

Biallelic, and not monoallelic, loss of function variants in *TRIM63* most likely cause cardiomyopathy

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Introduction: *Tripartite motif-containing 63 (TRIM63)*, also known as *Muscle RING finger protein 1 (MURF1)*, encodes a skeletal and cardiac muscle specific E3 ubiquitin ligase that maintains the integrity and stability of the sarcomere. Heterozygous loss of function variants in *TRIM63* have been reported to cause hypertrophic cardiomyopathy (HCM) in humans [Chen SN, *et al.* (2012) *Circ Res* 111(7):907-919]. However, the reported families were small, the role of one of the variants in the report, p.Q247*, was questioned by another study [Ploski R, *et al.* (2014) *Circ Res* 114(2):e2-5], and two out of the three variants in the initial report (p.Q247* and p.A48V) have high allele frequencies in the Genome Aggregation Database (gnomAD) that are incompatible with the estimated prevalence of HCM. Additionally, the Exome Aggregation Consortium (ExAC) reports that this gene is tolerant of heterozygous loss of function variants (pLI=0.00). Animal models support a biallelic loss of function mechanism of disease because unlike wild-type mice, homozygous *Murf1* knockout mice develop an exaggerated cardiac hypertrophic response after pressure overload [Willis MS, *et al.* (2007) *Circ Res* 100(4):456-459]. *In-vitro* studies have also shown that depleting *Murf1* in neonatal rat ventricular myocytes by short interfering RNAs causes a significant increase in cell size and upregulation of markers of hypertrophy [Arya R, *et al.* (2004) *J Cell Biol* 167(6):1147-1159]. Finally, there is a report of one adult patient from a consanguineous family with HCM who was homozygous for the p.Q247* loss of function variant but whose heterozygous siblings were asymptomatic [Olivé M, *et al.* (2015) *Hum Mol Genet* 24(13):3638-3650]. The patient also carried a heterozygous missense variant in another cardiac related gene, *TRIM54*. However, the contribution of this missense variant to HCM is likely minimal because of the observation that introduction of wild-type *TRIM63* in the patient's cultured myocytes was able to rescue the disrupted organization of the microtubule network. The patient's older half-sister with HCM was also homozygous for p.Q247*. However, she had a history of hypertension which could also have contributed to HCM. This set of observations, together with a complete absence of homozygous loss of function variants in gnomAD in *TRIM63*, strongly indicates that biallelic disruption of *TRIM63* can cause cardiomyopathy. Here we present an additional adult patient from a consanguineous family with cardiomyopathy who was found to be homozygous for a loss of function variant in *TRIM63* via diagnostic exome sequencing (DES) performed at our clinical laboratory.

Methods: DES and candidate gene analysis were carried out as described previously [Farwell Hagman KD, *et al.* (2017) *Genet Med* 19(2): 224-235].

Results: The patient was diagnosed with HCM at 26 years of age. He also had bilateral avascular necrosis of the hips, arthritis, and ataxic gait, and was homozygous for the p.Q247*

nonsense variant in *TRIM63* with no variants identified in other cardiac genes. His older brother was diagnosed with HCM as well, and is currently being genotyped.

Conclusion: Biallelic, rather than monoallelic, loss of function of *TRIM63* most likely causes HCM and we recommend that this gene be sequenced in patients presenting with these cardiac conditions.