

CO-05

A NOVEL MISSENSE MUTATION IN THE ALPHA-TROPOMYOSIN (*TPM1*) GENE IN A FAMILY AFFECTED WITH HYPERTROPHIC CARDIOMYOPATHY

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Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disorder that affects 1/500 individuals. The clinical and pathological manifestations are diverse and range from asymptomatic to severe clinical courses with heart failure and sudden cardiac death. To date, a large number of genetic studies have established that HCM is caused by mutations in over 11 genes encoding thick and thin contractile myofibrillar components of the sarcomere, or adjacent Z-disc, which are expressed primarily or exclusively in the heart. The 2 most commonly involved genes - β -myosin heavy chain (*MYH7*) and myosin binding protein-C (*MYBPC3*) - account for 50-70% of the cases, whereas several other genes are much less common, together accounting for fewer than 5% of the patients. The frequency of α -tropomyosin (*TPM1*) mutations causing HCM is no higher than 1 %.

We describe a family with five affected members, one of whom suffered sudden cardiac death at the age of 12. In the index case, a nine year old girl with symptomatic HCM, systematic screening for mutations was performed by Next Generation Sequencing (NGS) in all coding regions of the following genes: *MYH7*, *MYBPC3*, *TPM1*, troponin T2 (*TNNT2*), troponin I (*TNNI3*), myosin light chain 2 (*MYL2*), myosin light chain 3 (*MYL3*), α actin (*ACTC1*), cysteine and glycine rich protein 3 (*CSRP3*), and telethonin (*TCAP*).

A new nucleotide substitution c.388A>C was identified in the *TPM1* gene, predictably resulting in an amino acid change (p.Ile130Leu). The mutation was present in all clinically affected family members, as well as in the proband's sister who was clinically characterized as unaffected. No DNA sample was available of the individual who had suffered sudden death, but his father presented a mild HCM and also carried the familial mutation.

In silico analysis yielded somewhat contradictory results as to the pathogenicity of the c.388A>C mutation in *TPM1*,

predicted as probably deleterious by Mutation Taster and Polyphen-2's HumanVar model, yet tolerated by SIFT. However, our analysis suggests that this mutation causes HCM, because firstly it co-segregated with the disease and secondly the substituted amino acid is seen to be conserved among vertebrate species and among all alpha-tropomyosin isoforms. The clinical data suggest a variable clinical manifestation and variable penetrance caused by this mutation in this family.

Although it may be argued that genetic testing in HCM is of limited clinical and prognostic value, elucidation of the underlying pathogenic mutation not only confirms the diagnosis (of particular relevance in ambiguous cases) but, most importantly, it enables the identification of high risk patients, even before the occurrence of overt hypertrophy, thereby improving healthcare provision with adequate and timely intervention.