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P06.45.B

Milder form of Vici syndrome due to novel missense variant affecting splicing

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Introduction: Vici syndrome is a rare autosomal recessive syndrome caused by mutations in the gene *EPG5* encoding ectopic P granules protein involved in autophagy. It is a neurodevelopmental disorder with multisystem involvement including corpus callosum agenesis, cataracts, hypopigmentation, cardiomyopathy, and immunodeficiency. It has been hypothesized that the severity of phenotype is related to residual level of functional EPG5.

Patient: A 4 years old boy of Roma ethnicity with preterm birth, hypotonia, severe hypotrophy and growth retardation, developmental delay, mild brain atrophy, and urine organic acid profile suggesting mitochondrial disease was referred for whole-exome sequencing.

Results: We have found a novel variant c.4205G>A (p. Arg1402Lys) in the *EPG5* gene. As it is the last base of exon 23, we performed a mini-gene assay to estimate its effect on splicing. This has shown decreased inclusion of exon 23 compared to wild-type (40% vs. 72%, respectively). RNA sequencing confirmed only presence of the correctly spliced transcript. The patient was further examined for symptoms common in Vici syndrome and hypopigmented skin areas and immunodeficiency were confirmed. Interestingly, the patient has present corpus callosum, although thin, no seizures, no cataracts and no cardiomyopathy. Additionally, he has hemodynamically important stenosis of left pulmonary artery. The typical sign - pale skin and hair were also not present.

Conclusions: Novel variant c.4205G>A causes aberrant splicing only in a proportion of transcripts, therefore, milder presentation of Vici syndrome in our patient is probably due to the residual presence of the EPG5 protein. Supported by VEGA 2/083/17 and APVV-17-0296.

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P07 Immunology and Hematopoietic System

P07.05.A

A rare pair in one patient - Bernard-Soulier syndrome unraveled by 22q11.2 microdeletion syndrome

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Introduction: The 22q11.2 deletion syndrome is one of the most common microdeletion syndromes. Bernard-Soulier syndrome, in turn, is a rare autosomal recessive bleeding disorder (prevalence <1:1 000 000) with dysfunctional glycoprotein Ib-V-IX complex, responsible for the adhesion activity of platelets. We report a patient having both diseases.

Case report: A boy who was admitted to hospital on the third day of life due to epistaxis, petechias and umbilical cord bleeding. Brain MRI showed subdural hematoma among cerebellar lobes. Blood count revealed severe thrombocytopenia (8 x 10^3/uL), that required several platelet infusions and did not improve with immunoglobulin treatment. An NGS analysis for Bleeding disorder gene panel was ordered, with CNV analysis. On the second month of life flow cytometry revealed reduced CD42b expressivity.

Results: The NGS gene panel results revealed a heterozygous pathogenic 22q11.2 microdeletion, encompassing 73 genes with *GP1BB* gene included. The analysis also showed a heterozygous likely pathogenic variant in *GP1BB* gene c.395T>A, p.(Leu132Gln). The combination of the microdeletion on one and the mutation on the other *GP1BB* allele explains the bleeding disorder of our patient and confirms in him Bernard-Soulier syndrome. 22q11.2 microdeletion syndrome was not suspected before the DNA analysis. Afterwards at a repeated consultation the patient demonstrated signs of velopharyngeal insufficiency but as yet no other signs of the Velocardiofacial syndrome.

Conclusions: In patients with early onset bleeding disorder genetic testing with CNV analysis must be performed in order to not miss an autosomal recessive disease unmasked by a seemingly presymptomatic frequent microdeletion syndrome.

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