Clinical Case
A 59-year-old female with a personal and family history of dilated cardiomyopathy (DCM) was referred by her cardiologist for genetic testing and counseling. The patient was initially diagnosed with DCM after presenting with dyspnea and fatigue. Her symptoms also included mild bilateral pedal edema, but she denied orthopnea, paroxysmal nocturnal dyspnea, palpitations, presyncope, or syncope. An electrocardiogram showed sinus rhythm and a left bundle branch block morphology (Figure 1). She underwent a gadolinium-enhanced cardiac magnetic resonance imaging that showed an enlarged left ventricle (LV; internal diameter at end diastole and systole were 6.5 cm and 5.4 cm, respectively), and the LV ejection fraction was ≈25%. Abnormal septal wall motion consistent with a bundle branch block was noted. All other walls of the LV were diffusely hypokinetic. Mild midmyocardial hyperenhancement suggestive of idiopathic DCM was present. The right ventricle was normal in size and function. There were no valvular abnormalities. Left heart catheterization showed no significant epicardial coronary artery disease. She was treated with a β-adrenergic antagonist, an angiotensinogen inhibitor, a mineralocorticoid antagonist, and a loop diuretic. Her symptoms improved; however, the LV remained enlarged and had poor systolic function with an ejection fraction of ≈30%. She subsequently underwent biventricular implantable cardioverter-defibrillator implantation.

At the time of her initial diagnosis, the patient’s family history was notable for a 86-year-old mother who had atrial fibrillation, the patient underwent targeted genetic testing that identified abnormalities (Figure 3). She was treated with a β-adrenergic antagonist, an angiotensinogen inhibitor, a mineralocorticoid antagonist, and a loop diuretic. Her symptoms improved; however, the LV remained enlarged and had poor systolic function with an ejection fraction of ≈30%. She subsequently underwent biventricular implantable cardioverter-defibrillator implantation.

During her initial evaluation, the patient underwent genetic testing that revealed a missense mutation (Thr220Ile) in the type V α subunit of the voltage-gated sodium channel (SCN5A). Variants in SCN5A have been shown to impair the sodium ion channel and are associated with DCM with and without conduction disease, Brugada syndrome, and other arrhythmias.1-4 The SCN5A Thr220Ile variant (dbSNP ID rs45620037) has reported allele frequencies of 0.1% (allele count of 78 of 22,106) in an aggregate population and 0.7% (allele count of 29 of 4,160) in the Non-Finnish European population according to the Exome Aggregation Consortium (http://exac.broadinstitute.org/variant/3-38655278-G-A).5 Probands that carry the SCN5A Thr220Ile variant have been reported to carry additional potentially pathogenic variants. In addition, ClinVar, an archive of reports of relationships among medically important variants and phenotypes, described conflicting interpretation of the pathogenicity of SCN5A Thr220Ile among seven submissions—two likely benign, 3 pathogenic, and 2 of uncertain significance (http://www.ncbi.nlm.nih.gov/clinvar/variation/9396/#clinical-assertions). Therefore, the contribution of the SCN5A Thr220Ile variant to the phenotype was unclear, suggesting that other genetic variants probably were contributing to the niece’s presentation. A more comprehensive panel was obtained, and a second variant was identified (Thr1507Ile) in the Titin (TTN) gene. In light of her niece’s test results, the patient was referred to our Adult Cardiovascular Genetics Clinic. After genetic counseling, the patient underwent targeted genetic testing that identified the SCN5A Thr220Ile variant; however, she did not harbor the TTN Thr1507Ile variant. The niece’s mother (proband’s sister) had a history of hypertension and was asymptomatic. Cardiac evaluation revealed an ECG with left axis deviation. Echocardiography showed normal LV dimensions.

Genetic Test Results
Four years after the patient’s initial diagnosis of DCM, her 27-year-old niece who lived out of state developed clinical left-sided congestive heart failure and DCM. Her echocardiogram revealed moderate LV enlargement, severe functional mitral regurgitation, and severe LV systolic dysfunction with ejection fraction of <20%. ECG had incomplete left bundle branch block, left axis deviation, and diffuse T-wave abnormalities (Figure 3). She was treated with a β-adrenergic antagonist, an angiotensinogen inhibitor, a mineralocorticoid antagonist, and a loop diuretic. Her symptoms resolved and at 9 months her LV size, systolic dysfunction, and functional mitral regurgitation were normalized.

Her niece underwent genetic testing that revealed a missense mutation (Thr220Ile) in the type V α subunit of the voltage-gated sodium channel (SCN5A). Variants in SCN5A have been shown to impair the sodium ion channel and are associated with DCM with and without conduction disease, Brugada syndrome, and other arrhythmias.1-4 The SCN5A Thr220Ile variant (dbSNP ID rs45620037) has reported allele frequencies of 0.1% (allele count of 78 of 22,106) in an aggregate population and 0.7% (allele count of 29 of 4,160) in the Non-Finnish European population according to the Exome Aggregation Consortium (http://exac.broadinstitute.org/variant/3-38655278-G-A).5 Probands that carry the SCN5A Thr220Ile variant have been reported to carry additional potentially pathogenic variants. In addition, ClinVar, an archive of reports of relationships among medically important variants and phenotypes, described conflicting interpretation of the pathogenicity of SCN5A Thr220Ile among seven submissions—two likely benign, 3 pathogenic, and 2 of uncertain significance (http://www.ncbi.nlm.nih.gov/clinvar/variation/9396/#clinical-assertions). Therefore, the contribution of the SCN5A Thr220Ile variant to the phenotype was unclear, suggesting that other genetic variants probably were contributing to the niece’s presentation. A more comprehensive panel was obtained, and a second variant was identified (Thr1507Ile) in the Titin (TTN) gene. In light of her niece’s test results, the patient was referred to our Adult Cardiovascular Genetics Clinic. After genetic counseling, the patient underwent targeted genetic testing that identified the SCN5A Thr220Ile variant; however, she did not harbor the TTN Thr1507Ile variant. The niece’s mother (proband’s sister) had a history of hypertension and was asymptomatic. Cardiac evaluation revealed an ECG with left axis deviation. Echocardiography showed normal LV dimensions.
depending on the panel; comprehensive cardiomyopathy panels that are not specific to DCM can range to >70 genes. The sensitivity (ie, the likelihood of identifying a genetic variant using these panels in DCM) of testing remains about the same; however, ranging from 25% in DCM without conduction disease to as high as 40% in DCM with conduction disease.

Figure 1. ECG of proband. Heart rate (HR) in bpm, P–R interval (PR) in milliseconds (ms), QRS duration (QRS) in ms, Q–T interval (QT) in ms, and corrected Q–T interval using Bazett formula (QTc) in ms are shown. aVF indicates augmented vector foot; aVL, augmented vector left; and aVR, augmented vector right.

Figure 2. Pedigree. Ages and clinical data are shown. Arrow denotes the proband. CAD indicates coronary artery disease. CVA indicates cerebrovascular accident.
Among patients who present with unexplained cardiomyopathy, \( \approx 50\% \) are attributed to idiopathic DCM.\(^8\) A familial component has been estimated to occur in \( \leq 40\% \) of these idiopathic DCM cases.\(^8\) The identification of an inheritance pattern in multiple affected individuals in a family supports further genetic testing. The most important initial step in evaluating a patient who may have familial DCM is to obtain a careful family history for at least 3 generations with a goal of elucidating relatives with histories of early-onset heart failure, syncope, sudden cardiac death without coronary involvement, and other muscular disease. The most common inheritance pattern observed with DCM with or without conduction disease is autosomal dominant; however, this pattern may be masked by variable clinical expressivity, reduced penetrance, and heterogeneous genetic involvement. The presence of other affected family members (eg, a pedigree consistent with familial DCM) may be the best predictor of informative genetic testing.

Interpreting Variants of Uncertain Significance

Variant interpretation, that is, classifying genetic changes identified from sequencing as pathogenic, likely pathogenic, or variants of uncertain significance (VUS), can vary at each laboratory offering such testing. This clinical scenario demonstrates several important and complex issues pertaining to the evaluation of a genetic cause of DCM. The *SCN5A* Thr220Ile variant replaces the polar threonine amino acid with an isoleucine amino acid in the transmembrane region of the sodium channel, and it has been associated with DCM. It was considered a pathogenic variant by the initial testing laboratory and a VUS by the second testing laboratory. This difference in assignment of genetic variants by testing laboratories highlights a challenge to clinicians. As mentioned, segregation analyses of variants may provide some insight into the potential pathogenicity of a VUS. In addition, the field of human genetics is rapidly evolving and variants that were initially classified as VUS may be reclassified as pathogenic in light of advances in knowledge.\(^11\text{-}13\) In cases of well-documented pathogenic variants, the clinician should consider predictive genetic testing in other family members. Importantly, cascade screening of VUS is not recommended.

The families that have been studied with the *SCN5A* Thr220Ile variant have been complex, and a clear causative role has not been established with certainty; thus, there is room for differences in interpretation of this variant. This is highlighted by the conflicting interpretation of the pathogenicity of the *SCN5A* Thr220Ile listed in the ClinVar database.

Titin is an essential component of the sarcomere and mutations in *TTN* have been implicated in several diseases, including limb-girdle muscular dystrophy, Salih myopathy, tibial muscular dystrophy, hereditary myopathy with early respiratory failure, and DCM.\(^14\text{-}15\) *TTN* Thr15072SerfsX6 is a truncating variant; changes that cause truncation of TTN have been implicated in \( \approx 25\% \) of familial cases of DCM and in \( \approx 18\% \) of sporadic cases of DCM. Conversely, TTN truncating variants have been found in \( \approx 3\% \) of healthy controls.\(^14\) The *TTN* Thr15072SerfsX6 is a novel genetic change that has not previously been published, but was classified as a pathogenic variant by the testing laboratory.

The proband did not carry the *TTN* Thr15072SerfsX6 suggesting that this variant may represent a VUS, underscoring the complexities of variant interpretation. The designation of pathological variants, either de novo or inherited, requires additional supportive data. In the de novo setting, negative clinical data in both patients and the absence of the variant (with confirmed paternity) is required. If the variant is
presumed not to be de novo, then her mother or father has a 50% chance of passing the variant to the proband. The mother was evaluated clinically and did not have DCM. However, the father has not been evaluated and we recommended clinical screening.

The use of multiple laboratories highlights the differences in available testing panels. The interpretation of variants can be complex; our patient’s SCN5A variant was downgraded to a VUS by the second laboratory. Given our patient’s clinical history and lack of carriage of the TTN variant along with evidence in the literature, one interpretation is that the SCN5A Thr220Ile variant is responsible for the DCM presentation in our patient. Alternatively, an unidentified variant in a gene other than SCN5A could explain the clinical presentation. Moreover, TTN Thr15072SerfsX6 and SCN5A Thr220Ile potentially contribute to the niece’s presentation, which is supported by her DCM presentation at a younger age when compared with our patient. These issues highlight the importance of cardiovascular genetics—namely the careful phenotyping of all at risk relatives, identifying as many variants as possible, and testing unaffected relatives to understand the potential segregation of variants.

Importance of Formal Evaluation of Relatives

Guidelines for genetic testing in familial DCM have been established. Genetic testing provides important information and can be complex; our patient’s SCN5A variant was downgraded to a VUS by the second laboratory. Given our patient’s clinical history and lack of carriage of the TTN variant along with evidence in the literature, one interpretation is that the SCN5A Thr220Ile variant is responsible for the DCM presentation in our patient. Alternatively, an unidentified variant in a gene other than SCN5A could explain the clinical presentation. Moreover, TTN Thr15072SerfsX6 and SCN5A Thr220Ile potentially contribute to the niece’s presentation, which is supported by her DCM presentation at a younger age when compared with our patient. These issues highlight the importance of cardiovascular genetics—namely the careful phenotyping of all at risk relatives, identifying as many variants as possible, and testing unaffected relatives to understand the potential segregation of variants.

Conclusions

This clinical case highlights some of the complexity and issues involved with genetic testing in DCM. The understanding of the genetic basis of DCM is rapidly evolving, requires iterative re-evaluation of VUS identified during genetic testing, and interpreting VUS in light of new functional data from ongoing investigations to correlate genotype to phenotype. Regardless, the field of cardiovascular genetics is rapidly evolving and identification of patients who may have familial DCM is critical in improving the health and lives of patients and families. Genetic testing for familial DCM should be considered and if appropriate and desired by the patient, referral to a clinic with expertise in this disease, and capabilities for genetic counseling should be pursued.

Disclosures

None.

References


(http://www.bruгадadrugs.org/drug-lists). The patient’s genetic testing results also had implications for other family members. As a result of genetic testing and counseling, our patient’s 30-year-old daughter was evaluated in our Adult Cardiovascular Genetics Clinic and underwent genetic screening that showed that she did not inherit the SCN5A Thr220Ile variant as mentioned above. The other daughter is consider-


**Key Words:** cardiomyopathies ◼ dilated cardiomyopathy ◼ edema ◼ genetics ◼ genetic testing
Complexities of Genetic Testing in Familial Dilated Cardiomyopathy
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doi: 10.1161/CIRCGENETICS.115.001157
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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