FGB mutations leading to fibrinogen deficiency: four novel mutations

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Introduction

Mutations of *FGB* encoding the βb-chain are of particular interest since the βb-chain is considered the rate-limiting factor in the hepatic production of the fibrinogen hexamer.

Case reports

Case 1

A 30 year old patient from a consanguineous Algerian family was diagnosed with afibrinogenemia after a prolonged bleeding following circumcision. During childhood, he reported severe bleeds. Recently, he was hospitalized for an unprovoked PE. Both functional and immunologic fibrinogen were undetectable. The thrombophilia screening revealed a heterozygous Factor V Leiden mutation. Genetic analysis revealed a homozygous missense mutation in the fibrinogen Bβ-chain: c. 895T>C (exon 6) p.Tyr299His.

Case 2

A 49 year old Portuguese woman who was diagnosed with a severe hypofibrinogenemia (0.48 g/l for both functional and antigenic fibrinogen) during investigation of venous thrombosis. The thrombophilia screening was normal. Her personal thrombotic history included two pregnancy-related thromboses and one unprovoked deep venous thrombosis of the right leg. She reported two miscarriages and two full-term pregnancies without complications. Despite almost 10 years of anticoagulation, she never experienced bleeding. Genetic analysis revealed a homozygous missense mutation in the fibrinogen Bβ-chain: c.1415G>T (exon 8) p.Gly472Val.

Case 3

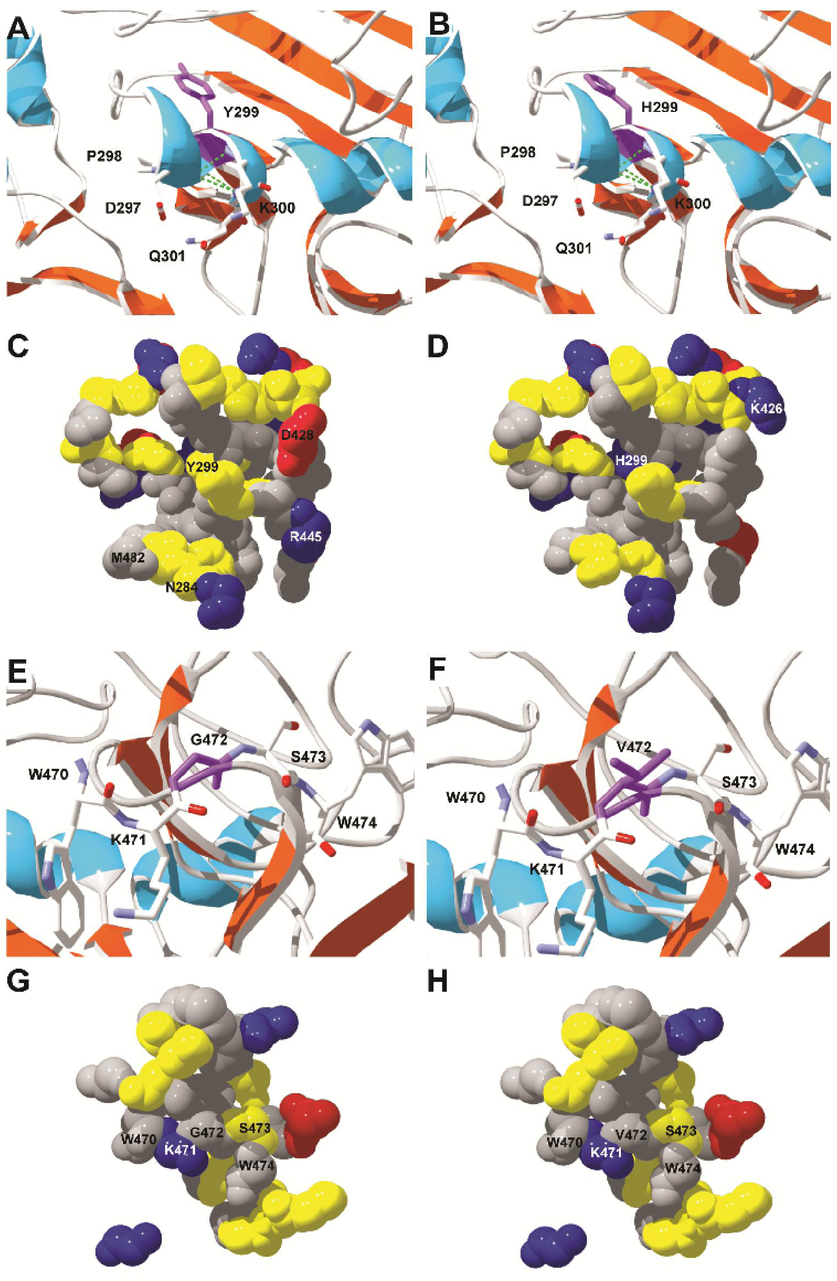
A Danish baby was diagnosed with afibrinogenemia following prolonged umbilical cord stump bleeding. Genetic analysis revealed a heterozygous nonsense mutation c.352C>T (exon 3) p.Glu118X and a heterozygous mutation at the acceptor splice site of intron 4: IVS4-1G>C (c719-1G>C). Each parent is a heterozygous asymptomatic carrier of one of the mutations (father: IVS4-1G>C; mother: Glu118X).

Discussion

The p.Tyr299His mutation replaces an uncharged aromatic amino acid side chain by a positively charged side chain (figure 1A and 1B) and is likely to impair the proper folding of the bC domain by modifying the subtle balance in the distribution of hydrophobic and hydrophilic of the 10 Å neighbourhood residues (figure 1C and 1D). The p.Gly472Val, while still predicted to be deleterious by SIFT analysis, replaces one non-charged aliphatic side chain by another (Figure 1E and 1F) and we did not observe any changes for the 10-Å region surrounding the Gly472Val mutation (Figure 1G and 1H). The p.Glu118X mutation leads to a severe premature termination codon. The IVS4-1G>C acceptor splice-site mutation may lead to skipping of exon 5 or usage of a cryptic acceptor site located upstream or downstream of the normal site

Conclusion

Missense mutations of *FGB* are the most frequent mutations leading to fibrinogen deficiency and are clustered in the highly conserved β-chain highlighting the importance of this structure for fibrinogen assembly and secretion. The continuous characterization of novel molecular defects responsible for fibrinogen deficiency combined with functional studies or modeling of mutant proteins will continue to provide a better comprehension of the complexity of fibrinogen synthesis and physiology.



Modelisation of the p.Tyr299His and p.Gly472Val mutations using the Swiss-Model platform (swissmodel.expasy.org/) in automated mode. The human fibrinogen beta chain precursor protein sequence (P02675) was obtained from the UniProt database. The resulting models were analysed in SwissPdbViewer 4.1 and POV-Ray 3.7. The 10-Å area surrounding each mutation site was isolated and compared with the wild type model.