

Piastrine: Alterazioni qualitative o quantitative

IDENTIFICATION OF A NEW VARIANT IN THE *RASGRP2* GENE IN A CHILD WITH SUSPECTED GLANZMANN THROMBASTHENIA

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Introduction. Congenital platelet disorders constitute a heterogeneous group of primary hemostatic defects that are often difficult to diagnose without an integrated approach that includes functional testing. We report the case of a child with suspected Glanzmann thrombasthenia, in whom a novel variant of the *RasGRP2* gene (NM_001098671.2) was identified that cosegregates with the clinical phenotype.

Methods. An 8-year-old boy, presenting with recurrent epistaxis and bruising and without a significant family history, was evaluated at our center. Initial tests showed normal PT and aPTT and impaired platelet function (PFA-100), suggesting a platelet disorder such as Glanzmann's thrombasthenia. However, the absence of aggregation tests and flow cytometric analysis prevented a definitive differential diagnosis. To identify the genetic cause and confirm the suspected diagnosis, clinical exome sequencing (6,600 genes) was performed using the NextSeq 550 platform (Illumina). Bioinformatic analysis included filtering based on allele frequency (<1%), phenotypic correlation, and information from major databases (ClinVar, gnomAD). All relevant variants were confirmed by Sanger sequencing.

Results. Exome sequencing identified a new homozygous missense variant (c.578T>C, p.Leu196Pro) in the *RasGRP2* gene, associated with a rare autosomal recessive hemorrhagic platelet disorder type 18 (OMIM-605577). Both parents are heterozygous carriers of the mutation. The variant is classified as a variant of uncertain significance according to ACMG guidelines, with a pathogenicity score of 4. Several in silico prediction algorithms (CADD, SIFT, PolyPhen-2) suggest a possible pathogenic effect of the variant on the protein. The frequency in the general population is less than 1%. Taken together, these data suggest a possible causal role of the variant in the patient's bleeding phenotype, ruling out a diagnosis of Glanzmann's thrombasthenia.

Discussion/Conclusion. In this study, we identified a new variant in the *RasGRP2* gene that is likely responsible for the patient's bleeding phenotype. The result highlights the importance of clinical exome sequencing as a complementary tool to functional and quantitative tests for an accurate differential diagnosis. An integrated approach allows for an accurate diagnosis and appropriate therapeutic management of patients with suspected congenital platelet disorders.

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