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CLINICAL LETTER

Genetic Dilated Cardiomyopathy Due to TTN Variants Without Known Familial Disease

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Dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement with reduced left ventricular ejection fraction.[1] Among those without coronary artery disease, ≈35% have a familial or genetic cause to their cardiomyopathy.[2] The majority of familial DCM is thought to be inherited in an autosomal dominant manner, and therefore, although it lacks specificity, family history is often used as a tool to both identify individuals who likely have a genetic cause and guide genetic testing, despite recent guidelines which highlight the insensitivity of this approach.[3] Isolated nonischemic DCM can have a genetic cause[4] due to a variety of factors including environmental contributions, de novo variants, limited availability of family history, recessive inheritance, and reduced penetrance. Genetic testing is often not considered in these individuals, especially if they present at age over 50 years. Therefore, there is limited information available regarding the frequency of genetic causes in these isolated cases.

After obtaining Institutional Review Board approval, we reviewed the family history and clinical characteristics of 83 probands with nonischemic DCM seen at the Johns Hopkins Center for Inherited Heart Disease between 2008 and 2020 whose genetic test results indicated a pathogenic or likely pathogenic variant. Participants either agreed to participate in a prospective registry (2018–2020) or fell into a retrospective review (2008–2017). Patients with known de novo variants were excluded. Twenty-seven of the identified individuals had pathogenic or likely pathogenic variants in the *TTN* gene. We report a case series of 6 patients presenting with nonischemic DCM with negative family histories in which subsequent genetic testing identified likely pathogenic variants in *TTN*. Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Patient demographics and clinical features are listed in Table 1A. Most commonly, patients presented with dyspnea and/or chest pain. Age of presentation ranged from 14 years to 64 years. Cardiac evaluations for all 6 individuals were consistent with nonischemic DCM. Stress tests and/or coronary angiographies were negative for ischemia for all except patient 6 who did not undergo specific evaluation for coronary artery disease given her young age. Of note, patient 6 did present in the context of marijuana use, but she denied use of other illicit drugs. Five of the 6 individuals had prominent arrhythmia, with either paroxysmal ventricular tachycardia or atrial fibrillation.

Three-generation family histories were obtained by a cardiac genetic counselor. None of the individuals had a known family history of cardiomyopathy, heart failure, or sudden death. Patient 4 did have a family history of coronary artery disease with her father undergoing coronary artery bypass surgery. Unfortunately, familial records were not available for review to confirm this negative history.

Patients 2, 3, 4, and 6 were referred for genetic counseling and genetic testing because they presented before the age of 50 years old without an alternative cause for heart failure which is standard procedure at our center. Patients 1 and 5 were self-referred for genetic

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Table 1A. Patient Demographics and Clinical Features Either

Study ID	Gender	Ethnicity	Age at presentation	Presenting feature	NYHA class	Ejection fraction	LVIDd, cm	ECG findings	Arrhythmias
1	Male	White	55	Dyspnea	II	20%	7.1	LBBB	…
2	Male	White	28	Dyspnea	II	45%	4.6	PVCs, AV block	VT
3	Male	Indian	48	Chest pain	I	40%	5.18	NSR	…
4	Female	White	64	PVCs	II	37%	5.68	PVCs, NSVT	…
5	Female	White	46	Dyspnea	IV	25%	5.9	PVCs	VT
6	Female	Black	14	Dyspnea, chest pain	IV	25%	5.45	PVCs, tachycardia	VT

Ejection fraction is either at the time of diagnosis or report available closest to the time of diagnosis. AV indicates ; LBBB, left bundle branch block; LVIDd, ; NSR, normal sinus rhythm; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular contraction; and VT, ventricular tachycardiac.

Table 1B. Pathogenic or Likely Pathogenic *TTN* Variant Identified

Study ID	Nucleotide change	Predicted amino acid change	Exon	PSI	ACMG criteria met	ACMG classification
1	c.98134G>T	p.Glu32712*	352	100	PVS1, PM2	Likely pathogenic
2	c.53901dupG	p.Arg17968AlafsX12	280	100	PVS1, PM2	Likely pathogenic
3	c.63025C>T	p.Arg21009*	304	100	PVS1, PM2	Likely pathogenic
4	c.96937C>T	p.Gln32313*	348	100	PVS1, PM2	Likely pathogenic
5	c.86627del	p.Pro28876fs	326	100	PVS1, PM2	Likely pathogenic
6	c.70162C>T	p.Arg23388*	326	100	PVS1, PM2	Likely pathogenic

The *TTN* gene transcript used is NM_001267550.2. ACMG indicates ; PM, pathogenic moderate; PSI, percent spliced in; and PVS, pathogenic very strong.

Table 1C. Other Variants of Uncertain Significance Identified

Study ID	Gene	Nucleotide change	Predicted amino acid change	ACMG criteria met	ACMG classification
1	*MYBPC3*	c.56T>C	p.Val19Ala	PM2, BP4	VUS
2	*TXNRD2*	c.591+1 G>T	IVS7+1 G>T	None	VUS
2	*KCNH2*	c.2854 C>T	p.Pro952Ser	BP4	VUS
2	*NKX2-5*	c.89 C>A	p.Ala30Asp	BP4	VUS
3	*LAMA4*	c.3796 T>G	p.Phe1266Val	PM2	VUS
3	*LAMA4*	c.3646 G>C	p.Val1216Leu	PM2	VUS
5	*DSG2*	c.1038_1040delGAA	p.Lys346del	BP3	VUS
6	*RBM20*	c.1024 C>A	p.Pro342Thr	PM2, BP4	VUS
6	*DMD*	c.652 G>A	p.Val218Ile	PM2, PM5, BP4	VUS

ACMG indicates ; BP, benign pathogenic; IVS, ; PM, pathogenic moderate; and VUS, variant of uncertain significance.

counseling based on personal concern of the cause for their cardiomyopathy. Genetic analysis was performed on either saliva or whole blood samples and included next-generation sequencing and deletion/duplication analysis. The specific genetic panel ordered varied between 2 commercial clinical laboratories, with a minimum of 50 genes associated with cardiomyopathy. Variants were classified using the American College of Medial Genetics Guidelines. Results are listed in Table 1B. In all 6 individuals, a pathogenic or likely pathogenic variant was identified in *TTN,* confirming a genetic cause for their cardiomyopathy. If a variant of uncertain significance was identified, these are listed in Table 1C as well.

Truncating variants in *TTN* are a common cause of DCM, particularly those occurring in the encoded A-band of titin, or in exons with constitutive expression and those spliced into a high proportion of left ventricular mRNA.[5] Additionally, they contribute to several other forms of DCM, including peripartum and those associated with alcohol and cancer chemotherapy.[4] Since ≈1% of people have truncating TTN variants, development of cardiac dysfunction probably involves genetic, or environmental modifiers in most of those with DCM.[4] Although familial DCM is considered a Mendelian trait, genetic DCM probably includes a much larger percentage of those whose cardiomyopathy would otherwise be considered idiopathic or due to prior viral infection.

Positive genetic test results not only have important implications for the patient but also have significant implications for family members.[3] In the 6 families reported here, genetic testing provided important information regarding familial risk, and allowed for

cascade screening. This case series illustrates that a negative family history should not exclude the possibility of a genetic cause for DCM as almost of quarter (22%) of patients with a pathogenic variant in *TTN* had an unremarkable family history. The older ages at the time of diagnosis for patients 1 and 5 suggest that neither age nor family history should exclude the consideration of genetic testing for nonischemic DCM.

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