Noncompaction Cardiomyopathy

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6.1 Introduction

Noncompaction of the left ventricle or *noncompaction cardiomyopathy* (*NCCM*) is a relatively new clinicopathologic entity, first described by Feldt et al. in 1969.[1] NCCM 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, thrombo-embolic events, and (potentially lethal) arrhythmias, including sudden cardiac death. NCCM 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 NCCM range from asymptomatic in adults to severe congenital forms.[4–7] Recently, NCCM was classified by the American Heart Association (AHA) as a separate primary, genetic cardiomyopathy, based on the predominant myocardial involvement and genetic etiology.[8] The European Society of Cardiology (ESC) considers NCCM as unclassified, due to the lack of consensus whether NCCM 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.[9] The majority of NCCM diagnosed in adults is isolated. Nonisolated forms of NCCM are more frequent in childhood and may co-occur with congenital heart malformations, or may be part of a malformation or chromosomal syndrome.[7] The combination of NCCM and neuromuscular disorders is observed in adults as well as in children.

The majority of NCCM, isolated and nonisolated, is hereditary and NCCM appears to be genetically heterogenous.[10,11] An important proportion of isolated NCCM 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 a genetic defect does not preclude a genetic cause of NCCM. In approximately half of the familial NCCM, the genetic defect remains unkown.[11] Shared sarcomere defects and the occurrence of HCM and DCM in families with NCCM patients indicate that at least some forms of NCCM 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. In analogy with the nomenclature of hypertrophic (HCM) and dilated cardiomyopathy (DCM), the term noncompaction cardiomyopathy is preferable. Therefore, noncompaction cardiomyopathy, abbreviated as NCCM, will be used in this chapter to denote this entity.

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6.1.1 Definition

NCCM is defined by prominent *trabeculations* on the luminal surface of the left ventricular 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 thrombo-embolic events.[12,13] Diagnosis of NCCM relies on two-dimensional transthoracic echocardiography and/or cardiac magnetic resonance imaging (MRI) (Table 6.1). Improvements in cardiac imaging techniques have led to increased recognition and diagnosis of NCCM. Figure 6.1 displays echocardiographic and cardiac MRI images of two NCCM patients, showing the abnormal segmental trabeculations as the hallmark of this new entity.

Features of noncompaction observed in cardiologic patients and normal controls illustrate the necessity of defining criteria in order to differentiate accurately normal physiological trabecularization from NCCM.[14]

Table 6.1 Echocardiographic diagnostic criteria for NCCM

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 NCCM 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.[12] 1. An excessively thickened left ventricular 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.[15] 1. More than three trabeculations protruding from the left ventricular 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

In 1990, the first diagnostic criteria for NCCM by Chin et al. were derived from the observations made in eight NCCM patients.[2] These diagnostic criteria defined NCCM 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 NCCM, consisting of four echocardiographic features: (1) an excessively thickened left ventricular 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.[12]

In 2002, Stollberger et al. proposed other diagnostic criteria for NCCM, wherein the diagnosis was a function of the number of trabeculations (>3) protruding from the left ventricular 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.[15]

More recently, MRI criteria for NCCM 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 NCCM.[16]

The most recent classification system of NCCM as proposed by Belanger et al. (2008) included dividing noncompaction into four categories (none, mild, moderate, and severe) according to noncompaction to compaction ratio and the size of the noncompaction area.[13] 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.

The Jenni echo criteria have been the most convenient to work with in daily clinical practice and have

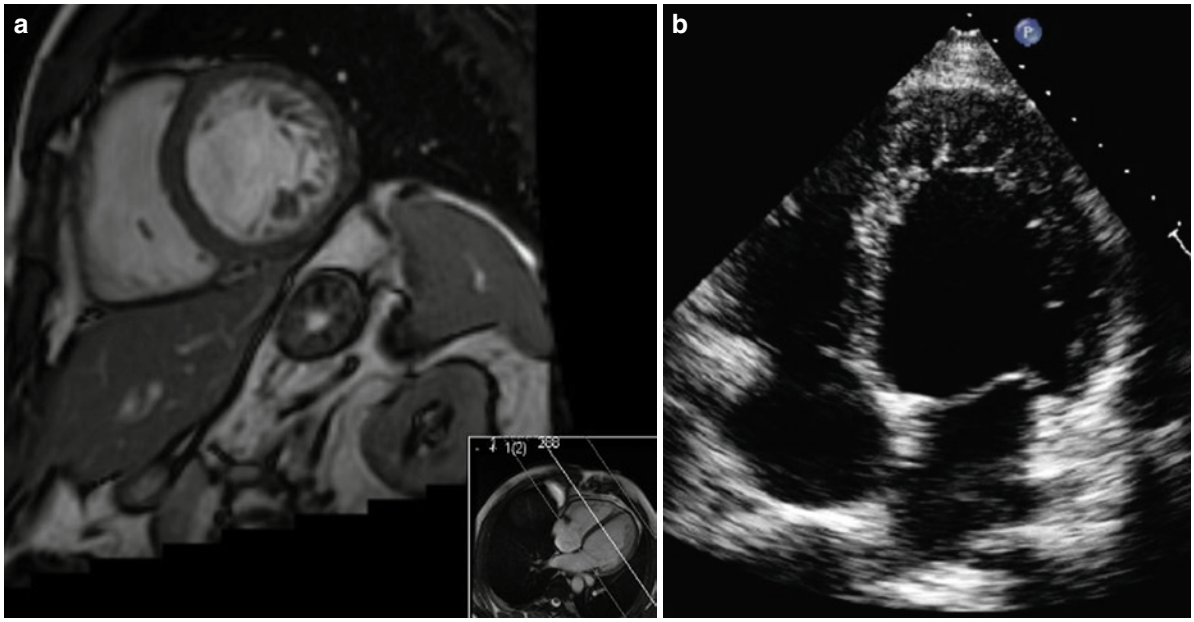

Fig. 6.1 (**a**, **b**) Cardiac MRI and echocardiography of a 43-year-old patient illustrating a two-layered myocardium with prominent intertrabecular recesses

been most widely applied in studies. However, further efforts to reach universal consensus with respect to the diagnosis of NCCM are clearly needed. A disparity in diagnosis has been observed when comparing the application of three different sets of NCCM 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% 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.[14]

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 NCCM family studies, a substantial proportion of (mostly asymptomatic) relatives showed mild to moderate features of NCCM.[11] Longitudinal studies of mild forms of NCCM will be needed to determine whether the current diagnostic criteria are suitable for diagnosis of family members in familial NCCM, or should be adapted in analogy to the criteria proposed for diagnosis of attenuated forms of familial HCM in relatives.

6.1.2 Pathology

6.1.2.1 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 left ventricular inferior and lateral wall are predominantly affected.[17, 18] In a pathoanatomical study of NCCM, Burke et al. described the morphology and microscopy of 14 pediatric NCCM cases.[18] 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; (3) interlacing smaller muscle bundles or relatively smooth endocardial surface with compressed invaginations, identified primarily microscopically (Fig. 6.2). In this study, no morphological differences were found between isolated and nonisolated NCCM.[18]

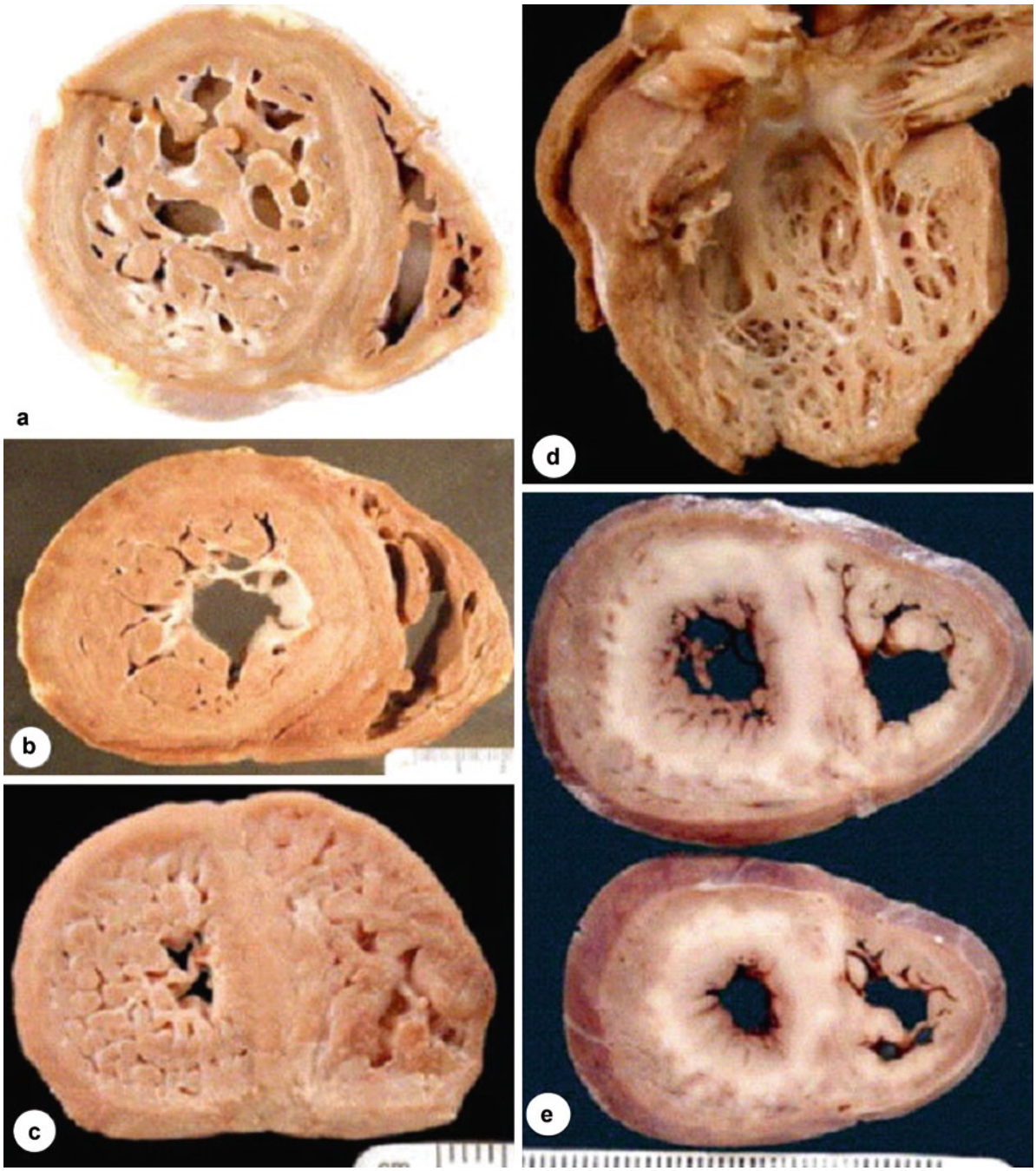

Fig. 6.2 NCCM gross pathology with a variety of NCCM patterns: (**a**) Anastomosing broad trabeculae. (**b**) Coarse trabeculae resembling multiple papillary muscles. (**c**) Interlacing smaller muscle bundles resembling a sponge. (**d**) Trabeculae viewed en face. (**e**) Subtle NCCM on gross section, requires histological confirmation (Reproduced from Burke et al.[18] With permission)

Jenni et al. described pathology of seven adult NCCM cases.[12] The pathoanatomical localization of the noncompacted myocardium corresponded to the echocardiographic findings. Two patients also showed involvement of the right ventricular apex.[12]

In a review of published pathology of NCCM, Stollberger et al. distinguished three particular morphologic features of NCCM 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. (3) Dysplastic thinned myocardium with excessive trabeculations.[19] 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%.[20]

6.1.2.2 Microscopy

Two patterns of myocardial structure in the superficial noncompacted layer in NCCM have been described by Burke et al.: (1) anastomosing muscle bundles forming irregularly branching endocardial recesses with a staghorn-like appearance; (2) multiple small papillary muscles, resulting in an irregular surface appearance (Fig. 6.3).[18] 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.[18] Right ventricular involvement was identified in six cases.[18]

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.[12] Interstitial fibrosis ranged from absence 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.[12]

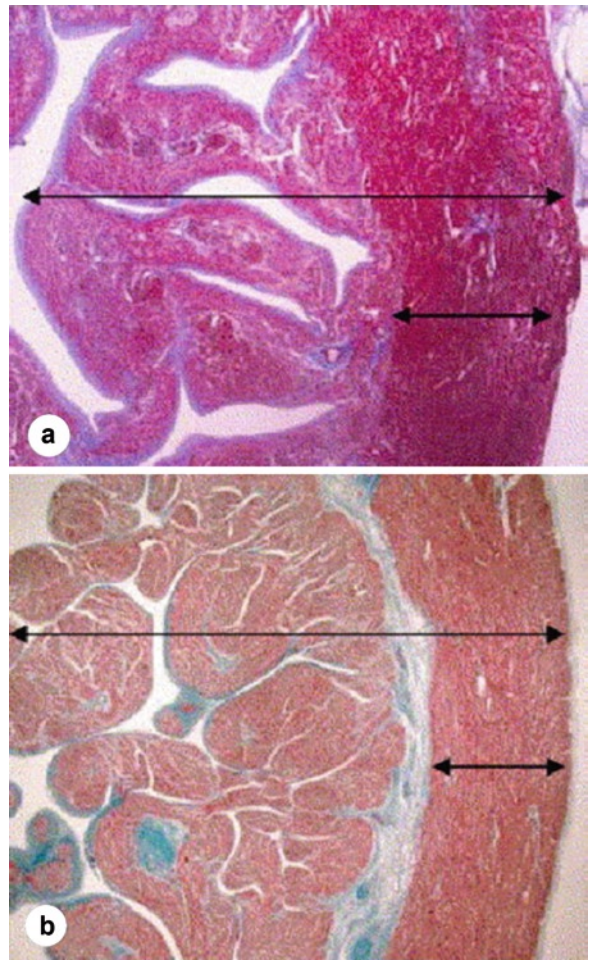

Fig. 6.3 Histological features in NCCMThe ratio of noncompact versus compact myocardium is larger than 2. (**a**) Relatively smooth endocardial surface (*left*) with anastomosing broad trabeculae. (**b**) Polypoid pattern of trabeculae; prominent fibrous band separating the noncompact from the compact myocardium (Reproduced from Burke et al.[18] With permission)

In one adult case report, abundant extracellular matrix and myocardial fiber disarray were reported.[21]

Freedom et al. proposed two criteria for the pathological diagnosis of NCCM: (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.[22]

6.2 Epidemiology

Estimates of prevalence of NCCM were derived from large retrospective studies of patients referred for echocardiography. Population studies for NCCM have not been performed. In 1997 Ritter et al. identified NCCM in 17 of 37,555 (0.045%) patients who had an echocardiographic exam.[23] 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 NCCM in 13/4,929 (0.26%) patients referred for echocardiography.[24,25] Prevalence was much higher (3.7%) in patients selected for a LV ejection fraction ≤45%.[25] Depending on the diagnostic criteria applied, even higher prevalence of NCCM (15.8% by Belanger; 23.6% by Kohli) were reported recently, indicating that NCCM may be more prevalent than previously indicated.[13,14] A substantial proportion of individuals is asymptomatic, suggesting that true prevalence of NCCM may be higher, because asymptomatic individuals may go unnoticed in the studies of cardiologic patients.[11,13] In a large study on childhood cardiomyopathies, NCCM was the most frequent cardiomyopathy after DCM and HCM, with an estimated prevalence of 9% in pediatric cardiomyopathies.[26]

6.3 Etiology and Molecular Genetics

The etiology of NCCM is rapidly being unravelled as more and more genetic defects in different genes are found, indicating that NCCM is genetically heterogeneous. Causes for acquired NCCM are scarce. One report suggested that candida sepsis was associated with cardiologic features mimicking NCCM.[27] Currently, genetic defects are identified in 42% of NCCM patients (35% of adults and 78% of children).[10] Most genetic defects are inherited as autosomal dominant trait (Table 6.2), with exception of rare genetic causes of syndromal NCCM, predominantly diagnosed in children. A small proportion of patients have a de novo mutation.

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 NCCM, indicating that further studies are needed to find additional genetic causes for NCCM.[11]

There is evidence that some forms of NCCM are part of a spectrum of cardiomyopathies, including hypertrophic, 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 NCCM, HCM, and DCM within families endorses a shared genetic susceptibility to these different forms of cardiomyopathy.[10,11] 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.

6.3.1 Molecular Defects in NCCM

Isolated NCCM has been associated with mutations in 14 different genes (Table 6.2). Defects in sarcomere genes have been identified to be the most prevalent genetic cause occurring in 33% of all patients with isolated NCCM.[11] In two DNA studies in cohorts of approximately 60 isolated NCCM patients, mutations were identified in 17–41% of the patients depending on the number and choice of analyzed genes.[10,28] In the study by Dooijes et al. of 56 patients, the yield was slightly higher 41% in all and 50% in case of confirmed familial disease.[11] In children with isolated NCCM, the yield of testing for sarcomere genes was as high as 75%.[10,11]

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 NCCM-associated gene, accounting for up to 21% of isolated NCCM (19% in adults and 25% in children).[10,28] Fifty percent of the *MYH7* mutations currently associated with NCCM cluster in the ATP-ase active site of the head-region in the N-terminal part of MYH7.[10] This is an evolutionary well-conserved region of MYH7. As the ATP-ase active site is required

Table 6.2 Genes associates with noncompaction cardiomyopathy (NCCM)

Gene	Locus	Protein	Other associated disorders	Reference
ACTC1	15q14	α-Cardiac actin	Hypertrophic and dilated cardiomyopathy Congenital myopathy with fiber-type disproportion	10,11,28,50
CASQ2	1p13.3-p11	Calsequestrin	Catecholaminergic polymorphic ventricular tachycardia Hypertrophic cardiomyopathy	10,11
DTNA	18q12.1-q12.2	α-Dystrobrevin		35,134
KCNH2	7q35-q36	Potassium voltage-gated channel, subfamily H, member 2	Long QT syndrome 2 Short QT syndrome	135
LDB3[a]	10q22.2-q23.3	LIM-Domain binding protein	Dilated cardiomyopathy Late onset distal myopathy Myofibrillar myopathy	10,11,36,134,136
LMNA	1q21.2	Lamin A/C	Dilated cardiomyopathy Emery--Dreifuss muscular dystrophy Lipodystrophy Restrictive dermopathy Werner syndrome Hutchinson--Gilford Progeria Limb girdle muscular dystrophy 1B Charcot--Marie--Tooth 2B1	10,11,61,62
MYBPC3	11p11.2	Cardiac myosin-binding protein C	Hypertrophic and dilated cardiomyopathy	10,11
MYH7	14q12	β-Myosin heavy chain	Hypertrophic, dilated, and restrictive cardiomyopathy Myosin storage myopathy Distal myopathy Scapuloperoneal myopathy	10,11,28,29
PLN	6q22.1	Phospholamban	Hypertrophic and dilated cardiomyopathy	10,11
SCN5A	3p21	Sodium channel type 5 α-subunit	Long QT syndrome 3 Brugada syndrome Sick sinus syndrome Familial heart block Paroxysmal ventricular fibrillation Cardiac conduction defect Dilated cardiomyopathy	137
TAZ[b]	Xq28	Taffazin	Barth syndrome Dilated cardiomyopathy	10,11,35,134,136,138–145
TNNI3	19p13.4	Cardiac troponin I	Hypertrophic, dilated, and restrictive cardiomyopathy	10,11
TNNT2	1q32	Cardiac troponin T	Hypertrophic, dilated, and restrictive cardiomyopathy	10,11,28
TPM1	15q22.1	A-tropomyosin	Hypertrophic and dilated cardiomyopathy	10,11

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

for normal force production, impaired force generation might play a role in the etiology of NCCM. Mutations in this region have been associated with NCCM with or without Ebstein anomaly.[28,29] 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.

Sarcomere mutations were common causes for NCCM in adults as well as in children.[10,11] Multiple or compound/double heterozygous mutations were identified in 25% of the children and in 10% of the adult NCCM patients.[10] HCM complex genotypes have been described in 7%.[30] In HCM, double heterozygosity for truncating sarcomere mutations have been previously associated with severe congenital forms mostly inherited in an autosomal recessive mode.[31–33] In NCCM, double mutations were associated with severe disease in two children and were also observed in adults.[10] Nonsarcomere genetic causes for isolated NCCM 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.[34–36] However, mutations in these genes were only rare causes of NCCM in single families.[37]

The absence of a mutation in approximately half of familial NCCM could be explained by phenotype assignment errors, the involvement of other yet unidentified genes, the presence of mutations in non-analyzed gene sequences, and incomplete sensitivity of the methods used.[10]

6.4 Pathogenesis

Mutations in different genes associated with NCCM affect different mechanisms in the cardiomyocyte leading to changes that may individually cause NCCM or lead to a common cellular disturbance resulting in NCCM.

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 either due to changes in calcium availability or myofibrillar sensitivity for calcium.[38]

The development of NCCM 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.

6.4.1 Isolated NCCM

The first hypothesis on the pathogenesis of NCCM stemmed from observations that the morphology of NCCM was reminiscent of the embryonic stages of cardiac development. Consequently, it was postulated that NCCM could be the result from an arrest of compaction of myocardial fibers.[39] Figure 6.4 illustrates the striking resemblance between NCCM and the physiological embryonic noncompaction in the 8th–10th 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.[40,41] 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 NCCM in knock out mice.[42–46] However, in human NCCM, no mutations in these genes have been described.

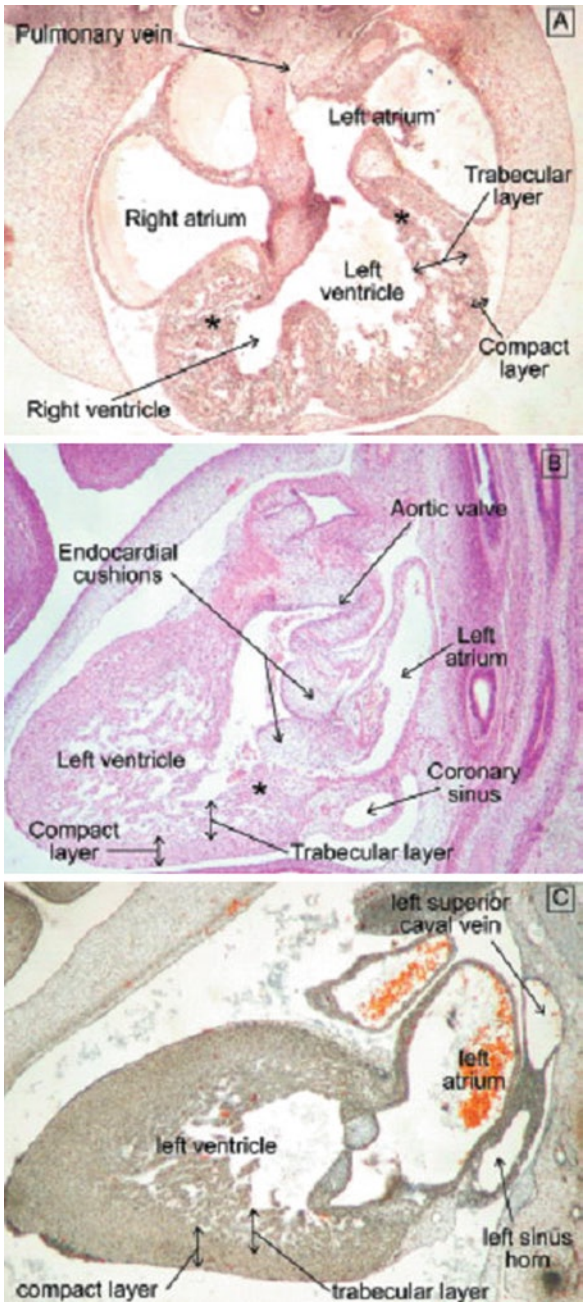

Fig. 6.4 Human embryos at Carnegie stage 16 (**a**), stage 18 (**b**) and after closing of the embryonic interventricular foramen (**c**). During development, there is an extensive trabecular layer forming the greater part of the ventricular wall thickness compared to the extent of the compact layer. The trabecular layer becomes compacted and forms the papillary muscles of the atrioventricular valves (*asterisks*) (Reproduced from Freedom et al.[22] With permission)

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

In the majority of patients, NCCM is diagnosed in adulthood, similar to HCM and DCM, which are rarely congenital.[47,48] Of course, it could be that in NCCM 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 NCCM 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 NCCM. 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.[38,49]

6.4.2 Nonisolated NCCM

NCCM 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 NCCM. Alternatively, NCCM 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 NCCM without a mutual etiology.

6.4.3 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 NCCM had a congenital heart defect.[7] The large number of structural heart malformations reported in association with noncompaction are presented in Table 6.3, indicating that septal defects, patent ductus arteriosus, and Ebstein's anomaly are the most prevalent congenital heart defects in NCCM.

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 NCCM) linked to sarcomere mutations, suggesting that these specific sarcomere defects may have been involved in cardiac morphogenesis.[11,29,50–54] But

Table 6.3 Congenital heart disease associated with noncompaction cardiomyopathy (NCCM)

Congenital heart disease in NCCM	Proportion of CHD		References
	In NCCM studies[a]	Case reports	
Aberrant origin of right/left subclavian artery	1/12 (8%)	1	146, 147
Absent aortic valve		1	148
Anomalous pulmonary venous return	2/26 (8%)		18, 146
Aortic coarctation	6/204 (3%)		7, 11, 113, 146, 149
Aortico-left ventricular tunnel		1	150
Aortic stenosis	2/46 (4%)	2	7, 22, 151
Aortopulmonary window	1/21 (5%)		113
Atrial septal defect	22/135 (16%)	3	7, 11, 29, 113, 152, 153
Atrio-ventricular diverticulum		1	154
Bicuspid aortic valves	3/64 (5%)	3	7, 113, 119, 155
Bicuspid pulmonary valve	1/14 (7%)		18
Cardiac aneurysms		4	81, 156–158
Coronary ostial stenosis	1/14 (7%)		18
Cor triatriatum	1/46 (2%)		7
Dextrocardia	2/58 (3%)	1	1, 7, 146
Dextro malposed great arteries	1/12 (8%)		146
Dextroversion		1	159
Double inlet left ventricle	1/46 (2%)		7
Double orifice mitral valve		4	160–162
Double outlet right ventricle	1/54 (2%)		149
Ebstein's anomaly	6/117 (5%)	10	7, 11, 153, 163–168
Fallot's tetralogy	1/71 (1%)	1	11, 147
Hypoplastic left heart syndrome	3/54 (6%)		149
Hypoplastic right ventricle	3/58 (5%)		7, 146
Isomerism of the left atrial appendage	4/66 (6%)	8	22, 146, 149, 169
Left-sided superior vena cava	1/46 (2%)		7
Mitral valve atresia		1	148
Mitral valve cleft	2/54 (4%)	1	149, 158

Table 6.3 (continued)

Congenital heart disease in NCCM	Proportion of CHD		References
	In NCCM studies[a]	Case reports	
Mitral valve dysplasia	2/14 (14%)		18
Mitral valve prolaps	1/46 (2%)		7
Patent ductus arteriosus	16/182 (9%)	1	7, 11, 149, 153
Persistent left superior vena cava	1/14 (7%)	1	18, 157
Pulmonary atresia	6/125 (5%)	1	11, 149, 153
Pulmonary valve dysplasia	2/14 (14%)		18
Pulmonary stenosis	4/97 (4%)	1	11, 18, 146, 153
Single ventricle	1/12 (8%)	1	146, 170
Subaortic membrane	2/55 (4%)		149
Transposition of the great arteries	1/46 (2%)	1	7, 171
Tricuspid atresia	2/54 (4%)		149
Tricuspid valve dysplasia	1/14 (7%)		18
Ventricular septal defect	23/218 (11 %)	3	1, 7, 11, 18, 113, 146, 149, 151, 157

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

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.

6.4.4 Neuromuscular Disease

Similar to HCM and DCM, NCCM has been associated with neuromuscular disorders. Stollberger and Finsterer identified NCCM-like morphological features in Duchenne and Becker muscular dystrophy and in myotonic dystrophy (see chapter *neuromuscular disorders*).[55–58] 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. A large proportion of patients and also female carriers have cardiac symptoms, including DCM.[59,60] 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 NCCM (Tables 6.1 and 6.4). 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 NCCM patients.[11,61,62] In one of them, there was familial limb girdle muscular dystrophy (LGMD) as well as DCM.[11] 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.[62] Up to 25% of patients with an LMNA mutation may remain cardiologically asymptomatic.[63] The β-myosin heavy chain is

Table 6.4 Neuromuscular disorders associated with noncompaction cardiomyopathy (NCCM)/hypertrabeculation

Neuromuscular disorders	Gene	Inheritance	Features	Reference
Adenosine Monophosphate Deaminase 1 (MADA deficiency)	*AMPD1*	AD	Exercise-induced myopathy, muscle weakness, cramps; prolonged fatigue after exertion; benign congenital hypotonia	172
Becker and Duchenne muscular dystrophy	*DMD*	XR	Muscle weakness and wasting; hypotonia; waddling gait; pseudohypertrophy; cognitive impairment; cardiomyopathy; respiratory failure	55–57, 132, 173, 174
Charcot-Marie-Tooth 1A (HMSN IA)	*PMP22*	AD	Distal limb muscle weakness and atrophy; distal sensory impairment	175
Myotonic dystrophy I	*DMPK*	AD	Myotonia; weakness; muscle wasting; adult cognitive deterioration; cataract; arrhythmia	58, 176, 177
Myotonic dystrophy II	*ZNF9*	AD	Muscle pain; myotonia; weakness (proximal/deep finger/neck flexor); cataract; cardiac conduction abnormalities; palpitations; tachycardia; hypogonadism; frontal balding	178
Infantile epilepsy-encephalopathy syndrome (Ohtahara syndrome)	*ARX*	XR	Age-dependent epileptic encephalopathy with "burst-suppression" on EEG; physical and mental retardation	179
Limb girdle muscular dystrophy 1B	*LMNA*	AD	Muscle weakness and wasting restricted to the limb musculature, proximal greater than distal	11, 132
Succinate dehydrogenase deficiency		AR	Encephalomyopathy; cardiomyopathy; generalized muscle weakness; cerebellar ataxia; optic atrophy; tumor formation in adulthood	180

AD autosomal dominant, *XR* X-linked recessive, *AR* autosomal recessive

part of type II myosin that generates the mechanical force needed for muscle contraction.

Tafazzins have no known similarities to other proteins. Two regions of the protein may be functionally significant, one serving as a membrane anchor and soluble cytoplasmic protein and the other may serve as an exposed loop, interacting with other proteins.

Table 6.4 presents a list of neuromuscular disorders in which NCCM has been identified. In addition, one case of noncompaction in a patient with Friedreich ataxia has been reported.[64] Friedreich ataxia is associated with symmetric, concentric, hypertrophic cardiomyopathy.

6.4.5 Syndromes

NCCM 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 6.5 or one of the *chromosomal defects* in Table 6.6 could be considered in the differential diagnosis.

6.4.6 Mitochondrial

Mitochondrial disorders often lead to multi-organ disease, including central and peripheral nervous system, eyes, heart, kidney, and endocrine organs. One of the cardiac features observed in mitochondrial disease is noncompaction cardiomyopathy. 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, NCCM was

Table 6.5 Syndromes associated with noncompaction cardiomyopathy (NCCM)/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	35, 37, 134, 136, 138–145
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	181
Congenital adrenal hypoplasia	*NR0B1*	XR	Failure to thrive; hypogonadotropic hypogonadism; cryptorchidism; hyperpigmentation; primary adrenocortical failure; adrenal insufficiency; gluco-mineralocorticoid insufficiency; salt-wasting; delayed puberty	66
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; kypkoscoliosis; hip/knee/elbow contractures; arachnodactyly; ulnar deviation of fingers; talipes equinovarus; hypoplastic calf muscles; motor development delay	182
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 2nd and 3d toes; single transverse palmar crease; cutis marmorata; hirsutism; low posterior hair line; mental retardation; language delay; automutilation	113
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	183
Melnick Needles osteodysplasty	*FLNA*	XD	Short stature; micrognathia; large ears; hypertelorism; exophthalmos; cleft palate; misaligned teeth; long neck; mitral/tricuspid valve prolapse; NCCM; 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	184
Nail Patella Syndrome	*LMX1B*	AD	Short stature; sensorineural hearing loss; ptosis; cataract; cleft lip/palate; malformed sternum; hypoplasia of first ribs; glomerulanephritis; renal failure; scoliosis; elbow deformities; hypoplastic or absent patella; clinodactyly; talipes equinovarus; longitudinal ridging nails; slow nail growth; koilonychias; anonychia; aplasia pectaralis minor/biceps/triceps/quadriceps	185, 186

(*continued*)

Table 6.5 (continued)

Syndrome	Gene	Inheritance	Features	Reference
Noonan syndrome	*PTPN11* *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	187
Roifman syndrome		XR	Short-trunk dwarfism; long philtrum; strabismus; narrow and downslanting palpebral fissures; long eyelashes; retinal dystrophy; narrow upturned nose; NCCM; hepato-splenomegaly; spondylo-epiphyseal dysplasia; eczema; hyperconvex nails; hypotonia; (mild) mental retardation; hypogonadotropic hypogonadism; recurrent infections; antibody deficiency	188
Syndromic microphtalmia/MIDAS syndrome (MIcrophtalmia, Dermal Aplasia, Sclerocornea)	*HCCS*	XD	Short stature; microcephaly; hearing loss; microphtalmia; 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	189, 190

AD autosomal dominant, *XD* X-linked dominant, *XR* X-linked recessive

Table 6.6 Chromosomal defects associated with noncompaction cardiomyopathy (NCCM)

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-oesophageal reflux; short fifth finger and clinodactyly; mental retardation (severe); seizures; hypotonia	191–194
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	195
5q35.1q35.3	Facial hirsutism; synophrys; downslanting palpebral fissures; atrial septal defect and patent ductus arteriosus; NCCM with sick sinus syndrome and second degree heart block; feeding problems; gastro-oesophageal reflux; joint hypermobility	196
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	66
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	197
Trisomy 13	Microcephaly; hypotelorism; cleft lip/palate; coloboma; low-set ears; septal defects; patent ductus arteriosus Polydactyly; overlapping fingers; mental retardation (severe); hypotonia; seizures	198

Table 6.6 (continued)

Chromosomal defects	Features	Reference
Trisomy 21	Short stature; bachycephaly; 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	11, 149
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	199
45,X0	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; lymph-edema of hands and feet; renal abnormalities: single horseshoe kidney; renal vascular abnormalities; delayed puberty; amenorrhea; infertility; hypothyroidism	200, 201
Loci		
6p24.3-21.1	NCCM; bradycardia; pulmonary valve stenosis; atrial septal defect; left bronchial isomerism; azygous continuation of the inferior vena cava; polysplenia; intestinal malrotation	153
11p15	NCCM; mild pulmonary stenosis; mild mitral valve prolapse; atrial septal defect	202

identified in 13%.[65] Pignatelli et al. showed that 5 of the 36 pediatric NCCM 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.[66] Mutations in mitochondrial DNA (mtDNA) and in nuclear DNA have been identified in the mitochondrial disorders associated with NCCM.[67–69]

6.4.7 Miscellaneous

NCCM has been described in patients with heterotaxy with polysplenia, polycystic kidney disease, congenital adrenal hyperplasia, nephropathic cystinosis, and myelofibrosis.[11, 66, 70–74] Whether these co-occurrences are coincidental or represent shared etiologies with NCCM is unknown.

Among the possibly acquired forms of NCCM, there are reports about an infectious cause.[27] Recently, an etiologic role for macro- and microvascular abnormalities was suggested.[75–84] NCCM has also been described in patients with coronary heart disease.[85–87] Since coronary artery disease is a frequent disorder, this association may well be coincidental. Aortic elasticity was significantly altered in a group of 20 NCCM patients (aortic stiffness index of 8.3 ± 5.2).[78]

Microvascular abnormalities in NCCM including decreased coronary flow reserve with wall motion abnormalities in more extended regions of the myocardium than the noncompacted area have been observed.[77] In addition, several case studies reported hypoperfusion of the noncompacted region in NCCM patients using myocardial perfusion SPECT, positron emission tomography, Thallium myocardial imaging, or MRI.[75, 76, 79, 80, 82, 83] It is thought that fibrosis, thrombus formation, hypokinesis, and necrosis may be the underlying mechanisms of hypoperfusion.[76, 79, 80]

Other pathogenic hypotheses for NCCM include adaptation to changes in the cardiovascular and/or hemodynamic climate; myocardial dissection or tearing of the inner layer of the cardiac muscle due to dilatation.[19, 22]

6.5 Clinical Aspects

Heart failure is among the most frequent presentations of NCCM, followed by supraventricular and ventricular arrhythmias, including sudden cardiac death, and thrombo-embolic 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.[6, 11, 88–93] Prenatal diagnostic imaging detects more often bilateral ventricular hypertrophy/*hypertrabeculation*s than the typical left ventricular morphologic changes observed postnatally and in adults (unpublished observation). The fourth to fifth decade is the median age for diagnosis in adult isolated NCCM, 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 NCCM.[11, 13] Symptomatic patients may present clinical symptoms of dyspnea, fatigue (atypical) chest pain, and/or (pre) syncope. NCCM may also present as a peripartum cardiomyopathy.[11, 94–96] Review of the literature revealed a male to female ratio of almost 2:1.[19] This gender difference cannot be fully explained by the occurrence of X-linked forms of NCCM.

Different *arrhythmias* and *conduction disorders* may occur in NCCM patients (Table 6.7). None of these arrhythmias is characteristic or pathognomonic for NCCM. Thrombo-embolic events may include stroke (cerebrovascular event or transient ischemic attack), peripheral embolism, and mesenterial thrombosis.

Table 6.7 Arrhythmia and conduction disorders associated with noncompaction cardiomyopathy (NCCM)

Arrhythmia/conduction disorders associated with NCCM	Reference
Atrial fibrillation	15, 113, 203
Atrioventricular nodal re-entrant tachycardia	204
Bigemini ventricular extra systole	146
Complete atrioventricular block	1, 158, 205, 206
Complete left bundle branch block	109, 146
Giant P-waves and focal atrial tachycardia	207
Long QT syndrome 2	135
Narrow QRS complex	106, 107, 110
Persistent atrial standstill	208
Sick sinus syndrome	209
Sinus bradycardia	153, 210
Supraventricular tachyarrhythmia	7, 113, 130, 146, 211
Ventricular fibrillation	106, 205, 212
Ventricular tachycardia	7, 79, 106, 109, 210
Wolff–Parkinson–White syndrome	2, 7, 146, 210, 213

6.6 Differential Diagnosis

The definitive diagnosis of NCCM 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 NCCM from normal physiological left ventricular 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 NCCM and the thickness of these physiological trabeculations does not exceed the thickness of the compact layer. Also, the area of noncompaction is larger in NCCM than in physiological trabeculations.[13]

Secondary forms of (acquired) NCCM may be the result of hypertension, chronic volume or pressure overload,[97] ischemic heart disease or extreme physical activity (i.e., athletes), leading to NCCM-like abnormalities. These are referred to as pseudo-noncompaction cardiomyopathy or an NCCM 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.[14]

Furthermore, dilated, hypertrophic, and ischemic cardiomyopathy may be mistaken for NCCM or vice versa, due to prominent trabeculations or abnormal myocardial thickening. Candida sepsis with intramyocardial abscesses and intramyocardial hematoma may mimic NCCM.[27, 98, 99]

The neuromuscular disorders, syndromes, and chromosomal abnormalities mentioned earlier (Tables 6.3–6.5) should be considered in the differential diagnosis of nonisolated NCCM, especially when NCCM occurs in patients with dysmorphism, growth retardation, or skeletal muscle weakness.

6.7 Therapy, Follow-up, and Prognosis

6.7.1 Therapy and Follow-up

Current guidelines for heart failure, arrhythmias, cardiac resynchronization therapy, and ICD implantation for primary and secondary prevention are applied for NCCM.[100–102] *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, based on case reports, small cohorts and clinical registries would be recommended since no randomized trials or studies on management of NCCM have been conducted, and clear-cut evidence-based clinical guidelines for this disorder are therefore missing.[103] An important issue is the use of prophylactic anticoagulants, in view of frequent thrombo-embolic events. The early case reports and case series emphasized the high risk of thrombo-embolism and advised routine anticoagulation therapy. However, a review of 22 publications addressing the issue concluded that thrombo-embolic events are rare in NCCM.[104] Fazio et al. came to the same conclusion.[105] Currently, in our hospital, anticoagulation therapy is advised only in patients with an ejection fraction less than 40% (cut off arbitrary), paroxysmal or persistent atrial fibrillation and/or previous thrombo-embolic events.

Successful cardiac resynchronization therapy has been described in several NCCM patients, leading to left ventricular reverse remodeling and an increase in left ventricular function.[106–110]

Heart transplantation has been performed in some NCCM patients with severe heart failure.[3, 11, 23, 111–117] Left ventricular restoration surgery has been reported successful in a single patient.[118] 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 NCCM is accompanied by hypertension or arrhythmias.

6.7.2 Prognosis

Initially, NCCM was reported to have a grave prognosis.[2, 3, 12, 19, 23, 119–125] However, the application of new imaging techniques allowing diagnosing NCCM in asymptomatic individuals suggests that the first observations were influenced by selection of the most severely affected individuals. It has become clear that prognosis of NCCM 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.[6, 88, 90, 92, 126, 127] Similarly, in some adult patients a rapid deterioration of heart function occurs, whereas in others the disease remains stable up to old age.[89] Malignant arrhythmias leading to sudden cardiac death and heart failure are the main indicators of poor prognosis. 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.

6.8 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 left ventricular 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 the risk factors and allow more appropriate risk stratification.[128]

Consensus and guidelines for prophylactic ICD treatment in NCCM patients are also needed. Regular ICD indications include primary and secondary prevention. For secondary prevention, i.e., 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 NCCM 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 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.[129] In another study, follow-up of 12 patients who received an ICD showed overall appropriate therapy in 42% in primary and secondary prevention combined.[130] In primary prevention, 25% of ICD therapy was appropriate opposed to 50% in secondary prevention.[130] This accentuates the need for further research of appropriate risk stratification of sudden cardiac death in patients with NCCM.

6.9 Cardiogenetic Aspects

6.9.1 Molecular and Cardiologic Family Screening

Familial NCCM has been estimated to occur in 18–71% of adults with isolated NCCM, mostly consistent with an autosomal dominant mode of inheritance, indicating the importance of informing and examining relatives of patients with isolated NCCM.[2, 11, 24, 66, 120, 131–133] 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.[11] 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.

Apart from NCCM, other cardiomyopathies may co-occur within families, like hypertrophic and dilated cardiomyopathy, so cardiac screening should aim at identifying all cardiomyopathies. Cardiac screening of relatives may show minor abnormalities not fulfilling NCCM criteria, which may be difficult to differentiate from normal physiologic trabecularization. Hypothetically, these minor abnormalities might develop into NCCM eventually. Longitudinal studies of patients with mild NCCM features are needed to investigate the natural history of these forms of noncompaction.

6.9.2 Genotype–Phenotype Correlations

Molecular studies of NCCM have thus far shown that there are few recurrent mutations.[10] Therefore, it is difficult to establish genotype-phenotype correlations. Additionally, intrafamilial phenotypic variability complicates predictions based on an identified mutation. Multiple (truncating) sarcomere mutations appear to result in a more severe phenotype with childhood onset.[10, 11] 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, 11] These observations may indicate that the combination of a sarcomere mutation and a nonsarcomere mutation causes a less severe phenotype than when a patient has two sarcomere mutations. Mutations in *DTNA* and *TAZ* seem to transfer the strongest predisposition to childhood onset NCCM.

6.9.3 Molecular Strategies

The proposed strategies for the molecular and cardiologic evaluation of NCCM are depicted in the flowchart in Fig. 6.5. Extensive genetic screening may lead to the identification of a molecular defect in over 40% of isolated NCCM patients and in half of these patients an *MYH7* mutation is found.[10] *MYH7* gene sequencing should be considered as an initial approach, being the most prevalent cause for NCCM in adults and children. Further molecular analyses of the other genes within the NCCM spectrum, which quantitatively have a relatively modest contribution to NCCM 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.[10] When an adult or pediatric patient is severely affected, screening for a

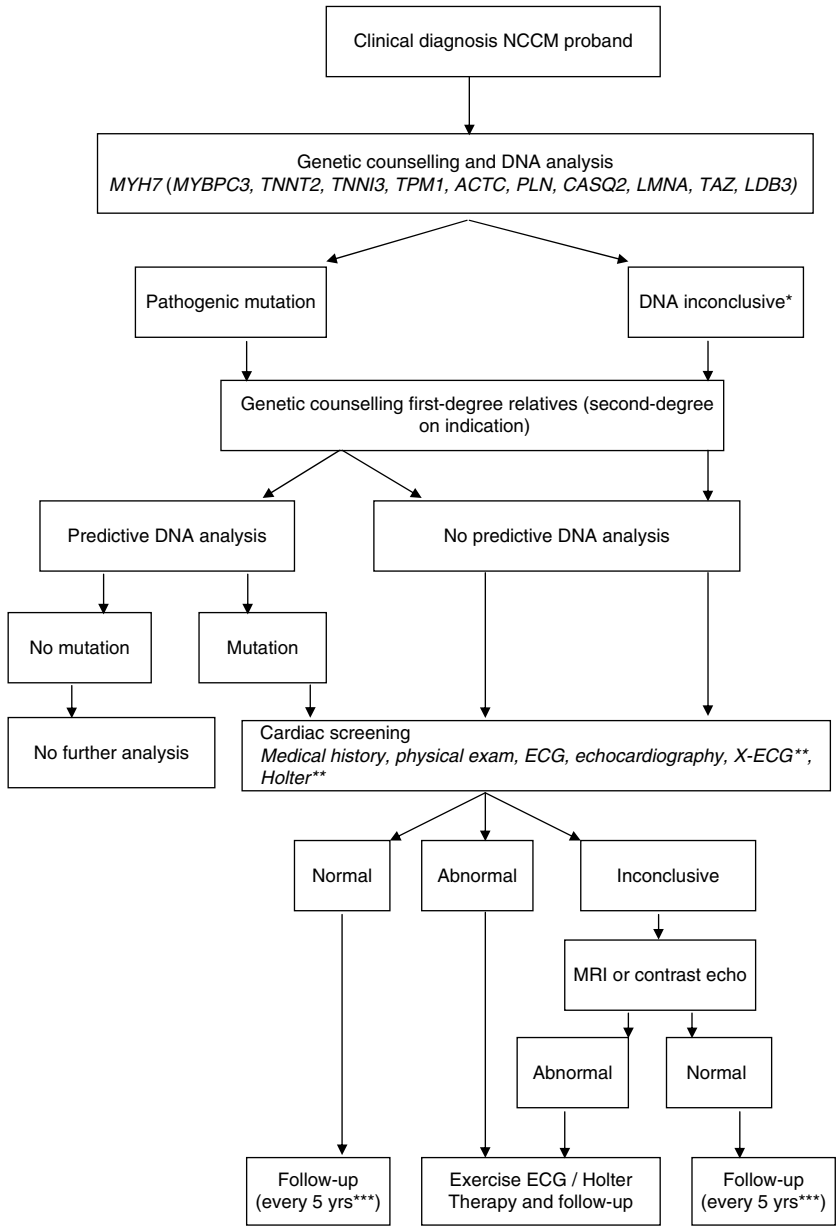

Fig. 6.5 Flowchart for family screening in NCCM * Including unclassified variants; ** if clinically indicated; *** earlier when symptomatic

second molecular defect is advised, given the high frequency of multiple mutations in NCCM.

6.10 Summary

NCCM 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. In adults, the majority of NCCM is isolated.

The first clinical presentation of NCCM may occur at all ages, even prenatally. In childhood, clinical features are often more severe and NCCM 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 NCCM population.

In as much as 41% of isolated NCCM, molecular testing may yield a genetic defect, mostly in sarcomere genes. The *MYH7* gene is the most prevalent disease gene. The nonisolated forms of NCCM are caused by a range of different (rare) genetic defects. Until now, in half of familial isolated NCCM, 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 NCCM may result from a wide range of pathophysiologic mechanisms.

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

The genetic etiology of NCCM 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.

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