The role of genetic sequencing in the diagnostic work up for chronic immune thrombocytopenia

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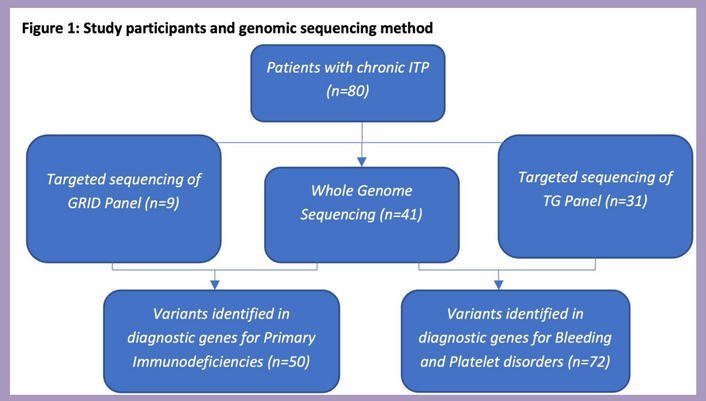
INTRODUCTION

Immune thrombocytopenia (ITP) is a heterogenous autoimmune disorder primarily diagnosed by excluding other conditions. Misdiagnosis can occur in patients with hereditary thrombocytopenia or ITP can present secondary to primary immunodeficiency syndromes. Can identification of these patients through genetic sequencing influence treatment decisions?

METHODS

This study investigates the pathogenicity of genetic variants in patients with chronic ITP. We performed whole genome sequencing or targeted panel sequencing on peripheral blood samples from 80 participants, utilising the ThromboGenomics (TG) Panel (n=72) and the Genomics of Rare Immune Disorders (GRID) panel (n=50). These panels consist of genes known to cause bleeding and platelet disorders or primary immunodeficiency syndromes respectively.

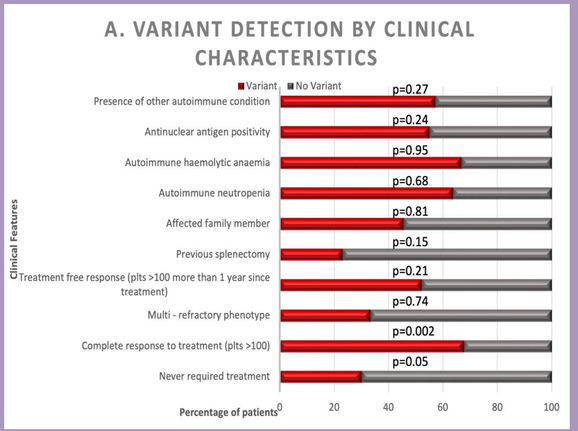
Figure 1: Study participants and genomic sequencing method



RESULTS

Variants were identified in 49% of patients. Known pathogenic, disease-causing, variants were identified in 5 patients; 4 in dominant platelet disorder genes from the TG panel and 1 compound heterozygote in an immune dysregulation gene from the GRID panel. Additionally, 4 patients had likely pathogenic variants, and 33 carried variants of uncertain significance (VUS). Genes in which variants were identified are shown in the table below.

	All patients (n=80)	**Bleeding and Platelet disorder Genes** (n=72)		**Primary Immunodeficiency genes** (n=50)			
	Number of patients	Number of patients	Specific genes	Number of patients	Specific genes		
Pathogenic variant	5 *(6.3%)*	4 (5.6%)	ANKRD26 ETV6 GP1BB TUBB1	1 (2%)	UNC13D (r)		
Likely pathogenic variant	4 *(5.0%)*	3 (4.2%)	VWF ANKRD26 ETV6	1 (2%)	NOD2		
Variant of Uncertain significance	31 *(38.8%)*	11 (15.3%)	RUNX1 ITGA2B TUBB1 MECOM SLFN14 ANKRD26 TBXA2R GP1BA ITGB3	23 (46%)	MEFV TINF2 NOD2 CTLA4 TLR3 CASP10 PLCG2 PIK3CD CHD7	NLRP3 TBK1 SERPING1 PARN NFKB2 POLA1 STAT3 NLRP12 TNFRSF1A	TICAM1 MALT1 ITGB2 IL17RA (r) ATM (r) LRBA (r) DOCK8 (r) STXBP2 (r)



More variants were identified in patients who respond to treatment, rather than multi-refractory patients. The only significantly associated clinical characteristic was patients who have a complete response to treatment with a platelet count of >100x109/L. The presence of family history, anti-nuclear antigen positivity or another autoimmune cytopenia was not associated with a variant.

DISCUSSION

Our findings highlight the role of integrating whole genome sequencing and targeted panel sequencing in the diagnostic pathway for chronic ITP. By identifying genetic variants, we can enhance diagnostic accuracy, tailor treatment strategies, and improve patient outcomes. The high frequency of variants of uncertain significance identified underscores the need for further research to determine the clinical utility of sequencing panels targeting specific thombocytopenia and immunodeficiency genes in the management of chronic ITP.