



Left ventricular noncompaction: a disorder with genotypic and phenotypic heterogeneity – a narrative review

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Background and Objective: Left ventricular noncompaction (LVNC) is a cardiomyopathy characterized by excessive trabecular formation and deep recesses in the ventricular wall, with a bilaminar structure consisting of an endocardial noncompaction layer and an epicardial compacted layer. Although genetic variants have been reported in patients with LVNC, understanding of LVNC and its pathogenesis has not yet been fully elucidated. We addressed the latest findings on genes reported to be associated with LVNC morphogenesis and possible pathologies to understand the diverse spectrum between genotype and phenotype in LVNC. Also, the latest findings and issues related to the diagnosis of LVNC were summarized.

Methods: This article is written as a commentary narrative review and will provide an update on the current literature and available data on common forms of LVNC published in the past 30 years in English through to May 2022 using PubMed.

Key Content and Findings: Familial forms of LVNC are frequent, and autosomal dominant mode of inheritance has been predominantly observed. Several of the candidate causative genes are also mutated in other cardiomyopathies, suggesting a possible shared molecular and/or cellular etiology. The most common gene functions were sarcomere function whereas genes in mice LVNC models were involved in heart development. Echocardiography and cardiac magnetic resonance imaging (CMR) are useful for diagnosis although there are no unified criteria due to overdiagnosis of imaging, poor consistency between techniques, and lack of association between trabecular severity and adverse clinical outcomes.

Conclusions: This review reflects the current lack of clarity regarding the pathogenesis and significance of LVNC and showed the complexity of imaging diagnostic criteria, interpretation of the role of LVNC as a cause, and uncertainty regarding the specific genetic basis of LVNC.

Keywords: Left ventricular noncompaction (LVNC); phenotype; genotype

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Introduction

Left ventricular noncompaction (LVNC), also used synonymously as hypertrabeculation, is a cardiomyopathy characterized morphologically by two layers of highly thickened myocardium, numerous prominent trabecular processes, and deep intertrabecular recesses that connect to

the left ventricular (LV) cavity (1,2). LVNC is the third most common cardiomyopathy after dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) (3). LVNC has a broad morphologic spectrum and can appear alone or in association with DCM, HCM, early onset of arrhythmias, and congenital heart disease (CHD) (4).

The clinical presentation of LVNC is highly variable, ranging from asymptomatic to severely symptomatic, including congestive heart failure (HF), arrhythmias, and thromboembolism (1,5-7). To date, genetic variants have been reported in patients with LVNC (5). Inheritance of LVNC is predominantly autosomal dominant, although X-linked recessive, autosomal recessive, and mitochondrial inheritance also occurs (6,8,9). However, despite the first clinical description of LVNC appearing 30 years ago (1), understanding of LVNC and its pathogenesis has not yet been fully elucidated, especially when compared to other cardiomyopathies such as HCM or DCM.

Therefore, we addressed the latest findings on genes reported to be associated with LVNC morphogenesis and possible pathologies in human or non-human model organisms to understand the diverse spectrum between genotype and phenotype in LVNC. Moreover, we summarized the latest findings and issues related to the diagnosis of LVNC. We present the following article in accordance with the Narrative Review reporting checklist (available at: <https://cdt.amegroups.com/article/view/10.21037/cdt-22-198/rc>).

Methods

Relevant studies published in the past 30 years to May 2022 were identified by PubMed searches using different combinations of the following search terms: “left ventricular noncompaction” and “hypertrabeculation”. The reference lists of relevant articles were also reviewed and additional articles were identified. Publications with relatively low reliability and non-English language publications were excluded. Data extraction was based on relevance to the topic rather than implementing a systematic approach to article extraction. This paper discusses existing data from the perspective of cardiologists caring for LVNC patients, is written as an expository narrative review, and provides an update on the current literature.

Epidemiology

The incidence of LVNC is reported to be 0.81 per 100,000 for infants, 0.12 per 100,000, and 50 per 100,000 for adults (3,10). Children are thought to account for 9.5% of all cardiomyopathies (5). LVNC is more common in males (62%) than in females (11).

Subtype

LVNC is often classified according to phenotype as follows (8,12,13).

- (I) Isolated LVNC: normal cardiac function, with relatively good prognosis;
- (II) LVNC with arrhythmias: normal cardiac function but with arrhythmias, often associated with ventricular arrhythmias, which is a poor prognostic factor. The arrhythmia phenotype is identified if a systolic function is preserved and LV size and wall thickness are normal but underlying arrhythmias are present, usually identified at diagnosis;
- (III) Dilated LVNC: as in DCM, but with LV dilation and reduced contractility; often a poorer prognostic factor than DCM;
- (IV) Hypertrophic LVNC: as in HCM, but with LV thickening and impaired diastolic function. The prognosis is often similar to that of HCM;
- (V) Restrictive LVNC: with enlargement of the left atrium or both atria and impairment of LV diastolic function. As with restrictive cardiomyopathy, the prognosis is often poor;
- (VI) LVNC associated with CHD: complications such as atrial septal defects, ventricular septal defects, and Epstein’s disease have been reported and present in 7% of patients (11). Compared to patients with CHD without LVNC, LV contractility is often reduced (14).

The MOGE(S) nomenclature may provide a clear basis for classifying phenotypic variations of LVNC. This nomenclature includes various aspects of cardiomyopathy, such as morphofunctional features (M), organ involvement (O), genetic patterns (G), etiologic annotation (E), and patient functional status by American college of cardiology/ American Heart association (ACC/AHA) staging or New York Heart Association (NYHA) functional class. MOGE(S) can be used to fix phenotypes at baseline and record follow-up data and may be useful to consider genotype-phenotype correlation (15).

Genetics

The genetic background of LVNC is both isolated and familial. A high percentage (28%) of familial cases were found to be characterized by genetic diversity, with autosomal dominant, autosomal recessive, or mitochondrial

gene abnormalities as well as X-linked inheritance suspected in some families (11,16). Approximately 40% are thought to have constant genetic variants (17). Many genes should be considered that the association with LVNC is weak since these are based on single reports and the data have not been replicated. van Waning *et al.* conducted a systematic review and found that 80 genes were genetic causes of LVNC (Table 1) (16). Most genetic causes were single variants (85%), of which autosomal dominant missense variants were the most common (55%) (16). X-linked genetic abnormalities accounted for 7% of patients, mostly *TAZ* (6%). More than 50% of the genetic defects were reported in sarcomere genes, the most common being *MYH7* (25%). Arrhythmia gene variants were found in 11%, especially in *HCN4* (4%). Rojanasopondist *et al.* sought to systematically analyze and score the strength of all published evidence linking each gene to LVNC, and then verified which molecular pathways are likely to be involved in the pathogenesis of LVNC (18). They identified 189 genes associated with LVNC; 11 were classified as definitive, 21 as moderate, 140 as limited, and 17 were classified as no evidence. Of the 32 genes classified as definitive or moderate, the most common gene functions were sarcomere function (34%), transcription/translation regulator (19%), mitochondrial function (9%), and cytoskeletal proteins (9%) (Table 1). In addition, 18 genes (56%) were involved in the presentation of noncardiac syndromes. In addition, there were 20 genes shared between LVNC and DCM, and 18 genes shared between LVNC and HCM. Analysis of pathways and protein-protein interactions suggested that LVNC, more than DCM and HCM, is responsible for abnormalities in cardiomyocyte development and differentiation during cardiomyogenesis.

Some mitochondrial DNA (mtDNA) variants may be associated with LVNC (19-23). Cardiomyopathy has been reported in up to 20% of patients with mitochondrial disease (24). The cardiac phenotype typically seen in patients with mtDNA variants is characterized by mild, usually concentric LV enlargement, while LVNC occurs rarely (20,21). mtDNA variants include nuclear gene variants in 51%, mtDNA point variants in 40%, mtDNA single large deletions in 5%, and chromosomal abnormalities in 4% (25).

Neuromuscular disorders were present in an average of 5% (11). In neuromuscular disorders, the DMD genetic abnormality causing Duchenne and Becker muscular dystrophy also causes LVNC in boys.

Complex and rare monogenic syndromes with cardiac

and non-cardiac abnormalities should be considered secondary to origin or cause of LVNC, such as Danon disease caused by *LAMP2* gene variants and Anderson-Fabry disease caused by *GLA* gene variants, which do not show typical LVNC (26-28). Periventricular dysplasia and rare syndromes, such as microcephaly, glucocorticoid deficiency, and Coffin-Lowry syndrome caused by *RPS6KA* gene variants, may occasionally manifest LVNC (29-37).

In addition to single gene abnormalities, LVNC can be seen in association with chromosomal disorders. Syndromes with LVNC have been reported in patients with chromosomal disorders, including 1p36 deletion syndrome, interstitial 1q43-q43del, del(1)(q) syndrome, del5q35; 7p14.3p14.1 deletion, 8p23.1 deletion, 1 del syndrome, 18p subtelomere deletion, 22q11.2 deletion syndrome, 22q11.2 distal deletion syndrome, 13 and 18 trisomy, tetrasomy 5q35.2-5q35, Robertson translocation 13;14, 45,X/46XX, and 45,X/46,X,i(Y)(p11), among others. Chromosomal abnormalities accounted for 6% of patients, and 88% of them were diagnosed in childhood. Most chromosomal aberrations are isolated cases (38,39).

Pathogenesis

Two hypothesized pathogenesis mechanisms are proposed for LVNC: the congenital hypothesis during the embryonic period, and the acquired hypothesis after birth.

Congenital hypothesis

In congenital LVNC, the process of compaction is thought to be arrested, leaving behind trabeculated fetal myocardium and, conversely, a hypoplastic compacted myocardium. During mammalian heart development, the ventricle undergoes a series of morphogenetic events (40-42), including trabeculation and compaction (Figure 1) (43). Ventricular formation consists of four steps and involves multiple signals originating from the endocardium, myocardium, and epicardium. The first step is the formation of a single cell layer of myocardium in early development (e.g., E8.5 in mouse embryos, corresponding to E19 in humans). The second stage is the formation of the trabecular myocardium in early mid-gestation (e.g., E9.5-E10.5 in mouse embryos, corresponding to E22-E28 in humans). As the loops form and the myocardium thickens, cardiomyocytes in specific areas along the inner wall of the heart form sheet-like projections into the lumen, forming trabecular myocardium. The outer layer of the myocardium remains as a base for the formation of compact

Table 1 Genes associated with LVNC

Group according to the molecular function	Gene	Locus	Protein	Inheritance	Associated conditions	Frequency*
Sarcomere genes	<i>ACTC1</i>	15q14	Actin alpha cardiac muscle 1	AD	HCM, DCM, ASD	7%
	<i>DES</i>	2q35	Desmin	AD	DCM, RCM	
	<i>LDB3</i>	10q23.2	LIM domain binding 3	AD	HCM, DCM	
	<i>MYBPC3</i>	11p11.2	Myosin binding protein C3	AD	HCM, DCM	7%
	<i>MYH7</i>	14q11.2	Myosin heavy chain 7	AD	HCM, DCM	25%
	<i>OBSCN</i>	1q42.13	Obscurin	AD	HCM, DCM	
	<i>PLN</i>	6q22.31	Phospholamban	AD	HCM, DCM	
	<i>RYR2</i>	1q43	Ryanodine receptor 2	AD	CPVT	2%
	<i>TNNT2</i>	1q32.1	Troponin T2, cardiac type	AD	DCM, HCM, RCM	2%
	<i>TPM1</i>	15q22.2	Tropomyosin 1	AD	DCM, HCM	3%
Transcriptional/translational regulator genes	<i>TTN</i>	2q31.2	Titin	AD	DCM	4%
	<i>NKX2-5</i>	5q35.1	NK2 homeobox 5	AD	CHD	
	<i>NONO</i>	Xq13.1	Non-POU domain-containing octamer-binding protein	XL	Intellectual developmental disorder, X-linked syndromic 34	
	<i>PRDM16</i>	1p36.32	PR/SET domain 16	AD	DCM	
	<i>RBM20</i>	10q25.2	RNA binding motif protein 20	AD	DCM	
Mitochondrial function genes	<i>TBX5</i>	12q24.21	T-box transcription factor 5	AD	Holt-Oram syndrome	
	<i>TBX20</i>	7p14.2	T-box transcription factor 20		CHD	
	<i>NNT</i>	5p12	Nicotinamide nucleotide transhydrogenase	AR	Glucocorticoid deficiency 4, with or without mineralocorticoid deficiency	
Cytoskeletal protein genes	<i>TAZ</i>	Xq28	Taffazin	XL	Barth syndrome	2%
	<i>TMEM70</i>	8q21.11	Transmembrane protein 70	AR	Mitochondrial complex V (ATP synthase) deficiency,	
	<i>DMD</i>	Xp21.2-p21.1	Dystrophin	XL	DCM, Duchenne/Becker muscular dystrophy	
Cellular junction protein genes	<i>DTNA</i>	18q12.1	Dystrobrevin alpha	AD	DCM	
	<i>LMNA</i>	1q22	Lamin A/C	AD	DCM	
Intracellular trafficking genes	<i>DSP</i>	6p24.3	Desmoplakin	AD	DCM	
	<i>PKP2</i>	12p11.21	Plakophilin 2	AR	ARVC	
Ion channel genes	<i>LAMP2</i>	Xq24	Lysosomal associated membrane protein 2	XL	Danon disease	
	<i>PLEKHM2</i>	1p36.21	Pleckstrin homology domain-containing family M member 2	AD		
Ion channel genes	<i>HCN4</i>	15q24.1	Hyperpolarization activated cyclic nucleotide gated potassium channel 4	AD	MVP, bradycardia, Brugada syndrome	4%
	<i>SCN5A</i>	3p22.2	Sodium voltage-gated channel alpha subunit 5	AD	Brugada syndrome, LQTS, DCM, AF, SSS	1%

Table 1 (continued)

Table 1 (continued)

Group according to the molecular function	Gene	Locus	Protein	Inheritance	Associated conditions	Frequency*
Signal transduction genes	<i>ALPK3</i>	15q25.3	Alpha kinase 3	AR	HCM (signal transduction)	
	<i>DMPK</i>	19q13.32	DM1 protein kinase	AD	Myotonic dystrophy 1	
Protein degradation gene	<i>MIB1</i>	18q11.2	MIB E3 ubiquitin protein ligase 1	AD		5%

*, proportion of all variants. AD, autosomal dominant; XL, X linked; AR, autosomal recessive; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ASD, atrial septal defect; RCM, restrictive cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; CHD, congenital heart disease; ATP, adenosine triphosphate; ARVC, arrhythmogenic right ventricular cardiomyopathy; MVP, mitral valve prolapse; LQTS, long QT syndrome; AF, atrial fibrillation; SSS, sick sinus syndrome.

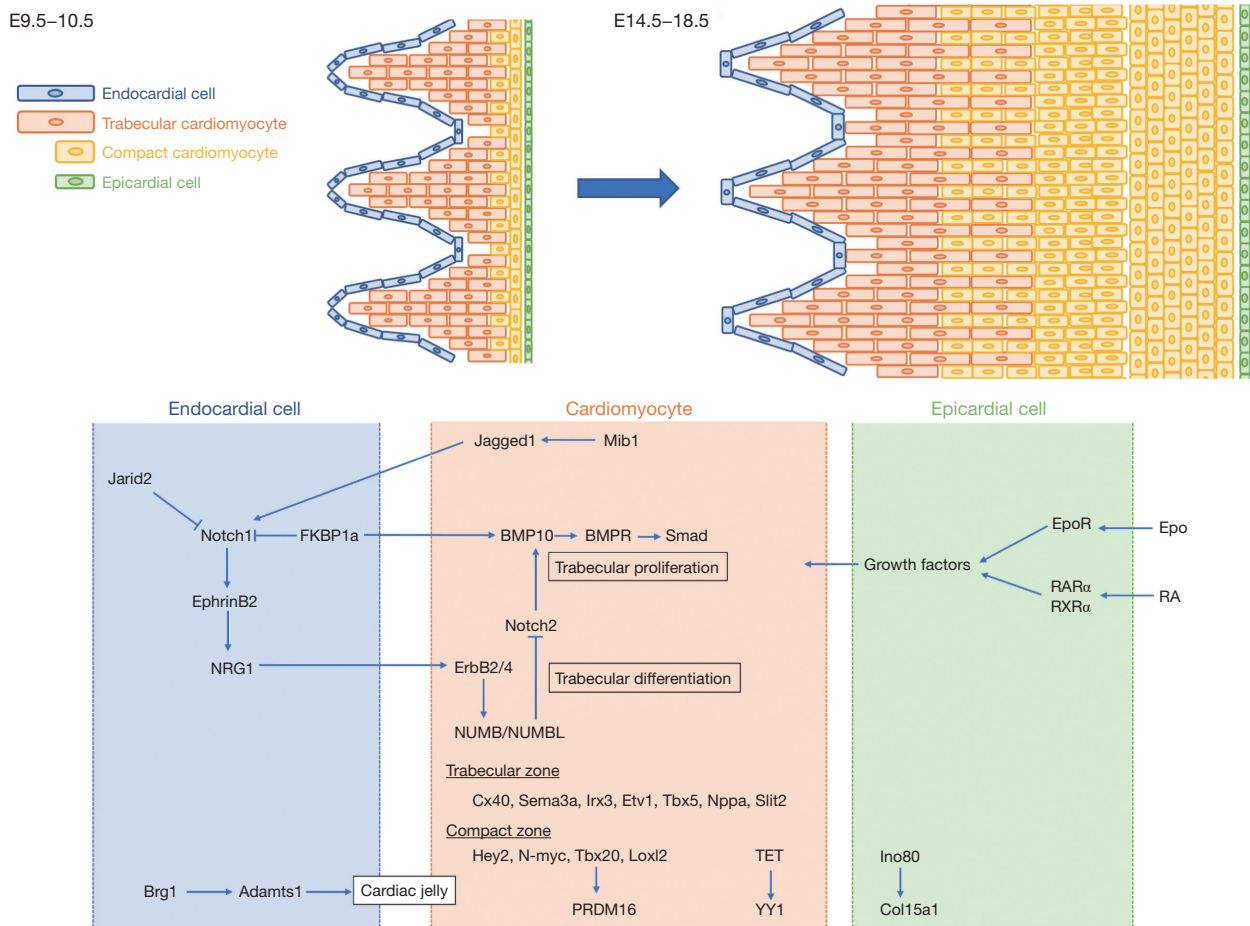


Figure 1 Schema of the formation (upper) and pathway (left lower) of ventricular trabeculation and compaction. The interactive regulation of endocardial, myocardial, and epicardial signaling networks is crucial to the ventricular trabeculation and compaction. BMP, bone morphogenetic protein; BMPR, bone morphogenetic protein receptor; TET, ten-eleven translocation; RA retinoic acid.

myocardium (43). The third stage is the compaction of the myocardium in the second half of gestation (e.g., E12.5–E13.5 in mouse embryos, corresponding to E40–E44 in humans). The fourth stage is the formation of the three-layered helical myocardium from late fetal to neonatal stages (41). Unlike skeletal muscle, ventricular myocardium is composed of a three-dimensional network of myocytes in the subendocardial, subepicardial, and intermediate layers (44–51). Patients with LVNC have little apical torsion and LV steric rotation, with basal and apical rotation in the same direction (52,53). The normal three-layer structure in the compacted myocardium may be disrupted because LVNC is a residual of embryonic trabecular myocardium.

During this heart developmental stage, trabeculation and compaction of the LV require interactions between cardiomyocytes and their surrounding environments, such as the endocardium, epicardium, extracellular matrix, other cardiomyocyte factors, and epigenetic factors according to genetic studies in mice (*Figure 1*). Disruption of this developmental process by defects in cardiac proliferation, impaired trabecular coalescence, or defects in myofibrillogenesis and polarization of cardiomyocytes leads to an abnormal trajectory of trabeculogenesis and ventricular wall compression that is subsequently theorized to cause LVNC (4,54).

Trabeculae formation requires an interaction between the endocardium and myocardium, which, late in development, contributes to ventricular compaction. These endocardial-myocardial pathways are largely driven by signaling from the neuregulin1/ErbB, Notch, and bone morphogenetic protein (BMP) 10 pathways. The Notch1 and neuregulin1 pathways interact dynamically to regulate extracellular matrix dynamics and trabecular growth, establishing a basis of trabecular architecture. The Dll4-Notch1 (55,56), Mib1 (57), BMP10 (58), and tumor growth factor (TGF)- β pathways (59), regulate trabecular compaction. *Hey2* or *Nppa* systems are involved in the Dll4-Notch1 variant. *Nrg1*, *Bmp10*, and *Hey2* have been reported to be Notch1-dependent (60,61). Recent studies have shown that Dll4-Notch1 signaling induces the formation of the trabeculae and coordinates their patterning and compaction with coronary formation to form mature chambers (55,56). Germline variants in human *MIB1*, encoding the E3 ubiquitin ligase that promotes endocytosis of the Notch ligands Delta and Jagged, cause LVNC, and those affected have decreased Notch1 activity and target genes (57). Kodo *et al.* showed that *Thx20* regulates the expression of TGF- β signaling regulators, including *Prdm16* (59), a SMAD2/3

repressor of TGF- β signaling through binding (62–64). Downregulation of *ErbB2* signaling in mature spongiosa has been shown to require the endocytosis-adaptive proteins Numb and Numbl (65).

The epicardium proliferates from the anterior pericardial organ at the venous pole of the heart beginning at E9.5 in mice (corresponding to E21 in humans), and the entire myocardial surface is covered by E11.0 (corresponding to E24 in humans) (66). The interaction between the epicardium and myocardium appears to be the primary driver of the compaction process (67,68). The epicardial-myocardial pathway includes retinoic acid (RA), erythropoietin (EPO), insulin-like growth factor (IGF-1), and fibroblast growth factor (FGF) signaling to support compaction. The underdevelopment of coronary artery is accompanied by abnormal growth of compact myocardium in several mouse models (55,69–72).

The extracellular matrix plays an important role in both trabeculae formation and compaction. The trabeculae require the chromatin-remodeling protein *Brg1* to require to suppress the expression of *Adamts1* in the endocardium above the developing trabeculae (73).

Other cardiomyocyte genes are involved in cardiomyocyte proliferation, but when or how their protein products facilitate interactions with surrounding cells remains unclear, although the cardiac transcription factor *Nkx2-5* is an important regulator of ventricular trabecular and conduction system development (74–76).

The regulation of chromatin levels, particularly DNA methylation, adenosine triphosphate (ATP)-dependent chromatin remodeling that alters nucleosome structure, and covalent histone modifications that alter DNA-histone interactions (77). Regulation of chromatin levels contributes to gene expression in cardiac development, including cardiomyocyte proliferation, trabecular structure, and compaction. *Jarid2* knockout mice exhibit HF, including trabecular hypertrophy with noncompaction of the ventricular wall. In *Jarid2* knockout mice, failure to properly regulate Notch signaling may lead to defects in the developing ventricle (78). Mice deficient in endothelial *Brg1*, a chromatin remodeler, do not form proper trabeculations due to premature degradation of the cardiac jelly, the extracellular matrix between the myocardium and endocardium (73). Tet protein-mediated DNA hydroxymethylation regulates chromatin accessibility (79). Cardiac-specific deletion of *Tet2* and *Tet3* in mice leads to LVNC with embryonic lethality (79). Deletion of the *Ino80* chromatin remodeler from embryonic

endothelial cells has been shown to result in LVNC (80).

Acquired hypothesis

The acquired hypothesis is that LVNC may be secondary to the process of myocardial remodeling. Acquired LVNC may occur in athletes (81-83), as well as those with sickle cell anemia (84,85), pregnancy (86), renal failure (87), and other conditions. There are increasing reports of healthy subjects showing trabecular hypertrophy in the LV with normal size, function, and wall thickness. Many studies have concluded that LV trabeculae may develop or hidden trabeculae may be exposed in some situations of cardiac remodeling that occurs because of preload and increased cardiac output. Considering acquired LVNC, an increase in trabeculae may provide an adaptive advantage. LV compliance is highest in the absence of trabeculae, but the apex is subjected to higher wall stresses and strains. The presence of apical trabeculae may redistribute apical wall stresses and protect the thin-walled apex from adverse aneurysmal remodeling (88). Increasing stroke volume comes at a considerable energy cost and requires progressively higher longitudinal strain in smooth and non-trabecular LV, whereas, in trabecular LV, higher stroke volume can be achieved without exponentially increasing strain (89). These observations may support the pathogenesis of acquired LVNC.

Theoretical gap among human and non-human models or congenital and acquired hypothesis

In mouse models, many of the genes associated with cardiomyocyte proliferation result in LVNC-like phenotype. Since the products of these genes also function in other cells, gene deletions are expected to cause embryonic lethality. In contrast, many variants associated with human LVNC are sarcomere genes, part of myofibrillar structures, and are associated with contractile function, and alter the resulting protein rather than eliminate its function. Indeed, we reported that sarcomere variants are most commonly identified in fetus-onset patients, and fetus-onset patients with LVNC are more likely to develop HF (90). Moreover, we found a time-dependent increase in the ratio of noncompacted to compressible layers (N/C) of the LV wall in patients with fetal-onset LVNC, with the N/C ratio being greater than 2 before and after birth (91). This change is in contrast to patients with DCM and HCM, suggesting that the formation of the trabeculated layer proceeds late in gestation. Thus, studies focusing on fetal LVNC provide new clues to previous hypotheses of mouse models and the development of LVNC in humans. Recent advances in the

generation of disease models of LVNC using genetically engineered mice may be expected to elucidate the etiology of LVNC.

LVNC exhibits several distinct forms, depending on the associated phenotype. Considering this vast etiologic heterogeneity, it makes sense that the genetics of LVNC are heterogeneous, with different causative genes and multiple disease-causing variants in each gene. The acquired and reversible morphology of LVNC poses a problem for the traditional interpretation that the noncompacted forms are genetic diseases (81,82,84-87).

Imaging

Echocardiography

Two-dimensional echocardiography is recommended as the first-line imaging modality for patients with LVNC because it is noninvasive, easy to perform, inexpensive, and, with the use of echo contrast agents, can delineate the presence of LV thrombus and trabeculae (92). Furthermore, as advances in tissue harmonics and image resolution in echocardiography have been made, there have been increasing reports of features consistent with even healthy populations. Excessive trabecular formation of the ventricular wall, deep recesses, and a two-layered structure with a trabeculated layer on the endocardial side and a compacted layer on the epicardial side can be observed by echocardiography (*Figure 2*). The trabeculated layer is often seen in the lateral, inferior, and posterior walls centered on the apex, and rarely on the ventricular septum or anterior wall (93). On color Doppler, blood flows in and out of the gaps in the reticular meatus formation centered on the apex, clearly differentiating this condition from apex HCM.

Cardiac magnetic resonance imaging (CMR)

CMR should be used to confirm the diagnosis of LVNC and rule out other cardiovascular diseases that may be present (94). CMR is capable of providing a detailed view of the cardiac structures in multiple image plans, including apical and lateral areas not easily seen on an echocardiogram (*Figure 3*). Multiple studies of late gadolinium enhancement (LGE) have been reported in LVNC on CMR. The most common LGE patterns are in the ventricular septum and right ventricular inflow region, similar to findings in DCM and HCM, and often differ from the apex, lateral, inferior, and posterior walls of the left ventricle, where trabeculation is most prominent (95). Moreover, the presence and extent of LGE are related to

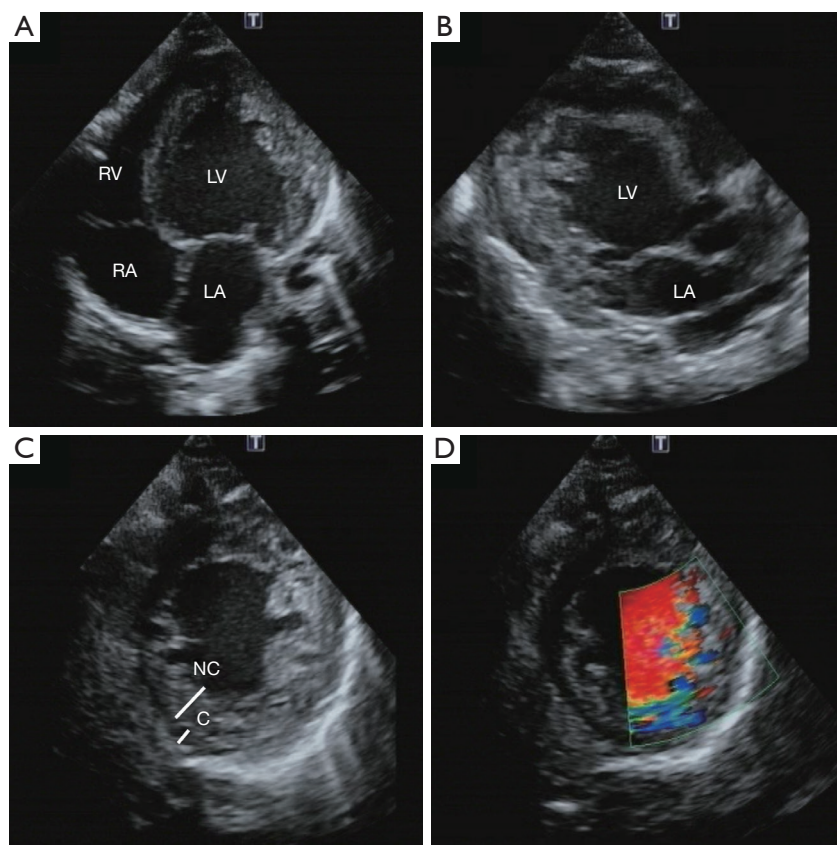


Figure 2 Characteristics of left ventricular noncompaction by echocardiography. (A) Four-chamber view image; (B) left ventricular long axis image; (C) left ventricular short axis image; (D) left ventricular short axis image with color Doppler view. (A,B) Prominent trabeculation and deep gaps are observed in the left ventricle. (C) The ventricular wall has a two-layered structure with noncompacted and compacted layers. (D) Color Doppler shows the blood flow between the recesses. LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium; NC, noncompacted layer; C, compacted layer.

the clinical features and LV systolic function (96). Patients with isolated LVNC and no LGE have a better prognosis than patients with LVNC and LGE (95).

In recent years, native T1 mapping has proven to be a useful tool to quantitatively measure myocardial tissue characteristics without the administration of exogenous contrast agents (97). Myocardial T1 values in patients with diffuse myocardial fibrosis have been reported to correlate well with fibrosis confirmed by myocardial biopsy (98). Native T1 mapping is superior for characterizing diffuse fibrosis and subtle focal lesions in comparison with LGE (97,99). Previous studies that applied T1 mapping to patients with LVNC and without LGE showed that LVNC patients had elevated native myocardial T1 values compared to normal controls, suggesting that native T1 mapping is a more useful indicator of early myocardial fibrosis than LGE

imaging in LVNC patients (100,101).

Thus, CMR provides morphological assessment and non-invasive tissue characterization and has been widely used in LVNC.

Electrocardiogram

Electrocardiographic abnormalities are present in approximately 90% of patients but are non-specific (54). LV hypertrophy, repolarization abnormalities, T wave negativity, ST changes, axial displacement, intraventricular conduction disturbances, and atrioventricular (AV) block are seen (102). Conduction disturbances such as AV block or bundle branch block are observed in 26% of patients, while supraventricular tachycardia is present in 17%. Sustained ventricular tachycardia occurs in 8%, and when non-

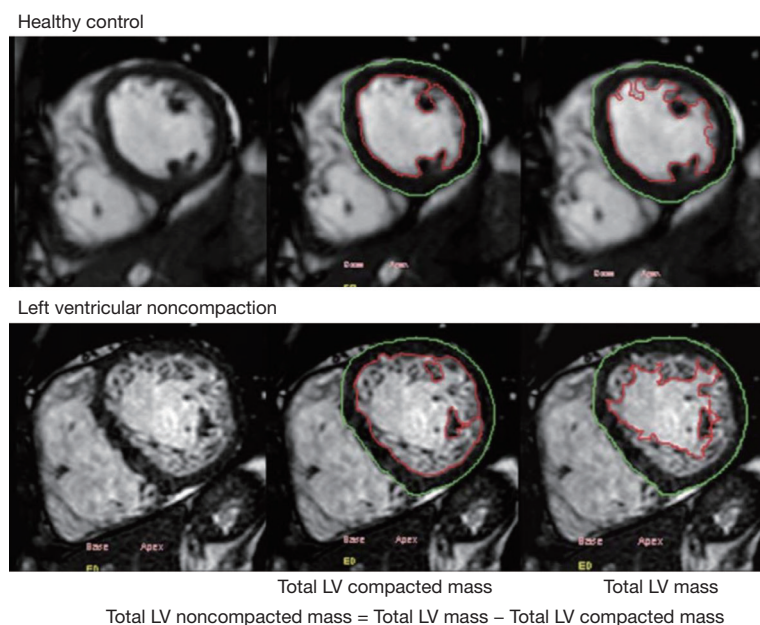


Figure 3 Characteristics of left ventricular noncompaction by cardiac magnetic resonance imaging. Normal case (upper row) and patient with left ventricular noncompaction (lower row). Compared to normal patients, patients with left ventricular noncompaction show marked trabecular formation of the left ventricle. LV, left ventricle.

sustained ventricular tachycardia is included, in 20% of cases (11). Certain arrhythmias are seen in patients with specific genetic variants, such as sinus failure syndrome in patients with LVNC with the *HCN4* gene variant.

Myocardial biopsy

Endocardial fibrosis or fibroblasts were the most frequently reported abnormalities in adult and pediatric LVNC (1,103-106). It is unclear whether endocardial fibrosis is caused by an immune response, the result of local blood flow abnormalities, or induced by hemodynamic and mechanical factors around the trabecular myocardium (107).

Often a mural thrombus is seen on the endocardial surface in the fine-walled column area. The myocardial layer shows various degrees of degeneration, mainly subendocardial, and up to moderate fibrosis (108,109). However, there is no extensive myocardial desmoplasia or foci of mottled fibrosis, as is often seen in DCM, and the histological findings are rather similar to those of endocardial fibroelastosis.

Diagnosis

Imaging studies are essential for diagnosis. Diagnostic

criteria based on echocardiography, CMR, and multidetector computed tomography (MDCT) have been proposed (Table 2) (1,5,52,110-124). Diagnostic criteria were created based on the ratio between noncompacted layer thickness (2,117), mass (118), volume (125), and compacted layer. The number of segments of the noncompacted layer provides information on LVNC dilation (119,126). Another approach integrates the assessment of counts or a global trabecular index (127). However, to date, there are no consensus criteria (128-130).

Echocardiography

Most studies on echocardiography use the diagnostic criteria of Chin, Jenni, and Stöllberger *et al.* (Table 2) (1,131). The first echocardiographic criteria were proposed by Chin *et al.* (1). This criterion proposed the ratio of the distance from the epicardium to the trabecular trough (X) to the trabecular peak (Y) is diagnostic of LVNC if X/Y is less than 0.5. Jenni *et al.* proposed a second criterion (2). They proposed a maximum ratio of N/C >2 as a diagnostic criterion for LVNC. Measurements in this study were made on the parasternal short-axis image at end-systole. Currently, this criterion is the most widely accepted and clinically applied echocardiographic criterion for the diagnosis of LVNC. Stöllberger *et al.* proposed the third

criterion (132). They proposed that the presence of three or more trabeculae at the tip of the papillary muscle and blood flow by color Doppler imaging or evidence of echo-enhancing agents in the interventricular recesses should be required.

Joong *et al.* compared the usefulness and reproducibility of the previously mentioned Chin, Jenni, and Stöllberger echocardiographic criteria and found that Chin's criterion has the highest reproducibility and interrater reliability for counting the parasternal short axis and apical trabeculae using the X/Y ratio in the apical anterolateral region (133). Jenni and Stöllberger's criteria are probably overdiagnosed in many adult HF cases that meet the diagnostic criteria. Moreover, echocardiography has several limitations. First, in the literature, echocardiographic diagnostic criteria vary widely and are based on a small number of studies using different research methods (134,135). Second, since myocardial thickness is greatest in systole and least in diastole, the cardiac cycle (end-systole or end-diastole) during which the uncompressed and compressed layers are measured is also important, which directly affects the N/C ratio. Paterick *et al.* suggest that the two-layer myocardium be measured at end-diastole because the thickness of each layer can be more accurately measured, and this approach is in line with the end-diastole. They proposed measuring the N/C ratio of the LV myocardium at end-diastole and diagnosing with a ratio >2 (136). This approach is consistent with the recommendation of the American Society of Echocardiography to measure wall thickness at the end of diastole (113).

Another common problem in echocardiographic criteria for LVNC is that interobserver reliability tends to be suboptimal. Saleeb *et al.* compared 104 LVNC cases with 100 controls and found that interobserver agreement in counts of trabeculations >3 and N/C ratio >2 ranged from 53% to 77% and did not statistically factor in the possibility of chance agreement (137). Stöllberger *et al.* recently evaluated the interobserver reliability among three observers evaluating 100 echocardiograms of LVNC patients and reported discordance in 35% of cases (128). Related to all LVNC diagnostic studies assessing the validity and inter-rater reliability is the lack of a gold standard for diagnosis, as many of these studies rely on the original echocardiographic diagnosis as their overarching criteria. Furthermore, these echocardiographic diagnostic tests may be too sensitive, as suggested by Kohli *et al.* They studied echocardiograms of patients referred for HF and found that 24% met one or more of the LVNC criteria (138).

CMR

If uncertainty still exists in the diagnosis of LVNC, additional diagnoses, such as CMR, are warranted (138). The most widely accepted criteria for CMR diagnosis of LVNC were proposed by Petersen *et al.* (117). They suggested a larger ratio (N/C >2.3) and measurements in diastole to better understand the bilayer myocardium and to improve accuracy. Jacquier *et al.* proposed another cross-sectional evaluation method by determining the mass of the trabecular LV (118). They proposed that trabecular LV mass be greater than 20% of the total hemispheric mass. Stacey *et al.* subsequently compared the Petersen and Jacquier criteria with the conventional end-systolic ratio N/C >2 proposed in the Jenni criterion and found the latter to be strongly associated with arrhythmia, HF, and subsequent hospitalization (120). Grothoff *et al.* presented a method to measure the LV myocardial mass index of uncompressed myocardium as an absolute value and as a percentage of total LV myocardial mass and proposed cutoffs of 15 g/m² and 25%, respectively (119).

Positano *et al.* found that the Grothoff method could more accurately depict trabecular tissue compared to the Jacquier method, but both methods had adequate reproducibility (139). Similarly, Ivanov *et al.* investigated the prevalence of LVNC in 700 patients using the Peterson, Stacy, Jacquier, and Captur CMR criteria, and the prevalence was found to be 39% by Peterson criteria, 23% by Stacey criteria, 25% by Jacquier criteria, and 3% by Captur criteria, respectively.

The current LVNC criteria produce substantial false-positive results when the LVNC criteria are applied to healthy or HF populations (140). Echocardiography shows a prevalence of 1.3%, while CMR shows a prevalence of 14.8% (140). In athletes, echocardiography showed a prevalence of 3.2%, whereas CMR showed a higher prevalence of 27.3% (140). Zemrak *et al.* studied echocardiograms from an American multi-ethnic study of an atherosclerosis cohort and demonstrated that 26% met Petersen's LVNC criterion. Interestingly, this population was reexamined during a 9.5-year follow-up period, which reaffirmed that the increased trabeculae in this healthy population were not associated with major adverse cardiac events (141). There have been several similar large cohort studies that have reached similar conclusions regarding possible overdiagnosis of imaging, poor consistency between techniques, and lack of association between trabecular severity and adverse clinical outcomes (142-145). Thus, while CMR can more easily identify changes in LVNC, it

Table 2 Imaging modalities with criteria to diagnose left ventricular noncompaction echocardiography

Modality	First author	Patients	Morphologic criteria (measurement) (cut-off for positive criteria)	Cardiac phase	Recommended section	
Echocardiography	Chin <i>et al.</i> (1), 1990	8	<ul style="list-style-type: none"> Distance (X) from the deepest trough of the trabecular recess to the epicardial surface Distance (Y) peak of trabeculations to the epicardial surface X/Y <0.5 considered potential LVNC 	<ul style="list-style-type: none"> End-diastole, parasternal long axis, or apical four-chamber view Sensitivity, 79–100%; specificity, 54–92% 	Long axis	
	Jenni <i>et al.</i> (110), 2002	34	<ul style="list-style-type: none"> N/C >2 Morphologic criteria: <ul style="list-style-type: none"> Absence of coexisting cardiac abnormalities Numerous excessively prominent trabeculations and deep intertrabecular recesses Intertrabecular spaces filled by direct blood flow from the ventricular cavity 	<ul style="list-style-type: none"> End systolic, parasternal short axis Insensitive 	Short axis	
	Stöllberger <i>et al.</i> (111), 2002	62	<ul style="list-style-type: none"> N/C ≥2 >3 Trabeculations protruding from the LV wall distal to the papillary muscles at the apex Perfusion of the intertrabecular recesses from the ventricular cavity Trabeculations must have the same echogenicity as the myocardium while moving in sync with ventricular contractions 	<ul style="list-style-type: none"> End-diastole, apical four-chamber view Sensitivity, 79–80%; specificity, 79–93% 	Lax (± short axis)	
	Pignatelli <i>et al.</i> (5), 2003	36	<ul style="list-style-type: none"> N/C >1.4 	<ul style="list-style-type: none"> End-diastole 	Long axis	
	Belanger <i>et al.</i> (112), 2008	60	<ul style="list-style-type: none"> N/C >2 + area >5 cm² 	<ul style="list-style-type: none"> End-systole 	Long axis + short axis	
	van Dalen <i>et al.</i> (52), 2008	10	<ul style="list-style-type: none"> LV twist—rigid body rotation 	<ul style="list-style-type: none"> Systole and diastole 	Short axis	
	Paterick <i>et al.</i> (113), 2012	0	<ul style="list-style-type: none"> N/C ≥2 	<ul style="list-style-type: none"> End-diastole 	Short axis	
	Gebhard <i>et al.</i> (114), 2012	41	<ul style="list-style-type: none"> Max systolic C layer <8.1 mm 	<ul style="list-style-type: none"> End-systole 	Short axis	
	Yubbu <i>et al.</i> (115), 2018	30	<ul style="list-style-type: none"> Circumferential strain <−24.5% 	<ul style="list-style-type: none"> Systole and diastole 	Short axis apical	
	Caselli <i>et al.</i> (116), 2012	17	<ul style="list-style-type: none"> TV >15.8 mL or TV% >12.8% 	<ul style="list-style-type: none"> End-diastole 	Long axis	
	CMR	Petersen <i>et al.</i> (117), 2005	7	<ul style="list-style-type: none"> N/C >2.3 in diastole N/C ratio >2.3 in 43% of subjects with no cardiac disease or hypertension 	<ul style="list-style-type: none"> End-diastole, long axis apical views Sensitivity, 86%; specificity, 99% 	Long axis
		Jacquier <i>et al.</i> (118), 2010	16	<ul style="list-style-type: none"> Total NC mass compared to the total LV mass Total NC mass >20% of the total LV mass 	<ul style="list-style-type: none"> End-diastole, short axis cine images Sensitivity, 93.7%; specificity, 93.7% 	Short axis
		Grothoff <i>et al.</i> (119), 2012	12	<ul style="list-style-type: none"> Total NC mass index of 15 g/m² of global LV mass with an NC mass >25% of the global LV mass 	<ul style="list-style-type: none"> End-diastole, short axis cine images High sensitivity and specificity 	Short axis
		Stacey <i>et al.</i> (120), 2013	122	<ul style="list-style-type: none"> N/C ratio >2 in end-systole End systolic criteria were shown to have a higher odds ratio for cardiac events compared to end diastolic criteria 	<ul style="list-style-type: none"> End-systole using short axis SSFP images 	Short axis
Captur <i>et al.</i> (121), 2013		30	<ul style="list-style-type: none"> FD max apical of ≥1.392 was considered diagnostic for LVNC FD was significantly higher in patients with LVNC compared to healthy volunteers 	<ul style="list-style-type: none"> Used fractal analysis to quantify the LVNC structure along the cardiac apex CMR short axis sine images were reviewed using a box counting method 	Short axis	
	Choi <i>et al.</i> (122), 2016	54	<ul style="list-style-type: none"> Ratio of the thickness of apical trabeculation to that of C myocardium in the apical lateral segments (apex/C ratio) measured during end-diastole in all three long axis views TV >35% total 	<ul style="list-style-type: none"> End-systole 	Short axis	
MDCT	Melendez-Ramirez <i>et al.</i> (123), 2012	10	<ul style="list-style-type: none"> N/C ratio >2.2 at end-diastole seen in >2 segments 	<ul style="list-style-type: none"> Diastole, visualization of 17 heart segments Sensitivity 100%, specificity 95% 	Short axis	

Table adapted with permission; for full references, see source Abela and D'Silva (124). CMR, cardiac magnetic resonance; MDCT, multidetector computed tomography; X, distance of the epicardial layer to the trabecular trough; Y, distance of the epicardial layer to the trabecular peak; NC, noncompacted layer; LV, left ventricle; FD, fractal dimension; C, compacted layer; Lax, long axis view; TV, trabeculated left ventricular volume; TV%, percentage trabeculated left ventricular volume as a proportion of the left ventricular end diastolic cavity; SSFP, steady-state free precession.

may also encompass healthy subjects.

Clinical symptoms

The major clinical manifestations of LVNC are HF, arrhythmias, and thromboembolism (10). HF is a complication in more than half of patients with LVNC, and LV systolic dysfunction is present in 84% of patients (146). LV diastolic dysfunction is also present and has been associated with marked trabeculation, myocardial ischemia, and abnormal relaxation and inflow limitation due to fibrosis (146). Hemodynamic features include decreased cardiac contractility with enlargement and thickening of the LV (146). The LV is also characterized by a high degree of cardiac contractility, with a high degree of LV hypertrophy. Arrhythmias are another common complication. Atrial fibrillation and ventricular tachycardia occur in 12.9% and 16.0% of adult patients, respectively (147). Sudden death occurs in approximately half of the patients with LVNC with arrhythmias (146). Wolff-Parkinson-White (WPW) syndrome has been reported in approximately 15% of pediatric patients with LVNC (6,146). Abnormal cardiac rhythm is frequently reported, with conduction defects in 26%, supraventricular tachycardia in 17%, and sustained or non-sustained ventricular tachycardia in 18% (11). Thromboembolism varies from 0% to 38% (5,6). Patients with reduced contractility and those with atrial fibrillation are at higher risk of systemic embolism, including cerebral emboli, and pulmonary infarction (11).

Chest pain and acute coronary syndromes are often present, which are thought to be due to decreased coronary blood flow and microcirculation (148-150). Recent studies have shown that LVNC has different symptoms depending on subtype and even genotype (16). These stratifications help predict the risk of LV systolic dysfunction and major adverse cardiac events.

Natural history

The onset of LVNC can range from neonatal to infancy, school age to adolescence, or adulthood, depending on the case, and the clinical presentation is diverse, making it easily overlooked. A recent meta-analysis estimates the prevalence, clinical presentation, natural history, and prognosis of LVNC. The cardiovascular mortality rate for children is 4.3 per 100 live births per year (151). The cardiovascular mortality rate for adults is 1.9 per 100 live births per year (152). The rate is 2.2 for those with LV ejection

fraction (EF) <45% and 1.2 for those with LVEF \geq 45% (152). The event rate for stroke and systemic embolism is 3.5 per 100 per year (152). The rate of ventricular arrhythmias is 2.2 per 100 person-years (152). We previously reported that neonatal and infantile-onset cases of dilated LVNC and LVNC with CHD are common, and some cases present with severe HF symptoms, subsequently half are indicated for heart transplantation or die within 10 to 15 years (17). The prognosis of newborns with mitochondrial disease or metabolic complications is worse, with a higher rate of heart transplantation compared to DCM in children (17). Additionally, fetal-onset cases have a high rate of HF and mortality (5,90,91). In contrast, young and adult-onset cases that are asymptomatic and detected by medical examination or incidentally often have isolated LVNC, are asymptomatic for a long time, and have a good prognosis (17). The arrhythmogenic form is also asymptomatic and is often diagnosed with an abnormal electrocardiogram, but the complication of lethal ventricular arrhythmias should be kept in mind (17). Screening of family members for LVNC by echocardiography and genetic testing is recommended.

Prognosis

Recent studies have reported risk factors for mortality in patients with LVNC. It appears that the prognosis may be different for children and adults. Kubik *et al.* suggested that the presence of atrial fibrillation, low LVEF, symptomatic HF, and enlargement of the dimensions and volume of the LV cavity, as in DCM and other cardiomyopathies were predictors of adverse outcomes in patients with LVNC (153). Sarma *et al.* noted that apart from lower LVEF (especially LVEF <31%), parameters such as atrial fibrillation, left atrial diameter >40 mm, advanced age, concomitant neuromuscular disease, and HF with LV dilation also lead to poor prognosis and increased mortality (154). Half of all deaths in patients with LVNC may be due to ventricular arrhythmias (155). Fragmented narrow or wide QRS complexes are associated with higher mortality and lower LVEF. The presence of a fragmented narrow QRS complex appears to be an independent predictor of all-cause mortality and heart transplantation (156). LBBB appears to be more frequent in patients with LVEF <35% (157). The LVEF, but not the degree of LV trabeculae, had an important influence on the variability of thrombolism. The risk of thromboembolism and ventricular arrhythmias in patients with LVNC was similar to that in patients with DCM (152). The presence

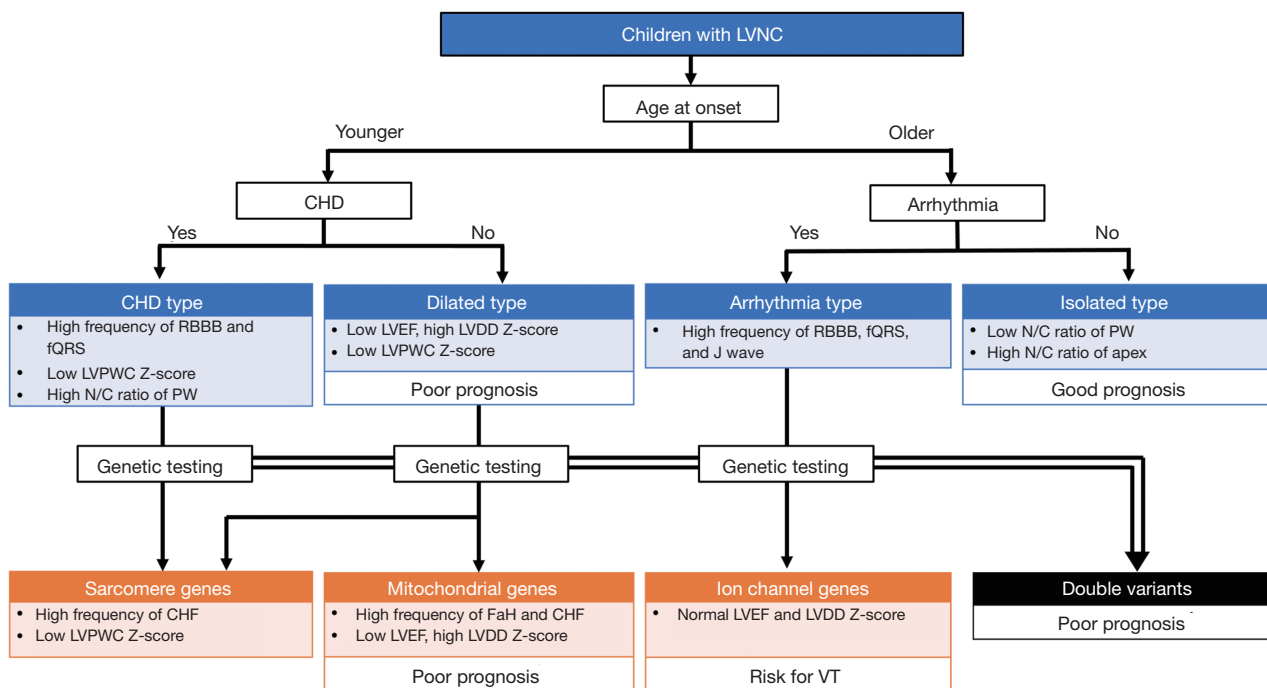


Figure 4 Summary of predominant phenotypic features in patients with LVNC. LVNC, left ventricular noncompaction; CHD, congenital heart disease; RBBB, right bundle branch block; fQRS, fragmented QRS; LVPWC, thickness of compacted layer of left ventricular posterior wall; N/C, noncompacted to compacted layer; PW, posterior wall; LVEF, left ventricular ejection fraction; LVDD, left ventricular diastolic diameter; CHF, chronic heart failure; FaH, family history; VT, ventricular tachycardia.

of LGE on CMR was associated with a higher incidence of premature ventricular contractions and non-sustained ventricular tachycardia (158). Patients presenting with LGE often have a poor prognosis (95). NYHA functional class III/IV, hospitalization for HF symptoms, sustained ventricular arrhythmia, and systemic embolism are predictors of adverse outcomes (159). Of the patients with a cardioembolic cause of LVNC, approximately 93% had either atrial fibrillation or LV systolic dysfunction with a fractional shortening rate of less than 25%, and approximately 29% had both atrial fibrillation and LV dysfunction.

Genetic diagnosis may help predict the outcome of LVNC. *MYH7* and *ACTC1* variants have been shown to have a lower risk of major adverse cardiac events than *MYBPC3* and *TTN* in adults (16). The cardiac phenotype of dilated LVNC was the most frequent subtype (56%) and was associated with an increased risk of major adverse cardiac events and a higher risk of LV systolic dysfunction. Moreover, *MYBPC3*, *TTN*, arrhythmia genes, and X-linked genes were genetic predictors of major adverse cardiac events (16). Recently, we found that genetic variants were

linked to age at diagnosis, LV systolic dysfunction, and risk of major adverse cardiac events in children (Figure 4) (17). The existence of multiple variants is a significant risk factor for MACE occurrence (17). Children with a variant were frequently diagnosed at <1 year old, and they exhibited cardiac symptoms, LV systolic dysfunction, and a high risk of major adverse cardiac events. Interestingly, most of them had either sarcomere or mitochondrial gene variants. Furthermore, patients with double variants developed the disease in the fetal or neonatal period and had a very poor prognosis. Thus, risk factors for major adverse cardiac events were linked to genetic status. Although further large-scale studies on patients with LVNC with variants are needed to confirm and refine the identified genotype-phenotype correlations to improve patient-tailored clinical management, the broad phenotypic classification of LVNC is consistent with a more accurate genotype-phenotype.

Management

There is no specific treatment for LVNC, and treatment for HF with diuretics, angiotensin-converting enzyme

inhibitors, and beta-blockers should be similar to that for DCM if cardiac enlargement or reduced cardiac function is observed. Newer HF therapies, such as angiotensin receptors and neprilysin inhibitors, are expected in the future. A high rate of arrhythmias may require antiarrhythmic drugs, pacemakers, or implantable cardioverter-defibrillators. Several studies have recommended the implantation of implantable cardioverter-defibrillator devices in patients with LVNC and ventricular arrhythmias, especially those with reduced systolic function as determined by LVEF <31% (160). However, there is insufficient evidence for implantable cardioverter-defibrillators implantation in primary prevention solely due to the presence of LVNC (161). In patients with HF or atrial fibrillation, it is important to use antiplatelet and anticoagulant therapy to prevent thromboembolism (147). In some cases of LVNC, cardiac resynchronization therapy may be effective because of dyssynchrony at the site of the meatus. cardiac resynchronization therapy should be considered to reverse LV regeneration and reduce the incidence of fatal ventricular arrhythmias and sudden cardiac death in the presence of severe systolic dysfunction (162). An increasing number of patients with severe HF are eligible for heart transplantation and are receiving ventricular assist devices and awaiting heart transplantation. The number of patients who have received a ventricular assist device remains low, and more large-scale studies are needed to chart a treatment strategy for severe HF cases.

Conclusions

This present review addressed the latest findings on genes reported to be associated with LVNC morphogenesis and possible pathologies in human or non-human model organisms. It reflects the current lack of clarity regarding the pathogenesis and significance of LVNC. This is due to the complexity of imaging diagnostic criteria, interpretation of the role of LVNC as a cause or contributor to cardiomyopathy, and uncertainty regarding the specific genetic basis of LVNC. Hence, the current review highlights both the complexity and heterogeneity of the disease and the continuing need for higher quality evidence. Further extensive genetic and imaging profiling of the patient population would help clarify the risk of LVNC. We hope that this review will not only serve to help with the current status and limitations of LVNC findings but will also help identify areas where current research is lacking and where future efforts may be of interest.

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