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Digenic inheritance of mutations in the cardiac troponin (*TNNT2*) and cardiac beta myosin heavy chain (*MYH7*) as the cause of severe dilated cardiomyopathy

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ABSTRACT

Familial dilated cardiomyopathy (DCM) is characterized by ventricular dilation and depressed myocardial performance. It is a genetically heterogeneous disorder associated with mutations in over 60 genes. We carried out whole exome sequencing in combination with cardiomyopathy-related gene-filtering on two affected family members to identify the possible causative mutation in a consanguineous Iranian family with DCM.

Two novel variants in cardiomyopathy-related genes were identified: c.247 A > C; p.N83H in the Troponin T Type 2 gene (*TNNT2*) and c.2863G > A; p.D955N in the Myosin Heavy Polypeptide 7 gene (*MYH7*). Sanger sequencing and co-segregation analysis in the remaining family members supported the coexistence of these digenic mutations in affected members of the family. Carriers of either variant alone were asymptomatic.

In summary, we find that digenic inheritance of two novel variants in DCM related genes is associated with a severe form of DCM. Exome sequencing has been shown to be very useful in identifying pathogenic mutations in cardiomyopathy families, and this report emphasizes the importance of comprehensive screening of DCM related genes, even after the identification of a single disease-causing mutation.

1. Introduction

Dilated cardiomyopathy (DCM) is a rare heart disorder, characterized by cardiac dilatation and reduced systolic function. It has an estimated prevalence of 1:2500 in the general population. Familial DCM is responsible for up to 50% of the cases reported (Haas et al., 2015) and an autosomal dominant pattern of inheritance is seen in most familiar DCM pedigrees (Mestroni et al., 1999). Mutations in over 60 genes encoding for cytoskeletal, sarcomeric, and desmosomal proteins have been found to cause different forms of DCM (Perez-Serra et al., 2016). We identified a consanguineous family of Iranian descent with characterised DCM (Table 1) in which we sought to identify the underlying mutation using a whole-exome sequencing (WES) approach in combination with cardiomyopathy-related gene-filtering.

2. Patient data

We identified a consanguineous family of Iranian descent (Fig. 1 and Table 1) with characterised DCM (including severe left ventricular dysfunction, normal heart valve function, no clinical evidence of ischemic heart disease). The proband, a 31-year-old man (IV-5) was diagnosed at age 30 with DCM. Echocardiography showed a mildly enlarged left ventricle (LV), global hypokinesia and severe impairment of the LV global function (ejection fraction 20–25%). Echocardiography in his 37-year old sister (IV-6) also diagnosed with DCM (since the age of 34) (IV-7) identified moderate global hypokinesia, grade I diastolic dysfuntion and her left ventricular ejection fraction (LVEF) was also moderately reduced (35%). The size of her left ventricle was normal and she had mild

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Table 1
Clinical characteristics of family members. Abbreviations: F, female; IVS, interventricular septum; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal end-diastolic diameter; LVIDs, left ventricular internal end-systolic diameter; M, male; MR, mitral regurgitation; n/a, not available; NYHA, New York Heart Association; PW, posterior wall; LBBB, left bundle branch block; TR, tricuspid regurgitation.

Pedigree ID	Sex	Current Age (yrs)	NYHA class	LVEF (%)	LVIDd (mm)	LVIDs (mm)	IVS (mm)	PW (mm)	Valves	ECG
III-9	M	65	n/a	n/a						
III-10	F	60	II	15-20%	5.6 cm	4.3 cm	0.7 cm	0.6 cm	Moderate secondary MR is seen, Moderate TR	LBBB
IV-4	M	42	I	60%	4.8 cm	3.0 cm	0.8 cm	0.8 cm	Normal	Normal sinus rhythm
IV-5	M	31	II	20-25%	5.7 cm	5.2 cm	0.8 cm	0.9 cm	Normal	Normal Sinus Rhythm
IV-6	F	37	I I	35%	5.2 cm	4.2 cm	0.9 cm	1.0 cm	Mild MR is seen	Normal Sinus Rhythm
IV-7	M	50	I	n/a						
IV-8	F	36	I	60%	5.0 cm	3.1 cm	0.7 cm	0.7 cm	Normal	Normal Sinus Rhythm
V-1	M	22	n/a	n/a						
V-2	F	20	n/a	n/a						
V-3	F	5	n/a	n/a						

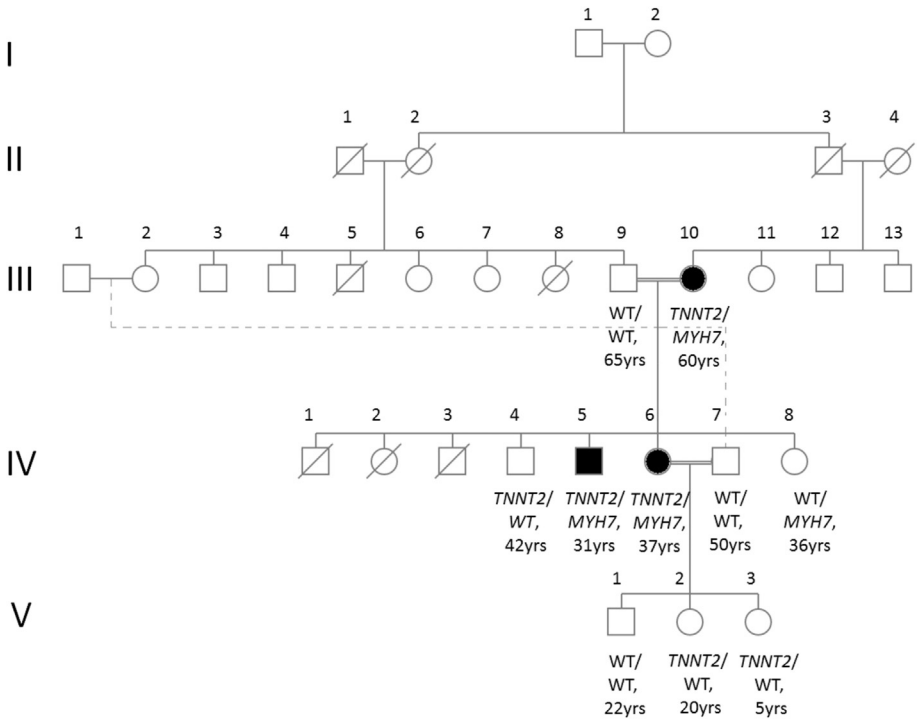

Fig. 1. Pedigree of family showing the age of individuals and segregation of the *TNNT2* and *MYH7* mutant alleles above and below respectively. WT=Wild-type alleles. Filled symbols indicate affected individuals. Diagonal lines across symbols indicate deceased individuals. IV-1, IV-2, IV-3 cause of death unknown, all <1 year of age.

mitral regurgitation (MR). Based on recent guidelines provided by the ESC working group on myocardial and pericardial diseases (Pinto et al., 2016), the phenotype in IV-5 and IV-6 can be more accurately defined as hypokinetic non-dilated cardiomyopathy as we did not observe significant dilatation and the left ventricular dysfunction could not be explained by abnormal loading conditions or coronary artery disease.

Their 60-year old mother (III-10) showed mildly enlarged left and right ventricles with severe systolic dysfunction, severe global hypokinesia, grade II diastolic dysfunction and severely reduced LVEF (15–20%). She underwent coronary artery bypass grafting (CABG) at the age of 52. Her mother had died at the age of 59 due to cardiac arrest, though the underlying cause is unknown and two of her siblings (III-11, III-12) underwent CABG at a similar age. III-11 a 60 y. o female was diagnosed with coronary artery disease at the age of 54. Echocardiography showed normal LV systolic function and size (LVEF:61%). RV and LA size were also normal and no other cardiac abnormalities were noted. III-12 a 56 y. o. male was diagnosed with coronary artery disease at the age of 50 and is hypertensive. Echocardiography showed good LV systolic function, LV size was normal, as was RV, LA and RA. No other cardiac abnormalities were noted. III-13 a 43 y. o. male showed normal systemic function by echocardiography at age 41, and is hypertensive. IV-1: died 28 days after birth (40 years ago), cause of death unknown and no additional medical data is available. IV-2: died 10 months after birth, cause of death unknown, no additional medical data available. IV-3: died shortly after birth, cause of death unknown, no additional medical data available. The two other living siblings of the proband (IV-4 and IV-8) appear to be healthy based on echocardiography and ECG, as do the three offspring of the affected sister (IV-6).

3. Methods

Genomic DNA samples from the two affected siblings (IV-5 and IV-7) were submitted for whole-exome sequencing (WES)

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