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ORIGINAL INVESTIGATIONS

Cardiac Phenotypes, Genetics, and Risks in Familial Noncompaction Cardiomyopathy

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ABSTRACT

BACKGROUND There is overlap in genetic causes and cardiac features in noncompaction cardiomyopathy (NCCM), hypertrophic cardiomyopathy (HCM), and dilated cardiomyopathy (DCM).

OBJECTIVES The goal of this study was to predict phenotype and outcome in relatives according to the clinical features and genotype of NCCM index cases.

METHODS Retrospective DNA and cardiac screening of relatives of 113 families from 143 index patients were used to classify NCCM cases according to the cardiac phenotype. These cases were classified as isolated NCCM, NCCM with left ventricular (LV) dilation (DCM), and NCCM with LV hypertrophy (HCM).

RESULTS In 58 (51%) families, screening identified 73 relatives with NCCM and 34 with DCM or HCM without NCCM. The yield of family screening was higher in families with a mutation ($p < 0.001$). Fifty-four families had a mutation. Nonpenetrance was observed in 37% of the relatives with a mutation. Index cases were more often symptomatic than affected relatives ($p < 0.001$). NCCM with DCM (53%) was associated with LV systolic dysfunction ($p < 0.001$), increased risk for major adverse cardiac events, mutations in the tail of *MYH7* ($p < 0.001$), and DCM without NCCM in relatives ($p < 0.001$). Isolated NCCM (43%) was associated with a milder course, mutations in the head of *MYH7,* asymptomatic NCCM (42%) ($p = 0.018$), and isolated NCCM in relatives ($p = 0.004$). NCCM with HCM (4%) was associated with *MYBPC3* and HCM without NCCM in relatives ($p < 0.001$).

CONCLUSIONS The phenotype of relatives may be predicted according to the NCCM phenotype and the mutation of index patients. NCCM phenotypes were related to outcome. In this way, clinical and genetic features of index patients may help prediction of outcome in relatives. (J Am Coll Cardiol 2019;73:1601–11) © 2019 by the American College of Cardiology Foundation.

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Noncompaction cardiomyopathy (NCCM), also known as left ventricular (LV) noncompaction, is a cardiomyopathy characterized by excessive trabeculations of the left ventricle (1,2). Current imaging diagnostic criteria, including the most frequently used echocardiographic Jenni criteria, are based on the ratio between a severely thickened myocardium, with a

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

DCM = dilated cardiomyopathy

DNA = deoxyribonucleic acid

HCM = hypertrophic cardiomyopathy

LV = left ventricular

LVEDD = left ventricular end-diastolic dimension

MACE = major adverse cardiac events

MYBPC3 = myosin binding protein C3

MYH7 = myosin heavy chain beta

NCCM = noncompaction cardiomyopathy

RV = right ventricular

TTN = titin

noncompacted layer that is at least twice as thick as the compacted layer, measured in systole in the short-axis view (3). Clinical features of NCCM range from asymptomatic patients with noncompaction of the left ventricle to patients with or without a mutation in a cardiomyopathy gene with symptoms of heart failure, arrhythmias, or major adverse cardiac events (MACE) (4).

In ~50% of patients with NCCM, there is evidence for a genetic cause because there is a mutation in a cardiomyopathy gene and/or at least 1 family member with a nonischemic cardiomyopathy (4,5). Mutations in mostly sarcomere genes explain ~32% of NCCM. In 15% of the patients, familial disease occurs without a mutation, indicating that many genetic causes are still unknown. Novel genetic causes conveying small risk for relatives or alternatively nongenetic, secondary causes for noncompaction of the left ventricle are expected in NCCM cases without a mutation and without familial disease. Among the NCCM genes, *MYH7*, *MYBPC3,* and *TTN* are the most prevalent and are also frequent causes for hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) (6,7). Previous family studies of NCCM occasionally reported relatives with HCM or DCM apparently without noncompaction in familial NCCM (8–12).

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Patients with NCCM may have additional ventricular dilatation or septal hypertrophy (13–17) similar to HCM and DCM. Subsequently, NCCM can be classified phenotypically into isolated NCCM, NCCM with DCM, and NCCM with HCM (18). In children, subtyping of NCCM according to cardiac phenotype is a good predictor for adverse events (19). Prediction of phenotype and associated clinical features for relatives is important, from the point of view of informing family members of NCCM patients and eventually guiding family screening and follow-up of relatives according to estimated risk.

The present study examined the clinical features, outcome, genetics, and familial recurrence of NCCM phenotypes (isolated NCCM, NCCM with DCM, and NCCM with HCM) by using the results of cardiac and genetic family screening comprising 473 family members of 143 index patients with NCCM. Our goal was to investigate if we could predict risk for relatives of patients with NCCM by establishing if cardiac NCCM phenotypes were related to outcome and to genotype, and if NCCM phenotype of the index case was related to cardiac features in relatives.

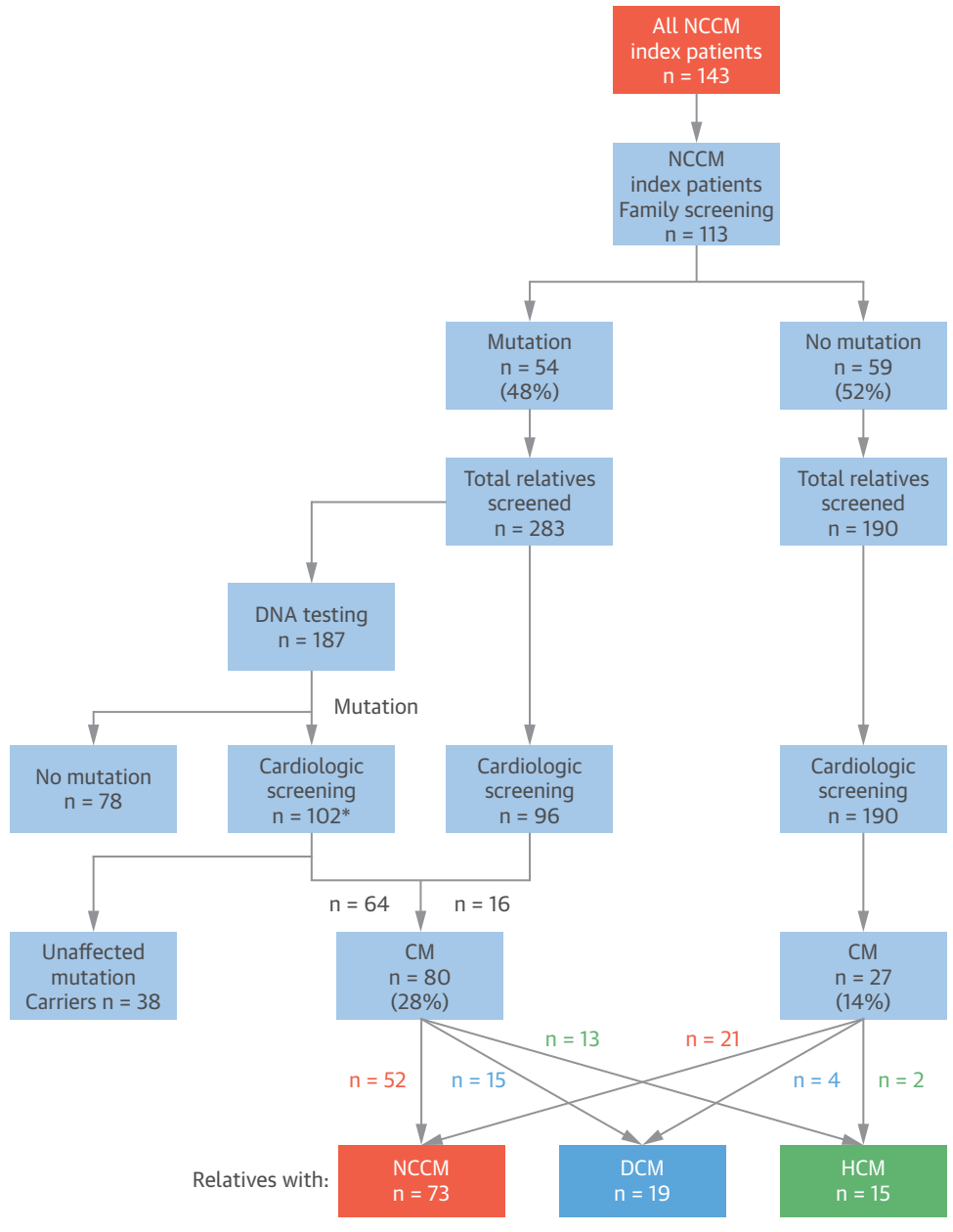
METHODS

STUDY POPULATION. The retrospective study population consisted of the families of 143 index patients diagnosed with NCCM between January 2005 and January 2017 at the Department of Cardiology and referred for genetic counseling to the Department of Clinical Genetics of the Erasmus Medical Center Rotterdam in the Netherlands. Genetic screening included deoxyribonucleic acid (DNA) testing of a cardiomyopathy gene panel, ascertainment of family history, and initiating cardiologic family screening.

FAMILY SCREENING. Family screening was initiated by asking the index patients to distribute a letter with information on heritability of NCCM and the recommendations for family screening (8,20). In families with a mutation, adult relatives were counseled about predictive DNA testing. For children at risk, cardiologic screening from the age of 10 years was recommended, with DNA testing in case of a cardiomyopathy. Cardiac screening for relatives consisted of physical examination, a 12-lead electrocardiography, and echocardiography. In families with a mutation, cardiologic screening was offered to relatives with the mutation and to adult relatives refusing DNA testing. In families without a mutation, relatives had cardiologic screening. Specifics regarding the DNA diagnostics for NCCM have been previously described (4). Online Table 1 presents the list of mutations in the participating patients with NCCM.

DIAGNOSTIC CRITERIA. NCCM diagnosis was based on consensus of evaluated echocardiographic and cardiac magnetic resonance (CMR) images according to the Jenni and Petersen criteria for NCCM by the lead author (J.I.V.W.) and a dedicated cardiomyopathy cardiologist (K.C., M.M., A.F.L.S., and M.D.) (3,21). All patients had echocardiographic images, and CMR data were available for 176 (82%) patients with NCCM. Patients were classified according to cardiac phenotype into isolated NCCM, NCCM with DCM, or NCCM with HCM. The NCCM with DCM phenotype was diagnosed in patients with NCCM according to dilatation criteria for DCM on echocardiography and was defined as a left ventricular end-diastolic dimension (LVEDD) >112% of predicted values (22). Predicted LVEDD was calculated according to the formula of Henry et al. (23): LVEDD = (45.3 × body surface area$^{0.3}$) − (0.03 × age) − 7.2. The NCCM with HCM phenotype was diagnosed in patients with NCCM by using the HCM criteria for adult family members: maximum LV wall thickness ≥13 mm, not explained by loading conditions (24). For children, we used either ventricular septal or LV posterior wall

FIGURE 1 Family Screening for Noncompaction Cardiomyopathy



*7 patients with a mutation had cardiologic screening elsewhere and were lost to follow-up. In 113 of 143 families (54 with a mutation), cardiologic screening identified 107 relatives with a cardiomyopathy: 73 with noncompaction cardiomyopathy (NCCM), 19 with dilated cardiomyopathy (DCM) without noncompaction, and 15 with hypertrophic cardiomyopathy (HCM) without noncompaction. Thirty-eight carriers of a familial mutation were unaffected. CM = cardiomyopathy; DNA = deoxyribonucleic acid.

thickness for body surface area >2 SDs different from the value for a normal population of children with similar body surface area, or the presence of localized LV hypertrophy in children (25). Patients were categorized in the NCCM with HCM category despite LV dilatation. The diagnosis of DCM or HCM in relatives without hypertrabeculation was made according to current European guidelines (2,24).

VENTRICULAR FUNCTION AND ADVERSE EVENTS. LV systolic dysfunction was defined as LV ejection

fraction <45% on CMR. Alternatively, LV systolic dysfunction was measured on echocardiography by using a wall motion score index that was lower than mildly reduced for patients without CMR imaging (n = 39). Systolic dysfunction was visually assessed by using the wall motion score index on echocardiography and was described as normal (≥55%), mildly reduced (45% to 54%), moderately reduced (30% to 44%), or poor (<30%) according to the echocardiography guidelines (26). Abnormal right ventricular (RV) systolic function was defined as RV ejection fraction <45% on CMR. For patients without CMR imaging (n = 39), tricuspid annular plane systolic excursion <17 mm on echocardiography was used to define RV systolic dysfunction (27). For children, dimensions of the ventricles >2 SDs from the reference range were classified as abnormal (28,29). We used the same definition for adverse cardiac events as described earlier (4). 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. For the hazard models, a combined endpoint for MACE was used because of the low incidence of death. Information on vital status of patients was retrieved from municipal registries.

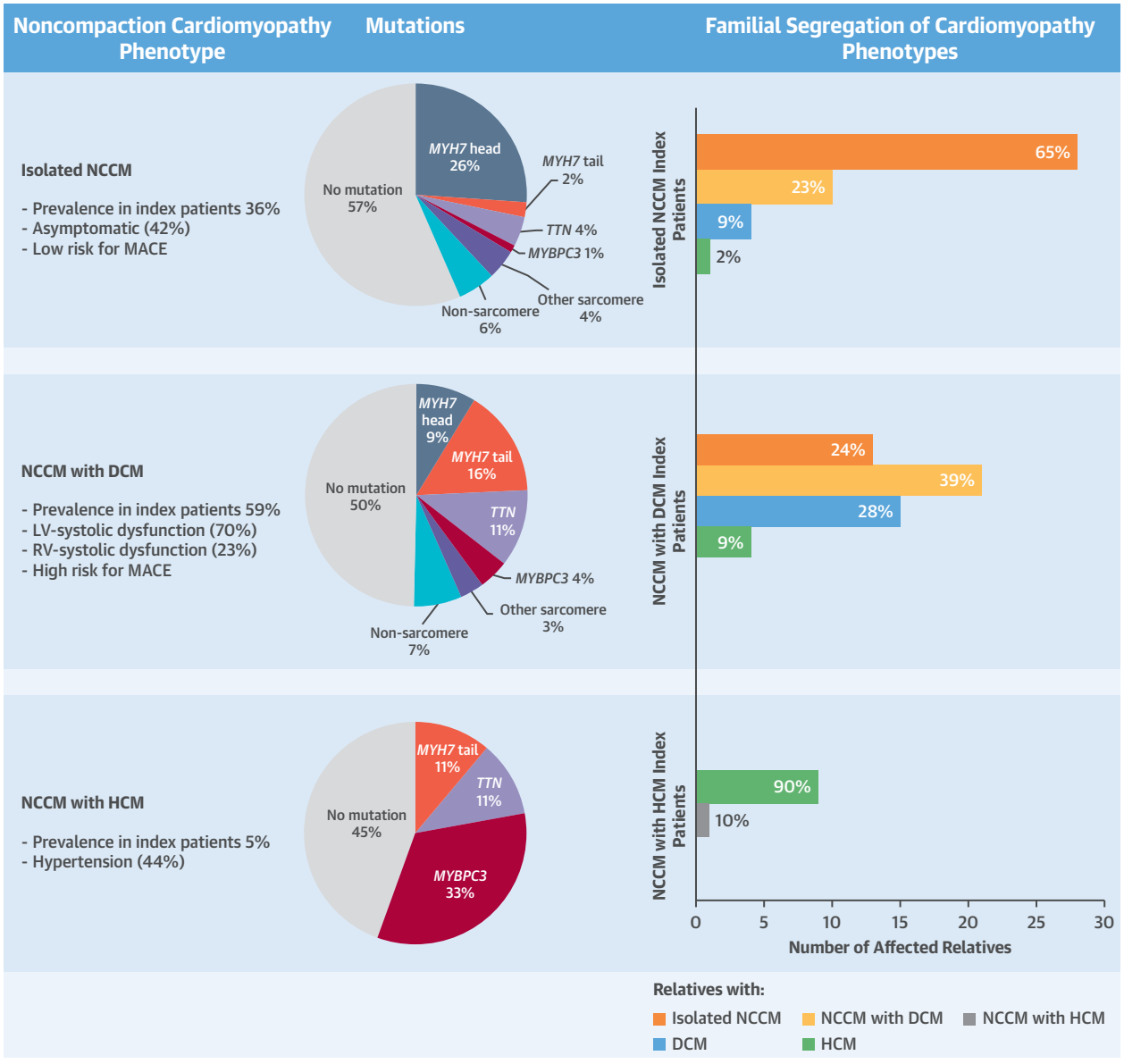
STATISTICAL ANALYSIS. Categorical data were compared with the Pearson chi-square test or Fisher exact test. For continuous variables, unpaired Student's *t*-tests were used for 2 groups and analysis of variance for >2 groups. Odds ratios were calculated by using binary logistic regression. Statistics for variables at follow-up were compared by using the log-rank test, using time at diagnosis as time zero. Hazard ratios for MACE were calculated according to Cox proportional hazards regression analysis and presented as MACE per 100 patient-years. Follow-up data were obtained in July 2017; 5 patients were lost to follow-up. Patients (lost to follow-up) were considered at risk until the date of last contact, at which time point they were censored. Statistical analysis was performed by using SPSS version 21.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

FAMILY SCREENING. Seventy-nine percent (113 of 143) of the families of NCCM index cases participated in genetic and cardiologic family screening (**Figure 1**). In total, 473 relatives were screened: 286 (60%) first-degree relatives, and 187 (40%) second-degree or more distantly related relatives. We found a mutation in 54 (48%) of 113 of the index patients. Subsequently, 187 (66%) of 283 relatives of the index cases with a mutation underwent genetic testing, revealing that 109 (58%) of the tested relatives had a mutation. In 78 relatives, a mutation was excluded. Cardiologic screening was performed in 102 of the 109 relatives with a mutation, revealing that 64 (63%) relatives with a mutation had a cardiomyopathy, and 38 (37%) did not have a cardiomyopathy. In addition, 16 relatives, who refused DNA testing, from the families with a mutation were diagnosed with a cardiomyopathy. In 39 (72%) of the 54 families with a mutation, 267 of 283 participating relatives underwent a cardiologic examination, revealing that 80 of the examined relatives were affected (29%). For 15 (28%) of the 54 families with a mutation, results of family screening were inconclusive. Family screening of 59 families without a mutation identified a cardiomyopathy in 27 (14%) of 190 relatives from 19 families. In total, family screening reported familial cardiomyopathy in 58 of the screened families with 107 (23%) affected relatives. In 34 families, all affected family members had NCCM. In 17 families, there were relatives with DCM without noncompaction, and in 7 families, relatives with HCM without noncompaction were observed. In families with a mutation, the yield of the family screening was higher than in families without a mutation (mutation 72%; without mutation 32%; p < 0.001) (**Central Illustration**, Online Table 2).

CHARACTERISTICS AND OUTCOME OF THE NCCM PHENOTYPES: ISOLATED NCCM, NCCM WITH DCM, AND NCCM WITH HCM. The 216 patients diagnosed with NCCM were classified according to NCCM phenotype into the following: 92 patients with isolated NCCM (51 index cases and 41 relatives), 115 NCCM with DCM patients (84 index cases and 31 relatives), and 9 NCCM with HCM patients (8 index cases and 1 relative) (**Table 1**). Affected relatives with NCCM had less severe clinical features at diagnosis and follow-up compared with NCCM index patients (**Tables 1 and 2**): 48% of the relatives with NCCM were asymptomatic compared with 24% of the index patients (p < 0.001). The NCCM with DCM phenotype was more frequent in index cases (p = 0.010), and LV systolic dysfunction was more frequent (p < 0.001) in index cases than in affected relatives. Patients with isolated NCCM had less RV and LV systolic dysfunction than NCCM patients with DCM or HCM (p = 0.023 and p < 0.001). Patients with NCCM and HCM more often had hypertension (p = 0.014). During a median follow-up of 44 months (interquartile range: 9 to 93 months), MACE occurred in 45 patients. The hazard ratios at follow-up showed that NCCM with DCM

CENTRAL ILLUSTRATION **Phenotypes in Familial Noncompaction Cardiomyopathy**



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Classification of noncompaction cardiomyopathy (NCCM) according to cardiac phenotype into isolated NCCM (51 index and 41 relatives), NCCM with dilated cardiomyopathy (DCM) (84 index and 31 relatives), and NCCM with hypertrophic cardiomyopathy (HCM) (8 index and 1 relative) in 39 families with a mutation and 19 families without a mutation. Genotyping and family screening revealed that isolated NCCM was linked to mutations in the head domain of *MYH7* ($p < 0.001$), isolated NCCM in relatives ($p < 0.001$), and a lower risk for left ventricular (LV) dysfunction ($p < 0.001$). NCCM with DCM was linked to the *MYH7* tail domain ($p < 0.001$) and *TTN*, and it was associated with relatives with DCM without signs of noncompaction ($p = 0.002$) and severe outcome ($p = 0.016$). The HCM phenotype was linked to *MYBPC3* in NCCM families ($p < 0.001$) and HCM without signs of noncompaction in relatives ($p < 0.001$). Factors reducing risk for relatives were absence of a mutation in index patients, nonpenetrance of familial mutations, or having asymptomatic disease. These findings underscore that the NCCM phenotype of the index case and the genotype are important predictors of risk in relatives. MACE = major adverse cardiac events; *MYBPC3* = myosin binding protein C3; *MYH7* = myosin heavy chain beta; RV = right ventricular; *TTN* = titin.

TABLE 1 Characteristics of NCCM Phenotypes

		Status			NCCM Phenotype			
	All NCCM (N = 216)	Index Patients (n = 143)	Relatives (n = 73)	p Value	Isolated (n = 92)	With DCM (n = 115)	With HCM (n = 9)	p Value
Index patient	116 (54)	143	73		51 (55)	84 (73)	8 (89)	0.010
Male	116 (54)	76 (53)	40 (55)	NS	44 (48)	66 (57)	6 (67)	NS
Age at presentation <18 yrs	35 (16)	25 (17)	10 (14)	NS	15 (16)	18 (16)	2 (22)	NS
Age at presentation, yrs	38 (23–52)	40 (24–54)	35 (22–48)	NS	34 (22–48)	40 (26–56)	36 (33–45)	NS
Mutation	104 (48)	63 (44)	41 (56)	NS	41 (45)	58 (50)	5 (56)	NS
Congenital heart defect	15 (7)	9 (6)	6 (8)	NS	6 (7)	7 (6)	2 (22)	NS
Comorbidity*	48 (22)	33 (23)	15 (21)	NS	15 (16)	18 (16)	5 (56)	0.009
Asymptomatic†	69 (32)	34 (24)	35 (48)	<0.001	39 (42)	28 (24)	2 (22)	0.018
Right bundle branch block	8 (4)	6 (4)	2 (3)	NS	3 (3)	5 (4)	0	NS
Left bundle branch block	27 (13)	25 (17)	2 (3)	0.002	7 (8)	18 (16)	2 (22)	NS
Left atrial diameter >45 mm	39 (20)	32 (25)	7 (10)	0.013	9 (12)	26 (24)	4 (44)	0.019
RV systolic dysfunction	38 (18)	28 (20)	10 (14)	NS	9 (10)	26 (23)	3 (33)	0.023
LV systolic dysfunction	113 (52)	87 (61)	26 (36)	<0.001	25 (27)	81 (70)	7 (78)	<0.001

Values are n (%) or median (interquartile range). *Hypertension, hypercholesterolemia, coronary artery disease, and diabetes. †At presentation.

DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LV = left ventricular; NCCM = noncompaction cardiomyopathy; NS = not significant; RV = right ventricular.

had highest risk for MACE (hazard ratio: 2.29; 95% CI: 1.17 to 4.47; p = 0.016) (Figure 2, Table 3).

FAMILIAL SEGREGATION OF NCCM PHENOTYPES. Of the 107 relatives diagnosed with a cardiomyopathy, 73 had NCCM. Fifty relatives had the same NCCM phenotype as the index patient in the family. The risk of having isolated NCCM was higher for relatives of index patients with isolated NCCM than for relatives of NCCM with DCM index cases (p < 0.001) (Central Illustration). NCCM with DCM in relatives occurred in families of index cases with isolated NCCM and NCCM with DCM. These patterns of familial segregation of NCCM phenotypes were observed in families with a mutation and in families without a mutation. In some families, all patients had the same phenotype; in 8 families, all patients had isolated NCCM, in 9 families all had NCCM with DCM, and in 1 family all had NCCM with HCM. In 17 families, relatives were diagnosed with DCM or HCM without noncompaction. Relatives with DCM (without noncompaction) were most frequently observed in the families of the NCCM with DCM index cases (p = 0.049). Relatives with HCM (without

TABLE 2 Event Rate per 100 Patient Years of Follow-Up of NCCM Phenotypes Since the Time of Diagnosis

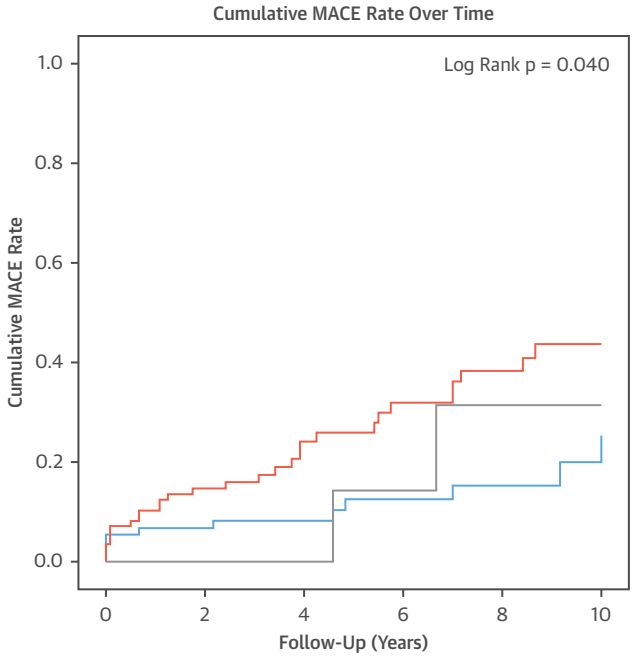
		Status			NCCM Phenotype			
	All NCCM (N = 216)	Index (n = 143)	Relatives (n = 73)	p Value	Isolated (n = 92)	With DCM (n = 115)	With HCM (n = 9)	p Value
Follow-up, months	44 (9–93)	42 (9–85)	50 (8–106)	NS	51 (10–93)	38 (8–93)	80 (55–120)	NS
Stroke*	0.85 (8)	0.84 (5)	0.86 (3)	NS	0.93 (4)	0.87 (4)	0	NS
Peripheral embolism*	1.06 (10)	1.67 (10)	0	0.010	0.93 (4)	1.31 (6)	0	NS
(Paroxysmal) atrial fibrillation*	2.65 (25)	3.68 (22)	0.86 (3)	0.004	1.40 (6)	3.28 (15)	6.89 (4)	0.034
VT*	2.65 (25)	3.85 (23)	0.58 (2)	0.001	1.86 (8)	3.49 (16)	1.72 (1)	NS
Sustained VF/VT*	1.38 (13)	2.01 (12)	0.29 (1)	NS	0.93 (4)	1.97 (9)	0	NS
Heart failure requiring hospitalization*	4.44 (42)	6.36 (38)	1.15 (4)	<0.001	1.63 (7)	7.21 (33)	3.44 (2)	<0.001
ICD (%)	71 (33)	57 (40)	14 (19)	0.001	19 (21)	51 (44)	1 (11)	<0.001
Secondary prevention, %†	11 (16)	11 (19)	0	NS	3 (16)	8 (16)	0	NS
Appropriate shock*†	0.53 (5)	0.84 (5)	0	NS	0	1.09 (5)	0	NS
Heart transplant*	0.74 (7)	1.17 (7)	0	0.043	0.23 (1)	1.31 (6)	0	NS
Deceased*	2.12 (20)	2.18 (13)	2.01 (7)	NS	0.93 (4)	3.06 (14)	3.44 (2)	NS
MACE*	4.76 (45)	5.86 (35)	2.88 (10)	NS	2.80 (12)	6.77 (31)	3.44 (2)	0.040

Values are median (interquartile range) or event rate (number of patients). *Having at least 1 of the following risk factors: hypertension, hypercholesterolemia, coronary artery disease, and diabetes. †Implantable-cardioverter defibrillator (ICD) carriers.

MACE = major adverse cardiac events; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

FIGURE 2 **Kaplan-Meier Curves of Major Adverse Cardiac Events for NCCM Phenotypes**

NCCM phenotype	MACE /100 patient years	HR (95% CI)	p-value
Isolated NCCM	2.80	1.00	NA
NCCM with DCM	6.77	2.29 (1.17 - 4.47)	0.016
NCCM with HCM	3.44	1.30 (0.29 - 5.81)	0.733



Number at risk						
Isolated NCCM	92	63	48	36	21	14
NCCM with DCM	115	71	43	33	18	13
NCCM with HCM	9	8	7	5	3	3

Isolated NCCM is shown in **blue**; NCCM with dilated cardiomyopathy (DCM) is shown in **orange**; and NCCM with hypertrophic cardiomyopathy (HCM) is shown in **gray**. CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; NA = not available; other abbreviations as in Figure 1.

noncompaction) occurred only in families of index cases with NCCM and HCM ($p < 0.001$). Mutations in the *MYH7* head domain predicted isolated NCCM (odds ratio: 7.5; 95% confidence interval [CI]: 2.9 to 19.5; $p < 0.001$), whereas *MYH7* tail domain mutations predicted NCCM with DCM (odds ratio: 9.8; 95% CI: 2.8 to 34.0; $p < 0.001$). *TTN* mutations predicted risk for DCM without noncompaction in relatives (odds ratio: 10.9; 95% CI: 2.3 to 51.1; $p = 0.002$). Risk for HCM without noncompaction in relatives was increased in families with *MYBPC3* mutations (odds ratio: 585.0; 95% CI: 49.5 to 6915.4; $p < 0.001$). In families of index cases without a mutation, fewer relatives were diagnosed with a cardiomyopathy because there are probably fewer cases with a genetic cause in this group of patients.

PHENOTYPES OF *MYH7* MUTATIONS. In total, 69 *MYH7* mutation carriers were identified, of whom 55 (23 index) had NCCM; 34 patients had a mutation in the head domain, and 21 patients had a mutation in the tail of *MYH7* (Table 4). Nearly one-half ($n = 24$ [44%]) of the patients with NCCM with an *MYH7* mutation were asymptomatic. Nonpenetrance was observed in 12 (17%) of the *MYH7* mutation carriers (50% with a mutation in the head and 50% in the tail domain). NCCM with DCM was associated with mutations in the tail domain of *MYH7* (outside of the *MYH7* p-loop) (29% isolated NCCM vs. 86% NCCM with DCM; $p < 0.001$) (Figure 3). Two relatives with a mutation in the tail domain of *MYH7* had DCM without noncompaction. Overall, patients with a mutation in the *MYH7* head were younger at

TABLE 3 MACE in NCCM Since Time of Diagnosis

	MACE/100 Patient-Years Characteristic Present*	MACE/100 Patient-Years Characteristic Absent*	Hazard Ratio (95% Confidence Interval)	p Value
Index patient	5.86 (35/143)	2.88 (10/73)	1.95 (0.96–3.95)	0.065
Male	4.44 (22/116)	5.11 (23/100)	0.91 (0.51–1.65)	0.763
Age <18 yrs at presentation	3.24 (7/35)	5.21 (38/181)	0.69 (0.31–1.55)	0.365
Mutation	4.93 (24/103)	4.58 (21/113)	1.2 (0.63–2.08)	0.646
Congenital heart disease	2.03 (2/15)	5.08 (43/201)	0.21 (0.03–1.53)	0.123
Cardiovascular comorbidities†	8.24 (13/32)	4.06 (38/178)	2.08 (1.09–3.97)	0.027
Asymptomatic at presentation	2.32 (7/69)	5.91 (38/147)	0.40 (0.18–0.90)	0.027
Right bundle branch block	0.00 (0/8)	5.06 (45/208)	0.05 (0.00–14.32)	0.292
Left bundle branch block	6.47 (9/27)	4.47 (36/189)	1.56 (0.75–3.24)	0.239
Left atrial diameter >45 mm	6.39 (12/39)	4.28 (29/156)	1.55 (0.79–3.05)	0.204
Reduced LV systolic function	7.34 (33/113)	2.42 (12/103)	3.16 (1.60–6.27)	0.001
Reduced RV systolic function	8.36 (14/38)	3.54 (27/178)	2.20 (1.17–4.15)	0.015

*Rates (no. of patients with event/no. of patients at risk). †Hypertension, hypercholesterolemia, coronary artery disease, and diabetes.
Abbreviations as in Tables 1 and 2.

presentation (p = 0.036). Mutations in the *MYH7* tail were associated with RV dysfunction (6% vs. 33%; p = 0.01). There was no difference in risk for MACE for patients with mutations in the head and tail domain of *MYH7*. Ebstein anomaly occurred in 4 of 34 of the patients with an *MYH7* mutation in the head domain: 2 patients with NCCM and Ebstein anomaly from 1 family, and 1 family with a patient with NCCM with Ebstein anomaly and 1 relative with Ebstein anomaly without noncompaction.

PHENOTYPES OF *TTN* MUTATIONS. *TTN* mutations occurred in 30 cases: 18 (15 index) with NCCM, and 12 relatives with DCM. Ten (67%) of the mutations occurred in the A-band (Table 4). Of the 5 patients with a mutation outside of the A-band, 2 had a complex genotype involving a *MIB1* mutation. Nine of the 14 relatives with a familial *TTN* mutation had no signs of a cardiomyopathy. For mutations outside of the A-band nonpenetrance (57% vs. 6%; p = 0.004), asymptomatic disease (2 of 3) and older age at diagnosis was observed (non-A-band 59 years vs. A-band 39 years; p = 0.006).

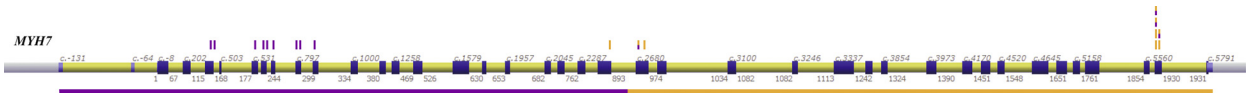
PHENOTYPES OF *MYBPC3* MUTATIONS. Eleven *MYBPC3* mutations in 8 families with 9 patients with NCCM were observed. Three NCCM index patients had 2 *MYBPC3* mutations (Table 4). Three patients with an *MYBPC3* mutation had NCCM with HCM. Five patients with an *MYBPC3* mutation had NCCM with DCM and 1 had isolated NCCM, 7 (78%) had LV dysfunction, and 5 (56%) had a MACE. Eleven (33%) of

TABLE 4 Mutations in *MYH7*, *TTN*, and *MYBPC3* in Familial NCCM

	MYH7				*TTN*				*MYBPC3*
	Head* (n = 40)	Tail* (n = 29)	Total (n = 69)	p Value	Non-A-Band (n = 14)	A-Band (n = 16)	Total (n = 30)	p Value	(n = 33)
NCCM index patient	11	12	23		5	10	15		8
Isolated NCCM	24	2	26		2	2	4		1
NCCM with DCM	10	18	28		3	10	13		5
NCCM with HCM	0	1	1		0	1	1		3
DCM	0	2	2		1	2	3		0
HCM	0	0	0		0	0	0		13
Non-penetrance	6	6	12		8	1	9		11
Patients with NCCM	34	21	55		5	13	18		9
Mean age at presentation, yrs	28	38	32	0.036	59	39	45	0.006	34
Asymptomatic	16 (47)	8 (38)	24 (44)	NS	1 (20)	2 (15)	3 (17)	NS	3 (33)
LV systolic dysfunction	14 (41)	14 (67)	28 (51)	NS	4 (80)	10 (77)	14	NS	7 (78)
RV systolic dysfunction	2 (6)	7 (33)	9 (17)	0.020	0	6 (15)	6 (33)	NS	0
MACE	3 (9)	3 (14)	6 (11)	NS	0	5 (38)	5 (28)	NS	5 (56)

Values are n or n (%) unless otherwise indicated. *Head is the p-loop of *MYH7* ending at c.2523, the tail was the rest of the *MYH7* gene.
MYBPC3 = myosin binding protein C3; *MYH7* = myosin heavy chain beta; *TTN* = titin; other abbreviations as in Tables 1 and 2.

FIGURE 3 ***MYH7*** **Mutations in NCCM**



Purple indicates the head domain and families with isolated NCCM. **Yellow** indicates the tail domain and the families with NCCM with DCM. Mixed **purple and yellow** mark indicates families with both isolated NCCM and NCCM with DCM. Mutations in the head, isolated NCCM phenotype versus in the tail, NCCM with DCM ($p < 0.001$). Figure adapted from Alamut Visual (Interactive Biosoftware, Rouen, France), 12-2016. Abbreviations as in **Figure 1**.

the relatives with a mutation, including 5 with the Dutch founder mutation c.2373dupG, had no signs of cardiomyopathy.

DISCUSSION

Prediction of risk for a cardiomyopathy phenotype and associated risk for adverse events is important for counseling the relatives of patients with NCCM and eventually tailoring cardiologic family screening. This study showed that the cardiac features and the genetic defect of index cases may help to predict the cardiomyopathy phenotype and associated risk for relatives. Familial segregation of isolated NCCM, NCCM with DCM, or NCCM with HCM was observed, as well as families in which a range of different NCCM phenotypes occurred. When the index case had isolated NCCM, relatives were more likely to have similarly isolated NCCM, linked to a better prognosis with less RV and LV systolic dysfunction and low risk for MACE. Almost one-half of the patients with isolated NCCM had a mutation, predominantly in the head domain of *MYH7*. NCCM with DCM was overall the most frequent NCCM phenotype and was associated with mutations in the tail domain of *MYH7* and in *TTN* with increased risk for LV systolic dysfunction and MACE in patients. Relatives of index cases with NCCM and DCM had an increased risk of having DCM without hypertrabeculation, compared with the relatives of the index cases with other NCCM features. For relatives of index cases with NCCM and HCM, the risk for HCM without noncompaction was increased.

NCCM PHENOTYPES. The cardiomyopathy phenotypes in relatives included DCM with no signs of NCCM, in particular in families of index cases with NCCM and DCM. It is unknown if LV dilation in NCCM with DCM is secondary to advanced NCCM or represents hypertrabeculation that may occur in a distinct subgroup of patients with DCM. In this study, 70% of the patients with NCCM and DCM had heart failure, indicating that in NCCM, as in other cardiac diseases, progressive heart failure may lead to LV dilatation. Conversely, normal LV function in ~30% of the patients with NCCM and DCM could not explain the LV dilatation. Similarly, the novel DCM diagnostic criteria include DCM without LV dysfunction (30). Our results suggest that mutations in the tail of *MYH7* and in *TTN* may predispose to LV dilatation, with or without LV dysfunction, and in some cases with RV dysfunction. Most important is that there was no apparent difference in outcome for DCM, with or without hypertrabeculation (31). Similarly, in a smaller number of cases, the nosology of concomitant NCCM with HCM remains part of the poorly understood spectrum of hypertrabeculation. In families with a mutation, relatives with DCM and HCM all had the familial mutation and therefore belong together with NCCM to a wider cardiomyopathy spectrum. The mechanism of hypertrabeculation needs to be explored by focusing on the role of additional genetic defects or nongenetic factors.

RISK FOR RELATIVES. Family screening showed that relatives had less severe cardiac features than the index patients among all subtypes of NCCM, which can be explained by early detection through screening that allows early treatment and prevention of severe complications. Risk for finding a cardiomyopathy in relatives was higher in families from index cases with a mutation than for families without a mutation. Nevertheless, cardiologic family screening is recommended for all cases because family screening may also identify asymptomatic relatives with a cardiomyopathy in families with no evidence of genetic disease (4). The fact that familial NCCM occurs in families with and without a mutation showed that not all genetic causes for NCCM have been identified. Although we cannot exclude unknown genetic defects in cases without a mutation, it is more likely that nongenetic causes with a low genetic risk are involved than unknown genetic causes because the relatives had low risk for cardiomyopathy.

GENES. NCCM phenotypes were related to genetic causes. The *MYH7* gene was a major genetic cause for NCCM. The location of the mutations in *MYH7* could predict cardiac phenotypes. An explanation for the association between mutations in the tail and NCCM with DCM could be that mutations in the tail domain might interfere with the binding site for *TTN*, and thus may have a similar effect as *TTN* mutations, which are important causes of DCM and also predict DCM without NCCM in relatives. Although mutations in the head of *MYH7* were previously associated with HCM, our study did not endorse that *MYH7* head mutations were related to NCCM with HCM (32). Our results endorse the previously reported association of concomitant Ebstein anomaly and NCCM with *MYH7* mutations. Similarly, *MYBPC3*, a major cause for HCM, was observed in families with NCCM and HCM and increased risk for HCM without hypertrabeculation in relatives.

STUDY LIMITATIONS. Not all participating NCCM index cases had next-generation sequencing DNA testing using the latest genetic cardio-panel, indicating the possibility of underreporting of genetic causes. Another cause of underreporting of familial disease might be that cardiomyopathy phenotypes in families may have been missed because not all relatives participated in testing. Given the retrospective design of the study, clinical data of index cases and relatives may be missing. Furthermore, age-dependent penetrance may play a role, rendering more relatives affected in the future.

CONCLUSIONS

NCCM phenotypes of index patients and the genetic defect may predict the cardiomyopathy phenotype and the severity of the disease in relatives. The strongest familial segregation of NCCM phenotypes was observed for isolated NCCM. NCCM with DCM was associated with *MYH7* tail domain and *TTN* mutations, with worse outcome and with DCM without NCCM in relatives. NCCM with HCM was related to *MYBPC3* and HCM without NCCM in relatives.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In familial NCCM, the genetic cause and the distinct NCCM phenotype (isolated NCCM, NCCM with DCM, or NCCM with HCM) of index cases may help predict risk for relatives.

TRANSLATIONAL OUTLOOK: The etiologic and genetic heterogeneity of NCCM demands stratification for genetic risk to distinguish families with a high genetic burden and high risk for relatives. Families of patients in whom NCCM may be caused by nongenetic causes or by (yet unknown) genetic causes with small effects (e.g., genetic modifiers) may have low risk for relatives. Ultimately, designing a risk model to predict risk for relatives with genetic and clinical data of the index case may be achieved by collecting data from large family screening studies.

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KEY WORDS family screening, genetics, left ventricular noncompaction, noncompaction cardiomyopathy, outcome

APPENDIX For supplemental tables, please see the online version of this paper.