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Beyond exclusion: the case for genetic screening in immune thrombocytopenia

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A key limitation in the management of immune thrombocytopenia (ITP) is the reliance on a 'diagnosis of exclusion' of other causes of thrombocytopenia. ITP has therefore become a catch-all for a biologically heterogeneous group of patients whose only shared feature is the absence of an alternative explanation for their thrombocytopenia.

There is now a growing body of evidence that genetic sequencing identifies both misdiagnosed inherited thrombocytopenia and underlying inborn errors of immunity (IEI) within presumed-ITP patient cohorts (Table 1). Targeted panels built around inherited thrombocytopenia (IT) genes have reported diagnostic yields ranging from 5% to over a quarter of patients tested in cohorts enriched for chronic disease and positive family history. Dedicated IEI screens in ITP have identified genetic disease in 0 - 10% in different adult and paediatric cohorts (Table 1).

Di Lieto et al (1), screening genes for both entities in 80 patients with presumed primary ITP, found pathogenic variants in 9% (7/80): two were reclassified as IT and five as IEI. This result is in keeping with the 11% reported by Joshi et al in an independent cohort of 80 patients with chronic ITP using a comparable dual panel strategy. (2) Convergence across two centres in two countries argues against single-centre artefact, and the wide range in Table 1 makes clear that findings depend on inclusion criteria with higher yields reported in populations enriched with chronic disease, autoimmune manifestations, Evan's syndrome (ES) or paediatric patients.

The clinical importance of correct reclassification are seen in both cohorts. Most of the patients with positive genetic findings in the Di Lieto cohort had received multiple lines of immunosuppression and four had undergone splenectomy, a procedure likely to increase the infection risk and unlikely to address the underlying process. In addition to avoiding splenectomy, confirmed IEI diagnosis can lead to targeted treatments such as abatacept for CTLA4 or LRBA related immune dysregulation, and in selected cases curative allogeneic stem cell transplantation.(2)

The article by Di Lieto et al also verifies variants of uncertain significance (VUS) with functional assays to prove pathogenicity. Two novel NFKB1 variants, initially of uncertain significance, were reclassified as pathogenic after the authors demonstrated loss of protein function in a cell-based luciferase reporter assay. This highlights one of the limitations of genetic screening; the high number of VUS generated by sequencing that, without functional work-up, remain unresolved. (8) Joshi et al identified 3 times higher number of VUSs (32.5%) compared to the 11% of pathogenic variants.(2) The reporting of VUS by clinical laboratories is variable, and may not be reported as they have no clinical relevance until reclassified. Family testing or functional testing can provide evidence for re-classification but this is not feasible in a clinical laboratory and is mostly limited to research settings. Interpreting pathogenicity of genetic variants is a particular challenge in the IEI field. Curated resources such as ClinGen and Genomics England's PanelApp provide guidance, but coverage is incomplete, advice is not always concordant, and both inevitably lag behind a fast-moving literature. Improved ability to classify VUS as pathogenic or benign is the essential next step to improve patient care and enhance our understanding of disease biology.

Exacerbating the problem is the fact that many IEI genes do not follow classical Mendelian inheritance, exhibiting incomplete penetrance complicating the assignment of pathogenicity. The two variants reported here in TNFRSF13B and TNFSF13 illustrate this well. Heterozygous variants in TNFRSF13B are treated as common risk alleles that predispose to, rather than causes, immune dysregulation, (9) and therefore it would not fulfil ACMG criteria for a monogenic gene-disease association. TNFSF13 has to date only been convincingly linked to disease through biallelic loss-of-function variants in the literature in one pedigree, (10) yet Di Lieto et al have classified a heterozygous variant as likely pathogenic. Both genes appear with only limited evidence for pathogenicity on Clinvar and PanelApp curated gene lists. However, both genes sit within the APRIL/BAFF signalling axis, a druggable target, warranting further investigation. A curated, ITP-specific gene list may help standardise this, but the pace of new gene discovery in the IEI space means such a list would need regular review to keep it up to date.

The question of when in the disease course patients should be tested, remains unresolved. Four out of five IEI-positive patients in this cohort had a multi-refractory phenotype (>2 lines of treatment and/or splenectomy). These patients did not have a lasting response to splenectomy in contrast to approximately 60% response rates reported in 'Primary' ITP patients. However, refractoriness alone is not a reliable discriminator; the association between genetic yield and a multi-refractory phenotype was not reproduced in the Joshi et al cohort. Where possible genetic screening should be performed before a splenectomy to avoid unnecessary surgery, however clinical need must be balanced with the patient's phenotype and access to testing in individual healthcare settings. Where genetic testing best fits in the pathway — at diagnosis, before second-line immunosuppression, or only once a patient becomes multi-refractory — is not yet established.

A universal first-line approach is neither practical nor cost-effective; however, a targeted framework has clinical value. Abnormal size platelets, leucocyte inclusions on blood film, as well as family history, lower platelet nadir and longstanding disease may all indicate an inherited thrombocytopenia.(4) Whereas personal or family history of autoimmunity, low immunoglobulins, lymphadenopathy or other cytopenias may indicate an underlying inborn error of immunity (Figure 1). Extended immunological testing may help to improve patient selection for genetic testing.

Another aspect to consider is the implications of genetic findings on the patient and their extended family. When a result reclassifies a longstanding ITP diagnosis as a syndromic immunodeficiency or returns a secondary finding with cancer-predisposition implications, the consequences extend beyond the patient in the room to family and future generations. Genetic counselling, both before and after testing, is a resource commitment that should be included into screening pathways from the outset to ensure patients fully understand the consequences of a positive finding.

The evidence supports a role for genetic screening in the ITP work-up for select patients. WGS is comprehensive but expensive and generates variants of uncertain significance that require infrastructure to interrogate and secondary findings which require a genetics service to manage. Further studies into phenotype and biomarker informed selection as well as interrogation of VUSs are indicated to provide further support for genetic testing in immune thrombocytopenia.

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Table 1: Published genetic studies in ITP patient cohorts

Study	Population	Genetic approach	Diagnostic yield of Pathogenic/Likely Pathogenic Variants*
Di Lieto et al (1) (this issue)	Primary ITP, all ages (n =80)	WGS, in silico IT panel (123 genes) + IEI panel (86 genes)	9% (7/80): 2 IT, 5 IEI
Joshi et al, Blood Adv, 2024 (2)	Chronic ITP, all ages (n=80)	WGS or gene panels – IT panel (123 genes) + IEI panel (>200 genes)	11% (9/80) 7 IT, 2 IEI
Sato et al, Pediatric H&O, 2024 (3)	Paediatric persistent or chronic ITP, enriched for positive FH (n=53)	WES with 56 IT gene panel and 9 IEI genes	23% (12/53) 10 IT, 2 IEI
Gurumurthy et al, BJH, 2025 (4)	21 adult ITP, enriched for positive FH	NGS Panel – 123 IT genes	29% (6/21)
Jiang et al, Blood Adv, 2023 (5)	ITP or Evans, adults (n=40)	NGS panel with >370 IEI genes	0
Downes et al, Blood, 2019 (6)	Chronic ITP, adults, (n=29)	WGS with in silico IT panel (107 IT genes)	24% (7/29)
Ma et al, Front Pediatr, 2020 (7)	Paediatric chronic ITP (n=229)	NGS Panel for both IT and IEI genes	7% 16/229 7 IT, 9 IEI

*Determined by ACMG Criteria, but as discussed interpretation can differ.

Figure 1: Features that should prompt consideration of genetic screening in patients with presumed ITP, before committing to splenectomy or additional lines of empiric immunosuppression.

Patient with presumed ITP

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graph TD; A[Patient with presumed ITP] --> B[Thrombocytopenia red flags: Family history thrombocytopenia Chronic disease Abnormal morphology Higher nadir platelet count]; A --> C[Immune red flags: Multi-lineage cytopenias Other autoimmune diseases Low immunoglobulins FH autoimmunity or haematological malignancy Recurrent infections]; B --> D[Consider genetic screen for inherited thrombocytopenia]; C --> E[Consider genetic screen for inborn error of immunity];
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Thrombocytopenia red flags:

Family history
thrombocytopenia
Chronic disease
Abnormal morphology
Higher nadir platelet count

Consider genetic screen for
inherited thrombocytopenia

Immune red flags:

Multi-lineage cytopenias
Other autoimmune diseases
Low immunoglobulins
FH autoimmunity or
haematological malignancy
Recurrent infections

Consider genetic screen for
inborn error of immunity