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Relationship between sex, shape, and substrate in hypertrophic cardiomyopathy

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Abstract

Background—Hypertrophic cardiomyopathy (HCM) is a disease characterized by substantial genetic, morphologic, and prognostic heterogeneity. Recently, sex-related differences in HCM were reported, with women being older at diagnosis and exhibiting greater left ventricular outflow tract obstruction than men. We sought to evaluate the influence of sex on the HCM phenotype in a large cohort of unrelated patients with genetically and morphologically classified HCM.

Methods—Comprehensive genotyping of 13 HCM-susceptibility genes encoding myofilament and Z-disc proteins of the cardiac sarcomere was performed previously on 382 unrelated patients with HCM. Blinded to the genotype, the septal morphology was graded as reverse-curvature, sigmoidal, apical, or neutral-contour HCM by echocardiography.

Results—Overall, women (*a*) were significantly older at diagnosis (45.1 ± 20 vs 35.8 ± 17 years, $P < .001$), (*b*) had greater left ventricular outflow tract obstruction (53.5 ± 45 vs 41.7 ± 42 mm Hg, $P = .009$), (*c*) were more likely to have concomitant hypertension (19% vs 11%, $P = .02$), and (*d*) had a higher rate of surgical myectomy (49% vs 36%, $P = .01$) than men. Interestingly, these sex-based differences were apparent only among patients with sigmoidal HCM ($P < .001$).

Conclusions—In this largest cohort of comprehensively genotyped and morphologically classified patients with clinically diagnosed HCM, we observed that the striking sex-related differences in the clinical phenotype are confined largely to the subset of mutation-negative sigmoidal HCM. Whereas mutations within the sarcomere appear to dominate the disease process, in their absence, sex has a significant modifying effect, specifically noted in cases of sigmoidal HCM.

Affecting 1 in 500 persons, hypertrophic cardiomyopathy (HCM) is a disease characterized by marked genetic and prognostic heterogeneity.[1] Characterized by unexplained myocardial hypertrophy in the absence of precipitating factors, HCM is the most common cause of sudden death in young athletes.[1,2] Since the sentinel discovery of the first locus linked to

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familial HCM[3] and the first HCM-associated mutations identified in the *MYH7*-encoded β-myosin heavy chain,[4] hundreds of mutations scattered among 20 HCM-associated genes encoding sarcomeric proteins have been identified.

In a pregenomics study by Lever et al, a striking correlation between the echocardiographically classified reverse and sigmoidal septal contour and age of onset was described.[5] This observation was followed by an early shape-genetic substrate analysis by Seidman et al showing a correlation between reverse septal curvature and the presence of an HCM-associated *MYH7* mutation.[6] Recently, a strong relationship between the genetic substrate comprised by all 8 myofilament genes underlying HCM and the morphologic subtype was elucidated in a large cohort of genotyped patients with HCM.[7] The morphology of the left ventricle and septum was much more closely related to the presence or absence of an underlying myofilament mutation than to the age of the patient. In fact, multivariate analysis revealed reverse septal contour to be the strongest independent predictor of a myofilament mutation, with an odds ratio of 21.[7]

Over the past several years, several studies have described sex differences in HCM.[8–11] Most recently, significant sex-related differences were reported in a large cohort of American and Italian patients with HCM. This study, in which women were underrepresented, showed that women were older and more symptomatic at the time of initial diagnosis.[11] Furthermore, the aforementioned study noted that women, usually with left ventricular outflow tract obstruction (LVOTO), were more likely to progress to advanced heart failure and stroke.[11] The relative contributions between sex, genetic substrate, and anatomical shape could not be ascertained because this analysis was performed on a cohort of genetically undefined and morphologically unclassified patients with HCM. Because of the heterogeneous nature both at the level of the genotype as well as the specific anatomical morphology, we sought to further evaluate the influence of sex on the HCM phenotype in a large cohort of unrelated patients with genetically and morphologically classified HCM.

Methods

Between April 1997 and December 2001, a total of 382 unrelated patients (210 male, mean maximum left ventricular wall thickness [MLVWT] 21.5 ± 6 mm) underwent clinical evaluation, including echocardiography in the Mayo Clinic's HCM Clinic, a tertiary referral center for HCM and surgical septal myectomies. Furthermore, comprehensive genetic testing for 8 myofilament and 5 Z-disc–associated, HCM-susceptibility genes was completed for all patients in Mayo Clinic's Windland Smith Rice Sudden Death Genomics Laboratory.[12–18] Informed consent for this Institutional Review Board–approved study was obtained from all patients or, if the patients were underage, from their parents. Evaluation of septal curvature and cavity contour was previously performed; and blinded to genotype, patients were classified morphologically into sigmoidal, reverse-curve, apical, and neutral-contour HCM.[7] The diagnosis of HCM was based on the echocardiographic demonstration of increased left ventricular wall thickness in the absence of clear etiology. Data on symptomatic status at initial visit (angina, dyspnea) was collected and scored in severity using the New York Heart Association (NYHA) class, while the overall NYHA class was assessed as well.

As hypertension is a common disease in the US population, some patients in this cohort also had mild concomitant hypertension. In these cases, the diagnosis of HCM was felt to be the appropriate diagnosis by experienced clinicians dedicated to the care of patients with HCM, as the severity of hypertrophy was out of proportion to the concomitant hypertension. As a reference, 317 patients were referred to the Mayo HCM clinic during this period and were

felt to have either significant hypertension or aortic valve stenosis rather than HCM, and were therefore not included in this cohort.

Statistical analysis

Student *t* tests and Fisher exact tests were applied to calculate overall differences between the men and women as well as sex differences for the 4 different morphologic subgroups using the JMP Statistical Software (JMP 6.0, 2005; SAS Institute Inc, Cary, NC). For characteristics with multiple levels, multivariate analyses (χ^2) were performed to assess the distribution of the given character between sexes; and therefore, a single *P* value was reported. Multiple logistic and linear regression analyses that included the sex-by-shape interaction effect were used to assess whether the difference between sexes were, in fact, dependent on morphology. A *P* value < .05 was considered statistically significant.

Results

The demographics of the entire cohort as well as the independent analysis of men and women are shown in Table I. Overall, there were 382 patients (210 male) diagnosed at an average age of 41.5 ± 19 years, with the women being significantly older at diagnosis than the men (45.1 ± 20 vs 35.8 ± 17 years, *P* < .001). As inquired during the interview, one third of patients had a family history of HCM; and 20% of patients had a family history of sudden cardiac arrest (SCA). Fifty-two patients (14%) were found to have concomitant hypertension at their evaluation at the Mayo Clinic (mean systolic blood pressure [SBP] 123 ± 17 mm Hg), which was more common in women. Nineteen percent of women (31/172) had concomitant hypertension compared with 10% of men (21/210, *P* = .02). Clinically, women were more symptomatic at diagnosis with respect to dyspnea (*P* = .002) and overall NYHA class (*P* = .0006). During mean follow-up of 24 months (range 0.1–88 months), 25 patients died of HCM-associated causes; but no sex differences were observed in these small numbers.

Although there was no difference in mean MLVWT between men and women (21.7 ± 6 vs 21.4 ± 7 mm, *P* = .7), a slightly greater portion of women than men (141/172 [82%] vs 153/210 [73%], *P* = .04) had obstructive HCM with a significantly higher LVOT gradient (53.5 ± 45 vs 41.7 ± 40 mm Hg, *P* = .009). Overall, sigmoidal HCM (181 patients, 47%) and reverse-curve HCM (131 patients, 35%) represented the 2 major morphologic subtypes (Figure 1); only 37 patients (10%) had apical HCM, and 33 patients (8%) had neutral-contour HCM. As shown previously, only 14% of patients with sigmoidal HCM had a probable disease-causing mutation after comprehensive open reading frame/splice site genetic testing of the 13 HCM-susceptibility genes compared with 79% of the patients with reverse-curve HCM.[7,17] Overall, there was no statistical difference in the distribution of each morphologic subtype of HCM or distribution of mutations between men and women.

To investigate the influence of septal contour, we subdivided the cohort into the 4 septal-contour subgroups and further analyzed the sex-related–based differences of the 2 major subgroups of sigmoidal and reverse-curve HCM. Strikingly, the effect of sex on clinical phenotype that was first observed for the cohort at large was present only among patients with sigmoidal HCM (Table II). Akin to the initial observations gleaned from the entire cohort, women with sigmoidal HCM were older at diagnosis (56.0 ± 15 vs 42.6 ± 16 years old, *P* < .001), were more likely to show obstructive HCM (75/79 [95%] vs 83/102 [84%], *P* = .007), had higher LVOT gradient (63.9 ± 40 vs 49.7 ± 42 mm Hg, *P* = .02), and were more likely to have concomitant hypertension (*P* = .05) compared to men with sigmoidal HCM. Although not statistically significant, more women (52%) than men (40%) underwent surgical septal myectomy (*P* = .1). In contrast to the overall observation, no statistical differences were seen in symptomatic status (angina, dyspnea, and overall NYHA class)

between sexes and the 2 morphologic subgroups. Specifically, the clinical presentation in women was similar between obstructive sigmoidal HCM and obstructive reverse-curve HCM, suggesting that symptoms stem from the degree of obstruction regardless of the morphologic substrate for that obstruction. No statistical differences were observed between men and women in MLVWT ($P = .6$), ejection fraction (.08), or the presence or location of an HCM-associated mutation ($P = .1$). Sex had no demonstrable effect for patients with reverse-curve HCM. To assess whether the observed differences between sexes were dependent specifically on the morphology, multiple linear and logistic regression analyses were performed. For women, age at diagnosis ($P = .01$), SBP ($P = .008$), and presence of LVOTO ($P = .04$) were in fact directly dependent on the sigmoidal morphology, whereas prevalence of myectomy no longer achieved statistical significance.

Our prior demonstration that reverse-curve HCM is predominantly genotype positive whereas sigmoidal HCM is mostly genotype negative prompted us to further homogenize the 2 most common subsets of morphologic/genetic HCM by comparing patients with mutation-positive/reverse-curve HCM (n = 105) with patients with mutation-negative/sigmoidal HCM (n = 156). Herein, sex-based differences in age at diagnosis, LVOT gradient, and presence of concomitant hypertension were significantly higher among women than men for the largest subtype of HCM, that is, mutation-negative/sigmoidal HCM (Figure 2).

To investigate the potential confounding influence of concomitant hypertension, the analysis of sex differences per septal subgroup was repeated excluding the patients diagnosed with concomitant hypertension. As shown in Table III, all previously observed statistically significant differences that were confined to the sigmoidal-HCM subgroup—age at diagnosis, number of patients with obstruction, degree of LVOT obstruction, and rate of surgical myectomies—persisted; and no new statistically significant differences were seen (data not shown). Again, logistic regression models showed a clear female sex–sigmoidal shape dependence with respect to age at diagnosis ($P = .006$) and presence of LVOTO ($P = .02$). Overall, patients with sigmoidal HCM and concomitant hypertension were less likely to undergo surgical myectomy than patients without hypertension (21% vs 52%, $P < .001$), explaining the increase of significance in surgical myectomies when hypertension was excluded from the analysis.

Discussion

Long considered a disease of the sarcomere or, more specifically, a disease of the myofilament, the discovery of mutations in multiple proteins outside the myofilament has caused an expansion of the spectrum of genetically mediated pathways, culminating in the disease phenotype that clinicians diagnose as HCM. Currently, >18 HCM-susceptibility genes have been published, with 8 of these genes encoding the essential cardiac myofilaments for which HCM genetic testing is now commercially available. With this large number of putative pathogenetic genes, a variety of genes yielding rare mutations, it is intriguing that 30% to 50% of adults with clinically diagnosed HCM remain genetically unexplained.[19] Binder et al recently described an important genotype-phenotype relationship linking the genotypic substrate to the morphologic shape. The analysis of a large cohort of genotyped and echocardiographically characterized patients reveals that nearly 80% of patients with reverse-curve HCM have a positive genetic test for myofilament HCM, whereas the same genetic test is positive in fewer than 10% of patients clinically diagnosed with HCM, but having a sigmoidal contour (ie, sigmoidal HCM).[7] More recently, the yield for sigmoidal HCM increased from 8% to 14% with the inclusion of 5 Z-disc–associated genes.[17] Conversely, myofilament HCM preferentially yields reverse-curve HCM, whereas Z-disc HCM predisposes to the development of sigmoidal HCM.[20]

Now, this present study examines the influence of sex in the interplay between genetic substrate and anatomical shape. Overall, this cohort mirrors previously published studies that examined the effect of sex on a presumably heterogeneous cohort of HCM lacking both morphologic and genetic subclassification.[9–11] Moreover, the data presented herein suggest that the differences are largely confined to sigmoidal HCM, which constitutes the anatomical phenotype of nearly half of the patients with clinically diagnosed HCM in our institution. Furthermore, it shows that specifically for age at diagnosis, SBP, and presence of LVOTO, there is a direct sex-by-morphology interaction for women with sigmoidal HCM.

These observations among distinct subtypes of HCM generate several questions regarding the influence of sex in the phenotypic expression of disease. More specifically, it suggests that sex does not seem to be a significant modifier in reverse-curve HCM. This is supported by our original morphologic data that the underlying genotype rather than sex appears to be the predominant determinant of septal morphology.[7] Thus, in reverse-curve HCM, the presence of a structural myofilament mutation is the driver of the phenotype, whereas in sigmoidal HCM, a multifactorial process culminates in a clinical expression of HCM, with significant male-female differences.

The presence of mild, concomitant hypertension may be a contributing factor in the pathogenesis of sigmoidal HCM in women because 1 of 4 women within this morphologic classification of HCM was mildly hypertensive. Several studies have shown that in response to pressure overload, sex differences in the hypertrophic response patterns can be seen. Krumholz et al showed that in isolated hypertension, significant sex differences can be observed in cardiac adaptation. In contrast to our findings, they show that women predominantly develop a concentric hypertrophy, whereas a more eccentric pattern was observed in men.[21] Similar patterns of sex-dependent hypertrophy were observed in aortic stenosis[22,23] and as a response to hemodynamic overload after myocardial infarction.[24]

Furthermore, the presence of concomitant hypertension could mean there has always been a presence of low-grade hypertension and therefore a higher afterload in these patients. These factors combined with a (undefined) genetic susceptibility for HCM by means of a pathogenetic mutation or a left ventricular hypertrophy–promoting polymorphism[25] or endocrine factors[26] could all converge in the phenotype of clinically diagnosed sigmoidal HCM.

Although recent studies have shown that LVOTO is far more prevalent than previously believed,[28,29] our study may be biased with its higher prevalence of patients with obstructive HCM at rest because of our role as tertiary referral center for the surgical treatment of HCM. This is reflected in a higher prevalence of patients with resting LVOTO (75% vs ~35%–40% in other published HCM cohorts)[27,28] as well as a higher rate of surgical myectomies (42% vs ~5%–10% in other published HCM cohorts).[29] Our observations might therefore be less applicable to a broader spectrum of patients with HCM, particularly nonobstructive HCM. On the other hand, the conclusions regarding these important sex-substrate differences appear robust for the subset of patients with obstructive disease.

Conclusions

In this large cohort of comprehensively genotyped and morphologically classified unrelated patients with clinically diagnosed HCM, we observed that the striking and previously noted sex-related differences in HCM are confined largely to the subset of patients with mutation-negative, sigmoidal HCM. Sex does not appear to be a significant genetic modifier in myofilament HCM.

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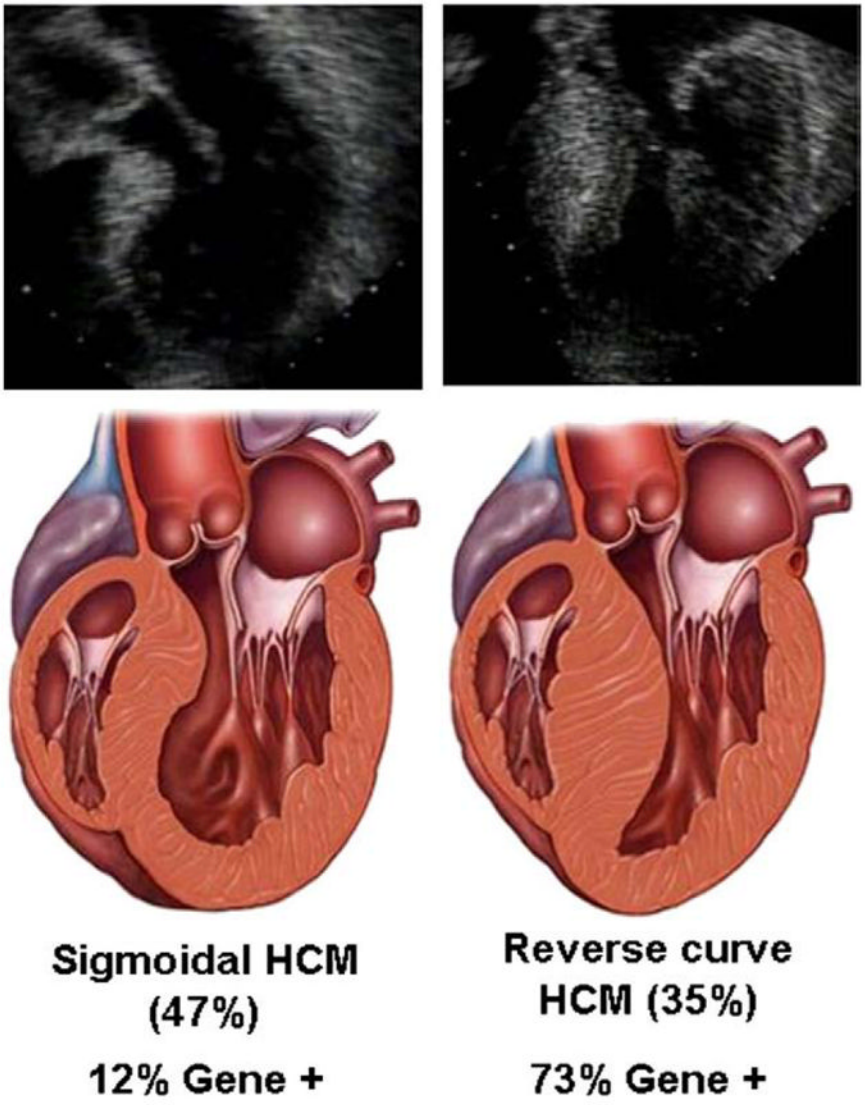

Figure 1.
Two most common morphologic subtypes of HCM. Echocardiographic picture and graphic depiction of the 2 most common morphologic subtypes of HCM: sigmoidal HCM (47%) and reverse-curve HCM (35%). *Gene+*, Presence of HCM-associated mutation.

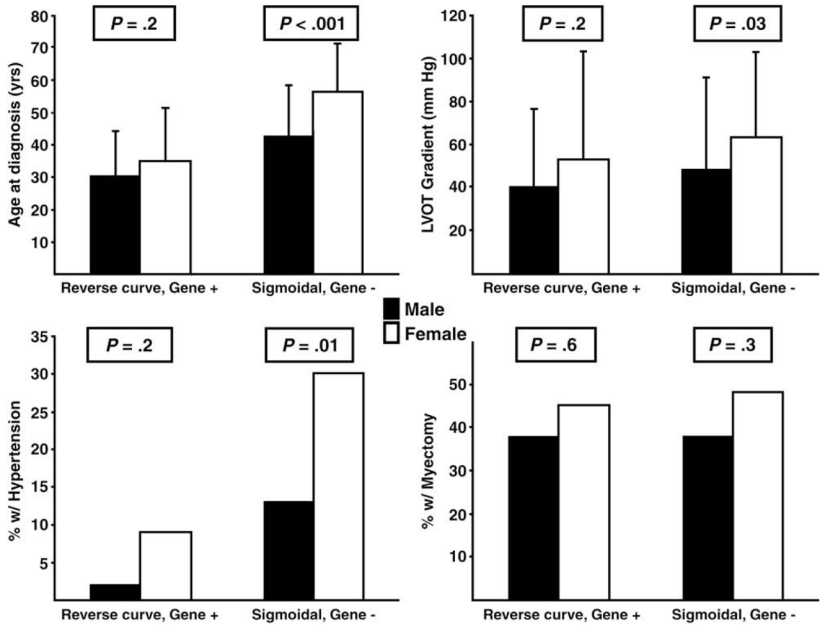

Figure 2.

Male-female comparisons among patients with genotype-positive, reverse-curve HCM and patients with genotype-negative, sigmoidal HCM. Bar diagrams showing the sex differences between men and women with HCM in the specific subgoups of genotype-positive (gene+)/ reverse-curve HCM and genotype-negative (gene−)/sigmoidal HCM on age at diagnosis (top left panel), resting left ventricular outflow tract gradient (top right panel), percentage with surgical myectomy (bottom right panel), and percentage with mild hypertension (bottom left panel).

Table I

Sex differences among patients with clinically diagnosed HCM

	Total	Male	Female	*P*
n	382	210	172	
Age at Dx (y)	41.5 ± 19	35.8 ± 17	45.1 ± 20	<.001
Age >50 n (%)	125 (33)	55 (26)	70 (41)	.003
Angina * n (%)	151 (40)	80 (38)	71 (45)	.2
Dyspnea * n (%)	250 (65)	126 (60)	134 (78)	.002
NYHA class n (%)				
Class I	116 (30)	82 (39)	34 (20)	.0006
Class II	74 (19)	48 (23)	26 (45)	
Class III	164 (43)	76 (36)	88 (51)	
Class IV	8 (2)	4 (2)	4 (2)	
FH HCM† n (%)	117 (31)	62 (30)	55 (32)	.7
FH SCA† n (%)	53 (14)	34 (17)	19 (11)	.2
Hypertension n (%)	52 (14)	21 (10)	31 (19)	.02
SBP (mm Hg)	123 ± 17	122 ± 16	124 ± 19	.4
DBP (mm Hg)	72 ± 11	73 ± 11	71 ± 12	.1
Septal myectomy n (%)	159 (42)	75 (36)	84 (49)	.01
Septal ablation n (%)	15 (4)	5 (2)	10 (6)	.1
Echocardiography				
MLVWT (mm)	21.5 ± 6	21.7 ± 6	21.4 ± 7	.7
Patients with obstruction n (%)	294/382 (77)	153 (73)	141 (82)	.04
Resting gradient (mm Hg)	47.3 ± 42	41.7 ± 40	53.5 ± 45	.009
EF (%)	72.7 ± 8	72.5 ± 8	73.1 ± 8	.4
Morphology n (%)				
Sigmoid	181 (47)	102 (49)	79 (46)	.83
Reverse	131 (35)	69 (33)	62 (36)	
Apical	37 (10)	22 (10)	15 (9)	
Neutral	33 (8)	17 (8)	16 (9)	
Genotype positive n (%)	157 (41)	86 (41)	71 (41)	1.0
Mutation location n (%)				
Thick filament	57 (15)	23 (11)	34 (20)	.06
Intermediate filament	57 (15)	37 (18)	20 (11)	
Thin filament	12 (3)	9 (5)	3 (2)	
Z-disc	12 (3)	7 (3)	5 (3)	
Multiple‡	19 (5)	10 (4)	9 (5)	

Thick filament: *MYH7*-encoded β-myosin heavy chain, *MYL2*-encoded regulatory myosin light chain, *MYL3*-encoded essential myosin light chain. Intermediate filament: *MYBPC3*-encoded cardiac myosin binding protein C. Thin filament: *ACTC*-encoded cardiac actin, *TNNI3*-encoded cardiac troponin I, *TNNT2*-encoded cardiac troponin T, *TPM1*-encoded α-tropomyosin. Z-disc: *ACTN2*-encoded α-actinin 2, *CSRP3*-encoded muscle LIM protein, *LBD3*-encoded LIM binding domain 3, *TCAP*-encoded telethonin, *VCL*-encoded (meta)vinculin. *Dx*, Diagnosis; *FH*, family history; *SCA*, *sudden cardiac death* defined as unexpected death, nocturnal or within 1 hour of witnessed collapse; *DBP*, diastolic blood pressure; *EF*, ejection fraction.

[*] Symptomatic status as classified by NYHA class. Data shown are classes II, III, and IV combined.

[†] In a first-degree relative.

[‡] Patients harboring >1 HCM mutation (double/compound heterozygotes).

Table II

Sex differences in the 2 most common morphologic subgroups

	Sigmoidal HCM (n = 181)			Reverse-curve HCM (n = 131)			Multiple regression models (*P*)
	Male	**Female**	***P***	**Male**	**Female**	***P***	
n	102	79		69	62		
Age at Dx (y)	42.6 ±16	56.0 ± 15	<.001	29.2 ± 16	33.3 ± 18	.2	.01
Age >50 n (%)	36 (35)	47 (59)	.002	5 (7)	10 (16)	.2	.9
Angina * n (%)	49 (48)	35 (44)	.8	20 (29)	27 (44)	.4	.2
Dyspnea * n (%)	73 (72)	67 (85)	.1	35 (51)	43 (69)	.03	.4
NYHA class n (%)							
Class I	29 (28)	10 (13)	.07	33 (48)	17 (27)	.07	.7
Class II	23 (23)	21 (26)		18 (26)	19 (31)		
Class III	49 (48)	47 (59)		16 (23)	25 (40)		
Class IV	1 (1)	2 (3)		2 (3)	1 (2)		
FH HCM§ (%)	25 (25)	14 (18)	.4	29 (42)	30 (48)	.5	.2
FH SCA§ (%)	13 (13)	5 (6)	.2	15 (22)	10 (16)	.5	.5
Hypertension n (%)	13 (13)	20 (26)	.05	2 (3)	4 (7)	.4	.1
SBP (mm Hg)	124 ± 16	131 ± 30	.01	118 ± 17	115 ± 13	.2	.008
DBP (mm Hg)	73 ± 10	73 ± 11	.6	71 ± 11	69 ± 11	.3	.7
Septal myectomy n (%)	41 (40)	41 (52)	.1	27 (39)	26 (42)	.9	.4
Echocardiography							
MLVWT (mm)	19.8 ± 5	19.4 ± 5	.6	24.5 ± 7	24.6 ± 7	.9	.9
Patients with obstruction n (%)	83 (84)	75 (95)	.007	51 (74)	47 (76)	.8	.04
Resting gradient (mm Hg)	49.7 ± 42	63.9 ± 40	.02	38.1 ± 37	50.3 ± 49	.1	.9
EF (%)	73.1 ± 6	74.6 ± 5	.08	71.7 ± 9	72.6 ± 9	.6	.8
Genotype positive n (%)	15 (15)	10 (13)	.8	58 (84)	47 (76)	.3	.6
Mutation location n (%)							
Thick filament	0 (0)	4 (5)	.04	17 (25)	23 (37)	.1	.3
Intermediate filament	6 (6)	2 (3)	.5	26 (38)	14 (23)	.09	
Thin filament	1 (1)	1 (1)	1.0	7 (10)	2 (3)	.2	
Z-disc	7 (7)	3 (4)	.5	0 (0)	0 (0)	–	

	Sigmoidal HCM (n = 181)			Reverse-curve HCM (n = 131)			Multiple regression models (*P*)
	Male	**Female**	***P***	**Male**	**Female**	***P***	
Multiple[†]	1 (1)	0 (0)	1.0	8 (12)	8 (13)	1.0	

[*] Symptomatic status as classified by NYHA class. Data shown are classes II, III, and IV combined.

[†] Patients harboring >1 HCM mutation (double/compound heterozygotes).

[§] In a first-degree relative.

Table III

Sex differences in the 2 most common morphologic subgroups after exclusion of patients with mild hypertension

	Sigmoidal HCM (n = 148)			Reverse-curve HCM (n = 125)			Multiple regression models (*P*)
	Male	**Female**	***P***	**Male**	**Female**	***P***	
n	89	59	–	67	58	–	–
Age at Dx (y)	40.9 ± 16	53.8 ± 15	.001	29.4 ± 16	31.6 ± 16	.5	.006
Patients with obstruction n (%)	72 (81)	57 (97)	.005	50 (75)	44 (75)	1.0	.02
Resting gradient (mm Hg)	50.0 ± 42	66.1 ± 39	.02	38.4 ± 37	49.0 ± 49	.2	.06
Septal myectomy n (%)	37 (42)	38 (64)	.008	26 (39)	24 (41)	.9	.1