Penetrance of Hypertrophic Cardiomyopathy in Children and Adolescents

A 12-Year Follow-up Study of Clinical Screening and Predictive Genetic Testing

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Background—The penetrance of hypertrophic cardiomyopathy (HCM) during childhood and adolescence has been only sparsely described. We studied the penetrance of HCM and the short- and long-term outcomes of clinical screening and predictive genetic testing of child relatives of patients with HCM.

Methods and Results—Ninety probands and 361 relatives were included in a family screening program for HCM (1994–2001). Eleven sarcomere genes, CRYAB, α-GAL, and titin were screened. Sixty-six relatives and 4 probands were <18 years of age at inclusion. Twelve child relatives were mutation carriers (age, 12±5 years), and 26 had unknown genetic status, ie, relatives from families without identified mutations (n=21) or not tested (n=5) (age, 11±5 years). Twenty-eight noncarriers (42%; age, 10±4 years) served as control subjects. Two of 38 child relatives (5%) at risk of developing HCM fulfilled diagnostic criteria for HCM at inclusion. After 12±1 years of follow-up, 2 of the 36 (6%; 95% confidence interval, 2–18) at-risk child relatives who were phenotype negative at inclusion had developed the HCM phenotype at 26 and 28 years of age. During follow-up, none of the child relatives experienced serious cardiac events. Participation in the screening program had no long-term negative psychological impact.

Conclusions—The penetrance of HCM in phenotype-negative child relatives at risk of developing HCM was 6% after 12 years of follow-up. The finding of phenotype conversion in the mid-20s warrants continued screening into adulthood. Forty-two percent of the child relatives were noncarriers, and repeat clinical follow-up could be safely limited to the remaining children. **(*Circulation*. 2013;127:48-54.)**

Key Words: child ■ echocardiography ■ genetic testing ■ mutation ■ penetrance ■ sarcomeres

Hypertrophic cardiomyopathy (HCM) is most often autosomal dominantly inherited with incomplete penetrance and variable expressivity.[1–3] The manifestations of this genetically heterogeneous disease vary from asymptomatic or mildly symptomatic patients to patients with severe heart failure symptoms, angina, arrhythmia, syncope, or sudden cardiac death (SCD). SCD may be the first manifestation of the disease.[4] The main purpose of family screening as recommended by American College of Cardiology and American Heart Association[5] is to identify undiagnosed HCM patients to allow clinical management of early symptoms and identification of patients with an increased risk of SCD. A disease-causing mutation can be identified in sarcomere genes in 30% to 60% of HCM patients.[3,6,7] Predictive genetic testing[8] of relatives identifies mutation carriers at risk of developing HCM and noncarriers without such a risk.

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The timing of clinical and genetic screening of children is based mainly on consensus opinions and clinical judgments and has been addressed in only a few studies.[9–11] It is largely unknown how many relatives <18 years of age are affected by HCM. The general recommendation is to screen child relatives beginning at 12 years of age.[5] The prognostic value of identifying sarcomere gene mutations in children without phenotypic manifestations of HCM is unclear.

We studied the outcome of clinical screening and predictive genetic testing of child relatives (<18 years of age) from families with HCM[3] and assessed the age-related

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penetrance of HCM during 12 years of follow-up in these young relatives.

Methods

Ethics

The local Ethics Committee approved the clinical and genetic family screening study (V92-213) and allowed clinical screening and predictive genetic testing of all children regardless of age after written informed consent had been obtained from parents or guardians. All families were offered genetic counseling. The children were included in the decision process according to their intellectual and emotional maturity and were given the opportunity to reject participation. The parents/guardians/children decided whether to accept the offered genetic test and whether they wanted to be informed about the genetic test result. These options were important to ensure that the study did not violate the best interest of the children.[12] Parents or guardians were informed about the children's right not to know[13] before deciding on the level of participation.

Study Cohort

From 1994 to 2001, 90 child and adult HCM probands were consecutively included in the family screening program at the Unit for Inherited Heart Diseases of the Heart Center in close collaboration with the Department of Clinical Genetics (National University Hospital, Rigshospitalet, Copenhagen, Denmark).[3,14–18] In 32 of the 90 probands (36%), 38 disease-causing mutations were identified. Each family was offered screening, and a total of 361 relatives (all ages) were included in the screening program. Four probands and 66 relatives (from 26 families) <18 years of age at the time of inclusion in the screening program (Figure 1) were included in the present long-term follow-up study.

Clinical and Genetic Family Screening

The first step in the screening process was clinical examination, including ECG recording and echocardiography in probands and relatives. The second step was genetic testing of the probands. All coding regions of 11 sarcomere genes (*MYH7*, *MYL2*, *MYL3*, *MYBPC3*, *TNNI3*, *TNNT2*, *TPM1*, *ACTC*, *CSRP3*, *TCAP*, and *TNNC1*), CRYAB, α-GAL, and 5 exons of titin were analyzed in all probands.[3,14–18] A sequence variant was considered disease causing if this had been shown in previous reports or if the following criteria were fulfilled: The mutation resulted in a missense mutation causing a nonsynonymous amino acid substitution or resulted in a frame shift or interference with a canonical splice site; the mutation affected an evolutionarily conserved amino acid; and the mutation was not found in 500 control alleles or in the database of single-nucleotide polymorphisms. Additionally, the mutations had to cosegregate with HCM in the family. In small families, in whom assessment of familial cosegregation was not possible, a disease association was presumed if the other criteria were met. In the case of a missense mutation in CRYAB, the pathogenicity was further supported by showing interference with correct folding of the protein, assessed by circular dichroism spectroscopy, and changes in amyloid properties, measured by changes in interaction with Congo red.

If a disease-causing gene mutation was identified in the proband, a selective genetic test for the identified mutation was offered to first-degree relatives. Relatives carrying a gene mutation and first-degree relatives from families without an identified gene mutation were referred for routine follow-up after the initial screening process. Noncarriers were reassured, and no further clinical follow-up was offered.

Carriers, Noncarriers, and Child Relatives With Unknown Genetic Status

The 66 child relatives were divided into 3 groups based on the genetic testing. The first group included 28 child relatives who were not carrying the gene mutation identified in their family (noncarriers). This group served as controls (Figure 1). The second group included 12 gene mutations carriers. The third group of 26 child relatives with unknown genetic status included 21 child relatives from families without identified gene mutations and 5 child relatives from families with identified gene mutations who declined genetic testing. Together, the second and third groups included 38 child relatives at risk of developing HCM.

Follow-up Assessment

The follow-up assessment included clinical, ECG, and echocardiographic evaluations, as well as questionnaire assessments of the long-term psychological impact of participation in the family screening program.[19–22] Vital status was available for all probands and relatives.

Echocardiography

At the time of inclusion, 2-dimensional echocardiography, M-mode, and Doppler evaluations and measurements were performed. Analyses were performed according to the American Society of Echocardiography guidelines[23] with Echopac Dimension software version 8. Echocardiograms were analyzed for left ventricular wall thickness, cavity dimensions, structural abnormalities, systolic anterior movement of mitral leaflets, and outflow tract gradients at

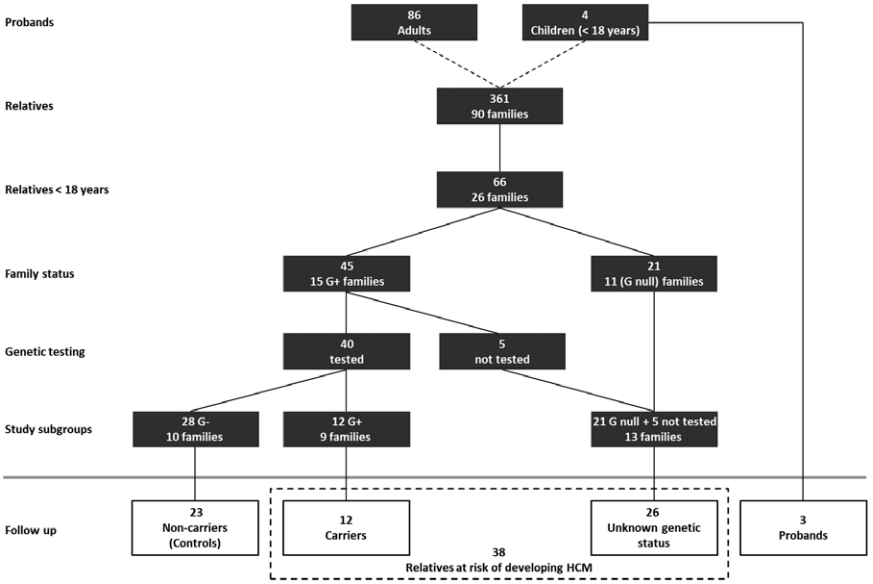

Figure 1. Study outline. Ninety probands with hypertrophic cardiomyopathy (HCM) and 361 relatives were included. Sixty-six relatives and 4 probands were <18 years of age. G– indicates genetically tested child relatives not carrying the disease-causing gene mutation (see Methods) identified in their family (ie, noncarriers or control subjects); G+, genetically tested child relatives carrying the disease-causing gene mutation identified in their family; and G null, child relatives from genetically tested families in whom a disease-causing gene mutation was not identified. White boxes represent study subgroups at follow-up.

rest and during the Valsalva maneuver. At the time of inclusion and at follow-up, left ventricular wall thickness was evaluated in all segments, including the apical segments. The maximal wall thickness (MWT) was defined as the maximal thickness of the left ventricular wall in any of the segments. In children (<18 years), the MWT was adjusted for body surface area (BSA) with the formula by Dubois and Dubois.[24]

Electrocardiograms

ECGs were recorded with commercially available 12-lead ECG recorders at the time of inclusion and at follow-up. The ECGs were analyzed for Q waves, T-wave abnormalities, and time intervals. The presence of Sokolow-Lyon voltage ≥35 mV,[25] a Cornell product >2440,[26] or a Romhilt-Estes[27] score ≥5 was considered suggestive of hypertrophy in adults.

Diagnostic Criteria for HCM

In child relatives (<18 years of age), a BSA-adjusted MWT greater than the mean BSA-adjusted wall thickness plus 2 times the standard deviation (ie, *Z* score >2) in the control group was considered diagnostic for HCM.[5] In adult relatives (≥18 years of age), an MWT ≥13 mm was considered diagnostic for HCM according to guidelines.[5] These criteria were used at inclusion and at follow-up.

Psychological Evaluation

See the online-only Data Supplement for a detailed description of the psychological testing.

Statistics

Data were analyzed with SAS statistical software version 9.1. Data are presented as mean ± SD. Unpaired comparisons were performed with the Student *t* test after confirmation of normal distribution. Normal values for the left ventricular wall thicknesses are available in the literature for the basal segments of the interventricular septum and posterior wall, but not for other segments. Therefore, *Z* scores for BSA-adjusted MWT were calculated on the basis of the standard deviation in control subjects. A *Z* score of 2 was considered the upper limit of normal for BSA-adjusted MWT in control subjects. The evaluation scores from questionnaires were handled as continuous variables, which enabled comparisons with the unpaired Student *t* test. Proportions are presented as percentages, and whenever relevant, confidence intervals (CIs) are reported. Proportions were compared by use of the χ^2 test or the Fisher exact test. A 2-sided value of $P<0.05$ was considered significant. Bonferroni correction of *P* values was used to adjust for multiple comparisons, leaving the level of significance unchanged at 0.05. Only corrected *P* values are given.

Results

Seventy children and adolescents (<18 years of age; 66 relatives and 4 probands) from 26 families were included in the family screening program (Figure 1). In 15 of these families (58%), a disease-causing sarcomere gene mutation was identified in the proband, and genetic testing was performed in 89% of their child relatives. In 87% of the genetically tested child relatives, parents/children wanted to know the genetic test result.

Genetic Findings

In the 12 carriers from 9 families, we identified mutations in 3 different genes (*MYH7*, *MYBPC3*, and *MYL2*; Table 1). One carrier had 2 mutations, as did the proband in the family (family T). The disease-causing mutation in the family was not present in 28 children from 10 families (control subjects). Two of the 4 child probands had *MYBPC3* mutations, and 1 child proband had a CRYAB mutation. In the last child proband, no mutations were found (Table 2).

Clinical Findings at Inclusion

There were no differences in BSA-adjusted MWT between control subjects (6.0 ± 1.6 mm/m^2) and carriers (5.7 ± 1.0 mm/m^2; *P* = NS) and relatives with unknown genetic status (5.7 ± 2.0 mm/m^2; *P* = NS). None of the carriers but 2 of 26 child relatives with unknown genetic status fulfilled the diagnostic criteria for HCM at the time of inclusion (*Z* score, 2.7 and 2.5; age, 5 and 7 years, respectively). Both were from families with known disease-causing sarcomere gene mutations, but these 2 children had not been genetically tested. In total, 2 of 38 (5%; 95% CI, 1–17) child relatives at risk of developing HCM fulfilled the diagnostic criteria for HCM at inclusion. Applying published and institutional references values for interventricular septal thickness and left ventricular posterior wall thickness at

Table 1. Identified Sarcomere Gene Mutations and Phenotypic Status After 12 Years of Follow-up of Child Relatives Included in the Family Screening Program for HCM

Family	Sex	Gene	cDNA Change	Protein	Age at follow-up, y	Age at HCM Diagnosis, y
T	M	*MYL2*	c.37G>A	p.A13T	22	–
		MYH7	c.3981C>A	p.N1327K		
B	M	*MYH7*	c.5134C>T	p.R1712W	26	–
A	F	*MYH7*	c.569G>C	p.R190T	19	–
A	M	*MYH7*	c.569G>C	p.R190T	27	26
G	F	*MYH7*	c.2080C>T	p.R694C	23	–
G	M	*MYH7*	c.2080C>T	p.R694C	22	–
ZJ	M	*MYBPC3*	c.682G>A	p.D228N	29	–
XD	F	*MYH7*	c.958G>A	p.V320M	26	–
ZL	M	*MYBPC3*	c.1153_1168del16	p.Val385Metfs*16	22	–
ZL	M	*MYBPC3*	c.1153_1168del16	p.Val385Metfs*16	28	28
ZH	M	*MYBPC3*	c.3491 to 14_3491-8delCCTGTCA	Splice variant	17	–
ZV	M	*MYBPC3*	c.281delT	p.Val94Alafs*2	13	–

HCM indicates hypertrophic cardiomyopathy; –, normal phenotype at follow-up. Reference sequence: *MYL2*, NM_000432.3; NP_000423.2; *MYH7*, NM_000257.2; NP_000248.2; and *MYBPC3*, NM_000256.3; NP_000247.2.

Table 2. Characteristics and Clinical Events During 12 Years of Follow-up in 4 Child Probands With HCM

Family	Age, y*	Sex	MWT, mm*	Gene	Mutation	Events During Follow-up
ZV	8	M	20	*MYBPC3*	g2430 delG	Myectomy/ICD
ZJ	15	F	13	*MYBPC3*	Asp230Asn	No events
YA	17	M	30	*CRYAB*	Q26X	Sudden death
ZN	5	F	14	–	–	ICD

HCM indicates hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; MWT, maximal wall thickness; and –, normal phenotype at follow-up.

*At inclusion.

The CRYAB mutation was a de novo mutation with confirmed maternity and paternity.

diastole to the left ventricular wall thicknesses measured in other projections did not change the diagnosis in any of the child relatives at risk of developing HCM.

Clinical Findings at Follow-up

All child relatives were alive at follow-up, and none had experienced any cardiovascular symptoms or any cardiac events during follow-up. Follow-up was performed in all carriers and all relatives with unknown genetic status (Table 3). Twenty-three control subjects were available for follow-up.

At follow-up, 2 of the 12 carriers (17%; 95% CI, 5–45) had developed HCM with an MWT of 15 and 17 mm (Table 1 and Figure 2B). One relative with unknown genetic status, diagnosed at inclusion, still fulfilled the diagnostic criteria for HCM at follow-up (MWT = 15 mm) (6%; 95% CI, 1–19). The other relative with unknown genetic status who fulfilled the criteria for HCM at inclusion (age 5 years) did not fulfill the diagnostic criteria for HCM at follow-up (MWT = 12 mm; *Z* score = −0.75; age, 17 years; weight, 110 kg). In total, 2 of 36 (6%; 95% CI, 2–18) child relatives at risk of developing HCM who were phenotype negative at inclusion developed HCM during 12 ± 1 years of follow-up.

The 3 child relatives who fulfilled the diagnostic criteria at follow-up had been evaluated repeatedly during the clinical follow-up. The 2 carriers who developed HCM during follow-up converted to the HCM phenotype at 26 and 28 years of age (Figure 3).

In the ECG recordings, abnormal Sokolow-Lyon voltage criteria, Cornell products, or Romhilt-Estes scores were present in a number of the at-risk children with normal echocardiograms and in some of the control subjects (Table 3). These false-positive findings indicate a reduced diagnostic value of ECG recordings in the screening program.

Psychological Findings at Follow-up

We did not find any differences in anxiety, depression, type D personality, or overall psychological impact of participation in the family screening program between the 3 groups (carriers, control subjects, and relatives with unknown genetic status; Table I in the online-only Data Supplement).

Discussion

To the best of our knowledge, this study is the largest series of child relatives of HCM probands followed up for the longest time period. Follow-up after 12 years revealed a very low penetrance of HCM in childhood and in early adulthood, and no cardiac events were seen in the child relatives. The low penetrance challenges the general perception that HCM develops predominantly during the growth spurt in childhood or adolescence.[10]

Table 3. Follow-up Characteristics of Relatives Included During Childhood in the Family Screening Program for Hypertrophic Cardiomyopathy

	Control Subjects (n = 23)	Unknown Genetic Status (n = 26)		Carriers (n = 12)	*P**
Demographics					
Age at follow-up, y	22 ± 4	22 ± 6	NS	23 ± 5	NS
Follow-up, y	12 ± 1	13 ± 2	NS	11 ± 2	0.02
Female sex, %	25	38	NS	25	NS
BSA at follow-up, m^2	1.9 ± 0.3	1.9 ± 0.2	NS	1.9 ± 0.2	NS
Echocardiography					
MWT (inclusion), mm	7 ± 2	8 ± 2	NS	8 ± 2	NS
MWT (follow-up), mm	10 ± 1	10 ± 1	NS	12 ± 3	NS
BSA-adjusted MWT, mm	5.3 ± 1	5.1 ± 1	NS	6.2 ± 1	0.02
IVSd, mm	9 ± 2	10 ± 2	NS	10 ± 3	NS
LVEDd, mm	46 ± 4	49 ± 5	NS	42 ± 5	0.01
LVPWd, mm	9 ± 1	10 ± 2	NS	10 ± 1	NS
LA dimension, mm	36 ± 5	38 ± 6	NS	36 ± 5	NS
LVEF, %	56 ± 7	54 ± 8	NS	55 ± 8	NS
Electrocardiogram, %					
Sokolow-Lyon >35 mm	13	15	NS	30	NS
Cornell product >2440	4	10	NS	10	NS
Romhilt-Estes score ≥5	13	5	NS	30	NS

BSA indicates body surface area; IVSd, interventricular septum thickness (diastolic); LA left atrium, LVEDd, left ventricular end-diastolic dimension (diastolic); LVEF left ventricular ejection fraction; LVPWd, left ventricular posterior wall thickness (diastolic); and MWT, maximal wall thickness.

**P* values for comparisons with the control group.

Diagnostic Yield and Penetrance

The initial screening revealed no affected carriers (n = 12), 2 affected children with unknown genetic status, and no affected control subjects. Two carriers (17%; 95% CI, 5–45) converted to the HCM phenotype during follow-up, but not until 26 and 28 years of age. At follow-up, only 1 child with unknown genetic status (6%; 95% CI, 1–19), already diagnosed at inclusion at the age of 5 years, fulfilled diagnostic criteria. Thus, only 3 (5%; 95% CI, 2–13) of the total group of child relatives (n = 66) or 3 (8%; 95% CI, 3–21) of the child relatives considered at risk of developing HCM, ie, carriers (n = 12) and relatives with unknown genetic status (n = 26), fulfilled the diagnostic criteria for HCM after 12 years of follow-up. With genetic screening, we identified 28 noncarriers (42%).

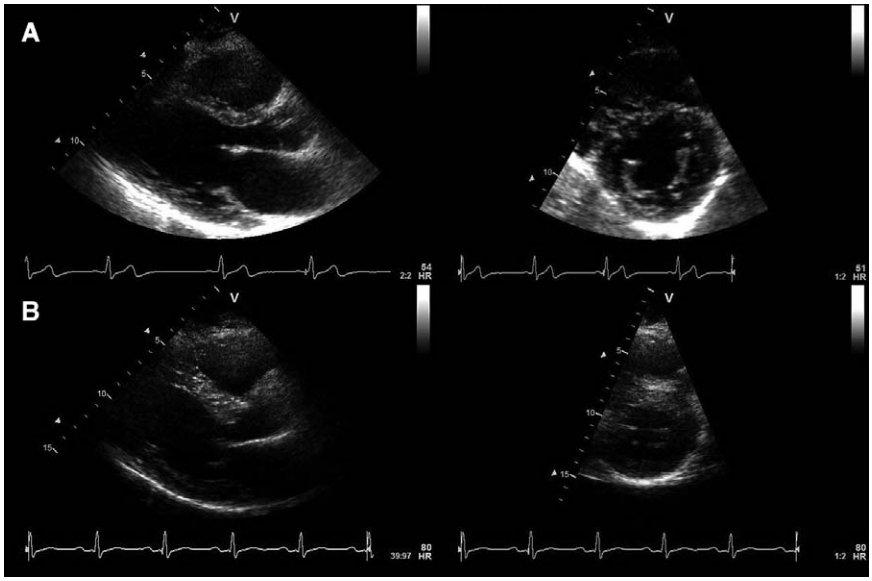

Figure 2. Echocardiographic images of 2 carriers with *MYH7* mutation at follow-up. **A**, Age 23 years; maximal wall thickness (MWT) = 9 mm. **B**, Age 27 years; MWT = 17 mm. Left, Parasternal long-axis view. Right, Sagittal axis view.

These children were reassured, and further clinical follow-up was ceased. Our youngest child proband was diagnosed at 5 years of age.

The observation that the HCM phenotype may not be present at birth but may develop during childhood was initially reported in 1986 by Maron et al,[10] who showed that in a group of phenotype-negative child relatives, at a mean age of 11 years, 5 of 16 child relatives (31%; 95% CI, 14–56) developed significant left ventricular hypertrophy during 4 years of follow-up. Considering the small study populations in the available studies, the low penetrance (6%; 95% CI, 2–18) during childhood and adolescence observed here may not differ significantly from the phenotype conversion rate reported by Maron et al. However, the penetrance observed here seems more in line with recent findings by Pasquale et al[28] of the penetrance of cardiac troponin T gene mutations in children <16 years of age. They reported development of HCM in only 2 of 13 children (15%; 95% CI, 4–42) at 19 and 29 years of age during 6.7 ± 3 years of follow-up. Taken together, in the majority of cases, the HCM phenotype does not seem to develop until adulthood.

Cardiac Events

The risk of SCD is the major driving force for cascade screening in HCM families. The observation that none of our child relatives experienced any cardiac events supports the general perception that cardiac events are rarely seen in phenotype-negative sarcomere gene mutation carriers.[29,30] This is reflected in the contemporary guidelines recommending risk stratification only in phenotype-positive patients.[5] The low event rates in phenotype-negative relatives are in contrast to high event rates in child probands, as illustrated in the present study (Table 2) and reported by others.[9,28] Ostman-Smith et al[9] have shown that SCD in symptomatic HCM children peaks at the age of 8 to 9 years, which is before the generally recommended age for beginning clinical screening of ~12 years.[5] However, a recent nationwide Danish study indicated a generally low risk of SCD in children with diagnosed or undiagnosed HCM of <0.1% per person-year.[31] Nevertheless, it is an ongoing lingering concern that children carrying a sarcomere gene mutation may be at risk of SCD even in the absence of any phenotypic manifestations. Pasquale et al[28] reported 1 cardiac event in 1 of 18 phenotype-negative children

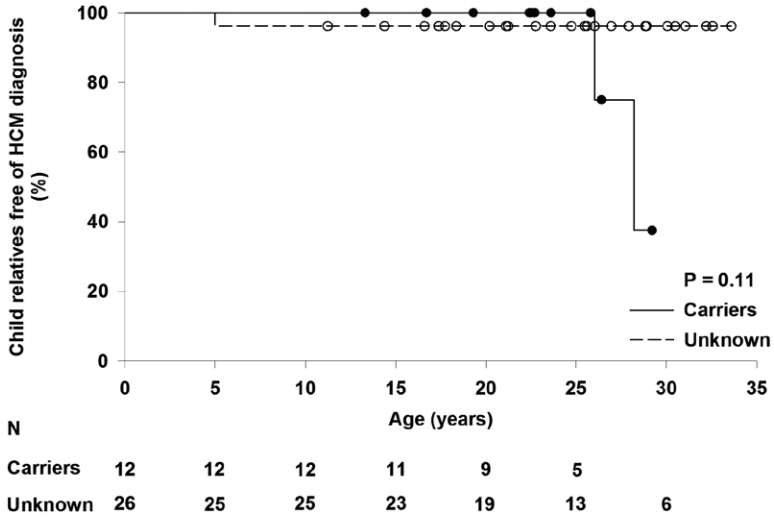

Figure 3. Age-related penetrance of hypertrophic cardiomyopathy (HCM) in sarcomere gene mutation carriers (carriers) and child relatives with unknown genetic status (unknown).

carrying troponin T mutations without echocardiographic signs of hypertrophy: A 16-year-old boy with an MWT of 9 mm died suddenly. No data on symptoms, ECG findings, or risk factors for SCD in this case were reported. This illustrates that even though the risk of major cardiac events is low in phenotype-negative mutation carriers, fatal cases can be seen, but at present, we have no tools to predict this risk.

Taken together, with repeated clinical and echocardiographic screening from the youngest age at which child relatives have been diagnosed by family screening, ie, early school age, it is possible to identify the few children with manifest HCM who are at risk of cardiac events. The recommended follow-up at 12- to 18-month intervals in children and adolescents[5] seems prudent, and the phenotype conversion in the 20s rather than during adolescence found in this and other studies[28] warrants continued screening into adulthood. This study does not provide data on the optimal screening intervals.

Psychological Impact of Screening

Data on the concerns of whether family screening programs and predictive genetic testing present a threat to the psychological development of children have been requested.[32]

Using formal testing, we did not identify apparent negative impacts of participating in the screening on the general psychological state in terms of anxiety, depression, and personality (Table I in the online-only Data Supplement). Thus, screening of children for HCM and possibly other inherited heart diseases may be considered safe if performed in an appropriate clinical setting and in the best interest of the child.[12]

Role of Genetic Testing for the Clinical Management

The decision on medical treatment, implantation of a cardioverter-defibrillator, or surgery of patients with HCM is not based on genetic findings but relies entirely on symptoms, clinical findings, and the presence of risk factors for SCD. At present, the value of genetic testing relates mainly to the decision to continue or discontinue clinical and echocardiographic follow-up. In this study, 42% of the child relatives were reassured of their noncarrier status, and follow-up could be safely limited to the remaining 58% of the child relatives. From clinical experience, a genotype-negative test result in a child relative is of major importance and provides considerable relief in these families.

Genetic testing in child relatives depends on the ability to identify the disease-causing mutation in the proband, which at present is possible in ~50% of cases.[5] Thus, genetic testing is technically possible in only half of the child relatives, but for families without an identified disease-causing mutation, it should be emphasized that, on the basis of the present findings and other data, there is no evidence that genetic testing per se improves safety or outcome in the children. Thus, whereas the clinical screening and follow-up are clearly justified in child relatives, predictive genetic testing is useful to differentiate between those with and those without a need for clinical follow-up. However, it is important to consider postponing the predictive genetic testing until adulthood to ensure the autonomy of the child and for legal reasons. It seems reasonable to suggest that the present findings provide some support for the general notion that genetic testing and clinical follow-up of children from families with inherited cardiac diseases are unlikely to have a significant negative impact on the psychological development of the child.

It should be emphasized that the present findings were obtained in a close multidisciplinary teamwork between expert cardiologist and clinical geneticists.

Limitations

The generalizability of the present findings is limited by the relatively small number of child relatives at risk of developing HCM included in the study. It should also be noted that phenotype conversion rates and timing might depend on a number of factors, eg, differences in genotype, ethnicity, or sex. In this study, the genotype-positive child relatives had mutations in the 2 most frequently involved genes in HCM, ie, *MYBPC3* and *MYH7*; all included children were white; and about one third of the children were at risk of developing HCM were male. However, although this is the largest series of child relatives followed up for the longest period, larger and more mixed populations of child relatives at risk of developing HCM should be followed up during childhood and adolescence to assess the timing and rate of phenotype conversion with more accuracy. This is of major importance for further development of recommendations for screening of child relatives to HCM patients.

Conclusions

The penetrance of HCM in phenotype-negative child relatives at risk of developing HCM was 6% after 12 years of follow-up. The observations of serious cardiac events in the few children with HCM strongly support clinical screening from early school age. The finding of phenotype conversion in the mid-20s warrants continued screening into adulthood. With contemporary genetic testing, almost half of the child relatives were excluded from being at risk of developing HCM. It was safe to limit the repeated clinical follow-up to the remaining children.

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Disclosures

None.

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CLINICAL PERSPECTIVE

It has been the general belief that hypertrophic cardiomyopathy (HCM) develops predominantly during the growth spurt in childhood or adolescence. This belief was based on few observations. We report that the vast majority of child carriers of sarcomere gene mutations and child relatives with unknown genetic status did not develop HCM during 12 years of follow-up. However, reports of serious cardiac events in the few children with HCM strongly support the American College of Cardiology/American Heart Association (ACC/AHA) recommendations of repeated clinical screening of children. We suggest that screening be initiated at early school age because affected child relatives have been identified at that age. The new knowledge of a low penetrance of HCM in childhood may be a great relief for affected families. The concern about a negative psychological impact of clinical and genetic screening of children was not confirmed. The low penetrance in children may influence the recommendations for screening of adults; if HCM does not develop primarily in childhood, then screening according to ACC/AHA recommendations of all phenotype-negative adults at 5-year intervals may be insufficient. Echocardiography is the diagnostic tool of choice in the clinical screening; ECG changes seem to be quite unspecific. With contemporary genetic testing, almost half of the relatives can be excluded from being at risk of developing HCM, and follow-up can be limited to the remaining relatives. Thus, our findings add to the importance of increased availability of genetic testing for cardiologists. This relates not only to HCM but also to other inherited cardiac diseases.

Penetrance of Hypertrophic Cardiomyopathy in Children and Adolescents: A 12-Year Follow-up Study of Clinical Screening and Predictive Genetic Testing

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SUPPLEMENTAL MATERIAL

Psychological evaluation

The possible psychological impact of including children and adolescents into the family screening program was evaluated by four self-reporting questionnaires. Primarily, the psychological impact of knowing the genetic test result (positive or negative) was evaluated. Secondly, the psychological impact of experiencing cardiovascular events in the family was evaluated. The questionnaires were sent to the relatives after they were informed about the long-term follow-up study and had accepted participation. Anxiety was evaluated by the State Trait Anxiety Inventory (STAI)[1]. STAI evaluates the temporary short-term (state) anxiety and the personality-related tendency to respond with anxiety (trait anxiety) with a cut off value of 42 indicating clinically significant levels of anxiety [1]. Anxiety was also evaluated by the Hospital Anxiety and Depression Scale (HADS) that evaluates depression as well[2]. For both anxiety and depression a HADS score of 0-7 was considered normal and >11 was considered highly suggestive of a mood disorder. The Impact of Event Scale (IES) was used to evaluate current subjective distress related to the family screening program[2, 3]. The IES was analyzed with respect to avoidance behavior, intrusive thoughts and hyper-arousal, and a higher score reflects a more affected psychological state. The DS14 questionnaire was used to evaluate negative affectivity and social inhibition, and a higher score reflects a more affected psychological state. The prevalence of type D personality[4] was estimated from these scores. Type D personality has been associated with increased cardiovascular risk[5, 6].

We used questionnaires developed for evaluation of adults. STAI is available for children, but the majority of relatives tested in this study were >18 years and only three children were < 15 years of age at follow-up. The adult STAI used in this study was written in a 6th grade reading level. HADS and IES were available in Danish. The STAI and DS14 were translated into Danish. To validate the

translation it was re-translated back into English by a second person, blinded with respect to the original English version. The original English version and the re-translated English version were compared by a third person (American with Danish as his second language). Disagreements between the two versions were then discussed in detail until consensus on a final Danish version was reached. When evaluating the psychological impact of the family screening program, persons not informed about the result of the genetic screening test were allocated to the group of relatives with unknown genetic status.

Table 1. Results of psychological evaluation of child relatives 12 years after inclusion to family screening for hypertrophic cardiomyopathy.

	Controls	Unknown genetic status	Carriers
N	**24**	**31**	**11**
Impact of Event Scale (IES)			
Intrusion	2±2	3±5	0.2±0.4
Avoidance behavior	3±4	7±6	3±4
Hyper-arousal	1±2	2±3	1±1
IES	6±7	12±12	4±4
Hospital Anxiety and Depression Scale (HADS)			
Anxiety score	13±2	12±2	13±2
Depression score	8±1	9±1	9±2
DS14			
Negative affectivity	7±5	7±5	9±3
Social inhibition	10±2	10±4	11±4
Type D personality	24%	22%	16%
State Trait Anxiety Inventory (STAI)			
STAI	45±5	45±4	45±2

All differences were non-significant after Bonferroni correction.

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