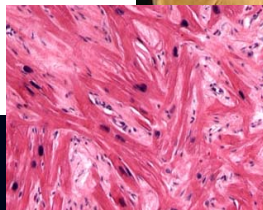
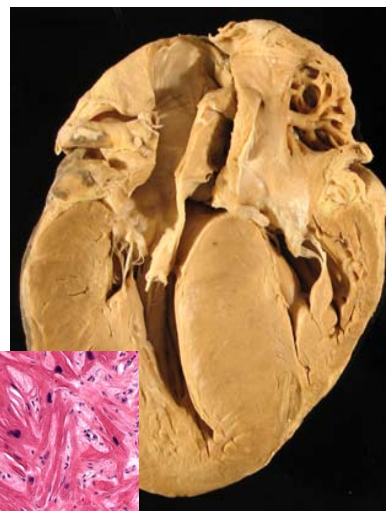
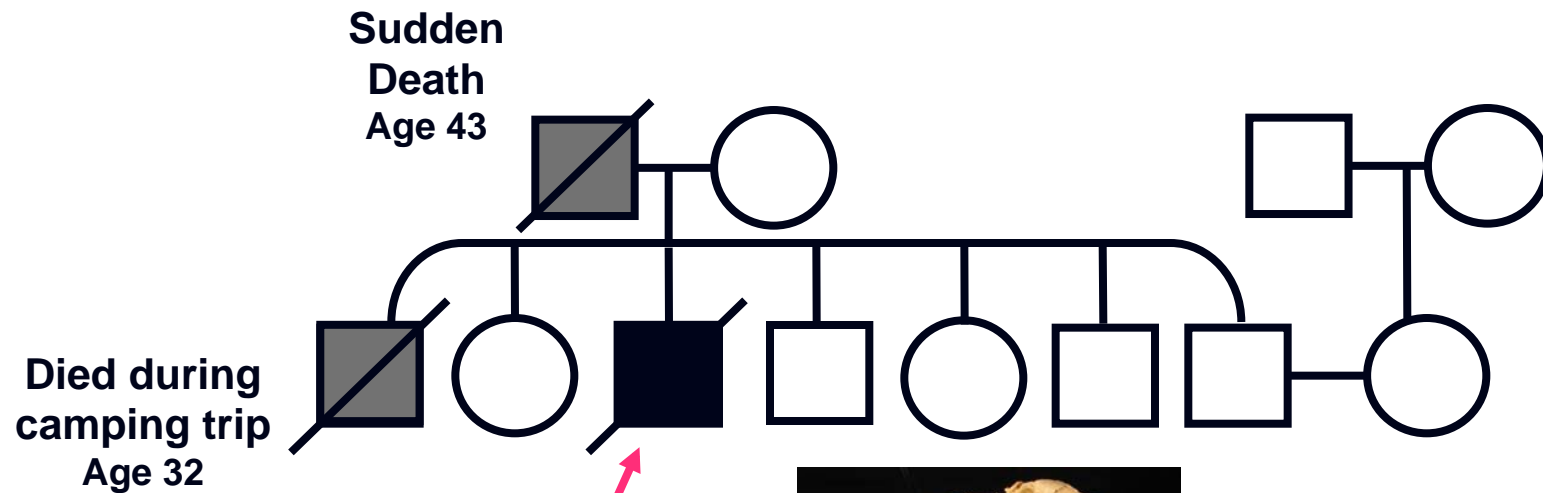


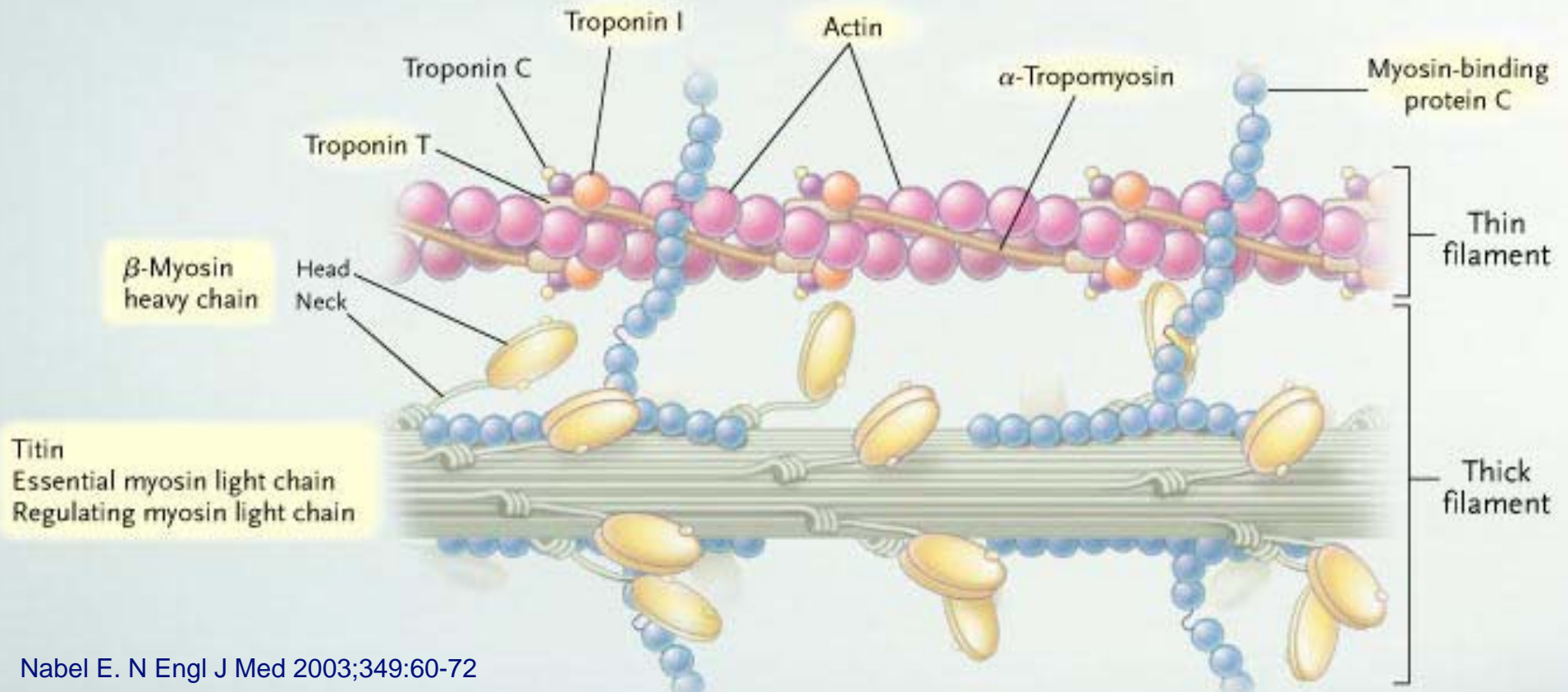
Genetics of Hypertrophic Cardiomyopathy

Carolyn Ho, MD
Cardiovascular Division
Brigham and Women's Hospital
Boston, MA

June 25, 2009



Hypertrophic Cardiomyopathy Caused by Sarcomere Gene Mutations



Nabel E. N Engl J Med 2003;349:60-72

Clinical Genetic Testing

Partners Center for Genetics and Genomics: Laboratory for Molecular Medicine
HPCGG.partners.org/LMM

Clinical Sensitivity (>1000 probands):

52% genotype (+)

40% if no FH

66% if +FH

Similar in adult and pediatric

~15% of Elderly and unselected

Of G(+):

~80% are MYH7 or MYBPC3

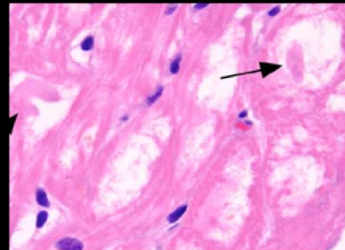
~2-8% have >1 mutation

~3-4% are non-sarcomere

Gene	Exons	Bases
MYH7	38	6548
MYBPC3	34	4485
TNNI3	8	773
TNNT2	15	1148
TPM1	11	1131
MYL2	7	621
MYL3	6	628
ACTC	6	1234
PRKAG2	16	2010
LAMP2	10	1543
GLA	7	1410
11	158	21591

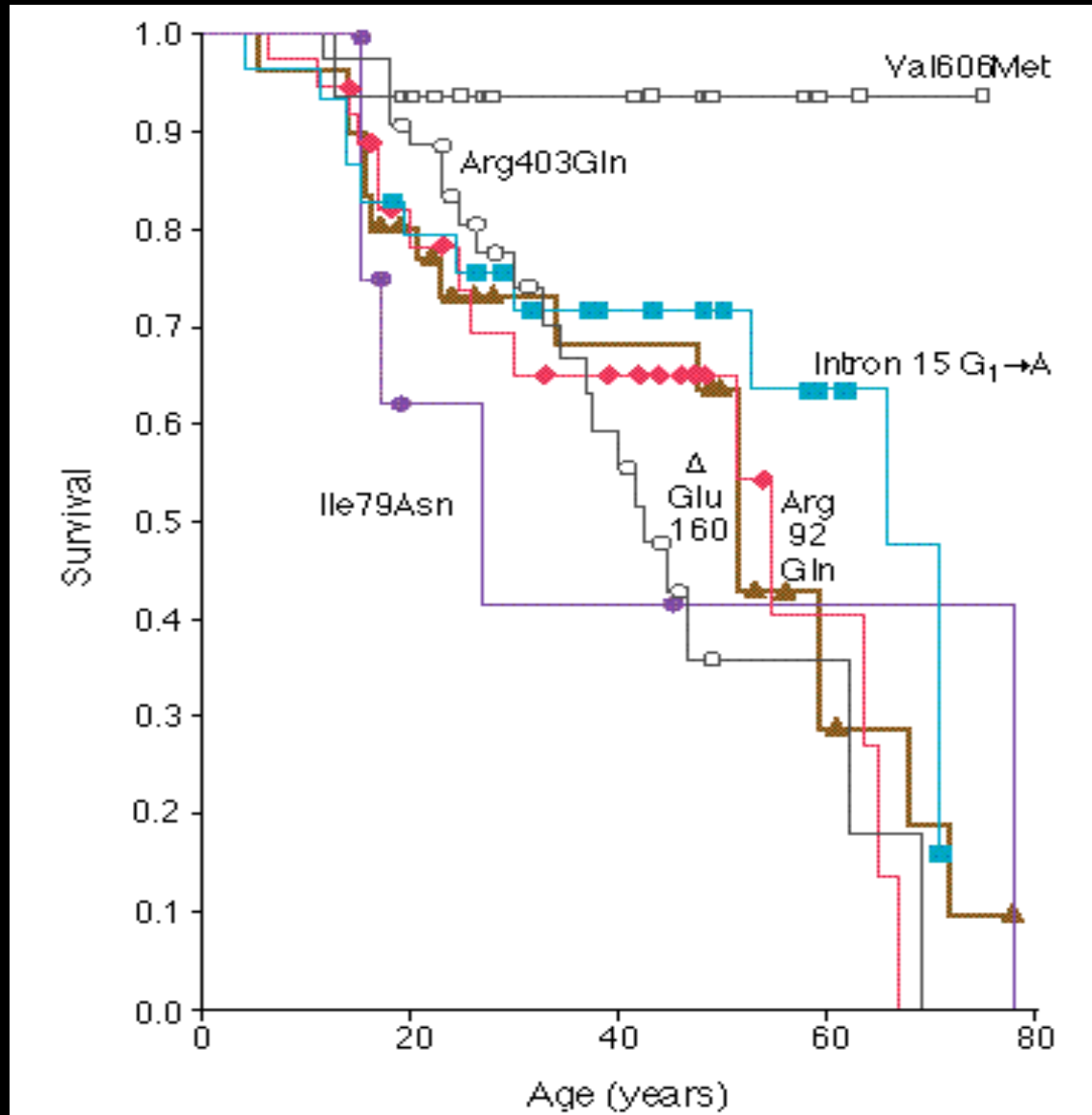
**Sarcomere
Genes**

**HCM Phenocopies
Metabolic/
Storage CMP**

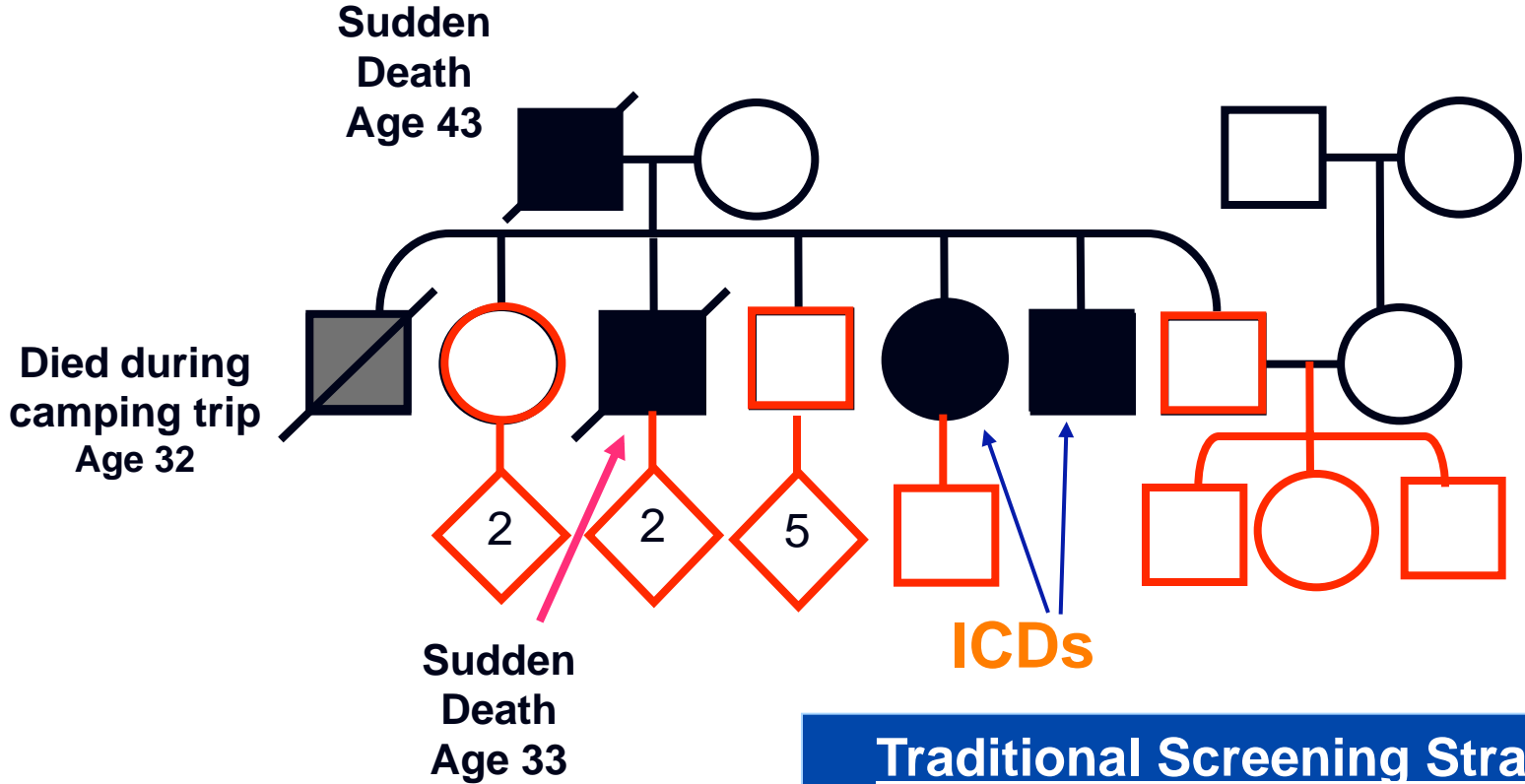


Genotype: Role in Prognosis?

- >800 Mutations
- 11 Genes
- Genotype-Phenotype correlations are not robust



Clinical Testing

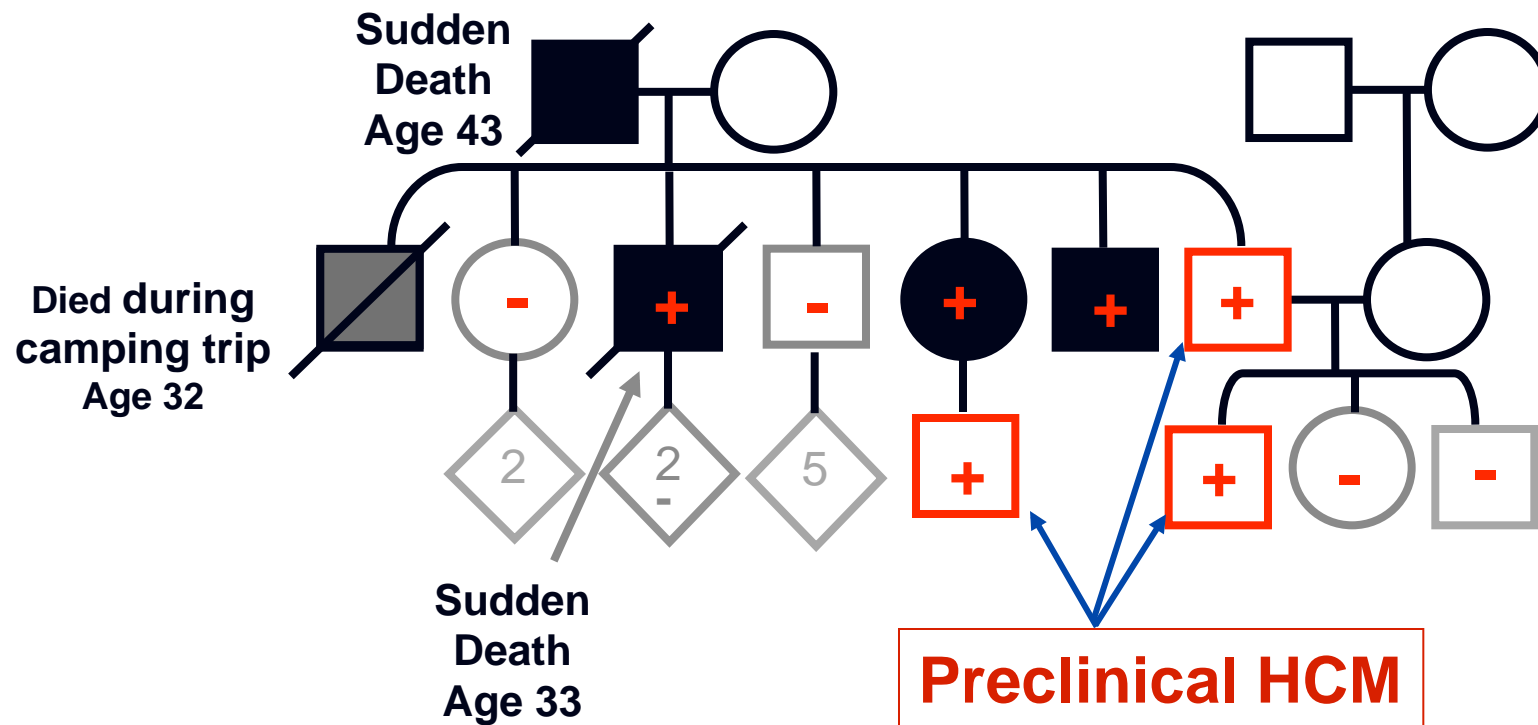


Traditional Screening Strategy
Clinical Exam
EKG, Echocardiogram
Holter, ETT, MRI
Serial Evaluation- Frequency Based on Age
Health Care Costs > \$1000/visit

MYH7 Mutation

Focused Longitudinal Follow up in Family Members

From 16 *possibly* to 3 *definitively* at risk relatives

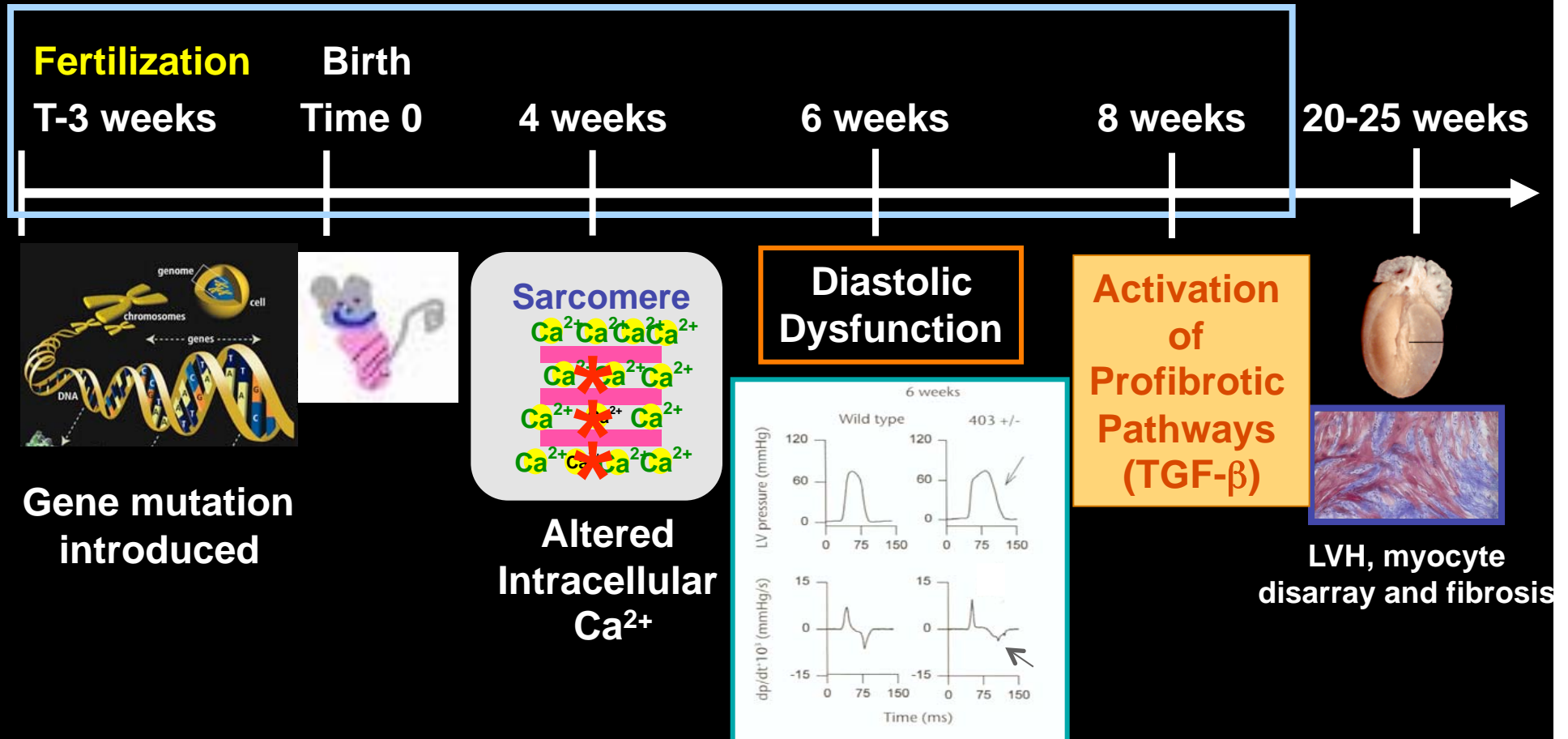


How can disease be defined?
Can phenotypic progression be changed?

Development of HCM Phenotype in Mouse Models

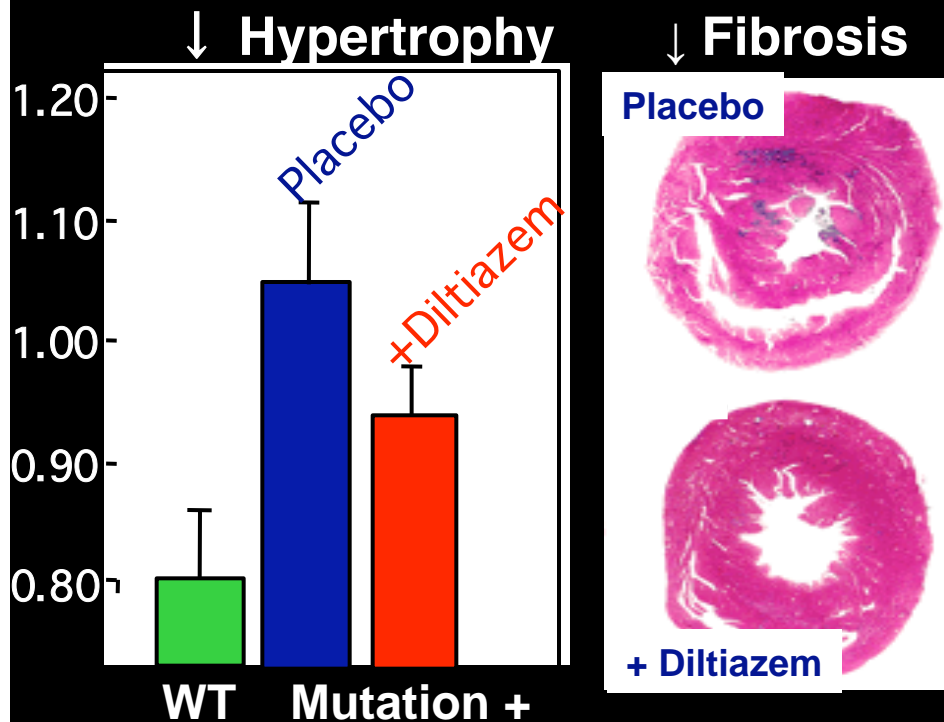
How do sarcomere mutations cause disease?
What are the earliest manifestations?

Preclinical HCM



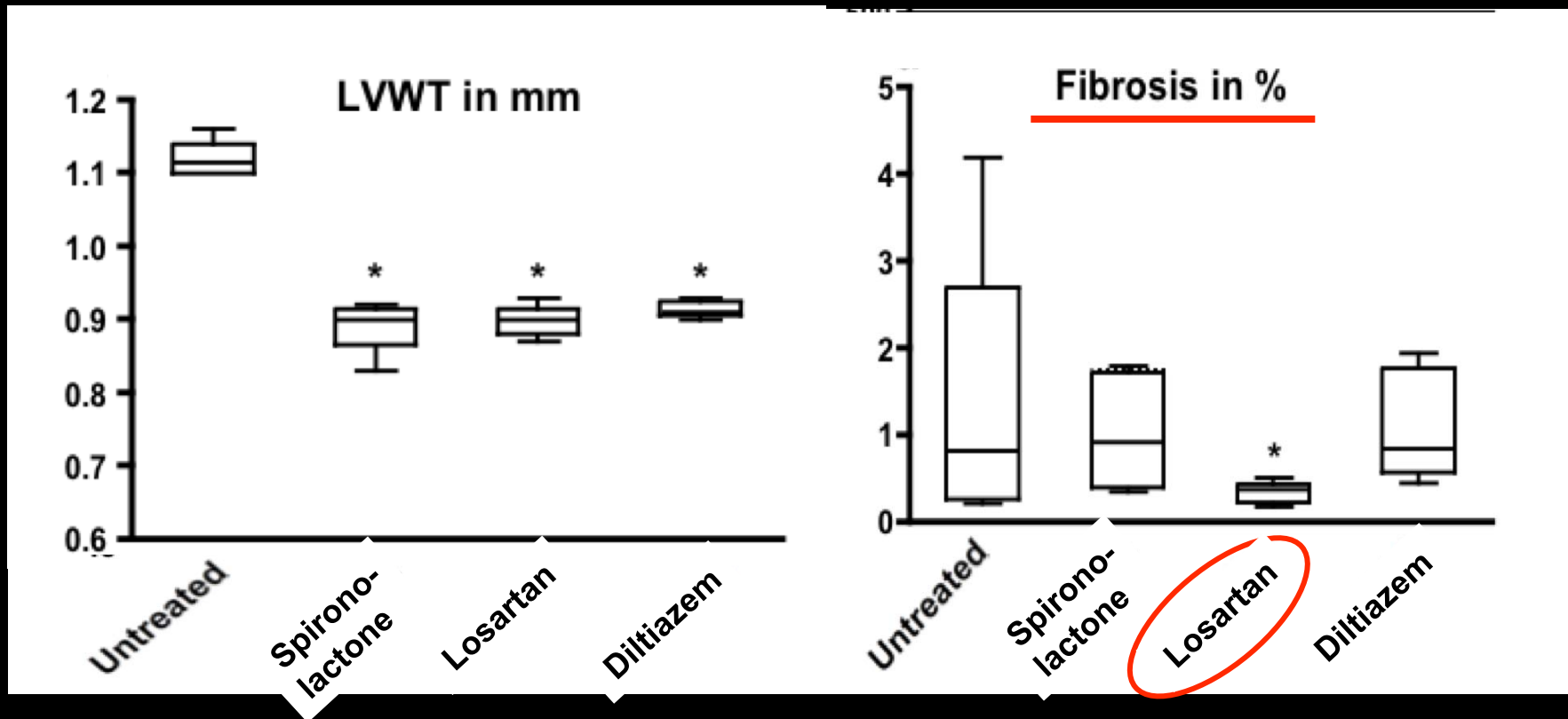
Phenotype Modification: Diltiazem treatment in Preclinical HCM

Reduces Hypertrophy
Improves Histopathology



- Suggests a mechanistic link: Ca^{2+} dysregulation and LVH
- No effect if treatment started after LVH developed
- Clinical Implications: Early pharmacologic intervention to improve Ca^{2+} balance may improve the natural history of HCM

Phenotype Modification: New Studies in mouse Preclinical HCM



From Mouse to Man



Mouse vs Man

Body Weight ~ 30 g vs 70 kg

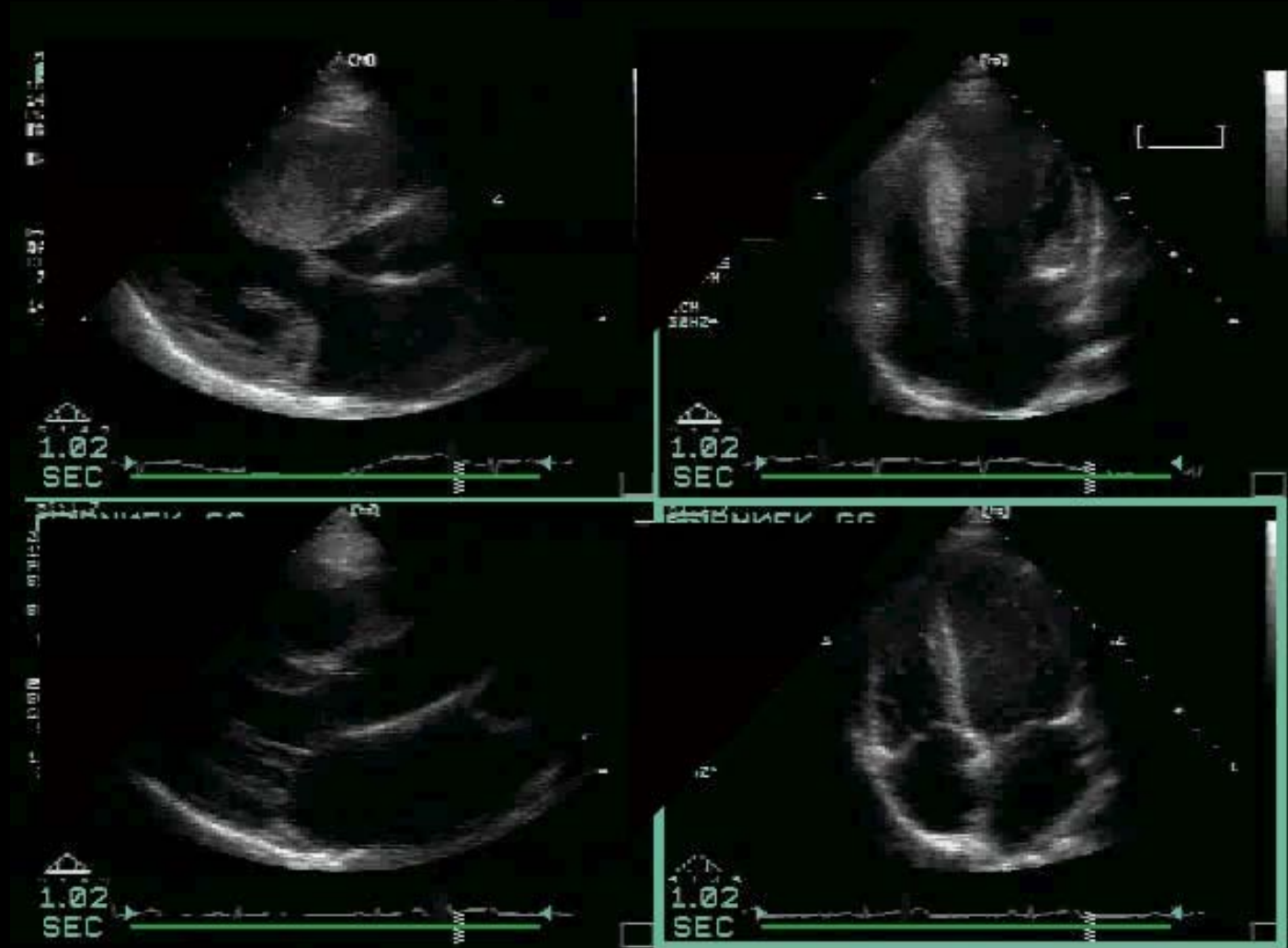
Heart Weight ~ 100 mg vs 300 g

Heart Rate > 500 vs 60 beats/minute

Translation to Human Preclinical HCM

Not identifiable by standard echocardiography

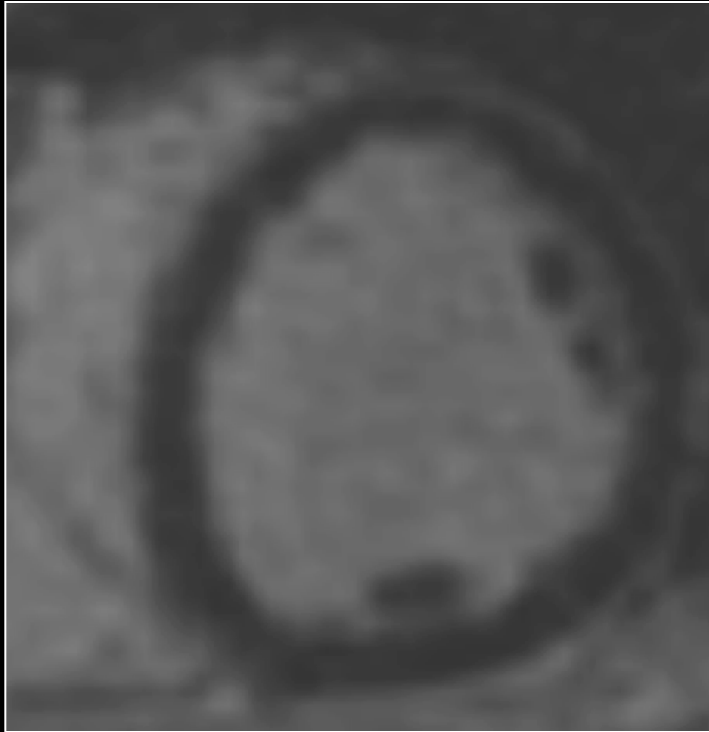
24F HCM:
MYH7 mutation



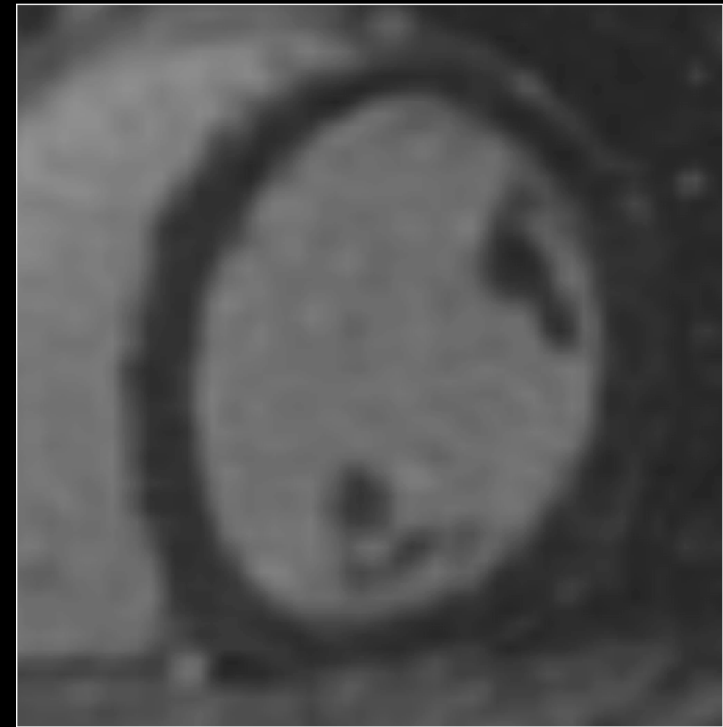
23F cousin:
MYH7 mutation
G+/LVH-
Preclinical HCM

Preclinical HCM

No abnormalities on cardiac MRI- absence of Delayed Gd



Resting Perfusion

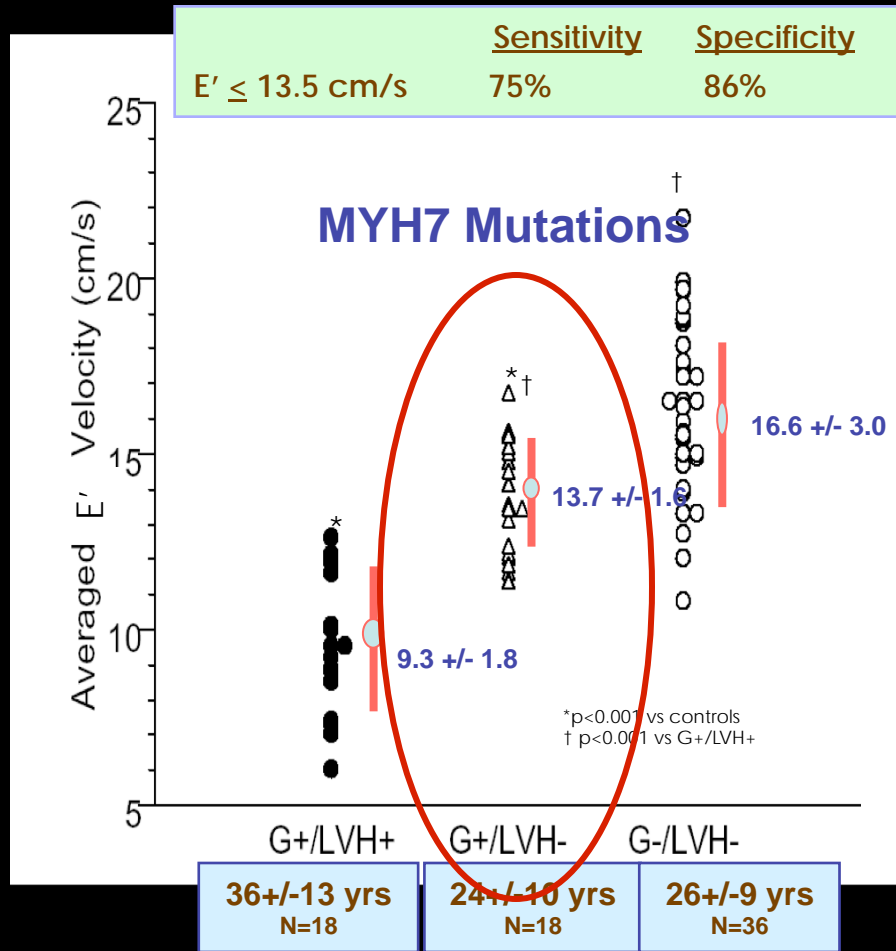


Delayed Perfusion

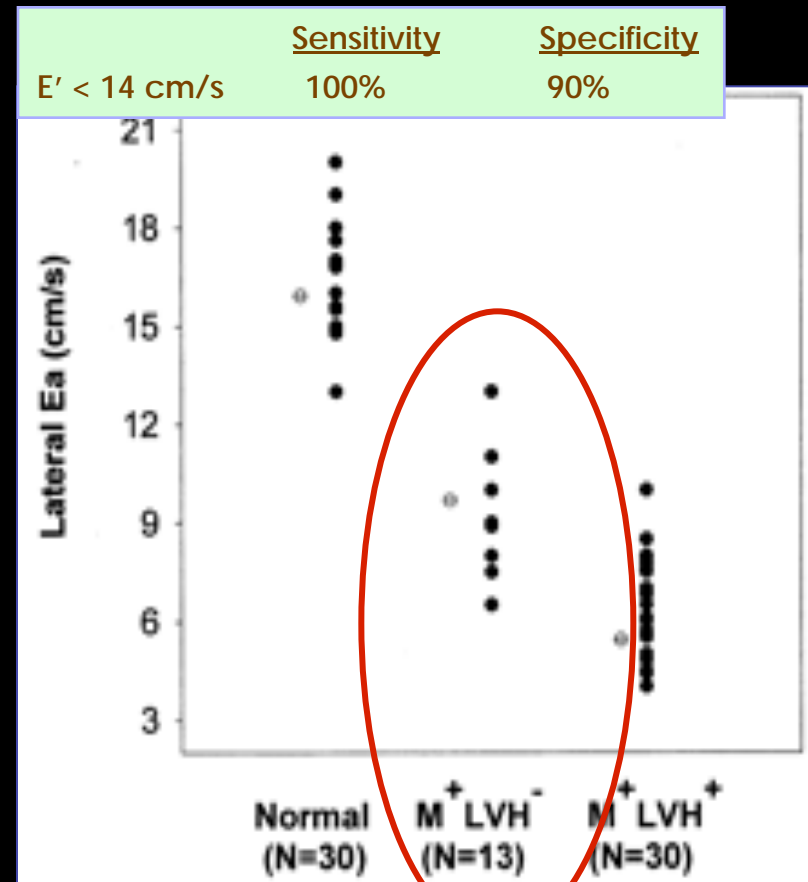
Genetic Testing is Required to Identify Preclinical HCM

Translation to Human HCM

Diastolic Dysfunction in Preclinical HCM



Ho, et al *Circulation* 2002: 2992-2997



Nagueh, et al *Circulation* 2001:128-30

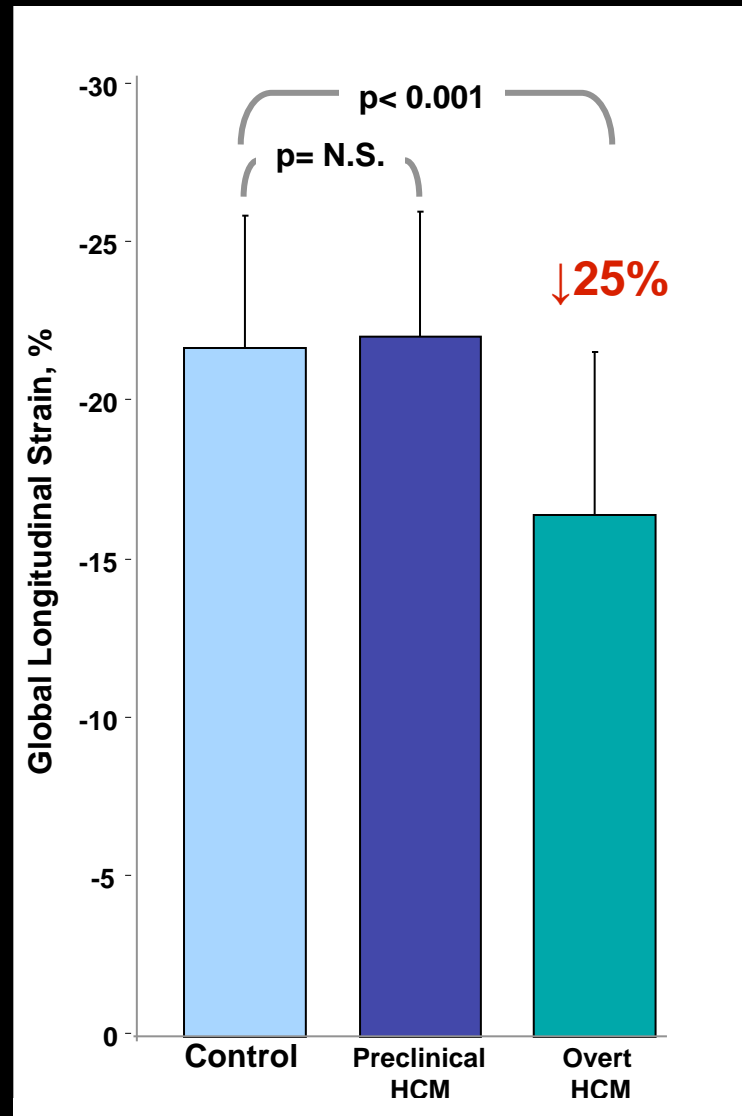
An early manifestation of sarcomere mutations

- Altered crossbridge kinetics?
- Delayed reuptake of Ca^{2+} into SR?

Translation to Human HCM

Longitudinal systolic strain and strain rate:

Preserved in preclinical HCM but Decreased in overt HCM



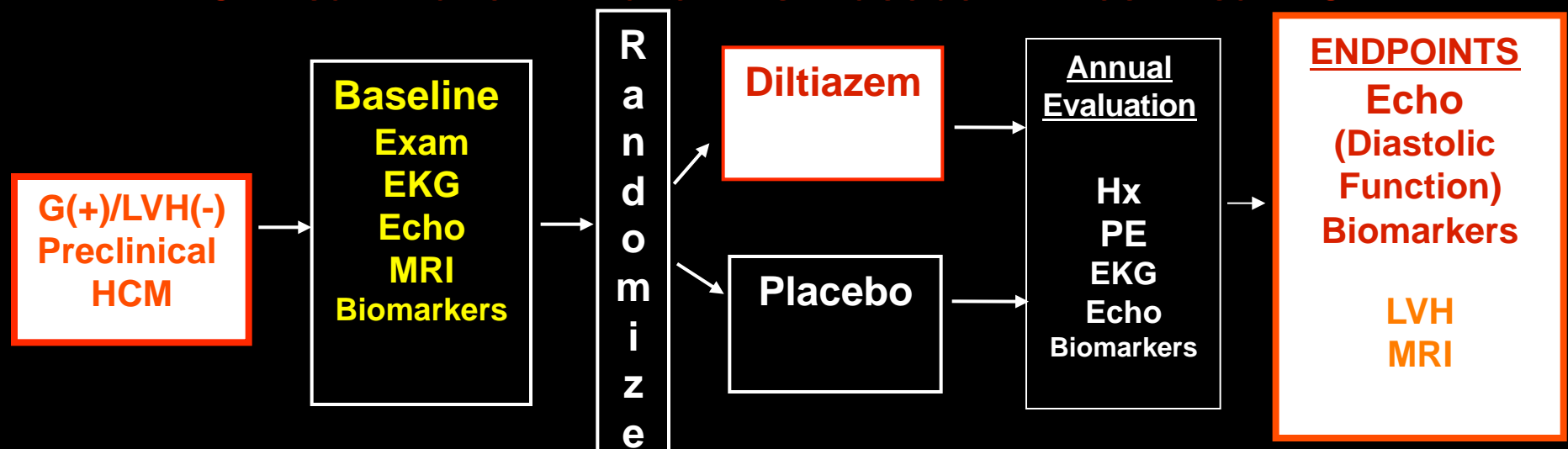
Normal LV EF

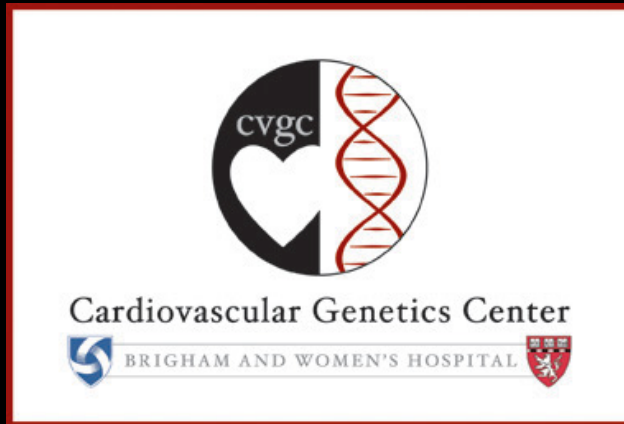
Translation to Human HCM

Future Goals

- **Proactive Management of Preclinical HCM**
 - Identify individuals at risk prior to clinical diagnosis by genetic testing (Preclinical HCM)
 - Characterize novel intermediate phenotypes of early disease and identify surrogate endpoints to monitor treatment response
 - Develop new treatment paradigms to attenuate or prevent phenotypic expression of sarcomere mutations by altering disease mechanism, not just symptoms or hemodynamics

Clinical Trial of Diltiazem vs Placebo in Preclinical HCM



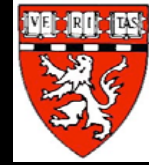


Allison Cirino
Akshay Desai
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Seidman Laboratory

Department of Genetics
Harvard Medical School

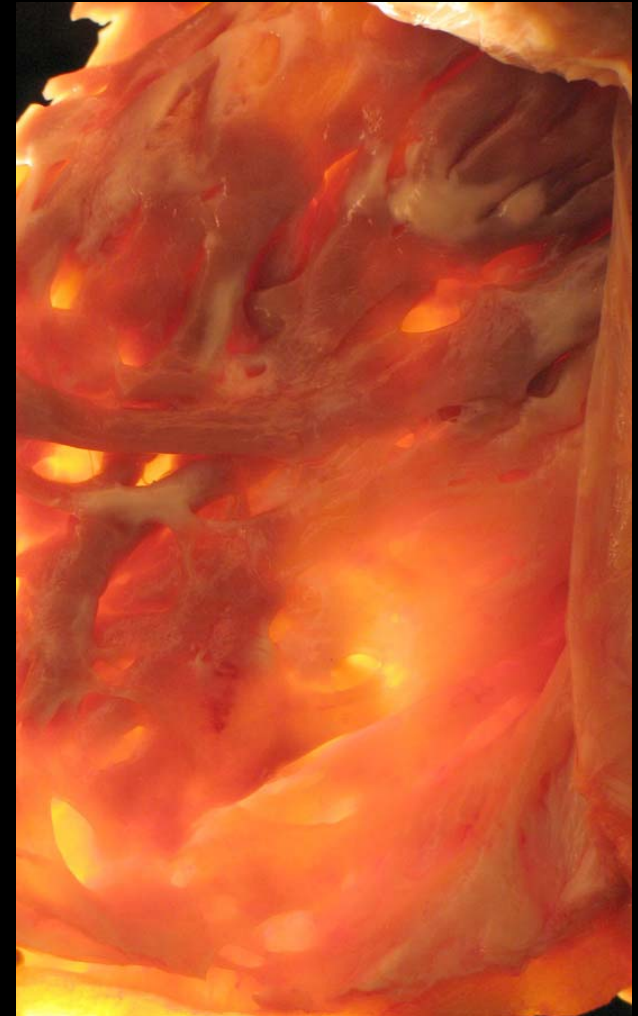
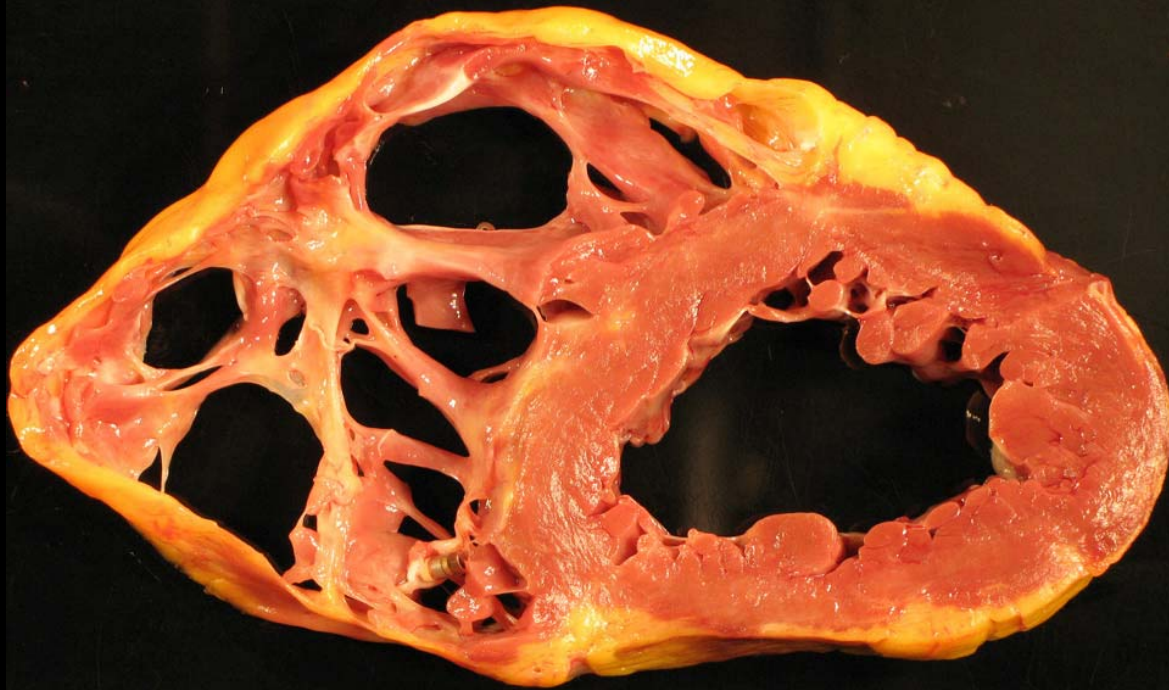


Diane Fatkin
Chris Semsarian
Hiroyuki Morita
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Libin Wang
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Dave Conner
Steve Greenaway
Kees Hovingh
Seda Eminaga

J.G. Seidman
Christine Seidman



Arrhythmogenic Right Ventricular Cardiomyopathy



- **Pathological Features**
 - Fibrofatty replacement of the RV myocardium at the end stage
 - Apical, inflow, and outflow portions of RV most commonly affected (thinnest regions)

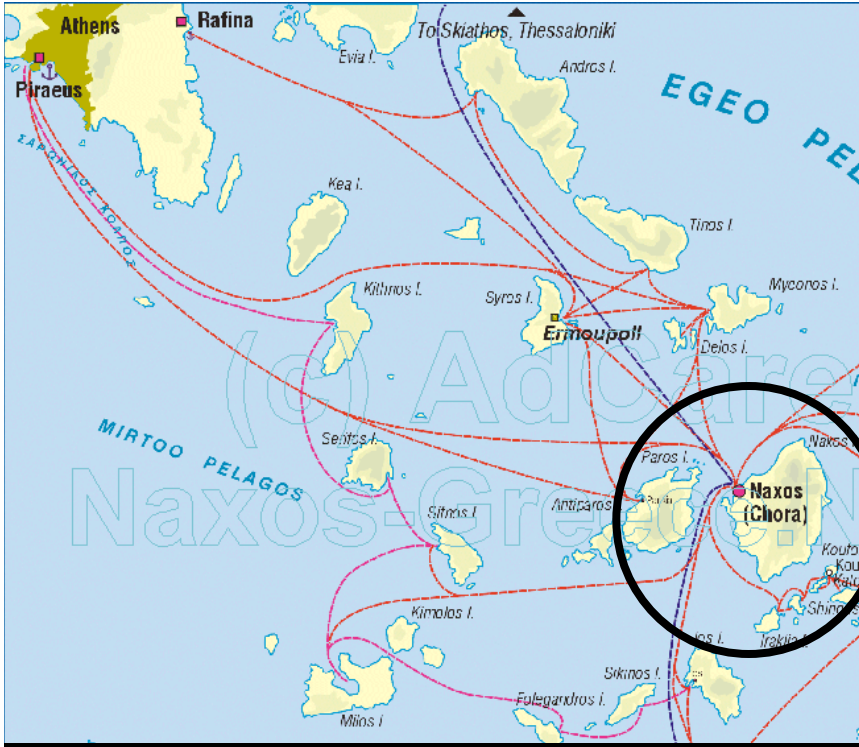
- **Clinical Features**

- **Electrical Instability: VT, syncope, SCD, especially early**
 - SCD 1st symptom in 50%
 - Important cause of SCD in young patients and competitive athletes
- **EKG changes: epsilon waves, TWI V1-3**
- **Cardiomyopathy and Heart Failure (later)**
- **SCD can occur at any time, even if no structural changes**
- **LV involvement in up to ~50%**

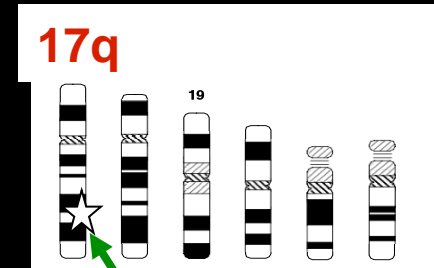
- **Prevalence**

- **~1:1000-5000**
- **Familial disease in >50%**
 - **Autosomal Dominant**
 - **Incomplete, age-dependent penetrance- often after puberty**
 - **Variable expression- difficult to recognize familial disease**
 - **Rare autosomal recessive cardiocutaneous syndromes**





Naxos, Greece
Population 20,000



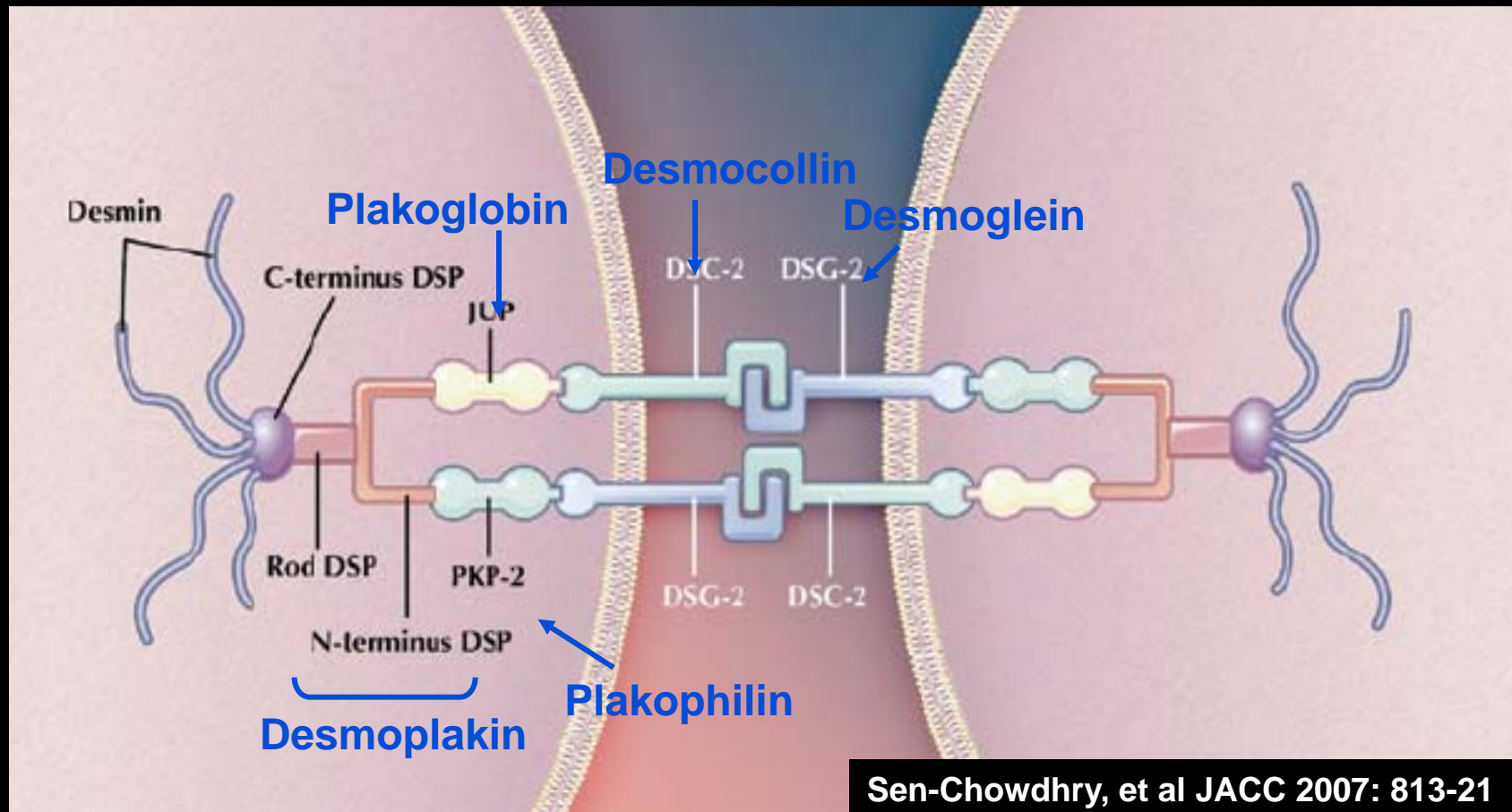
Linkage

Autosomal Recessive

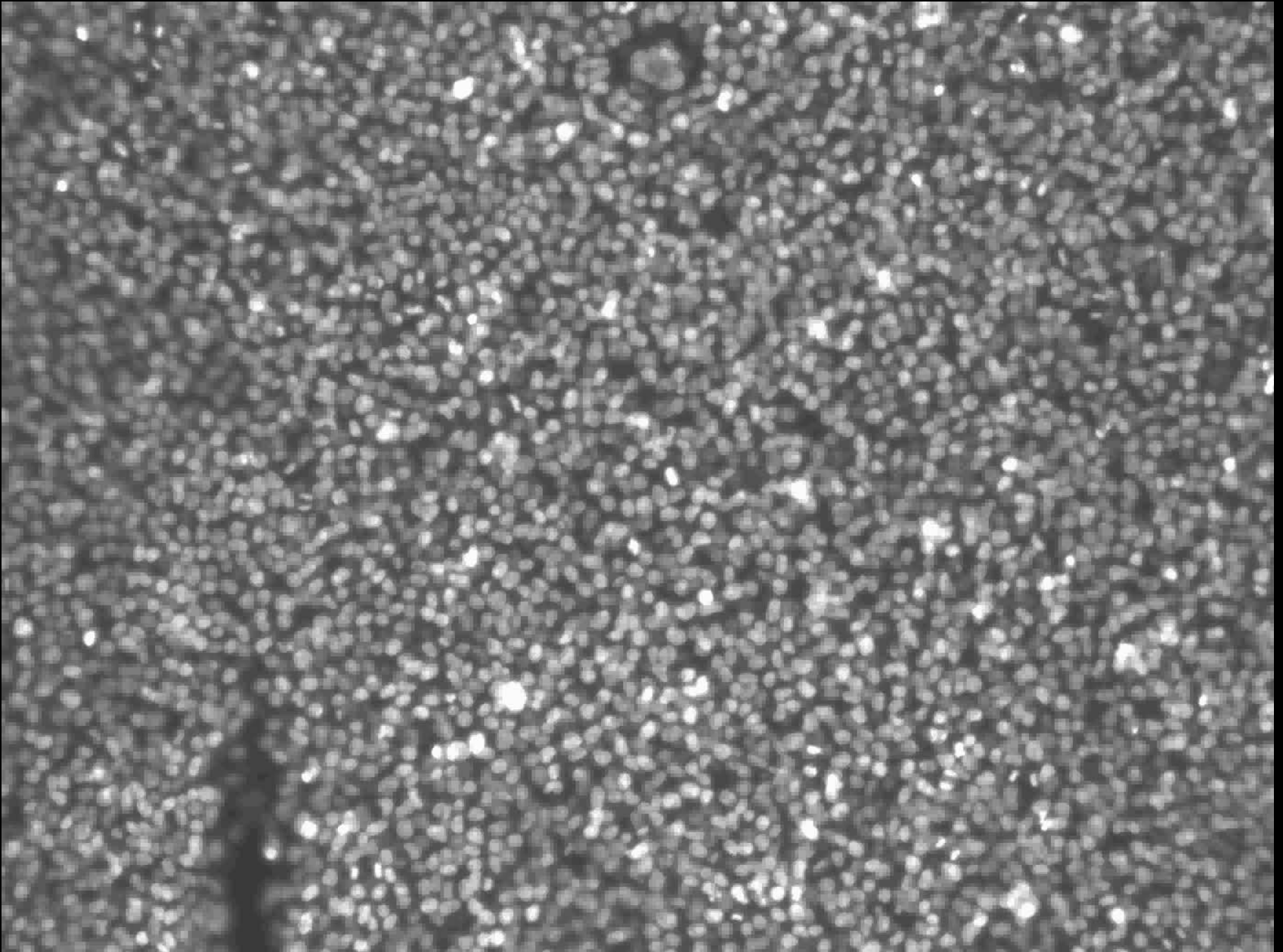
- **Woolly Hair**
- **Palmoplantar Keratoderma**
- **ARVC**
 - Cardiac manifestations in puberty
 - Annual SCD ~3%

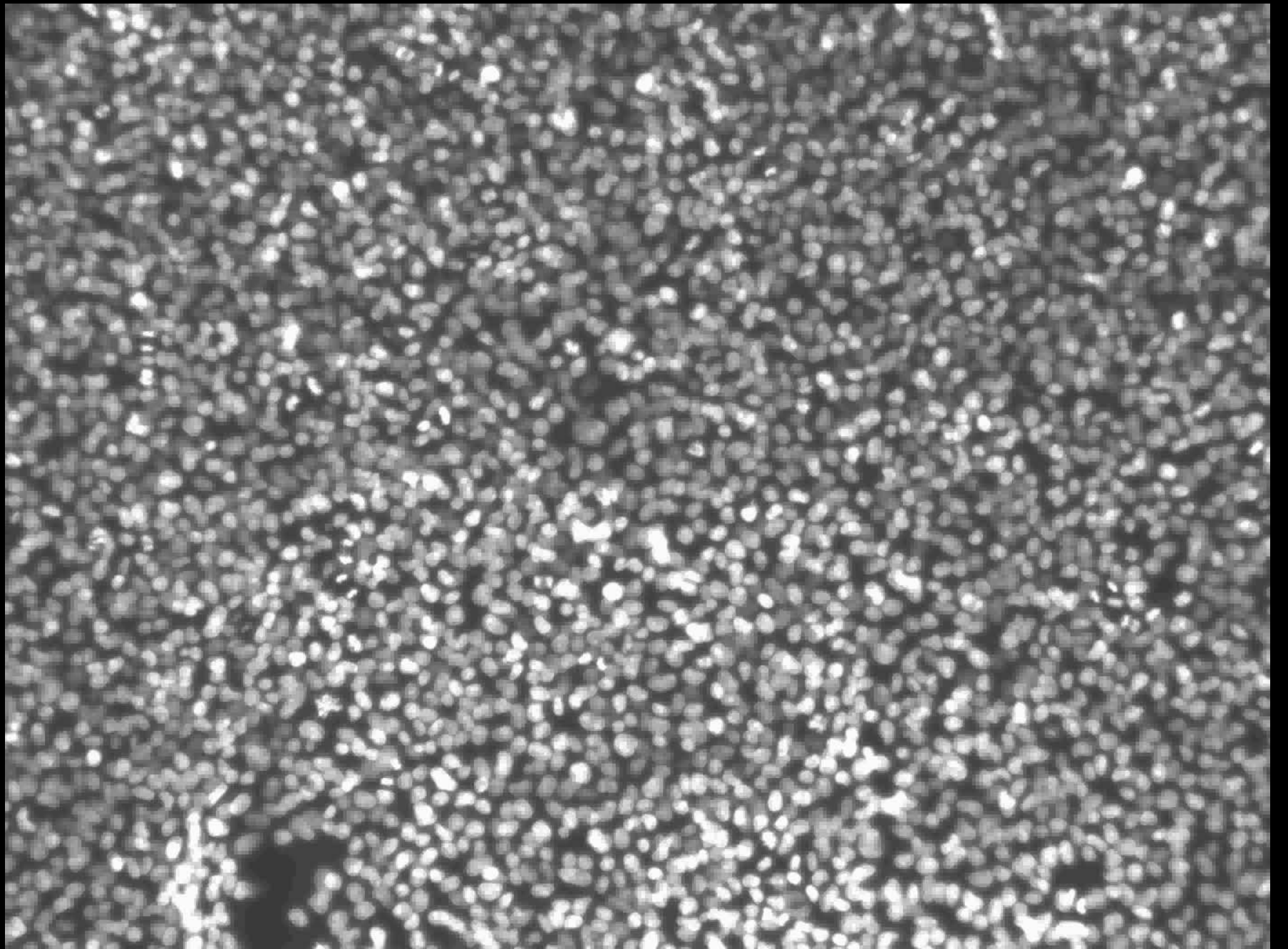
ARVC

A Disease of the Desmosome: Cell-Cell Adhesion Molecules



Anchor intermediate filaments between adjoining cells
Provide mechanical strength and transmit force
Most prevalent in tissues exposed to frictional/shear stress





ARVC: Genetic Testing

Gene (Symbol), Locus	Exons (n), Transcript Size (kb)	Mode of Inheritance	Number of Reported Mutations	Type of Reported Mutations	Associated Phenotype
Plakoglobin (JUP) 17q21	14, 2.4	AR	1	Deletion	Naxos disease
Desmoplakin (DSP) 6p24	~6-16%	AD	>10	Various	ARVC, LV involvement
		AR	3	Missense	ARVC, skin disorder, woolly hair
				Nonsense	ARVC, skin disorder, woolly hair
				Deletion	Carvajal syndrome
Plakophilin (PKP)-2 12p11	~11-43%	AD	>50	Various	ARVC
		AR	1	Cryptic splice site	ARVC
Desmoglein (DSG)-2 18q12	~10-40%	AD	>20	Various	ARVC
Desmocollin (DSC)-2 18q12	17, 3.1	AD	3	Deletion, insertion, splice site	ARVC

Pathogenic mutations found in 5 desmosome protein genes

- Overall Mutation Detection Rate: 40-50%
- Most commonly: Plakophilin, Desmoplakin, Desmoglein
- Penetrance and Expressivity are highly variable
- Genotype-Phenotype correlations have not been established
 - Desmoplakin mutations more commonly associated with LV involvement
 - Benign polymorphisms frequently seen- ?significance of novel variants
- May complement but not establish clinical diagnosis
- No independent prognostic information

