SciMedCentral

JSM Genetics & Genomics

Letter to the Editor

Re-Evaluation of Diagnosis Glycogen Storage Disease Type 1b Based on Familiar Co-Segregation Analysis and Whole Exome Sequencing Result

Vladimir Bzduch[1]*, Katarina Skalicka[2] and Gabriela Hrckova[2]

[1]*Department of Pediatrics, Comenius University, Limbova, Slovakia*

[2]*Laboratory of Clinical and Molecular Genetics, Comenius University, Limbova, Slovakia*

***Corresponding author**

Vladimir Bzduch, Department of Pediatrics, Comenius University, National Institute of Children´s Diseases, Limbova 1, 833 40 Bratislava, Slovakia

Submitted: 05 August, 2023

Accepted: 08 August, 2023

Published: 09 August, 2023

ISSN: 2334-1823

We presented case report „Fatal manifestation of glycogen storage disease type 1b as an e-poster in SSIEM meeting in Freiburg last year, which was published as an abstract in JIMD [1]. In this report, we described newborn with clinical features of progressive hepathopathy (hypoglycemia, hyperlactatemia, elevation of aspartate aminotransferase, hyperferritinemia, massive coagulopathy) with result of molecular genetic analysis (*SLC37A4*, c.527_528delG, p.Trp176Trpfs*35) as glycogen storage disease 1b. Genetic testing of the SLC37A4 and G6PC genes was primarily indicated by Sanger sequencing in 2020. Analysis consisted of all coding region of the gene and exon intron junction. Identified variant was not registered in population database (gnomAD) and human disease databases (ClinVar, HGMD). The result of the identified genetic change was a single nucleotide deletion leading to subsequent shortening of reading frame with premature termination of translation. Loss of function in SLC37A4 protein due to nonsense mediated decay is commonly known mechanisms for disease. At the time, we didn't classify variants according to the ACMG/AMP criteria, which are currently fully implemented in our routine practice. To clearly determine the diagnosis, we recommended carrying out a segregation analysis, examination of proband's parents. However, due to the death of the proband, the parents were not interested in this analysis at the time. Despite the not entirely clear genotype-phenotype correlations, we considered the identified variant to be a causal variant associated with the disease based on the available information that we had at the time. We reopened this case a few months ago at the parent's request due to determining the presence of a variant in their new offspring. The examination of parents ruled out the causality of the variant for the onset of the disease, as both were carriers of the same homozygous variant. Based on the latest recommendations for variant description at the DNA and protein levels and using the current GRCh38.p13 human genome sequence, we revised the variant description as follows: SLC37A4, ensembl canonical transcript (ENST00000357590.5): c.528del, p.(*Val177Trpfs*35*). Now, the variant is registered in the ClinVar database as benign. By searching medical databases, we found that the variant identified in our patient was published in 2021 as possibly pathogenic in association with sudden death syndrome [2]. However, based on the results of the segregation analysis of the proband's parents and the inclusion of simultaneously available information, we now reclassified the given variant as benign. In order to determine the exact etiology leading to the severe clinical manifestation of the disease leading to the death of the patient and the requirement of family planning, we performed whole-exome sequencing. We prepared the whole-exome sequencing from the archived DNA sample of the proband and identified a likely pathogenic variant in the deoxyguanosine kinase (DGUOK) gene in homozygous state (DGUOK, ENST00000264093.9, c.155C > T p.(Ser52Phe)). The variant was classified according to the ACMG/AMP criteria to class 4 based on the following criteria: PM2 (GnomAD genomes homozygous allele count = 0 is less than 2 for AR gene DGUOK), PP3 (MetaRNN = 0.988 is greater than 0.939 ⇒ strong pathogenic) and PP5 (ClinVar classifies this variant as Uncertain Significance). The results of the segregation analysis confirmed that both parents are asymptomatic carriers of the heterozygous variant in the DGUOK gene. The same mutation of DGUOK gene (c.155C > T p.(Ser52Phe) as our patient was published by Freisinger [3], in two patients, one German homozygous and one Russian heterozygous with the same phenotype of progressive hepatopathy. So we re-evaluated our previous diagnosis glycogen storage disease 1b [1], to DGUOK deficiency on the basis of whole exome sequencing.

Cite this article: *Bzduch V, Skalicka K, Hrckova G (2023) Re-Evaluation of Diagnosis Glycogen Storage Disease Type 1b Based on Familiar Co-Segregation Analysis and Whole Exome Sequencing Result. JSM Genet Genomics 8(1): 1032.*

REFERENCES

1. Bzduch V, Brennerova K, Ostrozlikova M, Hrckova G, Skalicka K, Letenayova I, et al. Fatal manifestation of glycogen storage disease type 1b in newborn with novel mutation of SLC37A4 gene. J Inherit Metab Dis. 2022; 45: 530.

2. Neubauer J, Wang S-Russo G, Haas C. Re-evaluation of single nucleotide variants and identification of structural variants in a cohort of 45 sudden unexplained death cases. Int J Legal Med. 2021; 135: 1341-1349.

3. Freisinger P, Futterer N, Lankes E, Klaus Gempel, Thomas M Berger, Johannes Spalinger, et al. Hepatocerebral Mitochondrial DNA Depletion Syndrome Caused by Deoxyguanosine Kinase (DGUOK) Mutations. Arch Neurol. 2006; 63:1129-1134.