THE GENETICS OF CARDIOMYOPATHY: OPTIMIZING PATIENT AND FAMILY CARE BY IDENTIFYING DISEASE ETIOLOGY

The Ohio-ACC Spring Summit
April 18, 2012

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The Heart Institute

Objectives

- Understand the variety of multi-gene panels available for cardiomyopathies
- Identify the utility of genetic testing for cardiomyopathy with regard to screening, diagnosis and management
- Determine appropriate genetic testing and/or referrals for patients with cardiomyopathies

Overview

- Genetic Counseling
- Review of published guidelines for genetic testing and screening of at-risk individuals
- Disease specific overview - HCM, DCM, RCM, ARVC, and LVNC
  - Etiology
  - Clinical genetic testing
  - Case examples

Genetic Counseling

- *…process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease.*
- In practice
  - Clinical care and support to families
    - Prenatal, Cancer, Pediatric, Adult, *Cardiovascular*
  - Education
  - Research
  - Policy
- Education:
  - M.Sc. in Genetic Counseling/Medical Genetics
    - 2-3 yr full time program, thesis requirement
  - Certification by the ABGC
  - Continuing Education

National Society of Genetic Counselors

nsgc.org

ACC/ESC EXPERT CONSENSUS DOCUMENT

American College of Cardiology/ European Society of Cardiology Clinical Expert Consensus Document on Hypertrophic Cardiomyopathy

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines

2003

A Contemporary Approach to Hypertrophic Cardiomyopathy

Carolyn Y. Ho and Christine E. Seidman

Circulation 2006;113:e858-e862

2006

Guidelines for the Diagnosis and Management of Hypertrophic Cardiomyopathy

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2007

MULTIDISCIPLINARY GUIDELINE

Genetic diagnostics and genetic counselling in Hypertrophic Cardiomyopathy (HCM)

ICIN working group on Hereditary Heart Diseases

2010

European Heart Journal (2010) **31**, 2715–2728
doi:10.1093/eurheartj/ehq271

CURRENT OPINION

Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

Philippe Charron[1], Michael Arad[2], Eloisa Arbustini[3], Cristina Basso[4], Zofia Bilinska[5], Perry Elliott[6], Tiina Helio[7], Andre Keren[8], William J. McKenna[6], Lorenzo Monserrat[9], Sabine Pankuweit[10], Andreas Perrot[11], Claudio Rapezzi[12], Arsen Ristic[13], Hubert Seggewiss[14], Irene van Langen[15], and Luigi Tavazzi[16]*

HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

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Heart Rhythm, Vol. 8 No. 8 August 2011

Genetic testing recommended:

HCM- confirmed clinical diagnosis
DCM- confirmed clinical diagnosis and CCD and/or family history of SUD
HCM, DCM, ARVC, RCM, LVNC- known mutation testing for relatives

Genetic testing can be useful:

ARVC- patients meeting the 2010 task force criteria
DCM- familial DCM to confirm the dx, recognize those at highest risk of arrhythmia, facilitate cascade screening
LVNC- confirmed clinical diagnosis

Genetic testing may be considered:

ARVC- patients with possible dx
RCM- clinical diagnosis

Genetic counseling *is recommended* for all patients and relatives with familial heart disease

Heart Rhythm, Vol. 8 No. 8 August 2011

Table 3 Yield and Signal-to-Noise Associated with Disease-Specific Genetic Testing

Section – Disease	Yield of Genetic Test*	% of Controls with a Rare VUS#
Section I – LQTS	75% (80%)	4%
Section II – CPVT	60% (70%)	3%
Section III – BrS	20% (30%)	2% (just *SCN5A*)
Section IV – CCD	Unknown	Unknown
Section V – SQTS	Unknown	3%
Section VI – AF	Unknown	Unknown
Section VII – HCM	60% (70%)	~5% (unpublished data)
Section VIII – ACM/ARVC	60%	16%
Section IX – DCM	30%	Unknown
Section IX – DCM + CCD	Unknown	4% (for SCN5A and LMNA)
Section X – LVNC	17%–41%	Unknown
Section XI – RCM	Unknown	Unknown

Heart Rhythm, Vol. 8 No. 8 August 2011

Logistics of genetic testing

- Large multi-gene panels
  - Multiple laboratories offer testing, specific panels may vary
  - www.genetests.org
- Test the most severely affected individual when possible
  - Blood, spit, tissue
- Turn around time typically 6-8 weeks
  - Communicated to the ordering provider
- Result interpretation
  - Positive, negative, variant of uncertain significance, other
  - Interpretation may vary between laboratories, and may change
  - Mutation prediction models, conserved amongst species, frequency in healthy control population, previous reports/publications

Clinical Screening Recommendations

- Genetic Evaluation of Cardiomyopathy-
  A Heart Failure Society of America Practice Guideline
  (Hershberger et al. *J Cardiac Fail* 2009;15:83-97)
- Clinical screening for cardiomyopathy is recommended
  - Asymptomatic at-risk relatives who are known to carry the disease-causing mutation(s)
  - Asymptomatic at-risk FDRs when genetic testing has not been performed or has not identified a disease-causing mutation

Clinical Screening Caveats

- Screening should also be initiated at any time signs or symptoms appear
- At-risk FDRs with any abnormal clinical screening tests (regardless of genotype) should be considered for repeat clinical screening at one year
- Clinical screening for HCM has also been recommended in “athletic SDRs” when genetic testing has not been performed or has not identified a disease-causing mutation*

Hershberger et al. *J Cardiac Fail* 2009, *Bos et al. *JACC* 2009

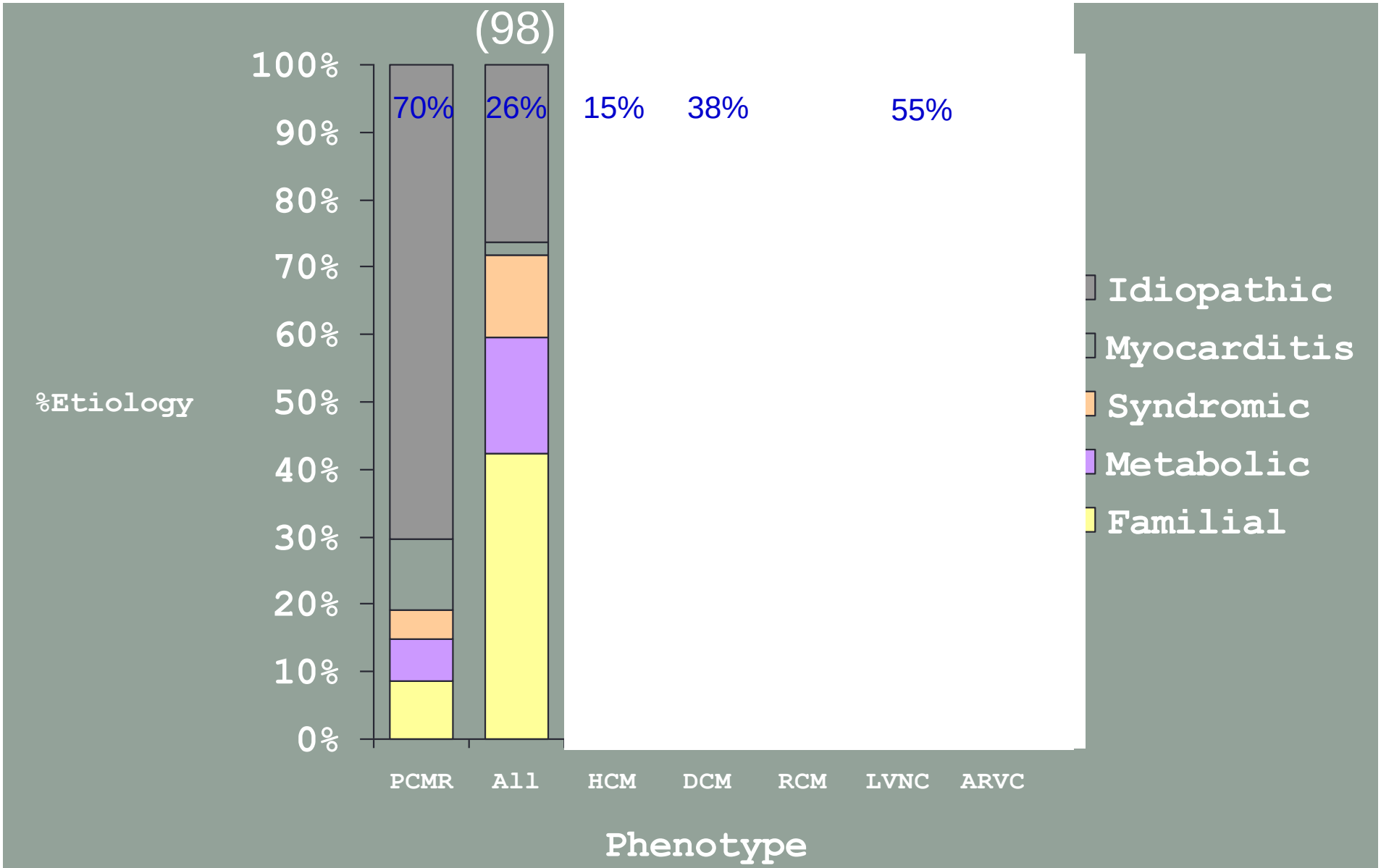
Inheritance, Penetrance and Disease Expression

- **Primarily autosomal dominant inheritance**
  - Mitochondrial, X-linked and AR inheritance observed
- **Penetrance**
  - Incomplete
  - Age-dependent
- **Variable disease expression**
  - Diverse clinical spectrum ranging from asymptomatic individuals, cardiovascular symptoms, congestive heart failure requiring transplant or resulting in death, and SCA/SCD
  - Heart muscle disease may present with overlapping features
- **Diverse etiologies and historically high rates of idiopathic disease**
  - Inability to identify underlying etiology has inhibited appropriate treatment, counseling and understanding of disease.

Genetic Diagnosis in Pediatric Cardiomyopathy Patients

- Aims:
  - Determine spectrum of etiologic diagnoses in PCM
  - Determine clinical diagnostic testing yield in a non-selected outpatient clinic population
- Methods:
  - Retrospective analysis of clinical test results
  - 98 consecutive probands
  - Excluded neuromuscular disease, chemotherapy mediated, and rhythm induced cardiomyopathies
  - All patients evaluated in Multidisciplinary Clinic
    - Full cardiac work-up including appropriate imaging
    - Clinical genetics evaluation
    - Molecular testing as indicated

Etiology in 98 Probands

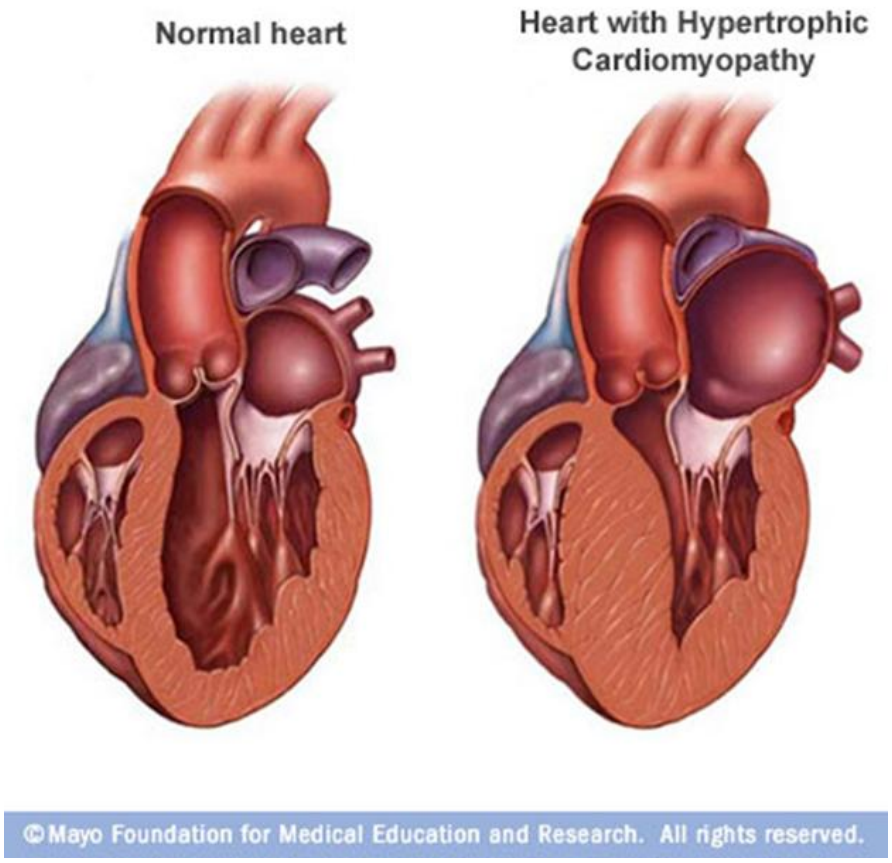


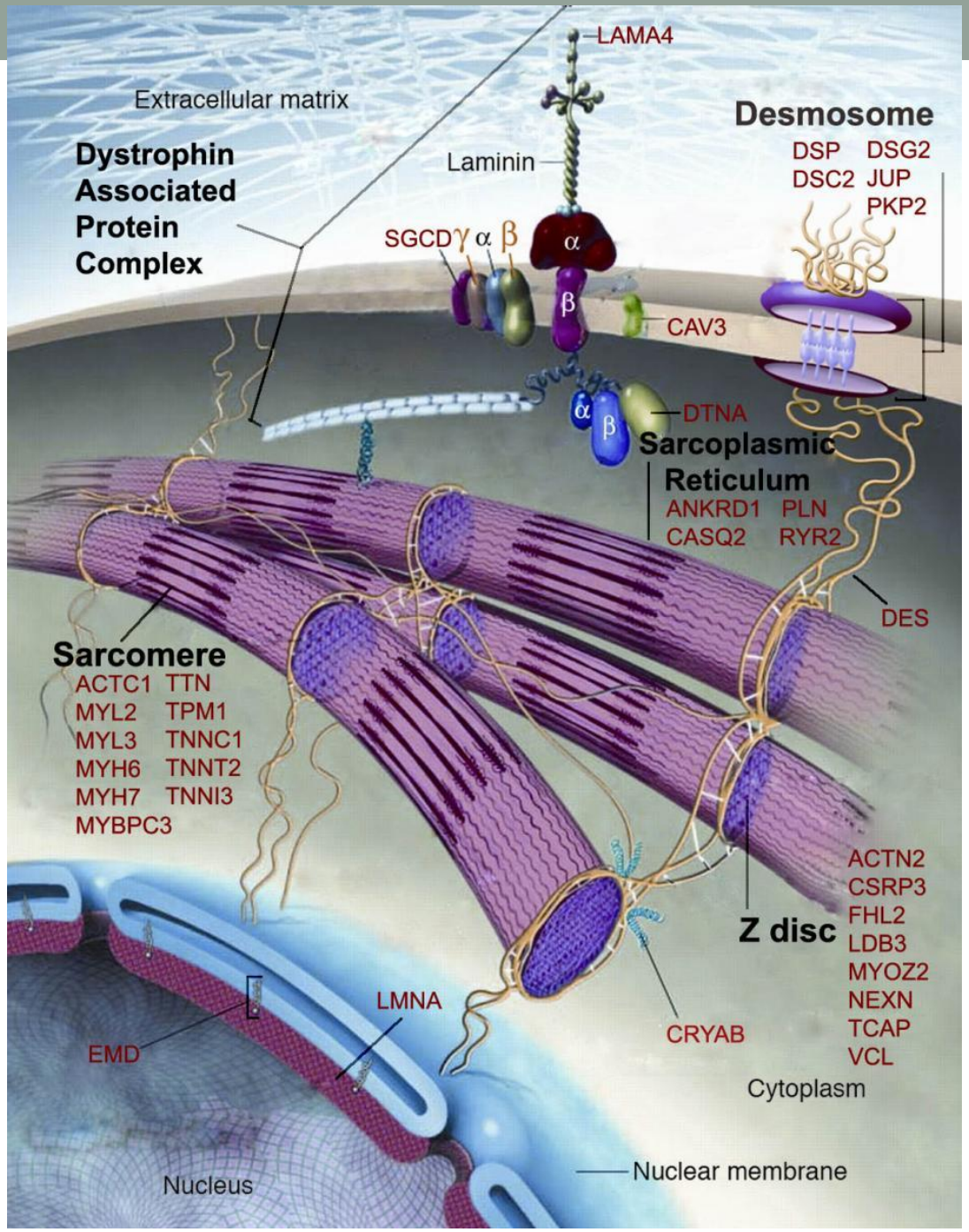
Results

- Significantly increased etiologic diagnosis
  - $p < 0.01$ when compared to PCMR data
- Familial disease most common etiology (42%)
  - True across phenotypic groups
  - Familial disease in infants in HCM and DCM
  - All RCM probands were familial
- Significant rates of metabolic and syndromic disease
  - All phenotypes: Metabolic = 17% Syndromic = 12%
  - Higher rates in HCM and DCM populations

Hypertrophic Cardiomyopathy (HCM)

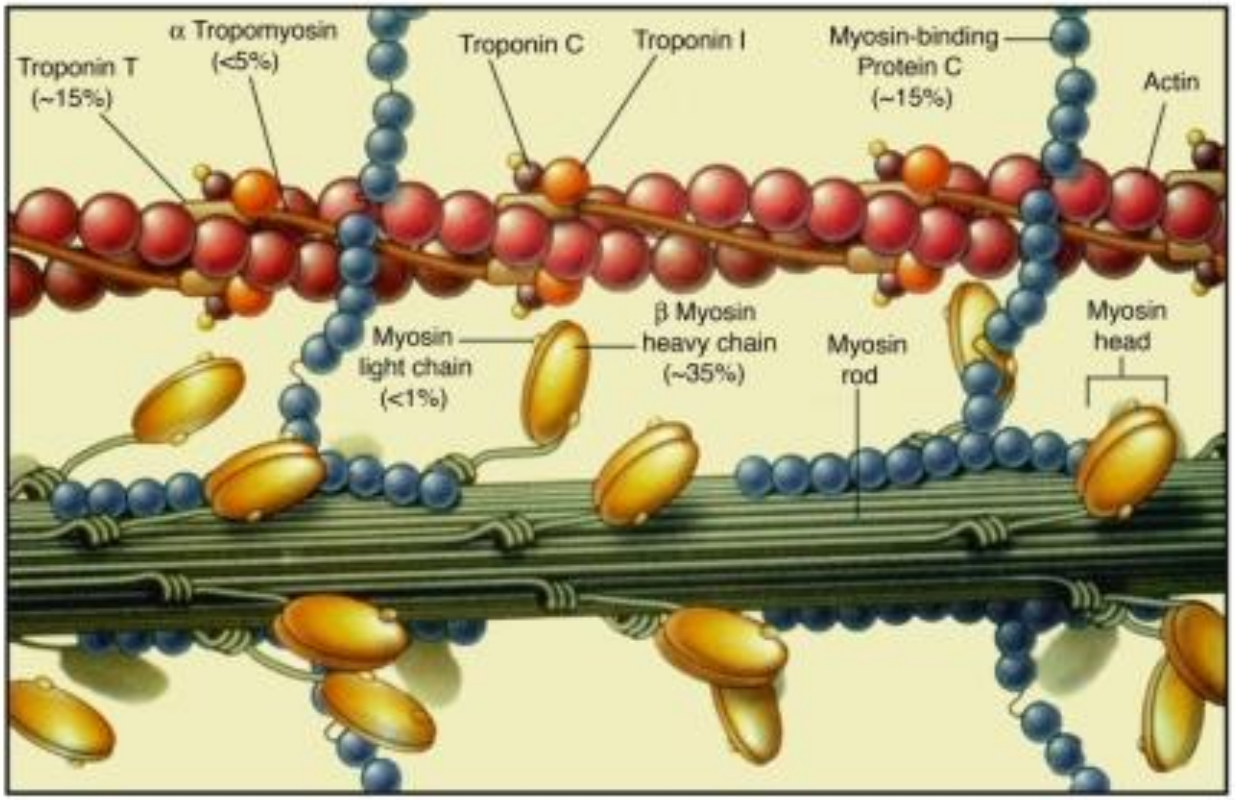
- Unexplained cardiac hypertrophy with systolic and possible diastolic dysfunction
  - Outflow tract obstruction possible
- Pathophysiology
  - Myocyte disarray
  - Fibrosis
- Prevalence 1 in 500
  - Most common inherited cardiac disorder
  - Major cause of sudden cardiac death (SCD) in competitive athletes
  - Acquired causes include systemic hypertension, athletes heart, etc.





Lab for Molecular Medicine-Harvard Partners
Adapted with permission from the American Society for Clinical Investigation; Morita et al (2005). American Society for Clinical Investigation. Journal of Clinical Investigation 2005 March 1.

HCM: A Disease of the Sarcomere



Thin filament

Thick filament

Seidman et al 1995

Genes Associated with HCM

Table 1 Hypertrophic cardiomyopathy: disease-causing genes and associated phenotypes.

Gene	Protein	Frequency in patients with HCM	Associated phenotype
MYH7	β-Myosin heavy chain	25–35%	Mild or severe HCM
MYBPC3	Myosin-binding protein C (cardiac type)	20–30%	Expression similar to MYH7, late onset
TNNT2	Troponin T (cardiac muscle)	3–5%	Mild hypertrophy, sudden death
TNNI3	Troponin I (cardiac muscle)	<5%	Extreme intrafamilial heterogeneity, no sudden death without severe disease
TPM1	Tropomyosin 1α	<5%	Variable prognosis, sudden death
MYL2	Regulatory myosin light chain 2 (ventricular/cardiac-muscle isoform)	<5%	Skeletal myopathy
MYL3	Essential myosin light chain 3	Rare	Skeletal myopathy
ACTC	α-Cardiac actin 1	Rare	Apical hypertrophy
TTN	Titin	Rare	Typical HCM
TNNC1	Troponin C, slow skeletal and cardiac muscles	Rare	Typical HCM
MYH6	α-Myosin heavy chain	Rare	Late onset
CSRP3	Muscle LIM protein	Rare	Late onset, variable penetrance
MYLK2	Myosin light chain kinase 2	Rare	Early onset
LDB3	LIM binding domain 3	Rare	Mainly sigmoidal HCM
TCAP	Telethonin	Rare	Typical HCM, variable penetrance
VCL	Vinculin/metavinculin	Rare	Obstructive midventricular hypertrophy
ACTN2	α-Actinin 2	Rare	Mainly sigmoidal HCM
PLN	Phospholamban	Rare	Typical HCM, variable penetrance
MYOZ2	Myozenin 2	Rare	Typical HCM
JPH2	Junctophilin 2	Rare	Typical HCM

Abbreviation: HCM, hypertrophic cardiomyopathy.

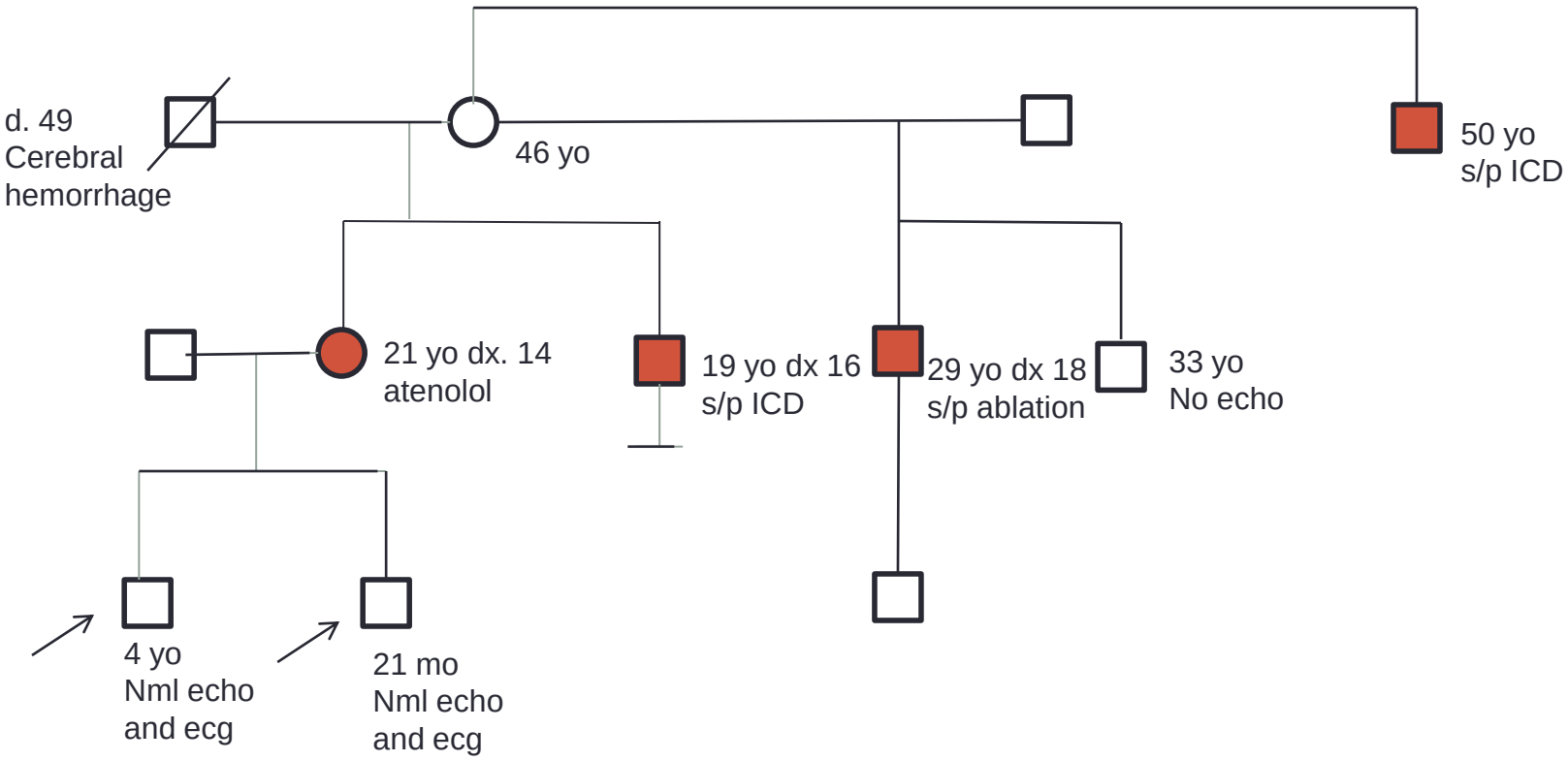
Keren et al. *Nature Clin Prac CV Med* 2008

Genetic Testing- HCM

- Clinical testing available through 6 clinical laboratories within the United States
  - HCM gene panel

- Large multi-gene panels due to significant genetic heterogeneity
  - Number of genes range from 8-18
  - MYBPC3 and MYH7 account for majority of cases;
    - many private mutations
    - Majority are inherited, de novo mutations reported
  - Heterozygous for two disease causing mutations in 3-5% of cases
  - Current detection rates vary; average 40% for isolated cases and 70% for cases with FH of HCM or SCD

Case Example 1 (KFM testing)



HCM Gene Panel
MYBPC3, IVS11-9 G>A

Genes Evaluated:
Disease: Protein (Gene)

HCM1: Myosin Heavy Chain (MYH7)
HCM2: Troponin T2 (TNNT2)
HCM3: Tropomyosin 1 (TPM1)
HCM4: Myosin-binding Protein C (MYBPC3)
HCM7: Troponin I (TNNI3)
HCM8: Myosin light chain 3 (MYL3)
HCM10: Myosin light chain 2 (MYL2)
HCM11: Alpha Actin Cardiac (ACTC)
Transthyretin amyloidosis: Transthyretin (TTR)

HCM/DCM: Troponin C1 (TNNC1)
HCM: Caveolin 3 (CAV3)
Danon disease: Lysosomal-associated Membrane Protein 2 (LAMP2)
Fabry disease: Alpha-galactosidase (GLA)
Glycogen Storage Disease:
Protein Kinase AMP-activated Gamma 2 (PRKAG2)
Mitochondrial HCM: tRNA glycine (MTTG)
Mitochondrial HCM: tRNA isoleucine (MTTI)
Mitochondrial HCM: tRNA lysine (MTTK)
Mitochondrial HCM: tRNA glutamine (MTTQ)

Result:

ABNORMAL (POSITIVE):
Heterozygous for IVS11-9 G>A in the MYBPC3 gene; published, disease-causing mutation (1).

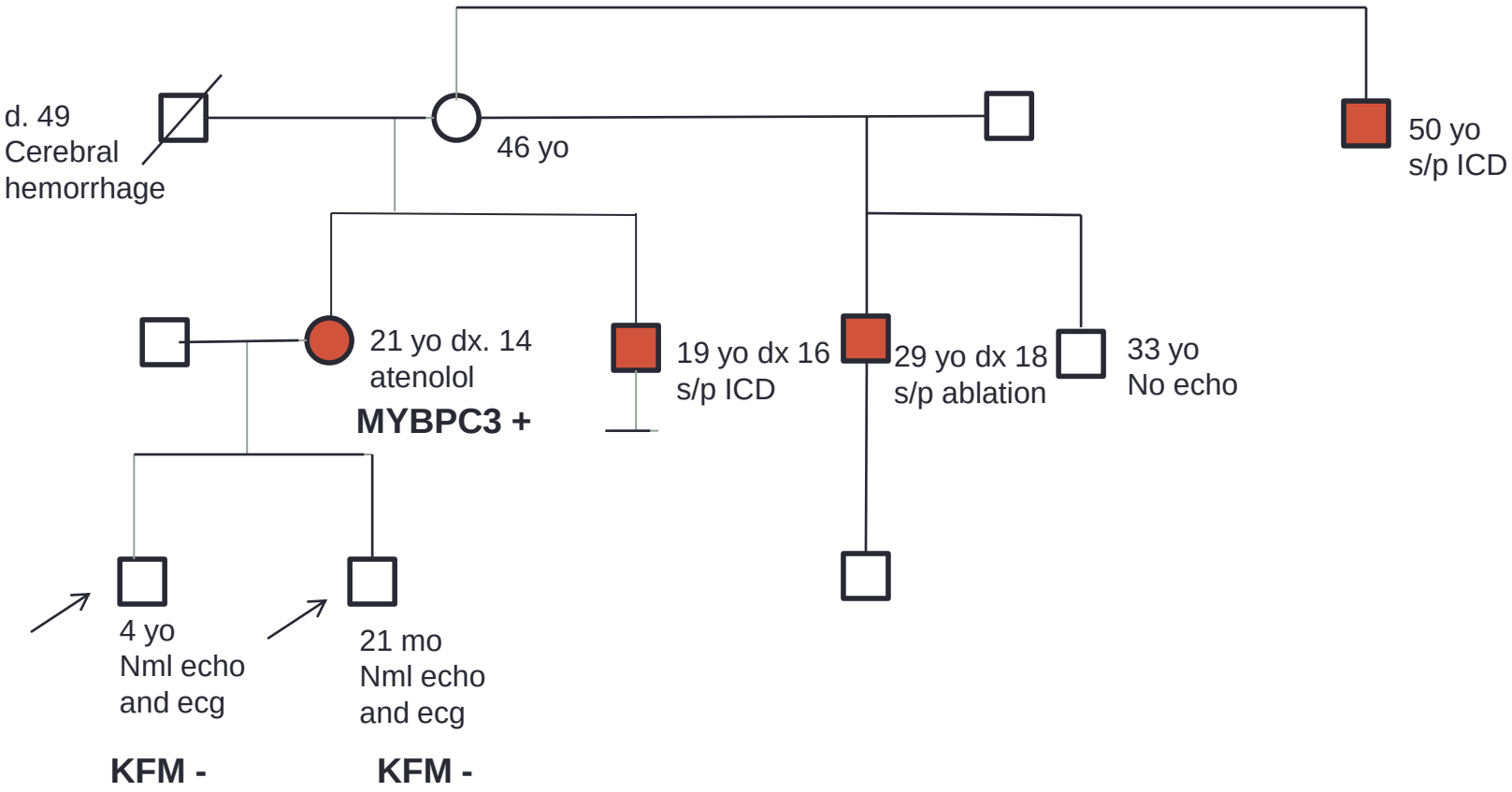
A heterozygous G>A nucleotide substitution was identified in intron 11 of the MYBPC3 gene, which is predicted to cause abnormal gene splicing. This mutation is denoted IVS11-9 G>A or c.927-9 G>A at the cDNA level.

No other disease-causing mutations were detected by sequence analysis of the 18 genes tested in this individual.

Interpretation:

This individual is heterozygous for a published splice site mutation in the MYBPC3 gene, consistent with an autosomal dominant form of HCM.

Case Example 1 (KFM testing)

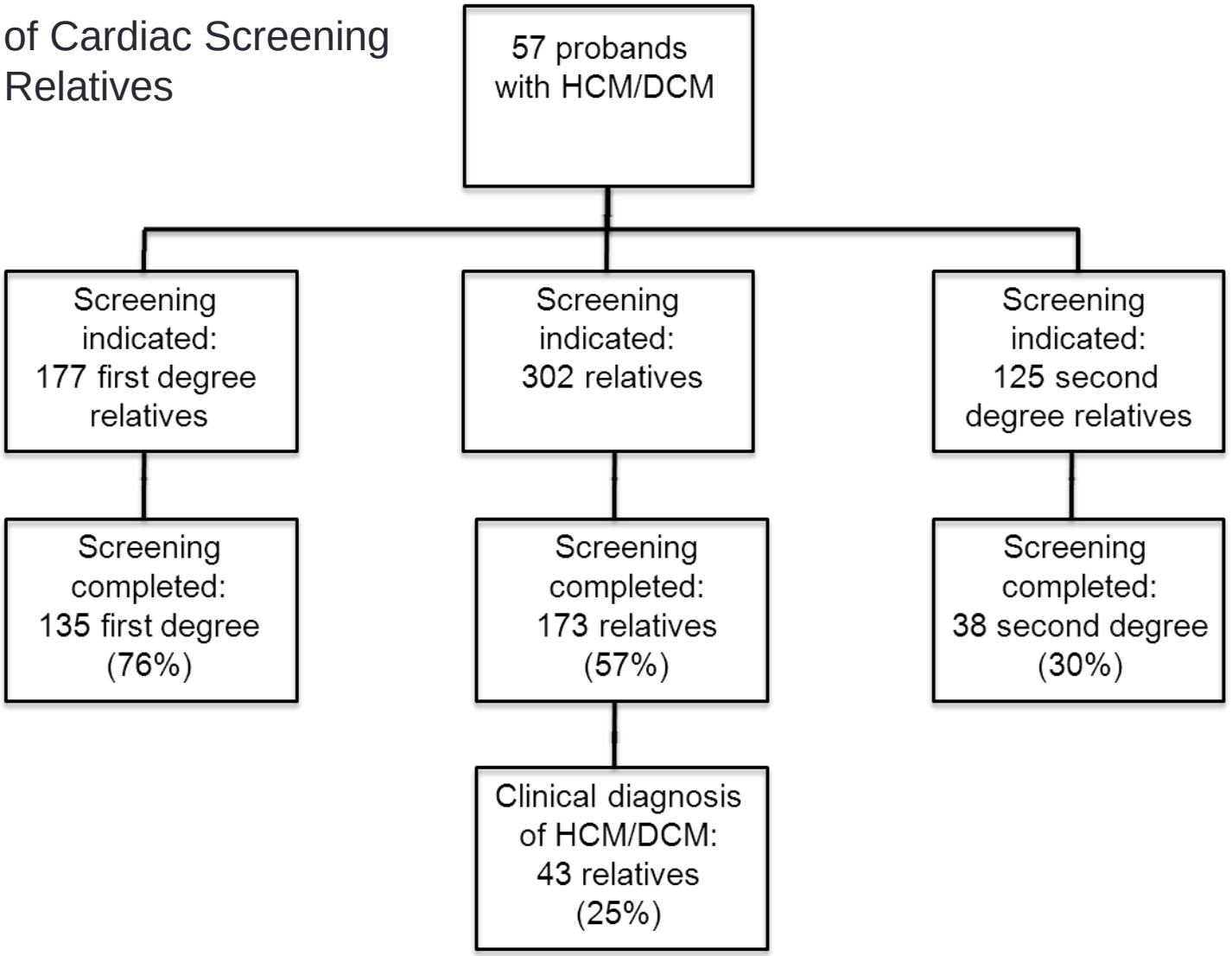


Uptake of Genetic Testing and Cardiac Screening among HCM and DCM Families

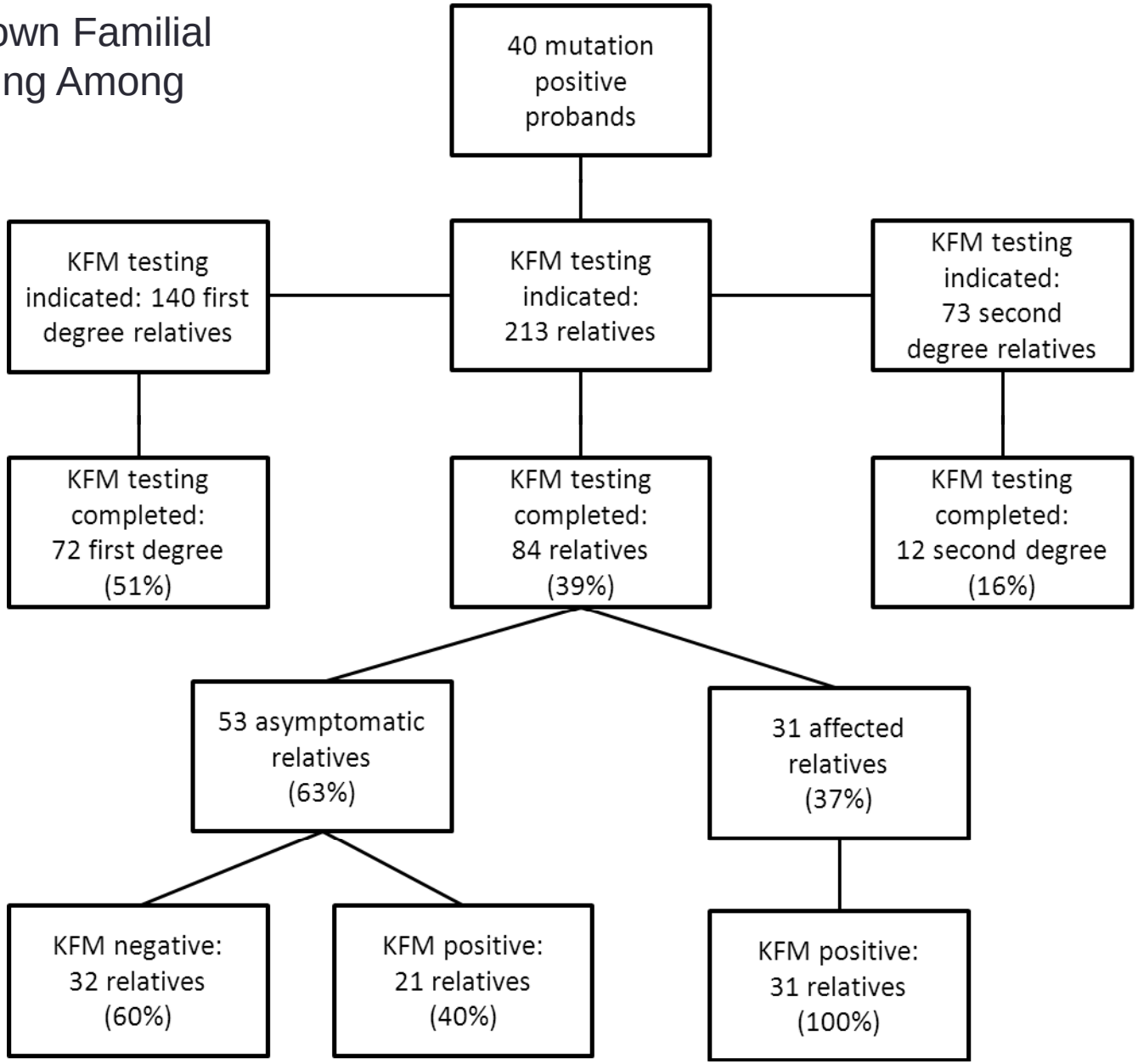
- METHODS
- Recent guidelines recommend genetic testing and cascade screening for at-risk relatives, clinical utility remains uncertain

- Reviewed >250 patients evaluated for cardiomyopathy between 10/2006 and 08/2010
  - Excluded patients with a genetic syndrome, underlying metabolic disease, myocarditis, chemotherapy induced CHF or other acquired causes
  - Excluded patients with RCM, ARVC and LVNC
  - 57 probands with a confirmed diagnosis of HCM or DCM who underwent genetic testing
  - 46 HCM, 11 DCM
- All patients underwent:
  - Full cardiac work-up including appropriate imaging
  - Clinical genetics evaluation and genetic counseling
  - Molecular genetic testing was discussed and offered as indicated
- IRB approval

Uptake of Cardiac Screening Among Relatives



Uptake of Known Familial Mutation Testing Among Relatives



PRECLINICAL

Family history status of patients with DCM and HCM

	FH status: Evaluation N (%)	**FH status: Current N (%)**
Positive Family History	28 (49)	41 (72)
Negative Family History	29 (51)	16 (28)

- 13 probands had additional family members diagnosed with cardiomyopathy after the initial evaluation
  - 9 probands; family members diagnosed as a direct result of recommendations for family screening
  - 2 probands; family members dx due to CV symptoms
  - 2 probands; uncertain why family members were dx

Summary: Uptake of Cardiac Screening and Genetic Testing

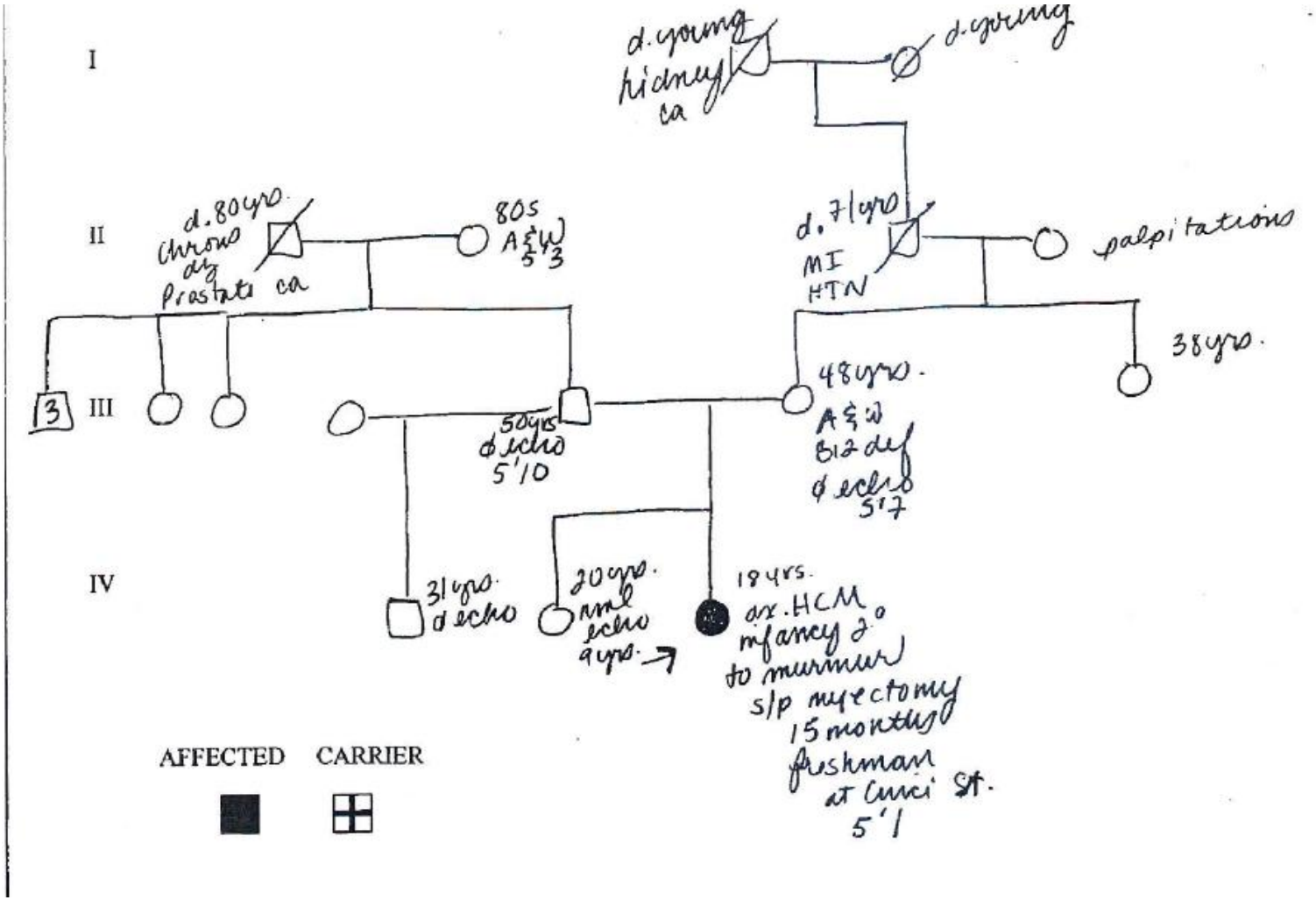
- 1st degree more likely than 2nd degree to complete screening and testing
- Uptake of cardiac surveillance was greater than genetic testing ($p<0.0001$)
- 40% of asymptomatic relatives were given a genetic diagnosis and 25% of relatives were given a clinical diagnosis
- 33 relatives negative KFM testing

- Data demonstrate role and utility of cascade screening and genetic testing
- Improved risk stratification
  - Psychological, economic and medical implications
    - Reduction in SCD, improved understanding of early signs/symptoms and disease progressing

Case Example 2 (confirming clinical dx)

- History:
  - Presented in infancy with a murmur
  - Status post resection of infundibular pulmonic stenosis and transannular patch enlargement of RV outflow tract (6/27/1994)
  - Surgical history: Status post ICD in July 2005

- Presented at 18 yoa in September of 2011
- Cardiac Evaluation:
  - HCM with severe asymmetric septal hypertrophy
  - LV mid-cavitary gradient of 7 mmHg, near obliteration of the LV cavity in systole
  - LV trabeculations
  - Supranormal LV systolic function, EF=72%



Relative short stature and Easy bruising
ADD, ADHD, difficult with reading comprehension
IEP in first grade; extra time for test taking
Nursing student

Differential Diagnosis

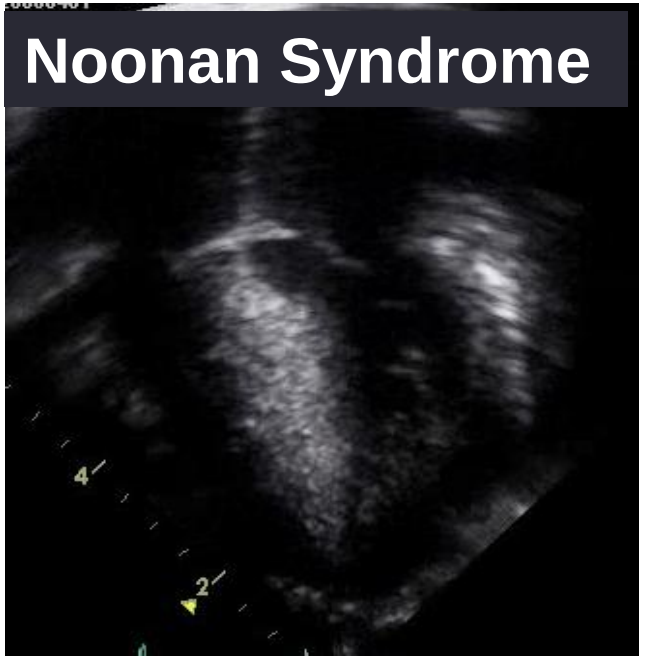
- Presentation of severe HCM in infancy with marked RV involvement
  - metabolic condition, inborn error of metabolism, genetic syndromic condition, or isolated (familial) cardiomyopathy.
- Familial HCM vs. Noonan syndrome
  - Some features of NS- PI, mild learning disabilities, easy bruising
- Noonan syndrome
  - CHD present in 50-80% (PVS 20-50%)
  - HCM present in 20-30% (present at birth, dev. in infancy
  - 1/3 have mild intellectual impairment, many normal cognitive function
  - Facial appearance changes considerably with age
    - Most striking in nb period, most subtle in adults
    - Low-set, posteriorly rotated ears, hypertelorism, thick or droopy eyelids

PTPN11 in 50% of affected individuals, *SOS1* in approximately 13%, *RAF1* in 3% to 17%, and *KRAS* in fewer than 5%. Other genes in which mutations have been reported to cause Noonan syndrome in fewer than 1% of cases include *NRAS*, *BRAF,* and *MAP2K1*.

Test(s) Requested:	Comprehensive Resequencing Array for Noonan, LEOPARD, Cardio-Facio-Cutaneous, and Costello Syndromes
Genes Included:	BRAF, HRAS, KRAS, MAP2K1, MAP2K2, PTPN11, RAF1, SHOC2, and SOS1
Result:	**POSITIVE. Heterozygous for the M504V Mutation in the PTPN11 Gene** This individual is heterozygous for the A>G nucleotide substitution in exon 13 of the PTPN11 gene, resulting in the replacement of a Methionine codon (ATG) with a Valine codon (GTG) at amino acid position 504. This mutation is denoted c.1510 A>G at the cDNA level or p.Met504Val (M504V) at the protein level.
Interpretation:	The M504V missense mutation observed in the submitted sample has been previously reported in association with Noonan syndrome and has also been seen many times at GeneDx (Tartaglia et al., 2001). The mutation lies within a region of the gene coding for the highly conserved PTP domain of the protein tyrosine phosphatase 11. The identification of the M504V mutation in this specimen is consistent with a diagnosis of autosomal dominant Noonan syndrome in the patient.

HCM

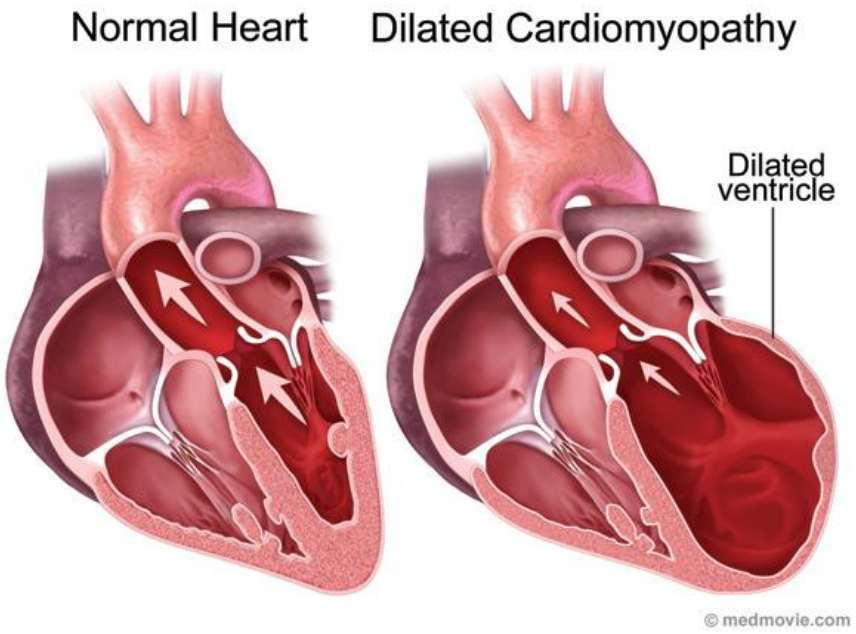
Case Example 1



Case Example 2

Dilated Cardiomyopathy (DCM)

- Left ventricular enlargement with systolic dysfunction
- The prevalence of DCM is ~1/2500, although it may be more common
  - 20-50% of individuals have a family history
  - Many acquired forms
- Common cause of CHF and cardiac transplantation



Genes Associated with DCM

Table 2. Genetic Causes of Dilated Cardiomyopathy

Gene*	Protein	OMIM	Frequency, Familial†	Frequency, Sporadic†	Comments‡
Autosomal Dominant FDC					
Dilated Cardiomyopathy Phenotype					
ACTC	Cardiac actin	102540	rare	rare	
DES	Desmin	125660	?	?	
LMNA	Lamin A/C	150330	7.3%	3.0%	5.5% overall (41/748, 6 studies, see text)
SGCD	δ-sarcoglycan	601411	rare	rare	
MYH7	β-myosin heavy chain	160760	6.3%	3.2%	4.8% overall (22/455, 3 studies)
TNNT2	Cardiac troponin T	191045	2.9%	1.6%	2.3% overall (15/644, 3 studies)
TPM1	α-tropomyosin	191010	rare	rare	
TTN	Titin	188840	?	?	
VCL	Metavinculin	193065	rare	rare	
MYBPC3	Myosin-binding protein C	600958	?	?	
CSRP3	Muscle LIM protein	600824	rare	rare	
ACTN2	α-actinin-2	102573	?	?	
PLN	Phospholamban	172405	rare	rare	
ZASP/ LDB3	Cypher/LIM binding domain 3	605906	?	?	
MYH6	α-myosin heavy chain	160710	?	?	
ABCC9	SUR2A	601439			
TNNC1	Cardiac troponin C	191040	?	?	
TCAP	Titin-cap or telethonin	604488	rare	rare	
SCN5A	Sodium channel	600163	?	?	2.3% overall (11/469, 2 studies)
EYA4	Eyes-absent 4	603550	?	?	
TMPO	Tthymopoietin	188380	?	?	
PSEN1	Presenilin 1 / 2	104311	?	?	
PSEN2		600759			
X-linked Familial Dilated Cardiomyopathy					
DMD	Dystrophin	300377			
TAZ/G4.5	Tafazzin	300394			
Autosomal Recessive Familial Dilated Cardiomyopathy					
TNNI3	Cardiac troponin I	191044	?	?	

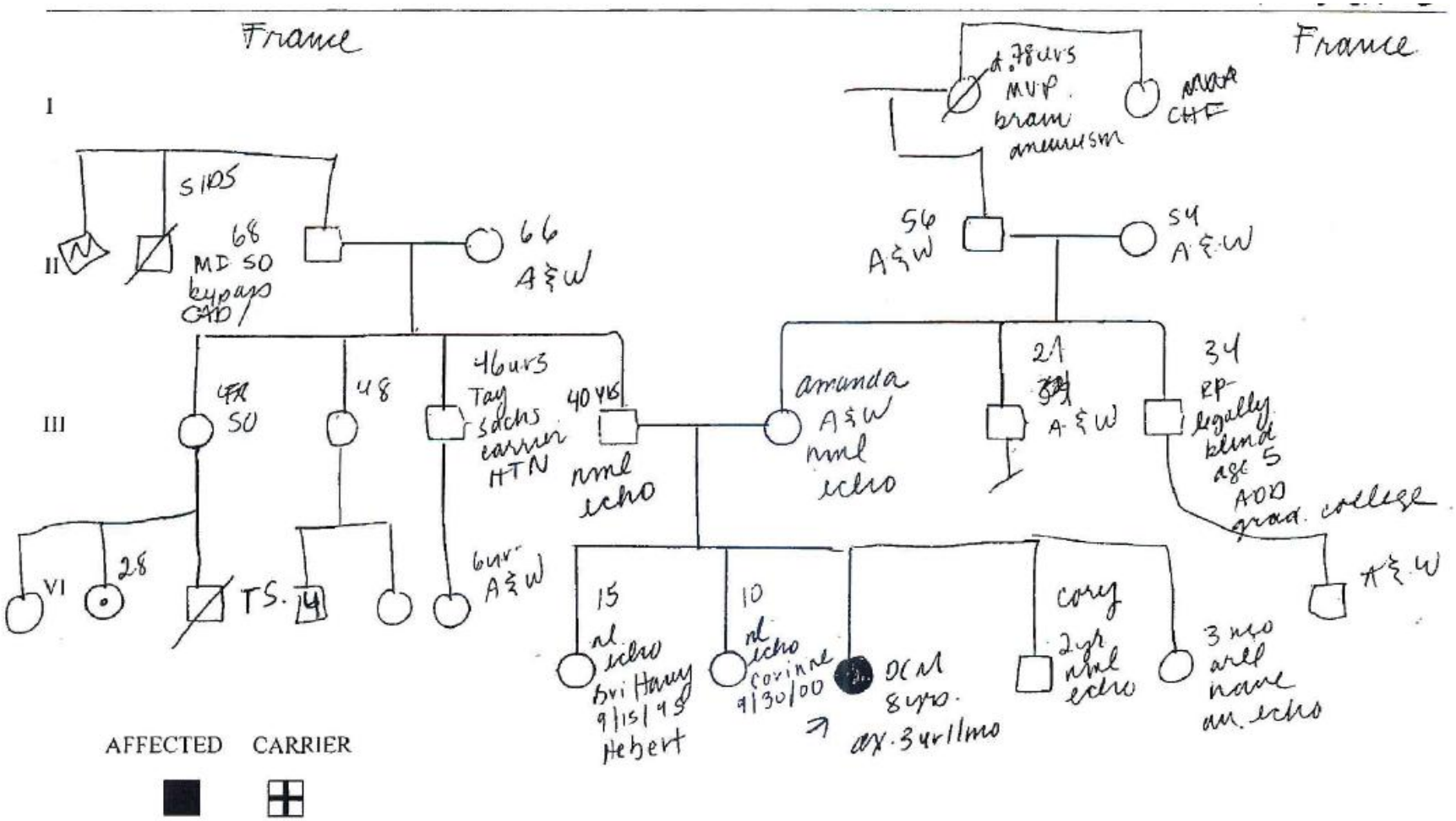
*Genes are ordered by publication year.
†Rare indicates less than 1%; frequencies are provided only with two or more publications.
‡Overall frequencies may include studies that did not distinguish between familial and sporadic cases.

Hershberger et al *J of Cardiac Failure* 2009

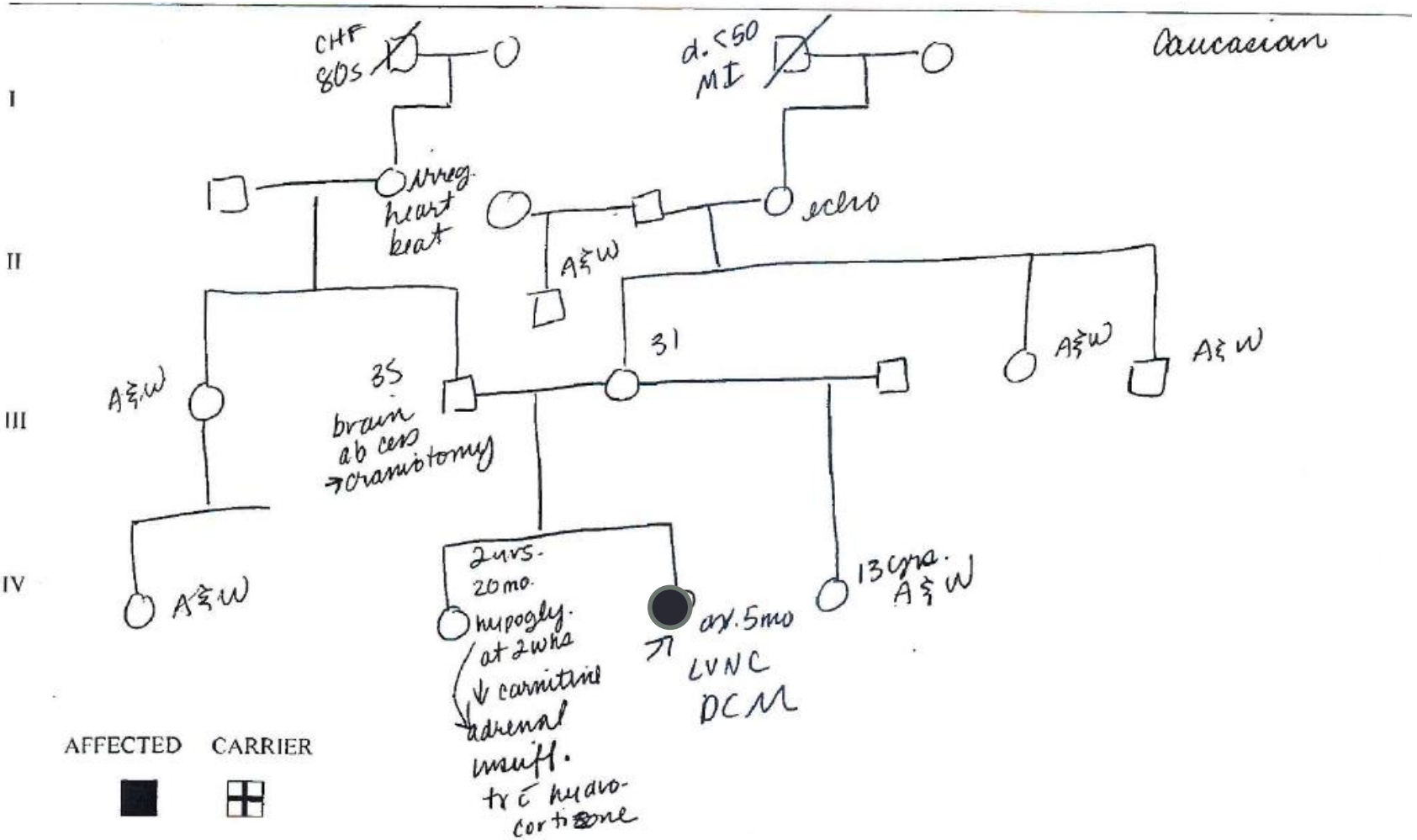
Genetic Testing- DCM

- Clinical genetic testing available; 4 laboratories offer comparable gene panels
  - DCM gene panel, DCM/LVNC gene panel
- Extensive genetic heterogeneity
  - Largest gene panel includes 27 genes
  - Relatively low frequency of involvement of any one gene
- Current detection rate approximately 20-30%

Case Example 3 (idiopathic DCM)

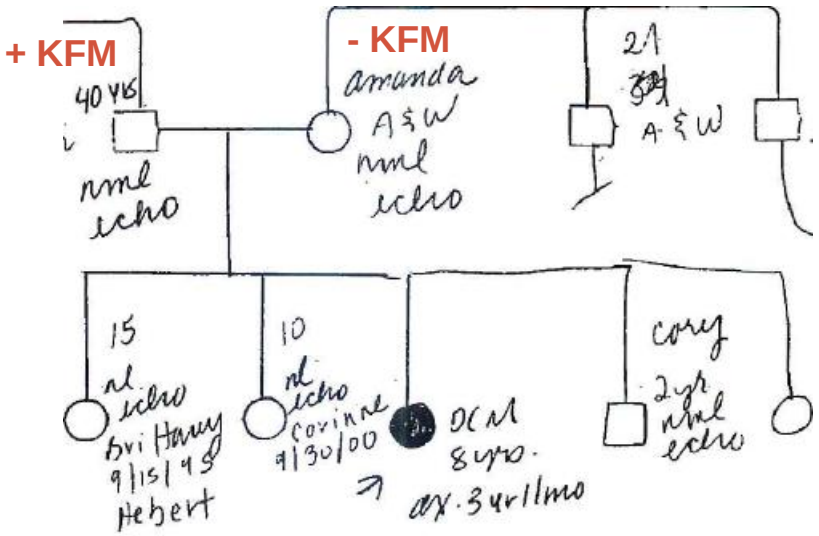


Case Example 4 (Idiopathic DCM)



DCM gene panel results

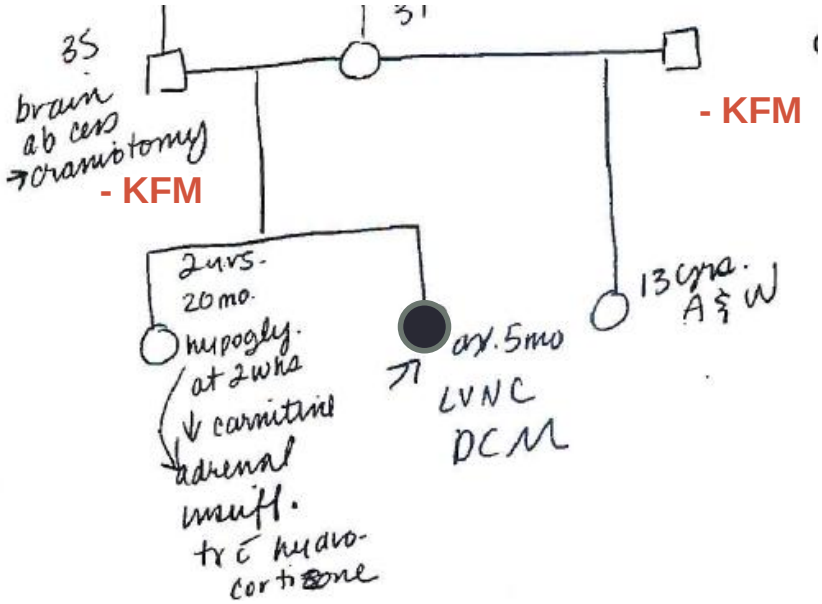
Case Example 3



MYH7, Gln1346Stop
Novel, predicted to cause loss of protein function

Risk stratification of relatives

Case Example 4



TPM1, Glu272Gly
Novel, variant of uncertain significance

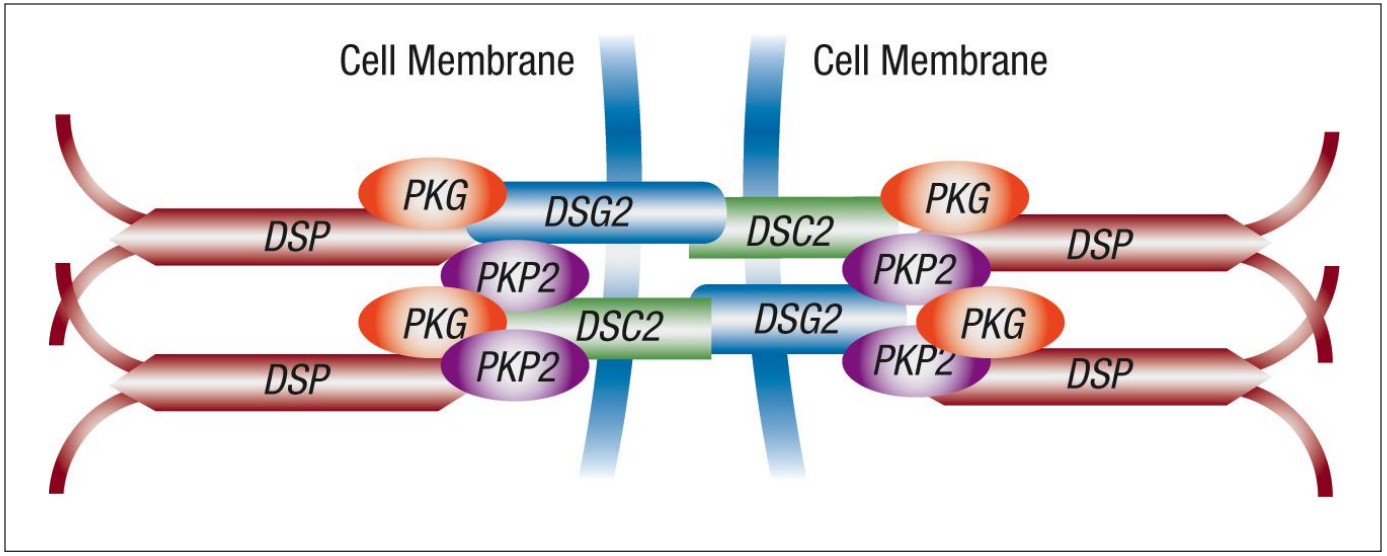
Likely de novo, confirms pathogenicity

Arrhythmogenic Right Ventricular Cardiomyopathy

- Characterized by progressive fibrofatty replacement of the myocardium predisposing to ventricular arrhythmia and sudden death
  - Bi-ventricular and LV presentation (20-40%) have been recognized
- Leading cause of ventricular arrhythmia and sudden cardiac in the young (<35 years)
- Prevalence unknown (1 in 1,250-5,000)
  - Approximately 50% have a positive family history

Genetic Basis of Disease

- ARVC regarded as a disease of the desmosome; form mechanical couplings that attach adjacent myocytes at the intercalated disc



DSG2, desmoglein-2; DSC2, desmocollin-2; PKP2, plakophilin-2; PKG, plakoglobin; DSP, desmoplakin.

Sen-Chowdhry S et al, *JACC* 2007

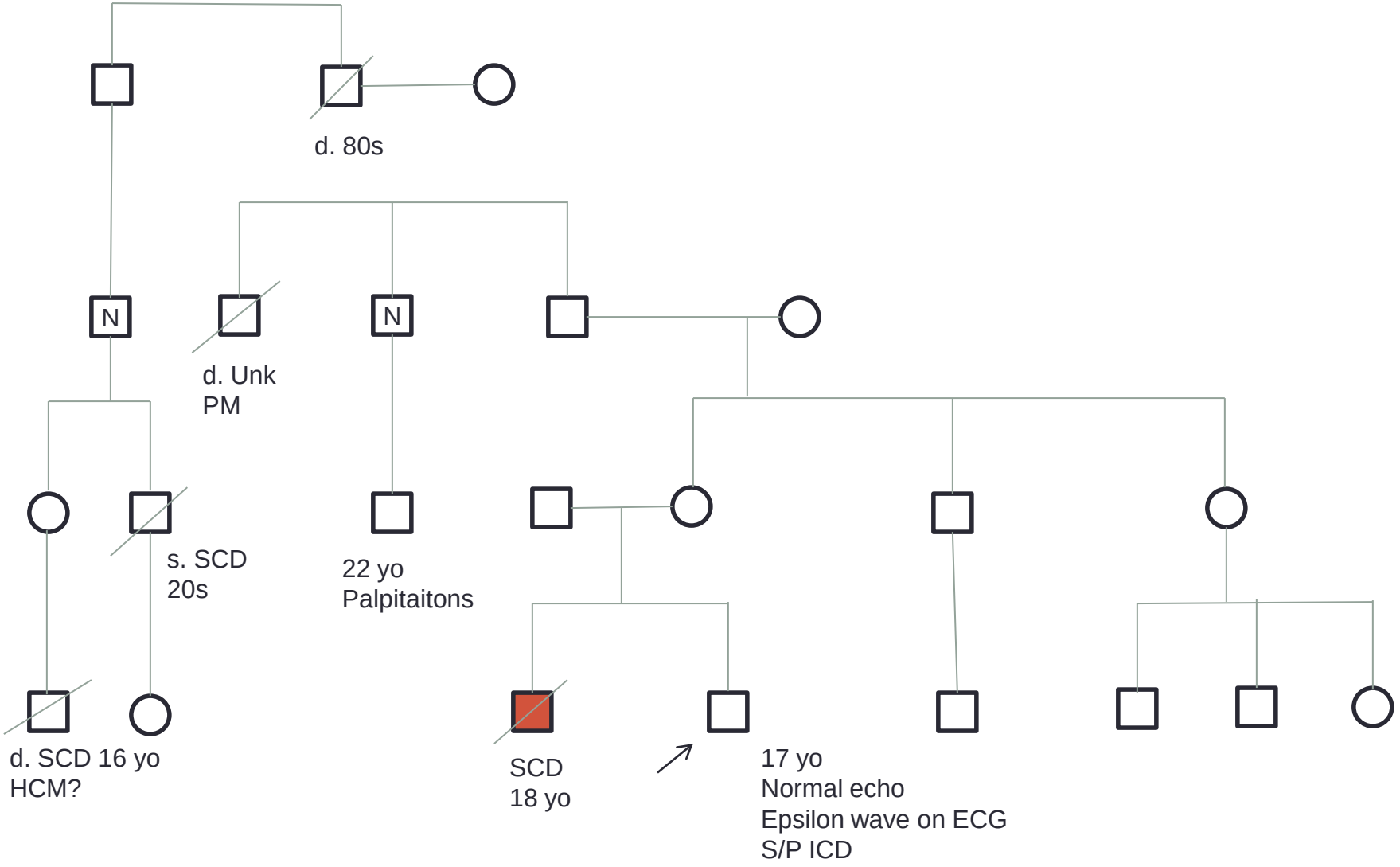
Genes Associated with ARVC

Gene	***Protein***	***Estimated Percentage of ARVC***
TGFB3	Transforming growth factor beta-3	rare
RYR2	Ryanodine receptor	rare
DSP	Desmoplakin	6-16%
PKP2	Plakophilin-2	11-43%
DSG2	Desmoglein-2	12-40%
DSC2	Desmocollin-2	rare
TMEM43	Transmembrane protein 43	unknown
JUP	Plakoglobin	rare

Genetic Testing

- Clinical testing available for all 8 genes
  - ARVC gene panel
- 40-50% of cases will have an underlying genetic mutation
  - Compound heterozygosity and digenic heterozygosity identified in up to 10% of cases
  - Disease modifying vs. disease causing?
- Some cases of autosomal recessive inheritance
  - Naxos disease
    - Palmoplantar keratoderma
    - Woolly, curly, dense, rough and bristly hair
    - Specific mutations in plakoglobin and desmoplakin

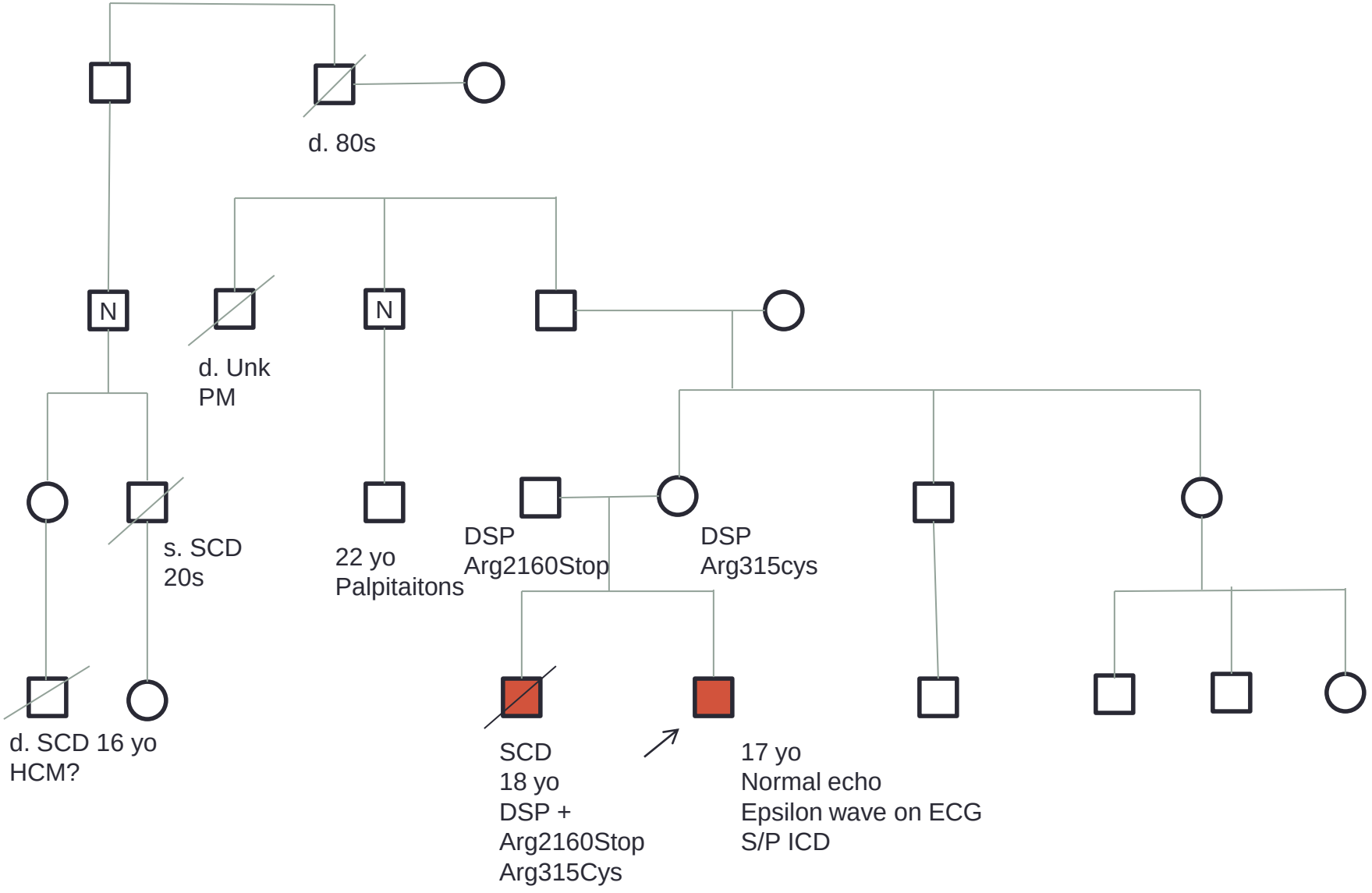
Case Example 5 (SCD and ARVC)



Genetic Testing Results

- Two variants were identified in DSP;
  - novel, disease-causing mutation, Arg2160Stop
  - variant of unknown significance, likely disease-causing, Arg315Cys.

Case Example 5 (SCD and ARVC)



Restrictive Cardiomyopathy

- RCM is characterized by impaired ventricular filling
  - Lack of flexibility, rigidity and stiffness
  - Normal LV wall thickness and systolic function
  - Atrial enlargement

- Rare- least common type of cardiomyopathy
  - Familial and Idiopathic cases
  - Infiltrative disease: Sarcoidosis, amyloidosis, Gaucher and Fabry disease

Genetics of RCM

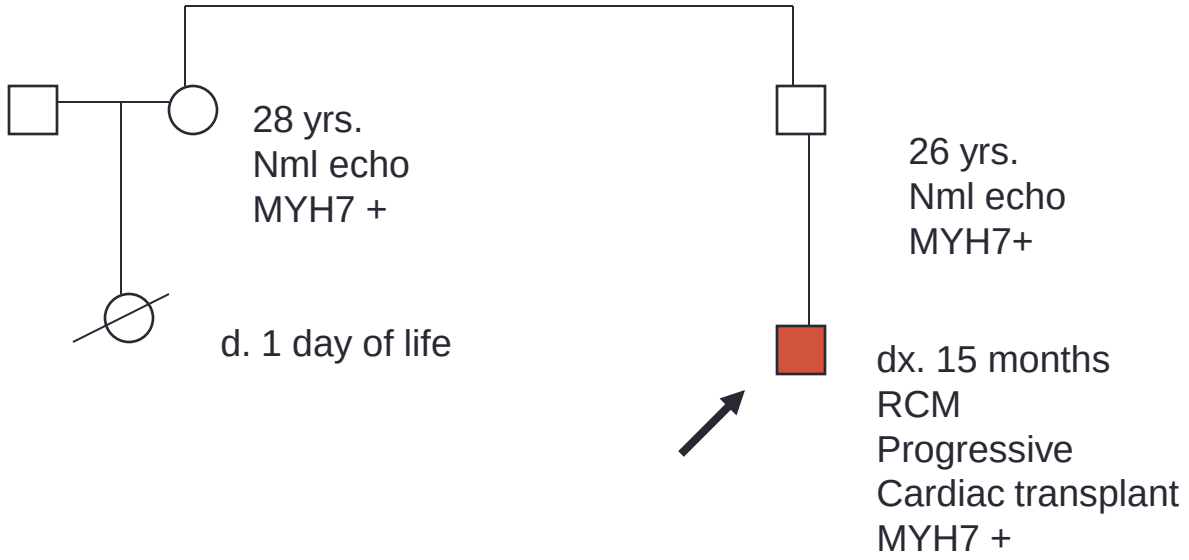
- Genetic basis largely unknown
  - Least common type of cardiomyopathy
  - Less commonly presents with familial disease
- Genes associated with RCM
  - *MYH7, TNNI3* and *DES*
  - *TNNT2, ACTC, MYBPC3, *TPMI, *MYL2* and **MYL3*

- Yield of testing unknown:
  - Kaski et al 2008 33% (4/12) of patients with idiopathic RCM had a mutation
  - Kubo et al 2007 53% (8/15) of patients with HCM and restrictive physiology had a mutation
  - Kindel et al 2012 (in press) 4 of 4 patients had positive FH, 1 with a mutation

*Caleshu C et al 2011

Case Example 6 (RCM)

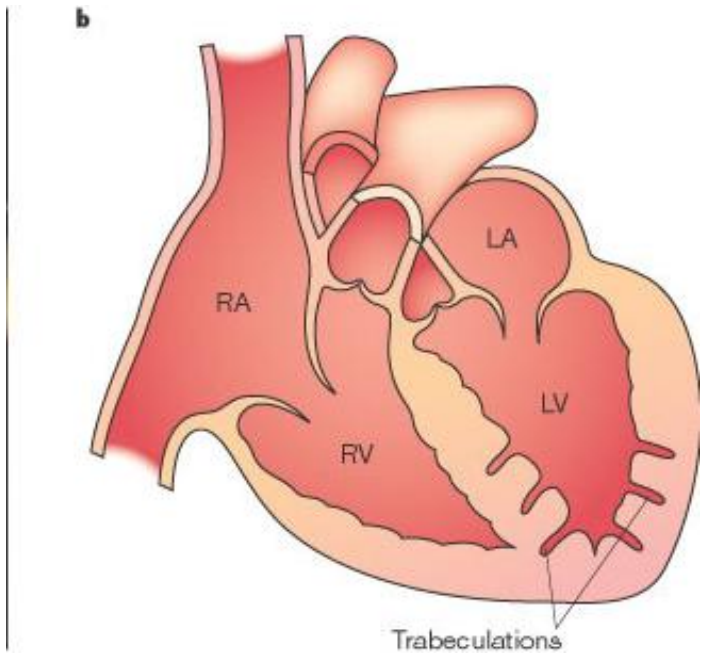
MYH7, G768R
Exon 21
aa 768 highly conserved
reported in literature as pathogenic
Adults with HCM – youngest age of dx 34



Ware, et al Clinical Genetics 2008

Left Ventricular Noncompaction (LVNC)

- Characterized by excessive prominent trabeculations and deep intratrabecular recesses of the normally smooth/compacted LV
- Recognized as a distinct form of cardiomyopathy in 2006*; previously referred to as spongiform or spongy myocardium
- Associated with heart failure, thromboembolism and arrhythmias



J. A. Towbin and N. E. Bowles
***Nature* 415**, 227-233(10 January 2002)
doi:10.1038/415227a

*Maron et al *Circ* 2006 ;113

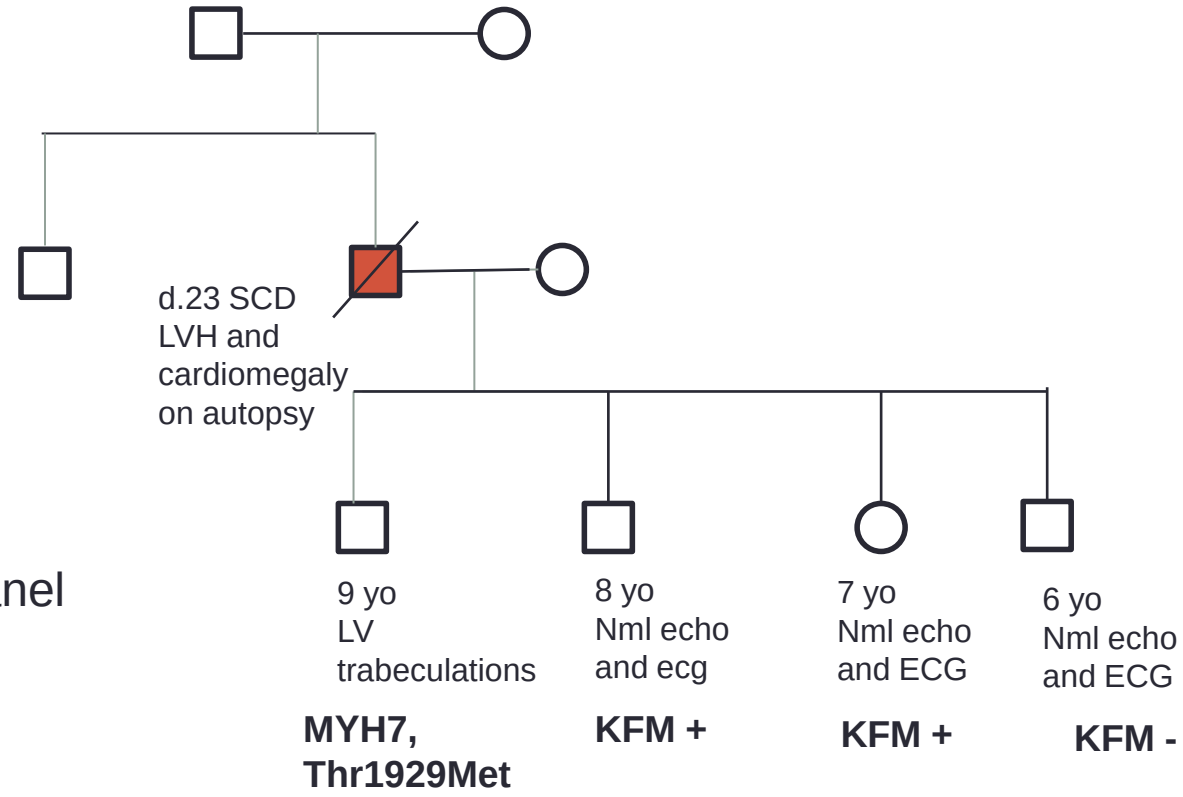
Genes Associated with LVNC

- Clinical Genetic Testing available
- 17-41%* will have an underlying mutation
  - Mutations in more than 15 genes identified
  - Sarcomeric, cytoskeletal and ion channel genes
  - Genes encoding the sarcomeric proteins most common
    - MYH7, ACTC1, TNNT2, MYBPC3, ZASP/LBD3

- Mitochondrial disease
- Barth syndrome
  - Mutations in TAZ result in x-linked form of LVNC and metabolic disease in infants

*Klaassen et al Circ 2008
Hoedemaekers et al Circ Cardiovasc Genet 2010

Case example 7



DCM/LVNC panel requested

Diagnostic Implications
Genetic testing

- Limited genotype-phenotype data given heterogeneity and frequency of private/novel mutations
- Challenges regarding result interpretation (i.e. multiple mutations, variants of uncertain significance, etc.)
- Confirmation of a clinical diagnosis and presumed etiology
  - Anticipation of syndromic features
- Identification of at-risk relatives when disease mutation identified

Prognostic and Therapeutic Implications Genetic Testing

- Identification of the underlying gene and mutation has limited role in cardiovascular risk assessment and management of the affected individual
  - GLA associated with Fabry disease – availability of ERT
  - Increased risk of arrhythmia associated with mutations in TNNT2, DES and LMNA
  - TTR associated with RCM secondary to amyloidosis
  - LAMP2 associated with Danon disease (x-linked)
  - PRKAG2 associated with WPW and conduction abnormalities
  - Noonan syndrome associated with extracardiac features
  - ARVC; LV involvement more common with DSP and PKP2 associated with earlier onset of symptoms and arrhythmia

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- The Cardiomyopathy/Heart Failure Team at CCHMC
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- Cardiovascular Genetic Counseling Colleagues

QUESTIONS AND COMMENTS

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