JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 7, 2018
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PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

Genetics, Clinical Features, and Long-Term Outcome of Noncompaction Cardiomyopathy

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ABSTRACT

BACKGROUND The clinical outcomes of noncompaction cardiomyopathy (NCCM) range from asymptomatic to heart failure, arrhythmias, and sudden cardiac death. Genetics play an important role in NCCM.

OBJECTIVES This study investigated the correlations among genetics, clinical features, and outcomes in adults and children diagnosed with NCCM.

METHODS A retrospective multicenter study from 4 cardiogenetic centers in the Netherlands classified 327 unrelated NCCM patients into 3 categories: 1) genetic, with a mutation in 32% (81 adults; 23 children) of patients; 2) probably genetic, familial cardiomyopathy without a mutation in 16% (45 adults; 8 children) of patients; or 3) sporadic, no family history, without mutation in 52% (149 adults; 21 children) of patients. Clinical features and major adverse cardiac events (MACE) during follow-up were compared across the children and adults.

RESULTS *MYH7*, *MYBPC3*, and *TTN* mutations were the most common mutations (71%) found in genetic NCCM. The risk of having reduced left ventricular (LV) systolic dysfunction was higher for genetic patients compared with the probably genetic and sporadic cases ($p = 0.024$), with the highest risk in patients with multiple mutations and *TTN* mutations. Mutations were more frequent in children ($p = 0.04$) and were associated with MACE ($p = 0.025$). Adults were more likely to have sporadic NCCM. High risk for cardiac events in children and adults was related to LV systolic dysfunction in mutation carriers, but not in sporadic cases. Patients with *MYH7* mutations had low risk for MACE ($p = 0.03$).

CONCLUSIONS NCCM is a heterogeneous condition, and genetic stratification has a role in clinical care. Distinguishing genetic from nongenetic NCCM complements prediction of outcome and may lead to management and follow-up tailored to genetic status. (J Am Coll Cardiol 2018;71:711–22) © 2018 by the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2017.12.019

ABBREVIATIONS AND ACRONYMS

ASD = atrial septal defect

CI = confidence interval

CHD = congenital heart defect

DCM = dilated cardiomyopathy

HCM = hypertrophic cardiomyopathy

HR = hazard ratio

IQR = interquartile range

LBBB = left bundle branch block

LV = left ventricular

MACE = major adverse cardiac events

MRI = magnetic resonance imaging

NCCM = noncompaction cardiomyopathy

RBBB = right bundle branch block

RV = right ventricular

VSD = ventricular septal defect

VUS = variant of unknown clinical significance

Noncompaction cardiomyopathy (NCCM), which is also known as left ventricular (LV) noncompaction, is a cardiomyopathy with excessive trabeculations of the LV, with a >2-fold thickening of the endocardial noncompacted layer compared with the epicardial compacted layer of the myocardium (NC/C >2) (1–3). Initially referred to as "spongy" heart, NCCM has gained attention because of improvements in cardiac imaging that allow more detailed visualization and increased clinical awareness of this syndrome (4,5). Clinical symptoms range from severe prenatal manifestations to asymptomatic cardiomyopathy presenting in adults (6,7).

Genetics play an important role in NCCM because 17% to 50% (8,9) of patients have a family member with cardiomyopathy, and the yield of DNA testing ranges from 17% to 41% depending on patient selection and the number of genes screened (10,11). In most families, an autosomal dominant pattern of inheritance is observed with variable penetrance (12). Most of the genetic defects associated with NCCM have also been reported in patients with hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) (10,13). In NCCM, mutations in the sarcomere genes, particular in *MYH7,* are the most common (10,11). However, the role of the sarcomere gene defects in the development of cardiac hypertrabeculation has not been established yet. The diagnosis of NCCM requires genetic counseling because timely screening and diagnosis of at-risk relatives is important. Finding a mutation allows prediction to identify accurately the relatives at risk for NCCM. Because NCCM is not as common as HCM and DCM, associations among mutations in cardiomyopathy genes, family history and the age of onset, LV systolic dysfunction, and long-term outcome have not been previously investigated in detail.

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We conducted a large multicenter study in 4 cardiogenetic centers in the Netherlands to investigate the role of genetics in NCCM. The focus of the study was to investigate the relationship between clinical and cardiologic features at diagnosis, the risk of LV systolic dysfunction, and the occurrence of major adverse cardiac events (MACE) during follow-up in NCCM patients diagnosed in childhood or adulthood. These insights may help to improve management of NCCM patients and their families.

METHODS

STUDY POPULATION. The retrospective study consisted of 327 unrelated NCCM patients referred to 1 of the participating departments of Clinical Genetics for genetic counseling and DNA testing (with informed consent) between January 2005 and January 2016. Sixteen patients who did not have DNA testing were excluded (Online Appendix). Diagnosis of NCCM was based on consensus of re-evaluated echocardiography and magnetic resonance imaging (MRI), according to the Jenni and Petersen criteria by J. van Waning and a dedicated participating cardiologist (3,5). Echocardiographic and MRI data were available for all patients, except for 34 patients with only MRI and 80 patients with only echocardiographic data. One patient was diagnosed at autopsy.

GENETICS. Specifics on the genes tested and methods of classification of variants are described in detail in the Online Methods. The core panel of tested cardiomyopathy genes included 45 cardiomyopathy genes. All variants were evaluated according to the current Dutch guidelines, and classification of each variant was achieved with consensus of the participating molecular geneticists. Patients were classified as genetic if they had a (likely) pathogenic mutation (Online Tables 1 and 2). Variants of unknown clinical significance (VUS) are reported in Online Table 3. Patients with only a VUS were not classified as genetic because these variants were not proven to be pathogenic. Patients were classified as probably genetic if they had a family history of cardiomyopathy and if DNA testing did not identify a mutation. Patients were classified as sporadic if patients had no mutation or family history of cardiomyopathy (**Figure 1**).

CLINICAL DATA. Clinical data were retrieved retrospectively from the medical records, including age, sex, cardiac diagnosis, electrocardiography, echocardiography, and cardiac MRI when available. If the images of the first echocardiographic examination were unavailable, more recent echocardiographic imaging was used.

VENTRICULAR FUNCTION. LV systolic dysfunction was defined as LV ejection fraction of <45% on MRI or

supported by a grant from the Jaap Schouten Foundation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 22, 2017; accepted December 8, 2017.

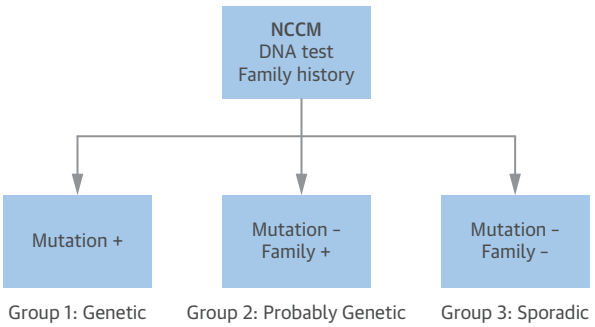
fractional shortening of <19% in men and of <21% in women on echocardiography if MRI images (n = 80) were missing (14). Abnormal right ventricular (RV) systolic function was defined as a tricuspid annular plane systolic excursion <17 mm on echo or RV ejection fraction <45% on MRI (15). For children, dimensions of the ventricles of <2 SDs from the reference range were classified as abnormal (16,17).

ADVERSE EVENTS. Information on the occurrence of clinical events at follow-up was collected from the medical records. Heart failure that required hospitalization was defined as new-onset or worsening signs of heart failure that required therapy and hospitalization. Sustained ventricular tachycardia/ventricular fibrillation was identified when at least 30 s of hemodynamically stable ventricular tachycardia or hemodynamically unstable ventricular tachycardia/ventricular fibrillation of any duration was documented by electrocardiograms, pacemaker, or defibrillator data. We used a combined endpoint for our hazard models because of the low incidence of death. The occurrence of cardiac death, implantation of a LV assistance device, heart transplantation, (aborted) sudden cardiac death, appropriate implantable cardioverter-defibrillator shock, or ischemic stroke were classified as MACE. Seventeen patients were lost to follow-up. Information on vital status was confirmed by checking municipal registries for all patients.

FAMILY HISTORY. Family histories were ascertained at the Departments of Clinical Genetics. Patients were classified as familial, if at least 1 first-degree or 2 second-degree relatives were reported to have cardiomyopathy. None of the patients had only 1 affected second-degree relative. Medical records confirmed the diagnosis of 82% of the relatives reported to have cardiomyopathy; no medical records were available for 18% of the affected relatives. The occurrence of (aborted) sudden cardiac death at age younger than 50 years in the family of the index patients was recorded. In families with multiple cases of NCCM, only 1 case per family, the first diagnosed, was included in the study.

STATISTICAL ANALYSIS. Categorical data were compared with Pearson's chi-square test or Fisher exact test. For continuous variables, unpaired Student's *t*-tests were used for 2 groups and analysis of variance tests for >2 groups. Logistic regression was used to find associations between genetic status and LV dysfunction at baseline. Kaplan-Meier survival curves were estimated and differences between groups were assessed by the log-rank test, using time at diagnosis as time zero. Risk factors for MACE were calculated by Cox proportional hazards regression analysis. Patients lost to follow-up were considered at risk until the date of last contact, at which time point they were censored. Analysis was performed with SPSS statistical software version 21.0 (IBM, Armonk, New York).

FIGURE 1 Noncompaction Cardiomyopathy Study Population



RESULTS

NCCM GENETICS. The 327 NCCM patients were categorized into the 3 groups: 104 genetic (32%; 81 adults, 23 children); 53 probably genetic (16%; 45 adults, 8 children); and 164 sporadic (52%; 149 adults, 21 children) (**Table 1, Figure 2**). The complete list of mutations in children and adult NCCM patients with reference to previous reported variants, the reported cardiomyopathy (NCCM, HCM, or DCM), and the yield per tested gene are presented in the Online Tables 1a and 2a, Online Figure 1). In addition, 192 VUS in cardiomyopathy genes were identified in 111 patients (Online Table 3); 13 (12%) patients with a mutation had an additional VUS. Of the patients without a mutation, 98 (30%) had a VUS. Seventy-one (41%) of the sporadic cases had a VUS, compared with 63% of the probably genetic cases (n = 27, p = 0.013).

Of the 104 genetic cases, 82% involved a sarcomere gene (**Figure 2**), most (71%) had a mutation in *MYH7*, *MYBPC3*, or *TTN*, and 11% had a mutation in *ACTC1, ACTN2, MYL2, TNNC1, TNNT2*, or *TPM1*. Mutations were more frequent in children (44%) than in adults (30%; p = 0.036) (**Table 1**). *MYH7* was the most frequently mutated gene in 19% (n = 10) of children and 11% (n = 29) of adults. *TTN* occurred frequently in adults (7%, n = 18), but not in children. Non-sarcomere gene mutations were detected in *DES, DSP, FKTN, HCN4, KCNQ1, LAMP2, LMNA, MIB1, NOTCH1, PLN, RYR2, SCN5A*, and *TAZ*. One patient classified as genetic had a 1p36 deletion. Mutations occurred more frequently in female patients irrespective of age at diagnosis (males: 27% vs. females:

TABLE 1 Baseline Characteristics and Clinical Features at Diagnosis of 327 NCCM Patients

	Children (n = 52)*				Adults (n = 275)				
		No Mutation (n = 29) (55%)				No Mutation (n = 194) (70%)			
	Mutation (n = 23) (45%)	Familial (n = 8) (15%)	Not Familial (n = 21) (40%)		Mutation (n = 81) (30%)	Familial (n = 45) (16%)	Not Familial (n = 149) (54%)		
	Genetic	Probably Genetic	Sporadic	Total	Genetic	Probably Genetic	Sporadic	Total	p Value
Male	8 (35)	4 (50)	15 (71)	27 (52)	39 (48)	39 (62)	80 (54)	148 (54)	NS
Median age, yrs	5 (0–14)	5 (0–13)	8 (1–15)	7 (0–14)	41 (31–54)	45 (34–57)	47 (35–57)	45 (33–56)	NS
Genetics									
Complex genotype	5 (22)			5 (10)	9 (11)			9 (3)	0.038†
Familial cardiomyopathy	13 (57)	8 (100)		21 (40)	54 (67)	45 (100)		99 (36)	<0.001‡
SCD before age 50 yrs in family	1 (4)	1 (13)		2 (4)	7 (9)	1 (2)	13 (9)	21 (8)	NS
Sanger, no NGS cardiopanel	15 (65)	3 (38)	3 (14)	21 (40)	36 (40)	16 (40)	45 (31)	97 (35)	NS
Comorbidities					19 (23)	16 (35)	49 (33)	84 (31)	NS
Coronary artery disease					1 (1)	2 (4)	9 (6)	12 (4)	NS
Hypertension					12 (15)	12 (27)	38 (26)	62 (23)	0.047‡
Diabetes	1 (4)			1 (2)	3 (4)	3 (7)	6 (4)	12 (4)	NS
Hypercholesterolemia					5 (6)	5 (11)	11 (7)	21 (8)	NS
COPD					6 (7)	5 (11)	9 (6)	20 (7)	NS
CHD	5 (22)	2 (25)	7 (33)	14 (27)	2 (3)	3 (7)	9 (6)	14 (5)	NS
ASD	2 (9)		4 (19)	6 (12)		1 (2)	5 (3)	6 (2)	NS
VSD	2 (9)	2 (25)	4 (19)	8 (15)			3 (2)	3 (1)	NS
Ebstein anomaly	2 (9)			2 (4)	2 (3)			2 (1)	NS
BAV	1 (4)			1 (2)		2 (4)	2 (1)	4 (2)	NS
CoA	1 (4)		1 (5)	2 (4)			1 (1)	1 (0)	NS
LBBB	1 (6)			1 (2)	7 (10)	4 (11)	40 (27)	51 (21)	0.010§
LV systolic dysfunction	16 (70)	4 (50)	2 (11)	22 (42)	49 (60)	23 (51)	80 (54)	152 (58)	0.001#
RV systolic dysfunction	4 (17)		1 (5)	5 (10)	17 (21)	7 (16)	15 (10)	39 (22)	0.029‡
LV and RV systolic dysfunction	4 (17)			4 (8)	16 (20)	5 (11)	11 (7)	32 (12)	0.020‡

Values are n (%) or n (interquartile range). *Diagnosis at age younger than 18 years. †Significant for children compared with adults. ‡Significant for adults with mutation compared with adults without a mutation. §Significant for (probably) genetic compared with sporadic adults. #Significant for children with mutation compared with children without a mutation.

ASD = atrial septal defect; BAV = bicuspid aortic valve; CHD = congenital heart disease; CoA = coarctation of the aorta; COPD = chronic pulmonary obstructive disease; LBBB = left bundle branch block; LV = left ventricular; NCCM = noncompaction cardiomyopathy; NGS = next-generation sequencing; RV = right ventricular; SCD = sudden cardiac death; VSD = ventricular septal defect.

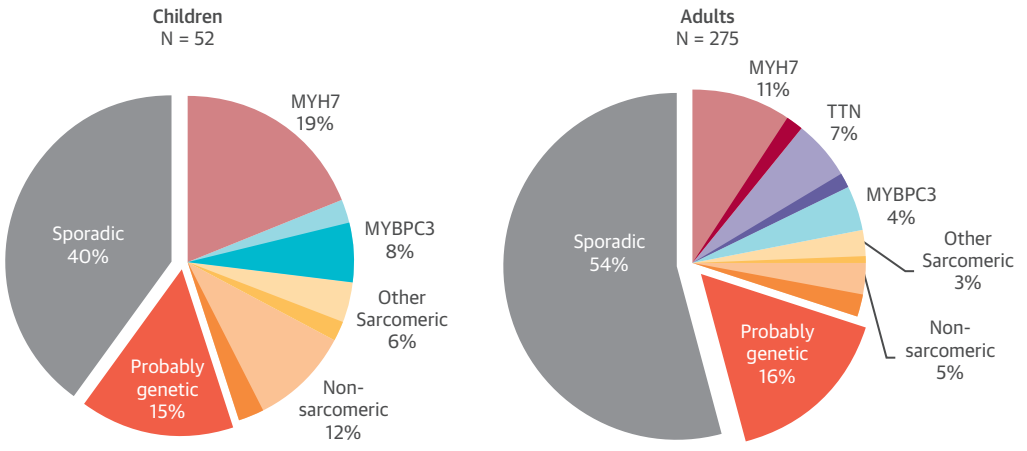
38%; p = 0.039). The yield per tested gene was highest for *MYH7* (13%), *TTN* (11%), and *MYBPC3* (5%).

Complex genotypes. Complex genotypes (multiple mutations in 1 patient) in cardiomyopathy genes were more prevalent in children (10%) than in adults (3%) (p = 0.038) (**Table 1,** Online Tables 1b and 2b). Three children with complex *MYBPC3* mutations presented with severe clinical phenotypes. Complex *MYBPC3* genotypes were not observed in adults. Four adult patients had the same 2 *MYH7* mutation in cis (c.1633G>A and c.2863G>A) that were not considered to be complex genotypes, and were expected to have a common ancestor. Three adult patients had the combination of a *MIB1* and a *TTN* mutation. One patient had 3 pathogenic mutations in 3 different genes: *FKTN*, *RBM20*, and *HCN4*. This 53-year-old patient was first admitted to the hospital for bradycardia. He had no structural heart defects and experienced serious adverse effects at end of follow-up (at 58 years).

DE NOVO MUTATIONS. De novo mutations involving *DES* and *PLN* were observed in 2 children, and de novo mutations involving *PRDM16* and *MYH7* were found in 2 adult patients. The children had severe heart failure and had a heart transplantation at a young age (the *DES* patient at the age of 10 years, the *PLN* patient at age 17 years). In contrast, the adult patients with a de novo mutation had a mild course of the disease without severe complications.

FAMILY HISTORY. Twenty-one (40%) of the children had a family history of cardiomyopathy, as well as 36% (n = 99) of the adults (**Table 1**). Of the 120 familial cases, 56% (n = 67) had a (likely) pathogenic

FIGURE 2 Genetics of NCCM



Darker shades indicate complex genotypes. DNA testing of approximately 45 cardiomyopathy genes and family histories showed that children were more likely to have a mutation (p = 0.036). *TTN* occurred only in adult cases. Complex *MYBPC3* genotypes occurred only in children **(teal).** Abbreviation as Figure 1.

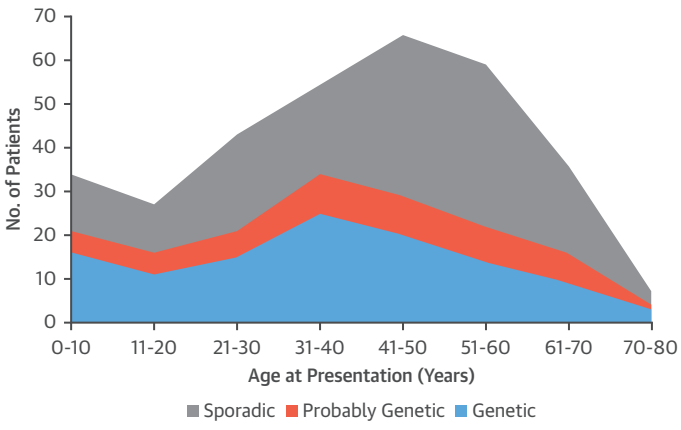
mutation. Of the 207 patients without a family history of cardiomyopathy, 18% (n = 37) had a mutation (p < 0.001). Overall, NCCM occurred in 23% (n = 76) of the affected relatives, in 12% (n = 39) of the families DCM was reported, in 3% (n = 11) HCM occurred in relatives, and in 1 family, a relative was diagnosed with arrhythmogenic cardiomyopathy. Sudden death at age younger than 50 years of a relative was reported by 7% (n = 23) of the patients, in 8% (n = 21) of the families of adult index cases, and in 4% (n = 2) of the families of pediatric index cases.

AGE AT DIAGNOSIS. The study population included 16% (n = 52) pediatric patients who were diagnosed at younger than 18 years of age, and 84% (n = 275) adult patients (Figure 3); the median age at diagnosis of NCCM was 41 years (range: 0 to 79 years; interquartile range [IQR]: 27 to 54 years), 44 years (range: 18 to 79 years: IQR: 33 to 56 years) for adult patients, and 8 years (range: 0 to 17 years; IQR: 0 to 14 years) for children (Table 1). Sixteen (30%) of the children were diagnosed at younger than 1 year of age. Age at diagnosis was inversely associated with the probability of finding a mutation (odds ratio: 0.983 per year; 95% confidence interval [CI]: 0.97 to 0.99; p = 0.01).

CONGENITAL HEART DEFECT. Congenital heart defect (CHD) was observed in 9% of the patients (n = 28). In particular, children (p = 0.027) (Table 1) had more atrial septal defects (ASD) (p = 0.005) and ventricular septal defects (VSD) (p < 0.001). Six of the 16 patients diagnosed at younger than 1 year of age had a CHD. Two children and 2 adults had Ebstein anomaly and an *MYH7* mutation (Central Illustration). Familial segregation of NCCM and Ebstein anomaly was observed in 1 family. *MYH7* was the only sarcomere gene associated with CHD. Two children with a CHD had a chromosomal defect: 1 with a 1p36 deletion had ASD, multiple VSDs, and an open ductus arteriosus; and a trisomy-21 patient with a *MYH7* mutation had ASD and VSD. The other CHDs were observed in patients with defects in nonsarcomere genes, in the probably genetic and the sporadic cases.

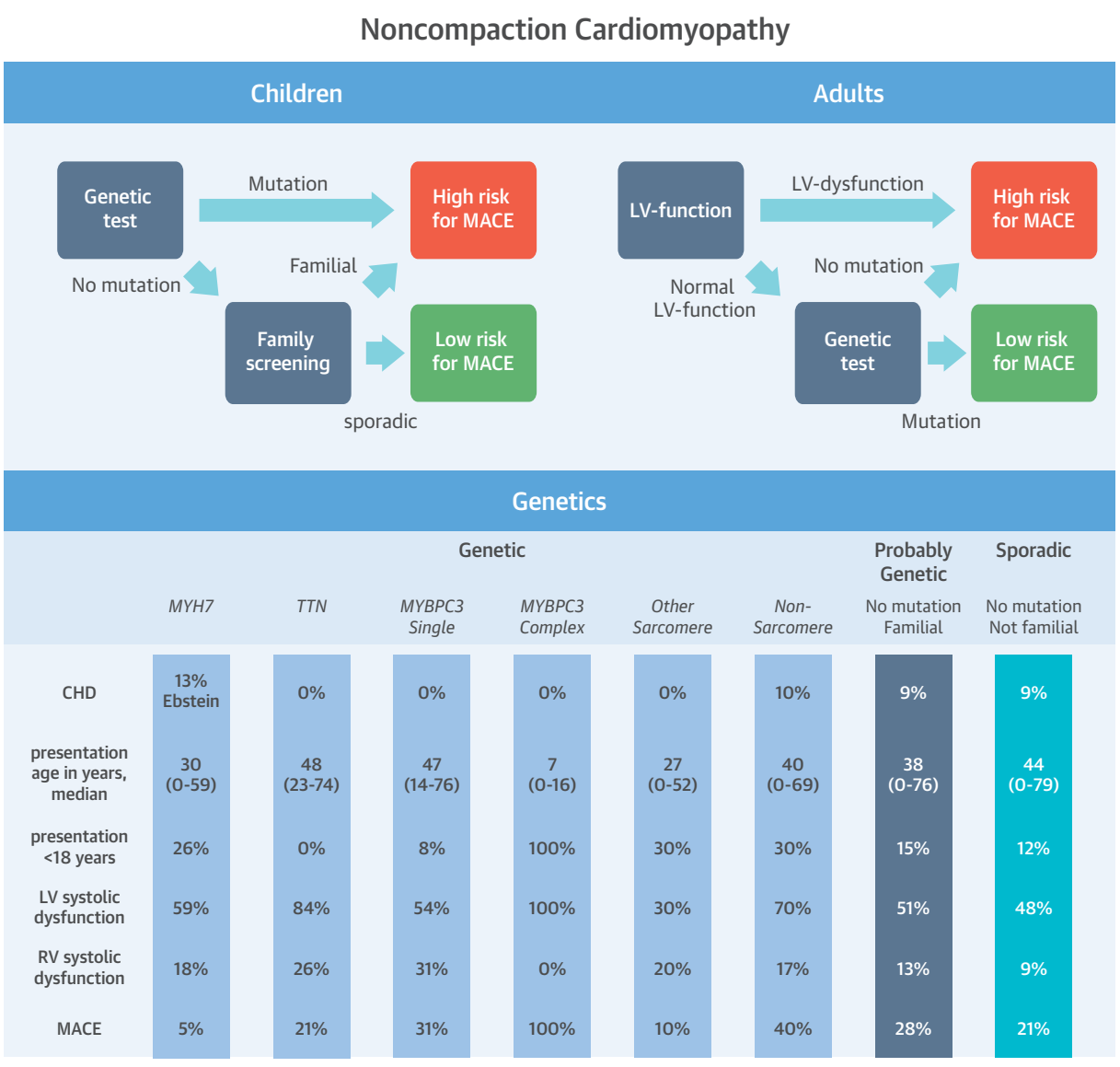
CLINICAL FEATURES. Eighty-three percent of the children and 85% of the adults were symptomatic at

FIGURE 3 Age at Diagnosis in 327 Dutch NCCM Cases



Chance of having a mutation decreased with age (odds ratio: 0.983 per year; 95% confidence interval: 0.97 to 0.99; p = 0.01). Abbreviation as in Figure 1.

CENTRAL ILLUSTRATION **Genetics and Outcome in NCCM**



van Waning, J.I. et al. J Am Coll Cardiol. 2018;71(7):711–22.

Noncompaction cardiomyopathy (NCCM) is a heterogeneous condition, and genetic stratification has a role in clinical care. In children, genetic causes with severe outcome are more common than in adults. In nongenetic NCCM, which occurs frequently in adults, acquired causes for NCCM may be involved. In adults with a normal left ventricular (LV) systolic function, genetics helps to predict cardiac events. *MYH7*, *MYBPC3*, and *TTN* mutations were the most common in genetic NCCM. Patients with *MYH7* mutations had low risk for cardiac events. Distinguishing genetic from nongenetic NCCM complements prediction of outcome and allows tailoring management to genetic status. MACE = major adverse cardiac events; RV = right ventricular.

presentation. Heart failure (27%) and arrhythmias (26%) were the most common presentations in children and adults (Online Figure 2). In 4% (n = 14), the primary presentation was cardiac arrest. Thromboembolic events were the first sign of NCCM in 3% (n = 10). Three patients had a CHD. Seven patients who presented with a thromboembolic event had a stroke, 2 had a kidney infarction, and 1 had a mesenteric occlusion. Thirty patients, of whom 16 had a mutation, were identified through family cardiologic family screening for HCM, DCM, sudden cardiac death, familial hypertension,

TABLE 2 Clinical Features at Long-Term Follow-Up of Pediatric and Adult Patients With NCCM

	Children (n = 52)				Adults n = 275				
		No Mutation (n = 29) (55%)				No Mutation (n = 194) (70%)			
	Mutation (n = 23) (45%)	Familial (n = 8) (15%)	Not Familial (n = 21) (40%)		Mutation (n = 81) (30%)	Familial (n = 45) (16%)	Not Familial n = 149 (54%)		
	Genetic	Probably Genetic	Sporadic	Total	Genetic	Probably Genetic	Sporadic	Total	p Value
Median follow-up, months	81 (13–114)	24 (1–102)	40 (19–120)	60 (18–113)	26 (6–69)	29 (10–71)	22 (4–49)	25 (4–58)	
Heart failure									
Heart failure requiring hospitalization	9 (39)	3 (38)	1 (5)	13 (25)	20 (25)	9 (20)	30 (20)	59 (21)	
Thromboembolic events									
TIA					2 (2)	1 (2)	5 (3)	8 (3)	
Stroke	1 (4)			1 (2)	1 (2)	4 (9)	12 (8)	17 (6)	
Peripheral thromboembolism	1 (4)			1 (2)	4 (5)	1 (2)	6 (4)	11 (4)	
Arrhythmias									
Atrial fibrillation	3 (13)	1 (13)	1 (5)	5 (10)	15 (19)	8 (18)	21 (14)	44 (16)	
Sustained VT/VF	1 (4)	2 (25)	1 (5)	3 (6)	3 (4)	2 (4)	11 (7)	16 (6)	
ICD	5 (22)	2 (25)	2 (10)	9 (17)*	34 (42)	15 (33)	57 (38)	106 (39)	0.004*
Secondary prevention (% of ICD)		1 (50)		1 (11)	3 (9)	2 (13)	5 (9)	12 (4)	
Appropriate shock (% of ICD)					1 (3)	3 (20)	6 (11)	10 (9)	
LVAD	1 (4)			1 (2)	2 (2)		1 (1)	3 (1)	
Heart transplantation	4 (17)			4 (8)	2 (2)	2 (4)	2 (1)	6 (2)	
Death	4 (17)	3 (38)	1 (5)	8 (16)	3 (4)	5 (11)	8 (5)	16 (6)	
MACE in patients with LV systolic dysfunction	8 (35)	3 (38)	0 (0)	11 (21)	12 (15)	6 (13)	18 (12)	36 (13)	
MACE in patients with normal LV function	1 (4)	1 (13)	1 (5)	3 (6)	1 (1)	5 (11)	16 (11)	22 (8)	0.027†

Values are n (interquartile range) or n (%). *Significant for children versus adults. †Significant for mutation carriers versus no mutation.

ICD = implantable cardioverter-defibrillator; LVAD = LV assist device; MACE = major adverse cardiac events; RV = right ventricular; TIA = transient ischemic attack; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

or hemochromatosis. Cardiologic screening for other reasons identified 42 patients, of whom 12 had a mutation. Twenty-four (34%) of these 42 patients were asymptomatic, and 7 asymptomatic cases had a mutation.

Hypertension occurred frequently in adults (n = 62; 23%), particularly in adults without a mutation (p = 0.047) (Table 1). Left bundle branch block (LBBB) was significantly more common in adult patients with sporadic NCCM (27%) compared with the adult genetic (10%) and probably genetic cases (11%; p = 0.01) (Table 1). Information on echocardiographic, electrocardiographic, and cardiac magnetic resonance characteristics of NCCM patients is presented in Online Table 4.

REDUCED VENTRICULAR SYSTOLIC FUNCTION. The risk of having LV systolic dysfunction was higher for genetic patients compared with the probably genetic and sporadic cases (p = 0.024), with the highest risk in patients with multiple mutations and *TTN* mutations (Tables 2 and 3 and the Central Illustration). LV systolic dysfunction occurred in 44% of the children and 58% of the adult patients (p = 0.067). LV dysfunction was observed more often than RV dysfunction (RV 14% and LV 53%). RV function was measured in 31 of the 52 pediatric patients (12 genetic, 5 probably genetic, and 14 sporadic) at admission; this assessment detected reduced RV function in 4 genetic cases (with *DES* de novo, *PLN* de novo, homozygous *MYL2*, and *MYH7* defects) who also had LV systolic dysfunction, and also in 1 sporadic patient with normal LV function. The risk of having reduced RV function was increased in genetic patients (p = 0.008).

MAJOR ADVERSE CARDIAC EVENTS. During a median follow-up of 60 months (IQR: 18 to 113 months), MACE occurred in 14 (27%) children, and 58 (21%) adults experienced MACE during a median follow-up of 25 months (IQR: 4 to 58 months) (Table 2). An increased risk of MACE was observed in children with (probable) genetic NCCM (p = 0.025) (Figure 4A), children diagnosed at age younger than 1 year (hazard ratio [HR]: 2.10; 95% CI: 1.00 to 4.40; p = 0.048)

TABLE 3 Risk for Ventricular Dysfunction in NCCM

	Reduced LV Function		Reduced RV Function	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Genetic	1.73 (1.07–2.78)	0.024	2.55 (1.28–5.06)	0.008
MYH7	1.30 (0.66–2.55)	0.456	1.74 (0.66–4.53)	0.258
MYBPC3 single	1.02 (0.34–3.10)	0.855	5.33 (1.15–24.79)	0.033
TTN	5.03 (1.44–17.61)	0.012	2.19 (0.70–6.92)	0.180
Other sarcomere	0.36 (0.10–1.43)	0.148	1.51 (0.28–8.03)	0.632
Nonsarcomere	2.10 (0.84–5.24)	0.113	1.53 (0.46–5.13)	0.491
Complex genetic defect	8.24 (1.03–65.78)	0.047	2.54 (0.41–15.69)	0.316
Probably genetic	0.89 (0.49–1.60)	0.698	0.87 (0.36–2.16)	0.770
Sporadic	0.67 (0.43–1.03)	0.069	0.45 (0.23–0.90)	0.024
LBBB	6.04 (2.73–13.38)	<0.001	0.77 (0.27–2.16)	0.620
Presentation at <1 yr	1.48 (0.53–4.18)	0.456	0.74 (0.08–6.46)	0.781

CI = confidence interval; LBBB = left bundle branch block; OR = odds ratio; other abbreviations as in Table 1.

(Table 4), and children with multiple mutations in *MYBPC3* (HR: 5.20; 95% CI: 1.62 to 16.50; p = 0.006). Risk of MACE in children was also associated with LV systolic dysfunction (HR: 7.70; 95% CI: 1.70 to 34.70; p = 0.008). The risk for adverse events in sporadic children was low (HR: 0.10; 95% CI: 0.02 to 0.93; p = 0.043). No difference in risk of MACE was observed among the adults with genetic, probable genetic, and sporadic NCCM (Figure 4B).

LV systolic dysfunction was associated with an increased risk of MACE (HR: 1.7; 95% CI: 1.1 to 2.8; p = 0.028). In line with these observations, genetic patients with good LV function had a low risk of adverse cardiac events (p = 0.002) (Figure 4C). A low risk of MACE was observed in patients with an *MYH7* mutation (HR: 0.17; 95% CI: 0.04 to 0.69; p = 0.013) (Table 4, Central Illustration). The reduced risk of MACE in patients with an *MYH7* mutation remained after correction of LV systolic function. In sporadic patients, the risk of MACE was not related to LV function (Figure 4D); patients without a mutation and normal LV function had a similar risk of MACE as patients with LV systolic dysfunction.

Cardiac arrest occurred significantly more in female patients than in male patients (11% vs. 2%; p = 0.003). More women had an ischemic stroke than men (9% vs. 3%; p = 0.045). Patients with CHDs experienced stroke more often (with CHD: 56% vs. without CHD: 5%; p = 0.001).

DISCUSSION

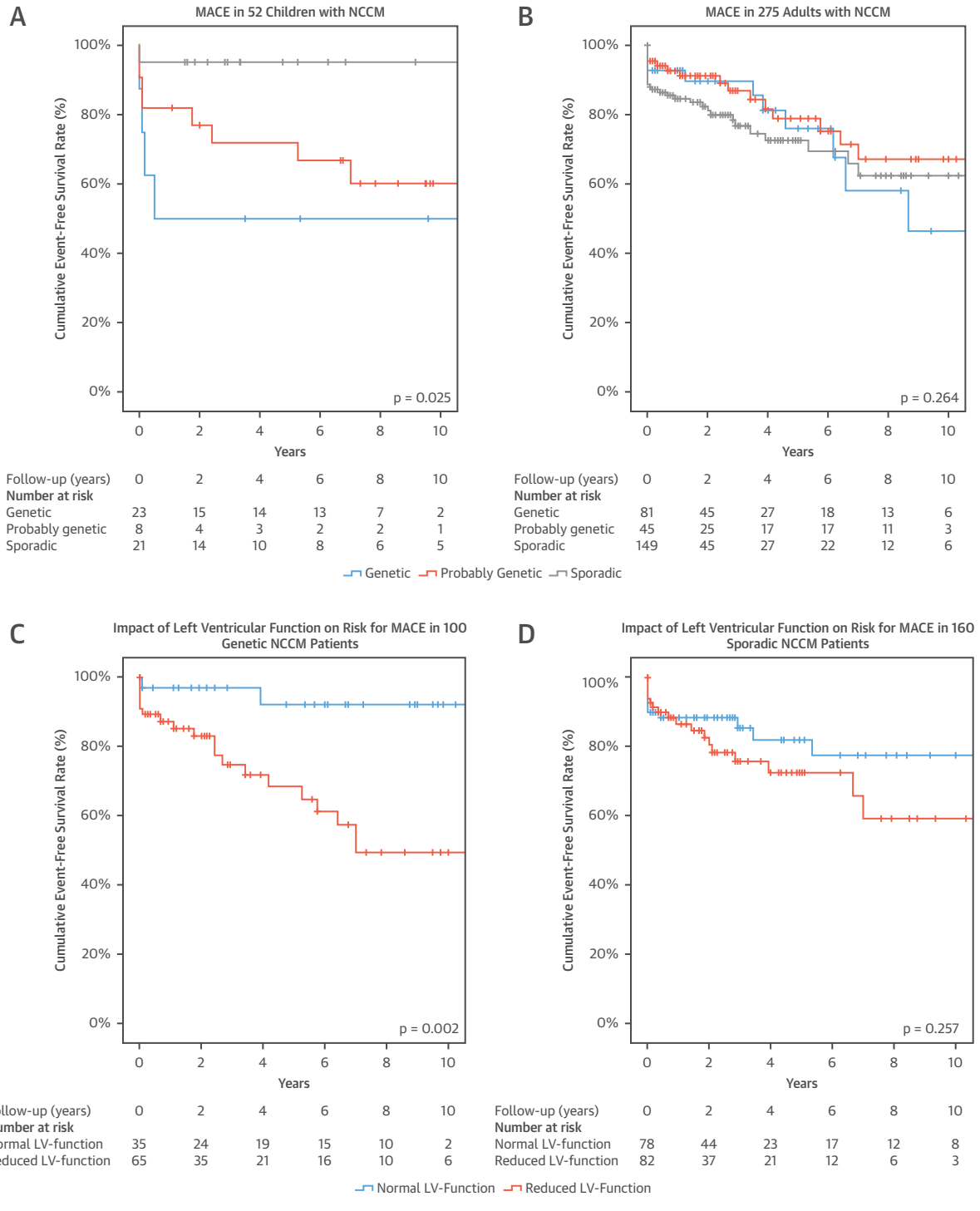
In this large cohort of NCCM patients, we investigated the correlations between genetics, clinical presentation, and long-term outcomes. We showed that nearly one-third of the NCCM patients had a mutation in a cardiomyopathy gene. In this heterogeneous cardiomyopathy, age at diagnosis, LV systolic dysfunction, and risk of MACE were linked to genetic status. Children diagnosed with NCCM more often had a genetic cause than adults. LV systolic dysfunction at presentation and long-term outcome were related to genetics.

It is important to distinguish genetic NCCM because genetic status may add to prediction of risk for MACE and may guide clinical management and intensity of follow-up for specific groups of patients and their relatives. Children with a mutation were diagnosed frequently at younger than 1 year of age; they had cardiac symptoms, LV systolic dysfunction, and a high risk for MACE. In contrast, children with sporadic NCCM were diagnosed incidentally, had normal cardiac function, and low risk of MACE. In adults with a mutation, a high risk of MACE was strongly correlated with LV systolic dysfunction. However, risk of MACE in adults with sporadic NCCM was not determined by LV systolic dysfunction.

In approximately one-half (48%) of the NCCM patients genetics played a role; 32% of the patients had a mutation and 16% of the patients had familial disease without a mutation. Sporadic NCCM was more prevalent in adults than in children. These results suggested that, apart from genetic causes for NCCM, acquired (nongenetic) causes for hypertrabeculation might play a role, particularly in the sporadic adult cases (18). In addition, our results endorsed the heterogeneity of NCCM and the importance of genetics, simultaneously evoking questions on different etiologies for hypertrabicularization in children and adults.

Three of the 22 different cardiomyopathy genes were not reported previously in NCCM, expanding the genetic spectrum of NCCM with the *DES, PLN*, and *RBM20* genes. In the genetic cases, mutations in *MYH7*, *MYBPC3*, and *TTN* genes were the most frequent. *MYH7* was the most affected gene, as described previously (7,10). The risk of MACE was lower in *MYH7* patients (5%). *MYH7* was the only sarcomere gene associated with CHD; 4 patients with the *MYH7* mutation had Ebstein anomaly (19). Compound heterozygosity of *MYBPC3* was associated with severe early-onset NCCM. In 3 patients, *TTN* mutations co-occurred with *MIB1* mutations, endorsing the hypothesis that a *TTN* mutation may not be a sufficient genetic cause for NCCM (20). *TTN* defects were not observed in pediatric cases. High prevalence of *TTN* mutations in women with a peripartum cardiomyopathy and in chemotherapy-induced cardiomyopathy (21–23) also suggested involvement of cofactors accumulated during life in the development of *TTN*-associated cardiomyopathies.

FIGURE 4 **Risk for MACE in NCCM**



Kaplan-Meier curves of major adverse cardiac events (MACE). **(A)** Genetics and freedom from MACE in children. **(B)** Genetics and freedom from MACE in adults. **(C)** Left ventricular systolic (LV) dysfunction and freedom from MACE in genetic NCCM. **(D)** LV systolic dysfunction and freedom from MACE in sporadic NCCM. Abbreviation as in Figure 1.

TABLE 4 Risk of MACE in NCCM

	All Patients	
	HR* (95% CI)	p Value
Genetic	0.83 (0.50–1.37)	0.459
MYH7	0.17 (0.04–0.69)	0.013
MYBPC3 single	1.44 (0.52–3.94)	0.482
MYBPC3 complex	5.17 (1.62–16.48)	0.006
TTN	1.02 (0.37–2.79)	0.973
Other sarcomere	0.41 (0.06–2.94)	0.374
Non-sarcomere	1.60 (0.77–3.34)	0.211
Complex genetic defect	2.11 (0.85–5.24)	0.108
Probably genetic	1.29 (0.73–2.29)	0.375
Sporadic	1.01 (0.63–1.61)	0.971
LBBB	1.20 (0.65–2.22)	0.563
Reduced LV	1.72 (1.06–2.80)	0.028
Reduced RV	1.73 (0.94–3.20)	0.080
Presentation at <1 yr†	2.11 (1.01–4.41)	0.048

*Hazard ratio (HR) (95% CI) for composite endpoint. †Presentation at <1 year HR in children.

Abbreviations as in Tables 1 to 3.

Acquired causes for NCCM are expected in a large proportion of patients, specifically, the sporadic adults. The role of acquired causes in late-onset NCCM challenges the general assumption of the embryological nature of hypertrabeculation. If NCCM is a developmental disorder, a higher rate of diagnosis would be expected shortly after birth or in childhood than the 16% of childhood cases we found in our cohort. Late-onset NCCM might be explained by an enhancement of a latent asymptomatic congenital defect by disruptions of cardiac homeostasis later in life. Recent studies endorsed the hypothesis that acquired causes might lead to characteristic hypertrabeculation. Conditions with an increased cardiac preload that are associated with hypertrabeculation include sickle cell anemia, pregnancy, and intensive sports (24–26). Our observation that LBBB was more prevalent in adults with sporadic NCCM might be explained by a role of increased cardiac preload in the development of hypertrabeculation. LBBB leads to higher end-diastolic volumes, which leads to an increased cardiac preload (27). Hypertension may also lead to increased preload and may be another secondary cause, because it was also more frequent in sporadic patients (28).

One-third of the mutations were found in patients who did not report relatives with a cardiomyopathy (i.e., when family history was negative). This illustrated that DNA testing should not be restricted to cases with a positive family history, and that DNA testing of patients without a family history is as important. DNA testing is important because when a mutation is found it allows families to have DNA testing and to accurately identify which relatives have a mutation and an increased risk. In this way, identifying the causative mutation facilitates genetic cascade screening. In addition, relatives who do not carry the mutation can be excluded from regular cardiac follow-up and can be reassured that there is no increased risk in their offspring.

The proportion of genetic patients is expected to be >48% because in 30% of the patients without a mutation, Sanger sequencing of a small number of cardiomyopathy genes was performed, and these might have a mutation in a cardiomyopathy gene that was not tested. Seventy-one (41%) of the sporadic cases had VUS that could be reclassified in the future as likely pathogenic. Moreover, cardiomyopathy genes, which have not been identified yet, might play a role in the familial cases without a mutation, as well as in the sporadic cases.

STUDY LIMITATIONS. A referral bias of more severe cases could not be excluded. Consequently, asymptomatic or mildly affected cases might be underrepresented, leading to an overestimation of severe clinical features. In addition, we might have introduced a selection bias of symptomatic NCCM by including only index cases (to control for overrepresentation of genetic causes). By doing so, we might have missed asymptomatic cases that would only be recognized by family screening. We might have underestimated the role of genetic causes for NCCM because not all patients were tested for the complete genetic cardio-panel (~45 genes). Some patients had a rare variant of unknown significance, which are currently not classified as disease-causing, but these might be reclassified as likely pathogenic in the future. In contrast, some variants, although they were classified by current stringent criteria as (likely) pathogenic, could turn out to be benign in the future.

We used the current, widely used diagnostic criteria for NCCM, despite the fact that they lack specificity, and that novel diagnostic criteria, preferably using both morphologic and genetic data, are needed. We could not currently rule out to have included patients with benign hypertrabeculation as NCCM. Family screening and obtaining accurate diagnosis of relatives was more difficult in families of adult patients; therefore, this might be one of the causes of the high prevalence of sporadic NCCM in adults. In addition, because of the retrospective design of our study, clinical data might have been missing. We might have underestimated heart failure–related events because we selected only patients with heart failure who required hospitalization.

CONCLUSIONS

NCCM is a heterogeneous condition, and genetic stratification has a role in clinical care. Distinguishing genetic from nongenetic NCCM might complement prediction of outcome and subsequently guide management of patients with follow-up tailored to genetic status.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: NCCM is heterogeneous, and genetic factors play a more important role in children than in adults with this condition. Adverse cardiac events occur more often in mutation carriers with left ventricular systolic dysfunction than in sporadic cases.

TRANSLATIONAL OUTLOOK: Large follow-up studies are needed to confirm the genotype-phenotype correlations and guide genetically tailored management strategies for patients with NCCM and their families.

REFERENCES

1. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006;113:1807–16.

2. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270–6.

3. Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart 2001;86:666–71.

4. Pignatelli RH, McMahon CJ, Dreyer WJ, et al. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. Circulation 2003;108:2672–8.

5. Petersen SE, Selvanayagam JB, Wiesmann F, et al. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. J Am Coll Cardiol 2005;46:101–5.

6. Brescia ST, Rossano JW, Pignatelli R, et al. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. Circulation 2013;127:2202–8.

7. Bhatia NL, Tajik AJ, Wilansky S, Steidley DE, Mookadam F. Isolated noncompaction of the left ventricular myocardium in adults: a systematic overview. J Card Fail 2011;17:771–8.

8. Weiford BC, Subbarao VD, Mulhern KM. Noncompaction of the ventricular myocardium. Circulation 2004;109:2965–71.

9. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 2000;36:493–500.

10. Hoedemaekers YM, Caliskan K, Michels M, et al. The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. Circ Cardiovasc Genet 2010;3:232–9.

11. Klaassen S, Probst S, Oechslin E, et al. Mutations in sarcomere protein genes in left ventricular noncompaction. Circulation 2008;117:2893–901.

12. Sasse-Klaassen S, Gerull B, Oechslin E, Jenni R, Thierfelder L. Isolated noncompaction of the left ventricular myocardium in the adult is an autosomal dominant disorder in the majority of patients. Am J Med Genet A 2003;119A:162–7.

13. Gati S, Rajani R, Carr-White GS, Chambers JB. Adult left ventricular noncompaction: reappraisal of current diagnostic imaging modalities. J Am Coll Cardiol Img 2014;7:1266–75.

14. Pieper JKPG. Normaalwaarden. In: Pieper JPMHPG, editor. Praktische echocardiografie. 3rd ed. Houten, The Netherlands: Bohn, stafleu van loghum springer media, 2015;391–410.

15. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–70.

16. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. J Am Soc Echocardiogr 2008;21:922–34.

17. Koestenberger M, Ravekes W, Everett AD, et al. Right ventricular function in infants, children and adolescents: reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiogr 2009;22:715–9.

18. Anderson RH, Jensen B, Mohun TJ, et al. Key questions relating to left ventricular noncompaction cardiomyopathy: is the emperor still wearing any clothes? Can J Cardiol 2017;33:747–57.

19. Vermeer AM, van Engelen K, Postma AV, et al. Ebstein anomaly associated with left ventricular noncompaction: an autosomal dominant condition that can be caused by mutations in MYH7. Am J Med Genet C Semin Med Genet 2013;163C:178–84.

20. Miszalski-Jamka K, Jefferies JL, Mazur W, et al. Novel genetic triggers and genotype-phenotype correlations in patients with left ventricular noncompaction. Circ Cardiovasc Genet 2017;10(4).

21. van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, et al. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. Eur Heart J 2014;35:2165–73.

22. Ware JS, Li J, Mazaika E, et al. Shared genetic predisposition in peripartum and dilated cardiomyopathies. N Engl J Med 2016;374:233–41.

23. Linschoten M, Teske AJ, Baas AF, et al. Truncating titin (TTN) variants in chemotherapy-induced cardiomyopathy. J Card Fail 2017;23:476–9.

24. Gati S, Papadakis M, Van Niekerk N, Reed M, Yeghen T, Sharma S. Increased left ventricular trabeculation in individuals with sickle cell anaemia: physiology or pathology? Int. J Cardiol 2013;168:1658–60.

25. Gati S, Papadakis M, Papamichael ND, et al. Reversible de novo left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular noncompaction in low-risk populations. Circulation 2014;130:475–83.

26. Gati S, Chandra N, Bennett RL, et al. Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes? Heart 2013;99:401–8.

27. Brunekreeft JA, Graauw M, de Milliano PA, Keijer JT. Influence of left bundle branch block on left ventricular volumes, ejection fraction and regional wall motion. Neth Heart J 2007;15:89–94.

28. Lavine SJ, Lavine JA. The effect of acute hypertension on left ventricular diastolic pressures in a canine model of left ventricular dysfunction with a preserved ejection fraction and elevated left ventricular filling pressures. J Am Soc Echocardiogr 2006;19:1350–8.

KEY WORDS genetics, LVNC, noncompaction cardiomyopathy, outcome, prognosis

APPENDIX For an expanded Methods section as well as the supplemental tables and figures, please see the online version of this paper.