Clinical Characteristics and Long-Term Outcome of Hypertrophic Cardiomyopathy in Individuals With a MYBPC3 (Myosin-Binding Protein C) Founder Mutation

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Background—*MYBPC3* (Myosin-binding protein C) founder mutations account for 35% of hypertrophic cardiomyopathy (HCM) cases in the Netherlands. We compared clinical characteristics and outcome of *MYBPC3* founder mutation (FG+) HCM with nonfounder genotype-positive (G+) and genotype-negative (G−) HCM.

Methods and Results—The study included 680 subjects: 271 FG+ carriers, 132 G+ probands with HCM, and 277 G− probands with HCM. FG+ carriers included 134 FG+ probands with HCM, 54 FG+ relatives diagnosed with HCM after family screening, 74 FG+/phenotype-negative relatives, and 9 with noncompaction or dilated cardiomyopathy. The clinical phenotype of FG+ and G+ probands with HCM was similar. FG+ and G+ probands were younger with less left ventricular outflow tract obstruction than G− probands, however, had more hypertrophy, and nonsustained ventricular tachycardia. FG+ relatives with HCM had less hypertrophy, smaller left atria, and less systolic and diastolic dysfunction than FG+ probands with HCM. After 8±6 years, cardiovascular mortality in FG+ probands with HCM was similar to G+ HCM (22% versus 14%; log-rank P=0.14), but higher than G− HCM (22% versus 6%; log-rank P<0.001) and FG+ relatives with HCM (22% versus 4%; P=0.009). Cardiac events were absent in FG+/phenotype-negative relatives; subtle HCM developed in 11% during 6 years of follow-up.

Conclusions—Clinical phenotype and outcome of FG+ HCM was similar to G+ HCM but worse than G− HCM and FG+ HCM diagnosed in the context of family screening. These findings indicate the need for more intensive follow-up of FG+ and G+ HCM versus G− HCM and FG+ HCM in relatives. **(*Circ Cardiovasc Genet*. 2017;10:e001660. DOI: 10.1161/CIRCGENETICS.116.001660.)**

Key Words: cardiomyopathy, hypertrophic ■ follow-up studies ■ genotype ■ myosins ■ phenotype

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disease with an estimated prevalence of 1:500 to 1:200.[1] More than 1500 mutations in at least 11 genes have been described in association with HCM.[2] *MYBPC3* (Myosin-binding protein C) is the most frequently mutated gene, representing 30% to 40% of all HCM mutations.[2] In the Netherlands, 35% of HCM cases are caused by 3 *MYBPC3* founder mutations: c.2373dupG (p.Trp792Valfs*41), c.2827C>T (p.Arg943*), and c.2864_2865delCT (p.Pro955fs*95).[3–5] These mutations cause C-terminally truncated protein, leading to haploinsufficiency.[6–8] Pathophysiologic studies have demonstrated that these mutations are associated with a reduced force-generating capacity of cardiomyocytes, cardiomyocyte hypertrophy, and reduced myofibril density.[8,9] The clinical phenotype of *MYBPC3* founder mutation (FG+) carriers varies.[10] Information on the clinical characteristics and long-term outcome of FG+ carriers is lacking.

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The aim of this study was to compare clinical characteristics and outcome of FG+ HCM with nonfounder mutation genotype-positive (G+) HCM and genotype-negative (G−) HCM.

Methods

Study Design and Population

This retrospective cohort study included a total of 680 subjects: 271 FG+ carriers (141 FG+ probands and 130 FG+ relatives) from 127 families, 132 G+ probands with HCM, and 277 G− probands with HCM, who underwent clinical evaluation between 1985 and 2015. Probands were defined as patients with HCM, dilated cardiomyopathy (DCM), or noncompaction cardiomyopathy (NCCM), presenting with signs or symptoms. Relatives were defined as subjects who were evaluated in the context of family screening. The study conforms to the principles of the Declaration of Helsinki. All patients gave informed consent for inclusion in the registry, and local institutional review board approval was obtained.

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Genetic Analysis

All subjects underwent genetic counseling. Before 2012, Sanger sequencing of all coding intron/exon boundaries of the following genes were available: *MYBPC3*, β-myosin heavy chain, cardiac troponin C, cardiac troponin T, cardiac troponin I, cardiac-regulatory myosin light chain, cardiac-essential myosin light chain, cardiac α-actin, α-tropomyosin, cysteine- and glycine-rich protein 3, and titin-cap/telethonin. After the identification of a pathogenic mutation, genotyping was extended at the discretion of the treating physician. Since 2012, next-generation sequencing covering 48 genes is used. Because of this change in DNA analysis over time, subjects underwent either extensive genotyping (≥6 sarcomeric genes) or limited genotyping (*MYBPC3* only). Extensive genotyping was performed in 77 (57%) FG+ probands with HCM, 57 (42%) G+ probands with HCM, and 244 (88%) G− probands with HCM. Next-generation sequencing was performed in 15 (11%) FG+ probands with HCM, 30 (22%) G+ probands with HCM, and 116 (60%) G− probands with HCM. Seven of 9 (78%) individuals with non-HCM phenotypes underwent extensive genotyping. Relatives in FG+ families were tested for the familial mutation and referred for cardiac screening if the mutation was present.[11] Genetic testing before adulthood was offered in families with severe HCM in childhood, when cardiac symptoms were present, or severe anxiety among parents existed.

Cardiac Evaluation

All individuals underwent periodic cardiac evaluation, including history, clinical examination, electrocardiography, and echocardiography. Echocardiographic studies were analyzed according to the American Society of Echocardiography guidelines.[12] In probands, HCM was diagnosed when maximal wall thickness (MWT) ≥15 mm, a cutoff value of 13 mm was used in relatives.[13] DCM was diagnosed based on left ventricular (LV) dilatation and LV systolic dysfunction.[14] NCCM diagnosis was based on the Jenni criteria.[15] MWT, LV end-diastolic diameter, left atrial size, and LV outflow tract (LVOT) velocity at rest and during provocation were measured. LVOT gradient was calculated with the Bernoulli equation. Systolic LV function was assessed using the wall motion score index and described as normal, mildly reduced, moderately reduced, or poor, which corresponded with LV ejection fractions of ≥55%, 45% to 54%, 30% to 44%, and <30%, respectively, according to echocardiography guidelines.[16] Systolic dysfunction was defined as mildly reduced, moderately reduced, or poor systolic function. Diastolic LV function was described as normal, abnormal relaxation (stage I), pseudonormal (stage II), and restrictive filling (stage III).[17] Clinical disease stages were defined according to Olivotto et al[18]: (1) nonhypertrophic (MWT <13 mm), (2) classic phenotype (MWT ≥13 mm and normal systolic LV function), (3) adverse remodeling (mildly reduced systolic LV function), and (4) overt cardiac dysfunction (moderately reduced or poor systolic LV function). After cardiomyopathy diagnosis, cardiac evaluation was extended with exercise testing and 24-hour ambulatory electrocardiographic monitoring. Nonsustained ventricular tachycardia was defined as ≥3 consecutive beats at ≥120/min lasting <30 seconds.[13]

Patient Follow-Up

Follow-up data were obtained in January 2016. Follow-up was complete for 99% of patients. Patients who were lost to follow-up were censored at the time of last follow-up. Mortality was retrieved from the civil service register and cause of death from the medical chart or the general practitioner. Septal reduction therapy and implantable cardioverter defibrillator (ICD) were registered. ICDs were implanted according to the guidelines.[13,19,20] Cardiovascular mortality was defined as the combined end point of sudden cardiac death (SCD)/aborted SCD, heart failure (HF)-related death (including heart transplantation), stroke-related death, coronary artery disease–related death, and procedure-related cardiac death. SCD/aborted SCD was defined as (1) instantaneous and unexpected death in patients who were previously in a stable condition, or nocturnal death with no antecedent history of worsening symptoms; (2) resuscitation after cardiac arrest; or (3) appropriate ICD intervention for ventricular fibrillation or ventricular tachycardia >200 bpm.

Statistical Analysis

Calculations were performed using SPSS 21 (IBM, Armonk, New York) and R Statistical Software, version 3.2.4., using packages survival and lme4. Normally distributed continuous data are expressed as mean + standard deviation and non-normally distributed data as median, followed by the interquartile range (IQR; IQ1–IQ3). For comparing categorical variables, Pearson χ^2 test was used. For comparing continuous variables, Student *t* test was used and Mann–Whitney *U* test in the case of non-normally distributed data. To make comparisons between FG+ probands and FG+ relatives, generalized linear mixed models were used, with random intercepts for family to account for family relatedness. Survival curves were constructed according to the Kaplan–Meier method. Comparisons of survival and other clinical outcomes between FG+ probands with HCM and FG+ relatives with HCM were performed by using Cox models. To estimate the standard errors of the hazard ratios while taking into account family relatedness, the grouped jackknife method was used. Fisher exact test was used in case of a zero cell count in either of the groups. Log-rank test was used for comparison of survival between FG+ patients and G+ or G− patients. For comparison of consecutive echocardiographic data, the paired *t* test and in case of non-normally distributed data, the Wilcoxon signed-rank test were used. Statistical significance was defined by $P<0.05$.

Results

Study Population

In 141 FG+ probands (age, 45±14 years; 66% men), HCM was diagnosed in 134 (95%), NCCM in 4 (3%), and DCM in 3 (2%). In 130 FG+ relatives (age, 42±15 years; 37% men), HCM was diagnosed in 54 (42%), NCCM in 1 (1%), and DCM in 1 (1%). The remaining 74 (57%) were FG+/phenotype-negative (Ph−). Baseline characteristics of the study population are presented in Table 1.

Genetic Test Results

In FG+ carriers, the c.2373dupG mutation was the most frequent (46%), followed by c.2827C>T (32%) and c.2864_2865delCT (22%). A complex genotype was present in 4 (1%); 3 probands and 1 relative. Complex genotypes were compound heterozygosity for the c.2373dupG and c.2827C>T mutations, homozygosity for the c.2827C>T mutation, compound heterozygosity for the c.2373dupG and c.442G>A (G148R) mutations in the *MYBPC3* gene, and a digenic mutation (c.2827C>T in the *MYBPC3* gene and c.222dupA; p.Leu75fs in the ankyrin repeat domain 1 gene).

In G+ probands, pathogenic mutations were present in the *MYBPC3* gene (45%), ß-myosin heavy chain (29%), cardiac troponin T (7%), cardiac-regulatory myosin light chain (6%), cardiac troponin I (5%), calreticulin 3 (2%), cardiac-essential myosin light chain (2%), andcysteine- and glycine-rich protein 3 (2%), and complex genotypes were present in 3 (2%). Complex genotypes were (1) compound heterozygosity for the c.913_914delTT and c.1468G>A mutations in the *MYBPC3* gene, (2) digenic mutations c.5135G>A in the ß-myosin heavy chain gene and c.2530_2532delTCTinsC in the mindbomb E3 ubiquitin protein ligase 1 gene, and (3) digenic mutations c.1000G>T in the *MYBPC3* gene and c.64G>A in the cardiac-regulatory myosin light chain gene.

Baseline Clinical and Echocardiographic Characteristics

Main reasons for evaluation in probands were cardiac symptoms (61%), systolic murmur (20%), and abnormal electrocardiography (16%). Five (1%) probands presented with cardiac arrest. All FG+ relatives were evaluated in the context of family screening. Men predominated in all groups. The clinical phenotype of FG+ probands with HCM was similar to G+ probands with

Table 1. Baseline Characteristics of the Study Population

Variable	FG+ Probands With HCM (n=134)	FG+ Relatives With HCM (n=54)	G+ HCM (n=132)	G– HCM (n=277)
Age, y (range)	44±14	47±16	47±15	55±15*†‡
<18	4 (3)	3 (6)	4 (4)	5 (2)
18–35	33 (25)	11 (20)	28 (21)	28 (10)*†‡
36–50	51 (38)	17 (32)	45 (35)	58 (21)*†
>50	46 (34)	23 (43)	55 (41)	187 (67)*†‡
Men, n (%)	91 (67)	31 (57)	89 (66)	171 (62)
Reasons for evaluation, n (%)				
Symptoms	75 (56)	0	70 (56)	181 (65)
Abnormal ECG	23 (17)	0	27 (22)	36 (13)
Systolic murmur	32 (24)	0	26 (21)	50 (18)
Sudden death	3 (2)§	0	1 (1)	1 (0.4)
Incidental finding	1 (1)	0	1 (1)	3 (1)
Familial evaluation	0	54 (100)	0	0
NYHA class ≥II, n (%)	48 (48)	3 (8)*	71 (56)	164 (61)*‡
History of AF, n (%)	28 (21)	4 (7)*	36 (27)	41 (15)†
History of stroke, n (%)	12 (9)	4 (8)	11 (8)	22 (8)
MWT, mm	20±5	16±4*	20±5	17±4*†‡
LA size, mm	45±8	40±7*	45±7	45±7‡
Systolic dysfunction	23 (17)	0*¶	22 (18)	30 (12)‡
Diastolic dysfunction	50 (56)	19 (38)*	53 (71)	159 (80)*‡
MWT ≥30 mm, n (%)	5 (4)	0¶	11 (9)	2 (1)*†
LVOTO ≥30 mm Hg	31 (28)	2 (4)*	36 (32)	101 (45)*†‡
LVOTO ≥50 mm Hg	18 (16)	2 (4)	24 (21)	85 (38)*†‡
Nonsustained VT, n (%)	44 (42)	6 (16)*	35 (32)	26 (13)*†

Data are expressed as mean±SD or as absolute and percentage. AF indicates atrial fibrillation; FG+, Dutch *MYBPC3* founder mutation; G+, genotype-positive; HCM, hypertrophic cardiomyopathy; LA, left atrial; LVOTO, left ventricular outflow tract obstruction at rest; MWT, maximal wall thickness; NYHA, New York Heart Association; SD, standard deviation; and VT, ventricular tachycardia.

*P<0.05 vs FG+ probands with HCM.

†P<0.05 vs G+ HCM.

‡P<0.05 vs FG+ relatives with HCM.

§One was not successfully resuscitated.

¶Fisher exact test was used because of zero cell count.

HCM. Both FG+ and G+ probands were younger than G– probands with HCM and had less LVOT obstruction; however, they had more hypertrophy and nonsustained ventricular tachycardia. FG+ relatives with HCM had less hypertrophy, smaller left atria, and less systolic and diastolic dysfunction in comparison with FG+ probands with HCM. Among FG+ relatives with HCM, MWT was not different between men and women after indexing for body surface area (6.6±2.1 versus 6.4±2.6 mm/m^2; P=0.776).

Echocardiographic Findings During Follow-Up of FG+ Carriers

Echocardiographic findings during 10±6 years of follow-up of FG+ probands and FG+ relatives with HCM are presented in Table 2. Figure 1 demonstrates the clinical HCM disease stages[18] at baseline and during follow-up of FG+ probands and FG+ relatives. A significant proportion of FG+ probands (29%) progressed to stage III (adverse remodeling) and 18% to stage IV (overt dysfunction); in FG+ relatives, only 5% progressed to stage III and none to stage IV. Systolic dysfunction during follow-up was frequently present in G+ and FG+ HCM (46% versus 46%; log-rank P=0.23) and less frequent in G– HCM than in FG+ HCM (31% versus 46%; log-rank P<0.001). Moderate-to-severe systolic dysfunction was also frequently present in G+ and FG+ HCM (15% versus 25%; log-rank P=0.54) and less frequent in G– HCM than in FG+ HCM (7% versus 25%; log-rank P<0.001).

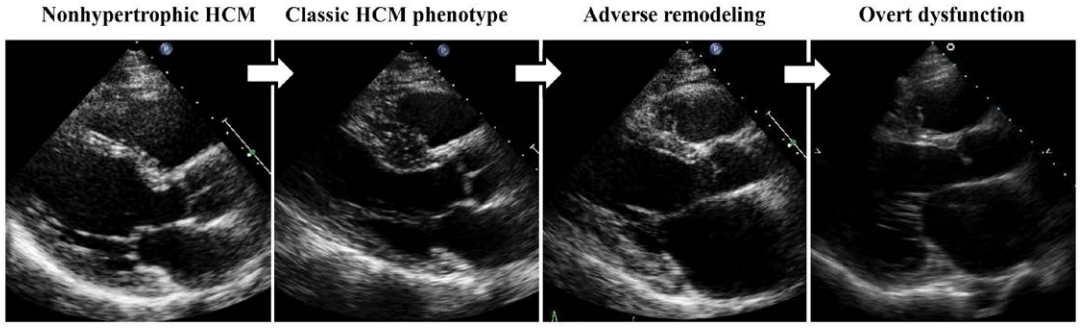
Mortality and Interventions During Follow-Up

Mortality and interventions are presented in Table 3. Cardiovascular mortality was 21% in FG+ probands with HCM and 14% in G+ probands (P=0.14), and cardiovascular mortality was significantly lower in FG+ relatives with HCM (4%) and G– probands (7%; Figure 2). During 8±6 years of follow-up, annual cardiovascular mortality was 2.1%, 1.6%, 1.0%, and 0.5% for FG+ probands with HCM, G+ probands, G– probands, and FG+ relatives with HCM, respectively. By multivariate Cox analysis taking into account age, sex, and family relatedness, FG+ relatives with HCM exhibited a lower risk of cardiovascular death than FG+ probands with HCM (hazard ratio, 0.15; 95% confidence interval, 0.04–0.64; P=0.01). Both HF-related death and SCD/aborted SCDs were more frequent in FG+ HCM than in G– HCM (8% versus 1%; log-rank P<0.001 and 14% versus 4%; log-rank P<0.001, respectively). In FG+ HCM, SCD/aborted SCD occurred at ages ranging from 11 to 77 years, and HF-related death generally occurred after the age of 50 years. Septal reduction therapy was performed more often in G– HCM than in FG+ HCM (33% versus 23%; P=0.004). ICDs for the

Table 2. Echocardiographic Findings During Follow-Up of FG+ Probands and FG+ Relatives With Hypertrophic Cardiomyopathy

	FG+ Probands With HCM			FG+ Relatives With HCM		
Variable	Baseline	Follow-Up	P Value	Baseline	Follow-Up	P Value
Maximal wall thickness, mm	20±5	17±4	<0.001	16±4	15±4	0.053
Left atrial size, mm	45±8	49±9	<0.001	40±7	41±6	0.044
LVEDD, mm	46±7	48±7	<0.001	47±5	45±6	0.107
LVOTO ≥30 mm Hg, n (%)	32 (28)	6 (6)	<0.001	2 (4)	2 (4)	1.000
LVOTO ≥50 mm Hg, n (%)	18 (16)	4 (4)	0.005	2 (4)	2 (4)	1.000
Systolic dysfunction, n (%)	23 (17)	47 (40)	<0.001	0	4 (8)	0.046
Diastolic dysfunction, n (%)	50 (56)	75 (84)	<0.001	18 (37)	26 (59)	0.011

Data are expressed as mean±SD or as absolute and percentage. FG+ indicates Dutch *MYBPC3* founder mutation; HCM, hypertrophic cardiomyopathy; LVEDD, left ventricular end-diastolic diameter; LVOTO, left ventricular outflow tract obstruction at rest; and SD, standard deviation.



FG+ Probands	Baseline	0	83% (111/134)	10% (14/134)	7% (9/134)
	Follow-up	0	53% (51/96)	29% (28/96)	18% (17/96)
FG+ Relatives	Baseline	58% (74/128)	42% (54/128)	0	0
	Follow-up	44% (38/86)	51% (44/86)	5% (4/86)	0

Figure 1. Clinical characteristics of individuals with a Dutch *MYBPC3* (myosin-binding protein C) founder mutation. Stage I: nonhypertrophic stage in a c.2864_2865delCT mutation carrier. Stage II: classic hypertrophic cardiomyopathy phenotype in a c.2373dupG mutation carrier. Stage III: adverse remodeling in a c.2373dupG mutation carrier. Stage IV: overt dysfunction (hypokinetic dilated form) in a c.2373dupG mutation carrier. FG+ indicates Dutch *MYBPC3* founder mutation; and HCM, hypertrophic cardiomyopathy.

primary and secondary prevention of SCD were implanted with similar proportions in all groups.

FG+/Ph– Relatives

Characteristics and outcomes of FG+/Ph– relatives versus FG+ HCM are presented in Table 4. FG+/Ph– relatives were predominantly women (63% versus 35%; $P<0.001$); there was no significant age difference. During 6±4 years of follow-up, there were no cardiovascular deaths among FG+/Ph– relatives. Echocardiographic follow-up was available in 44 (59%) FG+/Ph– relatives (Table 5). After 6±3 years, 5 (11%) FG+/Ph– subjects developed HCM. These 5 subjects were asymptomatic and without LVOT obstruction; conversion occurred at a median age of 37 (range, 25–71) years. Baseline electrocardiographic abnormalities were present in 3 (2 pathological Qs inferior/lateral and 1 nonpathological Q inferior), and anterior mitral valve leaflet elongation ≥30 mm in 1 (20%). Systolic anterior motion and diastolic dysfunction were absent in all 5. Hypertrophy developed at a pace of a median 0.5 (IQR, 0.2–0.8) mm per year during a median 6 (IQR, 3.5–9)-year follow-up, in which MWT increased from a median 11 (IQR, 9.5–11.5) to 13 (IQR, 13–13.5) mm.

Table 3. Long-Term Outcome of the Study Population

Variable	FG+ Probands With HCM (n=134)	FG+ Relatives With HCM (n=54)	G+ HCM (n=132)	G– HCM (n=277)
All-cause mortality, n (%)	39 (29)	3 (6)*	20 (15)*	38 (14)*†
CV mortality, n (%)	29 (22)	2 (4)*	19 (14)	20 (7)*
HF-related deaths, n (%)	10 (8)	0‡	10 (8)	4 (1)*†
Cardiac transplants, n (%)	1 (0.7)	0‡	3 (2)	2 (1)
SCD/aborted SCD, n (%)	18 (14)	2 (4)*	9 (7)	12 (4)*†
True SCD, n (%)	11 (8)	1 (2)	4 (3)	4 (1)*†
Stroke-related deaths, n (%)	0	0	0	2 (1)
Procedure-related deaths, n (%)	0	0	0	2 (1)
CAD-related deaths, n (%)	0	0	0	0
Noncardiac deaths, n (%)	8 (6)	1 (2)	1 (1)*	15 (5)
SRT, n (%)	31 (23)	2 (4)*	39 (30)	91 (33)*
ICD 1st prevention, n (%)	26 (19)	5 (10)	16 (12)	26 (9)
ICD 2nd prevention, n (%)	5 (4)	2 (4)	6 (5)	7 (3)

Data are expressed as mean±SD or as absolute and percentage. CAD indicates coronary artery disease; CV, cardiovascular; FG+, Dutch *MYBPC3* founder mutation; G+, genotype positive; HCM, hypertrophic cardiomyopathy; HF, heart failure; ICD, internal cardioverter defibrillator; SCD, sudden cardiac death; SD, standard deviation; and SRT, septal reduction therapy (alcohol septal ablation or surgical myectomy).

*$P<0.05$ vs FG+ probands with HCM.

†Log-rank $P<0.05$ vs G+ HCM.

‡Cox model with grouped jackknife method did not converge because of insufficient number of events.

Noncompaction and DCM in FG+ Carriers

NCCM was diagnosed in 5 (3%) FG+ carriers; 4 probands and 1 relative. A complex genotype was present in 3 (60%): 2 FG+ probands who experienced HF-related death within 2 months after birth and one 18-year-old asymptomatic FG+ relative. One NCCM patient experienced HF-related death at 50 years of age. DCM was diagnosed in 4 (2%) FG+ carriers; 3 probands and 1 relative. A complex genotype was present in 1 (25%), leading to cardiac transplantation at the age of 8 years. Another FG+ proband with DCM died of HF at 1 year of age. Figure 3 presents cardiac magnetic resonance and echocardiographic imaging, demonstrating the overlap of HCM and NCCM within 1 family and the presence of NCCM in an FG+ carrier.

Discussion

Key findings from the current long-term follow-up study are (1) clinical phenotype and outcome of FG+ HCM was similar to G+ HCM but worse than G– HCM and FG+ HCM diagnosed in the context of family screening and (2) cardiac events

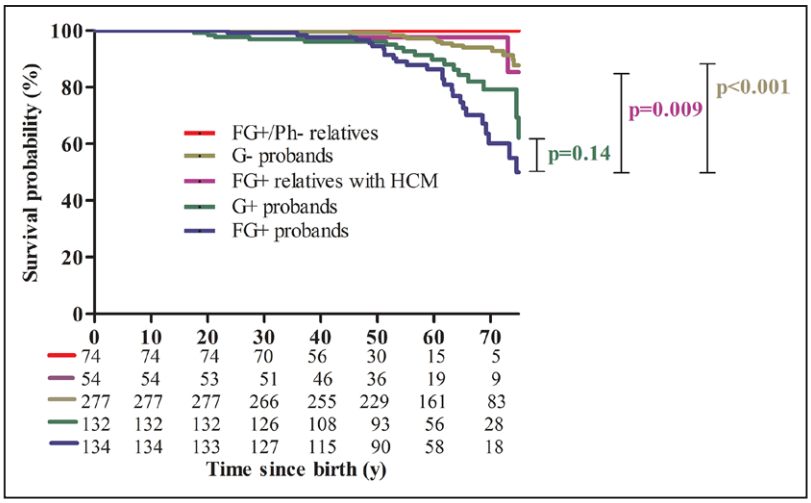


Figure 2. Kaplan–Meier survival analysis for cardiovascular mortality. *P* indicates the *P* value calculated with log-rank test in Dutch *MYBPC3* founder mutation (FG+) vs genotype-positive (G+) probands (in green) and in FG+ vs genotype-negative (G–) probands (in yellow). In FG+ probands vs FG+ relatives with hypertrophic cardiomyopathy (HCM), the *P* value (in purple) was calculated with a cox model with grouped jackknife method. In FG+/phenotype-negative (Ph–) relatives, the Cox model with grouped jackknife method did not converge because of insufficient number of events.

were absent in FG+/Ph– relatives; 11% of FG+/Ph– relatives developed HCM during 6±3 years of follow-up.

FG+ HCM

This study demonstrates that the prognosis of FG+ carriers is primarily defined by the presenting phenotype and the reason for evaluation. Cardiovascular mortality was significantly higher in FG+ HCM than in FG+/Ph– relatives and significantly lower in FG+ relatives diagnosed with HCM in the context of family screening. Adverse remodeling and progression to end-stage HCM was highly prevalent among FG+ probands with HCM, resulting in significantly more HF-related deaths in comparison with FG+ relatives with HCM. This finding is in line with the findings of Kubo et al.[21] We also observed a higher cardiovascular mortality rate in FG+ HCM in comparison with G– HCM. Several studies have previously demonstrated an increased risk of cardiac death in G+ versus G– HCM,[22–24] including studies of *MYBPC3* founder mutations.[25,26] G– probands in this study were older and more symptomatic most likely related to LVOT obstruction and diastolic dysfunction. Possibly, G– HCM represents a separate disease with a different pathophysiology. Unlike previous observations,[27] we did not observe a lower complication rate in FG+ versus G+ patients.

Initial cardiac screening revealed HCM in 42% of FG+ relatives, which is comparable with previous studies (24%–62%).[26,28–31] Extreme hypertrophy was absent in FG+ relatives, and there was less adverse remodeling. Identification of HCM leads to lifestyle modifications, periodic SCD risk stratification, and close clinical follow-up, with the opportunity to implant an ICD for primary prevention and timely referral for septal reduction therapy. In the future, early disease identification might lead to novel therapies to prevent hypertrophy[32] or delay progression to advanced disease stages.[33]

In this study, the clinical phenotypes of FG+ carriers showed substantial variation. The clinical heterogeneity in subjects carrying the same pathogenic mutation is intriguing. Basic studies have shown a decrease in the force-generating capacity of cardiomyocytes in G+ HCM patients.[8,9] For *MYBPC3* mutations, the force-generating capacity normalized after correction for myofibril density.[9] The drop in force was

Table 4. Characteristics of FG+/Ph– Relatives Versus FG+ HCM (Probands and Relatives Combined)

Variable	FG+ HCM (n=188)	FG+/Ph– relatives (n=74)	*P* Value
Baseline			
Age, y	45±15 (9–80)	42±15 (4–83)	0.077
<18	7 (4)	3 (4)	0.205
18–35	44 (23)	22 (30)	0.249
36–50	71 (38)	35 (47)	0.163
>50	66 (35)	14 (19)	0.013
Women, n (%)	66 (35)	47 (64)	<0.001
NYHA ≥II, n (%)	51 (37)	2 (3)	<0.001
History of stroke, n (%)	16 (9)	0	0.008*
History of AF, n (%)	32 (17)	1 (1)	0.008
Follow-up			
All-cause mortality, n (%)	43 (23)	1 (1)	0.036
Cardiovascular mortality, n (%)	31 (16)	0	†

Data are expressed as mean±SD or as absolute and percentage. AF indicates atrial fibrillation; FG+, Dutch *MYBPC3* founder mutation; HCM, hypertrophic cardiomyopathy; NYHA, New York Heart Association functional class; Ph–, phenotype negative; and SD, standard deviation.

*Fisher exact test was used because of zero cell count.

†Cox model with grouped jackknife method did not converge because of insufficient number of events.

Table 5. Echocardiographic Follow-Up of Dutch *MYBPC3* Founder Mutation/Phenotype-Negative Relatives

Variable	Baseline	Follow-Up	*P* Value
MWT, mm	9.9±1.6	10.2±2.0	0.188
LA size, mm	37±4	36±6	0.715
LVEDD, mm	48±4	46±4	0.021
Maximal LVOT gradient, mm Hg	5 [4–8]	6 [6–7]	0.072
Systolic dysfunction, n (%)	0	1 (2)	1.000
Diastolic dysfunction, n (%)	4 (10)	6 (15)	0.625

Data are expressed as mean±SD, median [interquartile range], or as absolute and percentage. LA indicates left atrial; LVEDD, left ventricular end-diastolic diameter; LVOT, left ventricular outflow tract; MWT, maximal wall thickness; and SD, standard deviation.

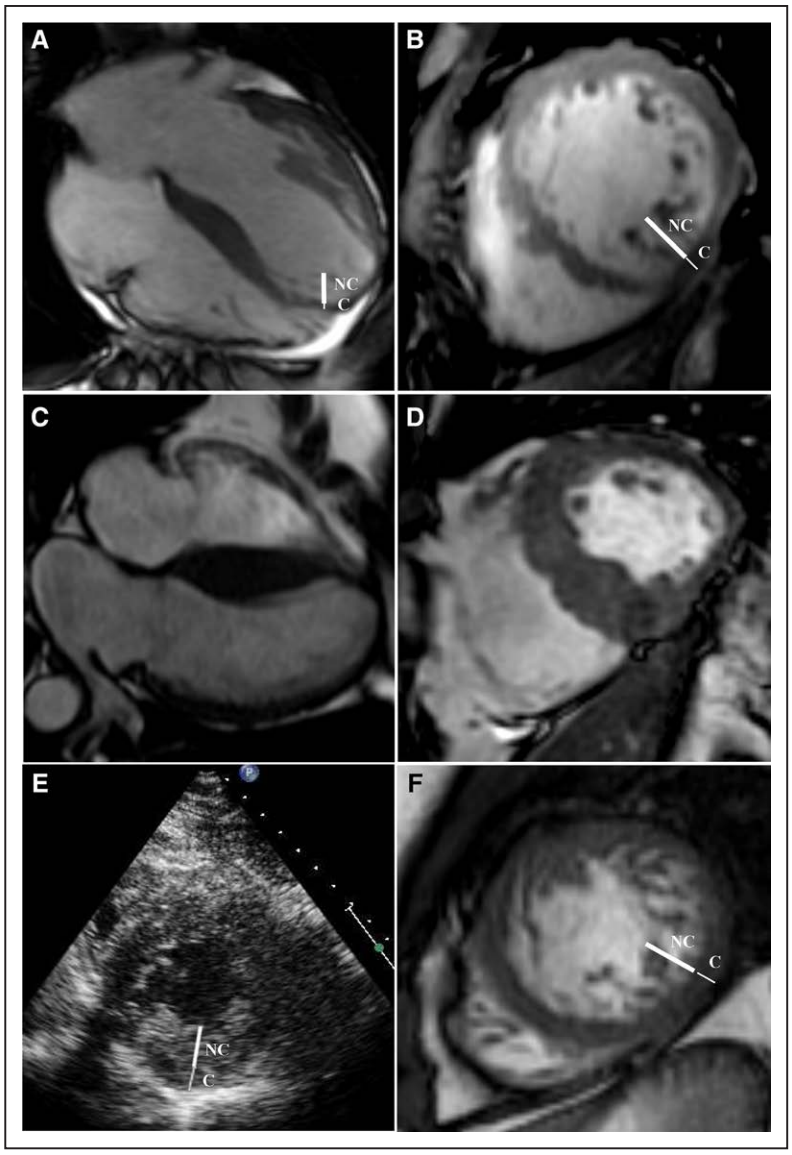


Figure 3. Cardiac magnetic resonance images of noncompaction cardiomyopathy and hypertrophic cardiomyopathy, measured in apical 3-chamber view and short-axis view at apical level during end diastole. Noncompaction cardiomyopathy was diagnosed in an 18-year-old Dutch *MYBPC3* founder mutation (FG+) relative (**A** and **B**) after family screening; asides from the familial mutation c.2827C>T, next-generation sequencing revealed a second mutation c.222dupA in the ankyrin repeat domain 1 gene. Mild hypertrophy (13 mm) of the left ventricular posterior wall was also present. His father (**C** and **D**) had hypertrophic cardiomyopathy based on the c.2827C>T mutation. Another FG+ individual presented with noncompaction cardiomyopathy on echocardiography (**E**) and cardiac magnetic resonance imaging (**F**); this individual carried the c.2827C>T mutation. Left ventricular systolic function was poor. **C** indicates compacted; and NC, noncompacted.

associated with cardiomyocyte hypertrophy and reduced myofibril density, suggesting sarcomere dysfunction is secondary to cardiomyocyte remodeling.[9] Other triggers, for example, altered Ca^{2+} handling and disturbances in myocardial energetics[34] are additionally being investigated. The exact pathways from mutation to disease remain largely unknown. The relatively large population of FG+ carriers is useful for translational research in which clinical data are combined with data from basic research to further unravel the pathomechanism and identify secondary disease modifiers, such as additional (epi)genetic variations and environmental disease triggers.

FG+/Ph− Individuals

Because of the known age-related penetrance in HCM,[29] long-term follow-up of FG+/Ph− subjects is recommended.[13,20,35] The interval at which clinical evaluation should be repeated is subject to debate. The American guideline recommends a 1- to 2-year interval for family members aged 10 to 20 years and 2- to 5-year interval for those >20 years, whereas the European guideline does not advise a specific interval.[13,20] In this study, 11% of FG+/Ph− relatives developed a subtle form of HCM after 6 years of follow-up. Additionally, comparable with previous studies,[31,36,37] the prognosis of FG+/Ph− relatives was good. These findings support cardiac follow-up of adult FG+/Ph− relatives with a low frequency, as advised by the American guideline.[20] The number of family members aged <18 years in our cohort was too small to propose screening intervals for this group. However, Jensen et al[36] reported a similarly low manifestation rate (6%) in 36 at-risk relatives <18 years of age during 12 years of follow-up. The main advantage of genetic testing in relatives is reassurance in case the mutation is absent. However, the identification of FG+/Ph− subjects currently has limited therapeutic and prognostic consequences because at present, no therapy is available to retard or prevent the development of HCM,[32,33] and clinical manifestation cannot be predicted.[35] Moreover, a FG+/Ph− status may have psychological and socioeconomic implications.[38] Clearly, cardiogenetic counseling of relatives should include a balanced discussion of the advantages and potential disadvantages of genetic testing.

NCCM and DCM in FG+ Carriers

MYBPC3 mutations are associated with various forms of cardiomyopathies, such as DCM and NCCM.[5] In this study, a significantly poor outcome was observed in a minority of young

NCCM and DCM patients, partly explained by homozygous and compound heterozygous mutations.[39] Because *MYBPC3* founder mutations are truncating mutations leading to haploinsufficiency,[8] compound heterozygous or homozygous mutations would theoretically result in human *MYBPC3* knockouts (no functional *MYBPC3* protein), leading to severe HF at a young age.[39] The likelihood of compound heterozygotes or homozygotes in countries with founder mutations is increased.[5] The finding of NCCM and DCM in the FG+ population and within 1 family supports previous suggestions that the various cardiomyopathies are part of a cardiomyopathy spectrum with similar pathogenesis. Lorca et al[40] similarly described the overlapping of HCM and NCCM phenotypes within 1 family.

Male Predominance in HCM

The male predominance in HCM patients was previously partly explained by a referral bias.[41] In this study, there was also a male predominance in FG+ relatives with HCM eliminating referral bias. Other theories explaining sex differences in HCM include differential gene regulation and the protective effect of estrogens.[41] Another explanation might be the use of the 13-mm cutoff value to diagnose HCM in relatives.[13] In this study, the difference in MWT between male and female relatives disappeared after indexing for body surface area, suggesting that women are clinically underdiagnosed or men over diagnosed. Recommendations for cardiac chamber quantification report different normal ranges for septal and posterior wall thickness in men (6–10 mm) and women (6–9 mm).[42] Therefore, either indexing to body surface area or creating sex-specific cutoff values for family members might lead to a higher diagnostic accuracy.

Limitations

This FG+ population is specific for the Netherlands, and, therefore, it might be difficult to extrapolate these findings to other countries. Follow-up echocardiography was not available in all subjects. Because of developments in genetic testing methodology over time, extended genotyping was not performed in all subjects. Because autopsy was not routinely performed in SCD cases, comorbidities such as coronary artery disease cannot be fully excluded.

Conclusions

Clinical phenotype and outcome of FG+ HCM was similar to G+ HCM but worse than G− HCM and FG+ HCM diagnosed in the context of family screening. These findings indicate the need for more intensive follow-up of FG+ and G+ HCM versus G− HCM and FG+ HCM in relatives.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In hypertrophic cardiomyopathy (HCM), extreme genetic and clinical heterogeneity challenge the use of genotype as a prognostic factor. The gene most frequently affected in HCM is *MYBPC3* (myosin-binding protein C). In the Netherlands, 3 *MYBPC3* founder mutations represent 35% of HCM cases. To investigate the impact of genotype on the clinical course of HCM, we compared clinical phenotype and outcome of *MYBPC3* founder mutation (FG+) HCM with nonfounder mutation genotype-positive (G+) HCM and genotype-negative (G–) HCM. Also, a distinction was made between FG+ HCM in probands who presented with signs or symptoms of disease, and in relatives who were diagnosed with HCM in the context of family screening. We observed a more severe phenotype at a younger age in FG+ and G+ HCM than in G– HCM and FG+ HCM in relatives, including more hypertrophy and nonsustained ventricular tachycardia, and more adverse remodeling during follow-up. Cardiovascular mortality was more frequent in FG+ and G+ HCM than in G– and FG+ HCM in relatives. FG+ relatives without a phenotype experienced no cardiac events; although 11% developed subtle HCM during 6 years of follow-up. The findings of the current study are important for the practicing clinician because they contradict previous reports that observed a more benign clinical course in FG+ HCM. The results indicate the need for more intensive follow-up of FG+ and G+ HCM versus G– HCM and FG+ HCM in relatives. Moreover, adult FG+ carriers without a phenotype can be screened at low frequency.

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Clinical Characteristics and Long-Term Outcome of Hypertrophic Cardiomyopathy in Individuals With a MYBPC3 (Myosin-Binding Protein C) Founder Mutation

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