PB1435 | Diagnostic Approach to Inherited Thrombocytopenias in a Low-Income Setting

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Background: Inherited thrombocytopenias (IT) remain a diagnostic challenge due to clinical and genetic heterogeneity. Although more than 30 genes have been identified, the underlying abnormality is unknown in half of the patients. Advent of next-generation technologies have represented significant advances although access is limited in low-income economies.

Aims: To rationalize resources for IT diagnosis in Argentina.

Methods: First, we applied a diagnostic algorithm (Balduini, 2003) based on phenotypic characterization followed by candidate gene sequencing and, second, whole exome sequencing (WES) was performed in an international center in undiagnosed patients after this algorithm.

Results: We included 114 patients from 50 pedigrees, 25 (0-73) years old, 68 (4-172) x10^9/L platelets; 68%, 30% and 2% had large, normal-sized and small platelets; 21% had syndromic forms: 11% hearing loss, 6% nephropathy, 7% hematologic malignancy, 2% myelofibrosis. By applying the algorithm, a conclusive diagnosis was reached in 27/50 (54%) pedigrees, 38% MYH9-RD; 4% Bernard-Soulier syndrome (1 monoallelic, 1 classic); 4% Gray Platelet Syndrome; 4% ANKRD26-RT; 2% FPD/AML; 2% Wiskott-Aldrich Syndrome. WES was undertaken in 8/23 (35%) pedigrees without diagnosis following the algorithm and known disorders were identified in 4 (1 FPD/AML, 1 ANKRD26-RT, 2 BSS:1 monoallelic, 1 biallelic), whereas no pathogenic variants in either known or new genes were detected in 4. Undiagnosed patients after the algorithm in whom WES was not performed suffered from mild isolated macrothrombocytopenia without distinctive features. Altogether, by this combined approach (algorithm+WES), a definitive diagnosis was identified in 31/50 (62%) pedigrees, which does not differ from the yield of NGS panels.

Conclusions: Careful clinical phenotyping allowed diagnosis in a substantial proportion of patients and MYH9-RD was the disorder most easily recognized by the algorithm. Restricting the application of NGS to patients with negative results after the algorithm allowed to optimize resources and improved the diagnostic yield, representing a feasible approach in low-income settings.

TABLE 1 Diagnostic yield in inherited thrombocytopenias

	1° step Algorithm (n=50)	2° step WES (n=8)	Combined approach Algorithm+WES (n=50)
MYH9-RD	19 (38%)	0 (0%)	19 (38%)
Classic BSS	1 (2%)	1 (12.5%)	2 (4%)
Monoallelic BSS	1 (2%)	1 (12.5%)	2 (4%)
Gray platelet syndrome	2 (4%)	0 (0%)	2 (4%)
FPD/AML	1 (2%)	1 (12.5%)	2 (4%)
ANKRD26-RT	2 (4%)	1 (12.5%)	3 (6%)
Wiskott-Aldrich	1 (2%)	0 (0%)	1 (2%)
With diagnosis	27 (54%)	4 (50%)	31 (62%)
Without diagnosis	23 (46%)	4 (50%)	19 (38%)

PB1436 | Highly Disturbed Platelet Ultrastructure in Two Families with Novel IKZF5 Variants and Inherited Thrombocytopenia

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Background: Heterozygous variants in the *IKZF5* gene, encoding transcription factor Pegasus, were recently discovered to be causal of inherited thrombocytopenia (IT). Platelets from patients with *IKZF5* variants were characterized by a paucity of alpha granules, empty vacuoles and empty membrane structures. Megakaryocytic proplatelet formation was impaired and light transmission aggregometry results varied from normal to reduced response to all agonists. It is currently unknown whether *IKZF5* variants could also be associated with immunodeficiency or developmental impairment.

Aims: We report two families with novel variants in *IKZF5* and present the results of platelet studies together with the results of immunodeficiency examination from one proband.

Methods: The study was approved by the regional ethics committee. Written informed consent was obtained from participants. Whole-genome sequencing of 101 genes, associated with platelet- and