Merits and Pitfalls of Genetic Testing in a Hypertrophic Cardiomyopathy Clinic

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ABSTRACT: **Background:** Hypertrophic cardiomyopathy (HCM) is a familial disease with autosomal dominant inheritance and age-dependent penetrance, caused primarily by mutations of sarcomere genes. Because the clinical variability of HCM is related to its genetic heterogeneity, genetic studies may improve the diagnosis and prognostic evaluation in HCM.

Objectives: To analyze the impact of genetic diagnosis on the clinical management of HCM.

Methods: Genetic studies were performed for either research or clinical reasons. Once the disease-causing mutation was identified, the management plan was reevaluated. Family members were invited to receive genetic counseling and encouraged to be tested for the mutation.

Results: Ten mutations in sarcomere protein genes were identified in 9 probands: 2 novel and 8 previously described. Advanced heart failure or sudden death in a young person prompted the genetic study in 8 of the 9 families. Of 98 relatives available for genotyping, only 53 (54%) agreed to be tested. The compliance was higher in families with sudden death and lower in what appeared to be sporadic HCM or elderly-onset disease. Among the healthy we identified 9 carriers and 19 non-carriers. In 6 individuals the test result resolved an uncertainty about "possible HCM." In several cases the genetic result was also used for family planning and played a role in decisions on cardioverter-defibrillator implantation.

Conclusions: Recurrence of a same mutation in different families created an opportunity to apply the information from the literature for risk stratification of individual patients. We suggest that the clinical context determines the indication for genetic testing and interpretation of the results.

IMAJ 2014; 16: 707–713

KEY WORDS: hypertrophic cardiomyopathy (HCM), gene testing, compliance, family planning, implantable cardioverter-defibrillator (ICD)

Hypertrophic cardiomyopathy (HCM) is a familial disease with autosomal dominant inheritance and age-dependent penetrance, usually caused by mutations in genes encoding the sarcomere proteins. Family history may be established in at least 50% of the patients. In others, familial clustering might be detected through screening family members and/or follow-up by echo and electrocardiogram. Disease-causing mutations may be found in up to 70% of families with HCM [1-4]. Some patients appear to have a sporadic disease. They are usually individuals with elderly-onset HCM or borderline hypertrophy. Some may have a different underlying disease etiology but some constitute a de novo mutation [2,5]. Once the disease-causing mutation is known, prospective genotyping of family members is expected to facilitate early diagnosis and simplify the follow-up of asymptomatic relatives. Position statements by professional societies endorse genetic studies in HCM, assuming a potential clinical benefit and potential cost containment [2,6-8]. Yet, most of the scientific evidence supporting these statements is based on genotyping of selected families with complicated or malignant outcome that do not reflect the real-life course of most families with HCM [5,8,9]. Reports describing the effect of genetic studies in the clinical setup are less abundant.

Performing genetic studies in HCM patients depends on reimbursement issues, the presence of an appropriate facility, and physician motivation. Interpretation of the results may be problematic, and this complexity is expected to increase with the introduction of novel techniques for gene testing [9-11]. The clinical application of the results, i.e., mutation testing among asymptomatic family members and implementation of the ensuing medical recommendations is a matter of compliance.

In his study we examine the clinical impact that resulted from obtaining genetic diagnoses in HCM families at our cardiomyopathy clinic. We provide data on the agreement of relatives to be tested for the mutation found in the index case and describe how the genetic data were applied with regard to family history and disease characteristics.

PATIENTS AND METHODS

All investigational procedures related to this study were approved by the Institutional Review Board. Established in

2004, the Cardiomyopathy Clinic of Leviev Heart Institute at Sheba Medical Center listed 296 families with HCM, comprising 360 individuals at the moment of data analysis. All patients being evaluated and their accompanying family members were informed about the genetic etiology of their disease, the need for cascade screening of relatives, and the availability of genetic testing. The potential implications of genetic diagnosis on the well-being and management of the proband and family members, as well as the limitations, were discussed [2]. Genetic studies related to HCM genes are not covered by Israel's National Health Service and are not reimbursed by most of the private insurance companies. However, once a mutation is found in the proband (index case), family members may be genotyped free of charge or for an easily affordable fee.

The decision to perform genetic testing could originate in a physician's interest in a familial disease or a peculiar phenotype. In such a case, after obtaining informed consent, a candidate gene screen was carried out in our laboratory or one of the collaborating research labs. If the patient requested to be tested, we assisted him or her by referral to a certified genetic service, filling the forms and preparing the DNA sample.

The clinical care of HCM patients follows established guidelines and recommendations [1-3] independently of the patient's interest in genetic testing. Once a disease-causing mutation is identified, the family is invited for another round of genetic counseling. We explain the result and encourage testing of the affected and non-affected family members by a cascade strategy. The management plan of every affected individual is reevaluated on a case-by-case basis regarding the disease gene, the mutation found, and the pertinent literature.

The laboratory procedures related to DNA extraction and sarcomere protein gene analysis are described elsewhere [9,10, and http://www.healthincode.com/index.php]. Candidate gene screen was performed by the Sanger method and/or by massive parallel (Next Generation) sequencing (Health in Code, A Coruna, Spain). Novel mutations were defined as such when producing a significant alteration of an evolutionary preserved residue in one of the established HCM-causing genes and absent from proprietary and the publicly available databases including Cardiogenomics [http://genepath.med.harvard.edu/~seidman/cg3/index.html and 1000 genomes and 5000 exomes http://www.ncbi.nlm.nih.gov/variation/tools/1000genomes, http://evs.gs.washington.edu/EVS/.] Segregation with the disease and, in particular, presence of mutation in all affected family members was confirmed when possible.

Table 1. The clinical phenotype

Family/ Proband	Main indication/ reason for genetic testing	Age at onset	Clinical characteristics					
			Massive LVH	HOCM	Sudden death	Severe HF	Heart Tx	Other
H1BD	Severe phenotype	Teenage	Yes		Yes	Yes	Yes	CSD
H13ABZ	Severe phenotype	Teenage	Yes		Yes	Yes	Yes	CSD
H7YY	Severe phenotype	Adult		Yes		Yes	Yes	
H18HF	Unique phenotype	Teenage	Yes			Yes		
H29OD	Family request	Elderly				Yes		CSD
H145RR	Unique phenotype	Elderly				Yes		Pulmonary vascular disease
H150SN	Reproduction counseling	Teenage			Yes			
H171GA	Sudden death*	Teenage		Yes	Yes	Yes		
H268LJ	Patient's request	Adult						

* Sudden death clearly related to HCM phenotype

LVH = left ventricular hypertrophy, HOCM = hypertrophic obstructive cardiomyopathy (left ventricular outflow tract obstruction), HF = congestive heart failure, Tx = transplantation, CSD = conduction system disease requiring pacing

STATISTICAL ANALYSIS

Our dataset includes the families where a disease-causing mutation was established between 2004 and 2011 and at least 2 years elapsed since contacting the family about the diagnosis. We describe the clinical characteristics, the indication to perform the genetic study, the results of testing for a mutation in family members, and the real-life application of the genetic data. Statistical comparisons were performed, when appropriate, using the chi-square test, with $P < 0.05$ regarded as statistically significant.

RESULTS

We identified 10 mutations in 9 probands. Table 1 presents the clinical characteristics of different pedigrees and the principal considerations that led to the genetic testing. Familial disease was present in six of the nine, while advanced heart failure or sudden death in a young family member was the phenotypic feature that prompted the testing in 8/9 families. Table 2 presents the mutations and the results of testing in family members. There were two novel and eight previously described mutations in the sarcomere protein genes. In six of the variants useful clinical data on at least two affected individuals were available in the literature. The literature on these mutations is summarized in the supplemental appendix (available online at: http://www.healthincode.com/index.php?option=com_content&view=article&id=138&Itemid=159&lang=en).

Cumulatively, 53 of the available 98 first-degree relatives agreed to be tested for the mutation found in the proband, resulting in 54% compliance with the formal recommendation provided through genetic counseling (range 0–100%) [Table 2].

It was dependent on the number of clinically affected individuals per family ($P = 0.003$) and age at disease onset ($P = 0.002$) and was strongly related to family history of sudden cardiac death ($P < 0.001$). Noteworthy, none of the relatives of a single affected proband agreed to undergo genetic testing. There was no relationship to history of heart failure, outflow obstruction, heart transplantation, or whether mutation was found in the context of research or through a formal study in a certified genetic lab.

Genetic testing confirmed the diagnosis by identifying a mutation in all six individuals with an uncertain diagnosis of HCM. Nine healthy carriers were identified in 4 families, while 19 individuals from 5 families could be reassured they were non-carriers. Table 3 summarizes the real-life clinical use made of the mutation data. The most common use was to validate the clinical diagnosis and provide prognostic information based on literature and family history. In several cases mutation data were used for family planning and played a decisive role regarding introduction of an implantation cardioverter-defibrillator (ICD).

Family H1BD represents a malignant phenotype of HCM characterized by early-disease onset, severe hypertrophy, high risk of sudden cardiac death, and development of heart failure due to hypokinetic transformation and/or severe diastolic dysfunction [Figure 1A]. Previous generations of this family were described by previous authors from our institution [12]. We have identified a β-myosin Arg719Trp mutation, which was previously found in at least 24 other families described in the literature [13,14]. These were characterized by similar phenotypic features in 78 affected carriers: 25 sudden deaths in young individuals, 4 heart failure-related deaths and 3 cardiac transplantations. Only two had a mutation but were clinically not affected.

Family H13ABZ represents a very similar disease course [Table 1 and Figure 1B]. Interestingly, a novel MYH7 Arg717Gly mutation identified in H13ABZ was also localized to the converter region of the protein, suggesting a potentially similar pathogenic mechanism. Genotyping of family members confirmed segregation with the disease among the affected. Furthermore, two teenage girls with a borderline phenotype were definitely classified as affected in order to guide appropriate management. Mutation data were used for prenatal diagnosis once in each of the above families. Nevertheless, about 40% of first-degree relatives refused to be tested.

In family H7YY the proband underwent heart transplantation at age 60 following two surgical procedures, pacemaker implantation and severe diastolic failure. Her son (age 37) suffers from severe outflow obstruction. Two healthy daughters aged 24 and 37 years tested positive but so far remain asymptomatic and disregard the genetic information regarding their lifestyle and reproduction decisions. There was a history of heart failure and sudden death in maternal uncles, but no other relatives were available for examination. Ratti et al. [15] subsequently showed in vitro that this mutation would affect the interaction between the myosin binding protein C and the regulatory light chain of myosin.

Family H150SN is another family described many years ago because of sudden death in an 18 year old soccer player and history of congestive heart failure in the mother and grandmother

Table 2. Mutations and genotyping results in the families

Family/ Proband	Mutation	No. of clinically affected*	Family members tested/ available (%)**	Clinical status and genotyping results in family members			
				Phen+ & Gen+	Phen uncertain & Gen+	Phen- & Gen+	Phen- & Gen-
H1BD	MYH7 R719W	6	7/12 (58)	3	1	0	3
H13ABZ	MYH7 R717G	9	14/23 (61)	7	1	2	4
H7YY	MyBPC3 R35W	2	9/14 (64)	1	0	2	6
H18HF	MYH7 R1344Q	1	0/7 (0)	0	0	0	0
H29OD	MyBPC3 Q208H TNNI3 L198V	2	2/12 (17)	0	0	1+1***	0
H145RR	MyBPC3 G596R	1	0/2 (0)	0	0	0	0
H150SN	TNNT2 E163del	3	3/3 (100)	1	1	0	2
H171GA	MYH7 V606M	10	17/22 (77)	7	3	3	4
H268LJ	MYH7 E497D	1	0/2 (0)	0	0	0	0
Total 9 families 10 mutations	35	53/98 (54)	19	6	9	19	

*No. of clinically affected: of those available for evaluation, including the proband

**Family members: those available for evaluation/genotyping according to a cascade strategy

% family members genotyped: individuals who agreed to be tested for a mutation found in the proband from those expected to undergo genotyping according to professional recommendations and the counseling provided

Note: there were no individuals who were Phen uncertain/Gen- or Phen+/Gen-

***One offspring carries both mutations while the second has only the MYBPC variant [Figure 1D]

Phen = phenotype, Phen+ = clinically affected, Phen- = clinically non-affected, Gen = genotype

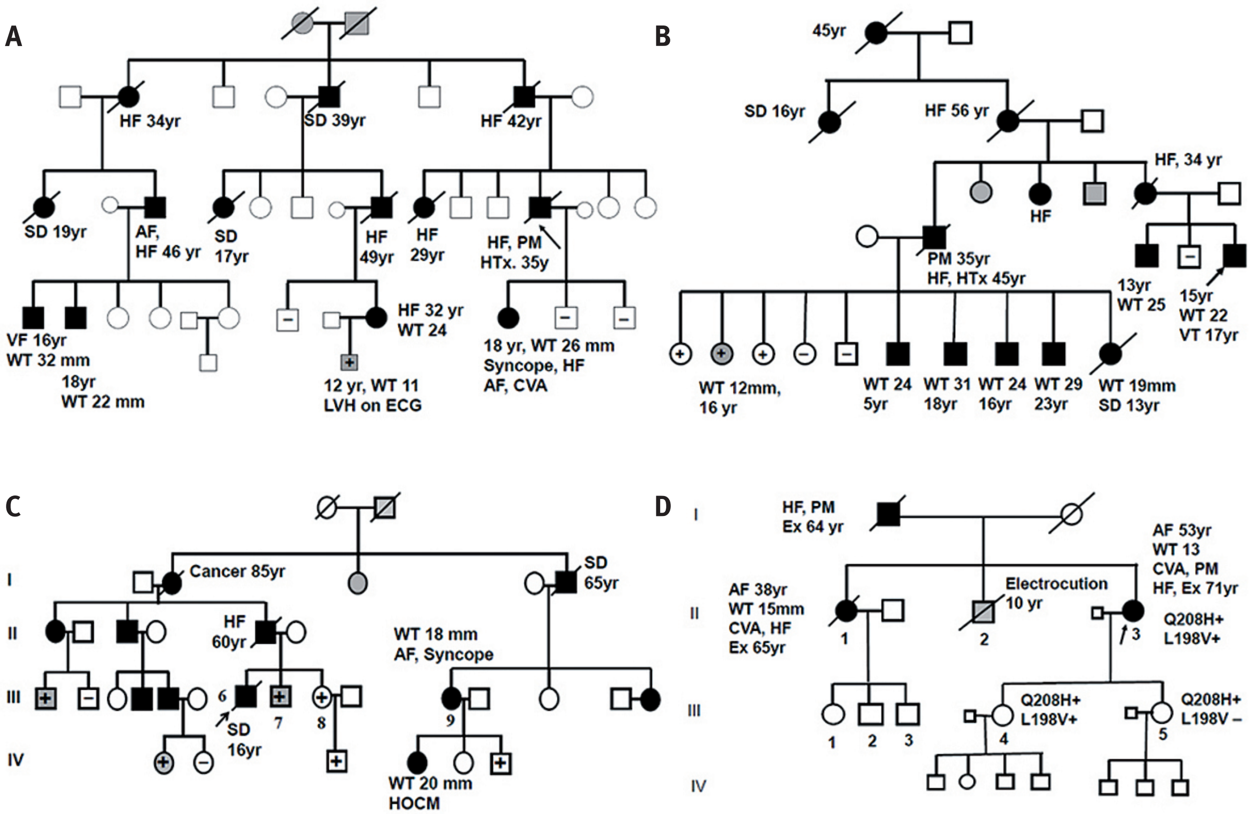
Table 3. Clinical outcome of genotyping according to mutation and the mode of diagnosis

Family/ Proband	Mutation	Testing setup	Clinical use of genetic diagnosis			
			Ascertain diagnosis	Prenatal diagnosis	Prognostic information	ICD implant
H1BD	MYH7 R719W	Research	Yes	Yes	Yes	
H13ABZ	MYH7 R717G	Research	Yes	Yes	Yes	
H7YY	Mybpc3 R35W	Research	Yes			
H18HF	MYH7 R1344Q	Research				
H29OD	Mybpc3 Q208H TNNI3 L198V	Service			Yes	
H145RR	Mybpc3 G596R	Research				
H150SN	TNNT2 E163del	Service	Yes	Yes	Yes	Yes
H171GA	MYH7 V606M	Research	Yes			Yes
H268LJ	MYH7 E497D	Service				

Research: genotyping was performed free of charge, for scientific purpose, after obtaining informed consent

Service: testing was done in a certified laboratory for a fee and following clinical recommendation and genetic counseling

Figure 1. [A] The H1BD family with a malignant phenotype caused by *MYH7* R719W mutation. **[B]** The H13ABZ family with malignant HCM caused by *MYH7* R717G mutation. **[C]** The H171GA family with MYH7 V606M mutation characterized by a marked phenotypic variability, where genetic diagnosis was prompted by sudden cardiac death in the proband. **[D]** The H29OD family with elderly-onset severe disease and multiple mutations



Dark symbols = clinically affected, white symbols = non-affected, grey symbols = clinical status unknown, + = mutation carrier, – = non-carrier, arrow = the proband.
HF = heart failure, SD = sudden death, AF = atrial fibrillation, PM = permanent pacemaker for conduction block, HTx = heart transplantation, VF = ventricular fibrillation, CVA = cerebrovascular accident, WT = maximal left ventricular wall thickness (mm), HOCM = hypertrophic obstructive cardiomyopathy.
The age of diseased persons (yr) represents the age at death, while in those alive it corresponds to the age of evaluation. Ex. age (yr) = age at expiry.

[16]. Following the autopsy result two teenage siblings of the proband were suspected to have HCM, and over the ensuing 30 years remained mildly symptomatic but developed wall thinning and mild left ventricular dysfunction. One of them was encouraged by his spouse to confirm the diagnosis and receive reproduction counseling. Genetic testing identified a malignant deletion mutation in troponin T (Glu163del), previously associated with a high incidence of sudden cardiac death. This mutation was previously identified in at least 43 carriers (40 with HCM and 3 healthy carriers) from 13 different families [17,18]. In 4 of those families there were 15 reported events of sudden death (9 with mutation and 6 without a genetic study). This critical information persuaded the patients (47 and 44 years old) and the medical team to have ICDs implanted. Genetic diagnosis allowed the birth of a healthy child.

Family H171GA is characterized by a highly variable HCM phenotype [Figure 1C]. Genetic diagnosis (mutation Val606Met in MYH7) was prompted by sudden cardiac death in a teenage boy (III-6 in Figure 1C). Numerous family members tested positive for the mutation, which confirmed the diagnosis in three with borderline hypertrophy and identified three asymptomatic carriers. A 16 year old athlete brother of the proband (III-7) had to discontinue competitive sports after being unequivocally diagnosed as affected. Because of severe anxiety in the family, he and his asymptomatic 17 year old sister (III-8, who had no cardiac hypertrophy) underwent ICD implantation. This decision was complicated by multiple inappropriate shocks and device infection in the young woman, who is now 25 years, still without an HCM phenotype. The Val606Met mutation has been described in at least 33 families comprising 82 carriers, 76 with HCM phenotype. Initially it was assumed to be a benign mutation, but additional families had adverse clinical manifestations and prognosis. The events reported in these 33 described families were: 16 sudden deaths, 2 heart failure-related deaths and 2 cardiac transplantations [17,19-21].

Family H29OD is characterized by severe heart failure caused by a mixed hypertrophic/restrictive phenotype developing in late adulthood [Figure 1D]. Despite genetic counseling, only after the death of II-1 did the daughters of II-3 become interested in the genetic study. Sarcomere gene screen in II-3 identified two mutations: MyBPC3 Gln208His and TNNI3 Leu198Val, both considered to be pathogenic [22]. Each was previously found in an individual with HCM, and TNNI3 Leu198Val was subsequently described in two additional patients with HCM (see supplemental appendix online). Attempts to genotype II-1 using DNA extracted from an archival paraffin-embedded liver biopsy failed. Both daughters of II-3, aged 50 and 54 years, are asymptomatic and have a normal echo-Doppler and ECG. III-4 carries both mutations, the III-5 the only MyBPC3 variant. At the current stage we are uncertain if both variants are pathogenic or if one is the principal cause of disease and the other a modifier.

A 69 year old woman, H145RR, was tested because of an unusual combination of elderly-onset HCM with severe pulmonary hypertension and pulmonary arterio-venous malformations. There was no family history of HCM, sudden death or vascular disease. A Gly596Arg variant in MyBPC3 was previously described in a patient with apical HCM and in six carriers of another HCM family [23]. No mutation was found in the *TGFβ R1* and *TGFβ R2* genes that were sequenced because of the vascular malformations. The proband died soon after being evaluated and her children so far refuse to be evaluated.

The 21 year old H18HF presented with congestive heart failure and growth delay due to severe distal hypertrophy. The symptoms started at about age 13. There was no family history of HCM. The novel MYH7 Arg1344Gln mutation was identified but the patient and her family were lost to follow-up.

H268LJ suffers from paroxysmal atrial fibrillation, septal and apical hypertrophy. After being informed about HCM genetics he became interested in genetic testing and the MYH7 Glu497Asp mutation was found. His two asymptomatic offspring are not willing to be tested. The same mutation was previously described in a 60 year old woman with apical hypertrophic cardiomyopathy whose relative had severe concentric hypertrophy [24].

DISCUSSION

Genetic studies have the potential to provide helpful information for the diagnosis and prognostic evaluation in HCM, because the clinical variability of HCM is strongly related to its genetic heterogeneity. Mutations in the main sarcomere genes (*MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC, TPM1, MYL2, MYL3*) account for 50–70% of the HCM cases [1,2,6,7,9]. More than 1000 mutations in these genes have been described. Multiple available data suggest that the genetic background is associated with the prognosis of the disease: some mutations are associated with higher risk, and complex genotypes are usually related to a more severe disease expression. Between 5% and 10% of patients with HCM present complex genotypes with two or more disease-associated mutations [2,17]. On the other hand, despite extensive gene testing, a disease-causing mutation is not found in 30–50% of HCM patients. To further increase the complexity, mutations in the same genes have been associated with other phenotypes, including dilated cardiomyopathy, restrictive cardiomyopathy, left ventricular non-compaction, septal defects and skeletal myopathies [1-3].

Genetic counseling is defined as the process by which patients or relatives at risk of an inherited disorder are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, and their options for management and family planning [2]. Potential benefits of genetic testing include not only early distinction between the affected and non-carriers (who do not require clinical follow-up); it may identify patients with particular high risk due to the presence of severe mutations or complex genotypes. Widespread application of genetic studies in HCM is limited by several problems including the costs, limited sensitivity, and a potential for false positive results, i.e., identifying a rare variant as a mutation or not detecting a mutation. When a study finds a "novel" mutation (such as MYH7 R1344Q in H18HF), the inability to perform segregation studies in small families and the limitations of various prediction methods challenge our capacity to correctly interpret the result. New-generation sequencing technologies offer a huge opportunity for a better diagnosis, but also increase the 'yield' of rare variants of unknown significance, thereby creating difficulty for correct interpretation of the genetic findings and for genetic counseling [9-11].

Our study demonstrates both the benefits and limitations of applying genetic studies in HCM. Table 3 summarizes the real-life use of genetic information in clinical practice according to the mode of testing and the mutation. Genetic diagnosis and the pertinent literature played a crucial role for the H150SN family. Finding the malignant TNNN2 E163del mutation and extending the clinical experience from a small nuclear family to 66 affected individuals from 13 families allowed the correct interpretation of clinical data and the subsequent provision of reasonable recommendations. Several members of families H1BD and H13ABZ suffering from malignant HCM also derived an immediate clinical benefit from genotyping in terms of early diagnosis in borderline cases and prenatal diagnosis. Clinical utilization of genetic information appeared to be independent of whether it was obtained for research or on a 'fee per service' basis.

The compliance of relatives was incomplete even when testing for a mutation (found in the proband) could be provided free of charge. The motivation to be tested might have been higher if we were allowed to directly contact all family members not treated in our institution. Compliance was better in families with a larger number of affected individuals and a severe disease phenotype [Table 2]. Sporadic HCM, the absence of family history of sudden cardiac death, and elderly age at disease onset appear to be associated with lack of motivation among family members to undergo testing. Apparently, the presence of familial clustering reinforces the impact of formal explanations and recommendations on the attitude of healthy family members. We suggest that practical considerations such as the family attitude and their expectations be taken into account when providing recommendations for performing genetic testing in HCM. It is the clinical context that will determine the indication and the potential uses of genetic testing in HCM.

The presence of complex genotypes is especially challenging regarding the estimation of risk of progression in the proband and recurrence of the disease in relatives. Finding multiple HCM mutations in a person predicts a severe phenotype, such as severe hypertrophy, advanced heart failure and progression to hypokinetic stage [2,6,19]. On the other hand, the presence of only one of the variants (III-5 in Figure 1D) creates a problem in predicting disease severity in the offspring of affected patients.

Compared to the extensive literature on genotype-phenotype correlation in HCM, the data on real-life implications of genetic testing for clinical decision making are more limited. The existence of many "private mutations" found in isolated families with unknown functional characteristics and variable disease severity, seen even among patients carrying identical mutations, limits the prognostic value of genetic testing [5]. Genetic counseling and clinical evaluation of first-degree family members will no doubt be integrated into HCM evaluation [1-3]. Genotyping of 'next of kin' once a causative mutation is found in the proband also appears to be straightforward. Yet, some experts remain skeptical of the role of genetic diagnosis in routine clinical management of HCM patients. Whereas genetic data may provide indispensible clinical information such as resolving controversy over borderline phenotypes, they can also lead to highly controversial decisions such as unjustified reproduction interventions or inappropriate ICD implantation. Mutation carrier combined with history of sudden death prompted unjustified ICD implant in a healthy MYH7 mutation carrier in the H171GA family [Figure 1C].

Decisions on primary arrhythmic prevention are individualized based on clinical criteria and at most implicate "malignant mutation" as a minor criterion [1,3]. Knowing the mutation may also lead to dramatic changes in reproduction planning, which may be driven by emotions rather than proper interpretation of disease severity. Besides in utero diagnosis, pre-gestational diagnosis has become widely available and may be the procedure of choice for couples who would not consider abortion. Reproduction decisions using genetic data will be individualized on a case-by-case basis depending on disease severity, personal preferences, and cultural, religious and legal considerations [2,25]. In general, mutation data should probably have a limited role in family planning in HCM, since this is often a rather benign disease with a near normal survival.

LIMITATIONS AND CONCLUSIONS

This is a relatively small observational study "enriched" by families with adverse outcomes. Because cardiac MRI was not routinely used, we could not assess its role in early HCM diagnosis compared to mutation testing. The net benefit of gene testing in HCM needs to be validated in prospective clinical studies.

Acknowledgment

We are grateful to Prof. Vardiella Meiner MD PhD, Chair of the Department of Genetics and Metabolic Diseases, and to Prof. Andre Keren, Head of the Heart Failure Center, Hadassah-Hebrew University Hospital, Jerusalem, for performing the genetic analysis in the H171GA family and for their helpful comments.

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