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Titin truncating mutations: A rare cause of dilated cardiomyopathy in the young

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ABSTRACT

Truncating mutations in the *TTN* gene are the most common genetic cause of dilated cardiomyopathy in adults but their role in young patients is unknown. We studied 82 young dilated cardiomyopathy subjects and found that the prevalence of truncating *TTN* mutations in adolescents was similar to adults, but surprisingly few truncating *TTN* mutations were identified in affected children, including one confirmed *de novo* variant. In several cases, truncating *TTN* mutations in children with dilated cardiomyopathy had evidence of additional clinical or genetic risk factors. These findings have implications for genetic testing and suggest that single truncating *TTN* mutations are insufficient alone to cause pediatric-onset dilated cardiomyopathy.

1. Introduction

Dilated cardiomyopathy (DCM) is the most common cardiomyopathy in the young with an annual incidence of 0.57 to 0.87 cases per 100,000 [1–3]. It is associated with high rates of cardiac transplantation and sudden death, particularly within the first year after diagnosis [2,3]. DCM may result from diverse inflammatory, metabolic, mitochondrial, neuromuscular or syndromic conditions, but in a majority of cases no specific cause can be identified. Up to 15% of young DCM patients have a positive family history suggesting a genetic etiology [1–4]. However, relatively few genetic analyses of primary early-onset DCM have been performed [5,6].

Truncating mutations in the gene encoding the giant sarcomeric protein titin (*TTN*tv) have recently been identified in 13% ambulatory, 22% end-stage and 27% familial cases of adult-onset non-ischemic DCM [7,8]. These findings indicate that *TTN*tv are the most common genetic cause of DCM in adults [9] and have profound implications for genetic testing of patients and their families. The contribution of *TTN*tv in young DCM patients is unknown. Here we report the results of genetic testing of cardiomyopathy-related genes, including the *TTN* gene, in 82 patients aged 21 years or less at the time of DCM diagnosis.

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2. Results

We enrolled 82 patients with early-onset DCM (age at diagnosis, birth to 21 years; mean age mean age, 10 years) for clinical and genetic studies, using protocols that were reviewed and approved by Boston Children's Hospital, the Royal Brompton and Harefield NHS Trust, the Kanuni Sultan Suleyman Training and Research Hospital, or the familial DCM research program at the Victor Chang Cardiac Research Institute. All subjects had clinical evaluations that included medical history, family history, ECG, and transthoracic echocardiography. Fifty-four subjects were male and 28 were females; all were of European ancestry.

All subjects had severe symptomatic heart failure: 63 subjects (77%) required heart transplantation (n = 52) or a left ventricular assist device (n = 11), and 4 subjects died prematurely. Twenty-seven subjects had a family history of DCM and 61 subjects (74%) had no identifiable clinical risk factors (Table 1, Supplemental Table 1).

Genes previously implicated in DCM, including *TTN*, were sequenced. Genomic DNA libraries that were constructed from subject samples were hybridized to custom capture probes and sequenced as described [7,8]. Seventy-seven (94%) patients were tested using one of two panels containing 66 or 69 genes, respectively. Sequencing data were aligned to the human reference genome hg19 and analyzed using a custom pipeline [7,8]. *TTN* variants were annotated using a Locus Reference Genomic sequence (LRG) and an inferred complete *TTN* meta-transcript (LRG_391_t1) [8]. Variant frequency was assessed using the ExAC database (http://exac.broadinstitute.org, accessed June 2015).

We also performed RNA sequencing of left ventricular tissue samples obtained from pediatric hearts (n = 6) and from control adult

Table 1
Clinical and genetic characteristics of subjects with childhood-onset DCM (0 to 14 years).

Subject	Sex	Age at diagnosis (or surgery)	Family history	DCM severity	ECG	Other risk factors	Truncating genetic variants[a]
DCM-2	M	Birth	No	Heart Tx			
DCM-25	M	Birth	No	Heart Tx		Ventricular septal defect	
DCM-26	F	Birth	No	Heart Tx		Ventricular septal defect	
DCM-33	M	Birth	No	Died 6 yr			
DCM-28	M	2 wks	No	LVEF 37%		Ventricular septal defect	*VCL* p.Q247X
DCM-21	F	6 wks	No	Heart Tx			
CW-III-1	F	6 wks	Yes	Heart Tx	1st degree heart block		
DCM-6	M	2 mth	No	Heart Tx		Atrial septal defect	*ACTN2* p.W259X
UK-1	M	(2 mth)	NA	Heart Tx			
UK-2	F	2 mth	No	Heart Tx			
DCM-1	F	3 mth	No	Heart Tx			
DCM-7	F	3 mth	No	Heart Tx			
DCM-20	F	3 mth	Yes	LVEF 32%			
DCM-27	F	3 mth	No	Heart Tx			
DCM-31	F	4 mth	NA	Heart Tx		Glycogen storage disease IV	
DCM-32	F	6 mth	No	LVEF 18%		Anomalous coronary arteries, Alagille syndrome	
UK-3	F	(10 mth)	NA	Heart Tx			
DCM-14	M	<12 mth	Yes	Heart Tx			
UK-4	F	(1 yr)	NA	Heart Tx			*TTN* p.R4749X
UK-5	M	1 yr	No	Heart Tx	Complete heart block		
DCM-22	M	18 mth	No	LVEF 16%			*TTN* p.Q4656X, *TBX20* p.297_-2 A > G
DCM-18	F	19 mth	Yes	Heart Tx			
DCM-29	M	22 mth	No	Heart Tx		Atrial septal defect	
TKC-14	F	23 mth	Yes	LVEF 56%			
UK-6	F	(2 yr)	NA	Heart Tx			
DCM-35	F	3 yr	No	Heart Tx		Ventricular septal defect	*PKP2* p.S837fs
UK-7	M	3 yr	No	Heart Tx			
DCM-5	M	6 yr	No	Heart Tx			
U-II-3	M	6 yr	Yes	Heart Tx			
DCM-16	F	7 yr	No	Heart Tx		Naxos syndrome[b]	
TKA-14	M	7 yr	Yes	Heart Tx			
TKE-12	M	7 yr	No	Heart Tx			
DCM-19	M	7 yr	No	Heart Tx		Juvenile polysaccharidosis	
DCM-17	F	8 yr	No	Heart Tx			
DCM-23	M	8 yr	Yes	LVEF 48%			
UK-8	M	8 yr	Yes	Heart Tx			*PKP2* p.L92X
DCM-4	F	9 yr	No	Heart Tx	1st degree heart block		
DCM-13	M	9 yr	NA	LVEF 12%			
TKZ-13	M	9 yr	No	Died 10 yr		LV non-compaction	
UK-9	F	9 yr	No	Heart Tx			
DCM-10	F	10 yr	Yes	Heart Tx			
UK-10	M	10 yr	No	Heart Tx		Chemotherapy	*TTN* p.T19345SfsX2
DCM-8	F	11 yr	No	Heart Tx		Glycogen storage disease IV	
UK-11	M	(11 yr)	NA	Heart Tx			
DCM-3	M	12 yr	No	Heart Tx, PPM	Complete heart block		
TKX-13	M	13 yr	Yes	LVEF >50%			
UK-12	M	13 yr	Yes	Heart Tx	Complete heart block		
UK-13	F	13 yr	No	Heart Tx			
DCM-12	M	14 yr	No	Heart Tx			
TKD-11	M	14 yr	No	LVEF 31%			
DCM-34	F	14 yr	No	Heart Tx			

LV, left ventricular; LVEF, left ventricular ejection fraction; NA, not available; PPM, permanent pacemaker; Tx, transplant.
[a] All patients were heterozygous for the variants listed, with the exception of DCM-35 who was homozygous for a *PKP2* p.S837fs variant.
[b] Clinical diagnosis of Naxos syndrome, *DSP* mutation-negative.