**Identification of a novel homozygous loss-of-function variant in JPH2 in two unrelated families affected by lethal Neonatal hypertrophic cardiomyopathy**

Authors

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Disclosures

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Abstract

Pediatric cardiomyopathies represent a clinically and genetically heterogeneous group of disorders affecting the ventricular myocardium, with an annual incidence of ~ 1.5 per 100,000 children. They are associated with substantial morbidity and mortality: up to 40% die or undergo transplantation. Here we studied two unrelated consanguineous families from the same geographic region of Iran, with 4 children who died due to infantile cardiomyopathy. Affected offspring presented with severe hypertrophic cardiomyopathy and right atrium enlargement in utero, at birth, or in early childhood. Whole exome sequencing (WES) of DNA from the proband of the first family led to identification of a novel homozygous frameshift variant (p.Glu641\*) in *JPH2*. The parents of the proband and a healthy sibling were heterozygous. Echocardiography revealed no abnormalities in the carriers. Due to unavailability of samples WES could only be carried out for the parents of the second family, however the same heterozygous frameshift variant was identified in both parents. The variant is novel and absent from population databases including gnomAD, the ethnically-matched GME variome, Iranome, and in ~1000 WES in-house control subjects from the same geographic region as the families investigated. The variant occurs in the protein C-terminal region of JPH2, just upstream of a 22-amino acid transmembrane anchor responsible for binding of the protein to the sarcoplasmic/endoplasmic reticulum, thereby potentially disrupting binding. Our findings add to the growing evidence that mutations in *JPH2* play a role in HCM; and suggest that this novel biallelic truncating mutation can give rise to severe, early-onset pediatric cardiomyopathy.