Systematic Review of Genotype-Phenotype Correlations in Noncompaction Cardiomyopathy

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Background—A genetic cause can be identified in 30% of noncompaction cardiomyopathy patients (NCCM) with clinical features ranging from asymptomatic cardiomyopathy to heart failure with major adverse cardiac events (MACE).

Methods and Results—To investigate genotype-phenotype correlations, the genotypes and clinical features of genetic NCCM patients were collected from the literature. We compared age at diagnosis, cardiac features and risk for MACE according to mode of inheritance and molecular effects for defects in the most common sarcomere genes and NCCM subtypes. Geno- and phenotypes of 561 NCCM patients from 172 studies showed increased risk in children for congenital heart defects ($P<0.001$) and MACE ($P<0.001$). In adult NCCM patients the main causes were single missense mutations in sarcomere genes. Children more frequently had an X-linked or mitochondrial inherited defect ($P=0.001$) or chromosomal anomalies ($P<0.001$). *MYH7* was involved in 48% of the sarcomere gene mutations. *MYH7* and *ACTC1* mutations had lower risk for MACE than *MYBPC3* and *TTN* ($P=0.001$). The NCCM/dilated cardiomyopathy cardiac phenotype was the most frequent subtype (56%; $P=0.022$) and was associated with an increased risk for MACE and high risk for left ventricular systolic dysfunction (<0.001). In multivariate binary logistic regression analysis *MYBPC3*, *TTN,* arrhythmia -, non-sarcomere non-arrhythmia cardiomyopathy—and X-linked genes were genetic predictors for MACE.

Conclusions—Sarcomere gene mutations were the most common cause in adult patients with lower risk of MACE. Children had multi-systemic disorders with severe outcome, suggesting that the diagnostic and clinical approaches should be adjusted to age at presentation. The observed genotype-phenotype correlations endorsed that DNA diagnostics for NCCM is important for clinical management and counseling of patients. **(*J Am Heart Assoc*. 2019;8:e012993. DOI: 10.1161/JAHA.119.012993.)**

Key Words: diagnostics • genetics • human • left ventricular noncompaction • noncompaction cardiomyopathy • outcome

Noncompaction cardiomyopathy (NCCM) is a rare cardiomyopathy characterized by excessive trabeculation of the left ventricle,[1] and is also known as left ventricular hypertrabeculation/noncompaction. Diagnostic criteria are based on cardiac imaging with echocardiography or cardiac magnetic resonance imaging requiring at least a 2-fold increase of ratio of endocardial hypertrabeculation.[1–3] Genetics plays an important role in NCCM in at least half the cases; 30% of the index patients have a mutation or chromosome defect. In addition, unknown genetic causes are expected in 20% of the index patients with familial disease who do not have a mutation.[4] In cardiomyopathy patients who do not have familial disease or a mutation, the cause of NCCM may involve unknown low penetrance genetic causes and/or cardiac stress induced mechanism.[5,6] In addition physiologic hypertrabeculation occurs in people without a cardiomyopathy.

The most prevalent genetic causes for NCCM are defects in the same sarcomere genes that are frequent causes for hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM); *MYH7*, *MYBPC3,* and *TTN*,[4,7] and are autosomal dominantly inherited with reduced penetrance. Less frequent are cases of NCCM inherited as X-linked or mitochondrial traits, or chromosome defects, which are, usually associated with complex congenital malformations in children.[8–10]

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Accompanying Data S1, Tables S1 through S4, and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.012993

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Clinical Perspective

What Is New?

- The most frequent causes of genetic noncompaction cardiomyopathy in adults are single sarcomere gene mutations, with a relatively low risk of adverse events.
- Children more often had rare X-linked and chromosome defects, with severe outcome.

What Are the Clinical Implications?

- Differences in causes between noncompaction cardiomyopathy patients presenting in adulthood and childhood should be considered in the clinic and when performing molecular diagnostics.
- Identifying the genetic cause allows risk stratification and may help clinical management and counseling of patients and their relatives.

Establishing genotype-phenotype correlations is important for genetic counseling and clinical management of NCCM. Previous studies suggested that the genetic defect, left ventricular systolic function, and age at diagnosis were important predictors of cardiac features and risk for major adverse cardiac.[4,11] Since NCCM is a relatively rare, genetically heterogonous cardiomyopathy, large studies are needed to establish a correlation between genetic defects and clinical outcome. By performing a systematic review of the NCCM literature for reports of NCCM patients with documented genotype and phenotypes, we could combine and analyze the results of smaller studies to determine the genetic spectrum of NCCM and establish if genetic causes could help predict high-risk profiles for major adverse cardiac events in NCCM.

Methods

Data Availability

The data of this study were extracted from publications, which were available online. The authors declare that all supporting data are available within the article and its online supplementary files. Since data were obtained from publications, no consent from an institutional review committee was required.

Data Collection

The collection of data included English-language publications from 1999 to March 2018. Inclusion criteria were that the complete results of DNA-testing or cytogenetic analysis and the cardiologic data of each individual patient were available. Only NCCM patients fulfilling the current diagnostic criteria were included in the study. Patients presumed to be reported more than once by different studies (based on mutation specifics: same amino acid change and base change in the same gene; sex; age, also with respect to date of publication; and corresponding authors) were included once. A detailed description of the search terms used for this study, the collection of studies, and inclusion of patient data are presented in Data S1 and Figure S1.

Specifics of the genetic defects of each patient and information on family histories of cardiomyopathies (NCCM, HCM, or DCM) or sudden death at <50 years old in relatives were collected. The included cardiologic data consisted of ECG, the applied diagnostic criteria used to diagnose NCCM, the modality of diagnosis (echocardiography, cardiac magnetic resonance imaging, computed tomography, and the cardiac symptoms). Information on the occurrence of congenital heart disease (CHD) and neuromuscular disease in NCCM patients was recorded. Patients were classified as having left ventricular dilatation when this was reported. In case this information was missing the occurrence of left ventricular (LV) dilatation was determined from presented LV measurements; patients were classified with LV dilation when left ventricular end diastolic diameter was ≥60 mm in males or ≥54 mm in females, or left ventricular end diastolic diameter index was ≥31 mm in males or ≥32 mm in females.[12] For children, dimensions of the left ventricle of <2 SDs from the reference range were classified as dilated.[13] Patients were classified as having left ventricular systolic dysfunction if reported, or if fractional shortening was <25% in males or <27% in females, or if LV ejection fraction was <55% in males and females. We recorded the occurrence and the age of a patient suffering sudden cardiac death, heart transplantation, having a left ventricular assist device, stroke, or heart failure requiring hospital admission.

NCCM Subtypes

NCCM patients were classified into the 4 NCCM subtypes (when LV diameters were known): isolated NCCM, NCCM/HCM, NCCM/DCM and NCCM/HCM/DCM. Patients were classified as isolated NCCM if they had normal LV dimensions without LV hypertrophy. NCCM patients were categorized into NCCM/HCM if they also had LV wall hypertrophy of ≥13 mm or the diagnosis of HCM was reported. An NCCM patient was classified as NCCM/DCM if the patient had LV dilatation. The NCCM patient was classified as NCCM/HCM/DCM if the patient had LV dilation and LV wall hypertrophy.

Genetic Causes

In total, 80 genes were reported as the genetic causes for NCCM, of which 14 were excluded from this review, because there was not sufficient evidence to support that these genes could be the cause of a cardiomyopathy. The genetic defects

were grouped according to the molecular function of the gene, into sarcomere- or arrhythmia cardiomyopathy genes, non-sarcomere and non-arrhythmia cardiomyopathy genes, genes involved in cardiac development, mitochondrial genes, X-linked inherited disorders, and chromosome defects. Figure 1 presents an overview of the genetic causes: the sarcomere genes were *ACTC1, ACTN2, DES, LDB3, MYBPC3, MYH7, MYL2, NEBL, OBSCN, TNNC1, TNNI3, TNNT2, TPM1,* and *TTN*. The arrhythmia genes were 10 genes associated with ion channels and transport: *ABCC9, ANK2, CACNA2D1, CASQ2, HCN4, KCNE3, KCNH2, KCNQ1, RYR2,* and *SCN5A*. The group of cardiomyopathy genes, which were not sarcomere or arrhythmia genes: *DMPK, DSP, DTNA, FKTN, HFE, JUP, LMNA, PKP2, PLEC, PLN, PRDM16, RBM20,* and *SGCD*. Eight genes were previously associated with developmental defect of the heart: *MIB1, MIB2, NKX2.5, NOTCH1, NSD1, PTPN11, TBX20* and *TBX5*. X-linked inherited NCCM included the *DMD, FHL1, GLA, LAMP2, RPS6KA3,* and *TAZ* genes. Mitochondrial dysfunction as the cause of NCCM was considered when a mutation occurred in a gene affecting mitochondrial functioning, including the nuclear genes with a mitochondrial function or the mitochondrial DNA genes: *HADHB, HMGCL, MIPEP, MLYCD, MT-ATP6, MT-CO1, MT-CO3, MTFMT, MT-ND1, MT-ND2, SDHA, SDHD, TMEM70,* and *VARS2*. Some additional genes were only reported in patients with complex genotypes, including: *BB2, BMPR1A, CSRP3, EMD, ITGA7, MT-TL1, MYH6, MYH7B, MYLK2, MYPN, PLEKHM2, RANGRF,* and *SH3PXD2B*. The current analysis did not include single cases of genetic causes for which there was little evidence for involvement in cardiomyopathy (*ARFGEF2, CYP2C9*2, GARS, LMX1B, MBL2, MMACHC, MSH6, NONO, PKD1, PKD2, PMP22, POMT2, SMC1A,* and *YWHAE*).

We compared the clinical features in patients according to the genetic causes, ie, in patients with sarcomere gene mutations, in patients with mutations in cardiomyopathy genes (ie, sarcomere, arrhythmia, and other cardiomyopathy genes). In patients with non-autosomal dominant inherited NCCM, the phenotypes of patients were compared according to the

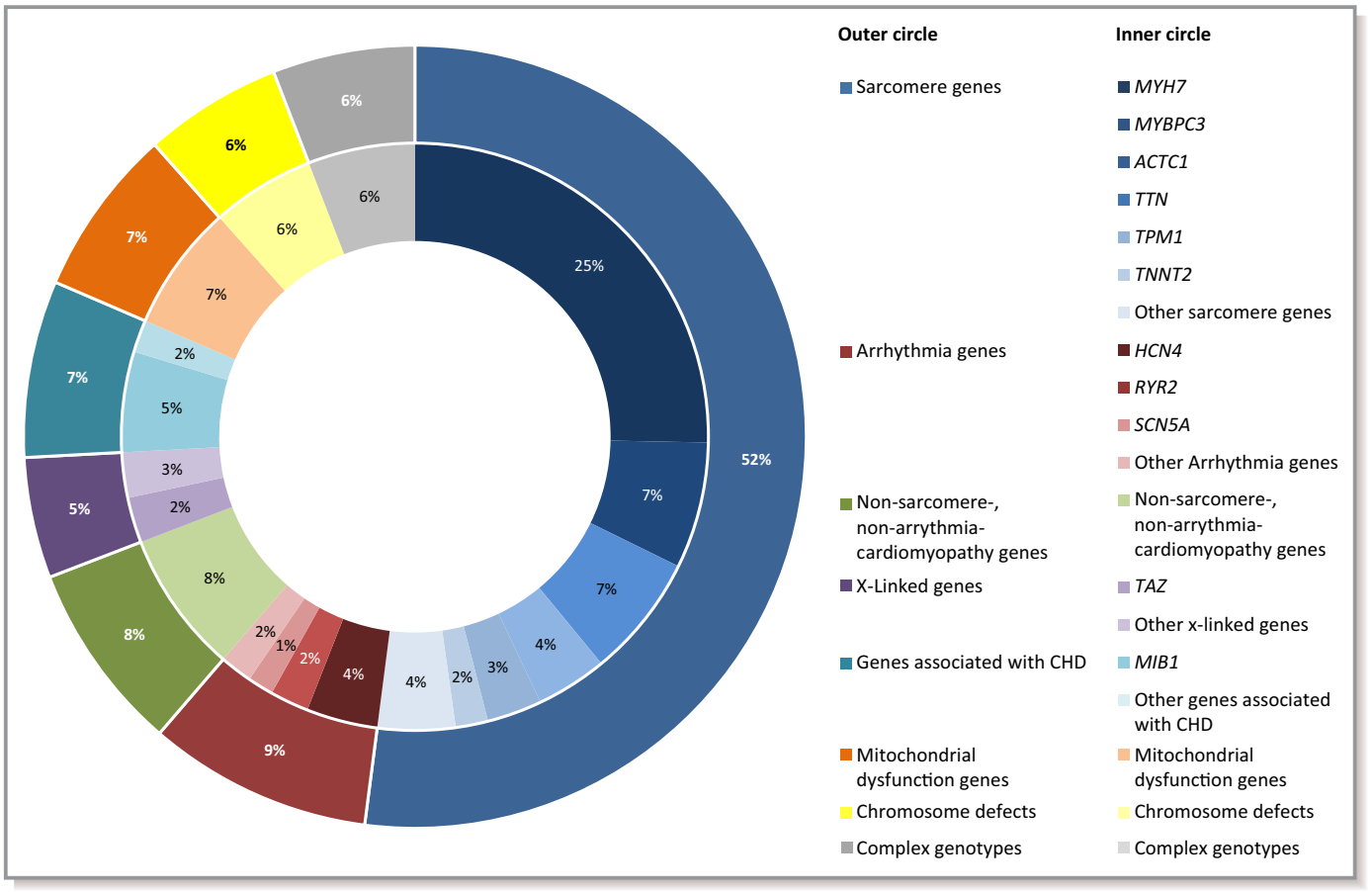

Figure 1. Genetic noncompaction cardiomyopathy. Other sarcomere genes: *ACTN2, DES, LDB3, MYL2, NEBL, OBSCN, TNNC1,* and *TNNI3*. Other arrhythmia genes: *ABCC9, ANK2, CACNA2D1, CASQ2, KCNE3, KCNH2,* and *KCNQ1*. Non-sarcomere, non-arrhythmia-cardiomyopathy genes: *DMPK, DSP, DTNA, FKTN, HFE, JUP, LMNA, PKP2, PLEC, PLN, PRDM16, RBM20,* and *SGCD*. Other X-linked genes: *DMD, FHL1, GLA, LAMP2,* and *RPS6KA3*. Other genes associated with CHD: *MIB2, NKX2.5, NOTCH1, NSD1, PTPN11, TBX20,* and *TBX5*. Mitochondrial-functioning: *HADHB, HMGCL, MIPEP, MLYCD, MT-ATP6, MT-CO1, MT-CO3, MTFMT, MT-ND1, MT-ND2, SDHA, SDHD, TMEM70,* and *VARS2*. Chromosome defect: see Table S3. Complex genotypes: see Table S2. CHD indicates congenital heart disease.

characteristics of the genetic cause (complex genotypes, X-linked, mitochondrial defects, and chromosome defects).

Statistical Analysis

Categorical data were analyzed with Pearson Chi-squared test or Fisher exact test. For comparison of medians the independent samples Kruskal–Wallis test was used. Odds ratios (OR) with 95% CI for MACE were calculated using binary logistic regression. To identify independent predictors for MACE, variables were tested in a multivariate logistic regression analysis using the enter method. Age, sex, and other parameters with a $P<0.05$ were stepwise entered into the multivariate model. Multiple imputation for the entered predictors was used to handle missing data in the multivariate regression models. Statistical analysis was performed with SPSS statistical software, version 21.0 (SPSS Inc, Chicago, IL).

Results

Study Population

The literature searches yielded 1978 publications reporting NCCM patients. After removing duplicates from the different searches 990 papers remained of which 172 fulfilled the inclusion criteria. In total 561 patients were included in this review (Figure S1). Age at presentation was reported in 541 of 561, and sex was reported in 554 cases. Among the NCCM patients 415 (72%) were index cases (the first patient diagnosed with NCCM in a family) and 159 (28%) were affected family members (Table 1). The study population consisted of 244 children, diagnosed before the age of 18 years and 297 adults. The diagnosis was based on echocardiography in 402 NCCM patients, cardiac magnetic resonance imaging in 66, 104 had an echocardiography and cardiac magnetic resonance imaging, and 2 patients were diagnosed at autopsy.

Table 1. Cardiac Features of 541 Genetic NCCM Patients*

	Children (<18 y) (n=244)	Adults (n=297)	Total (n=541)	*P* Value
NCCM index patients	195/244 (80%)	201/297 (68%)	396/541 (73%)	0.001
Male (%)	122/238 (51%)	154/297 (52%)	276/535 (52%)	ns
Median age at diagnosis in years (IQR)	0 (0–10)	41 (30–53)	23 (1–43)	NA
Congenital heart disease	45/244 (18%)	13/297 (4%)	58/541 (11%)	<0.001
Ebstein anomaly	11/45 (24%)	10/13 (77%)	21/58 (36%)	<0.001
Atrial septal defect	17/45 (38%)	7/13 (54%)	24/58 (41%)	ns
Ventricular septal defect	20/45 (44%)	2/13 (15%)	22/58 (38%)	ns
Patent ductus arteriosus	11/45 (24%)	1/13 (8%)	12/58 (21%)	ns
Patent foramen ovale	4/45 (9%)	1/13 (8%)	5/58 (9%)	ns
Hypoplastic left heart	2/45 (4%)	0/13 (0%)	2/58 (3%)	ns
Aortic coarctation	2/45 (4%)	0/13 (0%)	2/58 (3%)	ns
Heart failure	115/244 (47%)	153/297 (52%)	268/541 (50%)	ns
Left ventricular dilatation	101/150 (67%)	105/170 (62%)	206/326 (64%)	ns
Left ventricular systolic dysfunction	123/179 (69%)	131/233 (56%)	254/412 (62%)	0.010
Pacemaker	12/244 (5%)	14/297 (5%)	26/541 (5%)	ns
ICD	19/244 (8%)	63/297 (21%)	82/541 (15%)	<0.001
Major adverse cardiac events	94/244 (39%)	55/297 (18%)	149/541 (28%)	<0.001
Stroke	2/244 (1%)	6/297 (2%)	8/541 (1%)	ns
Heart failure requiring hospital admission	34/244 (14%)	6/297 (2%)	40/541 (8%)	<0.001
Left ventricular assist device	6/244 (3%)	2/297 (1%)	8/541 (1%)	ns
Heart transplantation	25/244 (10%)	5/297 (2%)	30/541 (5%)	<0.001
Sustained VT/VF or appropriate shock	30/244 (12%)	23/297 (8%)	53/541 (10%)	ns
Cardiac death	35/244 (14%)	10/297 (3%)	45/541 (9%)	<0.001
Neuromuscular symptoms	35/60 (58%)	15/83 (18%)	50/143 (35%)	<0.001

ICD indicates implantable cardiac device; IQR, interquartile range; LV, left ventricular; ns, not significant; NA, not applicable; NCCM, noncompaction cardiomyopathy; VT/VF, ventricular tachycardia/ventricular fibrillation.
*Age at diagnosis was missing for 20 cases.

Table 2. Genetics of 396 NCCM Index Patients

	Children (n=195)*	Adults (n=201)	Total (n=396)	*P* Value
Type of mutation				<0.001
Missense mutation	98 (50%)	119 (59%)	217 (55%)	
Other mutations†	56 (29%)	63 (31%)	119 (30%)	
Complex genotype‡	14 (7%)	15 (7%)	29 (7%)	
Chromosome defect	27 (14%)	4 (2%)	31 (8%)	
Mode of inheritance§				0.001
Autosomal dominant	105 (75%)	162 (89%)	267 (83%)	
X-linked	26 (19%)	10 (5%)	36 (11%)	
Mitochondrial	9 (6%)	10 (5%)	19 (6%)	
Familial cardiomyopathy	60 (31%)	109 (54%)	169 (43%)	<0.001
NCCM in family	38 (20%)	68 (34%)	106 (27%)	0.001
HCM/DCM in family	28 (14%)	49 (24%)	77 (19%)	0.012
SCD before age 50 y in family	34 (17%)	44 (22%)	78 (20%)	ns

DCM indicates dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death.
*Presentation before age 18 years.
†Nonsense- or frameshift mutations, small deletions or insertions.
‡At least 2 mutations.
§Chromosome defects and complex genotypes excluded.

Genetics of NCCM

In total 369 unique genetic defects in 66 genes were included. The majority of genetic causes were single mutations (85%) of which autosomal dominantly inherited missense mutation were the most frequent (55%; Table 2). In 7% of the patients an X-linked inherited genetic defect was reported, mostly in *TAZ* (n=31, 6%). In 32 (6%) of the patients a chromosome defect was reported, of whom 28 (88%) were diagnosed in childhood

Table 3. Genotype-Phenotype Correlations in 561 Genetic NCCM Patients

	Cardiomyopathy Genes*	Complex Genotype†	X-Linked	Mitochondrial	Chromosome Defects	
	n=416 (74%)	n=33 (6%)	n=41 (7%)	n=39 (7%)	n=32 (6%)	*P* Value
Male	203/411 (49%)	18/32 (44%)	35/41 (83%)	22/38 (58%)	7/32 (22%)	<0.001
Median age at diagnosis, y (IQR)	29 (10–45)	23 (0–45)	0 (0–29)	0 (0–27)	0 (0–9)	<0.001
Congenital heart disease	38/416 (9%)	2/33 (1%)	0/41 (0%)	6/39 (15%)	13/32 (41%)	…
Neuromuscular symptoms	12/90 (13%)	4/9 (44%)	14/16 (88%)	9/16 (56%)	11/12 (92%)	<0.001
LV dilatation	142/245 (58%)	14/16 (88%)	24/27 (89%)	17/18 (94%)	10/15 (67%)	<0.001
LV systolic dysfunction	177/307 (43%)	19/28 (68%)	27/36 (75%)	21/29 (72%)	11/21 (52%)	0.012
Major adverse cardiac events‡	97/416 (23%)	10/33 (30%)	21/41 (51%)	10/39 (26%)	11/32 (34%)	0.003
Stroke	6/416 (1%)	2/33 (6%)	0/41 (0%)	0/39 (0%)	0/32 (0%)	…
Heart failure requiring hospital admission	18/416 (4%)	2/33 (6%)	9/41 (22%)	3/39 (8%)	8/32 (25%)	…
Left ventricular assist device	6/4316 (1%)	0/33 (0%)	1/41 (2%)	1/39 (3%)	0/32 (0%)	…
Heart transplantation	21/416 (5%)	2/33 (6%)	4/41 (10%)	2/39 (5%)	1/32 (3%)	…
Sustained VT/VF or appropriate shock	38/416 (10%)	5/33 (15%)	5/41 (12%)	2/39 (5%)	3/32 (9%)	…
Cardiac death	23/416 (6%)	1/33 (3%)	9/41 (22%)	7/39 (18%)	5/32 (16%)	…

IQR indicates interquartile range; LV, left ventricular; NCCM, noncompaction cardiomyopathy; VT/VF, ventricular tachycardia/ventricular fibrillation.
*Cardiomyopathy genes: sarcomere-, arrhythmia-, non-sarcomere non-arrhythmia cardiomyopathy genes or an NCCM gene associated with congenital heart disease.
†Patients with multiple mutations.
‡Major adverse cardiac events were composed of stroke, heart failure requiring hospital admission, left ventricular assist device, heart transplantation, sustained VT/VF or appropriate shock, and cardiac death.

(Tables 2 and 3). Detailed descriptions of the reported mutations are presented in Table S1. More than 50% (292/651) of the genetic defects were reported in sarcomere genes, most prevalently in *MYH7* (n=142, 25%; Figure 1 and Tables 4, 5). Mutations in arrhythmia genes were observed in 11% of the patients, in particular in *HCN4* (n=22, 4%) (Table 4). Details of the complex genotypes are presented in Table S2. The complete list of reported chromosome defects is presented in Table S3, showing the 1p36 locus was the most frequently reported, in 13 patients, and 22q11 defects in 3 patients.

Children and Adult NCCM Patients

Overall genetic NCCM in children was associated with more severe features, CHD ($P<0.001$), LV systolic dysfunction ($P=0.010$), MACE ($P<0.001$), and neuromuscular signs ($P<0.001$; Table 1). The NCCM index cases diagnosed in childhood were more likely to have a chromosomal anomaly ($P<0.001$), an X-linked inherited disorder ($P=0.001$; Table 2), or mitochondrial defect. In 52% of the patients diagnosed before the age of 10 years there was an autosomal dominant inheritance, 37% had a sarcomere gene defects, 8% had an arrhythmia gene, 5% non-sarcomere non-arrhythmia cardiomyopathy genes, and 3% a gene associated with CHD. In contrast, 84% of the patients >20 years old had an autosomal dominant inheritance of which 64% had a sarcomere gene ($P<0.001$; Figure 2). Familial cardiomyopathy was reported more frequently in families of adult—than pediatric index patients (adults 54% versus children 31%, $P<0.001$; Table 2). In 93 (57%) families all affected relatives were reported to have NCCM. Sudden cardiac death (<50 years old) in relatives was reported in 78 (20%) of the families (Table 2).

Genotype-Phenotype Correlations Across the 5 Groups of Genetic Causes

Comparing the occurrence of cardiac features, risk for MACE, concomitant CHD, and neuromuscular signs in the 5 groups of genetic causes depicted in Table 3 showed that LV dilatation was most prominent in (94%) patients with a mitochondrial defect, and risk for MACE was highest in patients with X-linked inherited NCCM. Patients (23%) with a mutation in a cardiomyopathy gene had lowest risk for MACE ($P<0.001$). CHD occurred in 41% of the cases with a chromosome defect and in 9% of the patients with a mutation in a cardiomyopathy gene ($P<0.001$). No CHD were reported in patients with X-linked NCCM. Neuromuscular disease was more frequent in patients with X-linked NCCM and patients with a chromosome defect and was rarely reported in patients with a cardiomyopathy gene mutation ($P<0.001$).

Table 4. Genotype-Phenotype Correlations in 416 NCCM Patients With a Mutation in a Single Cardiomyopathy Gene

	Sarcomere Genes	Arrhythmia Genes	Non-Sarcomere Non-Arrhythmia Cardiomyopathy Genes	Genes Associated With CHD	
	n=292 (70%)	n=52 (12%)	n=44 (11%)	n=28 (7%)	*P* Value
Male	147/290 (51%)	21/52 (40%)	19/41 (46%)	16/28 (57%)	ns
Median age at diagnosis, y (IQR)	30 (13–44)	15 (4–43)	28 (13–46)	23 (13–47)	ns
Congenital heart disease	27/292 (9%)	1/65 (2%)	4/44 (9%)	6/28 (21%)	…
Neuromuscular symptoms	6/72 (8%)	0/4 (0%)	6/12 (50%)	0/2 (0%)	…
LV dilatation	112/199 (56%)	3/6 (50%)	18/22 (82%)	8/18 (44%)	…
LV systolic dysfunction	136/211 (65%)	9/35 (26%)	23/35 (66%)	9/26 (35%)	<0.001
Major adverse cardiac events*	57/292 (20%)	16/52 (31%)	18/44 (41%)	6/28 (21%)	0.009
Stroke	6/292 (2%)	0/52 (0%)	0/44 (0%)	0/28 (0%)	…
Heart failure requiring hospital admission	15/292 (5%)	0/52 (0%)	3/44 (7%)	0/28 (0%)	…
Left ventricular assist device	6/292 (2%)	0/52 (0%)	0/44 (0%)	0/28 (0%)	…
Heart transplantation	13/292 (5%)	0/52 (0%)	6/44 (14%)	2/28 (7%)	…
Sustained VT/VF or appropriate shock	15/292 (5%)	12/52 (23%)	9/44 (21%)	2/28 (7%)	…
Cardiac death	16/292 (6%)	2/52 (4%)	5/44 (11%)	0/28 (0%)	…

CHD indicates congenital heart disease; IQR indicates interquartile range; LV, left ventricular; MACE, major adverse cardiac event; NCCM, noncompaction cardiomyopathy; ns, not significant; VT/VF, ventricular tachycardia/ventricular fibrillation.

*Major adverse cardiac events were composed of stroke, heart failure requiring hospital admission, left ventricular assist device, heart transplantation, sustained VT/VF or appropriate shock, and cardiac death.

Table 5. Genotype-Phenotype Correlations in 292 NCCM Patients With a Mutation in a Sarcomere Gene

Total Number of Patients With a Mutation in a Sarcomere Gene	*MYH7* n=142 (48%)	*ACTC1* n=38 (13%)	*MYBPC3* n=39 (13%)	*TTN* n=22 (8%)	Other Sarcomere Genes* n=51 (17%)	*P* Value
Male	71/141 (50%)	20/38 (53%)	17/39 (44%)	15/21 (68%)	24/50 (48%)	ns
Median age at diagnosis, y (IQR)	30 (10–42)	26 (13–48)	28 (11–46)	43 (29–54)	30 (8–44)	0.043
Congenital heart disease	16/142 (11%)	6/38 (16%)	3/39 (8%)	1/22 (5%)	1/51 (2%)	…
Neuromuscular disease	4/32 (13%)	0/1 (0%)	1/13 (8%)	1/19 (5%)	0/7 (0%)	…
LV dilatation	49/80 (61%)	7/36 (19%)	17/24 (71%)	15/21 (71%)	24/38 (63%)	<0.001
LV systolic dysfunction	68/106 (64%)	8/14 (57%)	18/27 (67%)	16/21 (76%)	26/43 (61%)	ns
Major adverse cardiac events	19/142 (13%)	4/38 (10%)	16/39 (41%)	7/22 (32%)	11/51 (22%)	0.001
Stroke	4/142 (3%)	0/38 (0%)	1/39 (3%)	1/22 (4%)	0/51 (0%)	…
Heart failure requiring hospital admission	6/142 (4%)	1/38 (3%)	3/39 (8%)	1/22 (5%)	4/51 (8%)	…
Left ventricular assist device	0/142 (0%)	0/38 (0%)	4/39 (10%)	1/22 (5%)	1/51 (2%)	…
Heart transplantation	4/142 (3%)	1/38 (3%)	2/39 (5%)	2/22 (9%)	4/51 (8%)	…
Sustained VT/VF or appropriate shock	4/142 (3%)	2/38 (5%)	6/39 (15%)	1/22 (5%)	2/51 (4%)	…
Cardiac death	3/142 (2%)	0/38 (0%)	9/39 (23%)	2/22 (9%)	2/51 (4%)	…

IQR indicates interquartile range; LV, left ventricular; VT/VF, ventricular tachycardia/ventricular fibrillation; MACE, major adverse cardiac event; NCCM, noncompaction cardiomyopathy; ns, not significant.

**ACTN2, DES, LDB3, MYH7B, MYL2, NEBL, OBSCN, TNNC1, TNNC1, TNNI3, TNNT2,* and *TPM1.*

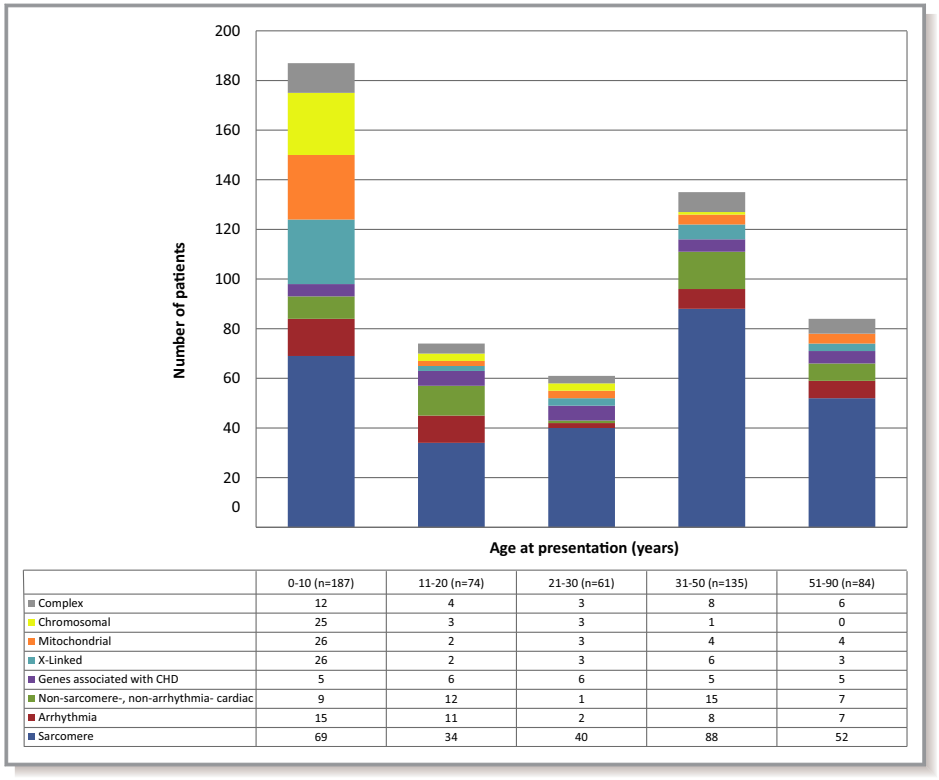

Figure 2. Genetic causes by age at diagnosis in 541 NCCM patients. CHD indicates congenital heart disease; NCCM, noncompaction cardiomyopathy.

Table 6. NCCM Subtypes in 349 Patients*

	Isolated NCCM	NCCM/HCM	NCCM/DCM		NCCM/HCM/DCM
	n=95 (27%)	n=47 (13%)	n=195 (56%)	*P* Value†	n=12 (3%)
Adult	54/95 (57%)	25/45 (58%)	104/194 (54%)	0.798	1/12 (8%)
Cardiomyopathy gene	84/95 (88%)	37/47 (80%)	139/195 (76%)	<0.001	3/12 (30%)
Sarcomere	72/95 (76%)	30/47 (81%)	110/195 (79%)	0.006	2/12 (67%)
Arrhythmia	3/95 (3%)	3/47 (8%)	3/195 (2%)	…	0/12 (0%)
Non-sarcomere-, non-arrhythmia-cardiac	4/95 (4%)	0/47 (0%)	17/195 (12%)	…	1/12 (33%)
Genes associated with CHD	5/95 (5%)	4/47 (11%)	9/195 (6%)	…	0/12 (0%)
X-linked	3/95 (3%)	3/47 (7%)	19/195 (10%)	…	5/12 (50%)
Mitochondrial	1/95 (1%)	3/47 (7%)	15/195 (8%)	…	2/12 (20%)
Chromosomal	5/95 (5%)	3/47 (7%)	10/195 (5%)	…	0/12 (0%)
Complex genotype	2/95 (2%)	1/47 (2%)	12/195 (6%)	…	2/12 (17%)
Left ventricular systolic dysfunction	42/86 (49%)	4/18 (22%)	148/185 (80%)	<0.001	11/12 (92%)
Major adverse cardiac events	21/95 (22%)	7/47 (15%)	66/195 (34%)	<0.001	9/12 (75%)
Stroke	1/95 (1%)	1/47 (2%)	3/195 (2%)	…	1/12 (8%)
Heart failure requiring hospital admission	6/95 (6%)	3/47 (6%)	16/195 (8%)	…	5/12 (42%)
Left ventricular assist device	0/95 (0%)	0/47 (0%)	3/195 (2%)	…	1/12 (8%)
Heart transplantation	4/95 (4%)	0/47 (0%)	15/195 (8%)	…	4/12 (33%)
Sustained VT/VF or appropriate shock	3/95 (3%)	4/47 (9%)	23/195 (12%)	…	2/12 (17%)
Cardiac death	5/95 (5%)	2/47 (4%)	28/195 (14%)	…	3/12 (25%)

CHD indicates congenital heart disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NCCM, noncompaction cardiomyopathy; VT/VF, ventricular tachycardia/ventricular fibrillation.

*Two hundred and twenty-five patients could not be classified because of missing data.

†Comparing isolated NCCN, NCCM/HCM, and NCCM/DCM.

Genotype-Phenotype Correlation: Cardiomyopathy Genes

Altogether 74% of the patients had a mutation in a cardiomyopathy gene, ie, in a sarcomere-, arrhythmia-, non-sarcomere non-arrhythmia cardiomyopathy, or a CHD gene (Table 4). LV systolic dysfunction was more frequent in patients with a mutation in a sarcomere gene, or in a non-sarcomere, non-arrhythmia cardiomyopathy gene mutation than in those with a mutation in an arrhythmia gene or a gene associated with CHD ($P<0.001$). In this group of patients defects in non-sarcomere, non-arrhythmia cardiomyopathy genes were associated with an increased risk for MACE ($P=0.009$).

Genotype-Phenotype Correlations: Sarcomere Genes

In 52% (n=292) NCCM was caused by a sarcomere gene mutation, in particular in *MYH7, MYBPC3, ACTC1,* and *TTN,* representing about 43% of the published genetic causes (Figure 1). Other sarcomere mutations were reported in the 10 genes: *ACTN2, DES, LDB3, MYL2, NEBL, OBSCN, TNNC1, TNNI3, TNNT2* and *TPM1*. The *TTN* mutations were reported in adult patients. Mutation in *ACTC1* had less LV dilatation ($P<0.001$; Table 5). Among the patients with a sarcomere gene defect, the *MYBPC3* mutations were associated with increased risk for MACE. Patients with a mutation in *MYH7* or *ACTC1* had the lowest risk of MACE of all patients with a sarcomere gene defect ($P=0.001$).

Noncompaction Cardiomyopathy Subtypes

The NCCM subtypes were isolated NCCM (n=95), NCCM with HCM (n=47), NCCM with DCM (n=195) and NCCM with HCM and DCM (n=12) (Table 6). In 225 patients there were insufficient data to classify the patients to the NCCM subtypes, and these patients were excluded from this analysis. The NCCM/HCM and NCCM/DCM cardiac phenotypes were mostly reported in patients with defects in sarcomere genes ($P=0.006$). Patients with mutations in the tail of *MYH7* (starting at c.2524) were more likely to have the NCCM/DCM subtype (83%), than patients with *MYH7* mutations in the head of the gene (42%). The NCCM/DCM

Table 7. Univariate and Multivariate Binary Logistic Regression for the Prediction of Major Adverse Cardiac Events in Genetic NCCM Patients

	Univariate risk prediction		Multivariate	
			Model 5*	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male	0.87 (0.60–1.28)	0.486	0.69 (0.41–1.15)	0.154
Age at diagnosis, y	0.98 (0.97–0.99)	<0.001	0.99 (0.97–1.00)	0.010
Congenital heart disease	1.24 (0.69–2.24)	0.469		
Neuromuscular symptoms	1.92 (0.92–3.99)	0.082		
LV dilatation	2.52 (1.45–4.37)	0.001	1.39 (0.19–10.23)	0.716
LV systolic dysfunction	3.65 (2.24–5.94)	<0.001	2.71 (1.19–6.15)	0.021
Isolated NCCM	1	…	1	…
NCCM/HCM	0.62 (0.24–1.58)	0.312	0.56 (0.07–4.65)	0.560
NCCM/DCM	1.80 (1.02–3.18)	0.042	0.87 (0.10–7.36)	0.883
NCCM/HCM/DCM	10.57 (2.62–42.60)	0.001	1.66 (0.04–62.08)	0.742
MYH7	1	…	1	…
ACTC1	0.76 (0.24–2.39)	0.641	1.05 (0.29–3.82)	0.936
MYBPC3	4.50 (2.02–10.03)	0.000	4.73 (1.98–11.26)	0.000
TTN	3.02 (1.09–8.37)	0.033	3.45 (1.17–10.22)	0.025
Other sarcomere genes	1.78 (0.78–4.06)	0.170	1.76 (0.75–4.15)	0.195
Arrhythmia genes	2.88 (1.34–6.16)	0.007	3.94 (1.71–9.08)	0.001
Non-sarcomere-, non-arrhythmia-cardiomyopathy	4.48 (2.07–9.69)	0.000	4.56 (2.00–10.42)	0.000
Genes associated with CHD	1.77 (0.63–4.92)	0.277	2.52 (0.83–7.63)	0.101
X-linked	6.80 (3.12–14.83)	0.000	5.65 (2.32–13.81)	0.000
Mitochondrial	2.23 (0.94–5.31)	0.069	1.67 (0.66–4.24)	0.284
Chromosome defect	3.39 (1.41–8.13)	0.006	2.41 (0.89–6.54)	0.083
Complex genotype	2.81 (1.16 –6.83)	0.022	2.58 (1.00–6.68)	0.051

CHD indicates congenital heart disease; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LV, left ventricular; NCCM, noncompaction cardiomyopathy.
*Model 5 included: sex, age, LV dilatation, LV systolic function, and NCCM subtype.

had more often LV systolic dysfunction ($P<0.001$). The patients with NCCM/HCM had the least often LV systolic dysfunction and had the lowest risk for MACE ($P<0.001$). The NCCM/HCM/DCM phenotype occurred mostly in children ($P=0.014$) with mutations in other than cardiomyopathy genes and was associated with severe outcome ($P<0.001$).

Patient Characteristics, Genetics, and Outcome

Univariate binary logistic regression analysis including both phenotype and genetic parameters predictors for MACE are presented in Table 7. Sex was missing in 1%, age at diagnosis in 4%, LV systolic function in 38%, NCCM subtype in 38%, and LV dilatation in 43%. In Table S4 we show stepwise multivariate regression. In the final model age (OR 0.99, 95% CI 0.97–1.00) LV systolic function (OR 2.71, 95% CI 1.19–6.15) and several genes were associated with MACE. These genes include *MYBPC3* (OR 4.73, 95% CI 1.98–11.26), *TTN* (OR 3.45 95% CI 1.17–10.22), arrhythmia genes (OR 3.94 95% CI 1.71–9.08), non-sarcomere non-arrhythmia cardiomyopathy genes (OR 4.56, 95% CI 2.00–10.42), and X-linked genes (OR 5.65, 95% CI 2.32–13.81) (Table 7). Complex genotypes and chromosome defects did not remain as significant predictors for MACE after correction.

Discussion

Many reported NCCM cases were reviewed to investigate if genetic cause could predict the clinical risk profile for age at diagnosis, NCCM subtype, clinical features, risk for MACE, and LV systolic dysfunction. The collected data concerned only reported genetic NCCM patients (ie, excluded about one third of the mutation carriers, who are expected to be non-penetrant carriers [without cardiomyopathy] who were not reported).[11,14] Of the reported patients, children were more

likely to have syndromic forms of NCCM with complex genotypes, X-linked inherited conditions, mitochondrial and chromosomal defects. These forms of NCCM had high risk for severe outcome, with congenital heart defects and neuromuscular symptoms. In contrast, patients diagnosed in adulthood had significantly less severe outcome associated with autosomal dominantly inherited mutations in predominantly sarcomere genes. The correlation between genetic causes, outcome, and age at diagnosis suggests that different diagnostic approaches and clinical care may be needed for children, for instance including neurological examinations. The application of testing of large numbers of genes with next generation sequencing, allowed identification of involvement of more than 80 genes. In case that the regular genetic testing of cardiomyopathy genes is inconclusive, a genetic cause cannot be excluded, and additional testing for rare causes, like mitochondrial genes—and chromosome analysis are important subsequent diagnostics steps, in particular when the NCCM is diagnosed in a child.

Genotype-Phenotype Correlations

Mutations in genes affecting sarcomere function represented more than half of the genetic causes of genetic NCCM, in particular in adults. Mutations in *MYH7* were most prevalent, followed by mutations in *ACTC1, MYBPC3,* and *TTN* as described previously.[4,15] Patients with a mutation in the sarcomere genes had lowest risk for MACE compared with patients with other genetic causes for NCCM. Comparing the clinical features of patients with different sarcomere gene mutation showed major differences for risk of MACE; patients with a mutation in *MYBPC3 and TTN* had a much higher risk for MACE than the patients with an *MYH7* mutation. This endorses the importance of DNA testing in NCCM because the DNA diagnosis may help to predict outcome. Secondly these results show that further large studies of NCCM patients with mutations are needed to confirm and refine the identified genotype-phenotype correlations for improved patient-tailored clinical management. Extensive phenotyping of NCCM may be the next step for finding more precise genotype-phenotype correlations. Recently, NCCM has been classified into subtypes based on concurrent occurrence of dilated and/or hypertrophic LV.[16] This subdivision improves prediction of genetic defect and helps to predict LV systolic dysfunction and risk for MACE.[11,14] This review shows that isolated NCCM was associated with defects in cardiomyopathy genes.

Family History

In genetic diseases a high prevalence of familial disease is expected. In this review familial cardiomyopathy was observed in 43% of genetic NCCM. The explanation for this low rate of familial cardiomyopathy may be that patients without familial disease had a de novo mutation or large chromosome defects. Another explanation might be that family histories were differentially ascertained across studies, or that patients may not have been aware that relatives had a cardiomyopathy or relatives were diagnosed after the completion of the study. In addition, the underreporting of familial disease may be explained because relatives may be asymptomatic carriers of a cardiomyopathy mutation. Previously we observed that 48% of affected relatives who were diagnosed by family screening were asymptomatic.[11] In NCCM 37% of relatives who are carriers of a mutation in a cardiomyopathy gene are asymptomatic and ≈30% of the carriers have no signs of cardiomyopathy (non-penetrance), which is similar to the rate of asymptomatic or unaffected carriers in families with HCM.[11,17] Familial cardiomyopathy was reported more frequent in adult index patients, although it is usually easier to attain genetic and/or cardiologic testing of the parents of young cases than of patients diagnosed in adulthood. An explanation for the discrepancy of familial disease could be that X-linked NCCM and chromosomal abnormalities were more frequent in children, and detection of patients in families with X-linked inheritance depends on the number of male relatives of the mother of the patient, and therefore it may be more difficult to detect affected relatives than in families with autosomal dominant inherited forms.

Noncompaction Phenotype

NCCM is associated with many mutations in a large number of genes, leading to different defective molecular functions in cardiomyocytes. This raises the question if these defects have a common final effect on the myocardium or that different pathogenic mechanisms are involved. For now, the observed differences in clinical features, NCCM phenotype and risk profiles suggest the latter. Future expansion of genetic testing with whole genome sequencing may identify regulatory influences on gene expression explaining the phenotype. In particular because many genetic defects occur also in HCM and DCM. It is expected that also the newly developed models using induced pluripotent stem cells differentiated into cardiomyocytes can be used to investigate genetic and epigenetic modifiers explaining cardiomyopathy phenotypes.

Limitations

Most of the included studies were case reports or small case series. Therefore, the included patients were expected to have been subject to referral, selection, and publication bias. We cannot exclude overrepresentation in reporting of rare genetic causes like, for instance, mutations in *TAZ* gene in children. This

review focused only on the genetically confirmed NCCM patients, which are approximately one third of all NCCM.[4] The design of this study precludes identifying differences in prognosis between known genetic and other causes for NCCM.

Conclusions

The most frequent causes of genetic NCCM are mutations in sarcomere genes, with a relatively low risk of adverse events, occurring mostly in adults. In general, age at diagnosis and cardiac outcome were related to specific genetic causes. Rare X-linked and chromosome defects were more frequent among children with severe outcome. These observations endorsed to adjust molecular diagnostics and clinical approaches to age at presentation. The observed genotype-phenotype correlations show that DNA diagnostics for NCCM are important. Identifying the genetic cause for NCCM allows risk stratification and may help clinical management and counseling of patients and their relatives.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1

Supplemental Methods

The online literature search was conducted in March 2018. The following online databases were used 'Embase.com (Embase incl. Medline)', 'Medline EPub (OVID)' and 'Web of Science'.

Web of Science

date of coverage: 1900 to 03-2018

Search term: *TS=(((noncompaction OR "non-compaction" OR LVNC)) AND ((gene* OR genetic* OR genotype* OR genom* OR DNA* OR mutat* OR chromosom* OR deletion*)) NOT ((animal* OR mouse OR mice OR rat OR rats) NOT (human* OR patient*))) AND DT=Article*.

Embase.com

date of coverage: 1947 to 03-2018

Search term: *('ventricular noncompaction'/de OR (noncompaction OR 'non-compaction' OR LVNC):ab,ti) AND ('molecular genetic phenomena and functions'/exp OR 'genotype'/exp OR 'chromosome deletion'/exp OR 'genetics'/exp OR (gene* OR genetic* OR genotype* OR genom* OR DNA* OR mutat* OR chromosom* OR deletion*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ('Conference abstract' OR 'Editorial')/it.*

Medline EPub:

date of coverage: 1946 to 03-2018

Search term: *(Isolated Noncompaction of the Ventricular Myocardium/ OR Noncompaction of Left Ventricular Myocardium with Congenital Heart Defects.mp. OR (noncompaction OR non-compaction OR LVNC).ab,ti.) AND (exp Genetic Phenomena/ OR exp Genetics/ OR (gene* OR genetic* OR genotype* OR genom* OR DNA* OR mutat* OR chromosom* OR deletion*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (congresses OR editorial)*

Table S1. Overview of reported mutations.

Gene	Transcript	Amino acid	Base	Genomic position GRCh37 (hg19)	Number of NCCM patients	Reference	Gene group †
ACTC1	NM_005159.4	p.(Tyr93His)	c.277T>C	g.35085623A>G	1	(1)	1
ACTC1	NM_005159.4	p.(Glu101Lys)	c.301G>A	g.35085599C>T	28	(2-4)	1
ACTC1	NM_005159.4	p.(Ala21Val)	c.62C>T	g.35086948G>A	1	(5)	1
ACTC1	NM_005159.4	p.(Thr231Arg)	c.692C>G	g.35084407G>C	1	(6)	1
ACTC1	NM_005159.4	p.(Met271Val)	c.811A>G	g.35083494T>C	2	(7, 8)	1
ACTC1	NM_005159.4	p.(Ile289Thr)	c.866T>C	g.35083439A>G	4	(9)	1
ACTC1	NM_005159.4	p.(Ile329Thr)	c.986T>C	g.35083319A>G	1	(10)	1
ACTN2	NM_001278343.1	p.(Ala119Thr)	c.355G>A	g.236882307G>A	1	(11)	1
ACTN2	NM_001103.2	p.(Asp196Thrfs*14)	c.586delG	g.236891027delG	1	(8)	1
ACTN2	NM_001103.2	p.(Met228Thr)	c.683T>C	g.236894600T>C	4	(12)	1
ACTN2	NM_001103.2	p.(Trp303*)	c.909G>A	g.236902634G>A	1	(8)	1
ANK2	NM_001148.5	p.(Arg321Trp)	c.961C>T	g.88677066G>T	1	(6)	2
CASQ2	NM_001232.3	p.(His244Arg)	c.731A>G	g.116269619T>C	1	(7)	2
DES	NM_001927.3	p.(Leu398Pro)	c.1193T>C	g.220286231T>C	1	(8)	1
DES	NM_001927.3	p.(Leu408Val)	c.1222C>G	g.220286260C>G	1	(8)	1
DMD	NM_004006.2	p.(Lys1615*)	c.4843A>T	g.32398629T>A	1	(13)	4
DMD	NM_004006.2		deletion exon 49-50		1	(14)	4
DMD	NM_004006.2		duplication exon 46-48		1	(13)	4
DMD	NM_004006.2		duplication Xp21		1	(15)	4
DMPK			1200-1900 CTG expansion		1	(16)	3
DMPK			140 CTG expansion		1	(17)	3
DMPK			300 CTG expansion		1	(17)	3
DMPK			700-800 CTG expansion		1	(18)	3
DSP	NM_004415.2	p.(Gln447*)	c.1339C>T	g.7568742C>T	6	(19)	3
DSP	NM_004415.2	p.(Ile560Phe)	c.1678A>T	g.7570773A>T	1	(20)	3
DSP	NM_004415.2	p.(?)	c.3084+1G>A	g.7578796G>A	1	(8)	3
DSP	NM_004415.2	p.(Gly1737Thrfs*7)	c.5208_5209del	g.7581631_7581632del	1	(21)	3
DSP	NM_004415.2	p.(Arg2229Serfs*32)	c.6687delA	g.7584182delA	1	(8)	3

DTNA	NM_001390.4	p.(Pro121Leu)	c.362C>T	g.32374214C>T	6	(22)	3
FHL1	NM_001159702.2	p.(Cys255Ser)	c.964G>C	g.135292105G>C	1	(23)	4
FKTN	NM_001198963.1	p.(Arg179Thr)	c.536G>C	g.108366662G>C	1	(24)	3
GLA	NM_000169.2	p.(Phe113Leu)	c.339T>A	g.100658829A>T	1	(25)	4
GLA	NM_000169.2	p.(Arg220*)	c.658C>T	g.100653916G>A	1	(26)	4
HADHB		p.(?)	c.1109+243_14338-703del		1	(27)	5
HCN4	NM_005477.2	p.(Ala414Gly)	c.1241C>G	g.73624602G>C	4	(8, 28)	2
HCN4	NM_005477.2	p.(Gly480Ser)	c.1438G>A	g.73622066C>T	1	(6)	2
HCN4	NM_005477.2	p.(Gly482Arg)	c.1444G>A	g.73622060C>T	4	(29, 30)	2
HCN4	NM_005477.2	p.(Gly482Arg)	c.1444G>C	g.73622060C>G	7	(28)	2
HCN4	NM_005477.2	p.(Glu695*)	c.2083G>T	g.73616490C>A	5	(31)	2
HCN4	NM_005477.2	p.(Pro883Arg)	c.2648C>G	g.73615786G>C	1	(31)	2
HFE	NM_139011.2	p.(His63Asp)	c.77-2168C>G	g.26091179C>G	1	(32)	3
HMGCL			deletion exon 3, 4		1	(33)	5
KCNH2	NM_000238.3	p.(Asp501Asn)	c.1501G>A	g.150649569C>T	1	(34)	2
KCNH2	NM_000238.3	p.(Ala561Thr)	c.1681G>A	g.150648800C>T	1	(6)	2
KCNH2	NM_000238.3	p.(Ala561Val)	c.1682C>T	g.150648799G>A	1	(34)	2
KCNH2	NM_000238.3	p.(Thr1019Profs*38)	c.3054del	g.150644514del	1	(35)	2
KCNQ1	NM_000218.2	p.(Asp611Tyr)	c.1831G>T	g.2869033G>T	1	(36)	2
KCNQ1	NM_000218.2	p.(Ley273Phe)	c.817C>T	g.2594112C>T	3	(37)	2
LAMP2	NM_001122606.1	p.(Arg293*)	c.877C>T	g.119576505G>A	1	(38)	4
LAMP2	NM_001122606.1	p.(Ala323Cysfs*27)	c.966dup	g.119575712dup	1	(8)	4
LDB3	NM_001080116.1	p.(Val55Ile)	c.163G>A	g.88439193G>A	2	(39, 40)	1
LDB3	NM_001080116.1	p.(Asp117Asn)	c.349G>A	g.88446830G>A	3	(41, 42)	1
LMNA	NM_170707.3	p.(Val445Glu)	c.1334T>A	g.156106181T>A	1	(43)	3
LMNA	NM_170707.3	p.(?)	c.1608+5G>C	g.156107028G>C	1	(8)	3
LMNA	NM_170707.3	p.(Arg644Cys)	c.1930C>T	g.156108510C>T	4	(44, 45)	3
LMNA	NM_170707.3	p.(Arg190Trp)	c.568C>T	g.156104248C>T	1	(46)	3
LMNA	NM_170707.3	p.(Ala244Val)	c.731C>T	g.156104687C>T	1	(6)	3
MIB1	NM_020774.3	p.(Arg530*)	c.1588C>T	g.19395685C>T	6	(47)	7
MIB1	NM_020774.3	p.(Val943Phe)	c.2827G>T	g.19438554G>T	7	(8, 47)	7
MIB2	NM_080875	p.(Val984Leu)	c.2950G>C	g.1565060G>C	1	(48)	7
MIPEP	NM_005932	p.(Lys343Glu)	c.1027A>G	g.24436467T>C	1	(49)	5
MIPEP	NM_005932	p.(His512Asp)	c.1534C>G	g.24411700G>C	1	(49)	5

MIPEP	NM_005932	p.(Leu582Arg)	c.1745T>G	g.24380192A>C	1	(49)	5
MIPEP	NM_005932	p.(Leu306Phe)	c.916C>T	g.24443458G>A	1	(49)	5
MLYCD	NM_012213.2	p.(Pro6Alafs*202)	c.15dup	g.83932764dup	1	(50)	5
MLYCD	NM_012213.2	p.(Leu133Alafs*72)	c.393_400del8	g.83933142_83933149del8	1	(51)	5
MT-ATP6	NC_012920.1	p.(ATP6:Thr112Ala)	c.334A>G	m.8860A>G	11	(52)	5
MT-CO1	NC_012920.1	p.(COX1:Ile254Val)	c.760A>G	m.6663A>G	1	(52)	5
MT-CO3	NC_012920.1	p.(COX3:Ile217Thr)	c.650T>C	m.9856T>C	1	(53)	5
MTFMT	NM_139242.3	p.(Arg332*)	c.994C>T	g.65295576G>A	1	(54)	5
MTFMT	NM_139242.3	p.(Pro151Leu)	c.452C>T	g.65316100G>A	1	(54)	5
MT-ND1	NC_012920.1	p.(ND1:Ala52Thr)	c.154G>A	m.3460G>A	2	(55)	5
MT-ND1	NC_012920.1	p.(?)	c.2T>C	m.3308T>C	1	(56)	5
MT-ND1	NC_012920.1	p.(ND1:Tyr30His)	c.88T>C	m.3394T>C	1	(52)	5
MT-ND1	NC_012920.1	p.(ND1:Met31Thr)	c.92T>C	m.3398T>C	1	(52)	5
MT-ND2	NC_012920.1	p.(ND2:Thr119Ala)	c.355A>G	m.4824A>G	1	(52)	5
MT-ND2	NC_012920.1	p.(ND2:Asn150Asp)	c.448A>G	m.4917A>G	1	(52)	5
MYBPC3	NM_000256.3	p.(Gly5Arg)	c.13G>C	g.47374186C>G	1	(57)	1
MYBPC3	NM_000256.3	p.(Gly490Arg)	c.1468G>A	g.47364285C>T	3	(57)	1
MYBPC3	NM_000256.3	p.(Arg495Gln)	c.1484G>A	g.47364269C>T	1	(8)	1
MYBPC3	NM_000256.3	p.(Arg502Trp)	c.1504C>T	g.47364249G>A	4	(58, 59)	1
MYBPC3	NM_000256.3	p.(Arg502Gln)	c.1505G>A	g.47364248C>T	1	(60)	1
MYBPC3	NM_000256.3	p.(Glu611Lys)	c.1831G>A	g.47362755C>T	1	(8)	1
MYBPC3	NM_000256.3	p.(Gly758Asp)	c.2273G>A	g.47360106C>T	1	(6)	1
MYBPC3	NM_000256.3	p.(Trp792Valfs*41)	c.2373dup	g.47359281dup	9	(7, 8, 61, 62)	1
MYBPC3	NM_000256.3	p.(Arg820Trp)	c.2458C>T	g.47359086G>A	2	(63)	1
MYBPC3	NM_000256.3	p.(Pro873Leu)	c.2618C>T	g.47357547G>A	1	(57)	1
MYBPC3	NM_000256.3	p.(Arg943*)	c.2827C>T	g.47356671G>A	4	(8, 61)	1
MYBPC3	NM_000256.3	p.(Pro955Argfs*95)	c.2864_2865del	g.47356633_47356634del	1	(57)	1
MYBPC3	NM_000256.3	p.(Arg1116Ser)	c.3346C>A	g.47354509G>T	1	(8)	1
MYBPC3	NM_000256.3	p.(Glu258Lys)	c.772G>A	g.47369975C>T	1	(8)	1
MYBPC3	NM_000256.3	p.(Gly263*)	c.787G>T	g.47369442C>A	2	(64)	1
MYBPC3	NM_000256.3	p.(Ser311*)	c.932C>A	g.47367916G>T	2	(8)	1
MYBPC3	NM_000256.2	p.(Lys505del)	c.1513_1515del	g.47364238_47364240del	1	(65)	1
MYBPC3	NM_000256.3	p.(Gly148Arg)	c.442G>C	g.47371628C>G	2	(7, 8)	1
MYBPC3	NM_000256.3	p.(Tyr1136*)	c.3408C>A	g.47354447G>T	1	(62)	1

MYBPC3	NM_000256.3	p.(Gln1259Argfs*72)	c.3776delA	g.47353661delT	1	(66)	1
MYH7	NM_000257.3	p.(Tyr350Asp)	c.1048T>G	g.23899074A>C	1	(67)	1
MYH7	NM_000257.3	p.(Met362Arg)	c.1085T>G	g.23899037A>C	2	(6, 68)	1
MYH7	NM_000257.3	p.(Arg369Gln)	c.1106G>A	g.23899016C>T	3	(8, 10, 66)	1
MYH7	NM_000257.3	p.(Leu390Pro)	c.1169T>C	g.23898526A>G	1	(67)	1
MYH7	NM_000257.3	p.(Arg403Gln)	c.1208G>A	g.23898487C>T	1	(69)	1
MYH7	NM_000257.3	p.(Arg403Pro)	c.1208G>C	g.23898487C>G	1	(8)	1
MYH7	NM_000257.3	p.(Met439Arg)	c.1316T>G	g.23898255A>C	1	(70)	1
MYH7	NM_000257.3	p.(Arg442His)	c.1325G>A	g.23898246C>T	1	(8)	1
MYH7	NM_000257.3	p.(Glu448Lys)	c.1342G>A	g.23898229C>T	1	(6)	1
MYH7	NM_000257.3	p.(Gln498Glu)	c.1492C>G	g.23897795G>C	2	(71)	1
MYH7	NM_000257.3	p.(Met531Arg)	c.1592T>G	g.23897090A>C	1	(72)	1
MYH7	NM_000257.3	p.(Lys542Thr)	c.1625A>C	g.23897057T>G	1	(73)	1
MYH7	NM_000257.3	p.(Lys542Asn)	c.1626G>T	g.23897056C>A	1	(6)	1
MYH7	NM_000257.3	p.(Leu620Pro)	c.1859T>C	g.23896823A>G	2	(6, 64)	1
MYH7	NM_000257.3	p.(Lys637Glu)	c.1909A>G	g.23896496T>C	1	(74)	1
MYH7	NM_000257.3	p.(Lys639Glu)	c.1915A>G	g.23896490T>C	1	(8)	1
MYH7	NM_000257.3	p.(Leu658Val)	c.1972C>G	g.23896058G>C	1	(7)	1
MYH7	NM_000257.3	p.(Arg671Glnfs*6)	c.2010_2031	g.23895997_23896018del	1	(75)	1
MYH7	NM_000257.3	p.(Glu677Val)	c.2030A>T	g.23896000T>A	1	(6)	1
MYH7	NM_000257.3	p.(Leu693Arg)	c.2078T>G	g.23895257A>C	1	(6)	1
MYH7	NM_000257.3	p.(Arg712His)	c.2135G>A	g.23895200C>T	1	(6)	1
MYH7	NM_000257.3	p.(Gly716Arg)	c.2146G>C	g.23895189C>G	1	(76)	1
MYH7	NM_000257.3	p.(Arg719Trp)	c.2155C>T	g.23895180G>A	1	(77)	1
MYH7	NM_000257.3	p.(Ile818Asn)	c.2453T>A	g.23894204A>T	2	(7)	1
MYH7	NM_000257.3	p.(Asp89Gly)	c.266A>G	g.23902372T>C	1	(8)	1
MYH7	NM_000257.3	p.(Ala893Val)	c.2678C>T	g.23893979G>A	1	(8)	1
MYH7	NM_000257.3	p.(Arg904Cys)	c.2710C>T	g.23893328G>A	2	(6, 8)	1
MYH7	NM_000257.3	p.(Cys905Arg)	c.2713T>C	g.23893325A>G	1	(8)	1
MYH7	NM_000257.3	p.(Glu929Lys)	c.2785G>A	g.23893253C>T	1	(10)	1
MYH7	NM_000257.3	p.(Arg941Cys)	c.2821C>T	g.23893217G>A	1	(6)	1
MYH7	NM_000257.3	p.(?)	c.3100-2A>C	g.23891536T>G	1	(8)	1
MYH7	NM_000257.3	p.(Leu1038Pro)	c.3113T>C	g.23891521A>G	2	(8)	1
MYH7	NM_000257.3	p.(1220delGlu)	c.3658_3660del	g.23889120_23889122del	1	(67)	1

MYH7	NM_000257.3	p.(Arg1250Trp)	c.3748C>T	g.23888797G>A	1	(66)	1
MYH7	NM_000257.3	p.(Glu1350del)	c.4048_4050del	g.23887538_23887540del	1	(7)	1
MYH7	NM_000257.3	p.(Arg1359Cys)	c.4075C>T	g.23887513G>A	2	(3, 8)	1
MYH7	NM_000257.3	p.(Tyr1375*)	c.4125T>A	g.23887463A>T	1	(8)	1
MYH7	NM_000257.3	p.(Val139Leu)	c.415G>T	g.23901935C>A	1	(8)	1
MYH7	NM_000257.3	p.(Lys1459Asn)	c.4377G>T	g.23886504C>A	2	(64)	1
MYH7	NM_000257.3	p.(Tyr1488Cys)	c.4463A>G	g.23886418T>C	1	(7)	1
MYH7	NM_000257.3	p.(Phe155del)	c.464_466delTCT	g.23901884_23901886delAGA	1	(10)	1
MYH7	NM_000257.3	p.(Met165Ile)	c.495G>A	g.23901855C>T	1	(8)	1
MYH7	NM_000257.3	p.(Ala1766Thr)	c.5296G>A	g.23884467C>T	1	(3)	1
MYH7	NM_000257.3	p.(Leu1793Pro)	c.5378T>C	g.23884385A>G	1	(78)	1
MYH7	NM_000257.3	p.(Glu1801Lys)	c.5401G>A	g.23884362C>T	5	(6, 79)	1
MYH7	NM_000257.3	p.(Glu1856Lys)	c.5566G>A	g.23883305C>T	1	(80)	1
MYH7	NM_000257.3	p.(Glu1914Lys)	c.5740G>A	g.23883018C>T	1	(6)	1
MYH7	NM_000257.3	p.(Asn1918Lys)	c.5754C>A	g.23883004G>T	4	(7)	1
MYH7	NM_000257.3	p.(Asn1918Lys)	c.5754C>G	g.23883004G>C	6	(8)	1
MYH7	NM_000257.3	p.(Asn1918Lys)	c.5754T>A	g.23883004A>T	4	(67)	1
MYH7	NM_000257.3	p.(Arg1925Gly)	c.5773C>G	g.23882985G>C	3	(8)	1
MYH7	NM_000257.3	p.(Ala223Val)	c.668C>T	g.23900858G>A	1	(6)	1
MYH7	NM_000257.3	p.(Arg23Trp)	c.67C>T	g.23902875G>A	1	(6)	1
MYH7	NM_000257.3	p.(Phe230Ser)	c.689T>C	g.23900837A>G	3	(6, 8)	1
MYH7	NM_000257.3	p.(Asp239del)	c.715_717delGAC	g.23900809_23900811del	2	(3, 8)	1
MYH7	NM_000257.3	p.(Arg243His)	c.728G>A	g.23900798C>T	4	(3, 8)	1
MYH7	NM_000257.3	p.(?)	c.732+1G>A	g.23900793C>T	6	(8, 81, 82)	1
MYH7	NM_000257.3	p.(Arg249Gly)	c.745C>G	g.23900678G>C	1	(10)	1
MYH7	NM_000257.3	p.(Phe252Leu)	c.754T>C	g.23900669A>G	1	(3)	1
MYH7	NM_000257.3	p.(Tyr266*)	c.798T>A	g.23900207A>T	2	(7, 8)	1
MYH7	NM_000257.3	p.(?)	c.818+1G>A	g.23900186C>T	9	(3)	1
MYH7	NM_000257.3	p.(?)	c.818+3G>C	g.23900184C>G	2	(3)	1
MYH7	NM_000257.3	p.(Arg281Thr)	c.842G>C	g.23900163C>G	9	(83)	1
MYH7	NM_000257.3	p.(Tyr283Asp)	c.847T>G	g.23900158A>C	7	(8, 67)	1
MYH7	NM_000257.3	p.(?)	c.896-1G>A	g.23899873C>T	1	(6)	1
MYH7	NM_000257.3	p.(Leu301Gln)	c.902T>A	g.23899866A>T	4	(8, 84)	1
MYH7	NM_000257.3	p.(Gln315Arg)	c.944A>G	g.23899824T>C	1	(6)	1

MYH7	NM_000257.3	p.(Ala326Pro)	c.976G>C	g.23899792C>G	1	(8)	1
MYH7	NM_000257.3	p.(Asp545Asn)	c.1633G>A	g.23897049C>T	7	(8, 84)	1
MYH7	NM_000257.3	p.(Asp955Asn)	c.2863G>A	g.23893175C>T	2	(8)	1
MYL2	NM_000432.3	p.(Glu88Lys)	c.262G>A	g.111352002C>T	1	(6)	1
MYL2	NM_000432.3	p.(Pro144Leufs*3)	c.431del	g.111348951del	1	(6)	1
MYL2	NM_000432.3	p.(?)	c.403-1G>C	g.111348980C>G	1	(8)	1
NEBL	NM_006393.2	p.(Pro916Leu)	c.2747C>T	g.21097453G>A	1	(85)	1
NKX2.5	NM_004387.3	p.(Ala172Argfs*5)	c.513_514insCG	g.172660033_172660034insCG	1	(86)	7
NKX2.5	NM_004387.3	p.(Lys183Asn)	c.549G>T	g.172659998C>A	2	(87)	7
NOTCH1	NM_017617.3	p.(Arg1263Cys)	c.3787C>T	g.139401282G>A	1	(8)	7
NSD1	NM_022455.4	p.(Tyr869Phefs*5)	c.2604-2605dupTT	g.176635399dupTT	1	(88)	7
NSD1	NM_022455.4	p.(Ala2074Serfs*39)	c.6218_6219insG	g.176715886_176715887insG	1	(88)	7
OBSCN	NM_001271223.2:	p.(Thr7266Argfs*53)	c.21796_23833del	g.228552765_228559441del	1	(89)	1
OBSCN	NM_001271223.2	p.(Ser7947Profs*82)	c.23839del	g.228559447del	1	(89)	1
OBSCN	NM_001271223.2	p.(?)	c.25367-1G>C	g.228562285G>C	1	(89)	1
PKP2			deletion: 32,936,266_33,056,189		1	(90)	3
PLEC	NM_201382.1	p.(Arg2351*)	c.6970C>T	g.144997127G>A	1	(91)	3
PLEKHM2	NM_015164.2	p.(Lys645Alafs*12)	c.1932_1933del	g.16055174_16055175del	2	(92)	3
PLN	NM_002667.3	p.(Arg9Cys)	c.25C>T	g.118880109C>T	1	(8)	3
PLN	NM_002667.3	p.(Arg14del)	c.40_42del	g.118880124_118880126del	1	(8)	3
PRDM16	NM_022114.3	p.(Lys702*)	c.2104A>T	g.3328865A>T	1	(93)	3
PRDM16	NM_022114.3	p.(Arg950*)	c.2848C>T	g.3334548C>T	1	(8)	3
PRDM16	NM_022114.3	p.(Asn19Ilefs*114)	c.56delA	g.3102707delA	1	(8)	3
PRDM16	NM_022114.3	p.(?)	c.676+1G>A	g.3313158G>A	1	(8)	3
PTPN11	NM_002834.	p.(Met504Val)	c.1510A>G	g.112926890A>G	1	(94)	7
PTPN11	NM_002834.3	p.(Asn58Lys)	c.174C>A	g.112888158C>A	1	(94)	7
PTPN11	NM_002834.3	p.(Tyr279Cys)	c.836A>G	g.112910827A>G	1	(95)	7
RBM20	NM_001134363.1	p.(Arg634Trp)	c.1900C>T	g.112572055C>T	1	(8)	3
RBM20	NM_001134363.1	p.(Arg634Leu)	c.1901G>T	g.112572056G>T	2	(96)	3
RPS6KA3	NM_004586.2	p.(?)	c.1000-2A>G	g.20194472T>C	1	(97)	4
RYR2	NM_001035.2	p.(Ile4855Met)	c.14565T>G	g.237982467T>G	2	(98)	2
RYR2	NM_001035.2	p.(?)	c.169-198_273+823del	g.237493980_237495105del	2	(8, 99)	2
RYR2	NM_001035.2		deletion 698bp, exon 3		1	(100)	2
RYR2	NM_001035.2		deletion exon 3		7	(101)	2

SCN5A	NM_198056.2	p.(Pro1090Leu)	c.3269C>T	g.38620946G>A	2	(102)	2
SCN5A	NM_198056.2	p.(Gly1262Ser)	c.3784G>A	g.38607956C>T	1	(8)	2
SCN5A	NM_198056.2	p.(Pro1332Pro)	c.3996G>A	g.38601887C>T	1	(102)	2
SCN5A	NM_198056.2	p.(Ile1660Val)	c.4978A>G	g.38592885T>C	1	(8)	2
SCN5A	NM_198056.2	p.(?)	c.1141-3C>A	g.38647642G>T	3	(102)	2
SDHA	NM_004168.2	p.(Gly555Glu)	c.1664G>A	g.251453G>A	7	(103)	5
SDHD	NM_003002.3	p.(Asp92Gly)	c.275A>G	g.111959696A>G	1	(104)	5
SGCD	NM_001128209.1	p.(Asn99His)	c.295A>C	g.156016244A>C	**1**	(6)	3
TAZ	NM_000116.3	p.(?)	c.109+1G>C	g.153640290G>C	3	(6, 105)	4
TAZ	NM_000116.3	p.(Thr43Pro)	c.127A>C	g.153640440A>C	1	(106)	4
TAZ	NM_000116.3	p.(His45Profs*38)	c.134_136delinsCC	g.153640447_153640449delinsCC	1	(107)	4
TAZ	NM_000116.3	p.(Tyr51*)	c.153C>G	g.153640466C>G	1	(108)	4
TAZ	NM_000116.3	p.(Leu53Profs*81)	c.157dup	g.153640470dup	1	(40)	4
TAZ	NM_000116.3	p.(Arg85Profs*49)	c.253dup	g.153641558dup	1	(109)	4
TAZ	NM_000116.3	p.(Cys118Arg)	c.352T>C	g.153641886T>C	1	(110)	4
TAZ	NM_000116.3	p.(Arg123*)	c.367C>T	g.153641901C>T	1	(107)	4
TAZ	NM_000116.3	p.(Phe128Ser)	c.383T>C	g.153642450T>C	1	(7, 111)	4
TAZ	NM_000116.3	p.(Gln159Pro)	c.476A>C	g.153647897A>C	1	(6)	4
TAZ	NM_000116.3	p.(Leu169Phe)	c.505C>T	g.153647926C>T	1	(6)	4
TAZ	NM_000116.3	p.(His176Arg)	c.527A>G	g.153647948A>G	1	(107)	4
TAZ	NM_000116.3	p.(Met185Val)	c.553A>G	g.153648055A>G	1	(6)	4
TAZ	NM_000116.3	p.(?)	c.583+5G>A	g.153648090G>A	1	(112)	4
TAZ	NM_000116.3	p.(Gly195*)	c.583G>T	g.153648085G>T	1	(113)	4
TAZ	NM_000116.3	p.(Gly197Arg)	c.589G>C	g.153648376G>C	1	(6)	4
TAZ	NM_000116.3	p.(Gly216Arg)	c.646G>A	g.153648433G>A	2	(8, 114)	4
TAZ	NM_000116.3	p.(Val237Alafs*73)	c.710_711delTG	g.153649007_153649008delTG	1	(107)	4
TAZ	NM_000116.3	p.(?)	c.777+2T>A	g.153649076T>A	3	(22, 110, 115)	4
TAZ	NM_000116.3	p.(Thr237Lys)	c.800C>A	g.153649264C>A	3	(116)	4
TAZ	NM_000116.3	p.(Arg292Aspfs*47)	c.873delG	g.153649337delG	1	(117)	4
TAZ	NM_000116.3	p.(?)	c.647-1G>C	g.153648550G>C	2	(40, 118)	4
TAZ			deletion exon 1-5		1	(119)	4
TBX20	NM_001077653.2	p.(Thr262Met)	c.785C>T	g.35280519G>A	1	(120)	7
TBX20	NM_001077653.2	p.(Tyr317*)	c.951C>A	g.35244134G>T	3	(120)	7
TBX5	NM_000192.3	p.(Arg279*)	c.835C>T	g.114804117G>A	1	(6)	7

TMEM70	NM_017866.5	p.(?)	c.317-2A>G	g.74893388A>G	1	(121)	5
TNNC1	NM_003280.2	p.(Gln50Arg)	c.149A>G	g.52486175T>C	1	(8)	1
TNNC1	NM_003280.2	p.(Glu94Ala)	c.281A>C	g.52485796T>G	1	(6)	1
TNNI3	NM_000363.4	p.(Arg162Trp)	c.484C>T	g.55665463G>A	1	(122)	1
TNNT2	NM_001001430.1	p.(Pro87Leu)	c.230C>T	g.201334772G>A	1	(7)	1
TNNT2	NM_001001430.1	p.(Arg92Gln)	c.245G>A	g.201334757C>T	1	(123)	1
TNNT2	NM_001001430.1	p.(Arg102Gln)	c.275G>A	g.201334425C>T	1	(10)	1
TNNT2	NM_001001430.1	p.(Glu96Lys)	c.286G>A	g.201334414C>T	3	(124)	1
TNNT2	NM_001001430.1	p.(Arg131Trp)	c.391C>T	g.201333494G>A	1	(3)	1
TNNT2	NM_001001430.1	p.(Lys210del)	c.629_631delAGA	g.201331099_201331101delTCT	1	(8)	1
TNNT2	NM_001001430.1	p.(Lys217del)	c.649_651del	g.201331079_201331081del	1	(125)	1
TNNT2	NM_001001430.1	p.(Glu39Lys)	c.85G>A	g.201337338C>T	1	(126)	1
TPM1	NM_001018005.1	p.(Lys37Glu)	c.109A>G	g.63335137A>G	3	(127)	1
TPM1	NM_001018005.1	p.(Asp84Asn)	c.250G>A	g.63349193G>A	3	(8, 128)	1
TPM1	NM_001018005.1	p.(Leu113Val)	c.337C>G	g.63349280C>G	4	(129)	1
TPM1	NM_001018005.1	p.(Asp159Asn)	c.475G>A	g.63351862G>A	1	(130)	1
TPM1	NM_001018005.1	p.(Arg160His)	c.479G>A	g.63351866G>A	1	(7)	1
TPM1	NM_001018005.1	p.(Glu192Lys)	c.574G>A	g.63353922G>A	1	(57)	1
TPM1	NM_001018005.1	p.(Arg238Gln)	c.713G>A	g.63354785G>A	1	(6)	1
TPM1	NM_001018005.1	p.(Lys248Glu)	c.742A>G	g.63354814A>G	3	(57)	1
TTN	NM_001267550.1	p.(Arg34807Serfs*8)	c.104421_104425del5	g.179396917_179396921del5	1	(8)	1
TTN	NM_133432.3	p.(Tyr6844*)	c.20532T>G	g.179482726A>C	1	(8)	1
TTN	NM_133432.3	p.(Arg12399*)	c.37195A>T	g.179451923T>A	1	(8)	1
TTN	NM_133432.3	p.(Arg14928*)	c.44782C>T	g.179439257G>A	1	(8)	1
TTN	NM_001267550.1	p.(Trp1528*)	c.4583G>A	g.179642209C>T	1	(8)	1
TTN	NM_001267550.1	p.(?)	c.48313-1G>A	g.179480516C>T	1	(8)	1
TTN	NM_001267550.1	p.(Ala178Asp)	c.533C>A	g.179665172G>T	5	(131)	1
TTN	NM_001267550.1	p.(Pro17886*)	c.53656_53663del8	g.179470359_179470366del8	1	(8)	1
TTN	NM_001267550.1	p.(Glu23066Glyfs*8)	c.69192dupC	g.179441870dupG	1	(8)	1
TTN	NM_133432.3	p.(Pro23065Alafs*11)	c.69192dupC	g.179408944dupG	1	(8)	1
TTN	NM_001267550.1	p.(Tyr24889*)	c.74666dupA	g.179436193dupT	1	(8)	1
TTN	NM_001267550.1	p.(Lys25752Valfs*18)	c.77254_77255delAA	g.179433604_179433605delTT	1	(8)	1
TTN	NM_001267550.1	p.(Val26839Leufs*5)	c.80514delA	g.179430345delT	1	(8)	1
TTN	NM_001267550.1	p.(Asn27438Argfs*2)	c.82309_82312dup4	g.179428547_179428550dup4	1	(8)	1

TTN	NM_001267550.1	p.(Tyr2951*)	c.8853C>A	g.179634455G>T	1	(8)	1
TTN	NM_001267550.1	p.(Pro29722Hisfs*20)	c.89165delC	g.179418673delG	1	(8)	1
TTN	NM_001267550.1	p.(Arg31606*)	c.94816C>T	g.179411339G>A	1	(8)	1
TTN	NM_001267550.1	p.(Glu2989Glufs*4)	c.9389G>C	g.179632568C>G	1	(132)	1
VARS2	NM_001167734.1	p.(Arg201Trp)	c.601C>T	g.30883762C>T	1	(133)	5

Table S2. Overview of reported complex genotypes.

Gene	Transcript	Amino acid	Base	Genomic position GRCh37 (hg19)	(n) NCCM patients	Reference
ABCC9	NM_020298.2	p.(Met1198Ile)	c.3486G>A	g.21981967C>T	1	(134)
TTN	NM_001256850.1	p.(Arg3120Gln)	c.93319C>T	g.179404550G>A		
ACTC1	NM_005159.4	p.(Ala21Val)	c.62C>T	g.35086948G>A	2	(5)
TTN	NM_001267550.1	p.(Thr9376Arg)	c.28127C>G	g.179575836G>C		
ACTN2	NM_001103.2	p.(Arg192*)	c.574C>T	g.236891015C>T	1	(8)
SCN5A	NM_198056.2	p.(Tyr1434Metfs*29)	c.4299delG	g.38598722delC		
BBS2	NM_031885.3	p.(Ser433Glufs*41)	c.1296-1297insG	g.56534866_56534867insC	1	(135)
BBS2			c.865T>C			
SH3PXD2B			c.970G>A			
TTN	NM_133378.4	p.(Glu17717Lys)	c.53149G>A	g.179455599C>T		
TTN	NM_001267550.1	p.(Ile14909Lys)	c.71345T>A	g.179439514A>T		
TTN			c.52151A>G			
CACNA2D1	NM_000722.2	p.(Arg652Argfs*3)	c.1956-13_1956-12delTT	g.81603880_81603881delAA	1	(136)
RANGRF	NM_016492.4	p.(Pro155Ser)	c.463C>T	g.8193156C>T		
CASQ2	NM_001232.3	p.(His244Arg)	c.731A>G	g.116269619T>C	1	(7)
LDB3	NM_001080116.1	p.(Lys204Arg)	c.611A>G	g.88451715A>G		
CASQ2	NM_001232.3	p.(His244Arg)	c.731A>G	g.116269619T>C	1	(7)
LDB3	NM_001080116.1	p.(Lys204Arg)	c.611A>G	g.88451715A>G		
CSRP3	NM_003476.4	p.(?)	c.*12G>A	g.19204205C>T		
DMD	NM_004006.2	p.(Ser2384Tyr)	c.7151C>A	g.31854884G>T	1	(137)
EMD	NM_000117.2	p.(Arg203His)	c.608G>A	g.153609400G>A		
HCN4	NM_005477.2	p.(Gly811Glu)	c.2432G>A	g.73616002C>T		
SCN5A	NM_198056.2	p.(Leu1988Arg)	c.5963T>G	g.38591900A>C		
HCN4	NM_005477.2	p.(Tyr481His)	c.1441T>C	g.73622063A>G	1	(8)
FKTN	NM_001079802.1	p.(Tyr371Cys)	c.1112A>G	g.108382282A>G		
HCN4	NM_005477.2	p.(Gly482Arg)	c.1444G>A	g.73622060C>T	3	(31)
CSRP3	NM_003476.4	p.(Trp4Arg)	c.10T>C	g.19213986A>G		
JUP	NM_021991.2	p.(Glu146Lys)	c.436G>A	g.39925702C>T	1	(6)
MYH7	NM_000257.3	p.(Lys542Asn)	c.1626G>T	g.23897056C>A		
KCNE3	NM_005472.4	p.(Arg99His)	c.296G>A	g.74168313C>T	1	(6)
TAZ	NM_000116.3	p.(His176Tyr)	c.526C>T	g.153647947C>T		
LMX1B			17-bp deletion exon 5		1	(138)
MT-TL1			m.3243A>G			
MYBPC3	NM_000256.3	p.(Ala216Thr)	c.646G>A	g.47371333C>T	1	(7)
ACTC1	NM_005159.4	p.(?)	c.*22C>T	g.35082591G>A		
MYBPC3	NM_000256.3	p.(Ser236Gly)	c.706A>G	g.47370041T>C	1	(139)
MYH6	NM_002471.3	p.(Arg860His)	c.2579G>A	g.23863383C>T		
TNNC1	NM_003280.2	p.(Asp88Asn)	c.262G>A	g.52485815C>T		
MYBPC3			5Mb deletion 11p11; 46,497,427 – 51,550,787			
MYH7	NM_000257.3	p.(Glu700Glnfs*37)	c.2081_2093dup	g.23895242_23895254dup	1	(8)
SCN5A	NM_001099404.1	p.(Gly579Arg)	c.1735G>A	g.38645358C>T		
MYH7	NM_000257.3	p.(Pro838Leu)	c.2513C>T	g.23894144G>A	1	(6)
BMPR1A	NM_004329.2	p.(Arg284Leu)	c.851G>T	g.88677066G>T		
MYH7B	NM_020884.3	p.(Arg890Cys)	c.2668C>T	g.33582046C>T	1	(140)

ITGA7	NM_002206.2	p.(Glu882Lys)	c.2644G>A	g.56086993C>T		
NONO	NM_001145408.1	p.(?)	c.1171+1G>T	g.70518359G>T	1	(141)
DSP	NM_004415.2	p.(Arg1302Cys)	c.3904C>T	g.7580327C>T		
MYPN	NM_032578.2	p.(?)	c.2926-2146C>T	g.69951974C>T		
MYLK2	NM_033118.3	p.(Tyr500Cys)	c.1499A>G	g.30419580A>G		
NONO			deletion exon 1-3		1	(142)
16p11.1			220kb recurrent copy number gain			
RYR2	NM_001035.2	p.(Arg169Gln)	c.506G>A	g.237540665G>A	1	(143)
CASQ2	NM_001232.3	p.(Asp398del)	c.1194_1196delTGA	g.116243866_116243868delTCA		
TTN	NM_133379.3	p.(Lys4455Arg)	c.13364A>G	g.179613763T>C		
SGCD	NM_001128209.1	p.(Asn99His)	c.295A>C	g.156016244A>C	1	(6)
TPM1	NM_001018005.1	p.(Asp14Gly)	c.41A>G	g.63335069A>G		
TAZ	NM_000116.3	p.(Phe128Ser)	c.383T>C	g.153642450T>C	1	(7)
LMNA	NM_170707.3	p.(?)	c.1968+26A>G	g.156108574A>G		
TAZ	NM_000116.3	p.(Glu202Valfs*15)	c.605_608del	g.153648392_153648395del	1	(144)
LDB3	NM_007078	p.(Thr350Ile)	c.1049C>T	g.86706683C>T		
TNNI3	NM_000363.4	p.(Asp180Gly)	c.539A>G	g.55665408T>C	1	(7)
TPM1	NM_001018005.1	p.(?)	c.241-12_241-11delinsTG	g.63349172_63349173delinsTG		
TNNT2	NM_001001430.1	p.(Pro87Leu)	c.230C>T	g.201334772G>A	1	(7)
LDB3	NM_001080116.1	p.(Asp117Asn)	c.349G>A	g.88446830G>A		
TNNT2	NM_001001430.1	p.(Arg161His)	c.452G>A	g.201333433C>T	1	(7)
TNNT2	NM_000364.2	p.(Val225Leu)	c.673G>C	g.201331078C>G		
CASQ2	NM_001232.3	p.(His244Arg)	c.731A>G	g.116269619T>C		
TTN	NM_001267550.1	p.(Glu1487*)	c.4459G>T	g.179642452C>A	1	(8)
MIB1	NM_020774.3	p.(Arg901*)	c.2701C>T	g.19437126C>T		
TTN	NM_133432.3	p.(Lys17258Ilefs*16)	c.51773_51774del	g.179432265_179432266del	1	(8)
MIB1	NM_020774.3	p.(Leu366Argfs*2)	c.1096_1097del	g.19378048_19378049del		
TTN	NM_001267550.1	p.(Gly2656Alafs*6)	c.7967delG	g.179636087delC	1	(8)
MIB1	NM_020774.3	p.(Glu864Valfs*31)	c.2589_2590dupTG	g.19433103_19433104dupTG		

Table S3. Chromosomal defects in NCCM.

Locus	Chromosome defect	(n) NCCM patients	Reference
16p11.2	244kb deletion 16p11.2; 28,807,417–29,051,191	1	(145)
1p36	1.51Mb deletion 1p36; 1,906,449–3,419,622	2	(146)
1p36	10.5-11.1Mb deletion; 1p36.21-p36.33	1	(147)
1p36	deletion	2	(8, 148)
1p36	3.49Mb deletion 1p36; 746,608–4,144,742	2	(149)
1p36	4.3Mb deletion; 1p36.32-1p36.33	1	(150)
1p36	4.6-5.9Mb terminal deletion	1	(151)
1p36	4.8Mb deletion; 1p36.33–1p36.32	1	(152)
1p36	5.5Mb deletion; 1p36.33-1p36.31(0-5,512,916)	1	(153)
1p36	Monosomy 1p36	1	(154)
1p36	2.5Mb deletion; 1p36.33p36.32 (834,101-3,284,340)x1	1	(155)
1q, 4q	Trisomy 4q31, monosomy 1q43; t(1;4)(q43;q31)	1	(156)
1q43	5.4Mb deletion; 46,XX,del(1q43q43)	1	(157)
22q11	22q11 deletion	1	(158)
22q11.2	22q11.2 deletion	1	(159)
22q11.21-q11.23	22q11.21-q11.23 deletion	1	(160)
5q35.1-3	5q35.1-3 deletion	1	(161)
5q35.2-5q35.3	6.56Mb interstitial gain 173,897,858-180,456,069; tetrasomy 5q35.2-5q35.3	1	(162)
7p, 13q	Balanced t(12;20)(q2433;p12.2); unbalanced der(13)t(7;13)(p21.3;q33.2)	1	(163)
7q11.23	1.45Mb duplication 7q11.23; 72,662,415–74,115,258	1	(164)
8p23.1	3.3Mb deletion; 8p23.1	1	(165)
Monosomy X	Mosaic 45,X(28)/46,X,+mar(21)/47,X,+2mar(1)	1	(166)
Monosomy X	Deletion exon 1-5 TAZ; mos 46,X,r(X)(p11.22q22.3)[35]/45,X[20]	1	(167)
Trisomy 13	Trisomy 13	2	(168)
Trisomy 18	Trisomy 18	1	(169)
Trisomy 21	Trisomy 21	1	(170)
Trisomy 22	47,XX,+22[16]/46,XX[5]	1	(171)
Trisomy 22	47,XX,+22[6]/46,XX[11]	1	(172)

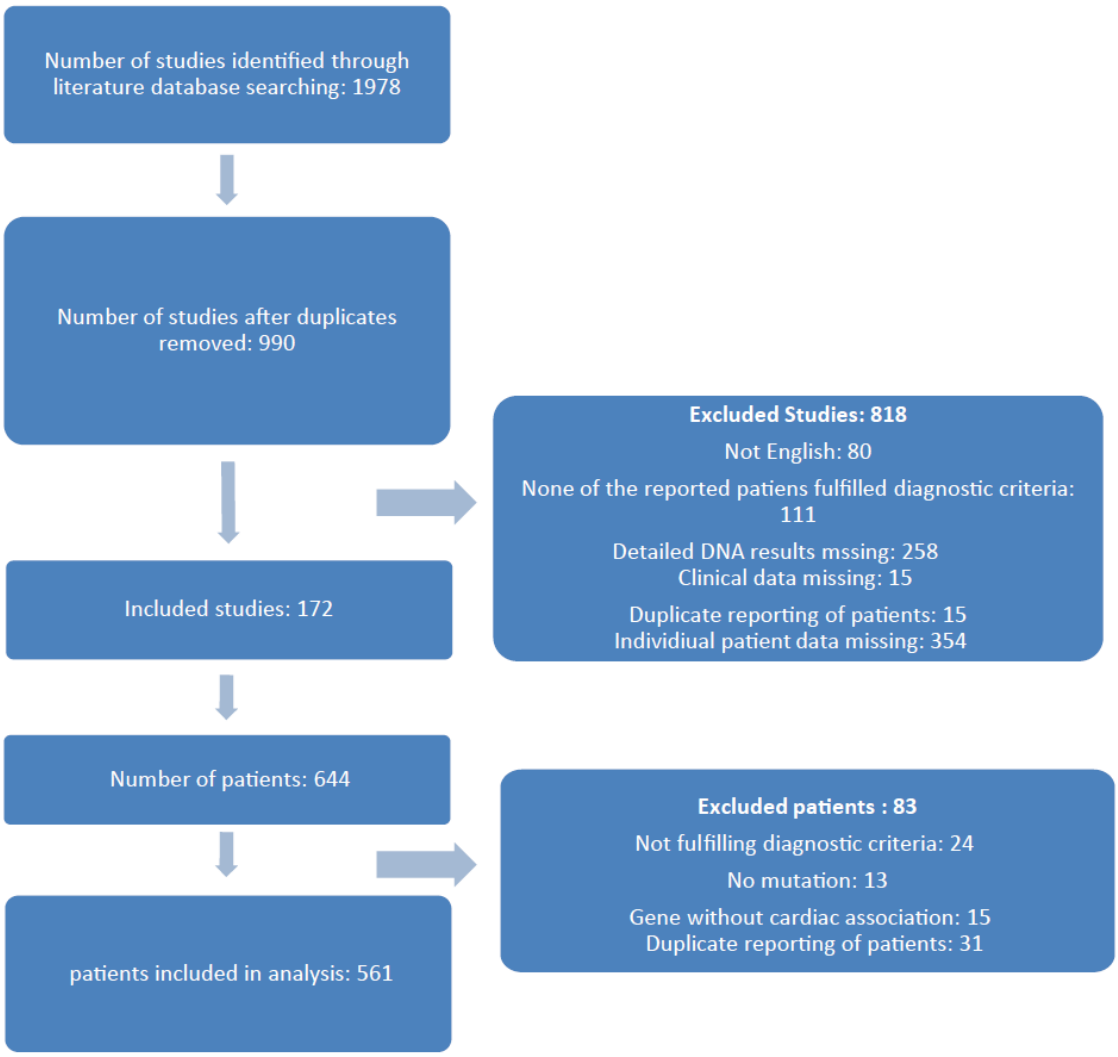
Table S4. Univariate and multivariate binary logistic regression for the prediction of major adverse cardiac events in genetic NCCM patients.

Variable	univariate		Multivariate analysis with missing data imputation									
			Model 1		Model 2		Model 3		Model 4		Model 5	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Male	0.87 (0.60-1.28)	0.486	0.74 (0.48-1.12)	0.153	0.75 (0.49-1.14)	0.175	0.71 (0.46-1.09)	0.113	0.73 (0.47-1.13)	0.158	0.69 (0.41-1.15)	0.154
Age at diagnosis in years	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	0.002	0.98 (0.97-0.99)	0.001	0.99 (0.97-1.00)	0.005	0.98 (0.97-0.99)	0.004	0.99 (0.97-1.00)	0.010
Congenital heart disease	1.24 (0.69-2.24)	0.469										
Neuromuscular symptoms	1.92 (0.92-3.99)	0.082										
LV dilatation	2.52 (1.45-4.37)	0.001			1.35 (0.82-2.22)	0.229					1.39 (0.19-10.23)	0.716
LV systolic dysfunction	3.65 (2.24-5.94)	<0.001					3.07 (1.66-5.65)	0.001			2.71 (1.19-6.15)	0.021
Isolated NCCM	1								1		1	
NCCM/HCM	0.62 (0.24-1.58)	0.312							0.63 (0.18-2.20)	0.448	0.56 (0.07-4.65)	0.560
NCCM/DCM	1.80 (1.02-3.18)	0.042							1.50 (0.62-3.61)	0.336	0.87 (0.10-7.36)	0.883
NCCM/HCM/DCM	10.57 (2.62-42.60)	0.001							2.07 (0.11-39.08)	0.568	1.66 (0.04-62.08)	0.742
MYH7	1		1		1		1		1		1	
ACTC1	0.76 (0.24-2.39)	0.641	0.77 (0.24-2.43)	0.651	0.87 (0.27-2.80)	0.812	0.96 (0.29-3.18)	0.951	0.95 (0.29-3.16)	0.939	1.05 (0.29-3.82)	0.936
MYBPC3	4.50 (2.02-10.03)	0.000	4.63 (2.06-10.44)	0.000	4.63 (2.05-10.46)	0.000	4.83 (2.08-11.23)	0.000	4.82 (2.08-11.18)	0.000	4.73 (1.98-11.26)	0.000
TTN	3.02 (1.09-8.37)	0.033	4.24 (1.48-12.15)	0.007	4.13 (1.44-11.83)	0.008	3.73 (1.28-10.87)	0.016	3.71 (1.26-10.92)	0.017	3.45 (1.17-10.22)	0.025
Other sarcomere genes	1.78 (0.78-4.06)	0.170	1.79 (0.78-4.12)	0.172	1.79 (0.78-4.15)	0.171	1.82 (0.78-4.28)	0.168	1.73 (0.74-4.04)	0.203	1.76 (0.75-4.15)	0.195
Arrhythmia genes	2.88 (1.34-6.16)	0.007	2.63 (1.21-5.71)	0.015	2.63 (1.22-5.71)	0.014	3.72 (1.63-8.49)	0.002	2.99 (1.30-6.88)	0.010	3.94 (1.71-9.08)	0.001
Non-sarcomere cardiomyopathy genes	4.48 (2.07-9.69)	0.000	4.72 (2.16-10.33)	0.000	4.58 (2.09-10.04)	0.000	4.71 (2.11-10.52)	0.000	4.52 (2.03-10.04)	0.000	4.56 (2.00-10.42)	0.000
Genes associated with CHD	1.77 (0.63-4.92)	0.277	1.83 (0.65-5.16)	0.252	1.83 (0.65-5.17)	0.256	2.47 (0.84-7.30)	0.101	1.93 (0.68-5.50)	0.220	2.52 (0.83-7.63)	0.101
X-linked	6.80 (3.12-14.83)	0.000	6.35 (2.82-14.30)	0.000	5.86 (2.58-13.28)	0.000	6.26 (2.70-14.48)	0.000	5.84 (2.42-14.09)	0.000	5.65 (2.32-13.81)	0.000
Mitochondrial	2.23 (0.94-5.31)	0.069	1.82 (0.75-4.42)	0.187	1.72 (0.70-4.20)	0.234	1.77 (0.71-4.40)	0.223	1.73 (0.68-4.38)	0.248	1.67 (0.66-4.24)	0.284
Chromosome defect	3.39 (1.41-8.13)	0.006	2.21 (0.89-5.49)	0.088	2.19 (0.88-5.46)	0.093	2.45 (0.94-6.37)	0.065	2.36 (0.94-5.91)	0.068	2.41 (0.89-6.54)	0.083
Complex genotype	2.81 (1.16 -6.83)	0.022	2.79 (1.13-6.85)	0.026	2.66 (1.08-6.56)	0.034	2.78 (1.11-6.99)	0.030	2.56 (1.00-6.54)	0.049	2.58 (1.00-6.68)	0.051

Multivariate analysis with missing data imputation, model 1: sex and age, model 2: sex, age and LV dilatation, model 3: sex, age and LV systolic dysfunction,

model 4: sex, age and NCCM subtype, model 5: sex, age, LV dilatation, LV systolic function and NCCM subtype

Figure S1. Flowchart of study selection and patient inclusion.



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