 c.1778C>T
16	139	F	Lebanese	9 Point	Missense	1778 c.1778C>T
17	140	F	Lebanese	9 Point	Missense	1778 c.1778C>T
18						
19	262		UK Populat	9 Point	Missense	1778 c.1778C>T
20	498	F		9 Point	Missense	1778 c.1778C>T
21	499	F		249 Point	Missense	1782 c.1782C>A
22	501			249 Point	Missense	1782 c.1782C>A
23						
24	500			249 Point	Missense	1782 c.1782C>A
25	502	28 F		181 Point	Missense	1789 c.1789G>A
26	31	85 F	Nantes	13 Point	Nonsense	1797 c.1797T>A
27	30	71 M	Nantes	13 Point	Nonsense	1797 c.1797T>A
28	503	44 M	Iranian	250 Point	Missense	1822 c.1822T>C
29						
30	265		UK Populat	27 Point	Nonsense	1824 c.1824C>A
31	181	32 F		27 Point	Nonsense	1824 c.1824C>A
32	157	72 F	Japanese	111 Point	Missense	1849 c.1849T>G
33	266		UK Populat	28 Point	Missense	1853 c.1853T>C
34	182	62 F		28 Point	Missense	1853 c.1853T>C
35	267		UK Populat	28 Point	Missense	1853 c.1853T>C
36						
37	514	F	Italian	260 Point	Missense	1856 c.1856T>C
38						
39						
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HGVS	Amino Acid	Protein Change	Domain	Other Variants	FXI:C%	FXI:Ag%	Inheritance	Clinical Severity
0	0		Promoter R	0	67		Heterozygous	Not Reported
0	0		Promoter R	0	29		Heterozygous	Not Reported
0	0		Serine Protease	0 <1			Homozygous	Severe
0	0			0	32		Heterozygous	Mild
1	-18	p.Met1Ile	Signal Peptide	0			Heterozygous	Not Reported
1	-18	p.Met1Ile	Signal Peptide	0	43		Heterozygous	Not Reported
15	-4	p.Ser15Leu	Signal Peptide	0	3		3 Homozygous	Not Reported
0	0		Linker	0	1		3 Homozygous	Not Reported
19	1	p.Glu19*	Linker	0	43		Heterozygous	Not Reported
0	0		Apple 1	0 <1	<1		Compound	Severe
0	0		Apple 1	0	20		32 Heterozygous	Not Reported
38	20	p.Val38Ala	Apple 1	0			32 Heterozygous	Not Reported
41	23	p.Pro41Gln	Apple 1	0	56		Heterozygous	Not Reported
41	23	p.Pro41Leu	Apple 1	0	30		39 Heterozygous	Not Reported
42	24	p.Ser42Arg	Apple 1	0	29		Heterozygous	Not Reported
42	24	p.Ser42Arg	Apple 1	1	2		Compound	Not Reported
46	28	p.Cys46Phe	Apple 1	0	24		35 Heterozygous	Mild
46	28	p.Cys46Phe	Apple 1	0	31		41 Heterozygous	Mild
46	28	p.Cys46Phe	Apple 1	0	26		Heterozygous	Mild
46	28	p.Cys46Phe	Apple 1	1	1		Compound	Not Reported
47	29	p.Gln47His	Apple 1	0			Heterozygous	Not Reported
51	33	p.Thr51Pro	Apple 1	0			Heterozygous	Not Reported
51	33	p.Thr51Pro	Apple 1	0			Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	1		Homozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	3		Homozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0 <1			Homozygous	Severe
56	38	p.Cys56Arg	Apple 1	0	40		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	44		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	44		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	41		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	37		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	37		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	34		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	28		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	42		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	49		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	40		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	68		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	58		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	42		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	25		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	41		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	36		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	30		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	38		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	41		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	42		Heterozygous	Not Reported
56	38	p.Cys56Arg	Apple 1	0	18		Heterozygous	Mild
56	38	p.Cys56Arg	Apple 1	0	30		Heterozygous	Mild

1					
2	56	38 p.Cys56Arg Apple 1	0	36	Heterozygo Mild
3	56	38 p.Cys56Arg Apple 1	0	40	Heterozygo Mild
4	56	38 p.Cys56Arg Apple 1	0	40	Heterozygo Mild
5	56	38 p.Cys56Arg Apple 1	0	45	Heterozygo Mild
6	56	38 p.Cys56Arg Apple 1	0	34	Heterozygo Mild
7	56	38 p.Cys56Arg Apple 1	0	40	Heterozygo Mild
8	56	38 p.Cys56Arg Apple 1	0	40	Heterozygo Mild
9	56	38 p.Cys56Arg Apple 1	1	2	Compound Not Report
10	56	38 p.Cys56Arg Apple 1	1 <1	<1	Compound Severe
11	56	38 p.Cys56Trp Apple 1	0	20	46 HeterozygoNot Report
12	72	54 p.Arg72Pro Apple 1	0	63	77 HeterozygoNot Report
13					
14	0	0 Intronic	0 <1		HomozygotNot Report
15	0	0 Intronic	0 <1		HomozygotNot Report
16	0	0 Intronic	0 <1		HeterozygoNot Report
17	76	58 p.Cys76Phe Apple 1	0 <1		Homozygot Severe
18	76	58 p.Cys76Tyr Apple 1	0	26	HeterozygoNot Report
19	99	81 p.Ser99Tyr Apple 1	0	57	Heterozygo Not Report
20	99	81 p.Ser99Tyr Apple 1	0	57	Heterozygo Not Report
21	99	81 p.Ser99Tyr Apple 1	0	57	Heterozygo Not Report
22	0	0 Apple 1	0	15	Heterozygo Severe
23	0	0 Apple 1	0	4	48 Heterozygo Severe
24					
25	101	83 p.Lys101Arg Apple 1	0	38	Heterozygo Mild
26	106	88 p.Gln106* Linker	0 <1		0 Homozygot Severe
27	106	88 p.Gln106* Linker	0 <1		0 Homozygot Severe
28	106	88 p.Gln106* Linker	0	60	51 Heterozygo Mild
29	106	88 p.Gln106* Linker	0	46	41 Heterozygo Mild
30	106	88 p.Gln106* Linker	1 <1		1 Compound Severe
31	109	91 p.Ala109Thr Linker	0		HeterozygoNot Report
32	109	91 p.Ala109Thr Linker	0		HeterozygoNot Report
33	109	91 p.Ala109Thr Linker	0	37	HeterozygoNot Report
34	109	91 p.Ala109Thr Linker	0	26	39 HeterozygoNot Report
35	109	91 p.Ala109Thr Linker	0	45	Heterozygo Not Report
36	109	91 p.Ala109Thr Linker	0	32	HeterozygoNot Report
37	109	91 p.Ala109Thr Linker	0	35	HeterozygoNot Report
38	109	91 p.Ala109Thr Linker	0	35	HeterozygoNot Report
39	109	91 p.Ala109Thr Linker	0 <1		Compound Not Report
40	109	91 p.Ala109Thr Linker	0 <1		Compound Not Report
41	0	0 Intronic	1 <1		Compound Not Report
42					
43	110	92 p.Cys110Gly Apple 2	0	47	40 Heterozygo Not Report
44	110	92 p.Cys110Gly Apple 2	0	21	44 HeterozygoNot Report
45	120	102 p.Met120Thr Apple 2	0		Heterozygo Not Report
46	120	102 p.Met120Thr Apple 2	0	40	HeterozygoNot Report
47	122	104 p.Gly122Asp Apple 2	0	42	HeterozygoNot Report
48	122	104 p.Gly122Asp Apple 2	0	35	Heterozygo Mild
49	122	104 p.Gly122Asp Apple 2	0	33	Heterozygo Mild
50	122	104 p.Gly122Asp Apple 2	0	58	61 Heterozygo Not Report
51	122	104 p.Gly122Asp Apple 2	0	44	Heterozygo Not Report
52	122	104 p.Gly122Asp Apple 2	0	45	Heterozygo Not Report
53	122	104 p.Gly122Asp Apple 2	1	2	Compound Not Report
54	122	104 p.Gly122Asp Apple 2	1	2	Compound Not Report
55	134	116 p.Gln134* Apple 2	0	52	43 Heterozygo Not Report
56	134	116 p.Gln134* Apple 2	1	1	4 Compound Severe
57	134	116 p.Gln134* Apple 2	0	10	Not Report
58	134	116 p.Gln134* Apple 2	0	16	HomozygotNot Report
59	135	117 p.Glu135* Apple 2	0	16	HomozygotNot Report
60	135	117 p.Glu135* Apple 2	0 <1		HomozygotNot Report

1						
2	135	117 p.Glu135* Apple 2	0 <1	<1		Homozygot Severe
3	135	117 p.Glu135* Apple 2	0 <1		4	Homozygot Severe
4	135	117 p.Glu135* Apple 2	0 <1			Homozygot Severe
5	135	117 p.Glu135* Apple 2	0	1	7	Homozygot Severe
6	135	117 p.Glu135* Apple 2	0	1	14	Homozygot Severe
7	135	117 p.Glu135* Apple 2	0	4		Homozygot Severe
8	135	117 p.Glu135* Apple 2	0	1		Homozygot Severe
9	135	117 p.Glu135* Apple 2	0	2		Homozygot Severe
10	135	117 p.Glu135* Apple 2	0			HeterozygoNot Report
11	135	117 p.Glu135* Apple 2	0			HeterozygoNot Report
12	135	117 p.Glu135* Apple 2	0	18		HeterozygoNot Report
13	135	117 p.Glu135* Apple 2	0	44		heterozygo Not Report
14	135	117 p.Glu135* Apple 2	0	62		Heterozygo Not Report
15	135	117 p.Glu135* Apple 2	0	35	33	HeterozygoNot Report
16	135	117 p.Glu135* Apple 2	0	32	39	HeterozygoNot Report
17	135	117 p.Glu135* Apple 2	0	38		HeterozygoNot Report
18	135	117 p.Glu135* Apple 2	0	42		HeterozygoNot Report
19	135	117 p.Glu135* Apple 2	0	34		HeterozygoNot Report
20	135	117 p.Glu135* Apple 2	0	47	88	Heterozygo Mild
21	135	117 p.Glu135* Apple 2	1 <10	<10		Compound Severe
22	135	117 p.Glu135* Apple 2	1 <10	<10		Compound Severe
23	135	117 p.Glu135* Apple 2	1 <10	<10		Compound Severe
24	135	117 p.Glu135* Apple 2	1 <10	<10		Compound Severe
25	135	117 p.Glu135* Apple 2	0			Compound Not Report
26	135	117 p.Glu135* Apple 2	1	1	3	Compound Not Report
27	135	117 p.Glu135* Apple 2	1 <0.5		4	Compound Severe
28	135	117 p.Glu135* Apple 2	1 <3	<5		Compound Severe
29	135	117 p.Glu135* Apple 2	1 <1	<3		Compound Severe
30	135	117 p.Glu135* Apple 2	1	0.02		Compound Severe
31	135	117 p.Glu135* Apple 2	0	0.02		Compound Severe
32	135	117 p.Glu135* Apple 2	0 <1			Compound Severe
33	135	117 p.Glu135* Apple 2	0 <1			Compound Severe
34	135	117 p.Glu135* Apple 2	0 <1	<1		Compound Severe
35	135	117 p.Glu135* Apple 2	1 <1			Compound Severe
36	135	117 p.Glu135* Apple 2	1 <1	<1		Compound Severe
37	135	117 p.Glu135* Apple 2	1 <1			Compound Severe
38	135	117 p.Glu135* Apple 2	1 <1	<1		Compound Severe
39	135	117 p.Glu135* Apple 2	1		3	Compound Not Report
40	135	117 p.Glu135* Apple 2	1	6		Compound Not Report
41	135	117 p.Glu135* Apple 2	1 <1			Compound Not Report
42	135	117 p.Glu135* Apple 2	0 <1		5	Compound Severe
43	135	117 p.Glu135* Apple 2	0 <1		5	Compound Severe
44	135	117 p.Glu135* Apple 2	1 <1		5	Compound Severe
45	135	117 p.Glu135* Apple 2	0			Compound Not Report
46	135	117 p.Glu135* Apple 2	1	2		Compound Not Report
47	135	117 p.Glu135* Apple 2	1 <1	<1		Compound Severe
48	135	117 p.Glu135* Apple 2	0 <1	<1		Compound Severe
49	135	117 p.Glu135* Apple 2	0	0		Severe
50	135	117 p.Glu135* Apple 2	0	42		Mild
51	135	117 p.Glu135* Apple 2	0	30		Mild
52	135	117 p.Glu135* Apple 2	0	1		Severe

1						
2	135	117 p.Glu135*	Apple 2	0	59	Mild
3	135	117 p.Glu135*	Apple 2	0	22	Mild
4	135	117 p.Glu135*	Apple 2	0	43	Mild
5	135	117 p.Glu135*	Apple 2	0 <1		0 Mild
6	135	117 p.Glu135*	Apple 2	0 <1		0 Severe
7	135	117 p.Glu135*	Apple 2	0 <1		1 Severe
8	135	117 p.Glu135*	Apple 2	0 <1		1 Severe
9	136	118 p.Cys136*	Apple 2	1 <1		Compound Severe
10	136	118 p.Cys136*	Apple 2	1 <1		Compound Severe
11	136	118 p.Cys136*	Apple 2	0 <1		0 Mild
12	136	118 p.Cys136*	Apple 2	0 <1		0 Mild
13	136	118 p.Cys136*	Apple 2	0 <1		0 Mild
14	140	122 p.Cys140Ty	Apple 2	0	4	3 Homozygot Not Report
15	140	122 p.Cys140Ty	Apple 2	0	25	Heterozygo Not Report
16	140	122 p.Cys140Ty	Apple 2	0	24	Heterozygo Not Report
17	140	122 p.Cys140Ty	Apple 2	0	31	Heterozygo Not Report
18	140	122 p.Cys140Ty	Apple 2	0		Compound Not Report
19	140	122 p.Cys140Ty	Apple 2	0		Compound Not Report
20	141	123 p.Thr141M	Apple 2	0	1	4 Compound Severe
21	143	125 p.Asp143Al	Apple 2	0	49	Heterozygo Not Report
22	143	125 p.Asp143Al	Apple 2	0	47	Heterozygo Not Report
23	143	125 p.Asp143Al	Apple 2	0		Heterozygo Not Report
24	143	125 p.Asp143Al	Apple 2	0		Heterozygo Not Report
25	145	127 p.His145Arj	Apple 2	0	27	125 Heterozygo Not Report
26	145	127 p.His145Arj	Apple 2	0	52	118 Heterozygo Not Report
27	145	127 p.His145Arj	Apple 2	0	56	157 Heterozygo Not Report
28	145	127 p.His145Arj	Apple 2	1	7	Compound Not Report
29	146	128 p.Cys146*	Apple 2	0 <1		Homozygot Severe
30	146	128 p.Cys146*	Apple 2	0 <1		Homozygot Severe
31	146	128 p.Cys146*	Apple 2	0 <1		Homozygot Severe
32	146	128 p.Cys146*	Apple 2	0	65	64 Heterozygo Mild
33	146	128 p.Cys146*	Apple 2	0	34	27 Heterozygo Mild
34	146	128 p.Cys146*	Apple 2	0	38	Heterozygo Not Report
35	146	128 p.Cys146*	Apple 2	0	45	Heterozygo Not Report
36	146	128 p.Cys146*	Apple 2	0	46	Heterozygo Not Report
37	146	128 p.Cys146*	Apple 2	0	46	Heterozygo Not Report
38	146	128 p.Cys146*	Apple 2	0	16	Heterozygo Not Report
39	146	128 p.Cys146*	Apple 2	0	49	41 Heterozygo Mild
40	146	128 p.Cys146*	Apple 2	0	61	Heterozygo Not Report
41	146	128 p.Cys146*	Apple 2	0 <2		Compound Severe
42	146	128 p.Cys146*	Apple 2	0 <1		Compound Severe
43	146	128 p.Cys146*	Apple 2	0 <1	<1	Compound Severe
44	146	128 p.Cys146*	Apple 2	1	4	Compound Severe
45	146	128 p.Cys146*	Apple 2	1 <2		Compound Severe
46	146	128 p.Cys146*	Apple 2	1	4	Compound Not Report
47	146	128 p.Cys146*	Apple 2	1	4	Compound Not Report
48	146	128 p.Cys146*	Apple 2	1 <1	<3	Compound Severe
49	146	128 p.Cys146*	Apple 2	1	2	Compound Not Report
50	146	128 p.Cys146*	Apple 2	1 <1		Compound Severe
51	146	128 p.Cys146*	Apple 2	0 <1		Compound Severe
52	146	128 p.Cys146*	Apple 2	0	29	29 Not Report
53	146	128 p.Cys146*	Apple 2	0	44	38 Not Report
54	146	128 p.Cys146*	Apple 2	0	41	Not Report
55	146	128 p.Cys146*	Apple 2	0	41	Not Report
56	150	132 p.Thr150M	Apple 2	0	23	Heterozygo Not Report
57	150	132 p.Thr150M	Apple 2	0	34	Heterozygo Not Report
58	150	132 p.Thr150M	Apple 2	0	52	Heterozygo Not Report
59	150	132 p.Thr150M	Apple 2	0	37	Heterozygo Not Report
60	150	132 p.Thr150M	Apple 2	0	43	Heterozygo Not Report



1					
2	151	133 p.Tyr151Cy Apple 2	0	47	Heterozygo Not Report
3	151	133 p.Tyr151Se Apple 2	0	38	Homozygot Mild
4	151	133 p.Tyr151Se Apple 2	0	50	Heterozygo Not Report
5	151	133 p.Tyr151Se Apple 2	0	36	Heterozygo Not Report
6	151	133 p.Tyr151Se Apple 2	0	38	Not Report
7	151	133 p.Tyr151Se Apple 2	0		
8	152	134 p.Ala152Pr Apple 2	0		Homozygot Not Report
9	152	134 p.Ala152Pr Apple 2	0 <1		Homozygot Severe
10	162	144 p.Arg162Cy Apple 2	0	35	Heterozygo Not Report
11	0	0 Intronic	0	3	Homozygot Severe
12	0	0 Intronic	0	56	Heterozygo Not Report
13	0	0 Intronic	0	36	25 Heterozygo Not Report
14	0	0 Intronic	0	36	25 Heterozygo Not Report
15	173	155 p.Gly173G Apple 2	0	41	Heterozygo Not Report
16	173	155 p.Gly173G Apple 2	0	43	64 Heterozygo Not Report
17	173	155 p.Gly173G Apple 2	0	30	Heterozygo Not Report
18	190	172 p.Leu190Pr Apple 2	0		Heterozygo Not Report
19	0	0 Intronic	0	33	Heterozygo Not Report
20	0	0 Intronic	0	51	Heterozygo Not Report
21	0	0 Intronic	0	85	Heterozygo Not Report
22	0	0 Intronic	0	35	Heterozygo Mild
23	0	0 Intronic	1	46	10 Compound Not Report
24	0	0 Apple 3	1	5	Compound Not Report
25	0	0 Apple 3	1	5	Compound Not Report
26	199	181 p.Ala199Va Apple 3	1	0.07	0.07 Compound Severe
27	200	182 p.Cys200Ty Apple 3	0	47	Heterozygo Not Report
28	200	182 p.Cys200Ty Apple 3	0	34	Heterozygo Not Report
29	200	182 p.Cys200Ty Apple 3	0	34	Heterozygo Not Report
30	200	182 p.Cys200Se Apple 3	0	34	Heterozygo Not Report
31	202	184 p.Arg202G Apple 3	0	69	121 Heterozygo Not Report
32	206	188 p.Pro206Se Apple 3	0	30	Heterozygo Not Report
33	0	0 p.Ile215_A Apple 3	0	39	34 Heterozygo Not Report
34	228	210 p.Arg228* Apple 3	1 <1		3 Compound Severe
35	230	212 p.Cys230Se Apple 3	0	38	Heterozygo Not Report
36	230	212 p.Cys230Se Apple 3	0	35	Heterozygo Not Report
37	230	212 p.Cys230Ar Apple 3	0	1	Homozygot Not Report
38	230	212 p.Cys230Ar Apple 3	0		Homozygot Severe
39	230	212 p.Cys230Ar Apple 3	0	34	Heterozygo Not Report
40	230	212 p.Cys230Ar Apple 3	0	34	Heterozygo Not Report
41	230	212 p.Cys230Ar Apple 3	0	34	Heterozygo Not Report
42	230	212 p.Cys230Ar Apple 3	0	34	Heterozygo Not Report
43	232	214 p.His232Pr Apple 3	0 <1		Homozygot Not Report
44	239	221 p.Phe239Se Apple 3	0 <3		7 Homozygot Severe
45	239	221 p.Phe239Se Apple 3	1		Compound Not Report
46	239	221 p.Phe239Se Apple 3	1		Compound Severe
47	239	221 p.Phe239Se Apple 3	1		Compound Severe
48	0	0 Apple 3	1	24	Compound Not Report
49	243	225 p.Ser243Ph Apple 3	0	22	22 Heterozygo Not Report
50	243	225 p.Ser243Ph Apple 3	0	25	25 Heterozygo Not Report
51	243	225 p.Ser243Ph Apple 3	0	25	25 Heterozygo Not Report
52	244	226 p.Gln244* Apple 3	0 <3		Heterozygo Severe
53	246	228 p.Trp246* Apple 3	0	62	64.1 Heterozygo Not Report
54	246	228 p.Trp246* Apple 3	0	40	48.3 Heterozygo Not Report
55	246	228 p.Trp246* Apple 3	0	38	44.8 Heterozygo Not Report
56	246	228 p.Trp246* Apple 3	0		Heterozygo Not Report
57	246	228 p.Trp246* Apple 3	0		Heterozygo Not Report
58	246	228 p.Trp246* Apple 3	1 <1		Compound Not Report
59	246	228 p.Trp246* Apple 3	0 <1		Compound Not Report
60	246	228 p.Trp246* Apple 3	1		Compound Not Report



1					
2	246	228 p.Trp246Cy Apple 3	0	2	Undetectable Homozygot Severe
3	246	228 p.Trp246Cy Apple 3	0	3	Homozygot Severe
4	246	228 p.Trp246Cy Apple 3	0	6	Homozygot Severe
5	246	228 p.Trp246Cy Apple 3	0	40	Heterozygo Mild
6	246	228 p.Trp246Cy Apple 3	0	36	Heterozygo Mild
7	246	228 p.Trp246Cy Apple 3	0	50	Heterozygo Mild
8	246	228 p.Trp246Cy Apple 3	0	31	Heterozygo Mild
9	246	228 p.Trp246Cy Apple 3	0	53	Heterozygo Mild
10	246	228 p.Trp246Cy Apple 3	0	41	Heterozygo Not Report
11	252	234 p.Arg252Ly Apple 3	0	42	Heterozygo Not Report
12	252	234 p.Arg252Se Apple 3	0	38	Heterozygo Not Report
13	252	234 p.Arg252Se Apple 3	0		
14	255	237 p.Cys255Ty Apple 3	0 <1		Compound Severe
15	255	237 p.Cys255Ty Apple 3	1 <1		Severe
16	0	0 Apple 3	0	3	Compound Not Report
17	261	243 p.Glu261As Apple 3	0	30	28 Heterozygo Not Report
18	263	245 p.Gly263Glu Apple 3	0	31	26 Heterozygo Mild
19	263	245 p.Gly263Glu Apple 3	0	61	Heterozygo Mild
20	266	248 p.Ser266As Apple 3	0	67	80 Heterozygo Not Report
21	266	248 p.Ser266As Apple 3	0	42	70 Compound Mild
22	268	250 p.Arg268Cy Apple 3	0		Homozygot Severe
23	268	250 p.Arg268Cy Apple 3	0	8	Homozygot Not Report
24	268	250 p.Arg268Cy Apple 3	0		Heterozygo Not Report
25	268	250 p.Arg268Cy Apple 3	0	35	Heterozygo Not Report
26	268	250 p.Arg268Cy Apple 3	0	53	Heterozygo Not Report
27	268	250 p.Arg268Hi Apple 3	0	24	Compound Not Report
28	270	252 p.Lys270Ile Apple 3	1	4	2 Compound Not Report
29	277	259 p.Gly277Se Apple 3	0	44	34 Heterozygo Not Report
30	281	263 p.Gln281* Apple 3	0	1	Homozygot Not Report
31	281	263 p.Gln281* Apple 3	0 <1		Homozygot Not Report
32	281	263 p.Gln281* Apple 3	0	1 <1	Homozygot Not Report
33	281	263 p.Gln281* Apple 3	0 <1		Undetectable Homozygot Severe
34	281	263 p.Gln281* Apple 3	0 <1		Homozygot Severe
35	281	263 p.Gln281* Apple 3	0	45	Heterozygo Mild
36	281	263 p.Gln281* Apple 3	0	49	Heterozygo Mild
37	281	263 p.Gln281* Apple 3	0	55	Heterozygo Mild
38	281	263 p.Gln281* Apple 3	0	40	Heterozygo Mild
39	281	263 p.Gln281* Apple 3	0	61	Heterozygo Mild
40	281	263 p.Gln281* Apple 3	0	40	Heterozygo Mild
41	281	263 p.Gln281* Apple 3	1	1	Compound Severe
42	281	263 p.Gln281* Apple 3	0 <1	<1	Compound Severe
43	281	263 p.Gln281* Apple 3	1	3	Compound Not Report
44	281	263 p.Gln281* Apple 3	1	4	Compound Not Report
45	281	263 p.Gln281* Apple 3	1 <1		Compound Not Report
46	281	263 p.Gln281* Apple 3	1	2	Compound Not Report
47	281	263 p.Gln281* Apple 3	0	260	3 Compound Not Report
48	301	283 p.Phe301Leu Apple 4	0 <10	<10	Homozygot Severe
49	301	283 p.Phe301Leu Apple 4	0	7	Homozygot Not Report
50	301	283 p.Phe301Leu Apple 4	0	76	Heterozygo Mild
51	301	283 p.Phe301Leu Apple 4	0	87	Heterozygo Mild
52	301	283 p.Phe301Leu Apple 4	0	35	Heterozygo Not Report

1						
2	301	283 p.Phe301Le	Apple 4	0	48	Heterozygo Not Report
3	301	283 p.Phe301Le	Apple 4	0	51	Heterozygo Not Report
4	301	283 p.Phe301Le	Apple 4	0	85	Heterozygo Not Report
5	301	283 p.Phe301Le	Apple 4	0	2	6 Compound Not Report
6	301	283 p.Phe301Le	Apple 4	1	2	2 Compound Not Report
7	301	283 p.Phe301Le	Apple 4	1	4	Compound Severe
8	301	283 p.Phe301Le	Apple 4	1	1 <1	Compound Not Report
9	301	283 p.Phe301Le	Apple 4	1	4	Compound Not Report
10	301	283 p.Phe301Le	Apple 4	1	6	Compound Not Report
11	301	283 p.Phe301Le	Apple 4	1	6	Compound Not Report
12	0	0	Apple 4	0	48	Heterozygo Mild
13	0	0	Apple 4	0	36	Not Report
14	0	0	Apple 4	0	66	Heterozygo Not Report
15	313	295 p.Ser313Ile	Apple 4	0	41	47.4 Heterozygo Not Report
16	313	295 p.Ser313Ile	Apple 4	0	58	63.1 Heterozygo Not Report
17	313	295 p.Ser313Ile	Apple 4	0	57	59.8 Heterozygo Not Report
18	313	295 p.Ser313Ile	Apple 4	1	2	5.4 Compound Not Report
19	315	297 p.Glu315Ly	Apple 4	0	40	Heterozygo Not Report
20	315	297 p.Glu315Ly	Apple 4	0	40	52 Heterozygo Not Report
21	315	297 p.Glu315Ly	Apple 4	0	38	39 Heterozygo Not Report
22	315	297 p.Glu315Ly	Apple 4	0	40	Heterozygo Not Report
23	315	297 p.Glu315Ly	Apple 4	0	39	Heterozygo Not Report
24	315	297 p.Glu315Ly	Apple 4	0	29	Heterozygo Not Report
25	315	297 p.Glu315Ly	Apple 4	1	4	Compound Not Report
26	315	297 p.Glu315Ly	Apple 4	1	7	Compound Not Report
27	315	297 p.Glu315Ly	Apple 4	1	34	Compound Not Report
28	315	297 p.Glu315Ly	Apple 4	1	36	Compound Not Report
29	315	297 p.Glu315Ly	Apple 4	1 <2	<5	Compound Severe
30	0	0 p.Cys321Hi	Apple 4	0 <1	<1	Homozygot Severe
31	0	0 p.Cys321Hi	Apple 4	0	57	Heterozygo Not Report
32	322	304 p.Thr322Ile	Apple 4	0	11	26 Homozygot Not Report
33	322	304 p.Thr322Ile	Apple 4	0	47	Heterozygo Not Report
34	322	304 p.Thr322Ile	Apple 4	0	51	Heterozygo Not Report
35	325	307 p.Val325Ph	Apple 4	0	50	Heterozygo Not Report
36	325	307 p.Val325Ph	Apple 4	0	55	Heterozygo Not Report
37	325	307 p.Val325Ph	Apple 4	0	52	Heterozygo Not Report
38	326	308 p.Arg326Cy	Apple 4	0	41	33 Heterozygo Mild
39	326	308 p.Arg326Cy	Apple 4	0	43	33 Heterozygo Not Report
40	326	308 p.Arg326Cy	Apple 4	0	36	Heterozygo Not Report
41	326	308 p.Arg326Cy	Apple 4	1	52	Compound Not Report
42	331	313 p.Thr331Ile	Apple 4	0 <1		Homozygot Severe
43	341	323 p.Glu341Ly	Apple 4	0		Heterozygo Not Report
44	341	323 p.Glu341Ly	Apple 4	1	9	Compound Not Report
45	341	323 p.Glu341Ly	Apple 4	1	9	9 Compound Not Report
46	0	0	Apple 4	0	56	Heterozygo Mild
47	342	324 p.Gly342=	Apple 4	1	1	5 Compound Severe
48	342	324 p.Gly342=	Apple 4	1	1	12 Compound Severe
49	342	324 p.Gly342=	Apple 4	1	2	Compound Not Report
50	0	0	Apple 4	0	45	Heterozygo Not Report
51	345	327 p.Lys345*	Apple 4	0	1 <1	Compound Not Report
52	354	336 p.Gly354Ar	Apple 4	0		Compound Not Report

1						
2	0	0	Apple 4	0	1	15 Homozygot Severe
3	0	0	Apple 4	1	2	Compound Not Report
4	359	341 p.Ile359Me	Apple 4	0		Heterozygo Not Report
5	360	342 p.Leu360Pr	Apple 4	0 <1		Homozygot Severe
6	362	344 p.Gly362Ar	Apple 4	0	38	Heterozygo Not Report
7	368	350 p.Gly368Gl	Apple 4	1	1	Compound Not Report
8	369	351 p.Tyr369Se	Apple 4	0 <1		Homozygot Severe
9	369	351 p.Tyr369*	Apple 4	0 <1		Homozygot Not Report
10	369	351 p.Tyr369*	Apple 4	0	53	Heterozygo Mild
11	369	351 p.Tyr369*	Apple 4	0	59	Heterozygo Mild
12	369	351 p.Tyr369*	Apple 4	1 <1		Compound Not Report
13	369	351 p.Tyr369*	Apple 4	1	2 <1	Compound Not Report
14	369	351 p.Tyr369*	Apple 4	1	1 <1	Compound Not Report
15	373	355 p.Leu373Se	Apple 4	0	67	Heterozygo Not Report
16	374	356 p.Cys374Ar	Apple 4	0	40	Heterozygo Not Report
17	0	0	Intronic	0 <1		Heterozygo Severe
18	0	0	Intronic	0	50	Heterozygo Not Report
19	378	360	Intronic	0	73	Heterozygo Not Report
20	0	0	Intronic	0 <10	<50	Homozygot Severe
21	0	0	Intronic	0 <10	<50	Homozygot Severe
22	0	0	Intronic	0 <10	<50	Homozygot Severe
23	0	0	Intronic	0	3	Compound Not Report
24	389	371 p.Val389Ile	Serine Prot	0	34	102 Heterozygo Not Report
25	393	375 p.Ala393Va	Serine Prot	0	35	69 Heterozygo Not Report
26	396	378 p.Arg396Cy	Serine Prot	0	61	83 Heterozygo Not Report
27	396	378 p.Arg396Cy	Serine Prot	0	44	Heterozygo Not Report
28	399	381 p.Trp399Le	Serine Prot	0	35	40 Heterozygo Not Report
29	404	386 p.Thr404As	Serine Prot	0	2	Decreased Homozygot Severe
30	404	386 p.Thr404As	Serine Prot	0	2	Decreased Homozygot Severe
31	404	386 p.Thr404As	Serine Prot	0	108	Normal Heterozygo Mild
32	406	388 p.His406Pr	Serine Prot	0	0.36	0.37 Heterozygo Severe
33	407	389 p.Thr407Pr	Serine Prot	0	35	Heterozygo Not Report
34	408	390 p.Thr408Pr	Serine Prot	0		Heterozygo Not Report
35	412	394 p.Gln412*	Serine Prot	0 <1		Homozygot Not Report
36	416	398 p.Cys416Ty	Serine Prot	0 <1		Homozygot Severe
37	416	398 p.Cys416Ty	Serine Prot	0 <1		Homozygot Severe
38	416	398 p.Cys416Ty	Serine Prot	0		Heterozygo Not Report
39	416	398 p.Cys416Ty	Serine Prot	0	28	Heterozygo Not Report
40	416	398 p.Cys416Ty	Serine Prot	0	22	Heterozygo Not Report
41	416	398 p.Cys416Ty	Serine Prot	0	34	Heterozygo Not Report
42	416	398 p.Cys416Ty	Serine Prot	0	26	Heterozygo Not Report
43	416	398 p.Cys416Ty	Serine Prot	0	37	Heterozygo Not Report
44	416	398 p.Cys416Ty	Serine Prot	0	33	Heterozygo Not Report
45	416	398 p.Cys416Ty	Serine Prot	0	40	Heterozygo Mild
46	416	398 p.Cys416Ty	Serine Prot	0	40	Heterozygo Mild
47	416	398 p.Cys416Ty	Serine Prot	0	25	25 Heterozygo Not Report
48	416	398 p.Cys416Ty	Serine Prot	0	58	Heterozygo Not Report
49	416	398 p.Cys416Ty	Serine Prot	0	43	Heterozygo Not Report
50	418	400 p.Gly418Va	Serine Prot	0 <2		Homozygot Severe
51	418	400 p.Gly418Va	Serine Prot	0		Heterozygo Not Report

1						
2	418	400 p.Gly418VaSerine Prot	0	15		HeterozygoNot Report
3	418	400 p.Gly418VaSerine Prot	0	15	Decreased	HeterozygoNot Report
4	418	400 p.Gly418VaSerine Prot	0	45		HeterozygoNot Report
5	418	400 p.Gly418VaSerine Prot	0 <3			10 Compound Severe
6	418	400 p.Gly418VaSerine Prot	1 <3			Compound Severe
7	418	400 p.Gly418VaSerine Prot	1	3		Compound Not Report
8	419	401 p.Ser419Al;Serine Prot	0	30		Not Report
9	424	406 p.Gln424* Serine Prot	0 <1			HomozygotNot Report
10	424	406 p.Gln424* Serine Prot	0	46		Heterozygo Not Report
11	425	407 p.Trp425CySerine Prot	0	0.22	0.27	Heterozygo Severe
12	426	408 p.Ile426ThrSerine Prot	0	28		HeterozygoNot Report
13	428	410 p.Thr428IleSerine Prot	0	25		HeterozygoNot Report
14	428	410 p.Thr428IleSerine Prot	0	38		Heterozygo Not Report
15	430	412 p.Ala430Se Serine Prot	0	35	35	Heterozygo Not Report
16	430	412 p.Ala430VaSerine Prot	0	45	39	Heterozygo Mild
17	430	412 p.Ala430VaSerine Prot	1 <1			1 Compound Severe
18	0	0 Intronic	0	50		Heterozygo Not Report
19	0	0 Intronic	0	1		Homozygot Severe
20	0	0 Serine Prot	0 <1			HomozygotNot Report
21	0	0 Serine Prot	1	1	4.1	Compound Not Report
22	443	425 p.Arg443CySerine Prot	0	46		Heterozygo Not Report
23	443	425 p.Arg443CySerine Prot	0	31	39	Heterozygo Not Report
24	460	442 p.Phe460V;Serine Prot	0	47	50	Heterozygo Mild
25	465	447 p.Glu465* Serine Prot	1	Undetecta	Undetecta	Compound Severe
26	451	433 p.Gln451GlSerine Prot	0	64		Heterozygo Not Report
27	451	433 p.Gln451GlSerine Prot	0	58		HeterozygoNot Report
28	478	460 p.Gly478ArSerine Prot	0			Homozygot Severe
29	478	460 p.Gly478ArSerine Prot	0 <1			Homozygot Severe
30	478	460 p.Gly478ArSerine Prot	0 <1			HomozygotNot Report
31	478	460 p.Gly478ArSerine Prot	0 <1			Homozygot Severe
32	478	460 p.Gly478ArSerine Prot	0	5		Homozygot Not Report
33	478	460 p.Gly478ArSerine Prot	0	51		HeterozygoNot Report
34	478	460 p.Gly478ArSerine Prot	0	42		Heterozygo Mild
35	478	460 p.Gly478ArSerine Prot	0	32		Heterozygo Not Report
36	478	460 p.Gly478ArSerine Prot	1	2		Compound Not Report
37	478	460 p.Gly478ArSerine Prot	1	18	13	Compound Not Report
38	478	460 p.Gly478ArSerine Prot	1	2	2	Compound Not Report
39	483	465 p.Leu483SeSerine Prot	0	34		HeterozygoNot Report
40	493	475 p.Thr493IleSerine Prot	0			Heterozygo Mild
41	493	475 p.Thr493IleSerine Prot	0	39	27	Heterozygo Mild
42	493	475 p.Thr493IleSerine Prot	0	46		Heterozygo Not Report
43	494	476 Serine Prot	0	38	20	HeterozygoNot Report
44	497	479 p.Arg497* Serine Prot	0	55		Heterozygo Not Report
45	500	482 p.Cys500ArSerine Prot	0	9		Heterozygo Not Report
46	500	482 p.Cys500TrSerine Prot	0	37		Heterozygo Not Report
47	503	485 p.Ser503PrSerine Prot	0 <1			Homozygot Severe
48	511	493 p.Tyr511Hi;Serine Prot	1	2		Compound Severe
49	511	493 p.Tyr511Hi;Serine Prot	1	1		Compound Severe
50	515	497 p.Trp515CySerine Prot	0	22	25	Heterozygo Not Report
51	515	497 p.Trp515CySerine Prot	0	36		HeterozygoNot Report

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2	515	497 p.Trp515CySerine Prot	0	36		HeterozygoNot Report
3	515	497 p.Trp515CySerine Prot	0	40		HeterozygoNot Report
4	516	498 p.Val516M <sub>1</sub> Serine Prot	1	1		Compound Not Report
5	0	0 Serine Prot	0	35		HeterozygoNot Report
6	0	0 Serine Prot	0	54		HeterozygoNot Report
7	0	0 Serine Prot	1 <1			Compound Severe
8	0	0 Serine Prot	1	4		Compound Not Report
9	519	501 p.Trp519* Serine Prot	0 <5		Undetectat	Homozygot Severe
10	519	501 p.Trp519* Serine Prot	0			HeterozygoNot Report
11	519	501 p.Trp519* Serine Prot	0			HeterozygoNot Report
12	519	501 p.Trp519* Serine Prot	0	114		HeterozygoNot Report
13	519	501 p.Trp519* Serine Prot	0	47		HeterozygoNot Report
14	519	501 p.Trp519* Serine Prot	0	36		HeterozygoNot Report
15	519	501 p.Trp519CySerine Prot	0	2 <1		Homozygot Severe
16	519	501 p.Trp519CySerine Prot	0	36	36	Heterozygo Mild
17	519	501 p.Trp519CySerine Prot	0	40	32	Heterozygo Mild
18	519	501 p.Trp519CySerine Prot	1	2 <1		Compound Not Report
19	521	503 p.Tyr521CySerine Prot	0	13	76	HomozygotNot Report
20	521	503 p.Tyr521CySerine Prot	0	38	93	HeterozygoNot Report
21	521	503 p.Tyr521CySerine Prot	0	42	102	HeterozygoNot Report
22	521	503 p.Tyr521CySerine Prot	0	37	98	HeterozygoNot Report
23	536	518 p.Lys536As Serine Prot	0			Heterozygo Mild
24	536	518 p.Lys536As Serine Prot	1	3		Compound Not Report
25	538	520 p.Pro538LeSerine Prot	0	20		HomozygotNot Report
26	538	520 p.Pro538LeSerine Prot	0	59		HeterozygoNot Report
27	538	520 p.Pro538LeSerine Prot	0	34		HeterozygoNot Report
28	538	520 p.Pro538LeSerine Prot	0	43	90	HeterozygoNot Report
29	538	520 p.Pro538LeSerine Prot	0	48		HeterozygoNot Report
30	538	520 p.Pro538LeSerine Prot	0	48	80	Heterozygo Not Report
31	538	520 p.Pro538LeSerine Prot	0	53		Heterozygo Not Report
32	538	520 p.Pro538LeSerine Prot	0	50	74	HeterozygoNot Report
33	538	520 p.Pro538LeSerine Prot	1	30		Compound Not Report
34	540	522 p.Val540G <sub>1</sub> Serine Prot	0			HeterozygoNot Report
35	562	544 p.Gly562SeSerine Prot	0	62		Heterozygo Not Report
36	562	544 p.Gly562SeSerine Prot	0	105		HeterozygoNot Report
37	565	547 p.Glu565LySerine Prot	0	30		HeterozygoNot Report
38	565	547 p.Glu565LySerine Prot	0	41		HeterozygoNot Report
39	565	547 p.Glu565LySerine Prot	0	36		HeterozygoNot Report
40	565	547 p.Glu565LySerine Prot	0	45		HeterozygoNot Report
41	565	547 p.Glu565LySerine Prot	0	32		HeterozygoNot Report
42	565	547 p.Glu565LySerine Prot	0	63		HeterozygoNot Report
43	565	547 p.Glu565LySerine Prot	0	49	37	Heterozygo Mild
44	565	547 p.Glu565LySerine Prot	0	25	18	Heterozygo Mild
45	565	547 p.Glu565LySerine Prot	0	23	32	HeterozygoNot Report
46	565	547 p.Glu565LySerine Prot	1	35		Compound Not Report
47	0	0 Serine Prot	1 <1	<10		Compound Severe
48	0	0 Intronic	0	37		HeterozygoNot Report
49	0	0 Intronic	0	60		HeterozygoNot Report
50	0	0 Serine Prot	0	71		Heterozygo Not Report
51	0	0 Serine Prot	1 <10	<10		Compound Severe



573	555 p.Gly573GlnSerine Prot	0 <1		100 Homozygot Severe
573	555 p.Gly573GlnSerine Prot	0	51	Heterozygo Not Report
574	556 p.Asp574AlSerine Prot	0 <1		Homozygot Not Report
581	563 p.Cys581ArSerine Prot	0		Homozygot Not Report
581	563 p.Cys581ArSerine Prot	0		Heterozygo Not Report
581	563 p.Cys581PhSerine Prot	0	45	Heterozygo Not Report
587	569 p.Trp587SeSerine Prot	0	15	Heterozygo Not Report
587	569 p.Trp587SeSerine Prot	0		Heterozygo Not Report
592	574 p.Ile592ThrSerine Prot	0	43	Heterozygo Not Report
593	575 p.Thr593MSerine Prot	0	2	105 Homozygot Not Report
593	575 p.Thr593MSerine Prot	0	38	83 Heterozygo Not Report
593	575 p.Thr593MSerine Prot	0	67	25 Heterozygo Not Report
593	575 p.Thr593MSerine Prot	0	43	106 Heterozygo Not Report
593	575 p.Thr593MSerine Prot	0	43	112 Heterozygo Not Report
593	575 p.Thr593MSerine Prot	0	51	85 Heterozygo Not Report
593	575 p.Thr593MSerine Prot	0	39	Heterozygo Not Report
594	576 p.Ser594ArSerine Prot	0	27	23 Heterozygo Mild
594	576 p.Ser594ArSerine Prot	0	27	23 Heterozygo Not Report
594	576 p.Ser594ArSerine Prot	0	46	71 Heterozygo Not Report
597	579 p.Glu597LySerine 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.Tyr608HisSerine 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.Trp617ArSerine Prot	0 <1	<1	Homozygot Severe
618	600 p.Ile618SerSerine Prot	0 <2		Homozygot Severe
618	600 p.Ile618SerSerine Prot	0	42	35 Heterozygo Not Report
618	600 p.Ile618SerSerine Prot	0	23	Heterozygo Not Report
619	601 p.Leu619PrSerine Prot	0 <1	<1	Homozygot Severe

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4	ed Saunders et al 2009
5	Patient's bl Zucker et al 2007
6	Mild bleedi Mitchell et al 2004
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8	ed Mitchell et al 2006
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10	ed Quelin et al 2006
11	No bleeding Castaman et al 2008
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13	ed Mitchell et al 2006
14	Gingival Zucker et al 2007
15	FXI:C/FXI:A Spena et al 2009
16	Asymptom: Zucker et al 2007
17	ed Mitchell et al 2006
18	ed Quelin et al 2005
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21	Bleeding fo Shao et al 2016
22	Menorrhag Hill et al 2005
23	Easy bruisir Hill et al 2005
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25	Bleeding pc Hill et al 2005
26	Easy bruisir Shao et al 2016
27	ed Mitchell et al 2006
28	Epistaxis Colakoglu et al 2018
29	Epistaxis Colakoglu et al 2018
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31	Esteban et al 2017
32	Esteban et al 2017
33	No bleeding Zivelin et al 2002
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35	Esteban et al 2017
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 ed Mitchell et al 2006  
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 8 Non-bleeding Ventura et al 2000  
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 10 Non-bleeding Ventura et al 2000  
 11 Epistaxis Colakoglu et al 2018  
 12 Asymptomatic Colakoglu et al 2018  
 13 Bleeding after Quelin et al 2006  
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 19 Superficial Tiscia et al 2017  
 20 Asymptomatic Tiscia et al 2017  
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 23 None Asakai et al 1989  
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 34 Post-operative Quelin et al 2009  
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 13 Bleeding after Quelin et al 2006  
 14 Easy bruising Quelin et al 2006  
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 17 Menorrhagia JerÄ iÄ et al 2020  
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 19 Asymptomatic JerÄ iÄ et al 2020  
 20 Asymptomatic Cataman et al 2013  
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 23 Easy bruising Lin et al 2020  
 24 Long APTT Bolton-Maggs et al 2004  
 25 Fall result in Zacharski & French 1978  
 26 Bleed after Bolton-Maggs et al 2004  
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 28 Cerebral hemorrhage Bolton-Maggs et al 2004  
 29 Easy bruising Bolton-Maggs et al 2004  
 30 Extensive bruising Bolton-Maggs et al 2004  
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 32 History of bleeding Imanaka et al 1995  
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 34 Patient also Bolton-Maggs et al 2004  
 35 Misdiagnosis Bolton-Maggs et al 2004  
 36 No active bruising Dai et al 2004  
 37 Patient has Duncan et al 2008  
 38 ed Mitchell et al 2006  
 39 Mitchell et al 2006  
 40 ed Mitchell et al 2006  
 41 Mitchell et al 2006  
 42 Menorrhagia Mitchell et al 2007  
 43 Post-Partum Hill et al 2005  
 44 Asymptomatic Hill et al 2005  
 45 Post Partum Hill et al 2005  
 46 ed Mitchell et al 2006  
 47 Epistaxis Tiscia et al 2017  
 48 Asymptomatic Tiscia et al 2017  
 49 Asymptomatic Tiscia et al 2017  
 50 Asymptomatic Tiscia et al 2017

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 5 No relevant Mitchell et al 2007  
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 11 Mitchell et al 2003  
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 20 None Dossenbach-Glaninger & Hopmeier 2006  
 21 ed Mitchell et al 2006  
 22 Asymptomatic Tiscia et al 2017  
 23 No bleeding Zivelin et al 2002  
 24 No Hx of bleeding Guella et al 2008  
 25 Easy bruising Shao et al 2016  
 26 Menorrhagia de Raucourt et al 2008  
 27 Patient has Duncan et al 2008  
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 29 ed Mitchell et al 2006  
 30 Lin et al 2020  
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 32 Asymptomatic Guella et al 2008  
 33 ed Quelin et al 2006  
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 35 No excessive Quelin et al 2004  
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 49 Patient has Duncan et al 2008  
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 3 Asymptom: Tiscia et al 2017  
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 5 Menorrhag Castaman et al 2008  
 6 Epistaxis, p Castaman et al 2008  
 7 Mild bleed: Dossenbach-Glaninger et al 2001  
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 9 Asymptom: Tiscia et al 2017  
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 11 No bleeding: Zivelin et al 2002  
 12 Menorrhag Hill et al 2005  
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 14 No bleeding: Wang et al 2019  
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 19 ed Quelin et al 2005  
 20 Epistaxis Quelin et al 2006  
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 22 Asymptom: Tiscia et al 2017  
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 24 No bleeding: Hopmeier et al 2004  
 25 Vaginal ble: Tiscia et al 2017  
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 37 History of e Mitchell et al 1999  
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 45 No evidenc: Dossenbach-Glaninger et al 2001  
 46 Excessive b Ventura et al 2000  
 47 Non-bleed: Ventura et al 2000  
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 49 ed Saunders et al 2009  
 50 No bleeding: Lin et al 2020  
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 2 No bleeding Zucker et al 2007  
 3 ed Mitchell et al 2006  
 4 Moderate Fard-Esfahani et al 2008  
 5 ed Mitchell et al 2006  
 6 Epistaxis Shao et al 2016  
 7 None Jayandharan et al 2005  
 8 Asymptomatic Lin et al 2020  
 9 No history Au et al 2003  
 10 Au et al 2003  
 11 Bleeding after Lin et al 2020  
 12 No bleeding Lin et al 2020  
 13 Epistaxis Lin et al 2020  
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 16 Bleeding at Hayashi et al 1997 Abstract  
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 27 Pt present Quelin et al 2009  
 28 No history Wistinghausen et al 1997  
 29 Minor bleeding Wistinghausen et al 1997  
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 3 Clinically, tl Kwon et al 2008  
 4 Prolonged l Fard-Esfahani et al 2008  
 5 Patient's h Ishikawa et al 2007  
 6 No history r Ishikawa et al 2007  
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 8 No apparer Iijima et al 2000  
 9 Bruising, bl Colakoglu et al 2018  
 10 Asymptom: Colakoglu et al 2018  
 11 Asymptom: Tiscia et al 2017  
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 27 Patient als Hill et al 2005  
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14 ed Germanos-Haddad et al 2005  
15 ed Germanos-Haddad et al 2005  
16 ed Germanos-Haddad et al 2005  
17 ed Germanos-Haddad et al 2005  
18 ed Mitchell et al 2006  
19 Menorrhag Mitchell et al 2007  
20 Patient suff Mitchell et al 1999  
21 ed Mitchell et al 2006  
22 ed O'Connell et al 2005  
23 No spontan Quelin et al 2006  
24 Patient suff Quelin et al 2004  
25 Patient reci Quelin et al 2004  
26 Moderate l Fard-Esfahani et al 2008  
27 ed Mitchell et al 2006  
28 Menorrhag Hill et al 2005  
29 Asymptom: Takamiya et al 2005  
30 Mitchell et al 2006  
31 Mild bleedi Hill et al 2005  
32 ed Mitchell et al 2006  
33 Menorrhag Spena et al 2009  
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Variant ID	No. of Case	Type	Effect	cDNA	Mutation (cAmino 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 11-1!	0	0	
284	1	Point	Missense	0 Unspecifiec	136	118	p.Cys136Ar
337	0	Point	Missense	0 Unspecifiec	326	308	p.Arg326Hi
273	0	Point	Missense	0 Unspecifiec	403	385	p.Val403M
338	0	Point	Missense	0 Unspecifiec	425	407	p.Trp425Le
339	0	Point	Missense	0 Unspecifiec	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_193in	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	

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2	221	0 Point	Missense	224 c.224C>T	75	57 p.Thr75Ile
3	154	0 Point	Missense	226 c.226G>C	76	58 p.Cys76Arg
4	102	1 Point	Missense	227 c.227G>A	76	58 p.Cys76Tyr
5	134	1 Point	Missense	227 c.227G>T	76	58 p.Cys76Phe
6	327	0 Point		250 c.1716+250	0	0
7	328	0 Point		252 c.1716+252	0	0
8	129	1 Point	Missense	259 c.259C>A	87	69 p.Pro87Thr
9	329	0 Point		265 c.*265A>G	0	0
10	187	1 Point	Missense	290 c.290G>C	97	79 p.Gly97Ala
11	330	0 Point		296 c.*296G>C	0	0
12	230	2 Point	Missense	296 c.296C>A	99	81 p.Ser99Tyr
13	36	2 Duplication	Frameshift	301 c.301_307c	0	0
14	114	1 Point	Missense	302 c.302A>G	101	83 p.Lys101Arg
15	8	5 Point	Nonsense	316 c.316C>T	106	88 p.Gln106*
16	364	1 Deletion		325 c.325+2del	0	0
17	135	11 Point	Missense	325 c.325G>A	109	91 p.Ala109Thr
18	341	4 Point		326 c.326-1G>A	0	0
19	346	0 Deletion	Frameshift	327 c.327delT	0	0
20	126	2 Point	Missense	328 c.328T>G	110	92 p.Cys110Gln
21	231	2 Point	Missense	359 c.359T>C	120	102 p.Met120Thr
22	60	7 Point	Missense	365 c.365G>A	122	104 p.Gly122Asp
23	104	3 Point	Nonsense	400 c.400C>T	134	116 p.Gln134*
24	58	61 Point	Nonsense	403 c.403G>T	135	117 p.Glu135*
25	105	4 Point	Nonsense	408 c.408C>A	136	118 p.Cys136*
26	121	5 Point	Missense	419 c.419G>A	140	122 p.Cys140Tyr
27	161	2 Point	Missense	422 c.422C>T	141	123 p.Thr141Met
28	304	0 Point	Silent	423 c.423G>A	141	123 p.Thr141=
29	353	3 Point	Missense	428 c.428A>C	143	125 p.Asp143Ala
30	39	0 Point	Silent	429 c.429C>T	143	125 p.Asp143=
31	232	4 Point	Missense	434 c.434A>G	145	127 p.His145Arg
32	20	22 Point	Nonsense	438 c.438C>A	146	128 p.Cys146*
33	138	6 Point	Missense	449 c.449C>T	150	132 p.Thr150Met
34	29	4 Point	Missense	452 c.452A>C	151	133 p.Tyr151Ser
35	139	2 Point	Missense	452 c.452A>G	151	133 p.Tyr151Cys
36	21	2 Point	Missense	454 c.454G>C	152	134 p.Ala152Pro
37	94	1 Point	Missense	484 c.484C>T	162	144 p.Arg162Cys
38	86	0 Point		485 c.485+23G>	0	0
39	342	0 Point		485 c.485+1G>A	0	0
40	70	0 Point		485 c.485+5G>C	0	0
41	317	0 Point		485 c.485+122T	0	0
42	318	0 Point		485 c.485+181T	0	0
43	80	0 Point		486 c.486-431G	0	0
44	319	0 Point		486 c.486-88T>A	0	0
45	320	0 Point		486 c.486-181C	0	0
46	87	0 Point		486 c.486-361C	0	0
47	71	3 Point		486 c.486-2A>G	0	0
48	238	3 Point	Missense	518 c.518G>A	173	155 p.Gly173Gln
49	97	1 Point	Missense	569 c.569T>C	190	172 p.Leu190Pro
50	69	6 Point		595 c.595+3A>C	0	0
51	343	1 Point		596 c.596-8T>A	0	0

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2	163	1 Point	Missense	596 c.596C>T	199	181 p.Ala199Va
3	22	2 Point	Missense	599 c.599G>A	200	182 p.Cys200Ty
4	336	1 Point	Missense	599 c.599G>C	200	182 p.Cys200Se
5	165	2 Point	Missense	604 c.604A>G	202	184 p.Arg202Gl
6	123	1 Point	Missense	616 c.616T>C	206	188 p.Pro206Se
7	119	2 Deletion	Inframe	644 c.644_649d	0	0 p.Ile215_As
8	234	0 Point	Missense	646 c.646G>A	216	198 p.Asp216As
9	11	1 Point	Nonsense	682 c.682C>T	228	210 p.Arg228*
10	23	4 Point	Missense	688 c.688T>C	230	212 p.Cys230Ar
11	222	4 Point	Missense	688 c.688T>A	230	212 p.Cys230Se
12	349	1 Point	Missense	695 c.695A>C	232	214 p.His232Pro
13	32	3 Point	Missense	716 c.716T>C	239	221 p.Phe239Se
14	209	1 Insertion	Frameshift	717 c.717insT	0	0
15	275	0 Point	Missense	723 c.723C>G	241	223 p.Phe241Le
16	101	2 Point	Missense	728 c.728C>T	243	225 p.Ser243Ph
17	155	3 Point	Nonsense	730 c.730C>T	244	226 p.Gln244*
18	64	0 Point	Missense	731 c.731A>G	244	226 p.Gln244Ar
19	41	8 Point	Missense	738 c.738G>C	246	228 p.Trp246Cy
20	95	9 Point	Nonsense	738 c.738G>A	246	228 p.Trp246*
21	140	1 Point	Nonsense	751 c.751C>T	251	233 p.Gln251*
22	25	0 Point	Missense	755 c.755G>T	252	234 p.Arg252Ile
23	235	1 Point	Missense	755 c.755G>A	252	234 p.Arg252Ly
24	141	2 Point	Missense	756 c.756A>T	252	234 p.Arg252Se
25	52	2 Point	Missense	764 c.764G>A	255	237 p.Cys255Ty
26	253	1 Deletion	Frameshift	769 c.769delC	0	0
27	128	2 Point	Missense	783 c.783G>C	261	243 p.Glu261As
28	115	2 Point	Missense	788 c.788G>A	263	245 p.Gly263Glu
29	63	2 Point	Missense	797 c.797G>A	266	248 p.Ser266As
30	55	0 Point	Silent	801 c.801A>G	267	249 p.Thr267=
31	30	5 Point	Missense	802 c.802C>T	268	250 p.Arg268Cy
32	210	2 Point	Missense	803 c.803G>A	268	250 p.Arg268Hi
33	40	4 Point	Missense	809 c.809A>T	270	252 p.Lys270Ile
34	255	1 Point	Missense	829 c.829G>A	277	259 p.Gly277Se
35	42	20 Point	Nonsense	841 c.841C>T	281	263 p.Gln281*
36	81	0 Point	Silent	861 c.861C>T	287	269 p.Ile287=
37	220	0 Deletion	Frameshift	865 c.865+2del,	0	0
38	99	1 Point	Missense	865 c.865G>C	289	271 p.Val289Le
39	65	22 Point	Missense	901 c.901T>C	301	283 p.Phe301Le
40	59	1 Deletion	Frameshift	907 c.907delG	0	0
41	116	1 Deletion	Frameshift	918 c.918delG	0	0
42	82	0 Point	Missense	922 c.922A>T	308	290 p.Ile308Phe
43	118	0 Point	Missense	923 c.923T>C	308	290 p.Ile308Thr
44	166	1 Duplication	Frameshift	933 c.933_951d	0	0
45	354	4 Point	Missense	938 c.938G>T	313	295 p.Ser313Ile
46	236	1 Point	Nonsense	943 c.943G>T	315	297 p.Glu315*
47	122	11 Point	Missense	943 c.943G>A	315	297 p.Glu315Ly
48	2	0 Point	Missense	959 c.959T>C	320	302 p.Leu320Pro
49	142	2 Deletion	Frameshift	961 c.961_962d	0	0 p.Cys321Hi
50	3	3 Point	Missense	965 c.965C>T	322	304 p.Thr322Ile
51	194	3 Point	Missense	973 c.973G>T	325	307 p.Val325Ph

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2	5	4 Point	Missense	976 c.976C>T	326	308 p.Arg326Cy
3	240	1 Point	Nonsense	981 c.981C>A	327	309 p.Cys327*
4	169	1 Point	Missense	992 c.992C>T	331	313 p.Thr331Ile
5	54	0 Point	Missense	1016 c.1016G>T	339	321 p.Cys339Ph
6	4	4 Point	Missense	1021 c.1021G>A	341	323 p.Glu341Ly
7	67	2 Duplication	Frameshift	1026 c.1026dupC	0	0
8	34	3 Point	Silent	1026 c.1026G>T	342	324 p.Gly342=
9	239	1 Point		1028 c.1028+5G>	0	0
10	72	0 Point		1029 c.1029-2A>	0	0
11						
12	361	1 Point	Nonsense	1033 c.1033A>T	345	327 p.Lys345*
13	12	2 Point	Missense	1060 c.1060G>A	354	336 p.Gly354Ar
14	37	2 Deletion	Frameshift	1072 c.1072delA	0	0
15	143	1 Point	Missense	1077 c.1077A>G	359	341 p.Ile359Me
16	170	1 Point	Missense	1079 c.1079T>C	360	342 p.Leu360Pr
17	144	1 Point	Missense	1084 c.1084G>A	362	344 p.Gly362Ar
18	223	1 Point	Missense	1102 c.1102G>A	368	350 p.Gly368Ar
19	14	1 Point	Missense	1103 c.1103G>C	368	350 p.Gly368Ala
20	18	1 Point	Missense	1103 c.1103G>A	368	350 p.Gly368Glu
21	100	1 Point	Missense	1106 c.1106A>C	369	351 p.Tyr369Se
22	360	3 Point	Silent	1107 c.1107C>T	369	351 p.Tyr369=
23	43	8 Point	Nonsense	1107 c.1107C>A	369	351 p.Tyr369*
24	145	1 Point	Missense	1118 c.1118T>C	373	355 p.Leu373Se
25	146	1 Point	Missense	1120 c.1120T>C	374	356 p.Cys374Ar
26	108	2 Point		1135 c.1135+1G>	0	0
27	147	1 Point	Missense	1135 c.1135+5G>	378	360
28	110	6 Deletion	Frameshift	1136 c.1136-4de	0	0
29	171	1 Point	Missense	1165 c.1165G>A	389	371 p.Val389Ile
30	196	1 Point	Missense	1169 c.1169G>C	390	372 p.Gly390Ala
31	241	1 Point	Missense	1178 c.1178C>T	393	375 p.Ala393Va
32	98	2 Point	Missense	1186 c.1186C>T	396	378 p.Arg396Cy
33	66	0 Point	Silent	1191 c.1191T>C	397	379 p.Gly397=
34	252	0 Point	Missense	1195 c.1195T>C	399	381 p.Trp399Ar
35	224	1 Point	Missense	1196 C.1196G>T	399	381 p.Trp399Le
36	106	3 Point	Missense	1199 c.1199C>T	400	382 p.Pro400Le
37	96	1 Point	Nonsense	1202 c.1202G>A	401	383 p.Trp401*
38	15	3 Point	Missense	1211 c.1211C>A	404	386 p.Thr404As
39	173	1 Point	Missense	1217 c.1217A>C	406	388 p.His406Pro
40	26	1 Point	Missense	1219 c.1219A>C	407	389 p.Thr407Pro
41	256	1 Point	Missense	1222 c.1222A>C	408	390 p.Thr408Pro
42	363	1 Point	Nonsense	1234 c.1234C>T	412	394 p.Gln412*
43	51	17 Point	Missense	1247 c.1247G>A	416	398 p.Cys416Ty
44	242	0 Point	Missense	1252 c.1252G>A	418	400 p.Gly418Se
45	16	8 Point	Missense	1253 c.1253G>T	418	400 p.Gly418Va
46	243	1 Point	Missense	1255 c.1255T>G	419	401 p.Ser419Ala
47	148	2 Point	Nonsense	1270 c.1270C>T	424	406 p.Gln424*
48	174	1 Point	Missense	1275 c.1275G>C	425	407 p.Trp425Cy
49	300	1 Point	Missense	1277 c.1277T>C	426	408 p.Ile426Thr
50	175	2 Point	Missense	1283 c.1283C>T	428	410 p.Thr428Ile
51	164	3 Point	Missense	1288 c.1288G>A	430	412 p.Ala430Th
52	244	1 Point	Missense	1288 c.1288G>T	430	412 p.Ala430Se



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2	6	2 Point	Missense	1289 c.1289C>T	430	412 p.Ala430Va
3	176	1 Point		1304 c.1304+12C	0	0
4	38	1 Point		1305 c.1305-10T	0	0
5	357	2 Deletion	Frameshift	1322 c.1322delT	0	0
6	347	0 Deletion	Frameshift	1325 c.1325delT	0	0 p.Leu442Cy
7						
8	156	2 Point	Missense	1327 c.1327C>T	443	425 p.Arg443Cy
9	103	2 Point	Missense	1334 c.1334A>G	445	427 p.Tyr445Cy
10	217	0 Point	Missense	1336 c.1336A>G	446	428 p.Ser446Gh
11	19	1 Point	Missense	1378 c.1378T>G	460	442 p.Phe460Va
12						
13	46	1 Point	Nonsense	1393 c.1393G>T	465	447 p.Glu465*
14	177	4 Point	Missense	1394 c.1394C>G	451	433 p.Gln451Gl
15	62	11 Point	Missense	1432 c.1432G>A	478	460 p.Gly478Ar
16	348	0 Deletion	Frameshift	1448 c.1448delT	0	0
17	351	1 Point	Missense	1448 c.1448T>C	483	465 p.Leu483Se
18	31	3 Point	Missense	1478 c.1478C>T	493	475 p.Thr493Ile
19						
20	344	0 Point	Missense	1480 c.1480+3A>	0	0
21	178	1 Point	Missense	1480 c.1480+2T>	494	476
22	322	0 Point		1481 c.1481-215	0	0
23	324	0 Point		1481 c.1481-34G	0	0
24						
25	303	0 Point		1481 c.1481-188	0	0
26	149	2 Point	Nonsense	1489 c.1489C>T	497	479 p.Arg497*
27	246	1 Point	Missense	1498 c.1498T>C	500	482 p.Cys500Ar
28	150	1 Point	Missense	1500 c.1500C>G	500	482 p.Cys500Tr
29	180	1 Point	Missense	1507 c.1507T>C	503	485 p.Ser503Pr
30						
31	53	2 Point	Missense	1531 c.1531T>C	511	493 p.Tyr511Hi
32	127	4 Point	Missense	1545 c.1545G>T	515	497 p.Trp515Cy
33	214	1 Point	Missense	1546 c.1546G>A	516	498 p.Val516M
34	47	7 Insertion	Frameshift	1556 c.1556insG	0	0
35	44	8 Point	Nonsense	1556 c.1556G>A	519	501 p.Trp519*
36	33	4 Point	Missense	1557 c.1557G>C	519	501 p.Trp519Cy
37						
38	215	1 Duplication	Frameshift	1560 c.1560dupC	0	0
39	331	4 Point	Missense	1562 c.1562A>G	521	503 p.Tyr521Cy
40	84	0 Duplication	Frameshift	1574 c.1574-93d	0	0
41	325	0 Point		1576 c.1576+51C	0	0
42						
43	35	4 Point	Missense	1608 c.1608G>C	536	518 p.Lys536As
44	50	9 Point	Missense	1613 c.1613C>T	538	520 p.Pro538Le
45	262	1 Point	Missense	1619 c.1619T>G	540	522 p.Val540Gh
46	167	1 Point	Missense	1634 c.1634G>A	545	527 p.Cys545Ty
47						
48	280	2 Point	Missense	1682 c.1682G>A	561	543 p.Ala561As
49	247	2 Point	Missense	1684 c.1684G>A	562	544 p.Gly562Se
50	117	10 Point	Missense	1693 c.1693G>A	565	547 p.Glu565Ly
51	332	0 Point	Missense	1694 c.1694T>A	454	436 p.Ile454Lys
52	85	0 Point	Silent	1707 c.1707C>T	569	551 p.Asp569=
53	45	1 Deletion		1714 c.1714_171	0	0
54	48	2 Point		1716 c.1716+1G>	0	0
55						
56	326	2 Point		1716 c.1716+248	0	0
57	83	0 Point		1717 c.1717-48A	0	0
58	206	0 Point		1717 c.1717-2A>	573	555
59	49	2 Point	Missense	1718 c.1718G>A	573	555 p.Gly573Gh
60	350	1 Point	Missense	1721 c.1721A>C	574	556 p.Asp574Al

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2	248	0 Point	Missense	1721 c.1721A>G	574	556 p.Asp574Gl
3	263	2 Point	Missense	1741 c.1741T>C	581	563 p.Cys581Ar
4	151	1 Point	Missense	1742 c.1742G>T	581	563 p.Cys581Ph
5	17	2 Point	Missense	1760 c.1760G>C	587	569 p.Trp587Se
6	301	1 Point	Missense	1775 c.1775T>C	592	574 p.Ile592Thr
7	9	8 Point	Missense	1778 c.1778C>T	593	575 p.Thr593M
8						
9	249	3 Point	Missense	1782 c.1782C>A	594	576 p.Ser594Ar
10	168	1 Point	Missense	1786 c.1786G>A	596	578 p.Gly596Cy
11	181	1 Point	Missense	1789 c.1789G>A	597	579 p.Glu597Ly
12						
13	299	1 Point	Missense	1796 c.1796G>A	599	581 p.Cys599Ty
14	13	2 Point	Nonsense	1797 c.1797T>A	599	581 p.Cys599*
15	56	0 Point	Silent	1812 c.1812G>T	604	586 p.Arg604=
16	250	1 Point	Missense	1822 c.1822T>C	608	590 p.Tyr608His
17	27	2 Point	Nonsense	1824 c.1824C>A	608	590 p.Tyr608*
18						
19	257	1 Point	Missense	1832 c.1832T>G	611	593 p.Val611Gly
20	57	0 Point	Silent	1839 c.1839G>A	613	595 p.Glu613=
21	311	0 Point	Missense	1843 c.1843G>A	615	597 p.Val615Met
22	111	1 Point	Missense	1849 c.1849T>G	617	599 p.Trp617Arg
23						
24	28	3 Point	Missense	1853 c.1853T>C	618	600 p.Ile618Ser
25	260	1 Point	Missense	1856 c.1856T>C	619	601 p.Leu619Pro
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