Molecular Genetics and Metabolism Reports 23 (2020) 100598

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

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The E273del variant of uncertain significance of the ornithine transcarbamylase gene - a case for reclassification

ARTICLE INFO

Keywords:
OTC
Variant of uncertain significance (VUS)
Hyperammonemia
Variant reclassification

Ornithine transcarbamylase deficiency (OTCD) is an X-linked urea cycle disorder (UCD) due to complete or partial deficit of ornithine transcarbamylase (OTC). OTCD is the most prevalent UCD and responsible for moderate to severe hyperammonemia (HA) resulting in substantial morbidity and mortality [1]. While ~80% of heterozygous females remain apparently "asymptomatic" [2], ~20% are thought to manifest symptoms, the risk of which are related to the time of onset, type of *OTC* variant, and severity of OTCD in their offspring or immediate relative [3]. Some heterozygous females exhibit severe HA as neonates or infants, while others manifest behavioral, hepatic, or neurologic symptoms including HA later in life or well into adulthood [4,5]. Evaluating risk of serious illness in female carriers is challenging due, in part, to the unpredictability of skewed X-inactivation [6,7] and imperfect predictability of severity based on enzyme activity in liver biopsies [8].

We present an 11 year-old male who at 7 years-of-age presented with initial symptoms of vomiting and lethargy during an intercurrent GI illness, with subsequent hyperammonemic coma (maximum ammonia 363 μM) requiring hemodialysis. At that time, he had low plasma citrulline and arginine, and high urine orotic acid, characteristic findings in OTCD [9]. *OTC* sequencing determined him to be hemizygous for the c.817_819delGAG (p.E273del) *OTC* variant. He has since returned to baseline without recurring symptoms, not requiring chronic nitrogen-scavenger therapy, citrulline supplementation or chronic dietary protein restriction, and with no learning delays. This patient's mother (who avoids beef and pork), maternal grandmother (who is vegetarian), older brother, maternal aunt, and maternal cousin are all asymptomatic with the same variant (as hetero- or hemizygote females or males, respectively) and normal plasma glutamine, citrulline and arginine, normal ammonia, and normal blood urea nitrogen (BUN) in mother and brother, normal BUN in maternal aunt, and normal BUN and plasma amino acids in maternal cousin. The maternal cousin had complete *OTC* sequencing and exonic deletion/duplication analysis, while other immediate family members had targeted testing for the familial variant.

The p.E273del variant is currently classified as a variant of uncertain significance. This variant has been reported in an unrelated male with late-onset hyperammonemic coma at 10 months-of-age and 5% OTC enzyme activity following liver biopsy [10]. These unrelated families suggest that though female heterozygotes with this variant appear asymptomatic, this variant seems to confer elevated risk of late-onset hyperammonemic crisis at least in males. It is crucial for proper genetic counseling, evaluation for appropriate therapeutic intervention (s), and prevention of complications that *OTC* variants be properly classified. Based on the American College of Medical Genetics and Genomics guidelines for variant classification [11], with one strong (PS3) *in vitro* enzyme deficit criterion and two supporting (PP4) phenotype-based criteria in two unrelated males, we propose that the p.E273del variant be considered for reclassification to likely pathogenic.

Acknowledgments

We are grateful to our patients and their immediate families for making this communication possible.

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https://doi.org/10.1016/j.ymgmr.2020.100598
Received 24 February 2020; Received in revised form 28 April 2020

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