Platelet storage pool disease with excessive bleeding associated with a novel *FLI1* variant.

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INTRODUCTION

Inherited platelet disorders (IPDs) are a heterogeneous group of disorders associated with normal or reduced platelet counts and bleeding diatheses of varying severities. The identification of the underlying cause of IPDs is clinically challenging due to the absence of a gold standard platelet test, and is often based on a clinical presentation and normal values in other haematology assays.

Dense granule disorders typically result in defective platelet aggregation of variable severity, specifically absent secondary aggregation response to exogenous stimuli and significant reduction in the content and ratio of ADP to ATP or a reduced ATP release.

Next-generation sequencing (NGS) technologies are allowing the rapid analysis of genes that have been previously implicated in IPDs or that are known to have a key role in platelet regulation, as well as novel genes that have not been previously implicated in platelet dysfunction.

PATIENT'S DETAILS

A 30 year old woman with a family history of platelet storage pool disorder was referred for investigation. She had a history of easy bruising, recurrent epistaxis and suffered increased post-partum bleeding after the birth of her second child. Her ISTH BAT score was 6. Routine coagulation tests were normal, platelet count was 212, platelet aggregation showed primary disaggregation to ADP at all concentrations, and ATP:ADP ratio was elevated at 7.0 (0.8 – 2.2).

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RESULTS

A variant in *the FLI1* gene (transcription factor friend leukaemia virus integration 1) was identified through Thrombogenomics, c.1019G>A p.(Arg340His). However the significance of the variant was initially unknown.

Further family testing was undertaken in 3 males and 2 female who all had a dense granule deficiency and a 2 males and a female who had normal platelets. The variant was only detected in the individuals with the dense granule deficiency and the mode of inheritance was autosomal dominant in this family. The variant was then reclassified as pathogenic and the family had bleeding disorder, platelet type 21.

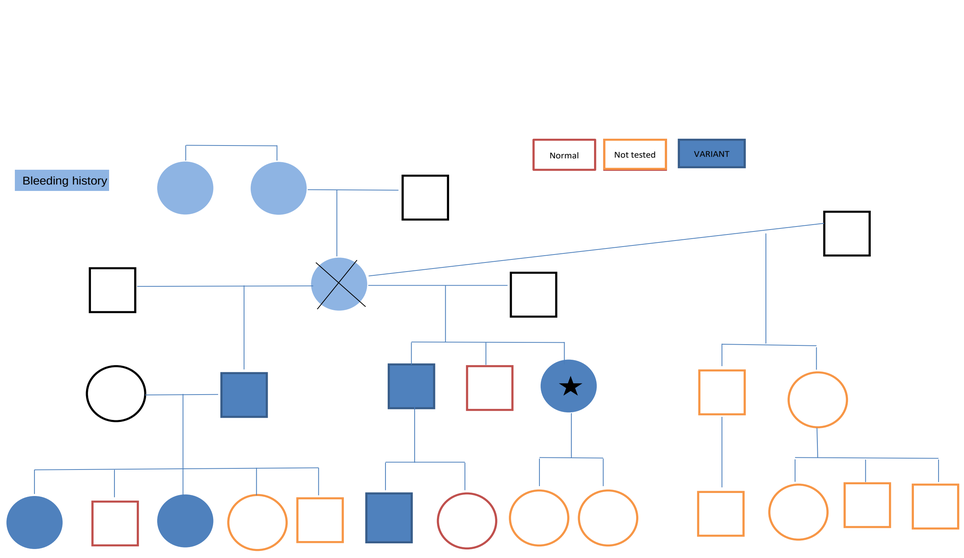
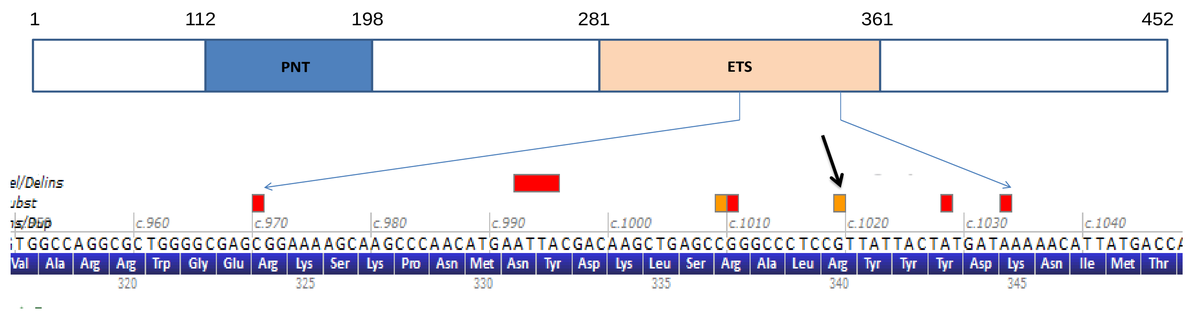


Fig 1: Family tree, proband highlighted with star



HGMD accession	HGMD codon change	HGMD amino acid change	HGVS (nucleotide)	HGVS (protein)	Variant class	Reported phenotype
CM1511325	CGG-TGG	Arg324Trp	c.970C>T	p.R324W	DM	Platelet dense granule secretion defect, excessive bleeding
CM176864	CGG-CAG	Arg337Gln	c.1010G>A	p.R337Q	DM	Macrothrombocytopaenia
CM1312701	CGG-TGG	Arg337Trp	c.1009C>T	p.R337W	DM	Platelet dense granule secretion defect, excessive bleeding
CM1715702	CGT-CCT	Arg340Pro	c.1019G>C	p.R340P	DM	Thrombocytopathy
CM1312702	TAT-TGT	Tyr343Cys	c.1028A>G	p.Y343C	DM	Platelet dense granule secretion defect, excessive bleeding
CM176865	AAA-GAA	Lys345Glu	c.1033A>G	p.K345E	DM	Macrothrombocytopaenia

Fig 2: Schematic diagram of the FLI1 protein. The functional N-terminal Pointed domain (PNT), and C-terminal ETS DNA-binding domain (ETS) are depicted. The positions of the alteration in FLI1 is indicated in black (alterations reported in this study) or blue (previously reported alterations) The table lists previously reported variants in HGMD

DISCUSSION

FLI1 belongs to the ETS-domain transcription factor family, in which members bind a specific DNA consensus sequence to control the expression of genes that are essential in the regulation of cellular proliferation, differentiation and programmed cell death.

To date a further 4 variants have been associated with platelet dense granule secretion defect and excessive bleeding, 2 variants have been associated with macrothrombocytopenia and 1 variant has been associated with thrombocytopathy.

Six of the 7 variants are missense mutations and 1 is a small deletion and they are all in the highly conserved C-terminal ETS DNA binding domain, in exon 9 between codons 324-345. These include another variant at codon 340, c.1019G>C p.Arg340Pro, which was found in an individual with macrothrombocytopenia and dense granule deficiency. Refer to Fig 2

CONCLUSIONS

As more individuals with platelet dense granule secretion defects are screened by NGS and their genetic cause is found, this will allow us to have a better understanding of the numerous platelet disorders and the effect they have on these individuals.