LETTER TO THE EDITOR

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# Analysis of Hereditary FXII Deficiency Caused by Three Mutations Including a Novel Mutation

## Biri Yeni Olmak Üzere Üç Mutasyon İlişkili Kalıtsal FXII Eksikliğinin Analizi

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**To the Editor,**

Congenital coagulation factor XII (FXII) deficiency is an autosomal disorder that primarily affects blood clotting. Patients exhibit prolonged activated partial thromboplastin time (aPTT) in vitro, but there is no significant predisposition to bleeding as expected. Most cases are typically identified incidentally during routine health checks or preoperative coagulation screening tests [1,2]. This report describes two Chinese patients with FXII deficiency, neither of whom had significant abnormal bleeding symptoms as expected. Both patients had prolonged aPTT, with FXII:C and FXII:Ag levels reduced to approximately 3% and 3.1 U/dL of normal, respectively. Relatives of the two affected patients had slightly prolonged aPTT, with FXII:Ag levels decreasing to approximately 50 U/dL of the normal range (Table 1). After conducting DNA analysis, it was discovered that Proband A carried homozygous deletion mutation c.303_304delCA (His82Glnfs*36) in exon 5 of the *F12* gene. The frequency of homozygous types ranges from 1 in 500,000 to 1 in 2 billion [3]. Consanguineous unions lead to the expression of traits associated with recessive genes in a homozygous state within a family [4]. The homozygous His82Glnfs*36 mutation in Proband A is likely to have originated from the parents due to their consanguineous marriage. Proband B was found to carry a compound heterozygous mutation consisting of the c.712_713insT (Cys219Leufs*73) mutation in exon 8 and the c.1792_1796delGTCTA (Val579Hisfs*32) deletion mutation in exon 14 (Figure 1).

Biological studies demonstrated that Cys219Leufs*73 and Val579Hisfs*32 were completely conserved in the homologous sequence, and His82Glnfs*36 was found to be highly conserved (Figure 1). MutationTaster predicted all three mutations to be pathogenic.

The His82Glnfs*36 and Cys219Leufs*73 mutations result in a partial truncation of the FXII protein. The Val579Hisfs*32 mutation is situated in the catalytic reaction site. These mutations alter the polarity of the amino acids and hydrogen bonding in this area. Previous in vitro expression studies have demonstrated that mutations at this site result in

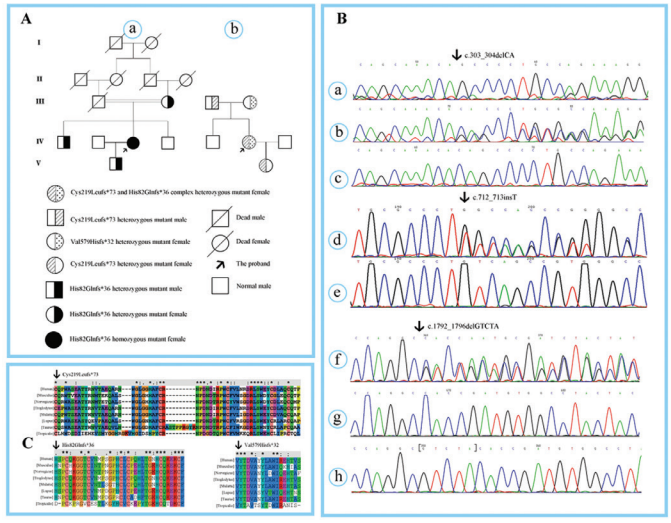


**Figure 1.** Genetic sequencing and conservation analysis of three FXII mutations. A) Pedigree investigation for two families. B) Chromatogram of DNA sequencing. (a) is a homozygous His82Glnfs*36 sequencing map, (b) is a heterozygous His82Glnfs*36 sequencing map, (c) is a wild-type forward sequencing of His82Glnfs*36, (d) is a heterozygous Cys219Leufs*73 sequencing map, (e) is a Cys219Leufs*73 wild-type forward sequencing, (f) is a heterozygous sequencing map of Val579Hisfs*32, (g) is a clonal sequencing map of Val579Hisfs*32, and (h) is a wild-type forward sequencing of Val579Hisfs*32. The position of the mutational base is indicated with an arrow. C) Conservation analysis of the three mutations. The target amino acids are indicated by arrows.

FXII: Congenital coagulation factor XII.

**Table 1. Phenotypes and genotypes of two families with hereditary FXII deficiency.**

| Family members | PT (s) | aPTT (s) | FXII:C (%) | FXII:Ag(U/dL) | AA substitution | Genotype |
|---|---|---|---|---|---|---|
| **Family A** | | | | | | |
| Mother ($III_2$) | 12.4 | 46.9 | 45 | 45.7 | His82Glnfs*36 | Heterozygous |
| Brother ($IV_1$) | 12.8 | 48.7 | 42 | 46.1 | His82Glnfs*36 | Heterozygous |
| Husband ($IV_2$) | 13.0 | 36.5 | 98 | 103.2 | - | Wild type |
| Proband ($IV_3$) | 14.1 | 145 | 3 | 3.1 | His82Glnfs*36 | Homozygous |
| Brother ($IV_4$) | 13.9 | 34.7 | 102 | 110.1 | - | Wild type |
| Son ($V_1$) | 12.9 | 49.8 | 46 | 49.7 | His82Glnfs*36 | Heterozygous |
| **Family B** | | | | | | |
| Father ($III_3$) | 13.4 | 49.7 | 45 | 46.7 | Cys219Leufs*73 | Heterozygous |
| Mother ($III_4$) | 13.7 | 46.5 | 43 | 50.7 | Val579Hisfs*32 | Heterozygous |
| Brother ($IV_5$) | 12.8 | 37.6 | 95 | 102.1 | - | - |
| Proband ($IV_6$) | 14.1 | 126.5 | 3 | 3.2 | Cys219Leufs*73 Val579Hisfs*32 | Compound heterozygous |
| Husband ($IV_7$) | 14.0 | 40.1 | 110 | 108.9 | - | - |
| Daughter ($V_2$) | 13.6 | 44.9 | 44 | 45.8 | Cys219Leufs*73 | Heterozygous |
| Normal range | 12.6-14.4 | 29.0-43.0 | 72-113 | 72-113 | - | - |

PT: Prothrombin time; aPTT: activated partial thromboplastin time; AA: amino acid; FXII: congenital coagulation factor XII.

the production and secretion of defective FXII proteins [5]. We hypothesized that the Val579Hisfs*32 mutation would also have deleterious effects. In addition, studies have shown that if the mutation is more than 50-55 nucleotides upstream of the last exon-exon junction after splicing, it can induce nonsense-mediated mRNA degradation [6]. It was hypothesized that the RNA surveillance systems of these two patients would eliminate some of the FXII mRNA from the alleles encoding the mutation.

By 2023, a total of 69 *F12* gene variants were registered in the Human Gene Variation Database (https://www.hgmd.cf.ac.uk/ac/all.php). These variants have fewer than 20 small insertions or deletions. It is important to note that the three mutations presented in this study are deletion/insertion mutations. Furthermore, the Cys219Leufs*73 mutation has never been reported before in the world. These mutations may have caused the FXII defect in the two pedigrees. However, the specific mechanism needs to be confirmed by further in vitro expression experiments.

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**Keywords:** Factor XII deficiency, Novel mutation, Genetic mutation

**Anahtar Sözcükler:** Faktör XII eksikliği, Yeni mutasyon, Genetik mutasyon

### Ethics

**Informed Consent:** Participants carefully read and fully understood the informed consent form for the research. This ensured that participants had a clear understanding of the purpose, procedures, and potential risks and benefits of the study and how personal information would be handled. The rights and privacy of participants were strictly respected.

### Authorship Contributions

Surgical and Medical Practices: L.Y.; Concept: Y.X.; Design: L.Y.; Data Collection or Processing: L.Y., M.W.; Analysis or Interpretation: L.Y., M.L.; Literature Search: Li.Y., L.Y.; Writing: L.Y.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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## References

1. Liu M, Wang H, Lin M, Jin Y, Yang L, Wang M. A novel homozygous missense mutation (Met527Ile) in a consanguineous marriage family with inherited factor XII deficiency. Hematology 2020;25:502-506.
2. Zhang H, Pan D, Shen W. Genetic analysis of a pedigree with hereditary coagulation factor XII deficiency. Blood Coagul Fibrinolysis 2021;32:406-410.

3. Peyvandi F, Palla R, Menegatti M, Mannucci PM. Introduction. Rare bleeding disorders: general aspects of clinical features, diagnosis, and management. Semin Thromb Hemost 2009;35:349-355.

4. Mansouritorghabeh H. Consanguineous marriage and rare bleeding disorders. Expert Rev Hematol 2021;14:467-472.

5. Xie H, Zhang H, Xu M, Zou A, Jin Y, Yang L, Pan J, Wang M. Identification of compound heterozygous variants of F12 gene in a pedigree affected with inherited coagulation factor XII deficiency. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2020;37:519-522.

6. Moret A, Zúñiga Á, Ibáñez M, Cid AR, Haya S, Ferrando F, Blanquer A, Cervera J, Bonanad S. Next generation sequencing in bleeding disorders: two novel variants in the *F5* gene (Valencia-1 and Valencia-2) associated with mild factor V deficiency. J Thromb Thrombolysis 2019;48:674-678.

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