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Insights into genotype–phenotype correlation in hypertrophic cardiomyopathy. Findings from 18 Spanish families with a single mutation in MYBPC3

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ABSTRACT

Background Mutations in the cardiac myosin-binding protein C (MYBPC3) gene are frequently found as a cause of hypertrophic cardiomyopathy (HCM). However, only a few studies have analysed genotype–phenotype correlations in small series of patients. The present study sought to determine the clinical characteristics, penetrance and prognosis of HCM with an identical mutation in MYBPC3.

Methods 154 non-related patients with HCM (aged 55±16 years, 100 (64.9%) males) were studied. 18 (11.7%) were found to have an identical mutation in the MYBPC3 gene (IVS23+1G→A). Pedigree analysis, including both clinical evaluation and genotyping, was performed.

Results 152 individuals (mean age 37±18 years, 53.3% males) from 18 families were evaluated. 65 carriers of the IVS23+1G→A mutation were identified, 61.5% of whom met HCM diagnostic criteria. Penetrance of the disease increased with age, with 50% affected at 46 years of age. Males tended to develop the disease earlier than females. 7 (15.6%) had systolic dysfunction. Compared with the rest of the HCM cohort, probands with the mutation had more hypertrophy and were younger at diagnosis. There was a trend towards a reduced survival free from sudden death (SD) (HR 1.71; 95% CI 0.98 to 2.98, p=0.059). There were 17 SD cases in 12 families with the mutation.

Conclusions The MYBPC3 IVS23+1G→A mutation is associated with middle-age onset disease and poor outcome, with a significant proportion of patients developing systolic impairment and a high SD risk profile.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with heterogeneous morphological, functional and clinical features and prognosis.[1–3] HCM is caused by mutations in nine genes that encode sarcomeric contractile proteins,[4] and less commonly associated with mutations in other genes.[5] One of the most common genetic causes of HCM in many populations studied involves mutations in MYBPC3, the gene encoding myosin-binding protein C.[6 7] Several studies have tried to define the phenotype associated with mutations in this gene. Although initially MYBPC3-HCM was associated with later onset, less hypertrophy, lower penetrance and better prognosis,[8–11] recent reports showed that the phenotype did not differ significantly from that of patients with other thick-filament HCM or thin-filament HCM with respect to age at diagnosis or severity.[12–14] Nevertheless, evidence is based on a few studies and reports from small groups of patients. Over 150 HCM-causing mutations in MYBPC3 have been reported to date. Information on genotype–phenotype correlation is still weak, and different mutations in the same gene seem to behave differently in terms of clinical presentation and outcomes.[15]

The main aim of this study was to report the clinical characteristics of affected patients who were found to have an identical mutation in the MYBPC3 gene (IVS23+1G→A),[16] and the penetrance of the disease in carriers. The secondary aim was to compare the clinical and risk profile of probands with the IVS23+1G→A mutation with an HCM population without this mutation.

METHODS

Study population

One hundred and fifty-four consecutive patients with HCM (aged 55±16, 100 (65.9%) males) were included. A pedigree was drawn for each patient and first-degree relatives were screened using the same protocol. Relatives were contacted by the probands and visited our clinic of their own free will. Blood samples were taken for genetic analysis and all patients and their relatives gave written consent. The evaluation of probands and relatives included medical history, physical examination, 12-lead ECG, M-mode, two-dimensional and Doppler echocardiography, and, in affected individuals, ambulatory 24 h Holter ECG and exercise test. The study was approved by the local Ethics Committee.

HCM was diagnosed by the presence of a hypertrophied left ventricle (maximum left ventricular wall thickness (MLVWT) ≥15 mm in adult index patients or ≥13 mm in adult relatives) in the absence of another cardiac or systemic disease able to cause left ventricular hypertrophy (LVH).[1]

Disease penetrance was determined by echocardiography and/or ECG criteria. Relatives with minor echocardiographic or ECG findings not sufficient to meet the diagnostic criteria were considered 'possible HCM'. All patients underwent risk stratification and were managed following recommended guidelines.[1]

Genetic study

A screening of all known HCM-causing mutations reported in the literature, up to January 2006, was performed. A platform based on single nucleotide polymorphism (SNP) technology (Sequenom MassARRAY SNP genotyping system) was available for the purpose of the study. Samples from all 154 probands were run in this platform. Positive results were confirmed by direct sequencing. Complete double strand direct sequencing of all the coding exons and flanking intronic regions of the five most prevalent genes associated with HCM (MYH7, MYBPC3, TNNT2, TNNI3 and TPM1) was carried out in the 18 probands with the MYBPC3 IVS23+1G→A mutation to evaluate the presence of additional mutations. Relatives from positive probands were offered genetic testing. DNA was extracted using standard protocols from peripheral blood samples. Four published markers that flank the MYBPC3 gene were used to investigate the presence of a founder effect in carriers of MYBPC3 IVS23+1G→A (MyBPC3-CA, D11S4109, D11S1784 and D11S1326)[13]

Statistical analysis

A dedicated (based on Access 2000, Microsoft) database was created for the study. The SPSS for PC statistical program (SPSS, Chicago, Illinois, USA, version 11.0) was used for the analysis. Continuous variables are presented as mean±SD. Two-tailed Student t test, χ^2 test or Fisher exact test were used to compare group data where appropriate. Two hundred and sixty-four living patients with HCM and 67 sudden death (SD) cases from the cohort of 154 families are included in the survival analysis (n=331). The age at death in SD cases and age at last follow-up in affected living patients were used for survival analysis. A Kaplan–Meier chart was produced and Cox regression analysis was employed for comparison in figure 3. A p value <0.05 was considered statistically significant.

RESULTS

Eighteen (11.7%) out of 154 apparently non-related HCM probands were carriers of the same mutation in the MYBPC3 gene: g15131G→A or IVS23+1G→A (reference sequence U91629.1 gi: 2920822), 13 (8.4%) had other described mutations (six MYBPC3, two MYH7, one TNNT2 and one TNNC1), and in the rest (123, 79.9%) genetic testing was negative. A founder effect was confirmed in the 18 probands with MYBPC3 IVS23+1G→A.

Table 1 summarises the clinical characteristics of probands with the IVS23+1G→A mutation compared with the rest of the cohort. Probands with the IVS23+1G→A mutation were more frequently males and younger at diagnosis, had more severe hypertrophy, more non-sustained ventricular tachycardia (NSVT) on Holter, a higher percentage of family history of sudden death, severe gradient and higher number of risk factors than the other probands. Four (22.2%) probands with the mutation had systolic dysfunction versus 15 (11.0%) from the group of non-carriers, (p=0.2).

A total of 152 individuals (mean age 37±18 years, 81 (53.3%) males) from the 18 families with the IVS23+1G→A mutation were evaluated. In the clinical study 45 (29.6%) met the diagnostic criteria for HCM, 8 (5.2%) were classified as possible HCM and 97 (63.8%) were considered clinically unaffected. Clinical characteristics of the 45 affected individuals are summarised in table 2. Of note, male patients had significantly more hypertrophy, more frequently had a reverse pattern of hypertrophy and had a worse risk profile than females. All seven patients who had systolic dysfunction were males (mean age 42 (15) years). Five cases in whom genetic testing was not possible (two died of heart failure and three refused to undergo the test) are included in this group.

Table 1 Characteristics of 154 hypertrophic cardiomyopathy probands evaluated regarding results of the genetic testing

		MYBPC3 IVS23+1G→A		
	p Value	Carriers n (%), mean (SD)	Non-carrriers n (%), mean (SD)	Total n (%), mean (SD)
n		18 (11.7%)	136 (88.3%)	154 (100%)
Male gender	0.02	16 (88.9%)	84 (61.8%)	100 (64.9%)
Age at diagnosis	0.02	39.1 (17.0)	48.9 (16.4)	47.7 (16.7)
Age at evaluation	0.06	48.6 (17.4)	56.2 (16.2)	55.3 (16.4)
Obstruction	0.2	8 (44.4%)	40 (29.6%)	48 (31.4%)
Severe obstruction	0.05	5 (27.8%)	14 (10.3%)	19 (12.3%)
Max LVH	0.01	23.3 (4.3)	20.4 (4.8)	20.7 (4.8)
Severe LVH	0.1	2 (11.1%)	4 (2.9%)	6 (3.9%)
Left atrium	0.8	45.3 (6.3)	44.7 (6.8)	44.8 (6.7)
Pattern 1				
No hypertrophy	–		6 (4.4%)	6 (3.9%)
ASH	0.2	15 (83.3%)	91 (66.9%)	106 (68.8%)
Concentric	0.9	3 (16.7%)	21 (15.4%)	24 (15.6%)
Apical	0.2		15 (11.0%)	15 (9.7%)
Others	–		3 (2.2%)	3 (1.9%)
Pattern 2				
No hypertrophy	–		6 (4.4%)	6 (3.9%)
Reverse	0.046	14 (77.8%)	72 (52.9%)	86 (55.8%)
Neutre	0.9	4 (22.2%)	33 (24.3%)	37 (24.0%)
Apical	–		11 (8.1%)	11 (7.1%)
Sigmoid	–		14 (10.3%)	14 (9.1%)
Systolic impairment	0.2	4 (22.2%)	15 (11.0%)	19 (12.3%)
Diastolic function				
Normal	–		8 (6.1%)	8 (5.4%)
Impaired relaxation	0.09	3 (18.8%)	54 (40.9%)	57 (38.5%)
Pseudonormal	<0.001	13 (81.3%)	35 (26.5%)	48 (32.4%)
Restrictive	–		6 (4.5%)	6 (4.1%)
Not possible	–		29 (21.3%)	29 (19.6%)
Atrial fibrillation	0.5	5 (27.8%)	49 (36.0%)	54 (35.1%)
NYHA	0.9			
I	0.7	7 (38.9%)	46 (33.8%)	53 (34.4%)
II	0.8	8 (44.4%)	56 (41.2%)	64 (41.6%)
III–IV	0.6	3 (16.7%)	34 (25.0%)	37 (24.0%)
Syncope	0.2	5 (29.4%)	22 (16.2%)	27 (17.6%)
NSVT	0.04	9 (52.9%)	33 (28.2%)	42 (31.3%)
ABPR	0.1	5 (41.7%)	16 (20.5%)	21 (23.3%)
FHSCD	0.03	6 (33.3%)	18 (13.2%)	24 (15.6%)
No. of risk factors*	<0.001	1.72 (1.23)	0.73 (0.81)	0.84 (0.9)
≥2 risk factors	0.002	9 (50.0%)	21 (15.4%)	30 (19.5%)

*Six risk factors of sudden death were considered: NSVT, ABPR if age <45 years old, FHSCD, syncope, severe LVH and severe gradient (>90 mm Hg).
ABPR, abnormal blood pressure response during upright exercise; ASH, asymmetrical septal hypertrophy; FHSCD, family history of sudden cardiac death; max LVH, maximal left ventricular wall thickness (mm); MYBPC, myosin-binding protein C gene; NSVT, non-sustained ventricular tachycardia on Holter monitoring; NYHA, New York Heart Association dyspnoea class; obstruction, left ventricular outflow tract gradient (>30 mm Hg).

Genetic study led to the identification of a total of 65 carriers and 64 non-carriers, whereas DNA samples were not available in 23 relatives. Figure 1 summarises the genotype–phenotype correlations. Forty carriers (61.5%) had HCM, 2 (3.1%) were considered possibly affected and 23 (35.4%) were considered clinically unaffected. Affected carriers were significantly older than unaffected carriers (43 (15) vs 32 (16) years, p=0.02). Penetrance of the disease increased with increasing age, with a 50% chance of developing the disease at 46 years of age (figure 2). Males tended to develop the disease earlier than females (the likelihood for developing HCM in 50% of cases was 42 years for males and 50 years for females, p=0.2).

Table 2 Characteristics of the 45 clinically affected patients

	Female n (%), mean (SD)	Male n (%), mean (SD)	Total n (%), mean (SD)	p Value
n	13 (28.9%)	32 (71.1%)	45 (100%)	
Age	52.9 (11.7)	44.8 (15.8)	47.1 (15.1)	0.1
Age at diagnosis	46.0 (13.2)	39.4 (16.0)	41.3 (15.4)	0.2
No. with age at diagnosis ≥50 years	6 (46.2%)	8 (25.0%)	14 (31.1%)	0.3
Reason for diagnosis				
Incidental	1 (7.7%)	7 (21.9%)	8 (17.8%)	0.4
Family screening	4 (30.8%)	11 (34.4%)	15 (33.3%)	0.9
Symptoms	8 (61.5%)	14 (43.8%)	22 (48.9%)	0.3
Hypertensive	5 (38.5%)	7 (21.9%)	12 (26.7%)	0.3
Abnormal ECG	13 (100%)	30 (93.7%)	43 (95.6%)	—
Q waves	5 (38.5%)	11 (34.4%)	16 (35.5%)	0.8
ST deviations	10 (76.9%)	19 (59.4%)	29 (64.4%)	0.4
T waves				
Negative	9 (69.2%)	20 (62.5%)	29 (64.4%)	0.9
Deep negative (>5 mm)	1 (7.7%)	3 (9.4%)	4 (8.9%)	0.9
Rmax+Smax	22.7 (7.5)	33.5 (16.4)	30.2 (15.1)	0.04
QRS duration	94.8 (15.3)	96.4 (15.9)	95.9 (15.5)	0.7
Atrial fibrillation	1 (7.7%)	2 (6.3%)	3 (6.7%)	0.9
Atrial fibrillation (FU)	2 (15.4%)	8 (25.0%)	10 (22.2%)	0.7
Max LVH	19.0 (3.9)	22.3 (5.2)	21.3 (5.0)	0.047
Severe LVH	0 (0%)	4 (12.9%)	4 (9.1%)	0.3
Obstruction	4 (30.8%)	10 (31.3%)	14 (31.1%)	0.9
Severe obstruction	2 (15.4%)	4 (12.5%)	6 (13.3%)	0.9
Pattern 1				
No hypertrophy	6 (46.2%)	6 (18.7%)	12 (26.7%)	0.1
ASH	4 (30.8%)	21 (65.6%)	25 (55.6%)	0.02
Concentric	2 (15.4%)	2 (6.2%)	4 (8.9%)	0.6
Pattern 2				
No hypertrophy	6 (46.2%)	6 (18.7%)	12 (26.7%)	0.1
Reverse	0 (0%)	17 (53.1%)	18 (40.0%)	0.001
Neutre	6 (46.2%)	5 (15.6%)	11 (24.4%)	0.052
Sigmoid	0 (0%)	1 (3.1%)	1 (2.2%)	—
Left atrium	43.4 (5.8)	43.7 (6.4)	43.6 (6.2)	0.9
LVEDd	40.7 (5.0)	45.2 (6.8)	44.1 (6.6)	0.1
Systolic impairment	0 (0%)	7 (21.9%)	7 (15.6%)	0.09
Diastolic function				
Normal	5 (38.5%)	6 (18.7%)	11 (24.4%)	0.2
Impaired relaxation	4 (30.8%)	7 (21.9%)	11 (24.4%)	0.7
Pseudonormal	1 (7.7%)	13 (40.6%)	14 (31.1%)	0.03
Restrictive	1 (7.7%)	0 (0%)	1 (2.2%)	—
Not possible/not available	2 (15.4%)	6 (18.7%)	8 (17.7%)	
NYHA				
I	6 (46.2%)	20 (62.5%)	26 (57.8%)	0.3
II	3 (23.1%)	9 (28.1%)	12 (26.7%)	0.7
III–IV	4 (30.8%)	3 (9.4%)	7 (15.6%)	0.2
Syncope	0 (0%)	8 (25.0%)	8 (17.8%)	0.08
Palpitations	4 (30.8%)	10 (31.2%)	14 (31.1%)	0.9
Chest pain	4 (30.8%)	4 (12.5%)	8 (17.8%)	0.2
NSVT	7 (53.8%)	11 (40.7%)	18 (45.0%)	0.4
ABPR	4 (44.4%)	6 (30.0%)	10 (34.5%)	0.7
No. of risk factors*				
0	2 (15.4%)	10 (31.3%)	12 (26.7%)	
1	11 (84.6%)	10 (31.3%)	21 (46.7%)	
2	0 (0%)	4 (12.5%)	4 (8.9%)	
≥3	0 (0%)	8 (25.1%)	8 (17.7%)	
Mean no. of risk factors	0.85 (0.38)	1.38 (1.29)	1.22 (1.1)	0.04
Events				
Sudden death	0 (0%)	1 (3.1%)	1 (2.2%)	—
Resuscitated cardiac arrest	1 (7.7%)	0 (0%)	1 (2.2%)	—
Heart failure death	0 (0%)	2 (6.2%)	2 (4.4%)	—
Stroke	0 (0%)	1 (3.1%)	1 (2.2%)	—

It was not possible to assess the pattern of hypertrophy in 4 patients.
*Six risk factors of sudden death were considered: NSVT, ABPR if age<45 years of age, FHSCD, syncope, severe LVH and severe gradient (>90 mm Hg).
ABPR, abnormal blood pressure response during upright exercise; ASH, asymmetrical septal hypertrophy; chest pain, exertional chest pain; FHSCD, family history of sudden cardiac death; FU, follow-up; left atrium, left atrial diameter (mm); LVEDd, left ventricular end diastolic diameter in mm; max LVH, maximal left ventricular wall thickness (mm); NSVT, non-sustained ventricular tachycardia on Holter monitoring; NYHA, New York Heart Association dyspnoea class; obstruction: left ventricular outflow tract gradient (>30 mm Hg).

There were two non-carriers who met the diagnostic criteria for HCM: one father of a proband (aged 81 years) with suspected HCM on the mother's side who had 24 mm non-obstructive LVH with clear LVH criteria in the ECG; and a young daughter of an affected patient (aged 22 years) with a diagnostic ECG (deep negative T waves in the precordial leads) but a normal echocardiogram.

There were 4 (8.8%) events during follow-up (mean 36 (28) months): two heart failure deaths, one SD and one resuscitated cardiac arrest. The two cases of heart failure death were males (aged 29 and 65 years), the SD case was a 33-year-old male with four of the traditional risk factors, and there was a women aged 53 who was successfully resuscitated at day 3 after a alcohol septal ablation procedure. An implanted cardioverter defibrillator (ICD) was implanted in eight high-risk patients (one secondary and seven for primary prevention) with no recorded treatments to date. Three patients (two female and one male) underwent alcohol septal ablation, one of whom also needed surgical myectomy for persisting obstruction and limiting symptoms.

Context of SD in families with the IVS23+1G→A mutation

There were 17 cases of SD in 12 (66.7%) families with the mutation. The mean age of SD cases was 45 (18) years, with 14 (82.4%) males. Four families accumulated more than one SD (F199, three cases; F40, F56 and F240, two cases).

SD happened prior to initiation of the study in 15 subjects, for which the context of death was obtained from interviews of relatives. In two cases, SD occurred during exercise (both were athletes, aged 21 and 27), seven occurred during daily normal

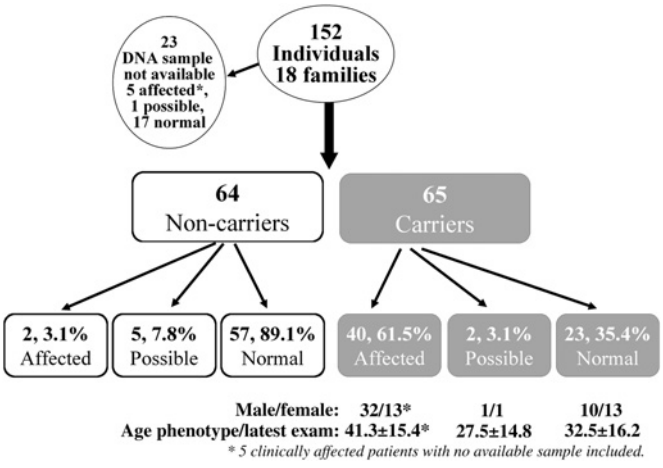


Figure 1 Summary of the results from clinical and genetic study of the population.

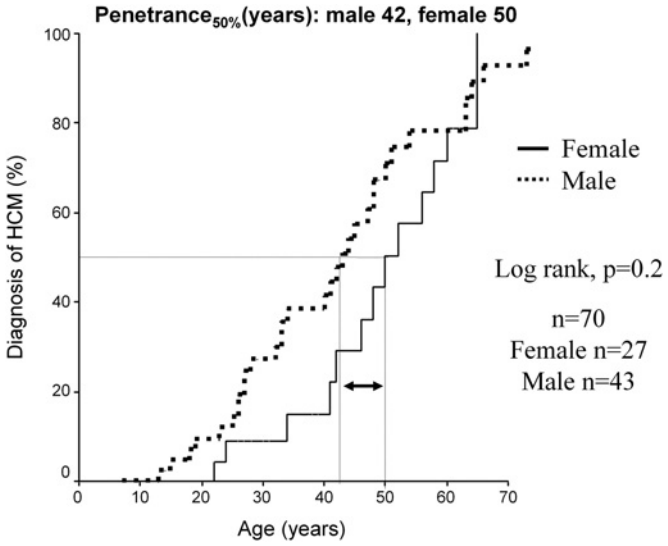


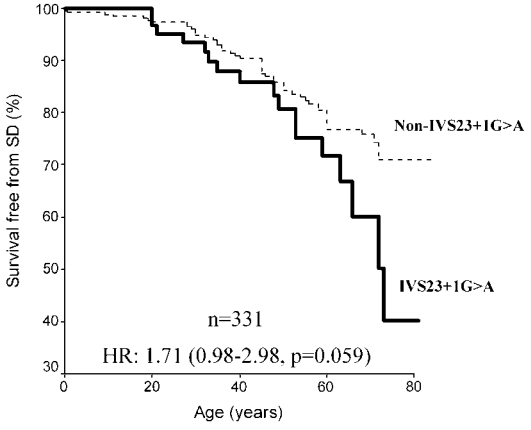
Figure 2 Penetrance of the disease (HCM) in carriers of MYBPC3 IVS23+1G>A.

activities, two at rest, one during sleep, one related to emotional stress and in four the context was unknown. In 6 (33.3%) patients HCM was diagnosed prior to death.

Genetic testing results in relatives with non-diagnostic ECG and echocardiographic features

Fourteen (13.3%) individuals out of 105 who did not meet HCM criteria had some suggestive ECG features. Four of them were carriers, nine non-carriers and in one a blood sample was not available for genetic testing. Similarly, 16 (15.2%) individuals had non-diagnostic echocardiographic features (three carriers, ten non-carriers and three with no available sample).

There were three carriers (two females and one male) older than 50 years of age with no evidence of HCM (a 75-year-old male had a flat T wave laterally and a 14 mm sigmoid septum with normal systolic function; a female aged 59 had a normal echocardiogram with non-diagnostic mild inferolateral repolarisation abnormalities; and the second female, aged 61, was hypertensive and had 13 mm of septal thickness with non-diagnostic ECG).



Number of patients at risk

MYBPC3 IVS23+1G>A	62		61		43		18		2
Non-MYBPC3 IVS23+1G>A	269		255		197		112		14

Figure 3 Survival free from Sudden Death in 2 groups regarding results from genetic testing in the proband.

Events and survival

There were a total of 67 SDs reported in 44 (28.6%) of the 154 families evaluated. There were six patients with HCM who died of heart failure, three were transplanted, there were three stroke-related deaths, two had an appropriate ICD discharge and two died of non-related causes.

When all living patients from the cohort and SD cases were included, survival analysis demonstrated a trend towards a reduced survival free from SD in the group with the IVS23 +1G→A mutation compared with the non-IVS23+1G→A group (HR 1.71, 95% CI 0.98 to 2.98, p=0.059) (figure 3).

DISCUSSION

The present study with 65 carriers from 18 families represents the largest series of patients with the same mutation in MYBPC3 reported to date.[11] Overall 60% of our carriers of IVS23 +1G→A had HCM. Our study confirms the association of the IVS23+1G→A mutation in the MYBPC3 gene with the development of HCM. This mutation has been previously described in four families from different countries, with partial information from a total of 19 carriers available,[16–18] (http://www.cardiogenomics.med.harvard.edu/home). Carrier *et al*[9 16] described a French family with four members affected out of seven carriers (mean age at diagnosis of 55 years), with all non-affected carriers being females, and two of them aged <18 years of age. No deaths or transplants were reported in this series. Later reports[18] have described a different prognosis, with three SDs in male relatives (aged 13, 33 and 42 years) of patients with this mutation. Other authors (http://www.cardiogenomics.med.harvard.edu/home) have found an association between the mutation and late onset of development of systolic impairment.

In agreement with a recent report from Kubo *et al*[13] with 39 carriers with another mutation in MYBPC3 (V592fs/8), our affected carriers with the IVS23+1G→A mutation described here were particularly prone to develop systolic dysfunction (18% and 15%, respectively). However, in our population, age at presentation of systolic dysfunction was remarkably younger and there was a clear male predominance compared with the Japanese study.

There were three carriers older than 50 years of age with no evidence of HCM. Regression of hypertrophy has been described in association with development of systolic dysfunction.[19 20] Systolic function and LV volumes were normal in all three cases. Other protective genetic or environmental factors could have played a role in these patients. Genetic diagnosis in these cases led to identification of other relatives.

It has recently been suggested that the pattern of hypertrophy can predict genetic testing success.[21] In keeping with this observation, the reverse type of pattern was highly prevalent within those affected with IVS23+1G→A and this percentage was significantly higher than in the group of patients with negative genetic testing. Nevertheless, different phenotypes were present in our population. Of note, three carriers exhibit features consistent with LV non-compaction (one proband and two relatives). This finding has been reported in patients with MYBPC3 mutations in a recent paper[22]

Possible mechanisms of disease

Information from earlier publications from Carrier *et al*[16] suggested that the IVS23+1G→A mutation involves DNA

splicing sites leading to the loss of the whole of exon 23. These authors also demonstrated that this mutation produces a truncated protein C which is unable to bind titin and myosin. Analysis of >600 healthy controls[6 16 17 23 24] and 236 hypertensive patients with no LVH from another ongoing project from our group (data not published) failed to identify this mutation.

Symptoms and outcomes

Similar to other series, the majority of affected carriers were in New York Heart Association (NYHA) class I–II (85%) and <20% reported syncope. In keeping with the literature, females had less maximal hypertrophy, smaller ventricles and were in a worse NYHA functional class.[19] The percentage of patients with atrial fibrillation in our series (24%) was similar to that reported by other authors.[25–27]

Males in our population accumulated significantly more risk factors of sudden death. Globally, differences in the risk profile between genders have not been demonstrated in large populations of patients with HCM.[28 29] In summary, male carriers of IVS23+1G→A express the disease earlier in life, the phenotype is more severe and they have a significantly worse risk profile than females.

Differences in patients with positive versus negative genetic testing

It has been reported in the literature that patients with a genetic diagnosis express more severe forms and worse outcomes.[12] Our study is consistent with this observation. Probands with the IVS23+1G→A mutation compared with probands with negative genetic testing had significantly more hypertrophy and exhibited a worse risk profile. Furthermore, survival free from SD tended to be poorer within families with IVS23+1G→A compared with other mutations or groups with negative genetic testing.

Limitations

Despite the fact that an important number of mutations in sarcomeric genes were screened, the success rate could have been improved with the strategy of sequencing of the most prevalent genes. Complete sequencing of the exons of the five most prevalent genes (MYH7, MYBPC3, TNNT2, TNNI3 and TPM1) was carried out in the 18 probands with the MYBPC3 IVS23+1G→A mutation. However, the presence of double mutations (new) in other related genes cannot be ruled out. A DNA sample was not available in some cases, and the genetic result could not be verified in some deceased patients. Diagnosis of cardiomyopathy could not be ascertained in all SD cases.

CONCLUSION

The MYBPC3 IVS23+1G→A mutation is associated with middle-age onset disease and poor outcome, with a significant proportion of patients developing systolic impairment and a high SD risk profile.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Ethics Committee of University Hospital Virgen Arrixaca, Murcia.

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