

openheart Sarcomere mutation negative hypertrophic cardiomyopathy is associated with ageing and obesity

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ABSTRACT

Background Despite advances in our understanding of the genetic causes of hypertrophic cardiomyopathy (HCM), a large portion of this patient population do not carry sarcomere gene mutations when screened. It remains largely unknown why patients without sarcomere mutations develop asymmetric myocardial hypertrophy.

Methods We performed a retrospective analysis of probands with HCM who underwent genetic testing to determine if clinical phenotypes were different depending on sarcomere mutation status. A medical history, three generation family history and clinical phenotyping were performed on 127 probands with HCM. Genetic screening was performed using clinically available HCM genetic testing panels.

Results We found that probands with HCM with pathogenic sarcomere mutations were over three times more likely to have a family history of HCM (66% vs 17%, $p < 0.0001$) and were diagnosed with HCM at a much younger age (32 vs 51 years old, $p < 0.0001$). In contrast, probands with HCM without sarcomere mutations were significantly more obese (body surface area $p = 0.003$, body mass index $p = 0.04$ adjusted for age) and were more likely to present with left ventricular outflow tract obstruction ($p = 0.0483$).

Conclusion Patients with sarcomere mutation negative HCM present at an older age and are more obese compared with patients with sarcomere mutation positive HCM. The role of ageing and obesity in asymmetric myocardial hypertrophy warrants further investigation.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM), a disease typically characterised by abnormal asymmetric growth of the ventricular myocardium, is a common genetic cause of heart failure and sudden death. The prevalence of this condition is $\approx 1:500$ and over the last 30 years there has been tremendous advancement in understanding the genetic underpinnings of this disorder.^{1–4} The genes implicated in HCM encode for a diverse array of proteins involved in the proper function of the cardiomyocyte sarcomere. Despite advances in understanding the genetics of this disease, the role of genetic testing in diagnosis and disease management continues to evolve.⁵

Key questions

What is already known about this subject?

- Sarcomere gene mutations are the primary genetic cause of hypertrophic cardiomyopathy (HCM).
- However, a large number of patients with HCM do not have sarcomere gene mutations and it remains poorly defined why these patients develop asymmetric myocardial hypertrophy.

What does this study add?

- We found that patients with sarcomere gene mutation negative HCM presented at an older age, were significantly more obese, and were much less likely to have a family history of HCM.

How might this impact on clinical practice?

- These findings suggest non-genetic risk factors such as obesity and ageing may contribute to asymmetric myocardial hypertrophy in some patients with HCM.
- Further studies will need to be performed to determine how these risk factors impact asymmetric myocardial remodelling and if targeted risk factor modification can impact disease progression.

Importantly, 30%–60% of individuals with HCM do not carry a germline mutation when screened for sarcomere gene mutations.⁶

The identification of sarcomere gene mutations provided a foundation from which to study the mechanisms controlling cardiomyocyte hypertrophy and pathological myocardial remodelling. Through research spanning two decades, sarcomere gene mutations have been shown to cause perturbations in cardiomyocyte calcium handling, energy utilisation and sarcomere function.^{7–12} Importantly, selective methods to correct these abnormalities are actively being pursued as therapeutic strategies in patients with HCM. It remains unclear why patients with sarcomere mutation negative HCM develop myocardial hypertrophy and if different treatment strategies are required for this patient population.

In order to explore these questions, we comprehensively evaluated a cohort of

proband with HCM to identify similarities and differences between subjects with sarcomere mutation positive and negative HCM.

METHODS

Study population

The diagnosis of HCM in proband subjects (n=127) was defined using the following criteria: left ventricular hypertrophy with a maximal wall thickness (LVWTmax) ≥ 15 mm in the absence of aortic stenosis or hypertension. In subjects with a previous diagnosis of hypertension, evidence of asymmetric myocardial hypertrophy as defined by an interventricular septal thickness to left ventricular posterior wall thickness ratio ≥ 1.5 and LVWTmax ≥ 15 mm were required. All patients met with a physician and genetic counsellor and a three generation family history was documented. All subjects had a comprehensive physical examination, seated non-invasive blood pressure measurement, 12-lead ECG and Doppler echocardiography performed. Subjects were excluded from our analysis if they were not screened for sarcomere gene mutations or if they did not have complete diagnostic imaging to verify phenotype status.

Evaluation for sarcomere gene mutations

After appropriate genetic counselling and following patient consent, blood samples were obtained and sent to either Harvard Partners Laboratory of Molecular Medicine (Boston, Massachusetts, USA) or GeneDx (Gaithersburg, Maryland, USA) for sequencing and variant classification following American College of Medical Genetics-accepted guidelines.¹³ The following genes were sequenced in all subjects: ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNC1, TNNI3, TNNT2, TPM1, PRKAG2, LAMP2, GLA and TTR.¹⁴ Subjects who tested positive for pathogenic DNA variants in PRKAG2, LAMP2, GLA or TTR genes were excluded from analysis (n=2). Sarcomere gene variants classified as pathogenic, or likely pathogenic, were considered sarcomere gene mutations. All DNA variants classified as sarcomere mutations had a minor allele frequency $< 1 \times 10^{-4}$.¹⁵

Echocardiographic imaging

Doppler echocardiography was performed on all subjects to assess LVWTmax, posterior or minimum left ventricular wall thickness, left ventricular function and the measurement of the peak left ventricular outflow tract (LVOT) gradient. LVOT obstruction was defined as peak gradient ≥ 30 mm Hg at rest or with exercise.

Statistical analysis

Mann-Whitney U test was used to assess continuous variables and Fisher's exact test was used to assess categorical data. To adjust for age, we performed multiple regression analyses for each outcome individually with sarcomere mutation as the main predictor. Age was adjusted for by entering into the model with non-linear effects using the restricted cubic spline.

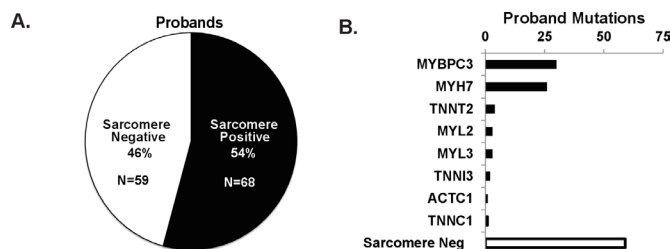


Figure 1 Sarcomere mutation status and family history of HCM. (A) Sarcomere mutation prevalence in subjects with a clinical diagnosis of HCM (n=127). (B) Distribution of mutations across sarcomere genes screened. HCM, hypertrophic cardiomyopathy.

RESULTS

Family history of HCM is much less common in subjects with sarcomere mutation negative HCM

Of the 127 probands with HCM who underwent genetic screening for sarcomere gene mutations, 54% (n=68) tested positive for a pathogenic sarcomere mutation and 46% (n=59) tested negative for a sarcomere mutation (figure 1A and online supplemental table S1). The most common sarcomere genes with mutations were Myosin Binding Protein C3 (MYBPC3) and Myosin Heavy Chain 7 (MYH7) (figure 1B). Family history of HCM was over three times more common in subjects with sarcomere positive HCM compared with subjects with sarcomere negative HCM (p<0.0001, figure 2).

Patients with sarcomere mutation negative HCM present at an older age

Proband subjects with sarcomere positive HCM (n=68) were diagnosed 18 years earlier than probands with sarcomere negative HCM (n=59) (median 32.5 vs 51

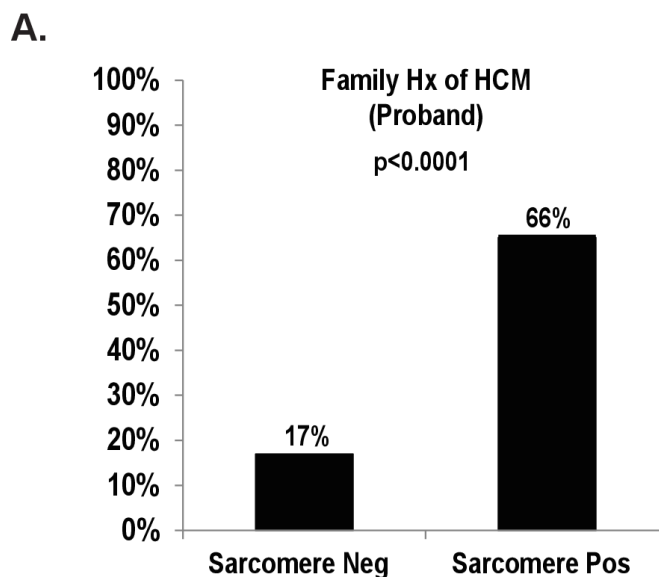


Figure 2 Family history of HCM in sarcomere mutation negative and positive probands. (A) Subjects with sarcomere mutation negative HCM and sarcomere mutation positive HCM with a family history of HCM (%). HCM, hypertrophic cardiomyopathy.

Table 1 Baseline characteristics of proband subjects with HCM

	Sarcomere negative N=59	Sarcomere positive N=68	P value	Adjusted p value
Age at diagnosis (years)	51.0 (39.5,59.0) 48±14.5	32.5 (16.8,46.3) 32±16.8	<0.0001	
Male (n)	38 (64%)	35 (51%)	0.15	
Systolic BP (mm Hg)	123 (112,137) 126.5±18.9	120 (107,128) 119±16.3	0.0253	0.398
Diastolic BP (mm Hg)	74 (67,81) 74.3±9.5	70 (62,78) 69.5±10.1	0.0242	0.196
Mean arterial pressure (mm Hg)	91.3 (83.3,99.2) 91.7±11.4	86.7 (78.3,93.3) 85.9±10.9	0.0163	0.232
BSA (m ²)	2.14 (1.95,2.22) 2.09±0.25	1.91 (1.73,2.11) 1.90±0.33	0.0008	0.003
BMI (kg/m ²)	31.1 (27.7,34.9) 31.7±5	27.7 (23.3,33.7) 28.2±6.9	0.0026	0.037

All values expressed as median (25% percentile, 75% percentile) and mean±SD.

BMI, body mass index; BP, blood pressure; BSA, body surface area; HCM, hypertrophic cardiomyopathy.

years old, $p<0.0001$, [table 1](#)). To control for an effect of family history on age of presentation, we performed a subgroup analysis of probands with only HCM with no family history of HCM (n=72). We found that probands with HCM with sarcomeric mutations but with no family history of HCM still presented 15 years earlier in life compared with probands with sarcomere negative HCM (median 37 vs 52 years old, $p=0.0004$). Therefore, probands with HCM with sarcomeric mutations presented at an earlier age regardless of family history. Both sarcomere positive and negative probands had a similar gender distribution. There was a slightly higher blood pressure in the probands with sarcomere negative HCM (~4 mm Hg), but when adjusted for age, this was not statistically different.

Patients with sarcomere mutation negative HCM are more obese

In addition to the sarcomere negative probands presenting at an older age, these subjects were also more obese with larger body surface area (BSA) and body mass index (BMI) ([table 1](#), age adjusted $p=0.003$ (BSA) and $p=0.037$ (BMI)).

Patients with sarcomere mutation negative HCM are more likely to have LVOT obstruction

The degree of asymmetric myocardial hypertrophy was less in the sarcomere mutation negative subjects and there was a trend to lower LVWTmax ([table 2](#)). When LVWTmax was indexed to BSA, there was a significant difference in the groups, reflective of the increased obesity

Table 2 Myocardial hypertrophy and LVOT obstruction

	Sarcomere negative N=59	Sarcomere positive N=68	P value
LVWTmax (mm)*	20 (18,22) 20.3±4.1	21 (18,27) 22.6±6.5	0.0686
Ratio LVWTmax:LVWTmin*	1.8 (1.57,2.1) 1.84±0.4	2.1 (1.66,3.0) 2.48±1.1	0.0011
LVWTmax/BSA (mm/mm ²)*	9.6 (8.1,10.7) 9.9±2.3	10.9 (8.9,13.8) 12.3±4.8	0.0006
LVOT obstruction (%)†	32 (54)	24 (35)	0.0483
LVOT gradient (mm Hg)*	105 (43,141) 98.5±56.3	71 (43,91) 75±51.3	0.1050

*Values expressed as median (25% percentile, 75% percentile) and mean±SD.

†LVOT obstruction defined as LVOT gradient ≥ 30 mm Hg.

BSA, body surface area; LVOT, left ventricular outflow tract; LVWTmax, maximum left ventricular wall thickness; LVWTmin, minimum left ventricular wall thickness.

in sarcomere mutation negative subjects (table 2). LVOT obstruction (>30 mm Hg) was more prevalent in subjects with sarcomere mutation negative HCM (table 2).

DISCUSSION

There have been significant advances in our understanding of the genetic and molecular mechanisms regulating the development of HCM caused by sarcomere gene mutations. However, approximately half of all patients with HCM who undergo genetic screening do not have a sarcomere mutation and the cause of HCM in these individuals remains poorly defined. We compared HCM with and without sarcomere mutations and discovered that family history, age of diagnosis and obesity were quite different between the cohorts.

We found that probands with sarcomere mutation positive HCM were much more likely to have a family history of HCM. This correlation between family history and sarcomere mutation status in HCM has also been reported in HCM cohorts from other centres.^{16–20} It would be logical that since sarcomere mutations are associated with an autosomal dominant inheritance pattern that patients who harbour sarcomere mutations would be likely to have a family history of disease. However, the much lower rate of clinically affected family members in pedigrees of patients with sarcomere negative HCM suggests that the cause of asymmetric myocardial hypertrophy may be related to multiple different factors. One possibility is that these patients harbour germline mutations with very low penetrance that are not routinely screened for. Alternatively, the more likely explanation is that there are non-heritable somatic mutations or non-genetic environmental factors (or a combination of these two factors) that contribute to the development of asymmetric myocardial hypertrophy in these patients. Our results suggest that ageing and obesity may serve as potential non-genetic factors that contribute to disease development in patients with sarcomere negative HCM.

We found that subjects with sarcomere negative HCM were more obese compared with subjects with sarcomere positive HCM. Supporting our results is earlier work which showed that obesity is independently associated with an increase in left ventricular mass and may affect progression of heart failure in a cohort of subjects with non-genotyped HCM.^{21 22} More recently, Fumagalli *et al* again demonstrated that obesity is associated with long-term adverse events in HCM overall.²³ Our results suggest that obesity may have a greater impact on disease development in the population with sarcomere negative HCM and this finding was independent of age. Obesity has been associated with increased heart mass and myocardial wall thickness in multiple studies and remains an independent risk factor for left ventricular hypertrophy after controlling for other comorbidities.^{24–26} In addition, myocardial hypertrophy has been shown to be reversible in morbidly obese individuals after aggressive weight loss.²⁷ These data further confirm that obesity contributes

to myocardial growth. Multiple mechanisms have been proposed for how obesity increases myocardial growth. These include changes in systemic haemodynamics and alterations in circulating hormone levels, both of which can directly alter cardiomyocyte growth. Further investigation is required to determine how obesity influences asymmetric myocardial growth in HCM and if aggressive weight loss can reverse this remodelling process.

In addition to obesity, we also found that patients with sarcomere negative HCM were diagnosed much later in life. Importantly, we found that the later age of presentation in probands with sarcomere negative HCM persisted even when individuals with a family history of HCM were excluded from the comparison. Therefore, family history does not appear to be confounder of this association. These results suggest that another potential driver of asymmetric myocardial hypertrophy in HCM may be related to normal ageing. Indeed, ageing has been associated with increasing left ventricular hypertrophic remodelling.^{28–30} Similar to obesity, there are multiple mechanisms through which ageing could increase left ventricular hypertrophy. Some proposed mechanisms are ageing-related increased vascular stiffness, myocardial fibrosis and ageing-related cardiomyocyte dysfunction.³⁰ It remains to be elucidated how ageing influences the asymmetric myocardial hypertrophy seen in HCM.

LIMITATIONS

This was a cohort that was collected from a single centre and therefore may not be representative of patient populations in other geographical areas. However, it should be noted that the distribution of sarcomere gene mutations in our cohort was similar to datasets from other cohorts in the USA and Europe, with MYBPC3 and MYH7 gene mutations accounting for ~80% of the identified mutations in our probands with HCM.⁶ In addition, we found a similar trend with other studies with regard to patients with sarcomere positive HCM being much more likely to have a family history of HCM.^{16–20}

CONCLUSION

A large portion of patients with HCM do not test positive for sarcomere gene mutations and the cause of disease in these individuals remains elusive. In our study, we found that patients with sarcomere negative HCM are much less likely to have a family history of HCM, present later in life and are more obese than patients with HCM with sarcomere gene mutations. It will be important to investigate how obesity and ageing influence asymmetric myocardial remodelling and if therapies targeting these pathways can benefit this patient population.

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Competing interests None declared.

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Table S1.

Gene	CDS	Protein	Total Number of HCM Probands With Mutation
ACTC1	698C>G	A233G	1
MYBPC3	1624G>C	E542Q	6
MYBPC3	2308G>A	D770N	1
MYBPC3	2374T>C	W792R	1
MYBPC3	2429G>A	R810H	1
MYBPC3	1624+4A>T		1
MYBPC3	2670G>A	W890X	2
MYBPC3	3330+2T>G		3
MYBPC3	3330+5G>A		1
MYBPC3	3330+5G>C		1
MYBPC3	833del>G	G278EfsX22	1
MYBPC3	1000G>A	E334K	1
MYBPC3	927-9G>A		3
MYBPC3	1504C>T	R502W	1
MYBPC3	2864_2865delCT	P955RfsX95	1
MYBPC3	3192_3193insC	K1065GlnfsX12	1
MYBPC3	3742_3759dup18	G1248_C1253dup	1
MYBPC3	2373_2374insG	W792VfsX41	1
MYBPC3	927-9G>A		1
MYH7	1166G>A	G389E	1
MYH7	1324C>T	R442C	2
MYH7	1357C>T	R453C	1
MYH7	1987C>T	R663C	1
MYH7	1988G>A	R663H	4
MYH7	2155C>T	R719W	4
MYH7	2221G>C	G741R	1
MYH7	2609G>A	R870H	1
MYH7	2770G>A	E924K	1
MYH7	2221G>T	G741W	1
MYH7	2788G>A	E930K	1
MYH7	2846A>T	E949V	1
MYH7	4130C>T	T1377M	1
MYH7	4487A>C	E1496A	1
MYH7	5135G>A	R1712Q	1

MYH7	739T>C	F247L	1
MYH7	799C>G	L267V	1
MYH7	1405G>A	D469N	1
MYH7	2156G>A	R719Q	1
MYH7	611G>A	R204H	1
MYL2	119G>A	R40K	1
MYL2	163G>T	A55S	1
MYL2	239C>A	T80N	1
MYL3	427G>A	E143K	2
MYL3	517A>G	M173V	1
TNNC1	8A>T	D3V	1
TNNI3	470C>T	A157V	1
TNNI3	509G>A	R170Q	1
TNNT2	487_489delGAG	E163del	1
TNNT2	814dupC	Q272PfsX11	1
TNNT2	536C>T	S179F	1