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Case Report

Phenotypic variations in carriers of predicted protein-truncating genetic variants in *MYBPC3*: an autopsy-based case series

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ABSTRACT

Our aim is to characterize predicted protein-truncating variants (PTVs) in *MYBPC3*, the gene most commonly associated with hypertrophic cardiomyopathy (HCM), found in a series of autopsied HCM cases after sudden unexpected cardiac death. All cases underwent death scene investigation, gross and microscopic autopsies, toxicological testing, a review of medical records, and a molecular analysis of 95 cardiac genes. We found four pathogenic PTVs in *MYBPC3* among male decedents. All variants were previously submitted to ClinVar without phenotype details. Two PTVs were located in the cardiac-specific myosin S2-binding (M) motif at the N-terminus of the *MYBPC3*-encoded cMyBP-C protein, and two PTVs were in the non-cardiac-specific C-terminus of the protein. The carriers of two cardiac-specific M-motif PTVs died at age 38 years; their heart weight (HW, g) and body mass index (BMI, kg/m^2) ratio were 34.90 (890/25.5) and 23.56 (980/41.6), respectively. In contrast, the carriers of two non-cardiac-specific C-terminal PTVs died at age 57 and 67 years, respectively; their HW and BMI ratio were 14.71 (450/30.6) and 13.98 (600/42.9), respectively. A detailed three-generation family study was conducted in one case. This study showed age-at-death variations among *MYBPC3* PTVs carriers in adult males.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is characterized by cardiac hypertrophy, myocyte hypertrophy and disarray, and interstitial fibrosis [1]. The prevalence of HCM is one in 500 [2]; it is an important cause of sudden unexpected cardiac death (SUCD) [3]. Several genes encoding sarcomere components have been linked to its pathogenesis, with disease-causing variants in *MYBPC3* accounting for the highest portion of clinically relevant cases [1]. While it has become evident that predicted protein-truncating variants (PTVs) in *MYBPC*3, encoding cardiac myosin binding protein C (cMyBP-C), are frequent causes of HCM [3], their genotype–phenotype relationship, particularly as it relates to risk of SUCD, is not well documented.

We characterize four cases of SUCD in which, at autopsy, the cause of death was determined to be sudden cardiac arrhythmia due to HCM. In each case, a PTV in *MYBPC3* was identified. We report a genotype–phenotype description with respect to the severity of the HCM and age at death. Case descriptions, including death circumstance, heart weight (HW) and body mass index (BMI) ratio, cardiac pathology, and toxicologic results, are presented first and followed by the molecular analysis of the PTVs in MYBPC3 for all cases.

At the New York City Office of Chief Medical Examiner, forensic investigation of sudden death includes:

1) Death scene investigation and family interview;
2) Complete gross autopsy; cardiac pathology and neuropathology examinations; microscopic examination of other important organs (e.g., liver, kidney, spleen, etc.).
3) Toxicologic testing;
4) Review of medical records; and
5) When indicated, microbiologic tests and metabolic screen.

In cases in which SUCD is suspected, next-generation sequencing of a panel of 95 genes associated with cardiac channelopathies and cardiomyopathies (Table S1) is routinely performed by an in-house College of American Pathologists-accredited Molecular Genetics Laboratory using methods previously described [4]. Following identification of a PTV, family testing was performed in conjunction with clinical evaluation at cardiogenetics clinics. The Institutional Review Board of New York

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City Department of Health and Mental Hygiene approved this study. Cases in this study were selected from a 2-year period of casework that met the criterion of an HCM phenotype with a pathogenic variant in *MYBPC3*. During this time, 268 SUCD cases were screened using the panel. Fifty-nine cases were noted to have hypertrophied hearts, of which 24 tested negative, one had a pathogenic variant in *LMNA*, one had a variant of uncertain significance (VUS) in *MYBPC3*, and five had PTVs in *MYBPC3*, four of which are featured in this report; one was removed because of drug overdose. The remainder had VUS in various genes.

2. Case descriptions

2.1. Case A

A 38-year-old black man with a past medical history (PMH) of hypertension and nonspecified psychiatric disorder collapsed while complaining of chest pain. At autopsy, his BMI was 25.5 kg/m^2 and his heart weighed 890 g (normal range 247–444 g for males with BMI of 25–29.9 kg/m^2) [5]. The heart was hypertrophied, with the lateral left ventricular wall measuring 2.4 cm, the right ventricular wall measuring 0.6 cm, and the interventricular septum measuring 3.6 cm thick, each greater than 95th percentile. Microscopically, the heart showed perivascular fibrosis, thickening of epicardial and intramyocardial blood vessels, and hypertrophy of the septal myocytes with disarray. Toxicology was negative. The cause of death was sudden cardiac arrhythmia due to HCM.

2.2. Case B

A 38-year-old Hispanic man with PMH of obesity, hypertension, and hyperlipidemia died during sleep while in bed with his wife. Medication found at the scene included multiple antihypertensive medications (hydroxyzine, hydrochlorthiazide, lisinopril, metoprolol, and amlodipine) and simvastatin, a cholesterol-lowering drug. At autopsy, his BMI was 41.6 kg/m^2 and his heart weighed 980 g (for males with BMI >30 kg/m^2, normal HW range is 273–575 g) [5]. The heart was dilated and asymmetrically hypertrophied with the thickness of lateral left and right ventricular walls measuring 2 cm and 0.8 cm, respectively, and the septum measuring 3.3 cm. Microscopically, the heart had myocyte hypertrophy, disarray, and interstitial fibrosis. Toxicology was negative. The cause of death was sudden cardiac arrhythmia due to HCM.

2.3. Case C

A 57-year-old Hispanic male with a PMH of hypertension and clinical suspicion of HCM was found unresponsive in his bedroom by family. A prescription for metoprolol was found in the home. On autopsy, his BMI was 30.6 kg/m^2. The gross measurement of the heart weighed 450 g, which is within the normal range of 273–575 g for BMI >30 kg/m^2 [5]. However, examination of the heart revealed pathognomonic signs of HCM: asymmetry of anterolateral septum, myocyte disarray, and biatrial cardiac dilation. The left ventricular wall was 1.3 cm thick; the right ventricle wall was 0.3 cm thick; and the interventricular septum was 1.3 cm thick, except in the anteroseptal area where it was 3 cm thick, showcasing asymmetrical hypertrophy with measurements that are above the normal range [6]. In addition, myxomatous degeneration of the tricuspid and mitral valve, and slight coronary artery atherosclerosis were found. The cause of death was sudden cardiac arrhythmia due to HCM.

2.4. Case D

A 67-year-old black male with a PMH of obesity, hyperlipidemia, chronic hepatitis B infection, and hypertension was found unresponsive on his kitchen floor by family. On autopsy, his BMI was 42.9 kg/m^2, and the heart weighed 600 g [5], well above normal range (normal range for males with BMI >30 is 273–575 g). The left ventricle wall measured 1.1 cm thick, and the right ventricle wall measured 0.2 cm in thickness, highlighting asymmetrical hypertrophy. The intraventricular septum measured 1.9 cm thick, which is above normal parameters [6]. The heart was hypertrophied, with asymmetric thickening of the interventricular free wall, a patchy focus of subendocardial fibrosis on the subaortic region of the outflow tract, and microscopically myocyte disarray with associated perivascular and interstitial fibrosis. There was also atherosclerotic cardiovascular disease. Toxicology was negative. The cause of death was sudden cardiac arrhythmia due to HCM.

3. Molecular analysis of the PTVs in *MYBPC3*

Four pathogenic PTV in *MYBPC3*, located in different functional domains of cMyBP-C (Fig. 1 and Table S2), were identified in the cases described.

Two PTVs in *MYBPC3*, p.Gly278GlufsTer22 and p.Phe295SerfsTer5, found in Case A and B, respectively, are frameshift variants located in

Case Information	Case A	Case B	Case C	Case D
Ratio (heart weight (g)/BMI (kg/m2))	34.90 (890/25.5)	23.56 (980/41.6)	14.71 (450/30.6)	13.98 (600/42.9)
Age-at-death, gender, ethnicity	38 years, male, African American	38 years, male, Hispanic	57 years, male, Hispanic	67 years, male, African American
PTVs in *MYBPC3*	p.Gly278GlufsTer22 g.11:47369221delC	p.Phe295SerfsTer5 g.11:47368998delA	p.Gln969Ter g.11:47356593G>A	c.3491-2A>T g.11:47354255T>A

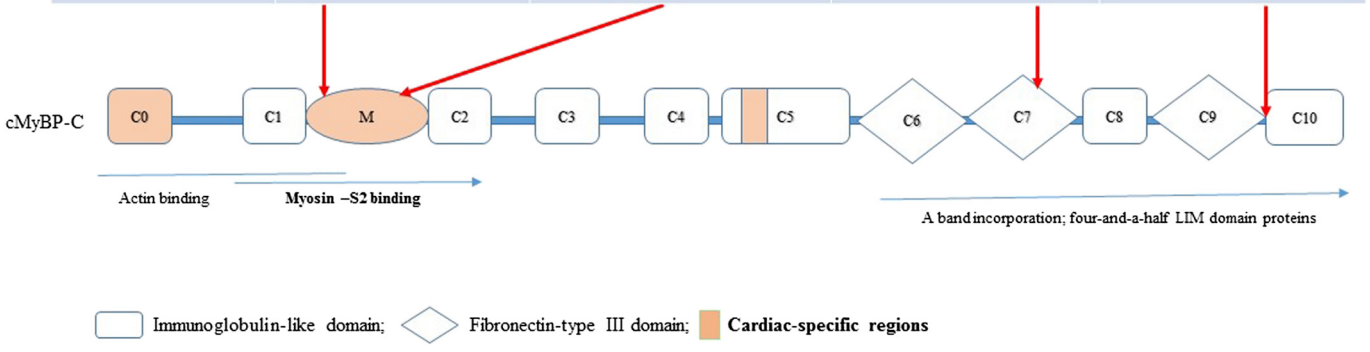

Fig. 1. Correlation of HCM phenotype with genotype of predicated PTVs located on the cMyBP-C protein. The ratio of HW (g) over BMI (kg/m^2), demographics (age at death, sex, ethnicity), and predicted PTV are indicated.