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A rare and unexpected case of Factor XIII deficiency

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Introduction

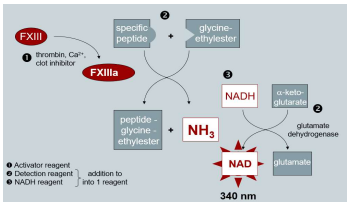
Factor XIII is a critical blood coagulation and fibrin stabilising enzyme. Deficiency of FXIII is one of the rarest inherited coagulation factor deficiencies, with a population incidence of 1 in 2-5,000,000. As a rare autosomal recessive disorder there is a higher prevalence in communities with a high degree of consanguinity. Most diagnoses are made during infancy often characterised by umbilical stump bleeding and intra cranial haemorrhage.

Patient clinical presentation

A 5 day old presented to a local DGH with bleeding from the umbilical cord. Initial clotting screen at the DGH showed normal PT and APTT. The case was then discussed with the on call Consultant at the Haemophilia Comprehensive Care centre and further samples were sent to the Specialist lab for FXIII and Fibrinogen antigen testing. This showed a **FXIII of 6.3% (NR 70-140%)**. The baby was treated with cryoprecitate and a blood transfusion.

Methodology

FXIII assays were performed on the baby and both parents using TCoag DT100 (Stago UK) analyser with Siemens Berichrom®FXIII (chromogenic FXIII)reagents.

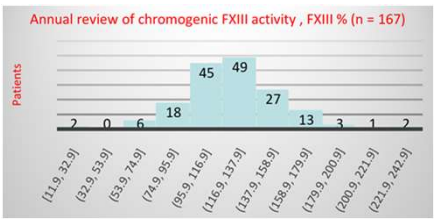


Genetic testing: The rare and inherited disease component of NHS England's Genomic Medicine Service (GMS) enables comprehensive genomic testing for bleeding disorders, provided as part of the specialist haematology service group and specified in the National Genomics Test Directory. For referrals from Central, South and South West regions, this service is provided by Oxford Genetics Laboratories, part of the Central & South Genomic Laboratory Hub (CSGLH). For patients with suspected Factor XIII deficiency (Clinical Indication R122 in the Test Directory), sequencing of the *F13A1* gene (and *F13B* gene if causative variant(s) not identified in *F13A1*) is appropriate. Therefore, Sanger sequencing of *F13A1* was undertaken in the baby. Targeted Sanger sequencing was then undertaken in the parents and sibling to test for the two variants identified.

Results

Haematological FXIII assays:

Individual	FXIII activity
Proband	6.3%
Mother	66.1%
Father	69.9%
Normal range	70-140%

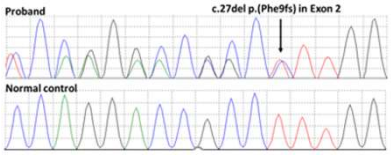


Genetics: Two heterozygous pathogenic *F13A1* variants were detected in the proband; see below.

Frameshift variant

The below figure shows a heterozygous deletion of a single thymine at nucleotide position c.27 in exon 2 of *F13A1*, c.27del, resulting in a frameshift at codon 9, p.(Phe9fs), detected in the proband:

- Predicted to lead to premature termination of translation and undergo nonsense-mediated mRNA decay.
- Previously reported in association with autosomal recessive FXIII deficiency in 2 unrelated individuals, one of whom was homozygous for the deletion.

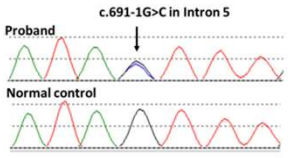


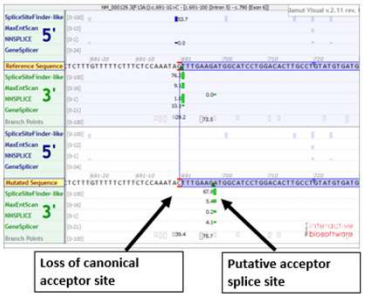
References
Alamut Visual 2.11 (Interactive Biosoftware, Rouen, France).
Schroeder V, Kohler HP. Factor XIII: Structure and Function. Semin Thromb Hemost. 2016 Jun;42(4):422-8

Novel splice site variant

The below figure shows a heterozygous nucleotide substitution, c.691-1G>C, at the canonical splice acceptor site in intron 5 of *F13A1* (left):

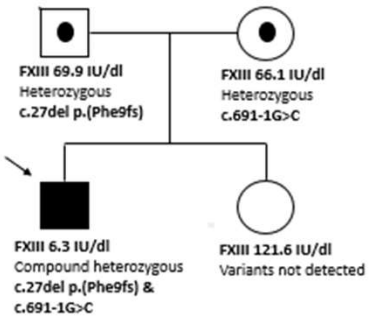
- Disrupts one of the two invariant nucleotides at a splice acceptor site; predicted by *in silico* splicing tools (see right) within the Alamut software to lead to aberrant splicing of intron 5, likely via use of a cryptic splice-site in exon 6 leading to a frameshift and nonsense mediated mRNA decay.
- Novel variant; not previously been detected in patients or in the large population databases.





Family Segregation Studies

- Each parent was found to be a carrier for one of the *F13A1* pathogenic variants; see pedigree.
- Confirming the proband to be compound heterozygous for the two variants and hence the genetic diagnosis of autosomal recessive FXIII deficiency.
- Co–segregation with reduced FXIII levels in the proband and in his parents.
- The proband's sister has normal FXIII levels and has not inherited either of the variants.



Molecular structure & function of FXIII

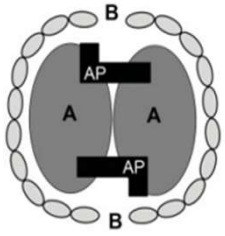


Figure from Schroeder & Kohler, 2016

In plasma, FXIII circulates as a tetramer of two A and two B subunits, encoded by *F13A1* and F13B respectively. **The figure** to the left displays the arrangement of the plasma FXIII A2B2 tetramer.

The A subunits have catalytic function and the B subunits are thought to act as a stabilising carrier protein for the A subunits.

Upon activation, the plasma FXIII dissociates its B subunits and catalyses the formation of gamma-glutamyl-epsilon-lysine crosslinking between fibrin molecules, to stabilise the fibrin clot.

Summary

- A rare case of autosomal recessive FXIII deficiency, due to compound heterozygous *F13A1* variants, was detected after unexpected bleeding from the umbilical cord.
- The *F13A1* gene encodes the catalytic subunit of FXIII required for crosslinking between the fibrin molecules which is required to stabilise the thrombus.
- The genetic findings in the baby and both parents corresponded with FXIII levels (summarised in the pedigree). There was no history of consanguinity and no bleeding symptoms in either parent.
- After discussion with the national paediatric haemophilia and inherited bleeding disorder MDT (initially via email correspondence, then formal presentation at the next meeting) the baby was started prophylaxis with FXIII concentrate (Fibrogammin, CSL), given every 4 weeks with the aim to keep levels above baseline. He has been well with no further bleeding episodes.
- This case illustrates the importance of combined FXIII haematological activity studies to support the molecular findings and confirm the clinical diagnosis of inherited autosomal recessive FXIII deficiency.