Left Ventricular Noncompaction

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Abstract

LVNC is a relatively new, genetically heterogeneous, cardiomyopathy. Clinical presentation and prognosis range from asymptomatic disease with no or slow progression, to severe disabling, rapidly progressive cardiac failure. Initial presentation includes the triad of heart failure (potentially lethal) arrhythmias and/or thrombo-embolism. LVNC may occur at all ages, even prenatally. In childhood, clinical features are often more severe and LVNC is frequently associated with congenital heart defects. In adults, the majority of LVNC is isolated. The echocardiographic diagnostic criteria as proposed by Jenni et al. are currently the most widely applied. General cardiac guidelines for chronic heart failure and ICDs are applicable to the LVNC population. In approximately 40 % of isolated LVNC, molecular testing may yield a genetic (mostly sarcomere) defect, with *MYH7* as the most prevalent disease gene. The nonisolated forms of LVNC are caused by a range of rare genetic defects. Until now, in half of familial isolated LVNC, the genetic defect remains unknown. Genetic defects in a large number of sarcomere and other cardiomyopathy genes and in genes primarily associated with skeletal myopathies indicate that LVNC may result from a wide range of pathophysiologic mechanisms. Shared genetic defects and familial aggregation of LVNC, HCM, and DCM indicates that LVNC may be part of a broad spectrum of cardiomyopathies. The genetic etiology of LVNC requires that patients and their relatives are offered genetic testing and counseling. This may include (predictive) molecular analysis of relatives, when applicable, and/or cardiac evaluation of at-risk relatives, even when they are as yet asymptomatic.

Introduction

Noncompaction of the left ventricle or left ventricular noncompaction (LVNC) is a relatively new clinicopathologic entity, first described by Feldt et al. in 1969 [1]. LVNC is characterized by a prominent trabecular meshwork and deep intertrabecular recesses communicating with the left ventricular (LV) cavity, morphologically reminiscent of early cardiac development, and is therefore thought to be caused by an arrest of normal embryogenesis of the myocardium [2, 3]. Initial presentation includes congestive heart failure, thromboembolic events, and (potentially lethal) arrhythmias, including sudden cardiac death. LVNC may be a part of a more generalized cardiomyopathy, involving both the morphologically normal and the predominantly apical, abnormal LV segments. The cardiologic features of LVNC range from asymptomatic in adults to severe congenital forms [4–6]. LVNC was classified by the American Heart Association (AHA) as a separate primary, genetic cardiomyopathy, based on the predominant myocardial involvement and genetic etiology [7]. The European Society of Cardiology (ESC)

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H.F. Baars et al. (eds.), *Clinical Cardiogenetics*, DOI 10.1007/978-3-319-44203-7_7

considers LVNC as unclassified, due to the lack of consensus whether LVNC is a separate individual cardiomyopathy or a nonspecific morphological trait that can be found solitary or in combination with other forms of cardiomyopathy like hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), or with congenital heart disease [8]. The overlap in phenotypes raises the question whether LVNC is in fact a distinct cardiomyopathy or whether it is a morphological expression of different underlying diseases [9]. The majority of LVNC diagnosed in adults is isolated. Nonisolated forms of LVNC are more frequent in childhood and may co-occur with congenital heart malformations, or may be part of a malformation or chromosomal syndrome [6]. The combination of LVNC and neuromuscular disorders is observed in adults as well as in children.

The majority of LVNC, both isolated and nonisolated, is hereditary and LVNC appears to be genetically heterogenous. An important proportion of isolated LVNC in children and adults has been associated with mutations in the same *sarcomere* genes that are involved in HCM, DCM, and restrictive cardiomyopathy (RCM) [10]. Absence of an identifiable genetic defect does not preclude a genetic cause of LVNC. In approximately half of the familial LVNC, the genetic defect remains unknown [10]. Shared sarcomere defects and the occurrence of HCM and DCM in families with LVNC patients indicate that at least some forms of LVNC are part of a broader cardiomyopathy spectrum.

The literature differentially refers to this form of cardiomyopathy as left ventricular noncompaction (LVNC), noncompaction cardiomyopathy (NCCM), noncompaction of the left ventricular myocardium (NCLVM), left ventricular hypertrabeculation (LVHT), spongiform cardiomyopathy, embryonic myocardium, honeycombed myocardium, persisting myocardial sinusoids, myocardial dysgenesis, ventricular dysplasia, or spongy myocardium.

Definition

LVNC is defined by prominent *trabeculations* on the luminal surface of the LV apex, the lateral wall, and rarely the septum in association with deep recesses that extend into the ventricular wall, which do not communicate with the coronary circulation. It is associated with a clinical triad of heart failure, arrhythmias, and/or thromboembolic events [11, 12].

Epidemiology

Estimates of prevalence of LVNC were derived from large retrospective studies of patients referred for echocardiography. Population studies for LVNC have not been performed. In 1997 Ritter et al. identified LVNC in 17 of 37,555 (0.045 %) patients who had an echocardiographic examination [13]. Similarly, in 2006 Aras et al. reported a prevalence of 0.14 % in over 42,000 patients and in 2008 Sandhu identified definite or possible LVNC in 13/4929 (0.26 %) patients referred for echocardiography [14, 15]. Prevalence was much higher (3.7 %) in patients selected for a LV ejection fraction ≤45 % [14]. Depending on the diagnostic criteria applied, even higher prevalence of LVNC (15.8 % by Belanger; 23.6 % by Kohli) was reported recently, indicating that LVNC may be more prevalent than previously indicated [12, 16]. A substantial proportion of individuals is asymptomatic, suggesting that true prevalence of LVNC may be higher, because asymptomatic individuals may go unnoticed in the studies of cardiologic patients [10, 12]. In a large study on childhood cardiomyopathies, LVNC was the most frequent cardiomyopathy after DCM and HCM, with an estimated prevalence of 9 % in pediatric cardiomyopathies [17].

Clinical Aspects

Heart failure is among the most frequent presentations of LVNC, followed by supraventricular and ventricular arrhythmias, including sudden cardiac death, and thromboembolic events. However, as in other cardiomyopathies, there is a great variability in presentation, even within families, ranging from a fully asymptomatic course to severe heart failure necessitating cardiac transplantation. The age of presentation is also highly variable varying from prenatal and neonatal diagnosis to diagnosis at the age of 94 years [5, 18, 19]. Prenatal diagnostic imaging more often detects bilateral ventricular hypertrophy/hypertrabeculations than the typical left ventricular morphologic changes observed postnatally and in adults [20]. The fourth to fifth decade is the median age for diagnosis in adult isolated LVNC, constituting a relatively young population in adult cardiologic practice. Many patients remain asymptomatic and may be detected due to an asymptomatic heart murmur, or by chance by preoperative cardiac evaluation or medical assessment for insurance or jobs or because they participated in cardiologic family screening, after a relative had been diagnosed with LVNC. Symptomatic patients may present clinical symptoms of dyspnea, fatigue (atypical) chest pain, and/or (pre) syncope. LVNC may also present as a peripartum cardiomyopathy [4, 21]. Review of the literature revealed a male to female ratio of almost 2:1 [22]. This gender difference cannot be fully explained by the occurrence of X-linked forms of LVNC.

Different arrhythmias and conduction disorders may occur in LVNC patients (Table 7.1) [23]. None of these arrhythmias is characteristic or pathognomonic for LVNC. Thromboembolic events may include stroke (cerebrovascular event or transient ischemic attack), peripheral embolism, and mesenterial thrombosis.

Clinical Diagnosis

Diagnosis of LVNC is still a challenge and relies on two-dimensional transthoracic echocardiography and/or cardiac magnetic resonance imaging (MRI) (Table 7.2). Improvements in cardiac imaging techniques have led to increased recognition and diagnosis of LVNC. Figure 7.1 displays echocardiographic and cardiac MRI images of two LVNC patients, showing the abnormal segmental trabeculations as the hallmark of this entity.

Table 7.1 Arrhythmia and conduction disorders associated with left ventricular noncompaction (LVNC)

Arrhythmia/conduction disorders associated with LVNC	Reference
Atrial fibrillation	[24–26]
Atrioventricular nodal reentrant tachycardia	[27]
Bigeminy ventricular extra systole	[28]
Complete atrioventricular block	[1, 29–31]
Complete left bundle branch block	[28, 32]
Early repolarization	[33]
Giant P-waves and focal atrial tachycardia	[34]
Long QT syndrome 2	[35]
Narrow QRS complex	[36–38]
Persistent atrial standstill	[39]
Sick sinus syndrome	[40, 41]
Sinus bradycardia	[41–44]
Supraventricular tachyarrhythmia	[6, 25, 28, 45, 46]
Ventricular fibrillation	[29, 36, 47]
Ventricular tachycardia	[6, 32, 36, 42, 48]
Wolff–Parkinson–White syndrome	[2, 6, 25, 28, 42]

Table 7.2 Echocardiographic diagnostic criteria for LVNC

I. Chin et al. [2]
Focusing on trabeculae localized at the LV apex on the parasternal short axis and apical views and on LV free-wall thickness at end-diastole LVNC is defined by a ratio of X/Y ≤ 0.5 with
X = distance from the epicardial surface to the trough of the trabecular recess
Y = distance from the epicardial surface to the peak of the trabeculation
II. Jenni et al. [11]
1. An excessively thickened LV myocardial wall with a two-layered structure consisting of a compact epicardial layer (C) and a noncompacted endocardial layer (NC) of prominent trabeculations and deep intertrabecular recesses
2. A maximal end-systolic NC/C ratio >2, measured at the parasternal short axis
3. Color Doppler evidence of deep perfused intertrabecular recesses
4. Absence of coexisting cardiac anomalies
III. Stollberger et al. [24]
1. More than three trabeculations protruding from the LV wall, apical to the papillary muscles and visible in a single image 2. Perfusion of the intertrabecular spaces from the ventricular cavity visualized on color Doppler imaging

Features of noncompaction observed in cardiologic patients and normal controls still illustrate the necessity of defining criteria in order to accurately differentiate between normal physiological trabecularization and LVNC [16].

In 1990, the first diagnostic criteria for LVNC by Chin et al. were derived from the observations made in eight LVNC patients [2]. These diagnostic criteria defined LVNC by the ratio of the distance from the epicardial surface to the trough of the trabecular recess (X) to the distance from the epicardial surface to the peak of the trabeculations (Y), with ratio X/Y ≤ 0.5.

More than a decade later, Jenni et al. proposed new diagnostic criteria for isolated LVNC, consisting of four echocardiographic features: (1) an excessively thickened LV myocardial wall with a two-layered structure consisting of a compact epicardial layer (C) and a noncompacted endocardial layer (NC) of prominent trabeculations and deep intertrabecular recesses; (2) a maximal end-systolic *NC/C ratio* > 2, measured at the parasternal short axis; (3) color-Doppler evidence of deeply perfused intertrabecular recesses; (4) absence of coexisting cardiac anomalies [11].

In 2002, Stollberger et al. proposed other diagnostic criteria for LVNC, wherein the diagnosis was a function of the number of trabeculations (>3) protruding from the LV wall, apically to the papillary muscles and visible in a single image plane with obligatory perfusion of the intertrabecular spaces from the ventricular cavity visualized on color-Doppler imaging [24].

More recently, MRI criteria for LVNC introduced by Petersen et al. indicated that a noncompacted/compacted ratio (NC/C) of >2.3, measured in end-diastole, can differentiate with sufficient sensitivity between the normal variation of noncompaction of the LV in the population, noncompaction in other cardiovascular disorders, and LVNC; the localization of noncompaction appeared to be more in the apical and lateral segments than in the basal and septal segments [49]. Jacquier et al. measured the trabeculated LV mass by MRI and postulated that a mass above 20 % is specific for the diagnosis of LVNC [50].

Belanger et al. proposed a classification system of LVNC by dividing noncompaction into four categories (none, mild, moderate, and severe) according to noncompaction to compaction ratio and the size of the noncompaction area [12]. This new classification scheme used the following criteria: (1) absence of congenital heart disease, hypertrophic or infiltrative cardiomyopathy, and coronary artery disease; (2) evidence of prominent trabeculations in the apex in any view (noncompacted to compacted ratio does not require to be >2); (3) concentration of the noncompacted area in the apex; (4) blood flow through the area of noncompaction.

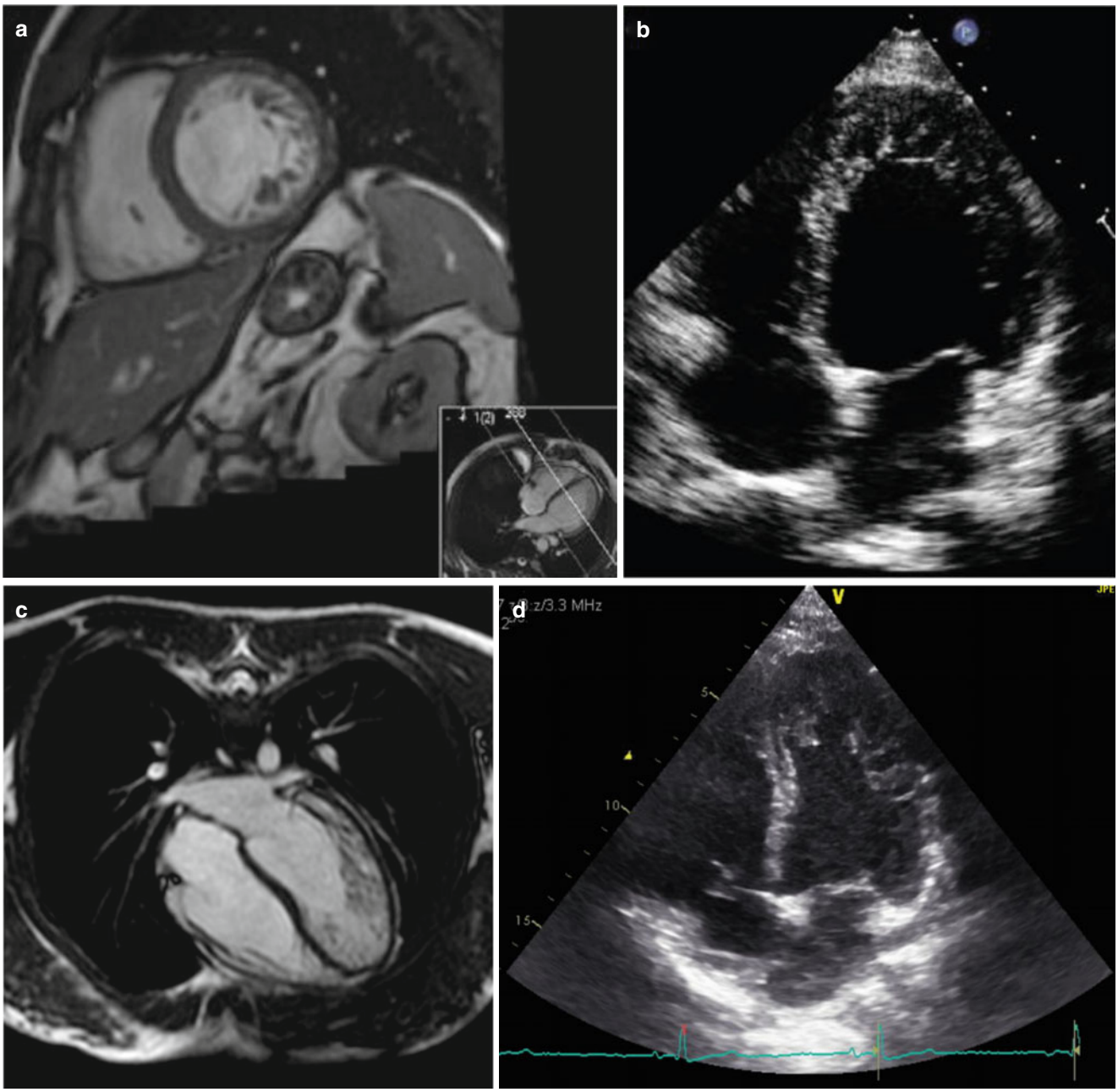


Fig. 7.1 (**a**, **b**) Cardiac MRI and echocardiography of a 43-year-old patient illustrating a two-layered myocardium with prominent intertrabecular recesses. (**c**, **d**) Cardiac MRI and echocardiography, four-chamber view each, of a 15-year-old patient with LVNC

The Jenni echo criteria have been the most convenient to work with in daily clinical practice and have been most widely applied in studies. However, further efforts to reach universal consensus with respect to the diagnosis of LVNC remain needed. A disparity in diagnosis has been observed when comparing the application of three different sets of LVNC criteria (Chin, Jenni, and Stollberger) in a cohort of 199 heart failure patients; 79 % fulfilled the Chin criteria, 64 % fulfilled the Jenni criteria, and 53 % fulfilled the criteria proposed by Stollberger. In only 30 % of patients, there was consensus among the three criteria on the diagnosis. Moreover, 8.3 % of normal controls fulfilled one or more criteria with a higher prevalence in black controls, and overdiagnosis is easily facilitated with the current diagnostic criteria [16, 51].

For now, it is disputable whether any of these diagnostic criteria are sufficiently sensitive to diagnose patients with mild noncompaction, and identify patients who may benefit from careful surveillance. For instance, in LVNC family studies, a substantial proportion of (mostly asymptomatic)

relatives showed mild to moderate features of LVNC [10]. Longitudinal studies of mild forms of LVNC are required to determine whether the current diagnostic criteria are suitable for diagnosis of family members in familial LVNC, or should be adapted in analogy to the criteria proposed for diagnosis of attenuated forms of familial HCM in relatives.

Pathology

Macroscopy

The noncompacted endocardial layer of the myocardium comprises excessively numerous and prominent trabeculations with deep intertrabecular recesses that extend into the compacted myocardial layer. The apical and mid ventricular segments of the LV inferior and lateral wall are predominantly affected [52, 53]. In a pathoanatomical study of LVNC, Burke et al. described the morphology and microscopy of 14 pediatric LVNC cases. The macroscopic appearance varied from anastomosing trabeculae to a relatively smooth endocardial surface, with narrow openings of the recesses to the ventricular cavity. Three types of recess patterns were distinguished: (1) anastomosing broad trabeculae, (2) coarse trabeculae resembling multiple papillary muscles, and (3) interlacing smaller muscle bundles or relatively smooth endocardial surface with compressed invaginations, identified primarily microscopically (Fig. 7.2). In this study, no morphological differences were found between isolated and nonisolated LVNC [52].

Jenni et al. described pathology of seven adult LVNC cases; the pathoanatomical localization of the noncompacted myocardium corresponded to the echocardiographic findings. Two patients also showed involvement of the right ventricular apex [11].

In a review of published pathology of LVNC, Stollberger et al. distinguished three particular morphologic features of LVNC in adults and children: (1) extensive spongiform transformation of the LV, (2) prominent coarse trabeculations and deep recesses, covered with endocardial tissue and not communicating with coronary arteries, and (3) dysplastic thinned myocardium with excessive trabeculations [22]. The first morphology was frequently associated with other cardiac malformations, compared to the second and third.

In 1987, in an autopsy study of 474 normal hearts of all ages, it was found that prominent trabeculations may be observed in as many as 68 % of the hearts, although more than three trabeculations were only identified in 3.4 % [54].

Microscopy

Two patterns of myocardial structure in the superficial noncompacted layer in LVNC have been described by Burke et al.: (1) anastomosing muscle bundles forming irregularly branching endocardial recesses with a staghorn-like appearance and (2) multiple small papillary muscles, resulting in an irregular surface appearance (Fig. 7.3). In most patients, these patterns overlapped. Endocardial fibrosis with prominent elastin deposition was found in all 14 cases, and subendocardial replacement fibrosis, consistent with microscopic ischemic infarcts, was present in 10; right ventricular involvement was identified in 6 cases [52].

Histological examination in another study showed that ventricular endocardium covered the recesses in continuity with the LV cavity and identified ischemic lesions in the thickened endocardium and the prominent trabeculae. Interstitial fibrosis ranged from being absent to severe. No fiber disarray was identified in any of these cases. Signs of chronic inflammation and abnormalities of intramyocardial blood vessels were present in some patients [11].

Freedom et al. proposed two criteria for the pathological diagnosis of LVNC: (1) absence of well-formed LV papillary muscles and (2) histological verification of more than 50 % penetration of invaginated endocardial recesses toward the epicardial surface. The endothelium that covers the recesses extends close to the surface of the compact layer. The recesses neither communicate nor connect with the coronary circulation [55].

Differential Diagnosis

The definitive diagnosis of LVNC relies on the morphological features of the LV myocardium, as defined by an imaging modality, like echocardiography, MRI, CT, or LV angiography. The variability in the extent of physiological trabecularization may complicate distinction of LVNC from normal physiological LV trabeculations. Especially in the area around the base of the papillary muscles of the mitral valve, more trabeculations may be present. However, in the normal heart, there is no excessive segmental thickening (due to hypertrabeculation) like in LVNC and the thickness of these physiological trabeculations does not exceed the thickness of the compact layer. Also, the area of noncompaction is larger in LVNC than in physiological trabeculations [12].

Secondary forms of (acquired) LVNC may be the result of hypertension, chronic volume or pressure overload, ischemic heart disease or extreme physical activity (i.e., athletes), leading to LVNC-like abnormalities. These are referred to as pseudo-left ventricular noncompaction or LVNC look-alike. Hypertensive patients are diagnostically challenging, because of the occurrence of LV hypertrophy due to hypertension. Further studies are needed to confirm whether excessive trabeculation is more prevalent in specific ethnic groups, as suggested by one study [16].

Furthermore, dilated, hypertrophic, and ischemic cardiomyopathy may be mistaken for LVNC or vice versa, due to

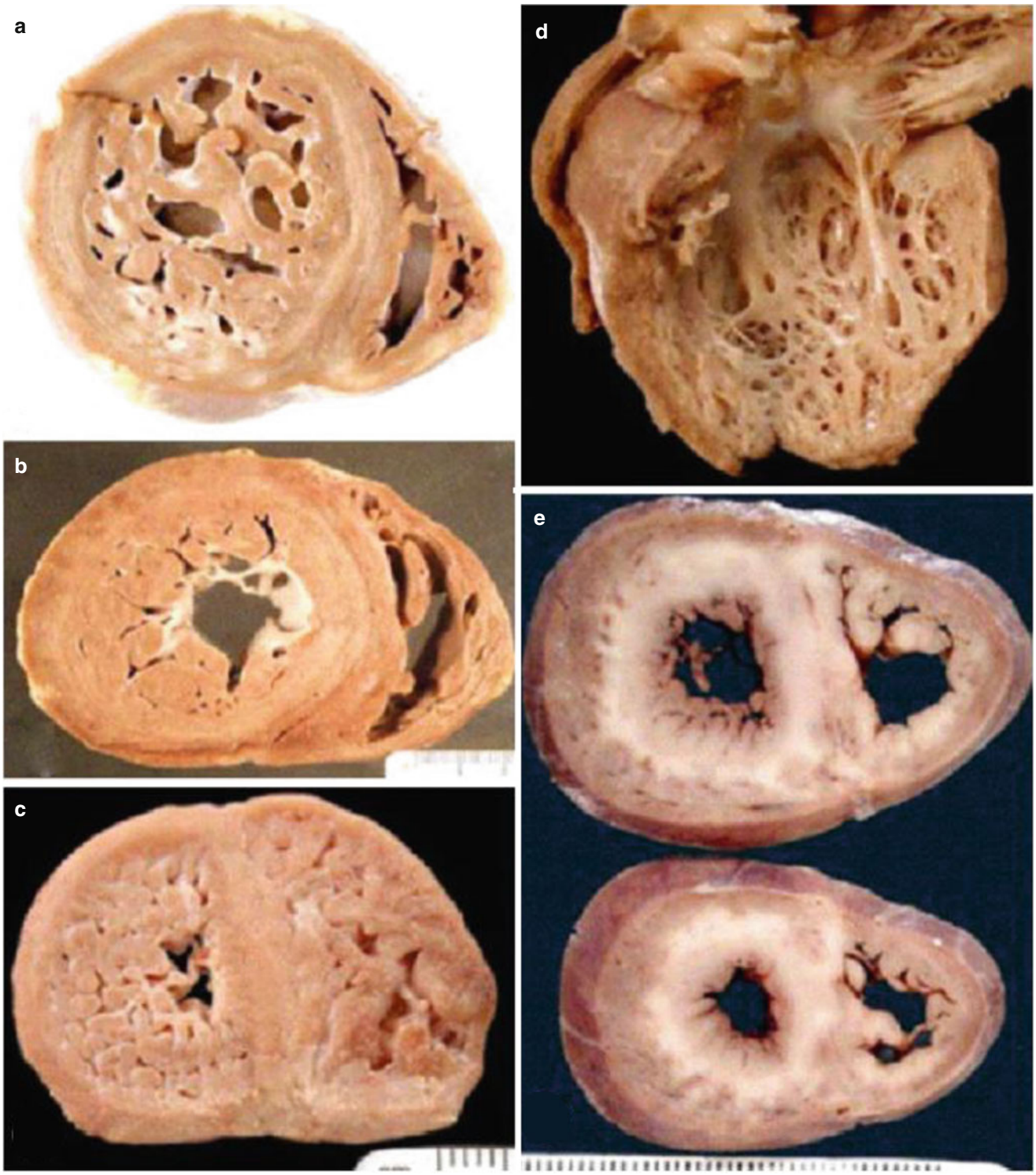


Fig. 7.2 LVNC gross pathology with a variety of LVNC patterns: (**a**) Anastomosing broad trabeculae. (**b**) Coarse trabeculae resembling multiple papillary muscles. (**c**) Interlacing smaller muscle bundles resembling a sponge. (**d**) Trabeculae viewed en face. (**e**) Subtle LVNC on gross section, requires histological confirmation (Reproduced from Burke et al. [52] with permission)

prominent trabeculations or abnormal myocardial thickening. Neuromuscular disorders, syndromes, and chromosomal abnormalities (Tables 7.3, 7.4, and 7.5) should be considered in the differential diagnosis of nonisolated LVNC, especially when LVNC occurs in patients with dysmorphism, growth retardation, or skeletal muscle weakness.

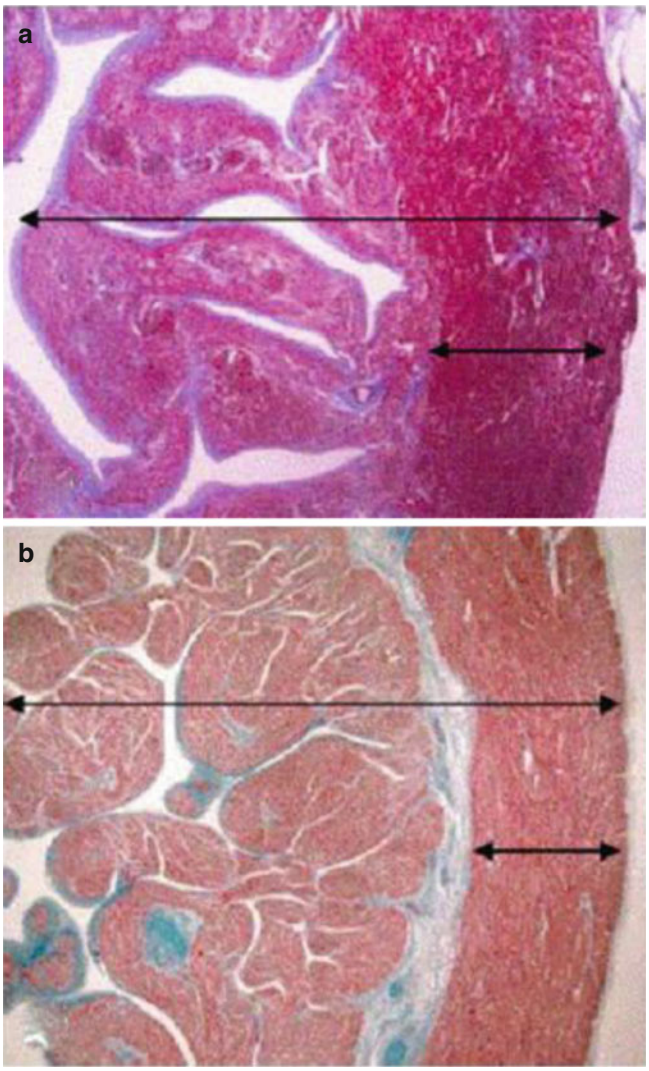


Fig. 7.3 Histological features in LVNC. The ratio of noncompact versus compact myocardium is larger than 2. (**a**) Relatively smooth endocardial surface (*left*) with anastomosing broad trabeculae. (**b**) Polypoid pattern of trabeculae; prominent fibrous band separating the noncompact from the compact myocardium (Reproduced from Burke et al. [52] with permission)

Work-Up, Therapy, Follow-Up, and Prognosis

Work-Up

Work-up of an LVNC patient should focus on identifying the underlying cause, either genetic or other (Table 7.3).

Therapy and Follow-Up

Current guidelines for heart failure, arrhythmias, cardiac resynchronization therapy, and ICD implantation for primary and secondary prevention are applied for LVNC [56–58]. β-Blockers and angiotensin-converting enzyme (ACE) inhibitors are the cornerstones of the treatment in the presence of LV dysfunction and/or arrhythmias. Establishing an expert consensus rapport, similar to HCM [59], based on case reports, small cohorts and clinical registries would be recommended since no randomized trials or studies on management of LVNC have been conducted, and clear-cut evidence-based clinical guidelines for this disorder are therefore missing. An important issue is the use of prophylactic anticoagulants, in view of frequent thromboembolic events. The early case reports and case series emphasized the high risk of thromboembolism and advised routine anticoagulation therapy. However, a review of 22 publications addressing the issue concluded that thromboembolic events are rare in LVNC [60]. Fazio et al. came to the same conclusion [61]. Therefore, anticoagulation therapy is advised only in patients with an ejection fraction less than 40 % (cutoff arbitrary), paroxysmal or persistent atrial fibrillation and/or previous thromboembolic events.

Successful cardiac resynchronization therapy has been described in several LVNC patients, leading to LV reverse remodeling and an increase in LV function [20, 36, 62–64].

Heart transplantation has been performed in some LVNC patients with severe heart failure [23, 65–67]. LV restoration surgery has been reported successful in a single patient [68]. Treatment with an *implantable cardioverter defibrillator* (ICD) will be discussed further on.

The indication for cardiologic follow-up depends on individual symptoms and cardiac abnormalities. In asymptomatic patients with preserved LV function, annual or biannual cardiologic follow-up is recommended, including ECG and echocardiography. If necessary, these could be extended with 24-h-Holter monitoring and exercise-testing. When EF is below 50 %, β-blocker therapy and ACE inhibitors should be prescribed, especially when LVNC is accompanied by hypertension or arrhythmias.

Risk Stratification and Indication for ICD

Patients at the highest risk for sudden death are patients who previously experienced (aborted) cardiac arrest, ventricular fibrillation, and sustained VF. Family history of sudden death, unexplained syncope (especially during exercise), abnormal blood pressure response during exercise tests, frequent premature ventricular beats on the resting ECG, and/or nonsustained ventricular tachycardia on Holter monitoring and significantly impaired LV function may be considered risk factors. The results from longitudinal studies and the understanding of underlying disease mechanisms will hopefully help to gain more insight into

Table 7.3 Proposed diagnostic work-up of a newly identified index patient with LVNC (Modified from the ACCF/AHA guidelines for the diagnosis and management of heart failure in adults [56])

History	Chest pain; palpitations; intake of alcohol, cocaine, medication; chemotherapy; radiation; deficiencies
Family history	Cardiomyopathy; conduction disease, arrhythmia, sudden cardiac or unexplained death; neuromuscular disease
ECG	Conduction disease; arrhythmia; sick sinus syndrome; prolonged QT; Q-waves; hypertrophy (see also Table 7.1)
Echocardiography	Congenital heart disease; Jenni criteria; LV ejection fraction
Laboratory	Complete blood count; serum electrolytes; blood urea nitrogen, serum creatinine, fasting blood glucose, lipids, liver function tests, thyroid function, CRP, iron status, creatine kinase, noradrenaline, cortisol, growth hormone
Viral work-up	Antibodies: Coxsackie-; influenza-; adeno-; echo-; cytomegalo-; human immunodeficiency virus
MRI	Myocardial infarction; infiltrative disease; myocarditis; dilated or hypertrophic cardiomyopathy, late gadolinium enhancement, NC/C ratio
Coronary angiography/ myocardial perfusion scintigraphy	Coronary artery disease
Mitochondrial work-up	When signs of mitochondrial disorder are present (e.g., myopathy; deafness; diabetes; encephalopathy; stroke-like episodes; ophthalmoplegia; retinopathy)
Neurologic examination	When signs of neuromuscular disease are present or when family history is positive for neuromuscular disease
Genetic counseling	Preferably for all cases
Genetic testing	Core panel when available; when unavailable ACTC1, MYBPC3, MYH7, TNNI3, TNNT2 and TPM1 (see also Fig. 7.5)

the risk factors and allow more appropriate risk stratification.

Consensus and guidelines for prophylactic ICD treatment in LVNC patients are also needed. Regular ICD indications include primary and secondary prevention. For secondary prevention, that is, after a previous episode of aborted cardiac death or collapse due to sustained VT or VF, current ICD guidelines advise ICD implantation. In the Rotterdam LVNC cohort of 67 patients, an ICD was indicated in 42 % according to the current ICD guidelines (n = 28; 21 primary and 7 for secondary prevention). After a long-term follow-up, appropriate ICD therapy occurred only in patients with secondary prevention (n = 3). Inappropriate ICD therapy occurred in 33 % of the patients with primary prevention and in 29 % of the patients with secondary prevention [69]. In another study, a follow-up of 12 patients who received an ICD showed overall appropriate therapy in 42 % in primary and secondary prevention combined. In primary prevention, 25 % of ICD therapy was appropriate opposed to 50 % in secondary prevention [45]. This accentuates the need for further research of appropriate risk stratification of sudden cardiac death in patients with LVNC.

Prognosis

Initially, LVNC was reported to have a grave prognosis. However, the application of new imaging techniques allowing diagnosing LVNC in asymptomatic individuals suggests that the first observations were influenced by selection of the most severely affected individuals. In children, age is not a predictor of the outcome [70]. New York Heart Association Class III or higher and presence of cardiovascular complications do seem to be a strong predictor [71]. It has become clear that prognosis of LVNC is as variable as the prognosis in other cardiomyopathies. Even in those with presentation in early childhood, gradual improvement in cardiac function may be observed, although in others evolvement to severe heart failure requiring heart transplantation does occur. Similarly, in some adult patients a rapid deterioration of heart function occurs, whereas in others the disease remains stable up to old age. Malignant arrhythmias leading to sudden cardiac death and heart failure are the main indicators of poor prognosis, also in children [72]. The establishment of appropriate risk stratification will be an important issue in the near future in order to identify patients at risk and to help prevent sudden cardiac death.

Etiology and Molecular Genetics

The etiology of LVNC is rapidly being unraveled as more and more genetic defects in different genes are found, indicating that LVNC is genetically heterogeneous. Currently, genetic defects are identified in approximately 40 % of LVNC patients [10, 63]. Most genetic defects are inherited as autosomal dominant trait (Table 7.4), with exception of rare genetic causes of syndromal LVNC, predominantly diagnosed in children. However, absence of a genetic defect does not exclude a genetic etiology. By performing systematic cardiologic family studies, it was shown that no genetic defect could be found in approximately half of the familial forms of LVNC, indicating that further studies are needed to find additional genetic causes for LVNC [10].

There is evidence that some forms of LVNC are part of a spectrum of cardiomyopathies, including hypertrophic,

Table 7.4 Genes associated with left ventricular noncompaction (LVNC)

Gene	Locus	Protein	Other associated disorders	Reference
ACTC1	15q14	α-Cardiac actin	Hypertrophic and dilated cardiomyopathy	[10, 64, 73]
			Congenital myopathy with fiber-type disproportion	
ACTN2	1q43	α-Actinin	Hypertrophic and dilated cardiomyopathy	[74]
CASQ2	1p13.3-p11	Calsequestrin	Catecholaminergic polymorphic ventricular tachycardia	[10]
			Hypertrophic cardiomyopathy	
DSP	6p24.3	Desmoplakin	Arrhythmogenic cardiomyopathy, dilated cardiomyopathy, epidermolysis bullosa, keratosis palmoplantaris striata, skin fragility–woolly hair syndrome	[65]
DTNA	18q12.1-q12.2	α-Dystrobrevin		[75, 76]
HCN4	15q24.1	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4	Brugada syndrome, sick sinus syndrome	[41, 44]
KCNH2	7q35-q36	Potassium voltage-gated channel, subfamily H, member 2	Long QT syndrome 2	[35]
			Short QT syndrome	
LDB3[a]	10q22.2-q23.3	LIM-Domain binding protein	Dilated cardiomyopathy	[10, 76–78]
			Late onset distal myopathy	
			Myofibrillar myopathy	
LMNA	1q21.2	Lamin A/C	Dilated cardiomyopathy	[10, 79, 80]
			Emery–Dreifuss muscular dystrophy	
			Lipodystrophy	
			Restrictive dermopathy	
			Werner syndrome	
			Hutchinson–Gilford Progeria	
			Limb girdle muscular dystrophy 1B	
			Charcot-Marie-Tooth 2B1	
MIB1	18q11.2	Mindbomb drosophila homolog 1	Left ventricular noncompaction	[66]
MYBPC3	11p11.2	Cardiac myosin-binding protein C	Hypertrophic and dilated cardiomyopathy	[10, 63]
MYH7	14q12	β-Myosin heavy chain	Hypertrophic, dilated, and restrictive cardiomyopathy	[10, 63, 64, 81, 82]
			Myosin storage myopathy	
			Distal myopathy	
			Scapuloperoneal myopathy	
NKX2.5	5q35.1	NK2 homeobox 5	Hypoplastic left heart syndrome; ventricular septal defect; atrial septal defect; Fallot; congenital hypothyroidism	[83]
PLN	6q22.1	Phospholamban	Hypertrophic and dilated cardiomyopathy	[10]
PRDM16	1p36	PR domain-containing protein 16	Dilated cardiomyopathy Del1p36 syndrome	[84]
SCN5A	3p21	Sodium channel type 5 α-subunit	Long QT syndrome 3	[85]
			Brugada syndrome	
			Sick sinus syndrome	
			Familial heart block	
			Paroxysmal ventricular fibrillation	
			Cardiac conduction defect	
			Dilated cardiomyopathy	
TAZ[b]	Xq28	Taffazin	Barth syndrome	[10, 75–77, 86–93]
			Dilated cardiomyopathy	
TNNI3	19p13.4	Cardiac troponin I	Hypertrophic, dilated, and restrictive cardiomyopathy	[10]
TNNT2	1q32	Cardiac troponin T	Hypertrophic, dilated, and restrictive cardiomyopathy	[10, 63, 64]
TPM1	15q22.1	A-tropomyosin	Hypertrophic and dilated cardiomyopathy	[10, 63]

Except *TAZ* related disorders, all are autosomal dominantly inherited
[a]Cypher/ZASP
[b]G4.5

dilated, and restrictive cardiomyopathy. A shared etiology consisting of genetic defects in the same sarcomere genes, sometimes even with identical mutations, has been found in these types of cardiomyopathy. Co-occurrence of LVNC, HCM, and DCM within families endorses a shared genetic susceptibility to these different forms of cardiomyopathy [10]. The phenotypic variability of cardiomyopathies within families, including variability in age at onset and severity of clinical features, might be explained by additional modifying factors, additional genetic variants or defects, or may depend on yet unidentified exogenous or systemic factors.

Molecular Defects in LVNC

Isolated LVNC has been associated with mutations in 20 different genes (Table 7.4). Defects in sarcomere genes have been identified to be the most prevalent genetic cause occurring in approximately 30 % of all patients with isolated LVNC [10, 63].

Over 40 different mutations in sarcomere genes encoding thick (*MYH7*), intermediate (*MYBPC3*), and thin filaments (*TNNT2*, *TNNI3*, *TPM1*, *ACTC*) have been described. In particular in *MYH7*, the most frequent LVNC-associated gene, accounting for up to 21 % of isolated LVNC [10, 63]. *MYH7* mutations currently associated with LVNC cluster in the ATP-ase active site of the head region in the N-terminal part of MYH7. This is an evolutionary well-conserved region of MYH7. As the ATP-ase active site is required for normal force production, impaired force generation might play a role in the etiology of LVNC. Mutations in this region have been associated with LVNC with or without Ebstein anomaly [64, 81]. Other *MYH7* mutations (30 %) were found in the C-terminal rod region of the MYH7 protein that plays an important role in the formation of the core of the thick filament. Mutations in this region of the gene are more commonly associated with skeletal myopathies. Relatively few cardiomyopathy mutations are situated in this region.

With the availability of targeted cardiomyopathy panels (next generation sequencing), more genes are and will be associated with LVNC, but as these data are still unpublished they are not mentioned here. Complex genotypes will become more common when more genes are analyzed per patient.

Multiple or compound/double heterozygous mutations were identified in 25 % of the children and in 10 % of the adult LVNC patients [10]. In hypertrophic cardiomyopathy, complex genotypes have been described in 7 % [94]. In HCM, double heterozygosity for truncating sarcomere mutations have been previously associated with severe congenital forms mostly inherited in an autosomal recessive mode [95–98]. Nonsarcomere genetic causes for isolated LVNC include mutations in the calcium-handling genes calsequestrin (*CASQ2*) and phospholamban (*PLN*), in taffazin (*TAZ*), α-dystrobrevin (*DTNA*), lamin A/C (*LMNA*) and LIM domain binding 3 (*LDB3*), potassium voltage-gated channel (*KCNH2*), and sodium channel type 5 (*SCN5A*) genes. However, mutations in these genes were only rare causes of LVNC in single families.

The absence of a mutation in approximately half of familial LVNC could be explained by phenotype assignment errors, the involvement of other yet unidentified genes, the presence of mutations in nonanalyzed gene sequences, and incomplete sensitivity of the methods used.

Pathogenesis

Mutations in different genes associated with LVNC affect different mechanisms in the cardiomyocyte leading to changes that may individually cause LVNC or lead to a common cellular disturbance resulting in LVNC. Cellular growth and differentiation signaling pathways are thought to be involved in LVNC pathogenesis [83, 99–101].

Mutations in sarcomere genes may have their effect through defective force generation (either by a dominant negative mechanism where the mutant protein acts as a "poison polypeptide" or by haploinsufficiency resulting in less protein); mutated cytoskeletal proteins may lead to a defective force transmission; myocardial energy deficits may be the result of mutations in ATP-regulatory genes and a fourth possible mechanism is abnormal calcium homeostasis due to either changes in calcium availability or myofibrillar sensitivity for calcium [102]. The development of LVNC features might be a compensatory response to dysfunction in one of these mechanisms.

The variable phenotypic expression of (sarcomere) gene mutations leading to different types of cardiomyopathy has not been explained. The localization of the mutations may partly explain phenotypic diversity. Another theory is "dose-effect"; the extent of the defective mechanism may determine which phenotype develops. Third, there might be independent pathways leading to the different cardiomyopathies. Finding identical mutations in different phenotypes suggests a role for additional factors, either environmental or molecular.

Isolated LVNC

The first hypothesis on the pathogenesis of LVNC stemmed from observations that the morphology of LVNC was reminiscent of the embryonic stages of cardiac development. Consequently, it was postulated that LVNC could be the result from an arrest of compaction of myocardial fibers [103]. Figure 7.4 illustrates the striking resemblance between LVNC and the physiological embryonic noncompaction in the eighth to tenth embryonic week. However, the possible mechanisms causing the arrest remain unclear. Epicardium-

derived cells are thought to play an important role in myocardial architecture and in the development of noncompaction [104, 105]. Mutations in genes involved in myocardial genesis like peroxisome proliferator activator receptor binding protein (*PBP*), jumonji (*JMJ*), FK506 binding protein (*FKBP12*), transcription factor specificity protein (*Sp3*), homeobox factor *NKX2.5*, bone morphogenetic protein 10 (*BMP10*) lead to congenital LVNC in knock out mice [106–111]. However, apart from the NKX2.5 gene, in human LVNC, no mutations in these genes have been described.

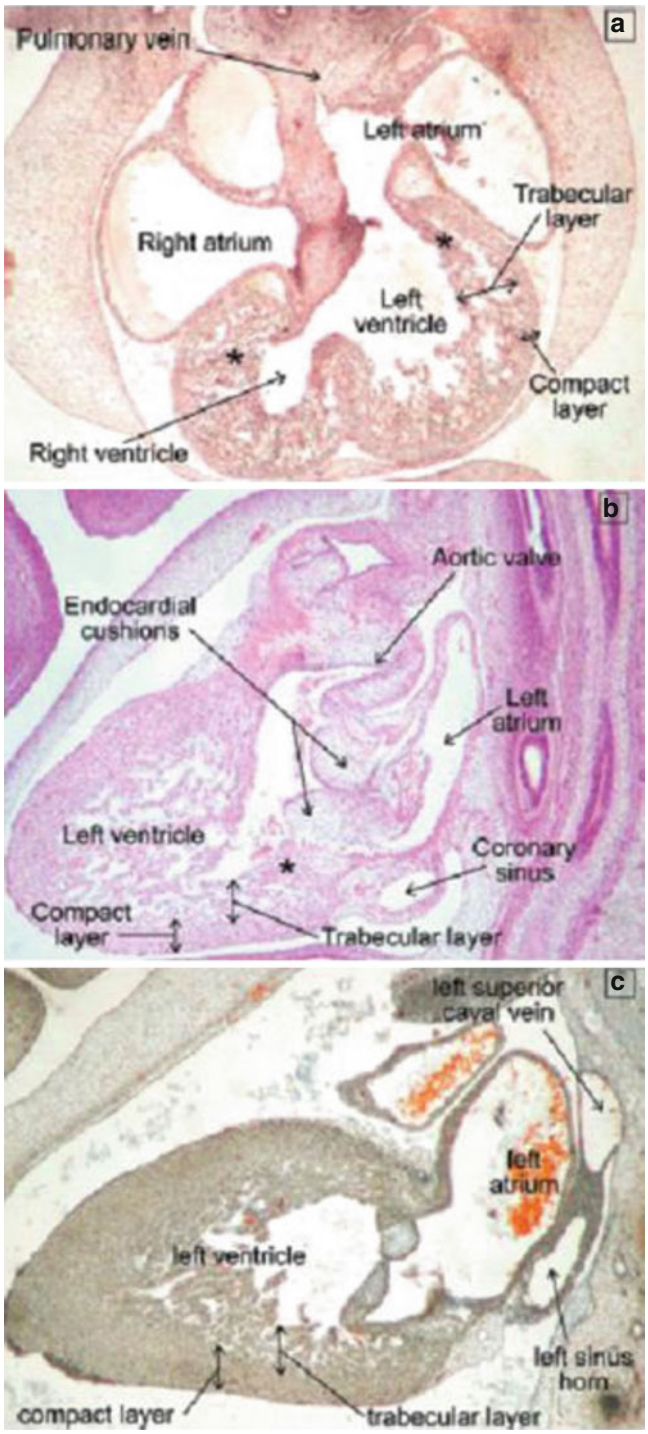


Fig. 7.4 Human embryos at Carnegie stage 16 (**a**), stage 18 (**b**) and after closing of the embryonic interventricular foramen (**c**). During development, there is an extensive trabecular layer forming the greater part of the ventricular wall thickness compared to the extent of the compact layer. The trabecular layer becomes compacted and forms the papillary muscles of the atrioventricular valves (*asterisks*) (Reproduced from Freedom et al. [55] with permission)

Until now, there is very little insight into factors that influence the variability in age at onset and severity of symptoms of LVNC, or any other familial form of cardiomyopathy.

In the majority of patients, LVNC is diagnosed in adulthood, similar to HCM and DCM, which are rarely congenital. Of course, it could be that in LVNC the lesions detected in adult patients were present from birth on, but remained unnoticed until symptoms developed and high-resolution cardiac imaging techniques were applied. However, the detection of sarcomere defects in LVNC patients may suggest otherwise, since mutations in sarcomere genes are known to cause late-onset HCM and DCM. Similarly, sarcomere mutations might lead to late onset LVNC. Longitudinal cardiologic studies of unaffected carriers of pathogenic mutations are necessary to provide insight whether noncompaction may develop later in life. The pathogenetic mechanism(s) of sarcomere defects in cardiomyopathies are not fully understood. It is possible that the pathological myocardial changes in the adult onset sarcomere related cardiomyopathies are caused by a compensatory response to impaired myocyte function resulting from mutations in the sarcomere genes [102, 112].

Nonisolated LVNC

LVNC has been observed in a number of neuromuscular disorders, metabolic and mitochondrial disease, congenital malformations, and chromosomal syndromes.

Some of these disorders may share pathogenetic mechanisms with LVNC. Alternatively, LVNC might be secondary to other cardiac malformations or other malformations or even vice versa. Another possibility is that the co-occurrence is coincidental. Congenital heart malformations, for instance, are relatively frequent (birth prevalence 0.008) and may therefore occasionally coincide with LVNC without a mutual etiology.

Congenital Heart Disease

The co-occurrence of congenital heart disease and noncompaction is predominantly observed in children. Tsai et al. showed that 78 % of 46 children with LVNC had a congenital heart defect [6]. Nevertheless, congenital heart defects and LVNC also co-occur in adults [113]. The large number of structural heart malformations reported in association with noncompaction is presented in Table 7.5, indi-

Table 7.5 Congenital heart disease associated with left ventricular noncompaction (LVNC)

Congenital heart disease in LVNC	Proportion of CHD		References
	In LVNC studies[a]	Case reports	
Aberrant origin of right/left subclavian artery	1/12 (8 %)	1	[28, 114]
Absent aortic valve		1	[115]
Anomalous pulmonary venous return	2/26 (8 %)		[28, 52]
Aortic coarctation	6/204 (3 %)		[6, 10, 25, 28, 116]
Aortico-LV tunnel		1	[117]
Aortic stenosis	2/46 (4 %)	2	[6, 55, 118]
Aortopulmonary window	1/21 (5 %)		[25]
Atrial septal defect	22/135 (16 %)	3	[6, 10, 25, 43, 81, 119]
Atrioventricular diverticulum		1	[120]
Bicuspid aortic valves	3/64 (5 %)	3	[6, 25, 121, 122]
Bicuspid pulmonary valve	1/14 (7 %)		[52]
Cardiac aneurysms		4	[31, 123–125]
Coronary ostial stenosis	1/14 (7 %)		[52]
Cor triatriatum	1/46 (2 %)		[6]
Dextrocardia	2/58 (3 %)	1	[1, 6, 28]
Dextro malposed great arteries	1/12 (8 %)		[28]
Dextroversion		1	[126]
Double inlet left ventricle	1/46 (2 %)		[6]
Double orifice mitral valve		4	[127–129]
Double outlet right ventricle	1/54 (2 %)		[116]
Ebstein's anomaly	11/130 (8 %)	14	[6, 10, 43, 82, 130–135]
Fallot's tetralogy	1/71 (1 %)	1	[10, 114]
Hypoplastic left heart syndrome	3/54 (6 %)		[116]
Hypoplastic right ventricle	3/58 (5 %)		[6, 28]
Isomerism of the left atrial appendage	4/66 (6 %)	8	[28, 55, 116, 136]
Left-sided superior vena cava	1/46 (2 %)		[6]
Mitral valve atresia		1	[115]
Mitral valve cleft	2/54 (4 %)	1	[31, 116]
Mitral valve dysplasia	2/14 (14 %)		[52]
Mitral valve prolaps	1/46 (2 %)		[6]
Patent ductus arteriosus	16/182 (9 %)	1	[6, 10, 43, 116]
Persistent left superior vena cava	1/14 (7 %)	1	[52, 125]
Pulmonary atresia	6/125 (5 %)	1	[10, 43, 116]
Pulmonary valve dysplasia	2/14 (14 %)		[52]
Pulmonary stenosis	4/97 (4 %)	1	[10, 28, 43, 52]
Single ventricle	1/12 (8 %)	1	[28, 137]
Subaortic membrane	2/55 (4 %)		[116]
Transposition of the great arteries	1/46 (2 %)	1	[6, 138]
Tricuspid atresia	2/54 (4 %)		[116]
Tricuspid valve dysplasia	1/14 (7 %)		[52]
Ventricular septal defect	23/218 (11 %)	3	[1, 6, 10, 25, 28, 52, 116, 118, 125]

[a]Cumulative number of LVNC patients with congenital heart defect (CHD) described in one or more LVNC studies

cating that septal defects, patent ductus arteriosus, and Ebstein's anomaly are the most prevalent congenital heart defects in LVNC.

Increasingly, *congenital cardiac malformations* (septal defects, Ebstein anomaly, patent ductus arteriosus, Fallot's tetralogy, aortic coarctation, and aortic aneurysms) are being reported in familial cardiomyopathies (HCM, DCM, and LVNC) linked to sarcomere mutations, suggesting that these specific sarcomere defects may have been involved in cardiac morphogenesis [10, 73, 81, 139–142]. But since there is rarely more than one patient with a congenital heart defect, even in families with multiple cardiomyopathy patients, the association of sarcomere defects and heart defects still demands further exploration.

Neuromuscular Disease

Similar to HCM and DCM, LVNC has been associated with neuromuscular disorders. Stollberger and Finsterer identified LVNC-like morphological features in Duchenne and Becker muscular dystrophy and in myotonic dystrophy (see section, "Neuromuscular Disorders") [143–145]. The gene mutated in Duchenne and Becker muscular dystrophy is a part of the dystrophine complex, a complex of muscle membrane associated proteins, connecting the cytoskeleton to the surrounding extracellular matrix and may also play a role in cell signaling. The dystrophine gene is expressed in skeletal and cardiac myocytes. Other genes previously associated with neuromuscular disorders, like adult onset myofibrillar myopathy (*LDB3* or *Cypher/ZASP*), limb girdle muscular dystrophy (LGMD) (*LMNA*), scapuloperoneal myopathy (*MYH7*), myosin storage distal myopathy (*MYH7*), and Barth syndrome (*TAZ*) have recently been associated with isolated LVNC (Table 7.4). ZASP, lamin A and C, β-myosin heavy chain, and taffazin are all expressed in cardiac and skeletal muscle tissue. ZASP has a function in cytoskeletal assembly. Mutations in ZASP can lead to DCM and to skeletal myopathy. Lamin A and C, proteins situated in the nuclear membrane, play an important role in maintaining nuclear architecture. *LMNA* mutations have been described in three LVNC patients [10, 79, 80]. In one of them, there was familial limb girdle muscular dystrophy (LGMD) as well as DCM [10]. Over 200 mutations have been described in *LMNA*, causing over 20 different phenotypes, including isolated DCM, LGMD, Emery–Dreifuss muscular dystrophy, Hutchinson–Gilford progeria, partial lipodystrophy, and peripheral neuropathy. For many of the phenotypes, there is no clear genotype–phenotype correlation, phenotypes may overlap, and different phenotypes are associated with single mutations. Up to 25 % of patients with an LMNA mutation may remain cardiologically asymptomatic [146].

Syndromes

LVNC can occur as part of a syndrome in combination with dysmorphic features and other congenital malformations. When there are other congenital defects or when there are dysmorphic features in a patient, one of the listed syndromes in Table 7.6 or one of the chromosomal defects in Table 7.7 could be considered in the differential diagnosis.

Table 7.6 Syndromes associated with left ventricular noncompaction (LVNC)/hypertrabeculation

Syndrome	Gene	Inheritance	Features	Reference
Barth syndrome/3-methylglutaconic aciduria	*TAZ*	XR	Growth retardation, dilated cardiomyopathy, skeletal myopathy, intermittent lactic acidemia, granulocytopenia, recurrent infections	[75–77, 86–93, 147]
Branchio-oto-renal syndrome I/ Melnick Fraser syndrome	*EYA1*	AD	Long narrow face; hearing loss (sensory/conductive/ mixed); preauricular pits; microtia; cup-shaped ears; lacrimal duct stenosis; cleft palate; bifid uvula; branchial cleft fistulas/cysts; renal dysplasia/aplasia; polycystic kidneys; vesico-ureteric reflux	[148]
Congenital adrenal hypoplasia	*NR0B1*	XR	Failure to thrive; hypogonadotropic hypogonadism; cryptorchidism; hyperpigmentation; primary adrenocortical failure; adrenal insufficiency; gluco-mineralocorticoid insufficiency; salt-wasting; delayed puberty	[149]
Contractural arachnodactyly/ Beals syndrome	*FBN2*	AD	Marfanoid habitus; micrognathia; frontal bossing; crumpled ear helices; ectopia lentis; high-arched palate; septal defects; bicuspid aortic valve; mitral valve prolapse; patent ductus arteriosus; aortic root dilatation; pectus carinatum; kyphoscoliosis; hip/knee/elbow contractures; arachnodactyly; ulnar deviation of fingers; talipes equinovarus; hypoplastic calf muscles; motor development delay	[150]
Cornelia de Lange syndrome I	*NIPBL*	AD	Short stature; microcephaly; long philtrum; micrognathia; low-set ears; sensorineural hearing loss; synophrys; myopia; long curly eyelashes; ptosis; anteverted nostrils; depressed nasal bridge; cleft lip/ palate; thin upper lip; widely spaced teeth; congenital heart defect; pyloric stenosis; hypoplastic male genitalia; structural renal anomalies; phocomelia; oligodactyly; syndactyly of second and third toes; single transverse palmar crease; cutis marmorata; hirsutism; low posterior hair line; mental retardation; language delay; automutilation	[25]

(continued)

Table 7.6 (continued)

Syndrome	Gene	Inheritance	Features	Reference
Leopard syndrome	*PTPN11* *RAF1*	AD	Short stature; triangular face; low-set ears; sensorineural hearing loss; hypertelorism; ptosis; epicanthal folds; broad flat nose; cleft palate; short neck; pulmonic stenosis; HCM; subaortic stenosis; complete heart block; bundle branch block; winged scapulae; hypospadia; absent/hypoplastic ovary; unilateral renal agenesis; spina bifida occulta; dark lentigines (mostly neck and trunk); café-au-lait spots	[151]
Melnick Needles osteodysplasty	*FLNA*	XD	Short stature; micrognathia; large ears; hypertelorism; exophthalmos; cleft palate; misaligned teeth; long neck; mitral/tricuspid valve prolapse; LVNC; pulmonary hypertension; pectus excavatum; omphalocele; hydronephrosis; tall vertebrae; bowing of humerus/radius/ulna/tibia; short distal phalanges of the fingers; pes planus; coarse hair; delayed motor development; hoarse voice	[152]
Nail Patella syndrome	*LMX1B*	AD	Short stature; sensorineural hearing loss; ptosis; cataract; cleft lip/palate; malformed sternum; hypoplasia of first ribs; glomerulonephritis; renal failure; kyphoscoliosis; elbow deformities; hypoplastic or absent patella; clinodactyly; talipes equinovarus; longitudinal ridging nails; slow nail growth; koilonychias; anonychia; aplasia pectoralis minor/biceps/triceps/quadriceps	[153]
Noonan syndrome	*PTPN11*[a] *KRAS* *SOS1* *RAF1*	AD	Short stature; triangular face; low-set ears; hypertelorism; downslanting palpebral fissures; epicanthal folds; myopia; micrognathia; high arched palate; low posterior hairline; webbed neck; septal defects; pulmonic stenosis; patent ductus arteriosus; pectus carinatum superiorly/pectus excavatum inferiorly; cryptorchidism; clinodactyly; woolly hair; mental retardation (mild); bleeding tendency; malignant schwannoma	[154]
Roifman syndrome		XR	Short-trunk dwarfism; long philtrum; strabismus; narrow and downslanting palpebral fissures; long eyelashes; retinal dystrophy; narrow upturned nose; LVNC; hepatosplenomegaly; spondyloepiphyseal dysplasia; eczema; hyperconvex nails; hypotonia; (mild) mental retardation; hypogonadotropic hypogonadism; recurrent infections; antibody deficiency	[155]
Syndromic microphthalmia/MIDAS syndrome (MIcrophthalmia, Dermal Aplasia, Sclerocornea)	*HCCS*	XD	Short stature; microcephaly; hearing loss; microphthalmia; sclerocornea; cataract; iris coloboma; retinopathy; septal defects; cardiac conduction defects; cardiomyopathy; overriding aorta; anteriorly placed anus; hypospadia; linear skin defects; corpus callosum agenesis; hydrocephalus; mental retardation; seizures	[156, 157]

AD autosomal dominant, *XD* X-linked dominant, *XR* X-linked recessive
[a]Most frequently involved genes

Mitochondrial

Mitochondrial disorders often lead to multiorgan disease, including the central and peripheral nervous system, eyes, heart, kidney, and endocrine organs. One of the cardiac features observed in mitochondrial disease is LVNC. Cardiac features may be the first or only feature in patients suffering from a mitochondrial disorder. In a study of 113 pediatric patients with mitochondrial disease, LVNC was identified in 13 % [171]. Pignatelli et al. showed that 5 of the 36 pediatric LVNC patients who underwent a skeletal muscular biopsy had morphologic and biochemical evidence for a mitochondrial defect, including a partial deficiency of complex I-III of the mitochondrial respiratory chain [149]. Mutations in mitochondrial DNA (mtDNA) and in nuclear DNA have been identified in the mitochondrial disorders associated with LVNC [172, 173].

Table 7.7 Chromosomal defects associated with left ventricular noncompaction (LVNC)

Chromosomal defects	Features	Reference
Deletion		
1p36	Microcephaly; sensorineural hearing loss; deep-set eyes; flat nose; cleft lip/palate; cardiomyopathy; septal defects; patent ductus arteriosus; dilated aortic root; feeding problems; gastro-esophageal reflux; short fifth finger and clinodactyly; mental retardation (severe); seizures; hypotonia	[84, 158–162]
1q43-q43	Microcephaly; upslanting palpebral fissures; epicanthus, broad nasal bridge, micrognathia; low set ears; bow-shaped upper lip; widely spaced teeth; short webbed neck; congenital heart defects; mental retardation (severe); speech impairment; seizures; corpus callosum agenesis	[163]
5q35.1q35.3	Facial hirsutism; synophrys; downslanting palpebral fissures; atrial septal defect and patent ductus arteriosus; LVNC with sick sinus syndrome and second degree heart block; feeding problems; gastro-esophageal reflux; joint hypermobility	[164]
7p14.3p14.1	Ventricular septal defect, atrial septal defect, aortic valve dysplasia, mental retardation, sacral fistula, growth retardation, microcephaly, facial dysmorphism	[162]
18p subtelomeric deletion	Esophageal atresia, otodysplasia, short stature, deafness, mental retardation, facial dysmorphism	[162]
22q11.2	Velo-cardio-facial syndrome: short stature; microcephaly; retrognathia; narrow palpebral fissures; square nasal root; prominent tubular nose; cleft palate; velopharyngeal insufficiency; congenital heart defect (85 %): ventricular septal defect; Fallot's tetralogy; inguinal/umbilical hernia; slender hands and digits; learning disability; mental retardation; schizophrenia; bipolar disorder	[149, 162]
Numeric		
4q trisomy/1q monosomy	Senile-like appearance; narrow palpebral fissures; telecanthus; epicanthus; broad nasal bridge; low-set ears; long philtrum; dimple below lower lip; anteriorly displaced anus; rocker-bottom feet; mental retardation; hypotonia, hypoplastic corpus callosum	[165]
Trisomy 13	Microcephaly; hypotelorism; cleft lip/palate; coloboma; low-set ears; septal defects; patent ductus arteriosus	[166]
	Polydactyly; overlapping fingers; mental retardation (severe); hypotonia; seizures	
Trisomy 21	Short stature; brachycephaly; flat facial profile; conductive hearing loss; epicanthal folds; upslant; iris brushfield spots; protruding tongue; congenital heart malformation; duodenal atresia; Hirschsprung disease; joint laxicity; single transverse palmar crease; excess nuchal skin; mental retardation; hypothyroidism; leukemia	[10, 116]
Mosaic trisomy 22	Microcephaly; hypertelorism; preauricular pits/tags; low-set ears; micrognathia, long philtrum; septal defects; double aortic arch; clinodactyly; hypoplastic nails; hemiatrophy; mental retardation	[167]
45,X0 (including mosaics)	Turner syndrome: short stature; short webbed neck; low hair line; broad nasal bridge; low-set ears; congenital heart defects: aortic coarctation; bicuspid aortic valves; aortic dilatation; lymphedema of hands and feet; renal abnormalities: single horseshoe kidney; renal vascular abnormalities; delayed puberty; amenorrhea; infertility; hypothyroidism	[162, 168, 169]
Translocation		
Robertsonian t13;14	Ventricular septal defect, mental retardation, linear cutaneous acromic lesions, growth retardation, toe syndactyly (II–III), facial dysmorphism	[162]
Loci		
6p24.3-21.1	LVNC; bradycardia; pulmonary valve stenosis; atrial septal defect; left bronchial isomerism; azygous continuation of the inferior vena cava; polysplenia; intestinal malrotation	[43]
11p15	LVNC; mild pulmonary stenosis; mild mitral valve prolapse; atrial septal defect	[170]

Cardiogenetic Aspects

Molecular and Cardiologic Family Screening

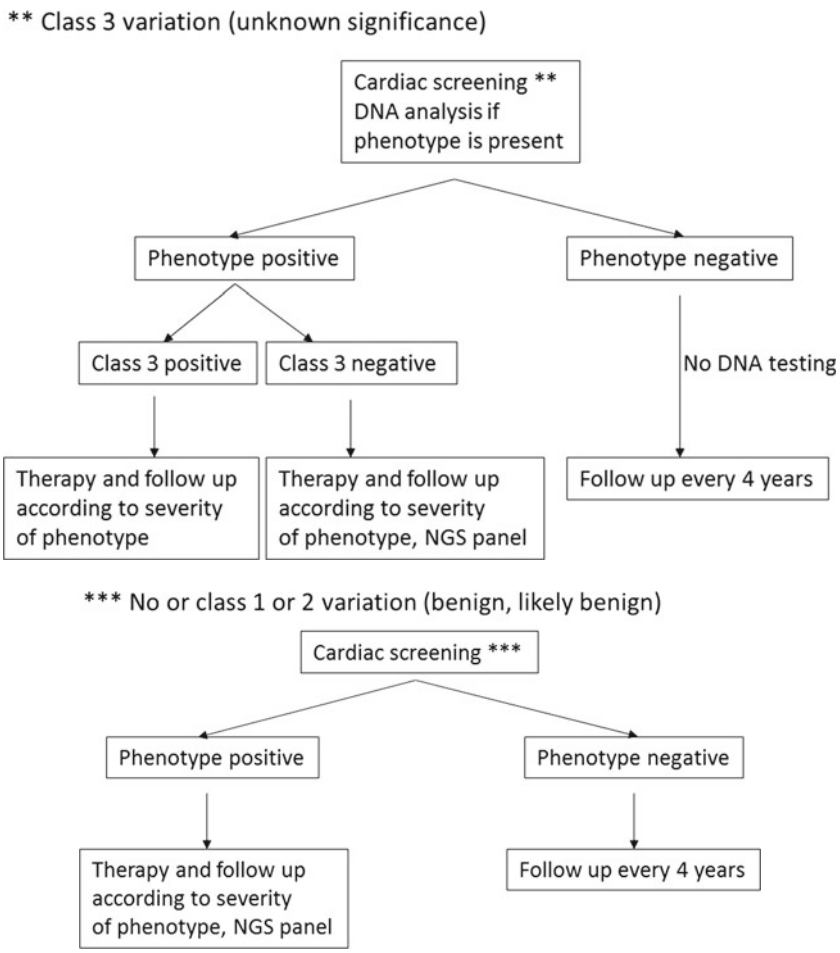
Familial LVNC has been estimated to occur in 18–71 % of adults with isolated LVNC, mostly consistent with an autosomal dominant mode of inheritance, indicating the importance of informing and examining relatives of patients with isolated LVNC [2, 10, 15, 149, 174–177]. Since extensive family studies showed that the majority of affected relatives are asymptomatic, cardiologic evaluation should include all adult relatives irrespective of medical history. Obviously, taking a family history is by itself insufficient to identify familial disease, given the high frequency of asymptomatic

disease in families [10]. In families where a pathogenic mutation has been identified, relatives can be offered predictive DNA analysis. In families without a pathogenic mutation, cardiac family screening remains the method of choice to identify relatives at risk of developing symptomatic cardiomyopathy, who may benefit from early treatment. In families where a variant (class 3 or 4) is identified, DNA analysis and cardiologic screening are advised as depicted in Fig. 7.5.

Apart from LVNC, other cardiomyopathies may co-occur within families, like hypertrophic and dilated cardiomyopa-

Fig. 7.5 Flowchart for family screening in LVNC including *likely pathogenic variants (class 4), **variants of unknown significance (class 3) and ***no variants or class 1 or 2 variants; # if clinically indicated; @ core panel: *ACTC1, ACTN2, ANKRD1, BAG3, CALR3, CAV3, CRYAB, CSRP3, CTNNA3, DES, DSC2, DSG2, DSP, EMD, FHL1, GLA, JPH2, JUP, LAMA4, LAMP2, LMNA, LDB3, MIB1, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEXN, PKP2, PLN, PRDM16, PRKAG2, RBM20, SCN5A, TAZ, TCAP, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL*

Fig. 7.5 (continued)



thy, so cardiac screening should aim at identifying all cardiomyopathies. Cardiac screening of relatives may show minor abnormalities not fulfilling LVNC criteria, which may be difficult to differentiate from normal physiologic trabecularization. Hypothetically, these minor abnormalities might develop into LVNC eventually. Longitudinal studies of patients with mild LVNC features are needed to investigate the natural history of these forms of noncompaction.

Genotype–Phenotype Correlations

Molecular studies of LVNC have thus far shown that there are few recurrent mutations. Therefore, it is difficult to establish genotype–phenotype correlations. Additionally, intrafamilial phenotypic variability complicates predictions based on an identified mutation. Te presence of multiple (truncating) sarcomere mutations in an individual appears to result in a more severe phenotype with childhood onset [10, 97]. Multiple mutations identified in adults mostly also comprise involvement of a nonsarcomere gene. Adult patients with multiple mutations seem to have more symptoms than adults with a single mutation [10].

The proposed strategies for the molecular and cardiologic evaluation of LVNC are depicted in the flowchart in Fig. 7.5. Extensive genetic screening, preferably with a targeted cardiomyopathy gene panel, may lead to the identification of a molecular defect in over 40 % of isolated LVNC patients and in half of these patients an *MYH7* mutation is found [10].

When no targeted panel is available, *MYH7* gene sequencing should be considered as an initial approach, being the most prevalent cause for LVNC in adults and children. Further molecular analyses of the other genes within the LVNC spectrum, which quantitatively have a relatively modest contribution to LVNC morbidity, may be considered when no mutation in *MYH7* can be identified. Sarcomere gene analysis is also warranted in pediatric patients, given the high percentage of sarcomere mutations in this group. When an adult or pediatric patient is severely affected, screening for a second molecular defect is advised, given the high frequency of multiple mutations in LVNC.

Summary

LVNC is a relatively new, genetically heterogeneous, cardiomyopathy. Clinical presentation and prognosis range from asymptomatic disease with no or slow progression to severe disabling, rapidly progressive cardiac failure. Initial presentation includes the triad of heart failure (potentially lethal)

arrhythmias and/or thromboembolism. In adults, the majority of LVNC is isolated.

The first clinical presentation of LVNC may occur at all ages, even prenatally. In childhood, clinical features are often more severe and LVNC is frequently associated with congenital heart defects. The echocardiographic diagnostic criteria as proposed by Jenni et al. are convenient in daily practice and currently the most widely applied. The general cardiac guidelines for chronic heart failure and ICDs are suitable and applicable to the LVNC population.

In as much as 40 % of isolated LVNC, molecular testing may yield a genetic defect, mostly in sarcomere genes. The *MYH7* gene is the most prevalent disease gene. The nonisolated forms of LVNC are caused by a range of different (rare) genetic defects. Until now, in half of familial isolated LVNC, the genetic defect remains unknown. Genetic defects in a large number of sarcomere and other cardiomyopathy genes and in genes primarily associated with skeletal myopathies indicate that LVNC may result from a wide range of pathophysiologic mechanisms.

Shared genetic defects and familial aggregation of LVNC, HCM, and DCM indicate that LVNC may be part of a broad spectrum of cardiomyopathies.

The genetic etiology of LVNC requires that patients and their relatives are offered genetic testing and counseling. This may include (predictive) molecular analysis of relatives, when applicable, and/or cardiac evaluation of at-risk relatives, even when they are as yet asymptomatic.

Take Home Messages

- LVNC is a difficult (clinical) diagnosis and is genetic/hereditary in the majority of cases.
- Sarcomere gene defects (especially in *MYH7*) are the most frequent cause of genetic isolated LVNC.
- Treatment consists of standard heart failure care and prevention of arrhythmia.
- Prognosis is highly variable, even within families.
- Relatives at risk may be asymptomatic, warranting active screening and a follow-up of first-degree relatives.

Acknowledgments The authors thank Kadir Calsikan and Danielle Majoor-Krakauer for their work on the first edition of this chapter.

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