The Turkish Journal of Pediatrics 2018; 60: 315-318
DOI: 10.24953/turkjped.2018.03.013

Case Report

A novel mutation of the MYH7 gene in a patient with hypertrophic cardiomyopathy

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Received: 5th February 2017, Accepted: 13th August 2017

SUMMARY: Goel N, Huddleston CB, Fiore AC. A novel mutation of the MYH7 gene in a patient with hypertrophic cardiomyopathy. Turk J Pediatr 2018; 60: 315-318.

Hypertrophic cardiomyopathy (HCM) is a genetic disorder characterized by asymmetric cardiac hypertrophy due to inherited mutations in genes that encode sarcomeric proteins. MYH7, which encodes β-myosin heavy chain, is among the most commonly mutated genes in patients affected by HCM. We aimed to identify the specific mutation responsible for HCM in a six-month old Caucasian patient. NextGen DNA sequencing revealed a novel p.Ala1328Thr (A1328T) mutation of MYH7 in the affected patient as well as his asymptomatic father and asymptomatic brother. The clinical details of this mutation are described for the first time in this report. The genetic variant affects a residue that is highly conserved across species. Theoretical analysis suggests that A1328T is very likely deleterious to β-myosin heavy chain protein structure and function. Furthermore, this novel mutation was not observed with any significant frequency in approximately 6,500 healthy individuals of European and African American ancestry in the NHLBI Exome Sequencing Project, underlining the potential pathogenicity of this variant.

Key words: hypertrophic cardiomyopathy, β-myosin, MYH7, pediatric cardiology, congenital heart defect.

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder characterized by unexplained asymmetric thickening of the interventricular septum and left ventricular free wall.[1-3] The prevalence of HCM is 1 in 500, greater than that of any other monogenic disease of the heart.[4] Moreover, it is the most common cause of sudden cardiac arrest (SCA) in individuals younger than 35.[5] HCM is inherited in an autosomal dominant pattern and exhibits vast genetic heterogeneity, with at least 12 causative genes documented to date, most of which encode cardiac sarcomeric proteins such β-myosin heavy chain (MYH7), myosin binding protein C (MYBPC3), cardiac troponin T (TNNT2), troponin I (TNNI3), cardiac alpha-actin (ACTC), and alpha-tropomyosin (TPM1).[6-8] Defects at MYH7 are among the most common, accounting for about 40% of sarcomeric mutations in HCM.[9,10] In general, mutations in MYH7 tend to cause earlier onset of severe disease and carry higher risk of SCA than other HCM-causing mutations.[11-13] Nonetheless, phenotypic expression resulting from mutations at MYH7 can be remarkably heterogeneous, with intra- and inter-familial variations ranging from severely malignant to entirely asymptomatic.[6] Even individuals with identical mutations may exhibit different clinical presentations, suggesting a role of modifier genes and environmental factors. The inherent complexity of HCM already encountered suggests there is still much to be learned about the genetic underpinnings of this disease, making it imperative to explore the genetic backgrounds of HCM patients when possible. Here we report a case of an affected 2-year old boy who is a carrier of a mutation at MYH7 that has yet to be reported in association with HCM.

Case Report

Clinical presentation

A 34-year old woman (G2P2) was referred for fetal echocardiography after the detection of enlarged right atrium and right ventricle in the

fetus on comprehensive obstetric ultrasound in the 32nd week of pregnancy. The fetal cardiac evaluation confirmed dilated right atrium and right ventricle, but no other abnormality was seen.

The patient was born at 38 weeks gestation by vaginal delivery and weighed 3.283 kg with Apgar scores of 8 and 9. Postnatal echocardiography revealed severe pulmonary hypertension, in addition to the previously noted dilation of the right atrium and right ventricle. The etiology of the pulmonary hypertension was not clear. Persistent neonatal pulmonary hypertension was the presumed diagnosis. The patient received supportive management for pulmonary hypertension in the neonatal intensive care unit. The pulmonary hypertension improved in 3-4 days, and the baby was discharged home with advice to follow up with pediatric cardiology in 3-4 months.

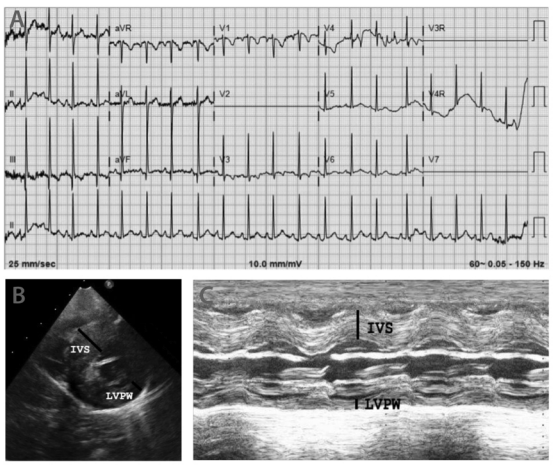

Fig. 1. (A) Standard 12-lead electrocardiogram shows high voltages and T-wave inversion, suggesting possible biventricular hypertrophy. (B, C) Echocardiogram of in parasternal short-axis view (B) and M mode (C) demonstrate marked asymmetrical thickening of the interventricular septum. IVS, interventricular septum; LVPW, left ventricular posterior wall.

The patient returned for routine cardiac follow-up at 6 months of age. He had no symptoms at that time. Development and weight gain were normal. An echocardiogram revealed marked asymmetrical septal hypertrophy suggestive of hypertrophic cardiomyopathy (Fig. 1B, Fig. 1C). No sub-aortic obstruction, mitral valve insufficiency, or sub-pulmonary obstruction was seen. His blood pressure was normal. An electrocardiogram revealed possible biventricular hypertrophy (Fig. 1A). A cardiac MRI was performed that revealed marked asymmetrical septal hypertrophy of the atrioventricular septum with no evidence of outflow tract obstruction or myocardial scarring. Storage disorder was considered unlikely. He underwent 24-hour Holter monitor which did not reveal any ventricular or supraventricular arrhythmia. An echocardiogram was performed on the baby's mother, father and only sibling. All three echocardiograms were normal. There was no evidence of hypertrophic cardiomyopathy in any of the family members.

Genetic analysis

After obtaining informed consent from the parents, blood and buccal cell samples obtained from the patient were submitted to the commercial lab GeneDx (GeneDx, Galthersburg, MD) for genetic analysis at 18 genes previously identified in association with HCM or HCM phenocopies. These were MYH7, TNNT2, MYBPC3, TNNI3, TPM1, ACTC, MYL3, MYL2, CAV3, MTTG, MTTI, MTTK, MTTQ, TNNC1, TTR, PRKAG2, LAMP2 (Danon disease), and GLA (Fabry disease). The coding regions and splice junctions of the 18 genes were enriched using a proprietary targeted capture system developed by GeneDx. These targeted regions were sequenced simultaneously by massively parallel (NextGen) sequencing on an Illumina platform (Illumina, San Diego, CA) with

Homo sapiens	sp|P12883|	LTRGKLTYTQ QLEDLKRQLE EEVKAKNALA HALQSARHDC DLLREQYEEE
Mus musculus	sp|Q91Z83|	LTRGKLTYTQ QLEDLKRQLE EEVKAKNALA HALQSARHDC DLLREQYEEE
Rattus norvegicus	sp|P02564|	LTRGKLTYTQ QLEDLKRQLE EEVKAKNALA HALQSARHDC DLLREQYEEE
Felis catus	sp|P49824|	LTRGKLTYTQ QLEDLKRQLE EEVKAKNALA HALQSARHDC DLLREQYEEE
Bos taurus	sp|Q9BE39|	LTRGKLTYTQ QLEDLKRQLE EEVKAKNALA HALQSARHDC DLLREQYEEE
Sus scrofa	sp|P79292|	LTRGKLTYTQ QLEDLKRQLE EEVKAKNALA HALQSARHDC DLLREQYEEE
Equus caballus	sp|Q8MJU9|	LTRGKLTYTQ QLEDLKRQLE EEVKAKNALA HALQSARHDC DLLREQYEEE

Fig. 2. The Ala 1328 residue of the cardiac MYH7 protein is highly conserved across species.

paired-end reads. Bi-directional sequence was assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing was used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads were achieved by NextGen sequencing.

Sequencing of the MYH7 gene identified a heterozygous G to A transition at nucleotide 3982 (p.Ala1328Thr or A1328T). The mutation had not been previously described in association with HCM. Genetic testing was performed on the patient's parents and only sibling. The father and brother were found to have the same mutation as the patient. The mutation was not seen in the mother.

Informed consent was obtained from all individual participants included in the study.

Discussion

This is the first report providing a detailed clinical presentation of a patient with a mutation, A1328T in MYH7, which has yet to be reported in association with HCM. The A1328T variant was identified once previously in an individual with dilated cardiomyopathy, but was classified as a variant of uncertain significance.[14] Our analysis aims to lend insight into the potential pathogenecity of this variant. The heterozygous G to A transition at nucleotide 3982, a position that is conserved across species (Fig. 2), results in the replacement of a non-polar, hydrophobic alanine residue with a polar, hydrophilic threonine residue. The A1328T variant was not observed with any significant frequency in approximately 6,500 healthy individuals of European and African American ancestry in the NHLBI Exome Sequencing Project (evs.gs.washington.edu/EVS), underlining the potential pathogenic nature of this mutation. PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), a program for predicting the potential impact of an amino acid substitution on the structure and function of a human protein, was used to evaluate the A1328T mutation. The resulting protein function score was 0.988, classified as "probably damaging" (benign: 0.00–0.20, possibly damaging: 0.20–0.85, probably damaging: 0.85–1.00). Furthermore, pathogenic variants in nearby residues (N1327K, A1332T) have been reported in the Human Gene Mutation Database in association with cardiomyopathy, supporting the functional importance of this region of the protein.[15] The effect of the N1327T mutation, in particular, on the structure and function of the beta-cardiac myosin protein has been shown to be more severe than the effects of other HCM-causing mutations at MYH7.[16]

In line with previous evidence on the great variability of phenotypic expression of the disease state in families affected by HCM8, we found that the presence of the responsible genetic mutation was not always associated with cardiac hypertrophy in this family. While the affected son was diagnosed with HCM at 6 months of age, the father and brother, both of whom also possessed the mutant gene, had normal echocardiograms at last evaluation (age 36 yr and 5 yr, respectively). This phenomenon has been correlated to the presence of modifier genes that may play a role in the phenotypic expression of cardiac hypertrophy in HCM.[17,18]

In conclusion, we describe a MYH7 gene mutation that has yet to be reported in a patient affected by HCM. The absence of the mutation from a control population and its theoretical effects on the physical properties of the coded protein suggest potential pathogenicity. Further studies are needed to better elucidate the role of this mutation in the development of HCM.

Acknowledgements

The authors thank the family for their participation in this study.

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