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Clinical characteristics and molecular background of congenital thrombocytopenia syndromes

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Introduction

Molecular analysis of congenital thrombocytopenia is one of the extensively developing branches of diagnostic research on hereditary bleeding disorders. The widespread use of next-generation sequencing (NGS) has enabled the identification of causative defects in nearly 50 genes. However, it is estimated that the molecular basis of inherited thrombocytopenia remains unidentified in approximately 45% of cases. The final diagnosis is often made only in adulthood due to the mild symptomatology and insufficient awareness of this group of diseases.

Objective and research hypothesis

The study aims to analyze the epidemiology of congenital thrombocytopenia in Poland, characterize their molecular background, and correlate it with the clinical presentation. The main research hypothesis is the significant impact of a causative genomic variant on the course of the disease.

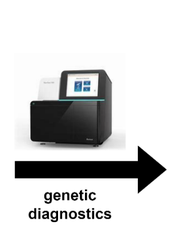
Materials and methods

All pediatric oncology and hematology clinics in Poland were invited to participate in the project. Collaboration letters were signed by 12 centers. To date, 132 patients with chronic thrombocytopenia since birth or childhood, referred between 2016 and 2023 to the Medical Laboratory of Pediatric Oncology and Hematology "Oncolab" in Łódź for genetic diagnostics of congenital thrombocytopenia, have been included in the study. Each of them underwent NGS testing using a panel of 750 genes associated with immunological and oncohematological disorders, including thrombocytopenias and thrombocytopathies, according to the Thrombogenomics Project standard. Some patients were also subjected to further analysis of copy number variation using high-resolution SNP (single nucleotide polymporphism) microarrays. Subsequently, the collected data underwent bioinformatic analysis. Collaborating centers received surveys on the clinical course of thrombocytopenia in the project participants.

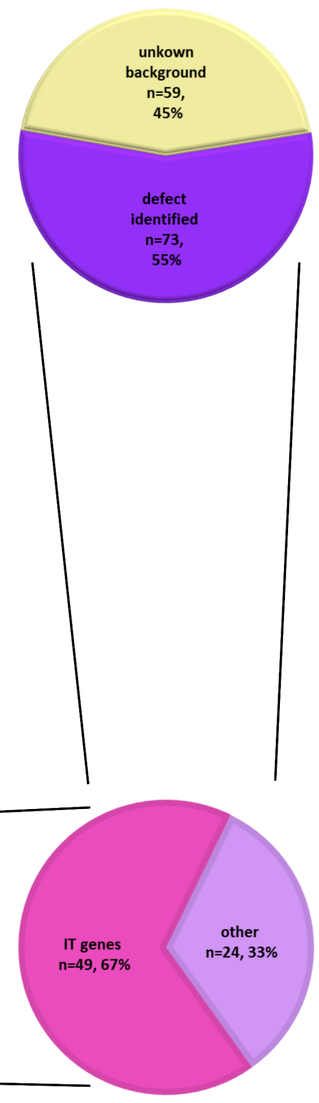
Results

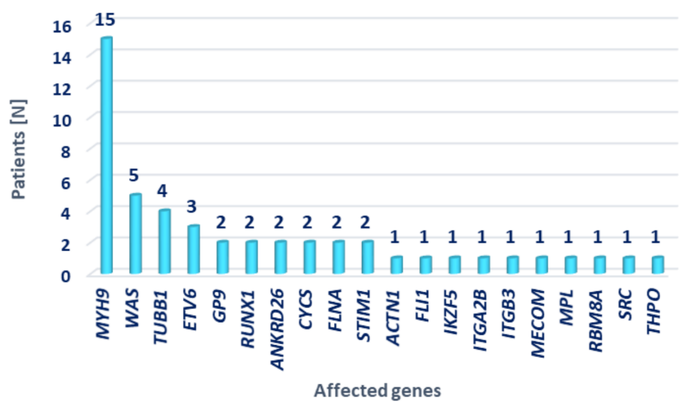
The median age of patients included in the study was 8.60 years (2.12-14.09), and pediatric patients accounted for 95% of the study group (n=126). The youngest patient was 9 days old, while the oldest was 68 years old. The male to female ratio in the study group was 1:1. The molecular basis of thrombocytopenia was identified in 73 patients (55%), including 38 men and 35 women, with a median age of 8.31 years (2.54-13.76). 49 defects diagnosed in this group were confirmed as pathogenic variants responsible for the development of congenital thrombocytopenia syndromes. The most common changes were detected in the *MYH9* gene (n=15), *WAS* gene (n=5), and *TUBB1* gene (n=4). Mutations predisposing to the development of tumors and bone marrow aplasia were diagnosed in 10 patients (14%), most frequently in the *ETV6* gene (n=3). In the remaining 24 cases, variants potentially related to thrombocytopenia were identified. The molecular basis of thrombocytopenia could not be determined in 59 patients (45%). Demographic characteristics of the study group and profile of detected mutations are presented in Figure 1.

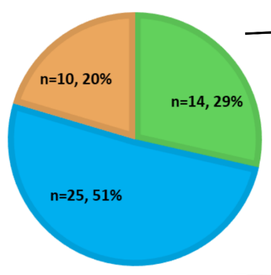
STUDY GROUP N=132	
Pediatric/adults (N)	126/6
Median age (years)	8.60 (2.12-14.09)
Sex (N;%)	F: 66 (50.00 %) M: 66 (50.00 %)



genetic diagnostics







isolated thrombocytopenia - *ACTN1, CYCS, FLI1, GP1BA, GP9, IKZF5, ITGA2B, ITGB3, SRC, TUBB1*

syndromic forms - *FLNA, RBM8A, MYH9, STIM1, WAS*

predisposing to malignancies/BM aplasia - *ANKRD26, ETV6, MECOM, MPL, RUNX1, THPO*

VARIANTS DETECTED
ANRKD26: NM_014915.2:c.[-118C>A];[=]
ETV6: NM_001987.4:c.[641C>T];[=]
MECOM: NM_004991.3:c.[1502A>G];[=]
MPL: NM_005373.2:c.[824C>T];[1675dup]
RUNX1: NM_001754.4:c.[601C>T];[=];
NM_001754.4:c.[155T>A];[=];
NM_001754.4:c.[1052delG];[=]
THPO: NM_000460.2:c.[596C>T];[=]

Figure 1. Study group characteristics and results of molecular testing

Conclusions

The development of molecular diagnostics of inherited platelet disorders in Poland aligns with global trends. Congenital thrombocytopenia is diagnosed in just over half of suspected patients, slightly more often in men than in women. A notable finding is the significant proportion of patients with mutations in the *TUBB1* gene, a very rare cause of congenital thrombocytopenia worldwide. A particular subgroup consists of individuals with variants predisposing to cancerogenesis, for whom early molecular diagnosis enables appropriate surveillance and genetic counseling, thereby acquiring crucial prognostic significance.

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