Benefits and pitfalls of genotyping HCM in cardiomyopathy clinic

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Disclosures

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Introduction

- Hypertrophic cardiomyopathy is considered to be 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 can be detected through family members' screening and longitudinal follow up.
- Disease-causing mutations may be found in up to 70% of families with HCM.

Introduction (II)

Recommendation on genetic testing, 2011 ACCF/AHA Guideline, Gersh et al.

- **Class I (level B)**
  - Evaluation of familial inheritance and genetic counseling is recommended as part of the patient assessment
  - Patients who undergo genetic testing should also undergo counseling so that results and their clinical significance can be appropriately reviewed
  - Screening (clinical, with/without genetic testing) is recommended in first-degree relatives of patients with HCM
  - Genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation or when another genetic condition is suspected
- **Class IIa (level B)**
  - Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM

Purpose

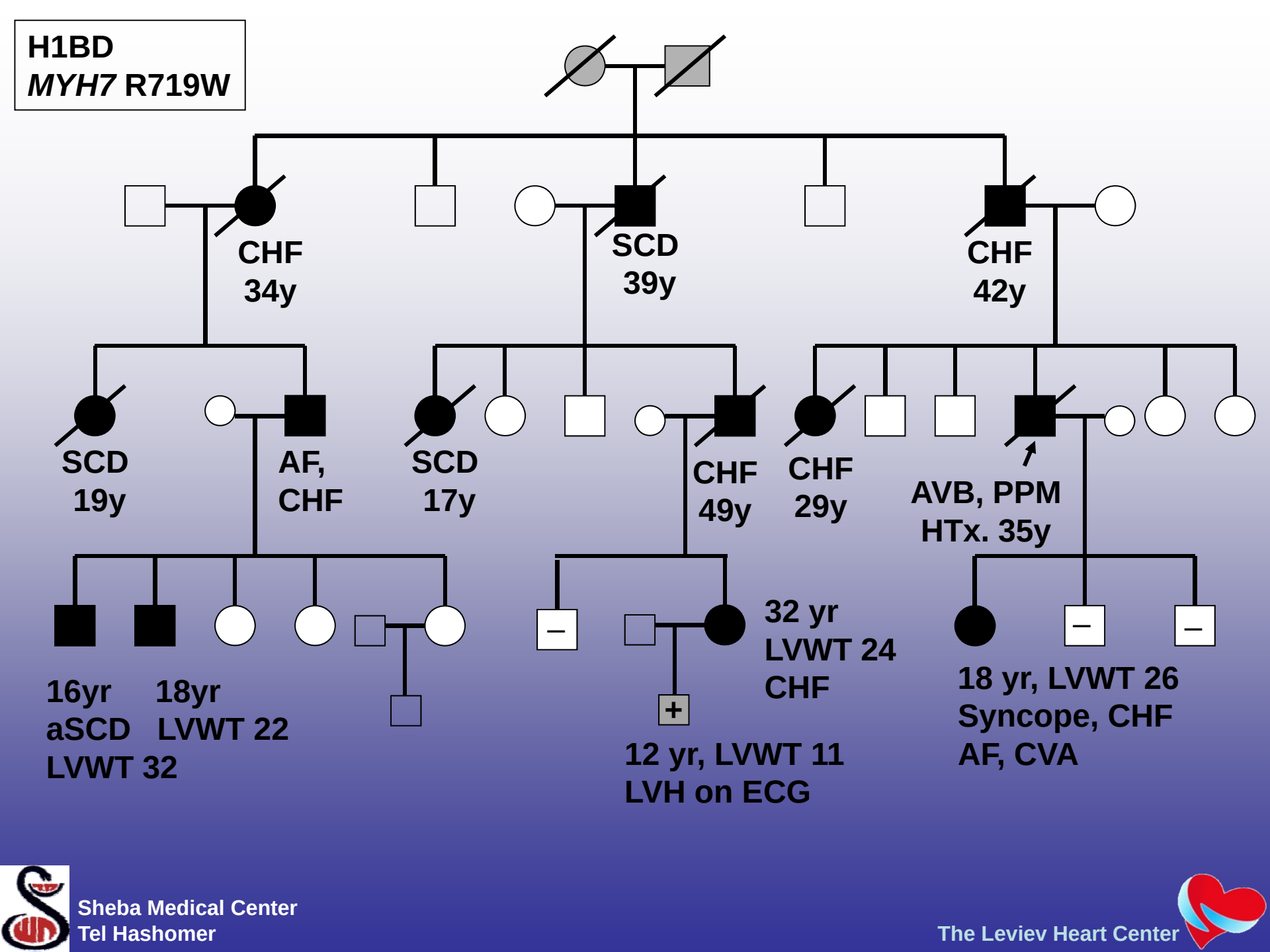
- To assess the effect of genetic diagnosis on clinical HCM management in cardiomyopathy clinic
- To evaluate the compliance of the relatives with the recommendation to undergo testing for the mutation found in HCM family

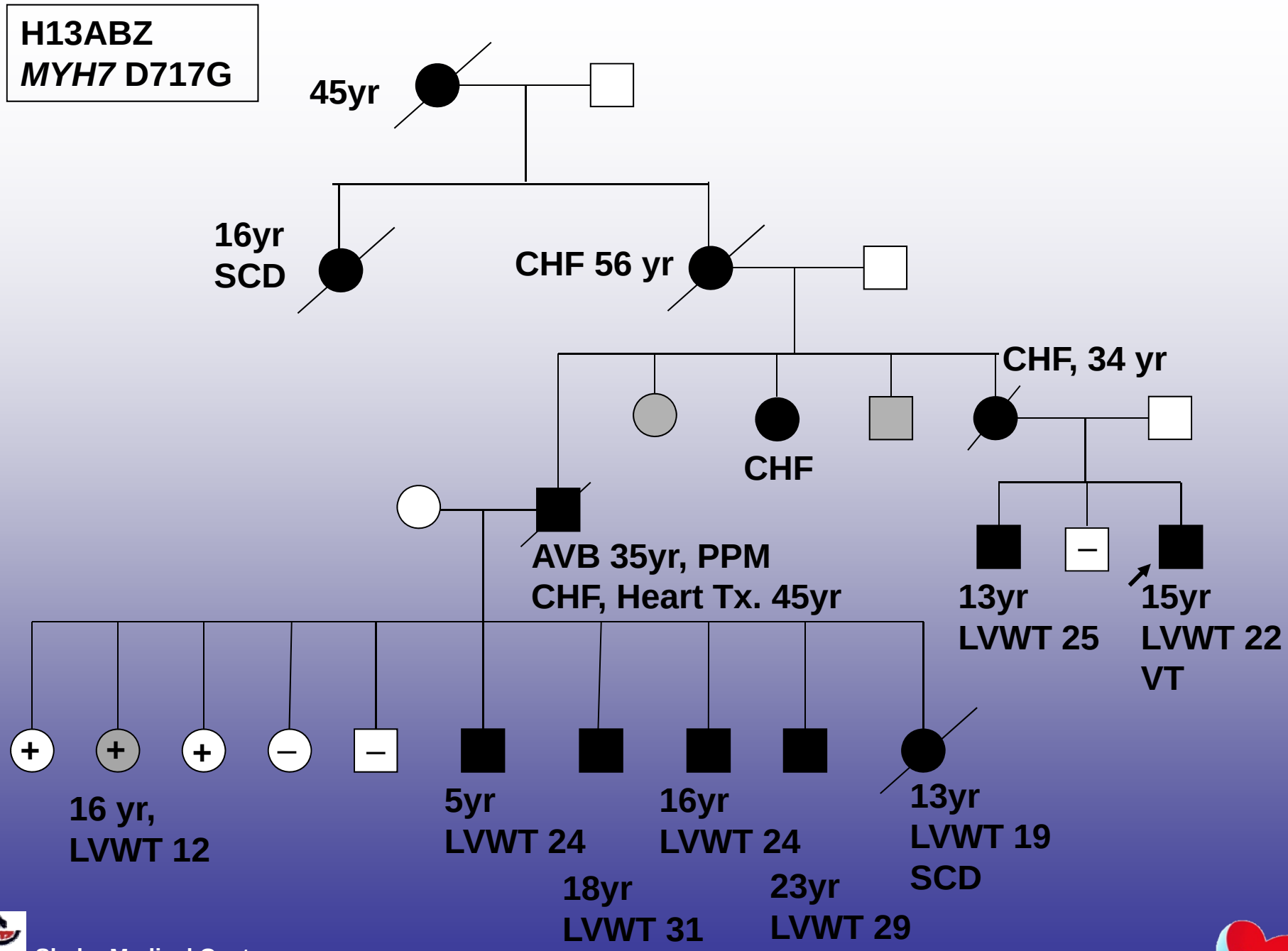
Methods

- **Cardiomyopathy Clinic of Leviev Heart Institute in Sheba Medical Center, listing at the moment of data analysis 360 HCM patients from 296 families.**
- **Patients and family members received genetic counseling and signed an informed consent when appropriate.**
- **Genetic diagnosis was established between 2004 and 2011 allowing at least 1 year of follow up after the test results were made available to the family.**
- **Results were accepted from research studies or from a certified genetic laboratory. Once mutation was found, genotyping of first degree family members was encouraged.**
- **Data on testing family members and on the clinical application of the genetic results was collected (descriptive and Chi square).**

Results: Clinical Characteristics

Family/ Proband	Indication/ Reason for referral	Age of onset	Disease Features					
			Massive LVH	LVOT Obstruct.	Sudden Death	Severe CHF	Heart Tx.	Other
H1BD	Severe Phenotype	teenage	Yes		Yes	Yes	Yes	CSD
H7YY	Severe Phenotype	adult		Yes		Yes	Yes	
H13ABZ	Severe Phenotype	teenage	Yes		Yes	Yes	Yes	CSD
H18HF	Unique Phenotype	teenage	Yes			Yes		
H29OD	Family Request	elderly				Yes		CSD
H145RR	Unique Phenotype	elderly				Yes		Pulmon. A-V mal
H150SN	Reproductive Counseling	teenage			Yes			
H171GA	Sudden Death	teenage			Yes	Yes		
H268LJ	Patient's Request	adult						


H1BD
MYH7 R719W
CHF
34y
SCD
39y
CHF
42y
SCD
19y
AF,
CHF
SCD
17y
CHF
49y
CHF
29y
AVB, PPM
HTx. 35y
16yr
aSCD
LVWT 32
18yr
LVWT 22
–
+
32 yr
LVWT 24
CHF
12 yr, LVWT 11
LVH on ECG
18 yr, LVWT 26
Syncope, CHF
AF, CVA
–
–



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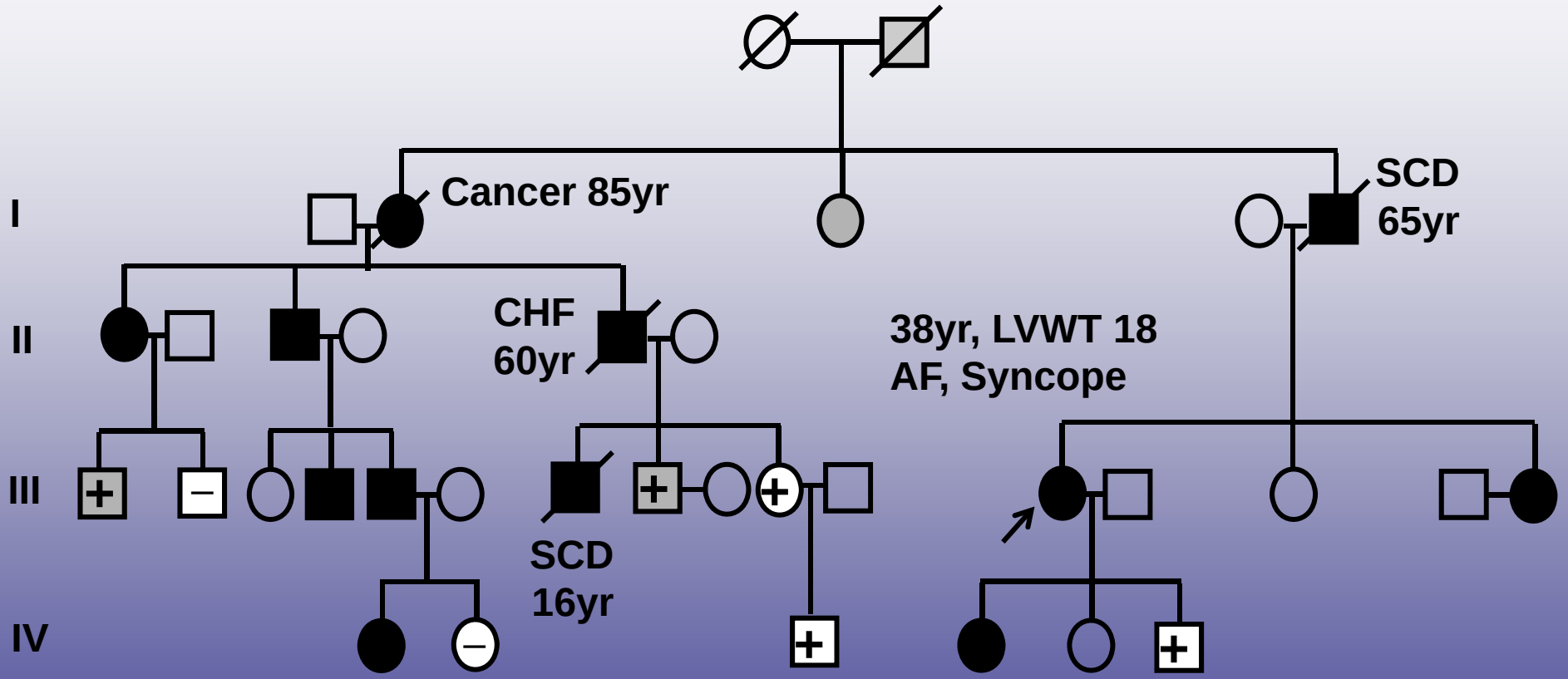
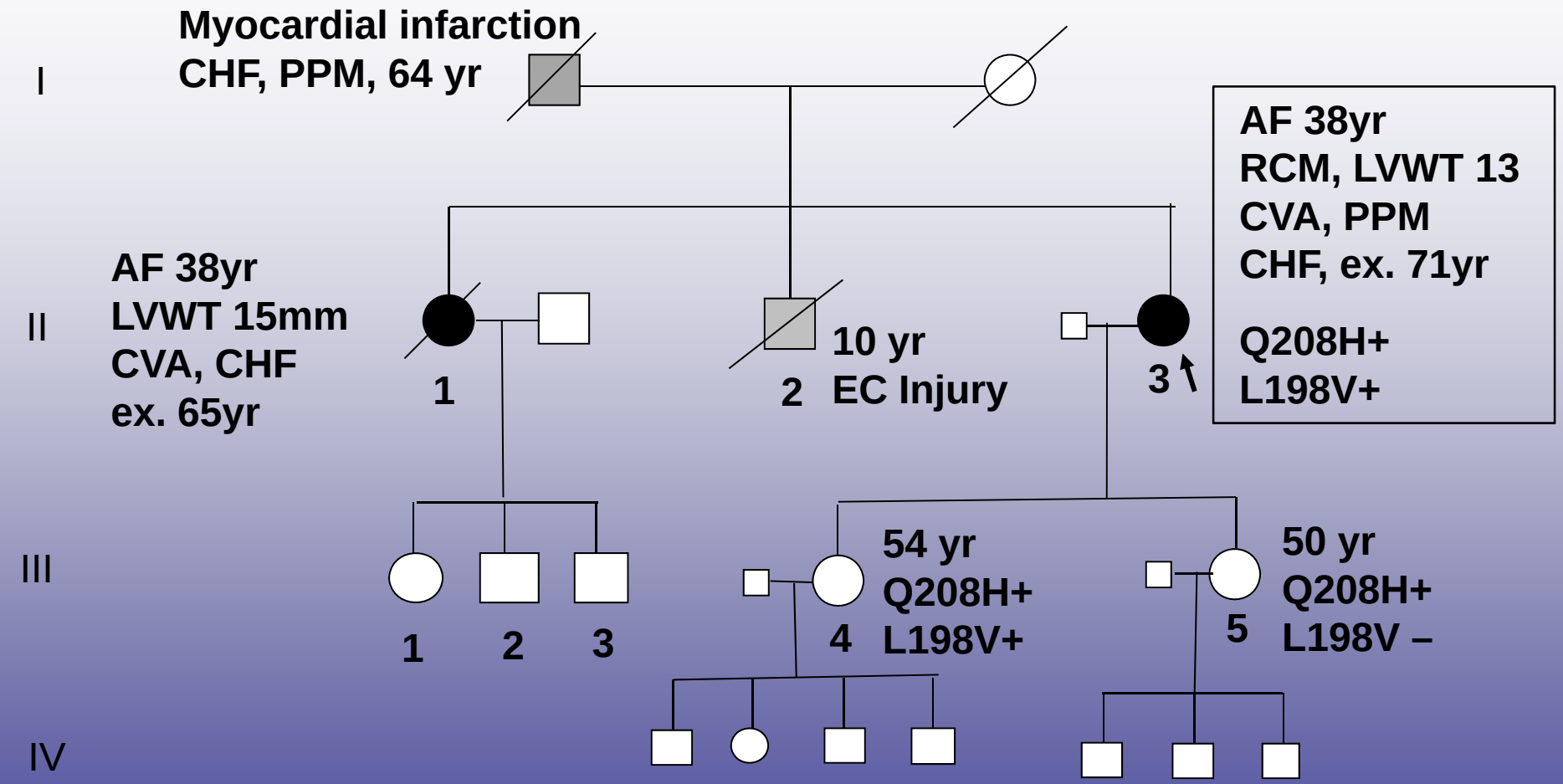
H171GA
***MYH7* V606M**



H29OD
***MyBPC3* Q208H, *TNNI3* L198V**



Results: Genetic Testing

Family	Mutation	No. of clinically affected	Family members tested (%)	Clinical status and genotyping results in family members			
				Affected & Positive	Unknown & positive	Non-affected & positive	Healthy & Negative
H1BD	MYH7 R719W	6	7/12 (58)	3	1	0	3
H7YY	MyBPC3 R35W	2	9/14 (64)	1	0	2	6
H13ABZ	MYH7 R717G	9	14/23 (61)	7	1	2	4
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)	8	3	2	4
H268LJ	MYH7 E497D	1	0/2 (0)	0	0	0	0

Results: What determines the % of family members willing to be tested?

- Higher rate in families with history of sudden cardiac death ($p<0.001$).
- Related to the number of clinically affected family members ($p=0.003$). No motivation in families with what appears to be a sporadic disease.
- Young age of disease onset ($p=0.002$). No motivation in families with elderly onset disease.
- No relationship to severe heart failure or family history of heart transplantation.

Results: Clinical Applications

Family/ Proband	Mutation	Testing Set up	Clinical use of genetic diagnosis			
			Ascertain Diagnosis	Prenatal Diagnosis	Prognostic information	ICD implant
H1BD	MYH7 R719W	Research	Y	Y	Y	
H7YY	MyBPC3 R35W	Research	Y			
H13ABZ	MYH7 R717G	Research	Y	Y	Y	
H18HF	MYH7 R1344Q	Research				
H29OD	MyBPC3 Q208H; TNNI3 L198V	Service			Y	
H145RR	MyBPC3 G596R	Research				
H150SN	TNNT2 E163del*	Service	Y	Y	Y	Y
H171GA	MYH7 V606M	Research	Y			Y
H268LJ	MYH7 E497D	Service				

Mutation has been previously described and there is clinical information available

*** - TNNT2 E163del previously found in 13 families, 43 subjects, 15 cases of sudden death**

Conclusions

- Genetic studies may improve the diagnosis and prognostic evaluation in HCM.
- The high recurrence rate of mutations in different families allows to apply the clinical information from the literature to risk-stratification of individual patients.
- Compliance with genetic testing was higher in families with sudden death and low in sporadic HCM or elderly-onset disease.
- Genetic diagnosis helps to resolve uncertainties over borderline phenotypes but may also lead to highly controversial decisions.
- We suggest that the clinical context should determine the indication and the interpretation of the genetic analysis.