Research Article

A Novel Myosin Essential Light Chain Mutation Causes Hypertrophic Cardiomyopathy with Late Onset and Low Expressivity

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Hypertrophic cardiomyopathy (HCM) is caused by mutations in genes encoding sarcomere proteins. Mutations in MYL3, encoding the essential light chain of myosin, are rare and have been associated with sudden death. Both recessive and dominant patterns of inheritance have been suggested. We studied a large family with a 38-year-old asymptomatic HCM-affected male referred because of a murmur. The patient had HCM with left ventricular hypertrophy (max WT 21 mm), a resting left ventricular outflow gradient of 36 mm Hg, and left atrial dilation (54 mm). Genotyping revealed heterozygosity for a novel missense mutation, p.V79I, in MYL3. The mutation was not found in 300 controls, and the patient had no mutations in 10 sarcomere genes. Cascade screening revealed a further nine heterozygote mutation carriers, three of whom had ECG and/or echocardiographic abnormalities but did not fulfil diagnostic criteria for HCM. The penetrance, if we consider this borderline HCM the phenotype of the p.V79I mutation, was 40%, but the mean age of the nonpenetrant mutation carriers is 15, while the mean age of the penetrant mutation carriers is 47. The mutation affects a conserved valine replacing it with a larger isoleucine residue in the region of contact between the light chain and the myosin lever arm. In conclusion, MYL3 mutations can present with low expressivity and late onset.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disease caused by mutations in genes which encode sarcomeric proteins [1–4]. The most frequently affected genes are MYH7 [5], MYBPC3 [6], and TNNT2 [7], coding for the heavy chain of myosin, the myosin-binding protein-C, and troponin T, respectively. More than 200 mutations have been described in these genes. Furthermore, mutations in a number of other genes, for example, mitochondrial genes [8] have been associated with HCM, albeit at a much lower frequency. Among the rare causes of HCM [9] are mutations in MYL3 which encodes the myosin essential light chain (ELC) of the sarcomere [4, 10–19]. The ELC is located at the lever arm of the myosin head and stabilises this region (Figure 1) through interaction with the IQ1 motif [20, 21] at aminoacid residues 781–810 [22] in beta myosin. The N-terminus of ELC interacts with actin [23]. Although the precise functional role of ELC has not been defined [24], the protein belongs to the EF-hand family of Ca2+-binding proteins [25] and appears to be involved in force development and fine tuning of muscle contraction [26, 27]. The phosphorylation of a C-terminal serine residue has recently been shown to be of major significance for cardiac contraction [28] in zebra fish.

Figure 1: The structure of the myosin S1 fragment (red) with the essential (ELC) (yellow) and regulatory (RLC) (blue) light chains marked. The structure is based on the X-ray crystallographic data available in the form of the 2MYS pdb file [43].

Exon: 1 2 3 4 5 6 7 
Mutation:  
E143K E149M R154H  
V79L E56G A57G H155D E152K R81H G128C  

Figure 2: The genomic structure of MYL3 with the localization of known disease causing mutations indicated.

The described phenotypes of ELC mutations vary considerably [24], from HCM with an autosomal dominant inheritance and sudden death events, as in p.A57G [13, 17] and p.M149V [10], to a recessive phenotype where only homozygosity was associated with sudden cardiac death [14]. The penetrance is high in middle-aged mutation carriers [24].

Here, we describe a family with a novel MYL3 mutation characterised by low expressivity and late onset of disease.

2. Materials and Methods

The proband and family members were subjected to a full clinical evaluation including family history, physical examination, echocardiography, stress test, and 12-lead electrocardiograph (ECG). Disease status for the proband and family members was determined using conventional diagnostic criteria [29, 30]. All family members gave informed consent for genetic testing, while for testing of children, consent was obtained from the parents.

Genomic DNA was extracted from blood samples using a QIAamp DNA purification kit (Qiagen, Germany). DNA from the proband was screened for mutations in the coding regions of MYH7, MYBPC3, TNNT2, TPM1, TNN13, MYL3, MYL2, ACTC, TCAP, and CSRP3, and exons 3, 7, 14, 18, and 49 of TTN, as detailed in a previous study [5]. The primers and conditions used for screening MYL3 have previously been described [9]. Three-hundred ethnically matched Caucasian controls were used to establish frequencies of genetic variants.

Polyphen2 (http://genetics.bwh.harvard.edu/pph2/) was used to predict the effect of the identified ELC variant (p.V79I) [31].

The modelling of ELC and regulatory domain of MYH7 was performed using PDB Protein Workshop (http://www.rcsb.org/) and the PDB file 1WDC [32]. Homology studies and gene-structure studies were performed using BioEdit vers 7.0.9 [33] and Ensembl (http://www.ensembl.org/).

3. Results

3.1. Family History. The proband, a 38-year-old obese (BMI=44) man, was referred for clinical assessment following the identification of a cardiac murmur during routine health check. He was asymptomatic and had never experienced cardiac symptoms, systemic hypertension, or syncope. Echocardiography demonstrated asymmetrical septal ventricular hypertrophy becoming more concentric towards the apex (max WT 21 mm), a resting left ventricular outflow gradient (36 mm Hg) and left atrial dilation (54 mm) (Table 1).

Genotyping of 11 sarcomere genes showed him to be heterozygous carrier of a novel missense mutation (c.235G>A), p.V79I, in MYL3, which encodes the ELC of the ventricle. PolyPhen2 prediction of the p.V79I mutation indicated this variant to be “possibly damaging.” The family was offered screening for the mutation and clinical evaluation (see Figure 3 for the pedigree and Table 1 for clinical data on family members).

Examination of the family members resulted in the identification of nine additional heterozygous carriers of the p.V79I mutation, none of whom fulfilled the diagnostic criteria for HCM. Three mutation carriers, see Figure 3 and Table 1, exhibited a borderline phenotype, either based on the presence of an angulated septum in combination with T-wave inversion in AVL on the ECG or diastolic dysfunction in association with left axis deviation (LAD) or LAD and...
QRS deviation on the ECG. One mutation carrier, a 29-year-old male, exhibited intraventricular conduction defect (IVCD) as an isolated abnormality. The three borderline cases were 58, 55, and 36 years of age, whereas the remaining asymptomatic mutation carriers were 3, 8, 11, 17, 23, and 29 years of age. None of the family members shown in the pedigree had experienced cardiac events or sudden death, but the grandfather of the proband (I-1) was said to have died suddenly and unexpectedly at the age of 55 years; while a sister (II-6) to the mother had died suddenly and unexpectedly at the age of 19 years. No information was available as to the cause of these deaths that occurred 4-5 decades ago, and no DNA was available for analysis. As none of the mutation carriers, including the patient with HCM, had any symptoms, severe disease expression, or risk markers, the mutation was considered benign. However, all mutation carriers were offered a follow-up evaluation.

The mutation was not found in 300 controls and had not been registered as a variant in the NCBI SNP databases (dbSNP). Furthermore, there were no clinically affected or borderline cases among the nonmutation carriers.

The p.V79I is a novel variant, which is located in exon 3 in the region where two other HCM-associated missense mutations have previously been identified (Figure 2). Multiple species alignment of MYL3 in seven species indicate that valine is strongly conserved at this position (Figure 4). We examined the location of the p.V79I mutation in the three-dimensional structure of ELC by interpolating the human structure on the structure established for the scallop myosin regulatory domain (Figure 5). The mutation is located on the linker connecting the N- and C-terminal lobes and it is located just two aminoacid residues from the N-C connecting-loop interacting with the first IQ1 motif on myosin (aa 780–810) [34]. It is possible that the more nonpolar, longer side chain of the isoleucine residue may disrupt interaction of ELC with the positively charged lysine and arginine residues of myosin heavy chain that interface with this ELC region [35].

4. Discussion

We have described a patient with mild HCM associated with a novel, dominantly inherited, MYL3 mutation p.V79I. The mutation segregates with disease and is absent in 600 control alleles in a family in which no other mutation was identified in known HCM-associated genes. The phenotypic mutations in MYL3 in seven species indicate that valine is strongly conserved at this position (Figure 4). We examined the location of the p.V79I mutation in the three-dimensional structure of ELC by interpolating the human structure on the structure established for the scallop myosin regulatory domain (Figure 5). The mutation is located on the linker connecting the N- and C-terminal lobes and it is located just two aminoacid residues from the N-C connecting-loop interacting with the first IQ1 motif on myosin (aa 780–810) [34]. It is possible that the more nonpolar, longer side chain of the isoleucine residue may disrupt interaction of ELC with the positively charged lysine and arginine residues of myosin heavy chain that interface with this ELC region [35].

4. Discussion

We have described a patient with mild HCM associated with a novel, dominantly inherited, MYL3 mutation p.V79I. The mutation segregates with disease and is absent in 600 control alleles in a family in which no other mutation was identified in known HCM-associated genes. The phenotypic
presentation of the p.V79I mutation is that of classical HCM with asymmetric septal hypertrophy, just as previously described for the p.A57G mutation in two unrelated Korean families [13, 17] but distinct from the rare midcavitary obstruction previously described in patients with p.E143K [14], p.M149V, and p.R154H mutations [15]. Expression was reduced and/or the disease exhibited late occurrence, as nine mutation carriers were asymptomatic and did not fulfill diagnostic criteria for HCM, and no mutation carriers below 35 years of age were affected or even borderline affected. However, four of the mutation carriers, all >35 years of age, exhibited either a borderline phenotype or ICVD. Strictly defined, the mutation has a penetrance of 10%, but as many of the carriers are below 25 years. If we define the phenotype as borderline HCM with a late onset, we can say that all mutation carriers above the age of 35 exhibit this phenotype. However, a more precise definition of the penetrance of disease will depend on followup studies. Unfortunately, it was not possible to obtain more information about the sudden deaths occurring in the two potential mutation carriers, I-1 and II-6, 4-5 decades ago. However, their existence supports that the mutation carriers are offered clinical follow-up.

The presence of beta myosin containing the IQ1 motif that interacts with the N-C-loop of ELC harbours a number of HCM-associated mutations, that are, p.S782D [36], p.S782N, and p.S782H [37]. Supporting the concept that interference with the interaction between ELC and myosin is a pathogenetic substrate of HCM.

However, the finding of a clinically silent mutation with low expressivity and late onset raises the question of whether it should entail a detailed followup of mutation carriers. However, as most mutations in MYL3 have been associated with sudden death [24], it would seem prudent to conduct a clinical followup of mutation carriers. The potential relation between a MYL3-based genetic predisposition, the hypertrophic phenotype and obesity in the proband should also strengthen the recommendation to the proband to lose weight.

Authors’ Contribution

P. Andersen and P. Hedley both contributed equally to the study.

References


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