HOMOZYGOUS ABCG8 MUTATION IN A 14-YEAR-OLD BOY WITH SITOSTEROLEMIA

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Introduction Sitosterolemia is a rare, inherited, autosomal recessive lipid disorder characterized by the accumulation of plant sterols and cholesterol in plasma and tissues as a consequence of hyperabsorption and impaired biliary secretion of sitosterol. It is caused by mutations in ABCG5 and/or ABCG8 genes that encode a pair of ABC half transporters and form a heterodimer (ABCG5/8), which then traffic to the surface of hepatocytes and enterocytes and promotes the secretion of sitosterol into the bile and the intestinal lumen. Here we report on a 14-year-old boy with hypercholesterolemia, failure to thrive and short stature.

Methods Patient was referred to us due to suspicion of familial hypercholesterolemia (FH). His father has hypercholesterolemia and arterial hypertension, grandfather on father’s side also has arterial hypertension and his mother and grandmother on mother’s side have thrombocytopenia. One of his two younger brothers has unilateral perceptual hearing loss, hypercholesterolemia, thrombocytopenia and short stature. NGS analysis of clinical exome (CES, Clinical Exome Sequencing) was performed using peripheral blood DNA obtained from patient and his parents. CES analysis in affected brother is ongoing.

Results CES revealed homozygous missense mutation ABCG8: c.584T>A, p.(Leu195Gln) in patient. His parents are heterozygous carriers of the same mutation. According to ACMG/AMP classification and publications data this variant is classified as likely pathogenic.

Discussion and Conclusion Leucine at codon 195 is highly conserved among all five human ABCG transporters. This mutation is localized within the nucleotide-binding domain (NBD) that powers the transport of substrates by binding and hydrolyzing ATP molecules. Phenotypically, sitosterolemia is very heterogeneous. It includes hypercholesterolemia, arterial coronary artery disease, xanthomas, hemolytic anemia, splenomegaly and elevated liver function test. Because of this it is considered extremely underdiagnosed with over 100 cases reported so far. According to rough estimations the frequency could be at least 1 in 200,000 individuals. It is also considered a recessive disorder, but recent studies have revealed that heterozygous carriers also exhibit milder manifestations as seen in this patient’s parents. Sitosterolemia is also often misdiagnosed as FH and mistreated with statins that are partially or completely ineffective. In conclusion, sitosterolemia should be considered in children with hyperlipidemia, especially with a significant hypercholesterolemia and increased low-density lipoprotein levels.

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