haematologica
Journal of the Ferrata Storti Foundation

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Received: March 3, 2026.
Accepted: July 13, 2026.

Citation: Delicia Di Lieto, Eva Birgitte Leinoe, Seyed Alireza Mahdaviani, Maria Rossing, Andreas Oerslev Rasmussen, Philipp Harald Richter, Alexandros Arvanitakis, Nadine Gretenkort Andersson, Annika Mårtensson, Jean-Laurent Casanova, Bertrand Boisson and Eva Zetterberg. Genetic screening alters diagnosis and management in patients with immune thrombocytopenia. Haematologica. 2026 July 23. doi: 10.3324/haematol.2026.300831 [Epub ahead of print]

Genetic screening alters diagnosis and management in patients with immune thrombocytopenia

Delicia Di Lieto[1], Eva Birgitte Leinoe[2,3], Seyed Alireza Mahdaviani[4,5], Maria Rossing[3], Andreas Oerslev Rasmussen[3], Philipp Harald Richter[3] , Alexandros Arvanitakis[6], Nadine Gretenkort Andersson[7], Annika Mårtensson[7] , Jean-Laurent Casanova[4,5,8,9,10], Bertrand Boisson[4,5,8], Eva Zetterberg[6]

[1]Lund University, Coagulation Unit, Skåne University Hospital, Malmö, Sweden.

[2] Department of Haematology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

[3]Department of Genomic Medicine, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

[4]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA

[5]Paris Cité University, Imagine Institute, Paris, France

[6]Department of Haematology, Oncology and Radiation Physics, Coagulation Unit, Skåne University Hospital, Malmö, Sweden.

[7]Department of Paediatrics and Coagulation, Skåne University Hospital, Malmö, Sweden.

[8]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM UMR1163, Paris, France

[9]Department of Paediatrics, Necker Hospital for Sick Children, Paris, France

[10]Howard Hughes Medical Institute, New York, NY, USA.

Corresponding author: Eva Zetterberg, M.D PhD

Corresponding author email address: eva.zetterberg@med.lu.se

Running short title: Up-front Genetic Testing in ITP

Key words: ITP, genetic sequencing, immune deficiency, NFKB1

Acknowledgements: We want to acknowledge the contributions of Elena Holm, MD PhD and Anders Lindblom, MD PhD for help with recruiting patients to the study as well as study nurse Amalia Sleiman for coordinating patient recruitment and blood sampling.

Conflict of interest disclosure: The authors have no conflicts of interest to disclose.

Data availability: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author contributions:

- Delicia Di Lieto, Eva Zetterberg, Eva Marie Leione, Andreas Oerslev Rasmussen, Philipp Harald Richter, Alexandros Arvanitakis, Nadine Gretenkort Andersson, Annika Mårtensson, Maria Rossing, Alireza Mahdaviani and Bertrand Boisson performed the research
- Eva Zetterberg designed the research study

- Maria Rossing and Jean-Laurent Casanova contributed essential reagents or tools
- Delicia Di Lieto, Eva Zetterberg, Eva Marie Leione, Andreas Oerslev Rasmusson, Philipp Harald Richter, Andrea Alireza Mahdaviani and Bertrand Boisson analyzed the data
- Delicia Di Lieto and Eva Zetterberg wrote the paper and it was critically reviewed by all authors

Funding information: Funding was provided by a non-conditional grant from Swedish Orphan Biovitrum, SOBI and by Skåne University Hospital funds and foundations. The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute, the Rockefeller University, the St. Giles Foundation, the National Center for Advancing Translational Sciences (NCATS), NIH Clinical and Translational Science Award (CTSA) programme (UL1TR001866), the French National Research Agency (ANR) under the "Investments for the Future" programme (ANR-10-IAHU-01), the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBEID), ANR AIDIRAK (ANR-23-CE15-0011), the Square Foundation, Grandir - Fonds de solidarité pour l'enfance, William E. Ford, General Atlantic's Chairman and Chief Executive Officer, Gabriel Caillaux, General Atlantic's Co-President, Managing Director and Head of Business in EMEA, and the General Atlantic Foundation, Institut National de la Santé et de la Recherche Médicale (INSERM), and the University of Paris Cité.

Since immune thrombocytopenia (ITP) is a diagnosis of exclusion it has been hypothesized that among patients with presumed ITP there are also cases of misdiagnosed patients with inherited platelet disorders (IPD) and inborn errors of immunity (IEI). In this study we wanted to determine the proportion of misdiagnosed ITP patients in a single center cohort. Out of 80 with presumed ITP, we show by performing whole genome sequencing (WGS), that two patients were misdiagnosed cases of inherited thrombocytopenia (IT) and five had pathogenic, or likely pathogenic variants, associated with IEI. In summary, 9% of ITP patients had clinically relevant genetic findings that would have altered management and treatment.

ITP remains a diagnosis of exclusion, as no confirmatory test exists. Thus, both rare IPD (causing isolated thrombocytopenia) and IEI (causing secondary thrombocytopenia), can mimic ITP. Distinguishing these conditions is critical as their management differs and many IPD are syndromic and require broader evaluation. Several IPD are also associated with increased cancer risk, necessitating long-term surveillance.

Genetic testing through high-throughput DNA sequencing has revolutionized early diagnosis of IPD and IEI with proven genetic background. Pathogenic variants in more than 40 different genes have been linked to IT and genetic screening has proven effective in suspected IT and bleeding disorders. [(1)] Approximately 10% of patients with common variable immunodeficiency (CVID) also harbor identifiable germline variants of diagnostic value.[(2)] We conducted a prospective cohort study to assess the diagnostic power of genetic screening in patients with ITP. We wanted to determine:

1. The proportion of patients with IT.
2. The proportion of patients with germline variants causing IEI associated to secondary ITP.

The study included patients of all ages diagnosed with primary ITP regularly followed at the Departments of Hematology and Pediatrics, at Skåne University Hospital (SUS), Sweden. The

inclusion period covered years 2021-2025. All stages of ITP, i.e. acute (<3 months), persistent (3-12 months) and chronic (>12 months) were included. Exclusion criteria were inability to understand patient information in Swedish or severe debilitation precluding participation. For details regarding the inclusion process, see supplementary figure S1.

Ethical approval was obtained from the Swedish Ethical Review Authority (2014/409 and 2019 03630) and the study adhered to the declaration of Helsinki.

Genetic analyses were performed using WGS that combined Illumina PCR-Free library preparation and Illumina platform sequencing. An *in silico* panel consisting of 123 diagnostic-grade genes associated with bleeding/thrombocytopenia was applied to identify variants causing IT (Table S1). Additionally, to detect variants associated with IEI, the VarSeq algorithm PhoRank was used to prioritize genes associated with either of two HPO terms: thrombocytopenia (HP:0001973) or purpura (HP:0000979). A cut-off value of 0.9 was used in PhoRank to select the top 10% genes best associated with either HPO term. Based on the results of PhoRank, an *in silico* gene panel was created consisting of 86 genes (Table S2). Variant interpretation and classification were performed according to recommendations from the American College of Medical Genetics [(3)] and the Clinical Genome Resource. [(4)] To determine pathogenicity of two previously undescribed variants in *NFKB1*, in Site-directed mutagenesis of full-length p105 (inserted into a pLenti-III-EF1alpha plasmid) was performed as described previously. [(5)] The luciferase reporter assay was performed as described previously. [(6)] WT and NFKB1$^{-/-}$HEK293T cells were transfected with a reporter plasmid (100 ng/well for a 96-well plate), the pRL-TK vector (10 ng/well), and a WT or mutant p105 and/or WT or mutant p65 in the presence of Lipofectamine 2000 Transfection Reagent (Thermo Fisher Scientific). After 24 h, cells were harvested and luciferase activity measured with the Dual-Glo Luciferase Assay System (Promega). [(6)]

Eighty patients were included in the study; four patients were children (below 18 years) at enrolment and 15 were children at diagnosis. For seven patients original records were not available and age of diagnosis could not be properly defined (Table 1). Out of 80 patients 26 were multi-refractory or needed continuous treatment to maintain response and 19/80 had autoimmune comorbidities (Table 1).

Two patients (Patient 1 and 2) harboured pathogenic or likely pathogenic variants leading to reclassification from ITP to IT (Table 2).

Patient 1 was a male patient who carried a pathogenic, X-linked hemizygous variant in the *WAS* gene, known to cause X-linked thrombocytopenia (XLT)(*WAS* c.167C>T p. Ala56Val). [7, 8] He was diagnosed with ITP in childhood and had a reduced platelet count of $57x10^9$/L. Blood smear revealed pale platelets with variable size and plenty of microcytes. The variant has been described in two families with XLT [7, 8] and was classified as pathogenic.

Patient 2 was of Chinese origin and carried a heterozygous missense variant in *SLFN14* (*SLFN14*c.667C>T, p. Arg223Trp), reported previously in two families with IT [9, 10] and therefore, classified as likely pathogenic. He was initially diagnosed with ITP in 2011 and remained untreated with stable platelet counts ($70–100 \times 10^9$/L). Blood smear revealed large, pale platelets. Pathogenic variants in *SLFN14* are associated with autosomal dominant *SLFN14*-related macrothrombocytopenia, characterized by secretion defects and abnormal platelet ultrastructure.

Five patients (Patients 3-7) had pathogenic/likely pathogenic variants associated with IEI (Table 2).

Patient 3 had a heterozygous variant initially classified as a variant of unknown significance (*NFKB1* c.802delinsTCAC, p. Glu268delinsSerGln), later reclassified as pathogenic, since

expression of the variant in a cell-based system demonstrated loss of protein function. The patient had a history of thrombocytopenia and neutropenia since childhood and was refractory to multiple ITP therapies, including splenectomy. He was repeatedly hospitalized because of infection and had an observed immunodeficiency with low levels of IgG and IgA for 20 years.

Patient 4 carried a previously undescribed heterozygous missense variant in *NFKB1* (*NFKB1*c.1043T>C p.Phe348Ser), predicted pathogenic by *in silico* analyses. Expression of the variant in a cell-based system demonstrated loss of protein function, confirming the *in silico* classification. He had a history of recurrent childhood infections and was found to have low IgA and IgG levels consistent with a CVID phenotype.

Patient 5 carried a heterozygous variant in *TNFRSF13B* (*TNFRSF13B* c.542C>A p. Ala181Glu)**,** considered a common polymorphism but associated with increased risk of CVID and pneumococcal infections.[11] He was diagnosed with ITP at age 53 and was refractory to multiple treatments including splenectomy. He had multiple infections, including pneumococcal sepsis post splenectomy, despite vaccination. Immunoglobulin levels were within normal range and CVID criteria were thus, not fulfilled. Despite this, the clinical course suggested the variant may have contributed to immune deficiency.

Patient 6 carried a previously undescribed heterozygous variant in *TNFSF13* (*TNFSF13*c.26_29del p. Leu9Profs*24). The patient was diagnosed with ITP in 1987. He had a fluctuating course with frequent relapses despite splenectomy and multiple lines of therapy. He had recurrent infections, found to have low IgA levels and was treated with intravenous immunoglobulin. The immunological findings and clinical course supported a diagnosis of CVID-associated ITP. The variant introduces a premature stop in codon 32, is expected to lead to truncated protein and was classified as likely pathogenic.

Patient 7 was a male born to consanguineous parents and diagnosed with ITP in 2001. He was refractory to multiple lines of therapy including splenectomy. Genetic analyses revealed *Del 3.5 Mb chromosome 22q11.2* consistent with a diagnosis of 22q11 deletion/DiGeorge's syndrome supported by displaying typical features such as autism, hypoparathyroidism and hypocalcaemia [(12)]. The clinical picture suggests that the patient had thrombocytopenia secondary to a syndromic IEI and not ITP.

This study demonstrates a high diagnostic yield when performing genetic screening in patients with presumed primary ITP. Pathogenic variants were found in 9% of cases (n= 7/80) with direct implications for diagnosis and management. Notably, we identified two previously undescribed *NFKB1* variants that proved deleterious *in vitro*. Importantly, four patients, all with hereditary immunodeficiency and thrombocytopenia, had been treated with splenectomy, a treatment likely not chosen had the genetic finding been known. It should be noted that the level of certainty of described variants in this study varied. Functional validation was not performed of the *TNFSF13* variant since we did not have access to proper validation assays. In addition, the *TNFRSF13B* (*TNFRSF13B* c.542C>A p. Ala181Glu) variant is considered a polymorphism and should rather be classified as a susceptibility allele.

It might be argued that the diagnostic yield is overestimated since patients with complex disease, in which most variants were found, may be more willing to participate in a scientific study. Furthermore, our cohort does not fully reflect the epidemiology of primary ITP reported in large population-based cohorts. Rather, it represents a real-world cohort from our center where many patients had been followed for a long period of time likely explaining the relatively high proportion of refractory disease. Diagnostic work-up prior to study inclusion was heterogeneous, reflecting changes in diagnostic guidelines over time and represents an important limitation of the study.

However, our results align with those of a recently published paper by Joshi et al. using a similar approach.[13] In this study, WGS or targeted panel sequencing was performed on peripheral blood samples in a cohort of 80 participants with chronic ITP, utilizing the ThromboGenomics panel and the Genomics of Rare Immune Disorders panel. In this cohort, known pathogenic or likely pathogenic variants were identified in nine patients of whom seven patients had variants in the ThromboGenomics panel and two patients had variants in the primary immunodeficiency gene panel. The small sample size and somewhat differing gene panels might explain the subtle differences in outcome.[13] Several diagnostic algorithms for patients with suspected ITP have been proposed. [14, 15] While informative and of practical value, these papers do not incorporate structured early genetic testing for IEI. In our cohort, 6/9 genetically diagnosed patients had clinical or laboratory abnormalities (hypogammaglobulinemia or abnormal blood smear), where IT/IEI could have been suspected if an updated diagnostic pathway had been used.

Considering results from our and previous studies we would like to suggest the diagnostic flow chart presented in Figure 1, underscoring the early use of genetic screening in the work-up (see legend for details). Notably, patients with pathogenic IEI variants had complicated disease courses and poor splenectomy outcomes, supporting the concept that refractory ITP may reflect an underlying genetic predisposition. Genetic testing may thus be most beneficial in patients with refractory ITP, complex disease courses, or comorbid autoimmune/immunodeficiency features. We suggest that genetic screening should be considered early in the diagnostic work-up of ITP, but if the use of genetic screening is cost-effective and if WGS or targeted sequences should be used, must be discussed at each center. In addition, early genetic diagnosis that may lead to later immunodeficiency, or later malignancy, may cause substantial worry and genetic counselling both before and after testing

must be available. Larger studies with curated and updated gene panels are needed to refine patient selection and further define the role of genetic screening in ITP.

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Tables

Table 1. Participants characteristics, n=80

	N (%)
Demographics	
Adults/children at enrollment	76/4 (95.0/5.0)
Adults/children at diagnosis*	58/15 (79.4/20.6)
Age at enrollment (median, range)	46 (7-88)
Age at diagnosis (median, range, n=73*)	1-90
Pediatric patients – age at enrollment (median, range)	13 (7-17)
Family history of bleeding	6 (7.5)
ITP diagnosis	
Newly diagnosed/persistent/chronic**	6/2/72 (7.5/2.5/90.0)
Treatment	
More than first line	45 (56.3)
Never required treatment	10 (12.5)
Complete response to treatment (platelet count>100 x10^9/L)	0 (0.0)
Multi-refractory phenotype***	13 (16.3)
Treatment free response (platelet count >100 x10^9/L more than 1 year since treatment)	36 (45.0)
Platelets<100 but treatment not indicated	8 (10.0)
Continuous treatment needed to maintain response	13 (16.3)
Previous splenectomy	16 (20.0)
Associated features and investigations	
Presence of autoimmune condition****	19 (23.7)
Autoimmune neutropenia	4 (5.0)
Prior genetic investigation	1 (1.3)

*Age at diagnosis could not be verified in 7 patients since original documents could not be retrieved ** Newly diagnosed (≤3 months), persistent (3–12 months), and chronic (>12 months) at time of enrollment ***More than 2 lines of treatment and/or splenectomy ****Neutropenia, autoimmune hemolytic anemia (Evans syndrome), positive antinuclear antigen, presence of other autoimmune condition

Table 2: Clinical features of patients with pathogenic/likely pathogenic variants identified.

Gene, mode of inheritance and variant classification	Age at diagnosis of ITP	Family history of thrombocytopenia	Ethnicity	Treatment for ITP	Effect on management	Reference re pathogenicity
Patient 1 *WAS* c.167C>T p.(Ala56Val) X-linked recessive missense variant Pathogenic	15	Yes, nephew with the same *WAS*-variant	White	Prednisolone during young adulthood	Stable without treatment but decline in platelets during infections. Genetic counselling to family members	Wu J, et al 2015; Villa A, et al 1995; Facchetti F, et al 1998[41-43]
Patient 2 *SLFN14* c.667C>T, p.(Arg223Trp) Autosomal dominant missense variant Likely pathogenic	51	No	Asian	Not required	Stable without treatment. Genetic counselling to family members.	Stefanucci L, et al 2023; Marconi S, et al 2016 [44,45]
Patient 3 *NFKB1* c.802delinsTCAC, p.(Glu268delinsSerGln) Autosomal dominant deletion-insertion variant Pathogenic	18	No	Mixed	Multi-refractory phenotype. Limited/no response to steroids, rituximab, TPO-RA and splenectomy. In remission with IVIG and rituximab.	Awareness of immunodeficiency and genetic counselling.	New variant
Patient 4 *NFKB1* c.1043T>C p.(Phe348Ser) Autosomal dominant missense variant Pathogenic	25	No	White	Multi-refractory phenotype. Response to steroids and TPO-agonist, but subsequently relapse. Currently in remission with rituximab.	Awareness of immunodeficiency and genetic counselling. Treated with immunoglobulins.	New variant
Patient 5 *TNFRSF13B* c.542C>A p.(Ala181Glu) Autosomal dominant/recessive missense variant, classified as a polymorphism but likely contributing to the patient's phenotype	53	No	White	Multi-refractory phenotype. No response to steroids, eltromopag, romiplastin, IVIG. Splenectomy inducing short-lived remission, thereafter pneumococcal sepsis. Relapse treated with steroids, romiplastin, avatrombog and rituximab.	Awareness of susceptibility to pneumococcal infections.	Castigli E, et al 2005[49]
Patient 6 *TNFSF13* c.26_29del p.(Leu9Profs*24) Autosomal dominant/recessive frameshift deletion variant Likely pathogenic	37	No	White	Multiple relapses after splenectomy. Partial response to steroids, danacrine, rituximab (induced remission for 8 years), thereafter romiplostim, rituximab. In remission with eltrombopag and romiplostim.	Awareness of immunodeficiency and genetic counselling.	New variant
Patient 7 22q11.2 Chromosomal microdeletion Pathogenic	21	No	Mixed	Multi-refractory phenotype. No response to first- and second-line treatment, including splenectomy. Limited response to cyclosporine and ATG. Relapse treated with avatrombopag.	Awareness of syndromic features.	Davies EG, et al 2013[50]

ITP, Immune thrombocytopenia; TPO-RA, Thrombopoietin Receptor Agonists; ATG, Anti thymocyte globulin

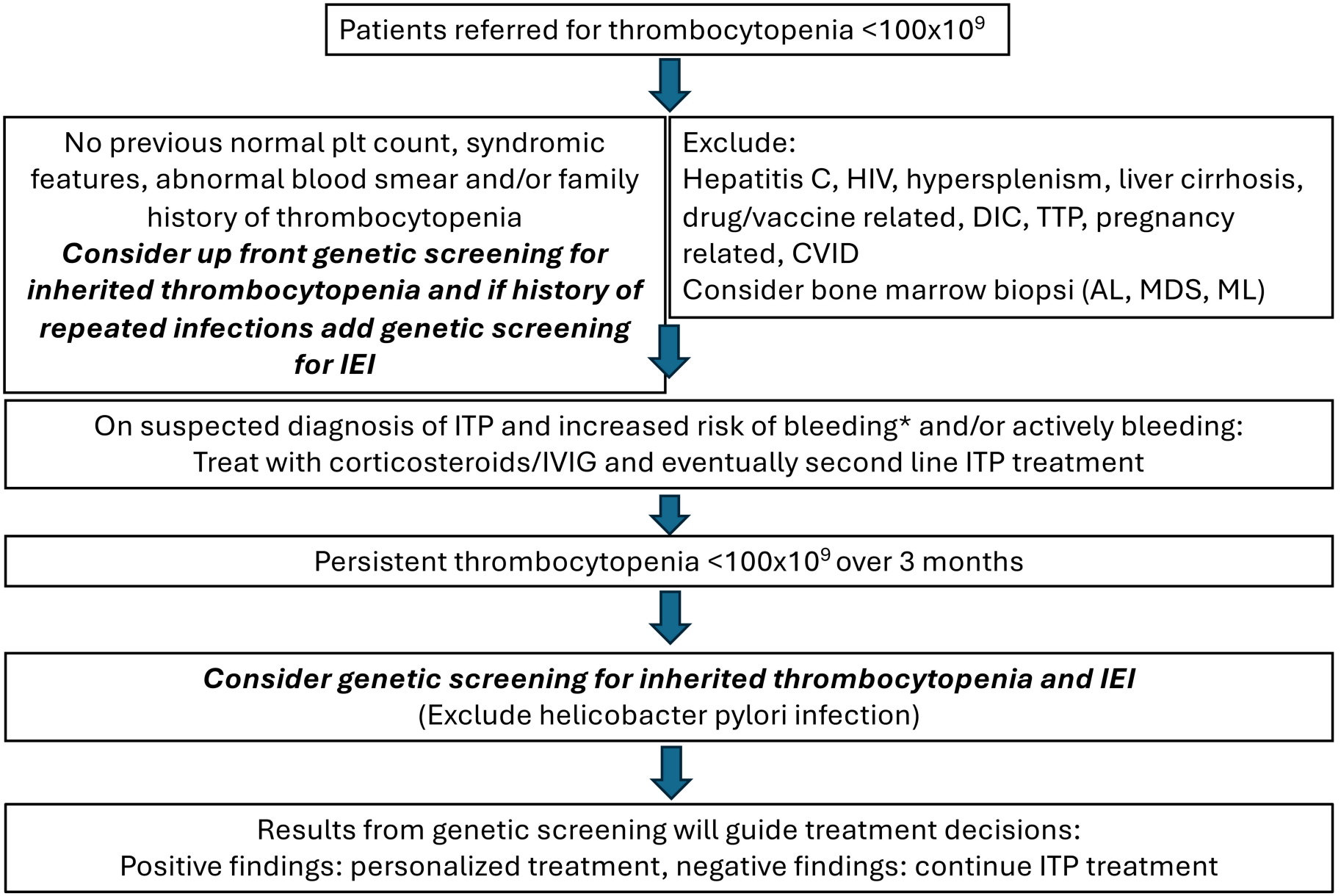
Figure legend

Figure 1. Proposed diagnostic flow chart for genetic screening in immune thrombocytopenia

Flow chart describing a clinical approach to genetic screening in patients referred for thrombocytopenia (<100 × 10μ/L). In patients with isolated thrombocytopenia relevant differential diagnoses should be excluded such as infections and disseminated intravascular coagulation or thrombotic thrombocytopenic purpura. Clinical features suggestive of inherited disease, including no previous normal platelet count, a strong family history or syndromic features should be assessed. In case of positive findings, up-front whole genome sequencing for inherited thrombocytopenia should be considered. If laboratory investigation and/or there is a history of repeated infections, genetic screening for inherited thrombocytopenia or inborn errors of immunity should be considered. In patients with suspected immune thrombocytopenia and bleeding risk, standard immune thrombocytopenia treatment should be initiated. Results from genetic screening will guide personalized management and avoid inappropriate therapies.

*Increased risk of bleeding defined as: Platelet counts below 20 x10μ/L or > 50 x10μ/L if concomitantly treated with anti-platelet agents)

ITP, Immune Thrombocytopenia; DIC, Disseminated Intravascular Coagulation; TTP, Thrombotic Thrombocytopenic Purpura; HUS, Hemolytic Uremic Syndrome; HIT, Heparin Induced Thrombocytopenia; HELLP, Hemolysis, Elevated Liver enzymes and Low Platelets; WGS, Whole Genome Sequencing; HIV, Human Immunodeficiency Virus; H. Pylori, Helicobacter Pylori; MDS, Myelodysplastic Syndrome; ML, malignant lymphoma, CLL, Chronic Lymphatic Leukemia, IgG, Immunoglobulin G; IgA, Immunoglobulin A; IVIG, Intravenous Immunoglobulin


Patients referred for thrombocytopenia <100x10^9
No previous normal plt count, syndromic features, abnormal blood smear and/or family history of thrombocytopenia
Consider up front genetic screening for inherited thrombocytopenia and if history of repeated infections add genetic screening for IEI
Exclude:
Hepatitis C, HIV, hypersplenism, liver cirrhosis, drug/vaccine related, DIC, TTP, pregnancy related, CVID
Consider bone marrow biopsi (AL, MDS, ML)
On suspected diagnosis of ITP and increased risk of bleeding* and/or actively bleeding:
Treat with corticosteroids/IVIG and eventually second line ITP treatment
Persistent thrombocytopenia <100x10^9 over 3 months
Consider genetic screening for inherited thrombocytopenia and IEI
(Exclude helicobacter pylori infection)
Results from genetic screening will guide treatment decisions:
Positive findings: personalized treatment, negative findings: continue ITP treatment

Supplementary files

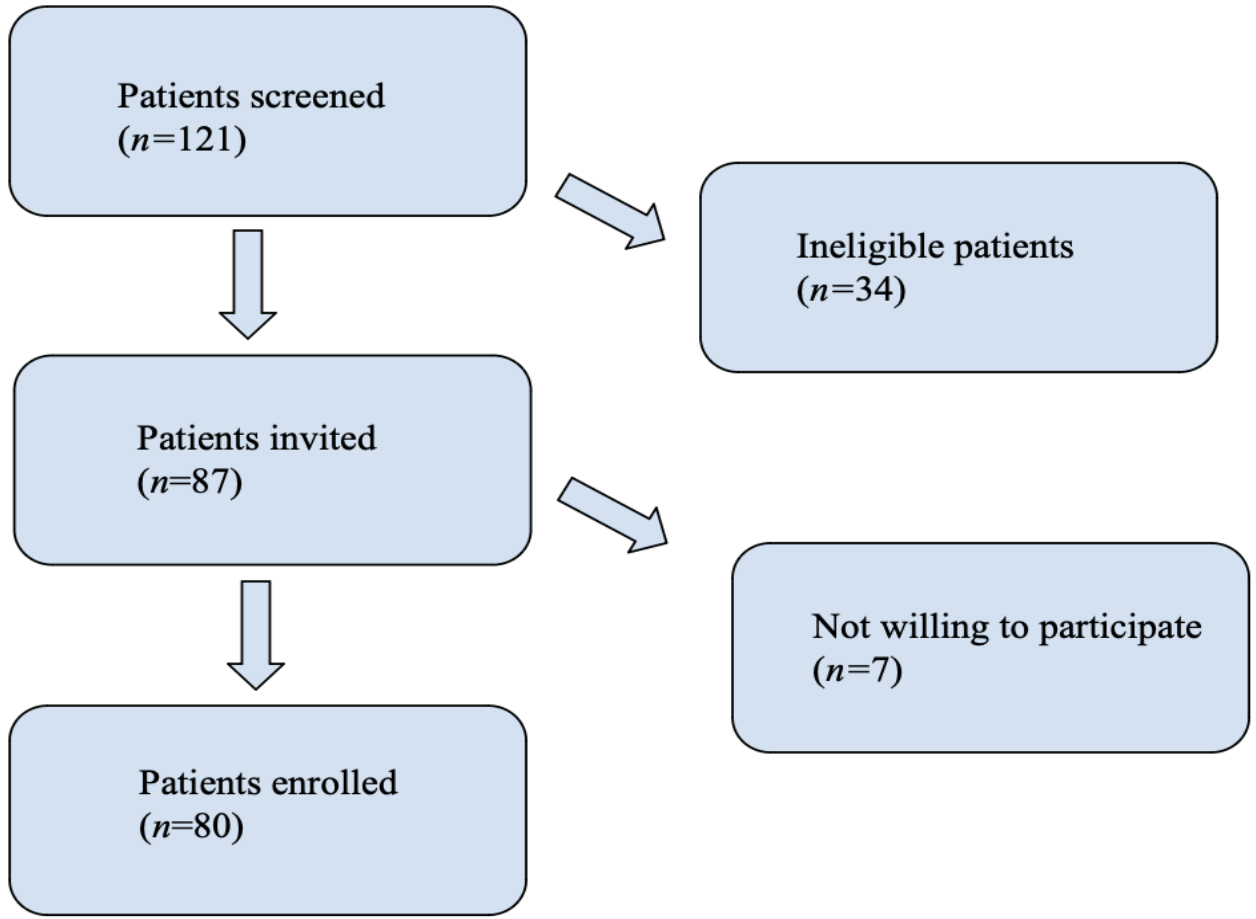
Legend to figure

Figure S1. Inclusion process of the ITP cohort
A total of 121 patients with ITP were screened for participation in the study and 80 patients were included. The main exclusion criteria were inability to read or understand patient information in Swedish or being too debilitated to participate. Out of 121 patients screened, 17 were excluded because of these criteria. Furthermore, there were 17 patients who were no longer followed by the department, making it 34 ineligible patients out of the 121 screened. Seven patients were not willing to participate.

Legend to tables **Please see Excel Supplementary Tables**

Table S1. 123 diagnostic-grade genes associated with bleeding/thrombocytopenia

Table S2. 86 genes associated with immunodeficiency
The VarSeq algorithm PhoRank was used to prioritize genes associated with either of two HPO terms: thrombocytopenia (HP:0001973) or purpura (HP:0000979). A cut-off value of 0.9 was used in PhoRank to select the top 10% genes best associated with either HPO term. Based on the results of PhoRank, an in silico gene panel was created consisting of 86 genes


Patients screened
(n=121)
Ineligible patients
(n=34)
Patients invited
(n=87)
Not willing to participate
(n=7)
Patients enrolled
(n=80)