# Navigating Genetic and Phenotypic Uncertainty in Left Ventricular Noncompaction

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Once called spongiform cardiomyopathy for its distinct lace-like morphology, left ventricular noncompaction (LVNC) describes a ventricular wall with a prominent noncompacted layer; the excessive trabeculations and deep intertrabecular recesses are separated by thin compacted myocardium.[1,2] The diagnosis of LVNC is made primarily by imaging studies to index the thickness of the trabeculated layer to that of the compacted layer. With the advent of cardiac magnetic resonance allowing for high-resolution imaging of the myocardium, hypertrabeculation in the LV has become increasingly recognized in clinical practice. Significant individual variability exists in the extent of trabeculation, however, making its diagnosis extremely challenging. In addition, LVNC frequently occurs in association with other cardiomyopathies,[2] congenital heart defects,[3] neuromuscular disorders, and genetic syndromes. As a result, there has been ongoing debate as to whether LVNC is an independent disease entity, a clinical phenotype shared among various cardiomyopathies, or a mere bystander.[2] Contributing to this debate is the little data on the genetic architecture underlying LVNC. Although the next-generation sequencing has facilitated comprehensive and cost-effective approaches to identify potentially causative genetic variation in LVNC, the ability to identify such variation has outpaced our capacity to clearly interpret its clinical significance. Thus, in this era of rapidly evolving clinical imaging and sequencing technologies, there is a pressing need to integrate the accumulating imaging and genetic data in a large cohort, to better understand the entity that is LVNC.

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In this issue of *Circulation: Cardiovascular Genetics*, Jefferies et al[4] expand on the known genetic causes of LVNC and provide insights into the genetic landscape of LVNC and LV hypertrabeculation (LVHT) in the largest prospective cohort to date. By leveraging whole exome sequencing and cardiac magnetic resonance, the research team has assembled a deeply genotyped and phenotyped study population of 174 unrelated families with suspected or known LVNC. The result is a significant contribution to the literature, most notably in the evidence providing support for an evolving genetic and clinical spectrum of LVNC.

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## Diagnosis and Clinical Features

The clinical manifestations of LVNC vary widely, from no symptoms, to thromboembolism, heart failure, arrhythmia, and sudden cardiac death. Echocardiography is the first-line diagnostic modality to detect abnormal trabeculations. Several echocardiographic diagnostic criteria[5–7] have been proposed to define LVNC, most of which focus on a noncompaction/compaction ratio. Cardiac magnetic resonance provides more detailed anatomic and functional information of the myocardium compared with echocardiography and has an added benefit of detecting fibrosis via late gadolinium enhancement. In 2005, Petersen et al[8] proposed cardiac magnetic resonance criteria to diagnose pathological noncompaction based on the presence of bilayered myocardium with the noncompaction/compaction ratio is >2.3 at the end diastole.[8] In the absence of consensus criteria for the diagnosis of LVNC, the Petersen criteria have become the most widely adopted in both clinical and research settings and are the criteria used in the present study by Jefferies et al.[4] Although many other criteria have since been proposed, including LV noncompacted mass >20% of the total mass, wide inconsistencies and poor specificity remain. For instance, in the MESA study (Multi-Ethnic Study of Atherosclerosis) which enrolled patients without clinically recognized cardiovascular disease,[9] ≤43% of participants satisfied LVNC diagnostic criteria, having at least 1 of 8 myocardial segments with a ratio >2.3. The variability in the extent of trabeculations is a key challenge in distinguishing normal variants from pathological trabeculations.[10] This heavy reliance on imaging description of trabeculations, without consensus on the diagnostic criteria, makes it difficult to understand the disease process and mechanism of LVNC.

## Molecular Underpinnings of LVNC

The underlying molecular mechanism for LVNC remains largely unknown, but may be related to a failure of compaction of trabecular myocardium during embryogenesis. This notion of developmental arrest, however, has been challenged because of a lack of evidence that the embryonic trabeculation directly contributes to the formation of the compacted layer of the myocardium.[10,11] In addition, recent reports of acquired, and potentially reversible, forms of prominent trabeculations in athletes[12] and pregnant women[13] raise a possibility of mechanistic heterogeneity and nongenetic contribution. Whether

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there is a final common pathway in the pathogenesis of LVNC is yet to be determined.

Presently, although controversial, LVNC is considered to be primarily a genetic condition. It frequently manifests as a monogenic disease, exhibiting various forms of inheritance with reduced penetrance and highly variable disease expression.[14] Approximately 20% to 30% of patients with LVNC currently have an underlying pathogenic variant identified, mostly in sarcomeric genes, and less frequently in Z-disc, cytoskeletal, or mitochondrial genes.[15,16]

To further delineate genetic causes of LVNC and establish genotype–phenotype relationships, Jefferies et al[4] performed whole exome sequencing along with detailed phenotypic/magnetic resonance imaging characterization on 190 patients from 174 unrelated families with LVNC or LVHT, and 425 control subjects. In whole exome sequencing analysis of each individual, the authors searched for rare and predicted damaging variants falling in 54 LVNC-associated genes, or genes previously implicated in other cardiomyopathies.

In 102 of 174 (59%) unrelated patients, they identified 138 rare, protein-altering variants in LVNC or other cardiomyopathy-associated genes. Importantly, these rare variants are considered potentially contributory, as opposed to established causative variants. Although many of the variants identified in this cohort will indeed be disease causing, others may not have sufficient evidence or may represent benign bystanders. Large scale sequencing analyses of the general population have firmly established that rare and private variation is common; thus, the vast majority of such variants are unlikely to individually cause rare, Mendelian conditions.[17]

To date, many established LVNC genes are also known hypertrophic cardiomyopathy and dilated cardiomyopathy genes.[14] Given wide clinical heterogeneity observed in this cohort, combined with interrogation of a broader set of genes, it is perhaps unsurprising that most genes (46/54) with identified rare candidate variants were cardiomyopathy genes, without a previously established link to LVNC. It is intriguing, however, that these rare candidate variants were found in only 8 previously established LVNC genes. Moreover, there was no significant difference in the proportion of the patients carrying the LVNC gene variants between the LVNC/LVHT and control groups (20.35% to 21.5%, $P$=0.74). We suspect that this apparent weak tie to the established LVNC genes could be related to various factors. First, this may stem from their broad inclusion criteria—patients were recruited if they had suspicious clinical presentations and imaging findings, without a set noncompaction/compaction ratio threshold on echocardiography. In addition, this may call into question the true significance of some of the previously well-characterized LVNC genes. In final, as the authors state, the ability to confidently identify copy number variants from whole exome sequencing data is currently challenging; therefore, it is possible that such variants involving LVNC genes could have been missed.

## Mutational Burden?

Independent of its previous link to LVNC, Jefferies et al[4] find clear correlation between overall mutational burden and the severity of the disease phenotype. The patients with rare candidate variants in LVNC or cardiomyopathy genes, compared with those without, were more likely to have preexisting neuromuscular disease and LV dysfunction. These patients were also more likely to satisfy LVNC diagnostic criteria, with more extensive trabeculation and fibrosis evidenced by the presence of late gadolinium enhancement. Although limited because of the small number of patients with ≥2 rare candidate variants (28 patients), a graded relationship was observed between the number of variants present and disease severity. This observation suggests that LVNC likely falls on a clinical spectrum that includes both a Mendelian disease and a more complex entity with variable clinical presentation and genetic risk contributors.

## Overlap With Sarcomeric Cardiomyopathy

Recognizing the clinical overlap between LVNC and other genetic cardiomyopathies, several studies have previously examined sarcomeric genes in LVNC cohorts and identified pathogenic variants in 17% to 29% of probands.[18,19] Consistent with these observations, sarcomeric variants were observed frequently (32%) in the present study by Jefferies et al.[4] Although the pathogenicity of many of these novel sarcomeric variants remains to be elucidated, the presence of sarcomeric variants was associated with increased trabeculations, late gadolinium enhancement, and a nonsignificant trend toward LV dysfunction. This is the first study suggesting the presence of sarcomeric variants as a predictor of worse clinical severity in LVNC. Additional studies are required to further explore this association.

## Titin and LVNC

Recently, Hastings et al[20] first described the potential role of *TTN*, the giant sarcomeric protein best known for its function as a molecular spring, in the development of LVNC. This study identified a missense variant, p.A178D, in *TTN* via whole genome sequencing and linkage analysis of a 3-generation family affected by autosomal dominant LVNC. The variant was found to result in structural changes in titin markedly impairing its binding to telethonin, a potentially important initiating step in the pathogenesis of LVNC.

Herein, Jefferies et al[4] identified truncating variants in *TTN* (*TTN*tv) in 14 of 174 LVNC/LVHT patients. Interestingly, 8 of these 14 patients had reduced LV ejection fraction. These truncating variants mainly appeared in the *TTN* A-band or other constitutively expressed exons, as is also reported in dilated cardiomyopathy.[21] In addition, they observed significant enrichment of *TTN*tv for co-occurrence with other rare candidate variants, which seems to be in alignment with accumulating data that a secondary factor (genetic or environmental) is often required for a clinical phenotype to manifest with *TTN*tv variants. To our knowledge, this is the first study demonstrating the association of *TTNtv* variants with LVNC, establishing the importance of this gene in LVNC. Moreover, considering the significant clinical and genetic overlap between LVNC and dilated cardiomyopathy, it is reasonable to speculate on shared pathogenesis.

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## Possible Link to Arrhythmia?

An intriguing finding of this study is the enrichment of variants observed in several genes associated with long-QT syndrome in this LVNC/LVHT cohort.[4] Twenty-seven patients (15%) were found to carry rare (minor allele frequency <1%), predicted deleterious variants in genes including *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1,* and others.

There have been only a small number of case reports describing potential associations between long-QT syndrome genes (eg, *KCNQ1* and *SCN5A*) and LVNC to date.[22] Variants in other primary arrhythmia genes such as *HCN4* and *RYR2*[23,24] have also been reported in association with LVNC. Excitation–contraction coupling, the fundamental myocardial process of electric stimulation triggering mechanical force generation, by definition implies a tight link between ion channels and sarcomeric contraction. Thus, one might anticipate that a primary ion channel defect could lead to dysfunction of cardiac muscle. One known example lies in *SCN5A*, the gene encoding sodium voltage-gated channel α-subunit 5, and implicated in arrhythmogenic dilated cardiomyopathy.[25] It is plausible that variants in this and potentially other ion channel genes could also play a role in LVNC. Thorough variant interpretation, while always required, is particularly critical in this scenario when attempting to establish new gene–disease relationships. For instance, Jefferies et al[4] observed 1 *SCN5A* variant, p.P1973A, to be particularly common in their cohort (7 of 174 patients). However, this variant is currently present in ClinVar (by an alternative name, p.P2006A; variation ID no. 68024),[26] where it is called likely benign by 4 clinical laboratories and a variant of uncertain significance by 1 clinical laboratory. In addition, *SCN5A* has been shown to have high background rates of rare variation.[27] Thus, although a potential modifying role could still be at play, this variant is unlikely to, by itself, represent a primary cause of LVNC. This highlights a key challenge in determining the clinical significance of identified sequence variants. Even in families harboring clear pathogenic variants causing Mendelian disease, we often observe widely variable phenotypes (eg, onset, severity, penetrance). Nongenetic factors and genetic modifiers likely play a role, but we have yet to develop approaches that can adequately determine their clinical impacts, both individually and cumulatively. Thus, until our ability to interpret clinical variants shifts and we can appropriately account for such variations when interpreting clinical variants, we will remain limited in our ability to incorporate these novel findings into clinical practice.

Although premature to establish a relationship between long-QT syndrome and LVNC, abnormal electric processes might indeed increase the LVNC myopathic susceptibility. As sequencing becomes increasingly ubiquitous, enabling interrogation of broader sets of genes not previously linked to LVNC, we cautiously anticipate that a link between primary arrhythmic variants and myopathic phenotypes will emerge. Further dissecting this link will yield invaluable insights into challenging clinical cases in which both electric and mechanical processes of the heart are disrupted.

## Clinical Implications

By assembling the largest cohort of LVNC patients with deep clinical imaging and genetic sequencing data to date, Jefferies et al[4] shed light on the evolving clinical entity that is LVNC and provide evidence that seems to support LVHT and LVNC as falling on a continuum of genotypic disease.

Important questions remain in understanding the genetic landscape of LVNC, before incorporating much of these findings into clinical practice. For instance, if LVNC exists on a clinical spectrum with mutational burden playing a key role, we must determine how to identify and interpret contributory rare variants and distinguish these from benign bystanders. Recent work by Homburger et al[28] and Alamo et al[29] demonstrate promising use cases to address this, by combining knowledge of the protein structure of several sarcomeric proteins, with computational comparisons of population and cardiomyopathy cohorts, to identify regions enriched for disease-causing variants. These identified critical regions can assist in adjudicating the significance of genetic variants, particularly the often-elusive novel missense variants. Although further efforts are required to better understand the mechanisms leading to LVNC, these types of approaches may help in interpreting complex phenotypic and genotypic presentations.

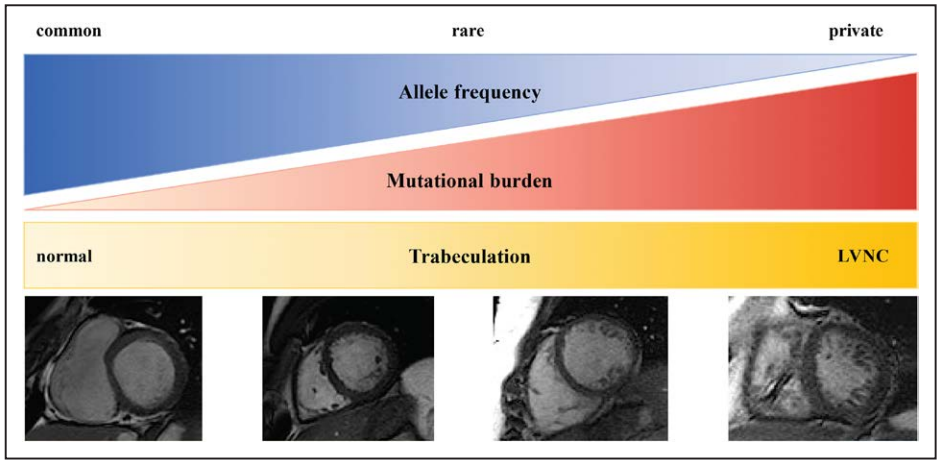


**Figure.** Allele frequency, mutational burden, and the risk of pathogenic trabeculation. LVNC indicates left ventricular noncompaction.

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As our understanding of LVNC evolves, applying this knowledge of potentially contributory genetic variants to conventional imaging studies may help distinguish pathogenic trabeculations from normal variants in the general population. In addition, given the observed association between LVNC and genes involved in sarcomeric cardiomyopathies and primary arrhythmias, the presence of LV dysfunction and arrhythmias may assist when determining significance of the observed trabeculation. When the clinical and family history points toward pathological trabeculation, one might consider ordering genetic testing panels that include the known genes implicated in various cardiomyopathies (such as a comprehensive cardiomyopathy panel). Until a better understanding of LVNC as a clinical and genetic entity is achieved, however, we currently caution against overly broad sequencing when ordering clinical genetic testing for this condition. Although evidence supporting several cardiomyopathy genes' involvement in LVNC is clear, the new link of arrhythmia genes and LVNC remains premature. In final, although Jefferies et al[4] did not specifically assess for clinical outcomes, recent studies suggest the presence of LV dysfunction and late gadolinium enhancement to be significant prognostic markers for LVNC.[30] Thus, one could postulate that the mutational burden and presence of specific gene variants (eg, in sarcomeric genes) may also be useful in further stratifying risk.

Although much remains to be elucidated, the findings from this study significantly contribute to the literature and identify key areas for future research. Jefferies et al[4] reinforce the importance of genetic contribution in the pathogenesis of LVNC/LVHT and highlight the significance of mutational burden in both establishing the diagnosis and predicting clinical manifestations (Figure).

## Disclosures

E.A. Ashley has an ownership interest and is an advisor for Personalis Inc. He is an advisor for Sequence Bio, Myokardia, Heart Metabolics, Genome Medical, and Avive. The other authors report no conflicts.

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