

## Case Report

# Novel Variants in *F10* and *DMGDH* Genes in a Child with Mild Factor X Deficiency and Familial Episodic Pain Syndrome

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### Abstract

**Purpose:** To describe the clinical, laboratory, genetic, and familial features of a child with mild factor X deficiency and associated multisystem findings. **Methods:** A 6-year-old boy with daily epistaxis underwent coagulation testing, family evaluation, pedigree analysis, and exome sequencing. **Findings:** Prothrombin time was prolonged, activated partial thromboplastin time was normal, and factor X activity was 20.3%. The father and sister also had prolonged prothrombin time, supporting familial inheritance. Exome sequencing identified a novel heterozygous *F10* variant, *F10* (NM\_000504.4):c.785G>A, p.(Gly262Asp), classified as likely pathogenic. Additional variants were detected in *DMGDH*, *TRPA1*, and *TNFRSF13B*, correlating with fish-like odor with muscle fatigue and familial episodic pain. No immunological work-up, including serum immunoglobulin measurements, was available in this report; therefore, the *TNFRSF13B* finding was interpreted cautiously and was not considered diagnostic of CVID or another primary immunodeficiency. Pedigree analysis showed recurrent bleeding and episodic pain on the paternal side. **Conclusions:** This case expands the molecular spectrum of *F10*-related disease and supports exome-based evaluation in families with bleeding and multisystem phenotypes when routine coagulation studies and family history suggest a broader inherited disorder in affected relatives.

### Key words

Dimethylglycine dehydrogenase; Exome sequencing; Factor X deficiency; Familial episodic pain syndrome; *TRPA1*

### Introduction

Factor X (FX) deficiency has a prevalence of 1 in 1,000,000 worldwide, and FX plays a crucial role in the coagulation cascade. The first sign of FX deficiency is a prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), which correct with a 50:50 mixing test. Chromogenic and immunologic assays are used to measure FX: C levels. Reduced FX: C activity correlates with bleeding severity. Several classifications exist for FX activity and bleeding severity. The European

Network of Rare Bleeding Disorders defined cut-off FX activity levels as 56, 40, 25, and 10 IU/dL for grades 1, 2, and 3 bleeding. Another classification states that FX activity levels >40, 10-40, and <10 IU/dL indicate clinical features: asymptomatic, minor triggered bleeding, or high risk of bleeding, respectively.<sup>1</sup>

Congenital FX deficiency is an autosomal recessive disorder with variable clinical severity, with inheritance patterns ranging from heterozygous to homozygous. Genetic mutations occur in the glutamic acid domain on exon two and at the catalytic site of F10 on exons 7 and 8. Missense mutations have been identified in certain patients or families. Severe cases of the disease result from homozygous or compound heterozygous mutations.<sup>2</sup>

Treatment indications include acute bleeding episodes, preparation for surgery, and prophylaxis against severe and recurrent bleeding. Therapeutic options include fresh-frozen plasma, cryoprecipitate, prothrombin complex concentrates, FIX/X, or FX replacement.<sup>3,4</sup> In this case

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report, we describe a rare cause of epistaxis, novel mutations in the *F10* and *DMDGH* genes, and the patient's family, with clinical features compatible with *TRPA1*-related familial episodic pain syndrome.

## Case Report

A 6-year-old boy, born in Turkey, with no known chronic medical conditions, was admitted to the paediatric haematology-oncology clinic due to epistaxis lasting about 10 minutes and occurring daily. There is no consanguinity in the family. His family history revealed prolonged bleeding episodes in his father, uncle, aunt, and his uncle's sister. The patient denied mucosal bleeding, spontaneous bruising, or prolonged bleeding after dental procedures. Physical exam showed a weight of 22 kg (50-75th percentile), a height of 127 cm (>95th percentile), and normal systemic findings. Additionally, he had a prolonged PT (21.1 seconds) with a normal aPTT. His family also showed prolonged PT in his father (16.9 seconds) and sister (13.7 seconds). Factor and coagulation levels, along with their normal ranges for age, are listed in Table 1. The exome study performed in the clinic identified the NM\_000504.4:c.785 G>A p.Gly262Asp heterozygous mutation in the *F10* gene, which is a nonsynonymous SNV effect causing factor X deficiency. This mutation is a new change not listed in Clinvar, with a DANN score of 0.988. Based on the ACMG guidelines (PP3, PM2, PP2), this mutation is classified as pathogenic (Figure 1).

The clinic exome study identified additional mutations (Table 2) associated with the patient's clinical features. For instance, the patient showed a fishy odor and muscle fatigue caused by dimethylglycine dehydrogenase deficiency. The patient also experienced episodic pain, including upper-body pain triggered by cold, physical stress, and fasting. Frequent fevers were reported clinically; however, no immunological investigations, including serum IgG, IgA, or IgM levels, had been performed at the time of this report. Therefore, the *TNFRSF13B* variant was recorded as a

genetic finding of potential relevance only, and no diagnosis of CVID or another primary immunodeficiency was made. Episodic pain syndrome was common in the patient's father's family, including an uncle, his sister, an aunt, a grandfather, and three of the aunt's children (Figure 2). However, an immune deficiency has not yet been diagnosed in the family. Family segregation analyses of the mutations are currently in progress.

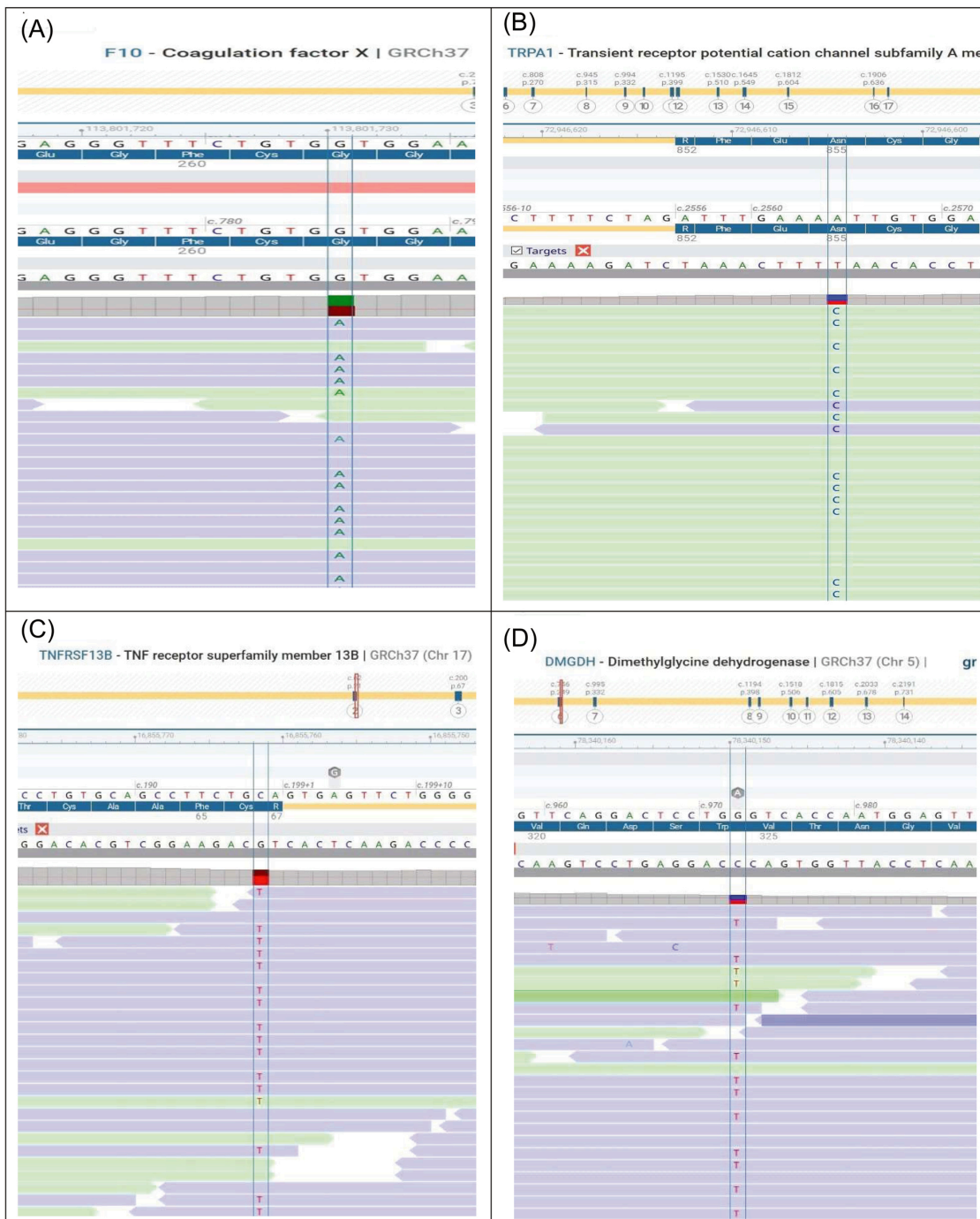
## Discussion

Factor X deficiency is a rare bleeding disorder. The severity of symptoms varies depending on different genetic mutations, mostly located in the glutamic domain of exon 2.<sup>1</sup> Gokcebay et al reported an infant homozygous for an *FX* gene mutation in exon 2 (Gly51Arg) and an FX serum level of 0.03 U/ml. This infant experienced umbilical cord bleeding and a cephalic hematoma and was treated with fresh frozen plasma and activated prothrombin complex concentrate (aPCC). PT (INR) was only elevated.<sup>5</sup> Nagaya et al identified four heterozygous mutations [p.Gly154Arg, p.Val236Met, p.Gly263Val, and p.Arg387Cys] and a compound heterozygous *F10* gene mutation (p.Gly406Ser and p.Val424Phe).<sup>6</sup> Another case report showed that a heterozygous nonsense mutation in the *F10* gene caused prolonged vaginal bleeding after polypectomy.<sup>7</sup>

In neonates, FX levels below 10% may cause severe bleeding such as CNS bleeding, gastrointestinal bleeding, hematomas, and hemarthroses. Additionally, a severe deficiency can lead to epistaxis and menorrhagia. The EN-RBD study results showed a target level range of 10% to 20%, up to 40%, to prevent bleeding. In addition to fresh-frozen plasma, APCC, FIX/FX, and FX concentrates are available for the treatment of FX deficiency. Treatment doses and schedules differ depending on surgery preparation, prophylaxis, or bleeding episodes. Tranexamic acid is preferred for menorrhagia, nosebleeds, and in preoperative and surgical settings to reduce excessive fibrinolysis.<sup>8</sup>

**Table 1** PT (prothrombin time), aPTT (activated partial thromboplastin time), and factor levels of the patient and his family

Severity of depressive symptoms (PHQ-9 score)	Patient	Father	Mother	Sister (7 years old)
PT (s)	21.1 (10.1-12.1)	16.9 (11-14)	13 (11-14)	13.7 (10-12.1)
APTT (s)	32.6 (26-36)	27.8 (27-40)	28.7 (27-40)	26.8 (26-36)
Factor VII (%)	75.3 (65-180)	97.7 (61-127)	97.7 (65-180)	69.4 (61-127)
Factor X (%)	<b>20.3</b> (88-94)	<b>65.9</b> (70-150)	78.5 (70-150)	<b>69.5</b> (88-94)

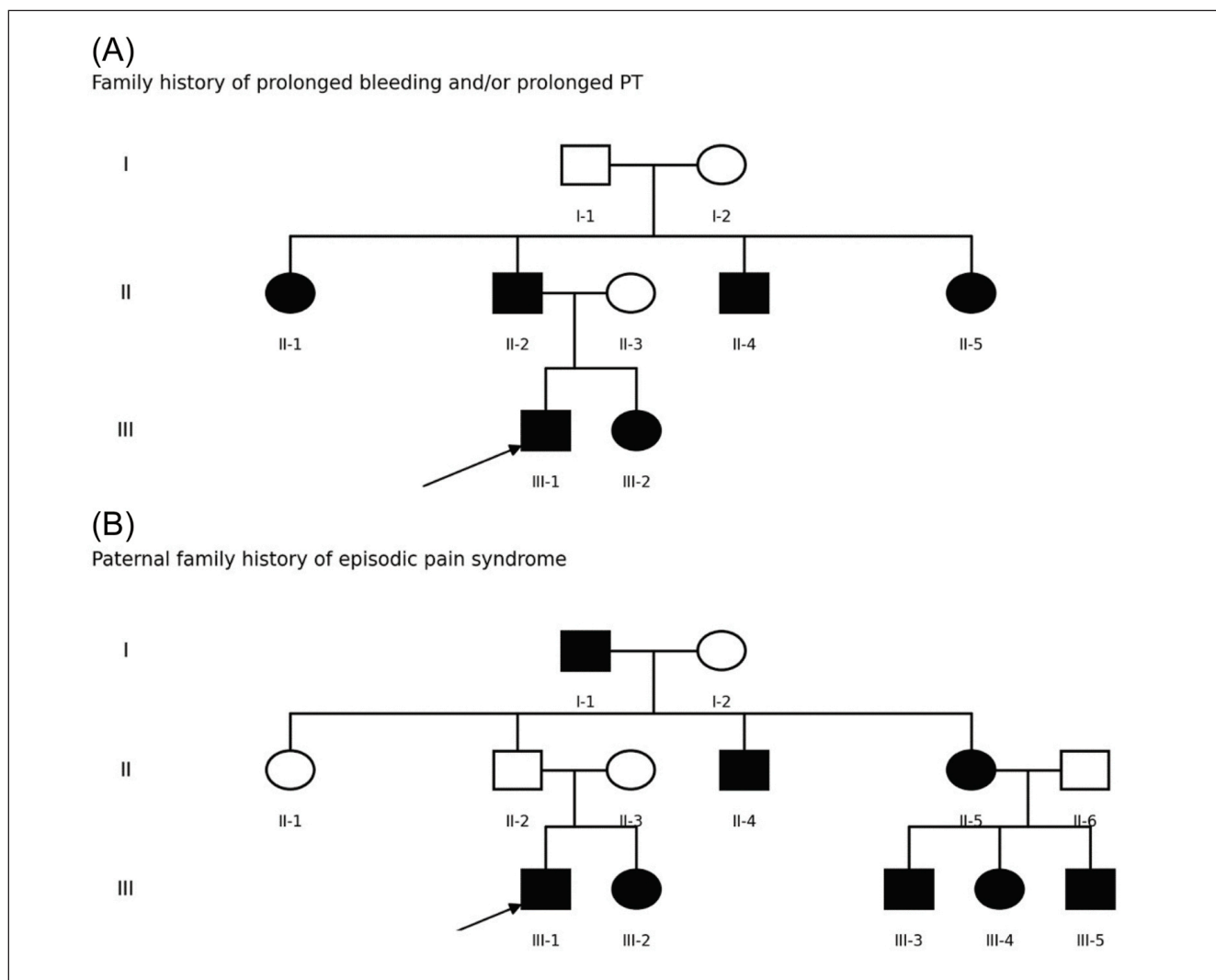


**Figure 1.** Next-generation sequencing shows: (A) NM\_000504.4:c.785 G>A p.Gly262Asp in *Factor X* gene; (B) *TRPA1* (Transient receptor potential cation channel subfamily A) gene mutation; (C) *TNFRSF13B* (Tumour necrosis factor receptor superfamily member 13; 604907) gene mutation; (D) *DMGDH* (Dimethylglycine dehydrogenase) gene mutation.

**Table 2** Genetic mutations in the index case

Gen	Nucleotide protein change	Zygosis	dbSNP	Effect	Variant classification	Disease (Dominance, OMIM#)
<i>F10</i>	NM_000504.4:c.785 G>A p.Gly262Asp	het	–	Nonsynonymous-SNV	–	Factor X Deficiency (AR; 227600)
<i>DMGDH</i>	NM_000504.4:c.785 G>A p.Gly262Asp	het	rs13904 4238	Stop gain	Pathogenic/VUS/Likely benign	Dimethylglislin dehydrogenase deficiency (AR; 605850)
<i>TRPA1</i>	NM_007332.3:c.2564 A>G p.Asn855Ser	het	rs39812 3010	Nonsynonymous-SNV	Pathogenic	Familial episodic pain syndrome (AD; 615040)
<i>TNFRSF13B</i>	NM_012452.3:c.198C>A p.Cys66Ter	het	rs14471 8007	Stop gain	Pathogenic	Tumour Necrosis Factor Receptor superfamily member 13B;604907

AR: autosomal recessive; AD: autosomal dominant; dbSNP: Single Nucleotide Polymorphism Database



**Figure 2.** (A) Pedigree for Factor X deficiency. (B) Pedigree for episodic pain syndrome.

Our study identified a mild FX deficiency linked to a nucleotide change NM\_000504.4:c.785 G>A p.Gly262Asp and a new mutation associated with FX deficiency. Recurrent episodes of epistaxis were treated with a nasal tampon. We plan to use tranexamic acid for uncontrolled nasal bleeding. During trauma and surgery, treatment options include fresh-frozen plasma and plasma-derived concentrates.<sup>9</sup>

Familial episodic pain syndrome type 1 (FEPS1) has been linked to *TRPA1* variants. In our patient, episodic upper-body pain was triggered by cold, physical stress, and fasting, and a similar pain pattern was present in multiple paternal relatives. These findings are clinically compatible with *TRPA1*-related FEPS1 syndrome. The pain is localised in the upper body, similar to that in his family.<sup>10</sup>

Dimethylglycine dehydrogenase deficiency, also known as fish-odor syndrome, is generally considered benign and is associated with mild muscle involvement.<sup>11</sup> We report a novel variant consistent with the clinical presentation: a heterozygous stop-gain in NM\_013391.3:c.972 G>A p.Trp324 mutation, classified as pathogenic/VUS/likely benign.

## Conclusion

This case describes a child with mild factor X deficiency due to a novel *F10* variant, additional *DMGDH* and *TRPA1* variants, and a family history suggestive of a broader multisystem inherited phenotype. The *TNFRSF13B* finding should be interpreted cautiously, as no immunological evaluation was available and no diagnosis of CVID or another primary immunodeficiency was established in this report.

## Conflicts of Interest

All authors have disclosed no conflicts of interest

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