

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Left Ventricular Noncompaction

A Distinct Genetic Cardiomyopathy?



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ABSTRACT

Left ventricular noncompaction (LVNC) describes a ventricular wall anatomy characterized by prominent left ventricular (LV) trabeculae, a thin compacted layer, and deep intertrabecular recesses. Individual variability is extreme, and trabeculae represent a sort of individual "cardioprinting." By itself, the diagnosis of LVNC does not coincide with that of a "cardiomyopathy" because it can be observed in healthy subjects with normal LV size and function, and it can be acquired and is reversible. Rarely, LVNC is intrinsically part of a cardiomyopathy; the paradigmatic examples are infantile tafazzinopathies. When associated with LV dilation and dysfunction, hypertrophy, or congenital heart disease, the genetic cause may overlap. The prevalence of LVNC in healthy athletes, its possible reversibility, and increasing diagnosis in healthy subjects suggests cautious use of the term LVNC cardiomyopathy, which describes the morphology but not the functional profile of the cardiomyopathy. (J Am Coll Cardiol 2016;68:949–66) © 2016 by the American College of Cardiology Foundation.

Left ventricular noncompaction (LVNC) describes a ventricular wall anatomy characterized by the presence of prominent left ventricular (LV) trabeculae, a thin compacted layer, and deep intertrabecular recesses that are continuous with the LV cavity and separated from the epicardial coronary arteries (1). By definition, noncompaction (NC) pertains to the left ventricle but may also involve the right ventricle, as either biventricular or an isolated right variant (2,3). The American Heart Association classification defines LVNC as a genetic cardiomyopathy (CMP) (4), and the European Society of Cardiology classification defines LVNC as a nonclassified entity (5). The recent MOGE(S) nosology proposes a simple description of the trait in subjects with either normal LV size and wall thickness and preserved systolic/diastolic function, or in combination with hypertrophic cardiomyopathy (HCM),

restrictive cardiomyopathy (RCM), dilated cardiomyopathy (DCM), or arrhythmogenic right ventricular cardiomyopathy (ARVC) (6). This more cautious, descriptive approach is the expression of clinical uncertainty regarding the unique interpretation of LVNC as a CMP (7). The requirements for the definition of a CMP in the American Heart Association guidelines indicate, "disease of the myocardium associated with mechanical and/or electrical dysfunction" (4), whereas the European Society of Cardiology guidelines define a CMP as "myocardial disease characterized by structurally and functionally abnormal heart muscle and absence of other diseases sufficient to cause the observed myocardial abnormality" (5). By itself, the diagnosis of LVNC is made on the basis of one of the attributes that define CMPs, namely the abnormal LV morphology, but does not obligatorily imply abnormal LV function (7).



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Manuscript received November 30, 2015; revised manuscript received May 9, 2016, accepted May 23, 2016.

**ABBREVIATIONS
AND ACRONYMS****AFD** = Anderson-Fabry disease**ARVC** = arrhythmogenic right ventricular cardiomyopathy**CHD** = congenital heart disease**CMP** = cardiomyopathy**CMR** = cardiac magnetic resonance**DCM** = dilated cardiomyopathy**DMD** = Duchenne muscular dystrophy**HCM** = hypertrophic cardiomyopathy**ILVNC** = isolated left ventricular noncompaction**LV** = left ventricular**LVNC** = left ventricular noncompaction**mtDNA** = mitochondrial deoxyribonucleic acid**NC** = noncompaction**RCM** = restrictive cardiomyopathy**RYR2** = ryanodine receptor 2

In normal hearts, trabeculae actively provide mechanical leverage during early systolic ejection through contraction (8,9). Trabeculae are formed during early embryonic development. The origin of LVNC is attributed to arrested compaction of the endomyocardial layer of the heart during early embryogenesis (8). This hypothesis may explain typical LVNC cardiomyopathies, such as infantile tafazzinopathies, in which both LVNC and LV dilation and dysfunction are part of the same disease (10), or LVNC in congenital heart disease (CHD) (11). The embryogenesis hypothesis is difficult to reconcile in acquired (12-19) and potentially reversible (15,17) LVNC. In fact, LVNC can be an incidental finding in screening studies (i.e., athletes) (15) and is not associated with deterioration in LV volumes or function during long-term follow-up in the asymptomatic population (20). The proportion of LVNC in asymptomatic subjects is increasingly described; up to 8% of consecutive athletes fulfill echocardiographic criteria for LVNC (15). Multiparametric evaluation (elec-

trocardiography, echocardiography, maximal stress test, 24-h Holter monitoring, and cardiac magnetic resonance [CMR]) can contribute to discriminate benign LVNC (18), which may represent a physiological adaptation to exercise conditioning and may be regarded as part of the spectrum of athlete's heart (21).

Cardiologists facing isolated LVNC morphology have to decide if they are observing a "CMP" or a variant of the LV wall anatomy. In most cases, especially in adult patients, the key element in the diagnostic decision is not the LVNC by itself, but the associated LV dilation and/or dysfunction, hypertrophy, right ventricular involvement, arrhythmias, and conduction disease. This review critically discusses the current knowledge on genetic LVNC as both an isolated trait and as part of other cardiac diseases or complex syndromes.

LVNC: THE DIAGNOSIS

The extreme variability of the LV trabecular anatomy is the manifestation of individual, dynamic "cardioprinting." The original definition of LVNC required the generation of echocardiography- and CMR-based quantitative indexes that measure ratios between noncompacted and compacted layers of the LV wall. Definition of cutoff values provided references for the imaging-based diagnosis of LVNC. Different methods

and normal reference values are currently used in clinical practice in the absence of consensus criteria (22-24).

The diagnostic criteria were created on the basis of ratios between thickness (25,26), mass (27), or volume (28) of NC and the compacted left ventricle. The number of NC segments provides information on the extension of LVNC (29,30); alternative methods integrate the count or evaluation of the global trabeculation index (31). Multidetector computed tomography angiography is useful when CMR is contraindicated or when echocardiography and CMR provide discordant data (32); it adds the advantage of noninvasive investigation of the coronary tree. In most diagnostic indexes, the ratios between compacted and noncompacted thickness/volume/mass drive the diagnosis. Although CMR is generally superior to echocardiography for identification of non-compacted myocardium, sensitivity and specificity of NC/compaction (C) ratios by echocardiography, CMR, and computed tomography are difficult to establish because of the absence of referral gold standards and guidelines for the diagnosis.

The role of the thin compacted layer, which is part of the definition of LVNC, is subordinated to that of the NC thickness. The compacted layer can be normal but disproportionately thinner than the NC layer; in this case, the NC/C ratio can reach cutoff values for the diagnosis. The weakness of a diagnosis based uniquely on proportions/ratios is demonstrated by using Anderson-Fabry disease (AFD) as an example. Hearts in patients with AFD may exhibit prominent papillary muscles and trabeculae (33) up to LVNC criteria (34,35), which are satisfied more for the trabecular thickness than for a thin compacted layer. Similarly, in hearts in patients with Danon disease with LVNC (36), the criteria for diagnosis of LVNC seem to be satisfied because of the prominent trabecular layer in hearts with a thickened compacted layer.

None of the current diagnostic indexes include LV dysfunction. LV function and hemodynamics can be normal. Tissue Doppler imaging studies of regional deformation seem to distinguish isolated left ventricular noncompaction (iLVNC) from DCM (37), and 2-dimensional speckle-tracking echocardiography seems to detect myocardial dysfunction in patients with LVNC and normal LV function by using conventional methods (38). The search for deformation indexes or early LV dysfunction in NC hearts is the expression of the clinical need to go beyond morphology in establishing whether the NC anatomy coincides with a diagnosis of CMP.

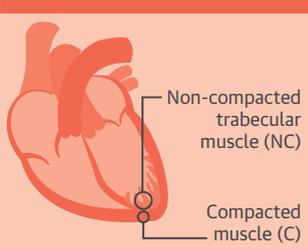
Lack of consensus on uniformly accepted standards of diagnosis influences both epidemiology and interpretation of imaging data. The prevalence of “hypertrabeculation” and LVNC is increasingly reported in large echocardiographic series (20). Overdiagnosis is one of the risks of forcing a morphologic marker in rigid numbers/ranges, being aware that the individual variability of the trabecular anatomy is vast. The opposite risk is underdiagnosing and missing early CMPs. Unfortunately, other diagnostic tools do not help; although commonly abnormal in LVNC associated with CMP, electrocardiography does not by itself contribute to the specific diagnosis of LVNC.

LVNC AS ISOLATED AND NONISOLATED TRAIT/DISEASE

LVNC can be regarded as an isolated entity or as one of the traits that may recur in cardiac and noncardiac diseases. As a marker, it can suggest specific diagnoses; that is, tafazzinopathies (caused by mutations in the *TAZ* [*Tafazzin*, or *G4.5*] gene) in male infants with a dilated, hypokinetic phenotype (10,39,40). As a structural trait with potential functional effects, it may contribute to LV dysfunction in coexisting morphofunctional disorders, such as CMP or CHD (Table 1 [34-36,41-76]). On the basis of current knowledge and terminology, LVNC can be grouped as follows:

1. iLVNC. NC morphology is observed in left ventricles with normal systolic and diastolic function, size, and wall thickness (20). The genetic basis of iLVNC in otherwise normal hearts is unknown. When the trabeculae are prominent in left ventricles with normal size and function, long-term follow-up may provide information regarding their potential role as either a predisposing factor or marker of risk for future progression through CMP (Figure 1).
2. LVNC associated with LV dilation and dysfunction at onset, such as in the paradigmatic infantile CMP of Barth syndrome (10,39,40). Tafazzinopathies represent a unique model of LVNC CMP and a reference for appropriate future nosology.
3. LVNC in hearts fulfilling the diagnostic criteria for DCM, HCM, RCM, or ARVC. In these cases, CMP and LVNC are both present. Family studies may contribute to unraveling whether the 2 traits can exist as independent entities or are part of the same phenotype in all or some affected family members (Figure 2). LVNC can be observed in cardiomyopathies with overlapping phenotypes, typically dilated HCM, such as in

CENTRAL ILLUSTRATION Spectrum of LVNC



The definition of LVNC is based on the ratio NC/C (usually ≥ 2.3). The ratio increases with either increased thickness of trabecular or decreased thickness of the compacted layer.

LVNC can be:

- Dynamic, changing with disease progression
- Emerging during the course of the disease
- Potentially reversible

LEFT VENTRICULAR NON COMPACTION (LVNC)

Hearts with normal LV size and function:

- Individual variability

Genetic LVNC associated with:

- Chromosomal anomalies
- Monogenic syndromes
- Congenital heart diseases
- Cardiomyopathies

Non-genetic LVNC also reported in:

- Athletes
- Sickle cell anemia
- Pregnancy
- Hematologic diseases
- Chronic renal failure
- Polycystic kidney

Arbustini, E. et al. J Am Coll Cardiol. 2016;68(9):949-66.

The 3 morphologic elements of left ventricular noncompaction (LVNC): the trabecular, the compacted layer, and the intertrabecular recesses. The high noncompaction/compaction (NC/C) ratio that defines the diagnostic criteria of LVNC can be obtained either in the presence of a very thin compacted layer (see Figure 6) or in the presence of prominent, disproportionate trabeculae even when the compacted layer is normally represented. The known and possible causes are displayed in the right part of the figure and include: individual variability in hearts with normal left ventricular size and function; genetic causes; and nongenetic causes.

mitochondrial deoxyribonucleic acid (MtDNA)-related CMPs (77).

4. LVNC associated with CHDs, ranging from patent ductus arteriosus or atrial/ventricular septal defects (Figure 3) to more severe diseases, such as the Ebstein anomaly or hypoplastic left heart syndrome (11,78). These disorders can be either sporadic or familial, with CHD in >1 family member.
5. Syndromes with LVNC, either sporadic or familial, in which the NC morphology is 1 of the cardiac traits associated with both monogenic defects and chromosomal anomalies. The former mostly include rare diseases, some of which are well known by cardiologists (i.e., Anderson-Fabry disease, Danon disease) (34-36) because the HCM phenotype is often the first recognized manifestation of the syndromes. Other monogenic syndromes are less commonly observed in the cardiology setting; patients are usually referred

TABLE 1 Genes Associated to Date With LVNC

Gene	Protein	MIM*	Inheritance	LVNC†	DCM and LVNC	HCM and LVNC	RCM and LVNC	ARVC and LVNC	Phenotypes
Genes associated with cardiomyopathies and or CHD and LVNC									
<i>ABCC9</i>	ATP-binding cassette, subfamily C members	601439	AD	X					DCM, AF, Cantu syndrome; 1 reported variant in LVNC (41)
<i>ACTC1</i>	Cardiac alpha-actin	102540	AD	X	X	X	X		LVNC4, HCM, DCM, ASD5 (2 members of the same family with LVNC [42])
<i>ACTN2</i>	Alpha-actinin 2	102573	AD	X	X	X			HCM and DCM with/without LVNC; the former (43) phenotype was observed in 4 of 11 mutation carriers in a family with HCM. The DCM phenotype (44) was observed in a female proband (22 years of age) with a history of syncope and a family history of premature sudden death
<i>CASQ2</i>	Calsequestrin 2	114251	AR	X					CPVT 2; LVNC described in a 5-year-old girl with suspected CPVT (45)
<i>DMPK</i>	Dystrophia myotonica protein kinase	160900	AD	X	X				LVNC is not typical of the disease (46)
<i>DSP</i>	Desmoplakin	125647	AD	X	X			X	1 patient with digenic DSP and TTN variants (41)
<i>DTNA</i>	Dystrobrevin	601239	AD	X					LVNC1 with or without CHD (47). A unique family with LVNC associated with 1 VSD, 1 PDA, 2 hypoplastic LV, and 1 isolated LVNC
<i>G4.5</i>	Tafazzin	300394	X-linked	X	X	X (rare)			Barth syndrome (confirmed); cardiophenotypes include endocardial fibrosis (10,39,40)
<i>HCN4</i>	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4	605206	AD	X					Brugada syndrome, SSS; LVNC and bradycardia: 1 report (48)
<i>LDB3</i>	Z-Band alternatively spliced PDZ motif-containing protein	605906	AD	X	X	X		X	LVNC3, HCM, DCM with or without LVNC, myofibrillar myopathy (DCM + LVNC) (49)
<i>LMNA</i>	Lamin AC	150330	AD	X	X			X	Nonisolated LVNC, LVNC + DCM† (50,51)
<i>MIB1</i>	Mindbomb, homolog of, <i>Drosophila</i>	608677	AD	X	X				LVNC7. 2 families; the heart of 1 proband (V934F) displays well-represented compacted layer and prominent trabeculae (52)
<i>MYBPC3</i>	Myosin-binding protein C	600958	AD	X	X	X	X		HCM, DCM, LVNC10 (53); compound mutations (54)
<i>MYH7</i>	Beta-myosin heavy chain 7	160760	AD	X	X	X	X		HCM, DCM, LVNC5; myopathies: AD and AR (55-57)
<i>PLEKHM2</i>	Pleckstrin homology domain-containing protein, family M, member 2	609613	AD	X	X				1 report (58)
<i>PKP2</i>	Plakophilin 2	602861	AR	X	X				2 siblings from consanguineous parents (59)
<i>PRDM16</i>	PR domain protein 16	605557	AD	X	X				DCM, LVNC8 (60) (identified in <i>1p36del</i>)
<i>RYR2</i>	RYR2	180902	AD	X				X	CPVT 1, ARVC; LVNC associated with exon 3 deletion (61,62)
<i>SCN5A</i>	Sodium channel, voltage-gated, type V, alpha subunit	600163	AD	X	X				Brugada syndrome, LQT3, AF, SSS, DCM, heart block, familial ventricular fibrillation; SIDS (63)

Continued on the next page

to cardiologists for consultation. The latter are complex syndromes that display several multi-organ defects; chromosomal abnormalities include deletions, translocations, and trisomy or tetrasomy.

6. Acquired and potentially reversible iLVNC, which has been reported in athletes (15,18,19); it has also been reported in sickle cell anemia (14,16), pregnancy (17), myopathies (12), and chronic renal failure (13). These observations expand the spectrum of the etiopathogenetic hypotheses from arrested maturation of the LV trabeculae during

embryogenesis to acquired pathogenetic mechanisms, including hemodynamics, phenotype-driven trabecular gene expression, or epigenetic factors, as in CHD (79).

7. Right ventricular NC, which can be concomitant with that of the left ventricle, or present as a unique anatomic area of NC (2,3).

Overall, the morphofunctional context in which the LVNC is observed is, by itself, heterogeneous, in terms of both heart diseases and systemic or multi-organ disorders, depending on the type of syndrome

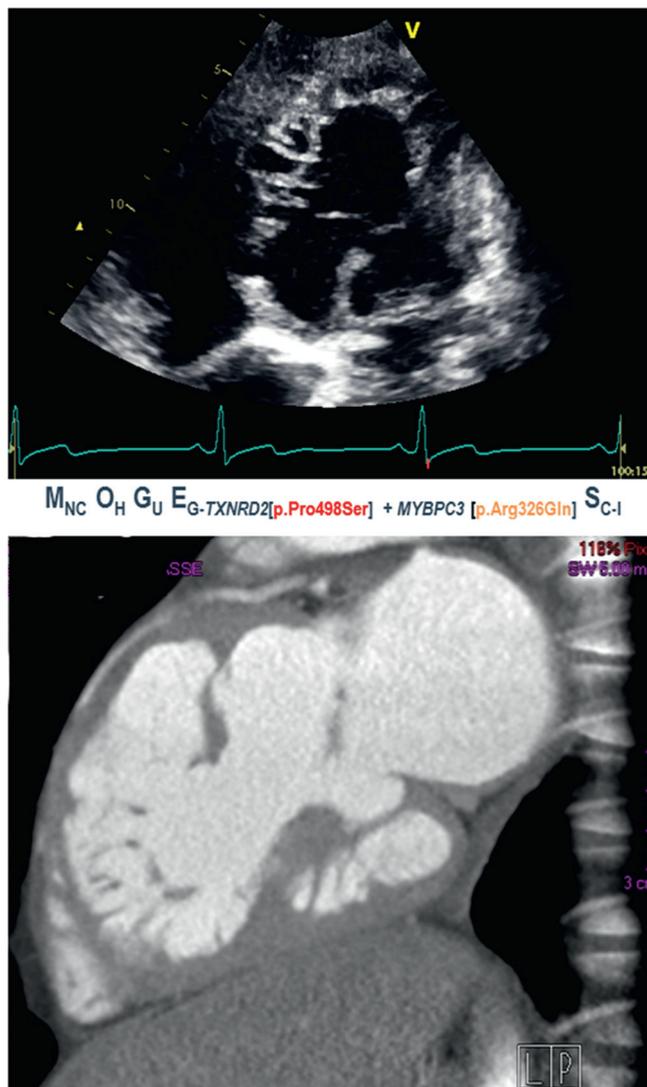
TABLE 1 Continued

Gene	Protein	MIM*	Inheritance	LVNC†	DCM and LVNC	HCM and LVNC	RCM and LVNC	ARVC and LVNC	Phenotypes
<i>TNNT2</i>	Cardiac troponin T2	191045	AD	X	X	X	X		DCM, HCM, RCM, LVNC6 (64)
<i>TPM1</i>	Tropomyosin 1	191010	AD	X	X	X			DCM, HCM, LVNC9 (65)
Monogenic syndromes with major extracardiac traits and cardiac involvement including LVNC									
<i>ARFGEF2</i>	ADP-ribosylation factor guanine nucleotide-exchange factor 2	605371	AR	X					Periventricular heterotopia with microcephaly (66)
<i>DNAJC19</i>	DNAJ/HSP40 homolog, subfamily c, member 19	608977	AR	X	X				DCM with ataxia (3-methylglutaconic aciduria type V) (67)
<i>GLA</i>	Alpha-galactosidase	300644	XL	X		X			Anderson-Fabry disease (34,35)
<i>LAMP2</i>	Lysosome-associated membrane protein 2	300257	XL			X			Danon disease (36)
<i>MLYCD</i>	Malonyl-coenzyme A decarboxylase deficiency	606761	AR	X	X				Developmental delay, metabolic acidosis hypoglycemia (1 case with LVNC and DCM) (68)
<i>MMACHC</i>	Cobalamin C deficiency; methylmalonic aciduria and homocystinuria, cblC type	609831	AR	X	X				Megaloblastic anemia, lethargy, failure to thrive, developmental delay, intellectual deficit, and seizures; >homocysteine (3 cases with LVNC) (69)
<i>NNT</i>	Nicotinamide nucleotide transhydrogenase	687878	AR	X					Glucocorticoid deficiency 4 (1 case with LVNC) (70)
<i>NSD1‡</i>	Nuclear receptor binding SET domain protein1	606681	Isolated cases	X					Sotos syndrome (Sotos cerebral gigantism) with or without CHD: 2 cases (71)
<i>RSK2</i>	Ribosomal S6 kinase 2	300075	XLD				X		Coffin-Lowry syndrome (facio-digital mental retardation syndrome); mental retardation (72)
<i>YWHAE(14-3-3ε)</i>	Monoxygenase activation protein, epsilon isoform	605066	AD	X	X				LVNC and hypoplasia of the corpus callosum (73); 1 case
Mitochondrial DNA mutations reported at least once as associated with cardiac phenotypes, including LVNC (74-77,101)									
<i>MTTL1</i>	tRNA leucine (UUR)	<i>tRNA^{Leu(UUR)}</i>	A3243G	X	X	X			MELAS
<i>MTTQ</i>	tRNA glutamine	<i>tRNA^{Glu}</i>	T4373C	X	X	X			Possibly LVNC-associated
<i>MTTD</i>	tRNA aspartic acid	<i>tRNA^{Asp}</i>	G7521A	X		X			Possibly LVNC-associated
<i>MTRNR1</i>	12S rRNA	<i>12S rRNA</i>	T921C	X	X				Possibly LVNC-associated
<i>MTRNR1</i>	12S rRNA	<i>12S rRNA</i>	T850C	X	X				Possibly LVNC-associated
<i>MTRNR1</i>	12S rRNA	<i>12S rRNA</i>	T961C	X	X				DEAF; possibly LVNC-associated
<i>MTRNR2</i>	16S rRNA	<i>16S rRNA</i>	T2352C	X	X				Possibly LVNC-associated
<i>MTRNR2</i>	16S rRNA	<i>16S rRNA</i>	G2361A	X	X				Possibly LVNC-associated
<i>MTRNR2</i>	16S rRNA	<i>16S rRNA</i>	A2755G	X	X	X			Possibly LVNC-associated
<i>MTND1</i>	NADH dehydrogenase subunit 1	<i>ND1</i>	T3308C	X					Possibly LVNC-associated; MELAS, DEAF, LVNC
<i>MTND1</i>	NADH dehydrogenase subunit 1	<i>ND1</i>	A3397G	X					Possibly LVNC-associated
<i>MTND1</i>	NADH dehydrogenase subunit 1	<i>ND1</i>	T4216C	X					LHON, possibly LVNC-associated
<i>MTATP8</i>	ATP synthase F _o subunit 8	<i>ATP8</i>	C8858T	X					Possibly LVNC-associated
<i>MTATP6</i>	ATP synthase F _o subunit 6	<i>ATP6</i>	A9058G	X					Possibly LVNC-associated
<i>MT-CO3</i>	Cytochrome c	<i>CO3</i>	A9299G(<i>syn</i>)	X					Provisional, possibly LVNC-associated
<i>MT-CO3</i>	Cytochrome c	<i>CO3</i>	G9300A	X					Provisional, possibly LVNC-associated
<i>MT-TG</i>	tRNA glycine	<i>tRNAGly</i>	T10034C	X					Provisional, possibly LVNC-associated
<i>MT-TG</i>	tRNA glycine	<i>tRNAGly</i>	A10042T	X					Provisional, possibly LVNC-associated
<i>MT-TG</i>	tRNA glycine	<i>tRNAGly</i>	C10043T	X					Provisional, possibly LVNC-associated
<i>MT-TG</i>	tRNA glycine (SIDS)	<i>tRNAGly</i>	A10044G	X					SIDS (mitomap) + provisional, possibly LVNC-associated (74)
<i>MTCYB</i>	Cytochrome b	<i>CytB</i>	T15693C (M-T)	X	X	X			Possibly LVNC-associated (1 case LVNC) (76)

In blue: 9 of the 10 left ventricular noncompaction (LVNC) phenotypes (#1,3-10) reported in the Online Mendelian Inheritance in Man (MIM) catalog. Unique cases or small series of diseases/syndromes in which LVNC was observed are referenced in the Phenotypes column. The concept of association does not imply a causal role of the genetic/chromosomal defect in LVNC. *Indicates the gene in the corresponding catalogue. †LVNC described in at least 1 patient/family. ‡NSD1 gene defects are also associated with acute myeloid leukemia and Beckwith-Wiedemann syndrome.

AD = autosomal dominant; AF = atrial fibrillation; AR = autosomal recessive; ARVC = arrhythmogenic right ventricular cardiomyopathy; ASD = atrial septal defect; ATP = adenosine triphosphate; CHD = congenital heart disease; CPVT = catecholaminergic polymorphic ventricular tachycardia (type 1 or 2); DCM = dilated cardiomyopathy; DEAF = maternally inherited or aminoglycoside-induced deafness; HCM = hypertrophic cardiomyopathy; LHON = Leber's hereditary optic neuropathy; LQTS = long QT syndrome type 3; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; PDA = patent ductus arteriosus; RCM = restrictive cardiomyopathy; rRNA = ribosomal ribonucleic acid; RYR2 = ryanodine receptor 2; SIDS = sudden infant death syndrome; SSS = sick sinus syndrome; tRNA = transfer ribonucleic acid; VSD = ventricular septal defect; XL = X-linked; XLD = X-linked dominant.

FIGURE 1 Apical 4-Chamber Echocardiographic View and CTA Scan Profile of a Heart That Meets LVNC Criteria



The heart has normal left ventricular diameter and left ventricular function. The 2 genetic variants identified in *TXNRD2* and in *MYBPC3* cannot be further investigated in family segregation studies because the patient is adopted. The *TXNRD2* gene encodes a selenocysteine-containing enzyme that is essential for mitochondrial oxygen radical scavenging. Mutations in this gene have been reported in dilated cardiomyopathy (118). The variant in *MYBPC3* is common and unlikely to be the cause of the left ventricular noncompaction. The morpho-functional description is according to MOGE(S) nosology (6). CTA = computed tomography angiography.

and related causes. A unifying pathogenetic hypothesis is unlikely.

CLINICAL GENETICS: FAMILY SCREENING

Genetic evaluation, including both counseling and genetic testing, is recommended for patients with

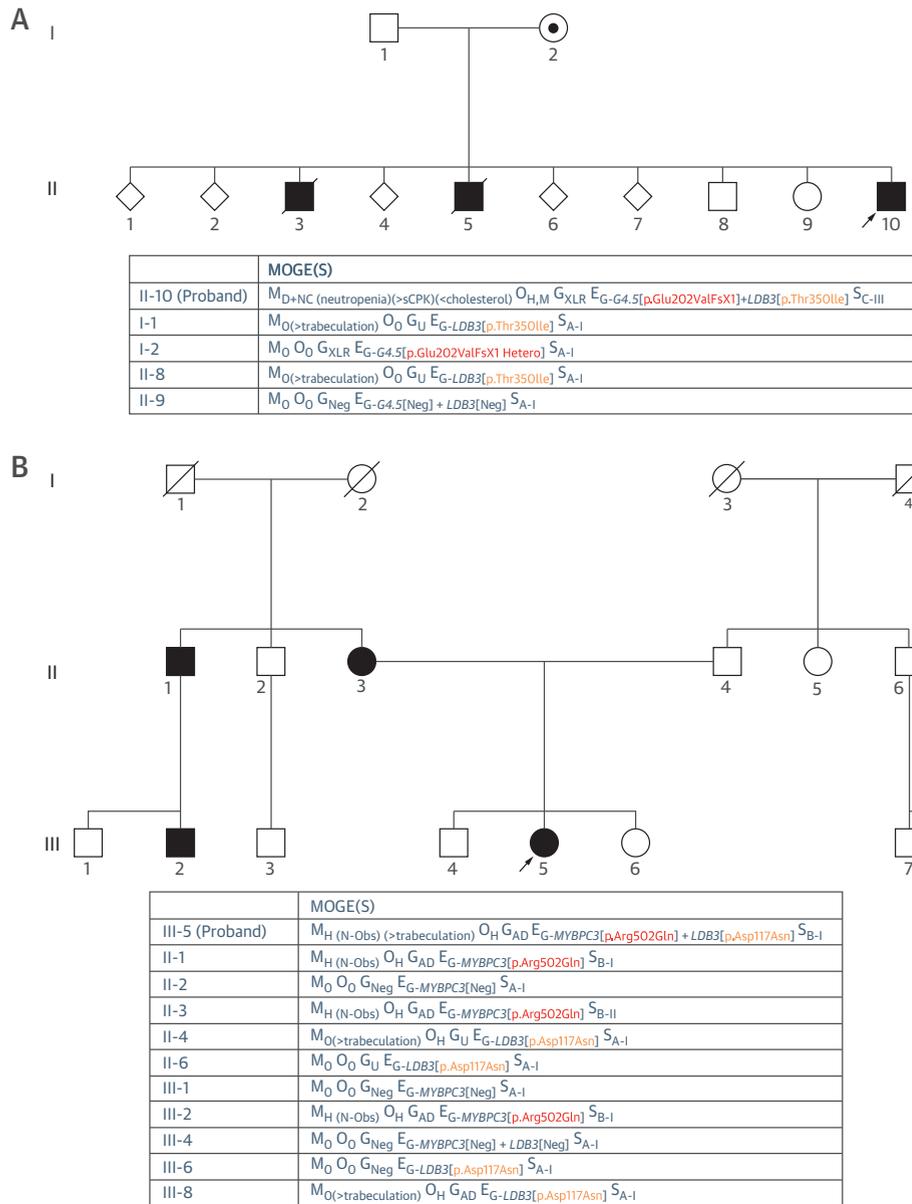
CMP and LVNC. This recommendation is for patients diagnosed with 1 of the syndromes in which LVNC may occur, as well as for subjects in whom LVNC is incidentally identified during medical screening (80,81).

The medical genetic examination explores anthropometric profiles, face, skin, eyes, hair, and the skeletal and nervous systems. This careful phenotypic evaluation may identify extracardiac traits that recur in syndromes with LVNC. [Online Table 1](#) summarizes electrocardiography, echocardiography, CMR, and biochemical information, along with extracardiac traits that are potentially useful for phenotypic characterization of patients and families in whom mutations of the listed genes are identified; each trait has been variably reported in patients carrying mutations in the corresponding genes and is part of the heterogeneous phenotypic manifestations. Clinical family screening can help identify if the trait is familial or sporadic (82). All data contribute to the generation of family pedigrees, which provide a graphic view of the mode of inheritance of the disease. In LVNC families, some relatives of affected members may have iLVNC (81), whereas others may have CHD or CMP with or without LVNC (47) ([Figure 4](#)). Therefore, the segregation of LVNC may not coincide with the segregation of a coexisting CMP ([Figures 2A and 2B](#)) (83). This scenario explains why segregation studies are major contributors to unraveling the role of mutations, especially in families with complex genetics characterized by the presence of >1 mutation/variant in the same person/patient. Clinical monitoring should be suggested to all family members exhibiting increased trabeculation or LVNC, irrespective of genetic testing ([Table 2](#)).

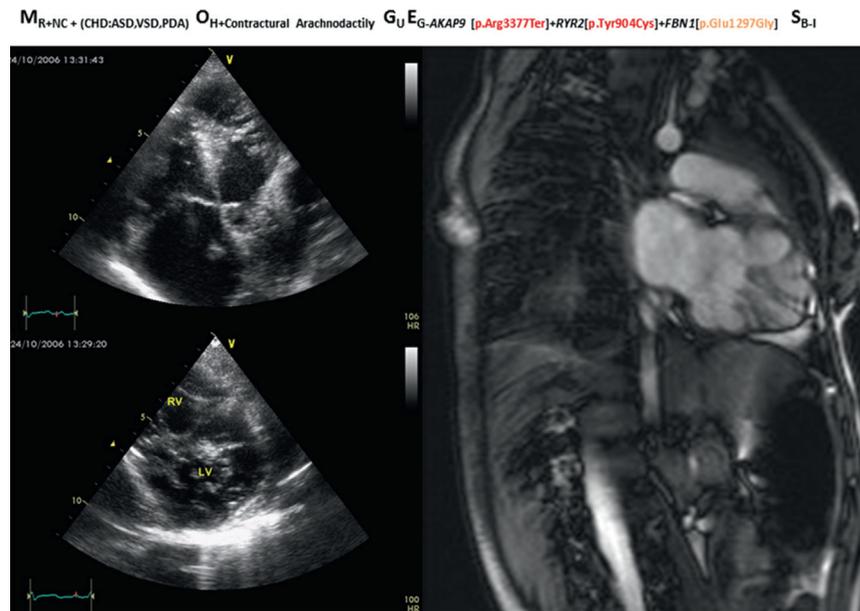
LVNC GENES

The genes reported to date in at least 1 patient/family with LVNC are listed in [Table 1](#) (34-36,41-76). Many genes should be considered provisional because they have been described in a single case/family, and data are not replicated. The genetic basis of LVNC is an expanding issue severely limited by the enrollment criteria, which reflect the current heterogeneous diagnostic definitions of LVNC. LVNC in patients with either DCM or HCM or with syndromic conditions should be distinguished from true iLVNC. In fact, when LV dilation and dysfunction are present, the diagnosis of LVNC CMP is supported more by the DCM phenotype than by the trabecular morphology. When LVNC is observed in hearts with HCM, the diagnosis of LVNC CMP is supported more by the HCM than by the LVNC criteria. When LVNC is observed in CHD,

FIGURE 2 Pedigrees and the MOGE(S) Tables Showing That Segregation of the Cardiomyopathy and Hypertrabeculation/LVNC May Not Coincide



(A) The proband (II-10) is affected by Barth syndrome (47). In infancy, the boy (II-10) demonstrated severe left ventricular noncompaction (LVNC)-dilated cardiomyopathy. After appropriate management of the early severe heart failure, he recovered and is now stable on optimal medical therapy. The mother is a healthy carrier of the G4.5 mutation and exhibits normal echocardiographic data. The father (I-1) is a carrier of the p.(Thr350Ile) in *LDB3*: he transmitted the variant to the proband (II-10) and to (II-8). Both I-1 and II-8 showed echocardiographic and cardiac magnetic resonance-prominent trabeculae but did not fulfill the criteria for LVNC (47). In the proband, clinical management was dictated by the early severe heart failure, irrespective of LVNC. **(B)** The proband (III-5) is affected by hypertrophic cardiomyopathy (HCM) with LVNC. The *MYBPC3* mutation that segregates with a mild form of nonobstructive HCM in the family was inherited from the affected mother, whereas the *LDB3* p.(Asp117Asn) mutation was inherited from the healthy father (II-4); the paternal echocardiographic study revealed prominent trabeculae but not LVNC. The paternal sister (II-5) did not accept screening and genetic testing, whereas her brother (II-6) had both clinical and genetic screening. The echocardiographic study showed normal trabecular anatomy, and LV size and function; the son (III-8) inherited the paternal *LDB3* variant and showed increased trabeculation, and normal LV size and function, but did not meet the criteria for LVNC. The proband's sister (III-6) inherited the *LDB3* variant and showed increased trabeculation but did not meet the criteria for LVNC. In both families, the 2 mutations/variants in *LDB3* do not seem to cause LV dilation and dysfunction because carriers only show hypertrabeculation of the LV wall. Long-term follow-up will help to elucidate the role, if any, of this genetic variant and the evolving phenotypes of family members showing only LV wall hypertrabeculation. The morpho-functional description is according to MOGE(S) nosology (6).

FIGURE 3 A 14-Year-Old Daughter of Healthy, Nonconsanguineous Parents

This female patient demonstrates congenital heart disease (CHD) (patent ductus arteriosus, atrial septal defect [ASD], ventricular septal defect [VSD] and papillary muscle abnormalities) with severe left ventricular noncompaction in the context of a restrictive, hypokinetic cardiomyopathy (left ventricular ejection fraction = 35%). The girl also displays contractural arachnodactyly. Her aorta and ocular apparatus are normal. Echocardiographic (apical 4-chamber and parasternal short-axis views) and cardiac magnetic resonance studies (2-chamber, long-axis) demonstrated prominent trabeculation of the left ventricle. The mother had normal results on electrocardiography and echocardiography studies. The father was not available for clinical and genetic studies. The incomplete family study prevents evaluation of the segregation of the genetic variants/mutations with the phenotype. The morpho-functional description is according to MOGE(S) nosology (6).

the diagnosis is driven by the congenital heart defect. Nonetheless, both descriptors (either leading or subordinating the LVNC to the CMP diagnosis) provide an immediate perception of the phenotype. Conversely, the diagnosis of “LVNC CMP” may limit clinical information and, in parallel, automatically assigns the LVNC a driving role in the diagnosis.

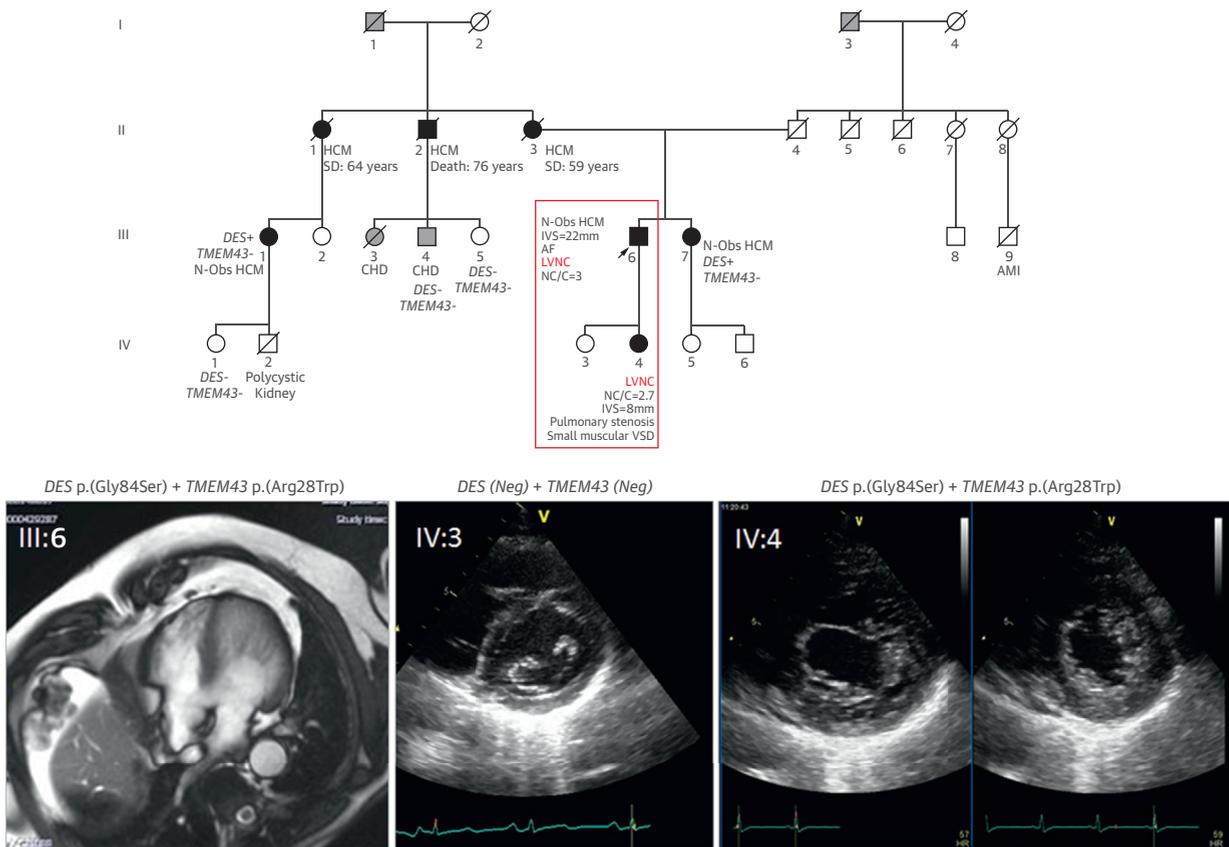
GENES AND LVNC. In 2001, Ichida et al. (47) identified a heterozygous mutation (p.Pro121Leu) in the *Dystrobrevin* (*DTNA*) gene segregating with LVNC in a 3-generation Japanese family with CHD and LVNC. This phenotype was labeled LVNC1 in the Online Mendelian Inheritance in Man catalog in which the LVNC abbreviation of the phenotype (#) is followed by a number (LVNC1, LVNC2, among others), each of which corresponds to a unique gene. In 2004, linkage analysis of a large family with autosomal dominant LVNC demonstrated a peak 2-point logarithm of odds score of 5.06 in 11p15. However, the 2 prime positional candidate genes (*CSR3* and *SOX6*) in the critical interval of 6.4 centimorgans (between markers D11S1794 and D11S928) tested negative (84). The locus

was labeled LVNC2 %609470; the symbol % indicates that the gene is still unknown. Since then, 8 additional loci have been included in the Online Mendelian Inheritance in Man catalog and labeled as LVNC loci. However, none of the reported genes is associated with iLVNC in hearts with normal dimensions and function.

GENES AND LVNC IN CMPs. It is not surprising that genes associated with LVNC coincide with those causing CMPs; in fact, the term LVNC CMP is usually assigned to DCM with LVNC or HCM with LVNC. These genes code for sarcomeric proteins, nuclear envelope and Z-band components, sarcolemma proteins, ion channels, and genes involved in signaling pathways, such as NOTCH (Table 1).

Sarcomeric genes have largely been investigated in CMP with LVNC. In 2008, Klaassen et al. (42) first associated mutations in *ACTC1* (cardiac alpha actin) with LVNC; the investigators identified the p.(Glu101Lys) mutation, described previously in apical HCM (85). Mutations in the same gene also cause DCM, RCM, and HCM, as well as CHD (86) (Figure 5).

FIGURE 4 Pedigree of a Family in Which the Proband Presented With Nonobstructive HCM and LVNC



The cardiomyopathy phenotype seems to segregate with the p.(Gly84Ser) in the *Desmin* (*DES*) gene. However, only the proband and his daughter (IV:4) fulfilled criteria for the diagnosis of LVNC. In other affected family members carrying the mutation, the trabecular anatomy was normal. The daughter exhibits mild pulmonic valve stenosis and 4 small, nonclinically and hemodynamically significant, interventricular muscular septal defects. The genetic cause of LVNC in III:6 and IV:4 is not clarified: it could be interpreted as possible modifier effect of the *TMEM43* variant. HCM = hypertrophic cardiomyopathy; LVNC = left ventricular noncompaction. Symbols as in Figure 2. Grey-filled symbols mean unknown status of the trabecular anatomy.

Mutations in the *MYH7* gene were reported in both children and adults with CMP and LVNC (55-57); 9 diseases are allelic at the same locus (LVNC5; HCM; DCM; RCM; familial autosomal dominant Ebstein anomaly with LVNC; autosomal dominant and recessive myosin storage myopathy; Laiang distal myopathy; and scapuloperoneal syndrome, myopathic type). Similar, but less complex, is the list of CMPs allelic at the *MYBPC3* locus (HCM, DCM, and LVNC) (53-55) (Figure 6), with lethal phenotypes in infants who carry compound heterozygous, double heterozygous, or homozygous truncating mutations (87). Mutations in *TNNT2* (LVNC) (64) and *TPM1* (LVNC) (65) are less common in CMPs associated with LVNC. The mechanisms by which mutations in sarcomeric genes cause LVNC remain to be elucidated.

Incomplete genotype is a possible explanation that will be unraveled in the near future with analysis of multigene panels and family segregation studies. Given the overlapping phenotypes associated with mutations of sarcomeric genes and the number of diseases allelic at the same loci, mutated members of a family may exhibit different cardiac profiles. Therefore, the diagnosis of “familial CMP” may not rely on the presence of an identical cardiac phenotype in all mutated and affected family members but on the presence of “CMP” with variable phenotypic characteristics in affected relatives.

Mutations in genes coding for nuclear envelope proteins (e.g., *LMNA*, which typically causes DCM and conduction disease) seem to be less common than those in sarcomeric genes. To date, 3 mutations

TABLE 2 Summary of the Possible Evaluation in Normal Subjects and Patients With LVNC

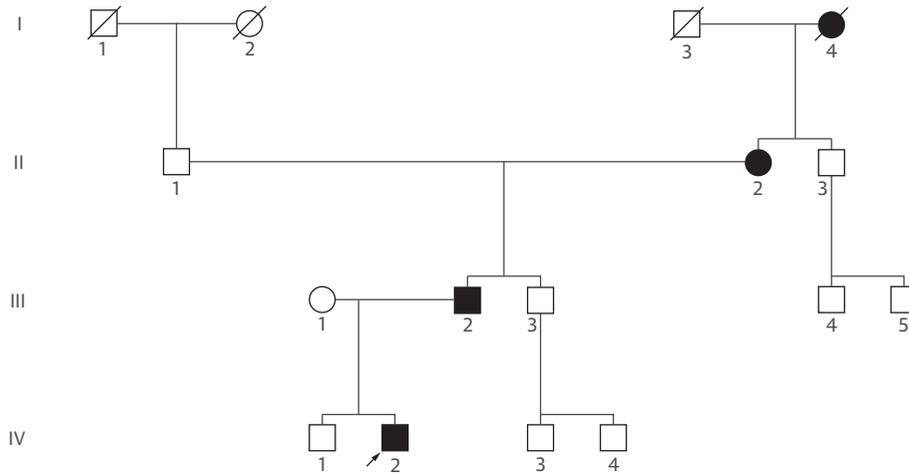
LVNC in Subjects With Normal LV Size and Function	LVNC in Patients With Cardiomyopathy: HCM, DCM, RCM, ACM	LVNC in Patients With Congenital Heart Disease	LVNC in Patients With Renal or Hematologic Disease	LVNC in Patients With Chromosomal Disorders That Do not Typically Affect the Heart	RVNC
Categories					
<ul style="list-style-type: none"> • Athletes* • Pregnant women 	<ul style="list-style-type: none"> • Isolated cardiomyopathies, all subtypes; • Monogenic syndromes with heart involvement presenting with cardiomyopathy phenotype (e.g. AFD, Danon disease); • Myopathies with LVNC, irrespective of associated LV remodeling and dysfunction. 	<ul style="list-style-type: none"> • Sporadic CHD • Familial CHD 	<ul style="list-style-type: none"> • Renal failure • Polycystic kidney† • Hypertension • Hematologic disorders 	<ul style="list-style-type: none"> • Known chromosomal defects with and without CHD or cardiomyopathy 	<ul style="list-style-type: none"> • Isolated RVNC • Biventricular NC
Clinical work-up					
<ul style="list-style-type: none"> • Monitoring • Genetic counseling • Family screening • Genetic testing when family screening demonstrates familial cardiomyopathy • Scheduling clinical controls in probands on individual basis • Interdisciplinary discussion with obstetricians and sport cardiologists 	<ul style="list-style-type: none"> • The management is dictated by the underlying cardiomyopathy/dystrophy. • Family screening • Genetic counseling • Genetic testing 	<ul style="list-style-type: none"> • The management is dictated by the underlying CHD. • Genetic counseling and family screening: to exclude minor asymptomatic congenital heart defects in relatives or assess the presence of isolated LVNC. • Genetic testing (cytogenetic and molecular genetics) 	<ul style="list-style-type: none"> • Exclude or assess LV dysfunction and abnormal dimensions • Monitoring during and after treatment of the non-cardiac disease • Genetic counseling • Family screening diseases affecting heart and kidney or associated with the primary disease† • Genetic testing when family screening demonstrates familial cardiac disease 	<ul style="list-style-type: none"> • The management is dictated by the underlying disease/syndrome • Annotation of novel traits associated with LVNC may help identification of LVNC genes • Genetic counseling • Genetic testing: to be evaluated on the basis of individual and family characteristics. 	<ul style="list-style-type: none"> • In patients with cardiomyopathy: the management is dictated by the phenotype according to guidelines. • In subjects with normal LV dimensions and function: monitoring ventricular size and function. CMR can be suggested. • Genetic counseling • Genetic testing in cardiomyopathies • Clinical family screening
<ul style="list-style-type: none"> • Cardiologic work-up includes individual examination, medical history (arrhythmias, syncope), family history (affected family members, SD of relatives) and screening, 12-lead ECG, 2D echocardiography. When indicated and possible: CMR with gadolinium contrast. Possible: stress echocardiography, ≥ 24-h Holter monitoring for arrhythmias. Personalized work-up contributes to tailoring individual clinical investigation. • Monitoring should be planned in patients with cardiomyopathy or CHD associated with LVNC as well as in asymptomatic subjects in whom LVNC/hypertrabeculation has been identified. 					
No indication to anticoagulation. Possible participation in competitive sports (112)	Anticoagulation in patients with LV dilation and dysfunction as per guidelines; atrial dilation; cardiac surgery related indications in CHD.		Anticoagulation: to be decided on individual needs in patients with LV dilation and dysfunction.		Anticoagulation in patients with ventricular dilation and dysfunction and atrial dilation.
<p>*African-American or African-Caribbean athletes have a higher risk. †Polycystic kidney disease (102-105). AFD = Anderson Fabry Disease; ACM = arrhythmogenic cardiomyopathy; CHD = congenital heart disease; CMR = cardiac magnetic resonance; ECG = electrocardiogram; RVNC = right ventricular non-compaction; other abbreviations as in Table 1.</p>					

([p.Arg644Cys]; p.[Arg190W] and p.[Val455Glu]) have been reported in patients with DCM and LVNC (51,52,88). Given the high risk of arrhythmia associated with LMNA mutations, these patients/families deserve the same monitoring and management strategies currently adopted for cardiomyopathies without LVNC. Recent guidelines on the prevention of sudden death recommend that implantable cardioverter-defibrillators should be considered in patients with DCM, a confirmed disease-causing LMNA mutation, and clinical risk factors (Class IIa, Level B) (89). Risk factors include nonsustained ventricular tachycardia during ambulatory

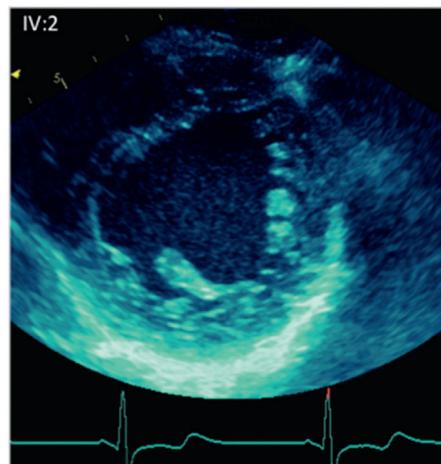
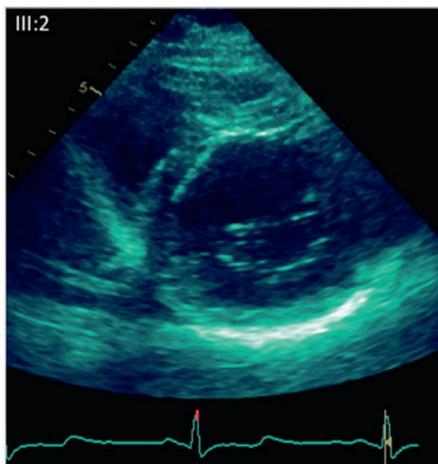
electrocardiographic monitoring, LV ejection fraction <45% at first evaluation, male sex, and non-missense mutations (insertions, deletions, truncations, or mutations affecting splicing). These factors correspond to those previously identified in a large European cohort of patients with dilated cardiomyopathy (90).

Genes encoding Z-line components in both skeletal and cardiac muscle include the CYPHER-ZASP (LDB3) gene that is a relevant candidate for LVNC (49). In fact, carriers of LDB3 mutations may exhibit DCM, LVNC, and, less commonly, HCM and ARVC (91,92). Mutations in the same gene also cause

FIGURE 5 Family With Autosomal Dominant "Cardiomyopathy"

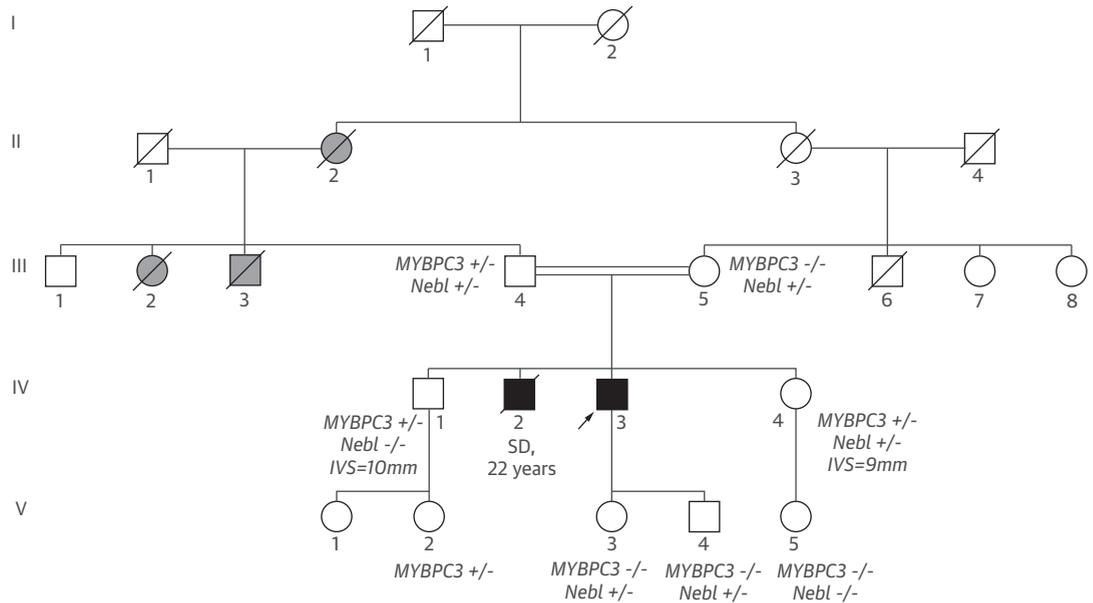


	MOGE(S)
IV-2 (Proband)	$M_{D+NC} O_H G_{AD} E_G-ACCTC1[p.Tyr296His] + DSC2[p.Ala897LysfsX4] + LAMA2[p.Ala921Glu] S_{C-II}$
I-4	$M_{H+D(Mahaim, ablation)} O_H G_{AD} E_G-ACCTC1[p.Tyr296His] S_{C-II}$
II-1	$M_O O_O G_U E_G-DSC2[p.Ala897LysfsX4] S_{A-I}$
II-2	$M_{H+D} O_H G_{AD} E_G-ACCTC1[p.Tyr296His] S_{C-II}$
II-3	$M_O O_O G_O E_G-ACCTC1[Neg] S_{A-I}$
III-1	$M_O O_O G_U E_G-LAMA2[p.Ala921Glu] S_{A-I}$
III-2	$M_D O_H G_{AD} E_G-ACCTC1[p.Tyr296His] + DSC2[p.Ala897LysfsX4] S_{C-II}$
III-3	$M_O O_O G_U E_G-DSC2[p.Ala897LysfsX4] S_{A-I}$
IV-1	$M_O O_O G_U E_G-LAMA2[p.Ala921Glu] S_{A-I}$

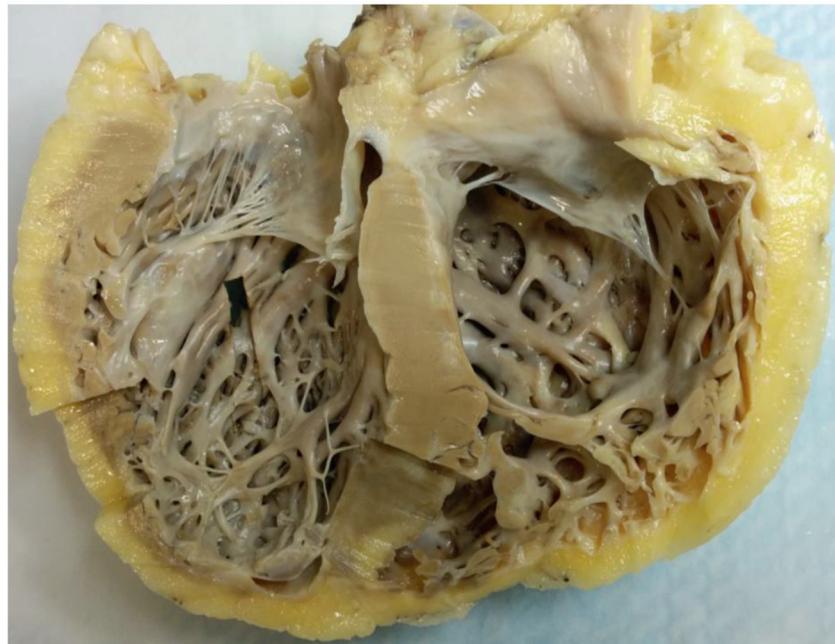


The affected family members demonstrate different phenotypes: the proband (IV:2) displays dilated cardiomyopathy (DCM) + LVNC and his father (III:2) shows dilated HCM, as do both his grandmother (II:2) and great-grandmother (I:4). This latter was the unique family member who had Mahaim fibers and tachycardia. She died at 88 years of age after a 30-year history of cardiomyopathy. In the proband, the left ventricular thickness (short-axis view) is normal (9 mm), left ventricular end-diastolic diameter is increased (58 mm), and left ventricular ejection fraction is 48%. His genetic profile is unique in the family: he inherited both the *ACTC1* mutation and the VUS in *DSC2* from the father and a further VUS in *LAMA2* from the mother, who demonstrated normal LV size, morphology, and function. The role of the *ACTC1* mutation seems to be confirmed by its segregation with the cardiomyopathy; the role of the *DSC2* and *LAMA2* variants is unclear. LVNC appears as a sporadic trait, whereas the cardiomyopathy is familial autosomal dominant. The morpho-functional description is according to MOGE(S) nosology (6). Abbreviations as in Figure 4.

FIGURE 6 Biventricular Dilated Cardiomyopathy With Compactless LV Wall



IV:3 → proband: MYBPC3 p.(Thr957Ser, +/-) and NEBL c.1008+5A>G (+/+)



The proband underwent heart transplantation for dilated cardiomyopathy; the heart excised at transplantation revealed left ventricular noncompaction, mostly because of the near absence of the compacted layer. Onset of the illness had occurred 10 years before transplantation with an episode of syncope sustained by ventricular tachycardia. The evolving phenotype was as in a biventricular dilated cardiomyopathy. The parents are consanguineous. We identified a MYBPC3 mutation that does not segregate with the phenotype because the carrier father is unaffected; in addition, both sister and brother are carriers of the same variant and have normal hearts. We also identified a rare splice variant in NEBL: both parents are carriers of the heterozygous variant. The proband is the only family member who carries both MYBPC3 and homozygous NEBL variants. -/- = noncarrier; +/- = heterozygous carrier; +/+ = homozygous carrier.

myofibrillar myopathy. Experimental ablation of Cypher, the PDZ-LIM domain Z-line protein, causes a severe form of congenital myopathy and DCM with premature death (93). Interpretation of the possible role of genetic variants in *LDB3* should be done cautiously; in fact, the p.(Asp117Asn) variant, which was originally described as causing DCM and LVNC (49), is now reported as a single-nucleotide polymorphism (Figure 2B) (94). This debated variant has been described in a patient with LVNC and conduction disturbances (95).

CMPs often coexist with muscle dystrophies/myopathies. Hypertrabeculation/NC of the left ventricle has been described in several neuromuscular disorders, including Duchenne muscular dystrophy (DMD) and mitochondrial myopathies (96). In a large CMR study including 96 patients with DMD, 27 (28%) fulfilled criteria for the diagnosis of LVNC (97). LVNC was defined as a diastolic NC/C ratio >2.3 and was measured according to the American Heart Association's 16-segment model. In patients with ejection fraction <55%, the median NC/C ratio was 2.46 versus 3.69 for patients with LVNC and 1.54 for normal control subjects. The relevant contribution of this study goes beyond the prevalence of LVNC in DMD: serial CMR in 78 boys with DMD demonstrated a mean rate of change in NC/C ratio per year of 0.36, resulting from the progressive decrease of the compacted and relative increase of NC layer. This information adds a dynamic view of NC anatomy in CMPs and potential prognostic information; in fact, LVNC was associated with worsening LV systolic function. The progressive thinning of the compacted layer may end in a relative increase in the ratio of the 2 layers. This scenario contributes to explaining the data reported by Kimura et al. (98), who found that LVNC is an independent negative prognostic factor in carriers of *DMD* defects. Mutations in alpha-dystrobrevin (*DTNA*), which is part of the cytoplasmic complex of dystrophin-associated proteins, have been reported in 1 family with CHD associated with LVNC (47).

Ion-channel genes (e.g., *SCN5A*), genes encoding calcium-release channels (e.g., the ryanodine receptor 2 [RYR2]), and calcium ion reservoir proteins (e.g., calsequestrin 2 [CASQ2, which is part of a protein complex that contains RYR2]) typically cause diseases affecting the QT-interval and catecholaminergic polymorphic ventricular tachycardia (types 1 and 2). Mutations in *SCN5A* have been reported in Japanese patients with LVNC (63). Similarly, mutations in *CASQ2* and *RYR2* have also been associated with LVNC (45,61,62); >80% of carriers of an exon 3 deletion in the *RYR2* gene demonstrated LVNC and

malignant arrhythmogenic phenotypes with syncope and catecholaminergic polymorphic ventricular tachycardia (61,62). A relevant contribution from *RYR2*-related LVNC is the demonstration that NC can develop during the evolution of the genetic disease: a young patient with a deletion of *RYR2* exon 3 exhibited normal LV function and structure at 14 years of age (when he presented with 2 episodes of exertional syncope) and LVNC with normal function 2 years later when he presented with a third episode of syncope (61).

Finally, the possible role of genes active in the Notch signaling pathway, which is involved in trabecular maturation, is supported by the description of mutations in the *MIB1* gene that encodes the Dapk-interacting protein 1 in 2 families with LVNC (1 proband underwent heart transplantation) (52). It has also been described in experimental studies in *Notch1*-deficient mice (failure of cardiac trabeculation) and in double-knockout suppressors (*Numb* and *Numblake*) of *Notch2* (hypertrabeculation, reduced compaction, and ventricular septum defects) (8,99).

In CMP, the interpretation of clinical, imaging, and genetic data does not meet LVNC-specific rules and criteria. Diagnoses such as dilated LVNC versus DCM with LVNC, or hypertrophic LVNC versus HCM with LVNC, are equally used to describe the phenotypes. However, when LVNC is associated with dilated or hypertrophic phenotype, the diagnosis should be driven by the type of CMP, followed by the description of LVNC.

MONOGENIC SYNDROMES WITH LVNC. Complex, rare monogenic syndromes with cardiac and noncardiac anomalies (Table 1) do not exclude an independent origin or cause of NC. Disorders such as Danon disease or Anderson-Fabry disease do not typically demonstrate LVNC; however, the association of typical hearts associated with AFD (34,35) or Danon disease (36) with NC of the left ventricle has been reported in a few cases. The possibility exists that unidentified mutations in genes other than *GLA* (Anderson-Fabry disease) or *LAMP2* (Danon disease) may coexist, thus explaining the associated trait. Rare syndromes, such as periventricular heterotopia with microcephaly, glucocorticoid deficiency, or Coffin-Lowry syndrome, may occasionally exhibit LVNC (66-73,100).

MtDNA AND LVNC. Several MtDNA variants are possibly associated with LVNC (74-77,101) (Table 1). Cardiac phenotypes that typically occur in patients who are carrier of mutations in MtDNA are characterized by mild, usually concentric, LV hypertrophy. The natural course of these HCMs is

characterized by evolution through LV dilation and dysfunction, similar to DCM. LVNC may occur but is uncommon (75,76). Studies exploring both MtDNA and nuclear genes are especially necessary to elucidate the causal or modifier roles of MtDNA mutations.

CHROMOSOMAL DISORDERS. Syndromes with LVNC have been described in patients with chromosomal anomalies [1p36 deletion syndrome; interstitial 1q43-q43del; del(1)(q) syndrome; del5q35; 7p14.3p14.1 deletion, 8p23.1 del syndrome; 18p subtelomeric deletion; 22q11.2 deletion syndrome; 22q11.2 distal deletion syndrome; trisomy 13 and 18; tetrasomy 5q35.2-5q35; Robertsonian translocation 13;14; mosaics, such as 45,X/46XX and 45,X/46,X,i(Y)(p11)]. Most chromosomal abnormalities represent isolated cases (11,78). Reasons of scientific and clinical interest include the possible identification of new disease or modifier genes when abnormal chromosomal regions include novel candidate genes in patients with the typical syndrome and LVNC.

ACQUIRED, NONGENETIC LVNC

The acquired and reversible forms of LVNC question the unique and a priori interpretation of the NC morphology as a genetic disease and CMP (13-19). An increasing number of reports describe normal subjects demonstrating hypertrabeculation up to NC in left ventricles with normal size, function, and wall thickness. When incidentally observed in young athletes, hypertrabeculation and NC morphology of the left ventricle prompt requests for genetic counseling and testing, often assigning the role of interpreting the possible pathological significance of the NC morphology to genetic testing, rather than to clinical data. Polycystic kidney is emerging as potentially associated with LVNC (102-105); the association can represent a comorbidity or may be similar to LVNC reported in chronic renal failure (13). Finally, hypertension seems to be associated with increased trabeculation, which is therefore influenced by cardiac loading conditions and comorbidities (106).

LVNC-SPECIFIC MANAGEMENT

Clinical family screening is indicated in LVNC associated with CMP, CHD, or rare syndromes with possible genetic causes (Table 2). Medical decisions do not vary in patients with LVNC and CMP or CHD with respect to the management of the corresponding disease without LVNC. In Barth syndrome, the administration of granulocyte-colony stimulating factor and prophylactic antibiotics during high-risk clinical occasions, such as surgeries or infections, is

dictated by the neutropenia (10). Risk stratification for arrhythmias and mural endocardial thrombosis is made on the basis of clinical, imaging, and biochemical data. Although there is concordance on high risk for heart transplantation in children with LVNC (107), and high arrhythmogenic and thromboembolic risk in patients with LVNC (108,109), major decisions (e.g., primary prevention of sudden death with implantable cardioverter-defibrillators) are made on the basis of individual risk estimates, according to current society guidelines (89,110). The prevention of mural endocardial thrombosis can eventually be a matter of earlier antiaggregation or anticoagulation therapy (7,111). The recent American Heart Association/American College of Cardiology Scientific Statement on Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities (112) introduced a modification from earlier guidelines (“it is most prudent to exclude athletes with these diseases from most competitive sports” [113]) and states: “Until more clinical information is available, participation in competitive sports may be considered for asymptomatic patients with a diagnosis of LVNC and normal systolic function, without important ventricular tachyarrhythmias on ambulatory monitoring or exercise testing, and specifically with no prior history of unexplained syncope (Class IIb; Level of Evidence C).” Conversely, “athletes with an unequivocal diagnosis of LVNC and impaired systolic function, or important atrial or ventricular tachyarrhythmias on ambulatory monitoring or exercise testing (or with a history of syncope) should not participate in competitive sports, with the possible exception of low-intensity class 1A sports, at least until more clinical information is available (Class III; Level of Evidence C).”

THE MOGE(S) NOSOLOGY: A DESCRIPTIVE STRATEGY

The novel MOGE(S) nosology endorsed by the World Heart Federation (6,114) provides a descriptive tool for the collection of precise genotype and phenotype data. Because the order of the abbreviations dictates the hierarchy of diagnostics and clinical evaluation of CMPs, and the system is flexible and implementable, MOGE(S) can be used to fix the phenotype at baseline and record follow-up data. In LVNC, the M descriptor of the morphofunctional phenotype can be NC (a Web app is available [115]; apps for smartphones or tablets are downloadable from Google Play or App Store) followed by additional specifications of further traits and markers. In DCM with LVNC, the descriptor integrates both DCM and NC ($M_D + NC$); in HCM with

LVNC, the descriptor includes both traits ($M_H + NC$). Isolated NC can be reported as M_{NC} , without further specification. In patients with LVNC associated with CHD, the description can include both conditions ($M_{Ebstein} + NC$). O describes the organs affected in the given patient (e.g., heart, muscle, auditory, ocular, skeletal systems). G defines whether the disease or the trait is genetic or nongenetic, and, when genetic, includes information on the pattern of inheritance (autosomal dominant [AD], autosomal recessive [AR], X-linked [XL], or matrilineal). In the case of chromosomal abnormalities (e.g., chromosome 1p36 deletion syndrome, which usually occurs as an isolated case in the family), the descriptor is either S (sporadic) or IC (isolated case), as reported in the Online Mendelian Inheritance in Man catalog. E (Etiology) is the precision diagnostic descriptor: in the case of genetic diseases, it specifies the disease gene(s) and the mutation(s) or the chromosomal anomaly. Finally, the (S) descriptor is optional, and it includes New York Heart Association functional class and American Heart Association stage. The system is being implemented for both annotation (116) and novel prognostic application (117); it is expected to provide extensive clinical and genetic data, in simple and large repositories, to be used for generating subgroups of cardiac phenotypes sharing the same causes and allowing for development of disease-specific drugs.

SUMMARY AND CONCLUSIONS

Our conclusions reflect the current uncertainties regarding the pathogenesis and significance of LVNC. By itself, LVNC is an imaging-based description of

the trabecular morphology of the LV wall. In rare syndromes/diseases, it is intrinsically part of the CMP. In the majority of cases, the current evidence supports more an association with CMP and/or CHD than a causal role. As such, the genetic basis is heterogeneous, often coinciding or overlapping with those that cause CMP or CHD. The acquired forms (the athlete example), the development of LVNC during the course of the disease (the RYR2 example), and its dynamic evolution (the DMD example) suggest that the origin is heterogeneous, and exclude arrest during embryogenesis as the unique pathogenetic hypothesis (Central Illustration). The complexity of the imaging-based diagnosis (nonconsensus criteria), interpretation of the role of NC as either cause or contributor to CMP, and the uncertainties as to the specific genetic basis of NC suggest the following:

- The need for consensus on diagnostic criteria from the scientific societies;
- Cautious diagnostic labeling of iLVNC as a CMP;
- The need for observational, prospective registries including probands and relatives with LVNC. The collection of precise data, both clinical and genetic, may positively influence interpretation of genotype-phenotype correlation, epidemiology, and clinical management.

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KEY WORDS congenital heart disease, genetic counseling, genetic testing, heart ventricles, mitochondrial myopathies, myocardium

APPENDIX For a supplemental table, please see the online version of this article.