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A rare genetic variant in a case of familial hypertrophic cardiomyopathy

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Obstructive and non-obstructive hypertrophic cardiomyopathy (HCM) is characterized by risk for sudden cardiac death (SCD) and progressive heart failure. Among the known genetic disorders affecting the cardio-vascular system, HCM leads the list and as many 11 genes and > 1400 mutations are implicated in the pathogenesis. The commonest mutation involves the myosin heavy chain (MYH) and myosin binding protein C (MYBC). Some of the rare mutations are associated with heterogeneous phenotypic manifestations ranging from asymptomatic phenotype (HCM with no symptoms) to SCD as the presenting symptom. We report a rare gene involved in the malignant form of HCM. According to our understanding this mutant variant is rarely reported in literature.

A 40-year-old female had been under our follow-up as a case of non-obstructive hypertrophic cardiomyopathy (HCM). The patient developed dilated cardiomyopathy (end-stage HCM). She underwent a percutaneous automated implantable cardioverter defibrillator (AICD) implantation for a resuscitated cardiac arrest with a documented ventricular tachycardia. Due to refractory symptoms of heart failure she underwent a successful heart transplant. This patient has a 42-year-old elder sister, who had a similar course of illness. She had a resuscitated cardiac arrest followed by AICD implantation and cardiac transplant. Both the sisters have a brother who is healthy. The sons of both these sisters also have the phenotype of HCM and are being followed-up closely. The mother of these sisters had suffered a sudden cardiac arrest due to unknown etiology at around the same age as these sisters.

Targeted gene sequencing was carried out in the present patient with the DNA extracted from blood using a custom capture kit on Illumina sequencing platform and analyzed using Picard and GATK version 3.6 (MedGenomeR). The following „heterozygous" mutations were identified: 1) MYH7 (-) at exon 23, and 2) MYL2 (-) at exon 7. A heterozygous missense variation in exon 23 of the MYH7 gene (chr14:23893268; C>C/T; Depth: 260x) that results in the amino acid substitution of lysine for glutamic acid at codon 924 (p.Glu924Lys; ENST00000355349) was detected. A heterozygous 5 base pair deletion in exon 7 of the MYL2 gene (chr12:111348887_111348891delCTTCT; Depth: 99x) that results in a frameshift and premature truncation of the protein 36 amino acids downstream to codon 164 (p.Glu164GlyfsTer36; ENST00000228841) was also detected.

Hypertrophic cardiomyopathy-1 (OMIM#192600) and dilated cardiomyopathy-1S (OMIM#613426) are caused by heterozygous mutations in the MYH7 gene (OMIM*160760). The observed variation has previously been reported in families affected with familial hypertrophic cardiomyopathy and is present in the myosin tail of the MYH7 protein. The Glu924Lys variant is not reported in both the 1000 genomes and ExAC databases. The in-silico predictions of the variant are possibly damaging by PolyPhen-2 (HumDiv) and damaging by SIFT and Mutation Taster2. Familial hypertrophic cardiomyopathy-10 (OMIM#608758) is caused by mutations in the MYL2 gene (OMIM*160781). This MYL2 variant is also not reported in both the 1000 genomes and ExAC databases. The in-silico prediction of the variant is benign by Mutation Taster2.

The case presents a classical example of „familial malignant hypertrophic cardiomyopathy". Genetic analysis has helped in detecting some rare variants of HCM genes in the family. Such testing is encouraged to understand the genetic basis of cardiovascular diseases and cardiomyopathy in particular. The in-silico testing of the interactions of such variants also help in understanding the molecular basis of cardiomyopathy

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