A rare and unexpected case of Factor XIII deficiency

H. LEWIS, P. WARE, S. MANGLES, P. BIGNELL

1. Haemophilia Haemostasis and Thrombosis Department, Hampshire Hospitals NHS Foundation Trust, Aldermaston Rd, Basingstoke, RG24 9NA.
2. Oxford Regional Genetics Laboratories, Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford OX3 7LE

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 cryoprecipitate 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 (CMSGH). 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:

<table>
<thead>
<tr>
<th>Individual</th>
<th>FXIII activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband</td>
<td>6.3%</td>
</tr>
<tr>
<td>Mother</td>
<td>66.1%</td>
</tr>
<tr>
<td>Father</td>
<td>69.9%</td>
</tr>
<tr>
<td>Normal range</td>
<td>70-140%</td>
</tr>
</tbody>
</table>

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:

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

Molecular structure & function of FXIII

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

1. A rare case of autosomal recessive FXIII deficiency, due to compound heterozygous F13A1 variants, was detected after unexpected bleeding from the umbilical cord.
2. The F13A1 gene encodes the catalytic subunit of FXIII required for crosslinking between the fibrin molecules which is required to stabilise the thrombus.
3. The genetic findings in the baby and both parents corresponded with FXIII levels and has not inherited either of the variants.
4. The proband’s sister has normal FXIII levels and has not inherited either of the variants.
5. Novel variant; not previously been detected in patients or in the large population databases.
6. 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.

References

Alamut Visual 2.11 (Interactive Biosoftware, Rouen, France).

Figure from Schroeder & Kohler, 2016

Figure 1: A schematic representation of the plasma FXIII A2B2 tetramer. 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.

Figure 2: An example of a classical frameshift variant. The below figure shows a heterozygous nucleotide substitution, c.691-1G>C, at the canonical splice acceptor site, leading 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.