Genetics of Cardiomyopathy

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Cardiomyopathies

- diseases of cardiac muscle associated with abnormalities of cardiac wall thickness, chamber size, contraction, relaxation, conduction, and rhythm.
- A major cause of morbidity and mortality at all ages and often result in heart failure
- The first primary cardiac disorders to be understood at the molecular level

Monogenic Cardiovascular Disorders

- **Cardiomyopathies :**
  - HCM
  - DCM
  - ARVC/D

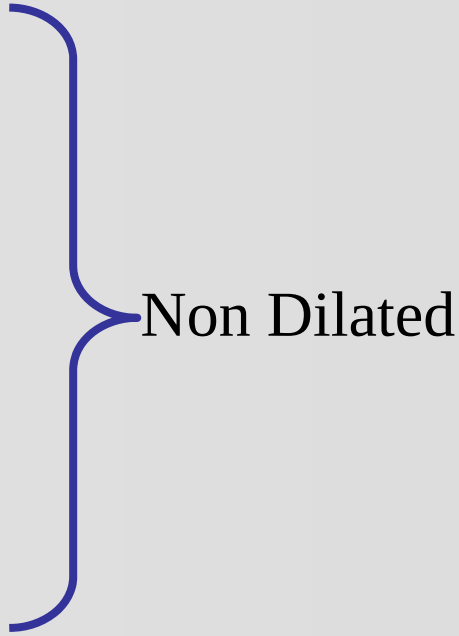
- **Arrhythmias**
  - LQTS
  - WPW
  - Atrial Fibrillation
  - Conduction Disease

- **Dyslipidemias**
  - Familial Hypercholesterolemia

- Congenital Heart Disease
- Familial Aortic Aneurysms

Cardiomyopathy Classification

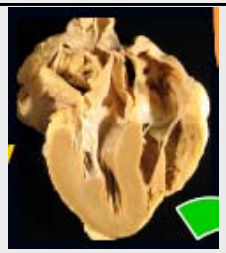
- **Dilated Cardiomyopathy**
- **Hypertrophic Cardiomyopathy**
- **Restrictive Cardiomyopathy**
- **Arrhythmogenic RV cardiomyopathy**
- **Unclassified Cardiomyopathy**

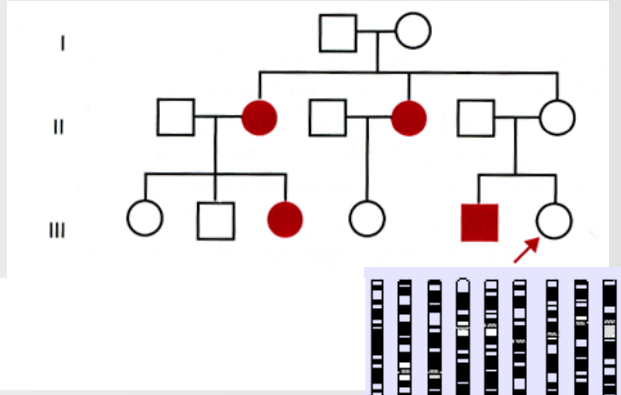


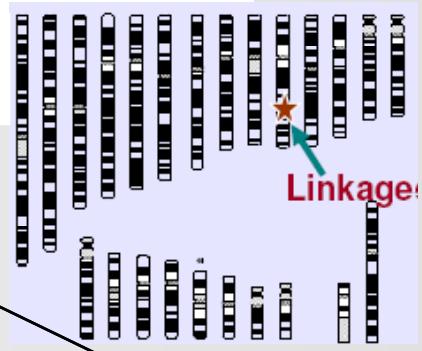
Cardiomyopathy

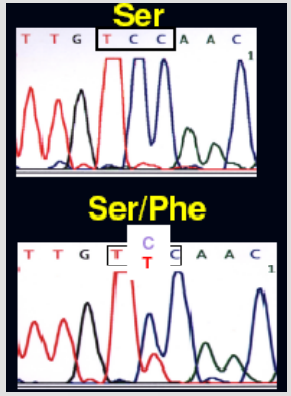
- 150 yrs since Mendel's breeding exp.
- 50 yrs since discovery of DNA structure by Watson and Crick
- 7 yrs since human DNA sequence draft by human genome project

Phenotype (Disease)





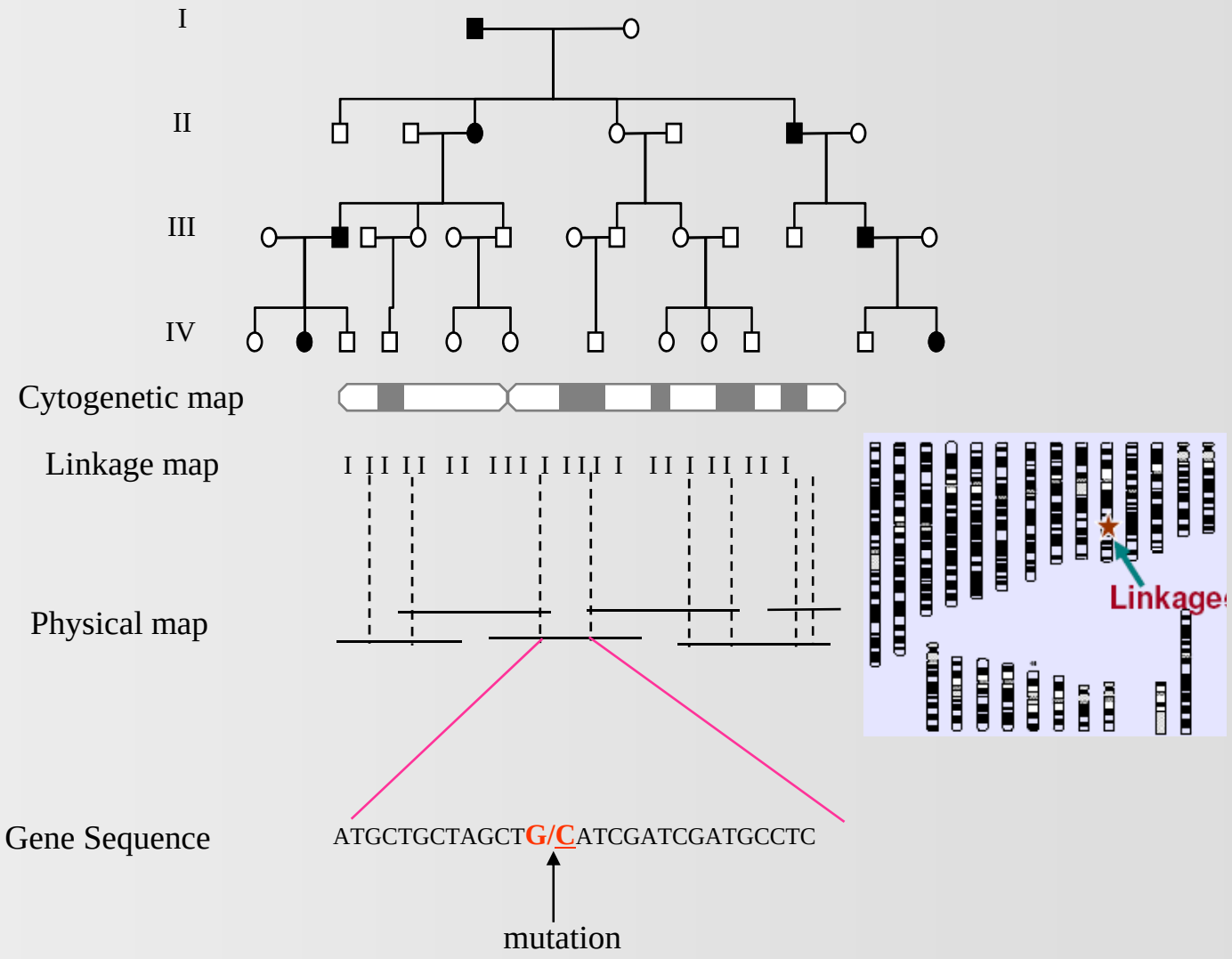


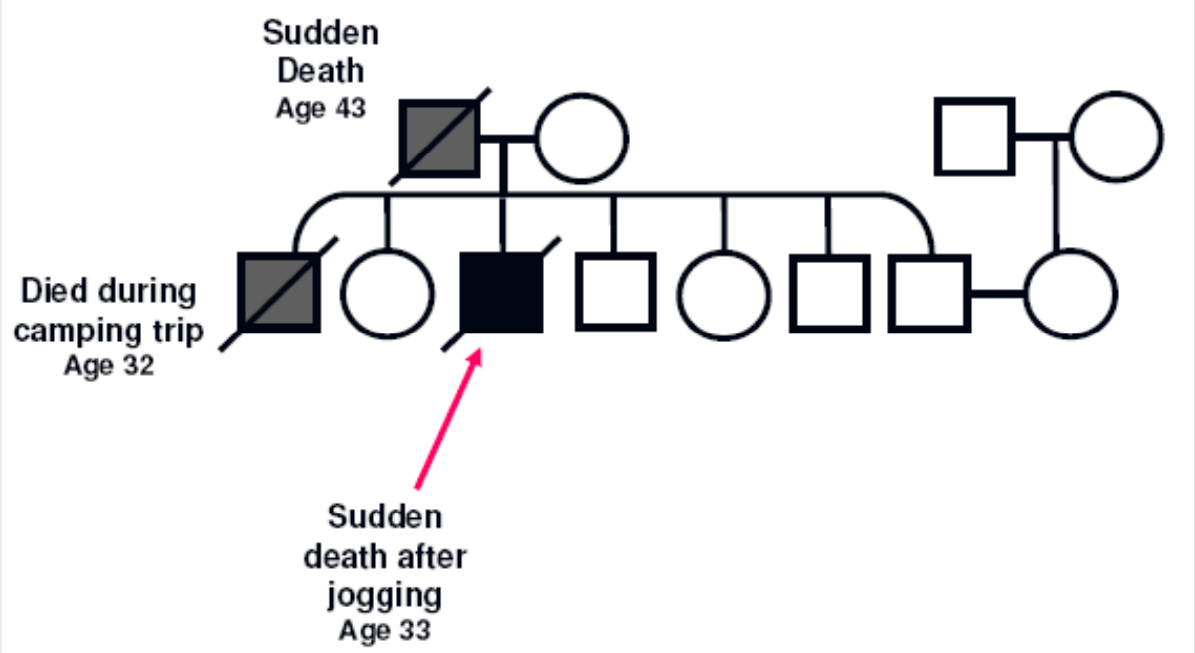


Disease Genes

Positional Cloning approach

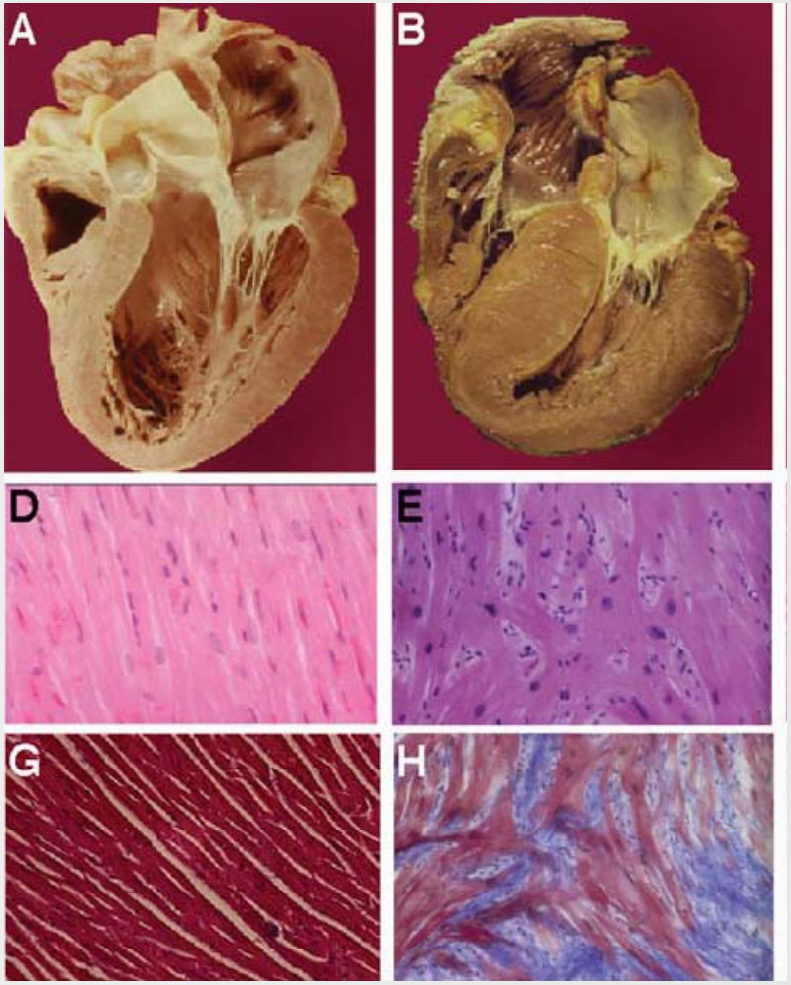
The identification of a gene based solely on its position in the genome




Sudden
Death
Age 43
Died during
camping trip
Age 32
Sudden
death after
jogging
Age 33

Hypertrophic Cardiomyopathy

Normal HCM



Ahmad et al. 2005 Ann. Rev. Genomics Hum. Genet

- **an inherited cardiac disorder**

Characterized by asymmetric left ventricular hypertrophy, myocyte disarray, and cardiac fib leading to heart failure and ventricular arrythn

the most common cause of sudden cardiac deat under 35 years

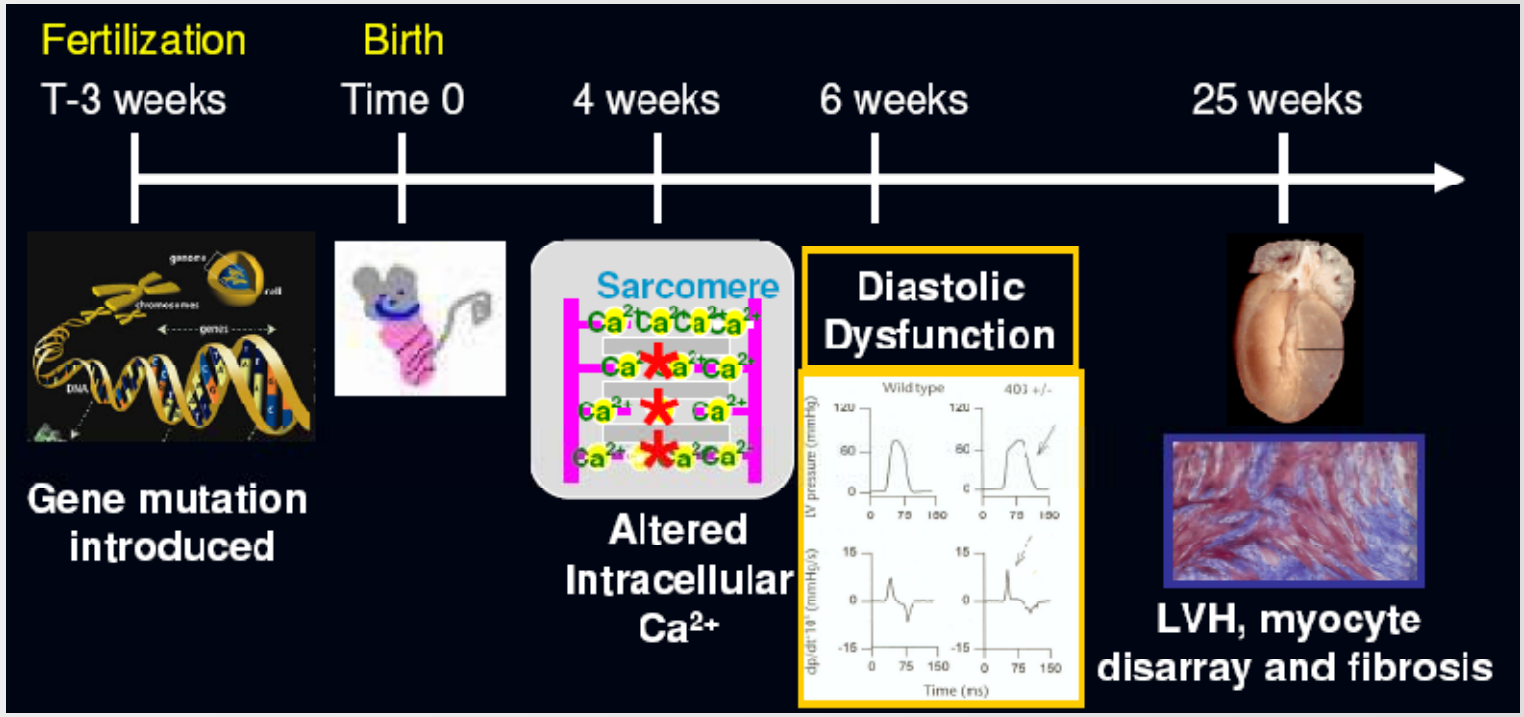
Prevalence: ~1:500
- At least 540,000 affected individuals in the US

Usually autosomal dominant
- Affected family members have 50% risk

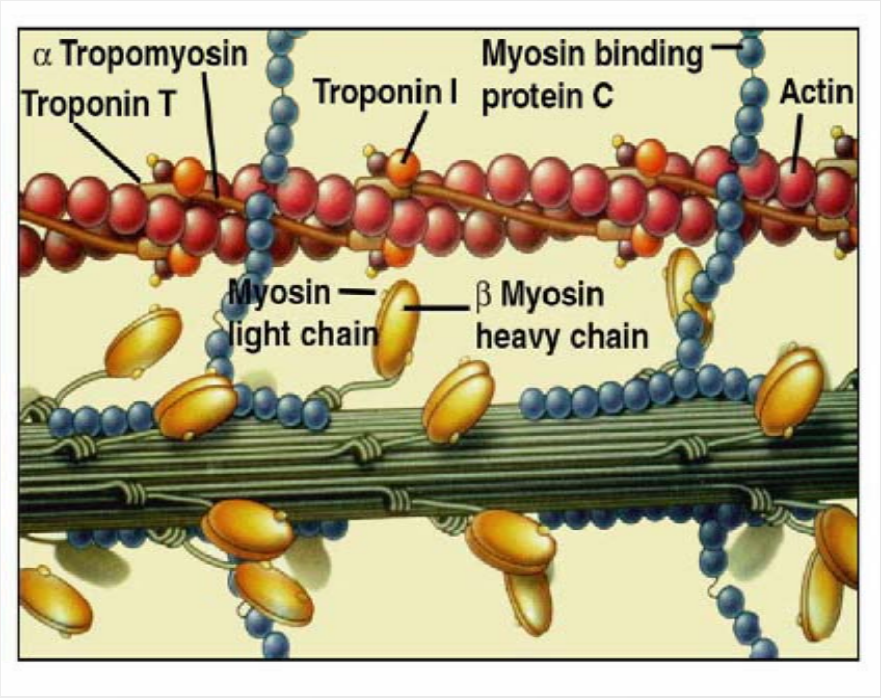
Heterogeneous with respect to:
- disease causing mutation
- presentation
- prognosis
- Treatment

Development of Hypertrophic Cardiomyopathy

Temporal sequence



Hypertrophic Cardiomyopathy



- **Prevalence of unexplained LVH : ~ 1: 500**
- **Traditionally an idiopathic disorders**
- **~ 60% attributed to sarcomere gene mutation**
- **Over 450 individual mutations detected**

Causative genes in Hypertrophic cardiomyopathy

Encoded Protein	Gene Symbol	Chromosome Locus	Sarcomere Component	No. of Cases	Percentage of All Cases
β-Myosin heavy chain	MYH7	14q12	Thick filament	212	44
Myosin-binding protein C	MYBPC3	11p11.2	Thick filament	165	35
Troponin T	TNNT2	1q32	Thin filament	33	7
Troponin I	TNNI3	19q13.4	Thin filament	27	5
α-Tropomyosin	TPM1	15q22.1	Thin filament	12	2.5
Regulatory Myosin light chain	MYL2	12q24.3	Thick filament	10	2
Essential Myosin light chain	MYL3	3p21	Thick filament	5	1
Actin	ACTC1	15q14	Thin filament	7	1
Titin	TTN	2q31	Thick filament/Z-Disc	2	< 1
Muscle LIM protein	CSRP3	11p15.1	Z-Disc	3	< 1
Telethonin	TCAP	17q12	Z-Disc	2	< 1
Myozenin 2	MYOZ2	4q26	Z-Disc	1	< 1
Vinculin	VCL	10q22.1	Intercalated disc	2	< 1

Alcalai et al. 2008 J. Cadiovascular Eletrophysiology

• Despite of these mutations, in about 40-50 % of patients with unexplained LVH, no mutations in a sarcomere gene is found.

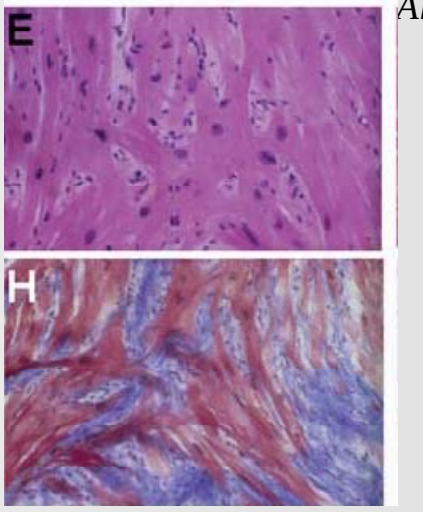
Sarcomeric HCM vs. Storage Cardiomyopathies

Major Characteristics of Genetic Cardiac Hypertrophy

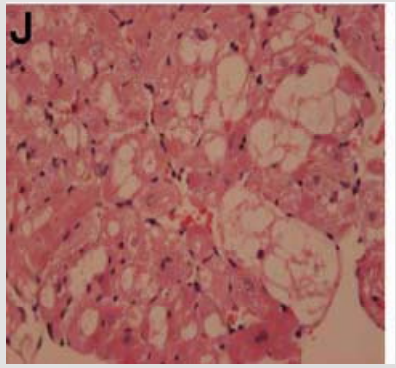
Characteristic	Sarcomeric HCM	Storage (metabolic) Cardiomyopathies
Inheritance	AD	AD, AR, X-lined
Degree of hypertrophy	Variable	Massive in LAMP2 mutations
Electric abnormalities	Nonsustained VT, atrial fibrillation	WPW, conduction system defects
Pathology	Disarray, fibrosis	Glycogen accumulation, abnormal vacuoles
Progression to heart failure	Variable, not common	Common, mainly in LAMP2 mutation

LVH + Electrophysiological abnormalites

Alcalai et al. 2008 J. Cadiovascular Eletrophysiology



Sarcomere

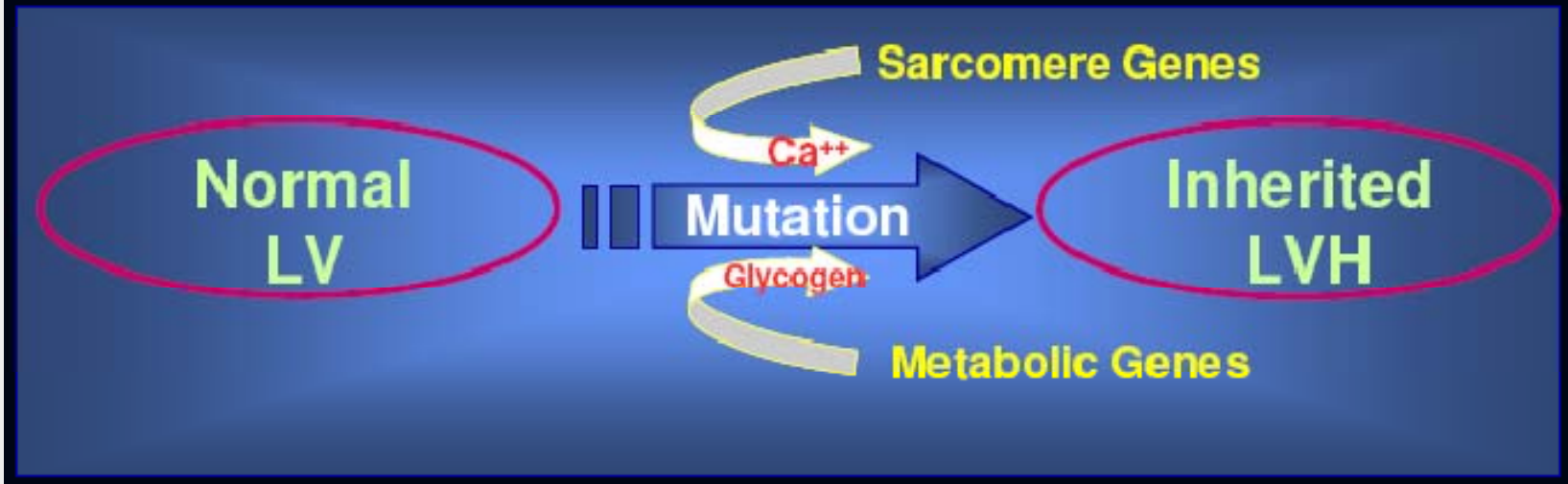


PRKAG2

Glycogen accumulation

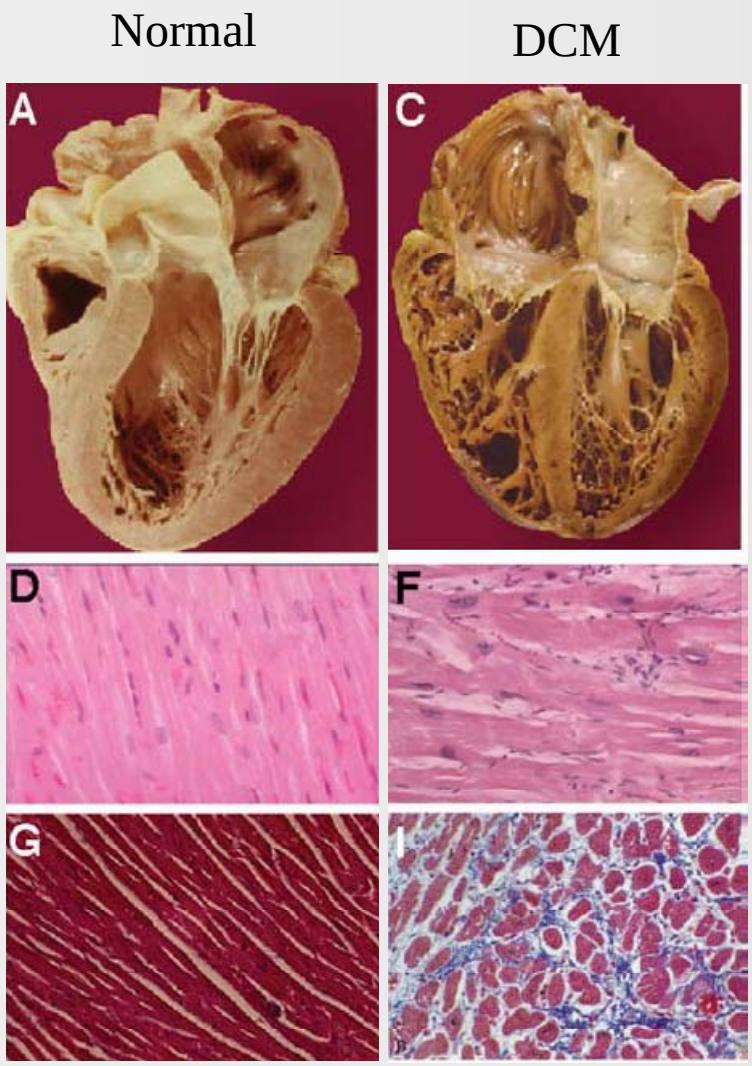
Vacuoles in myocytes

Sarcomere Protein and Metabolic Gene Mutations Are Common Causes of LVH



- 60% of Familial Hypertrophic Cardiomyopathy
- Gene-based Diagnosis is Important
  - →Clarify Diagnosis
  - →Identify at-risk family members
- Pathogenic Insights from studying familial HCM may
  - → Inform other forms of LVH
  - → Inspire novel preventive therapies

Dilated Cardiomyopathy



Ahmad et al. 2005 Ann. Rev. Genomics Hum. Genet

- **Unexplained dilation and impaired systolic function of LV or both ventricles and increased myocardial mass**
- **heart failure, palpitations, or sudden death**
- **Most common cardiomyopathies**
  - **Over 90% of cases**
  - **The most common reason for cardiac transplantation in the young**
- **Prevalence: ~1:2500**
- **Up to 50% of cases of idiopathic cardiomyopathy may have genetic causes**
- **Heterogeneous genetic causes**
  - **mostly autosomal dominant**
  - AR, X-linked, mitochondrial

Dilated Cardiomyopathy

- **Autosomal Dominant** **56%**
  - most common
  - High incidence of cardiac autoantibodies
  - 50 percent in families with autosomal dominant inheritance
- **Autosomal recessive** **16%**
  - Younger age, worse prognosis
- **X linked** **10%**
  - Different mutations in dystrophin gene
- Autosomal dominant + skeletal 7%
  - Restrictive pattern
- Familial DCM with conduction defects 2%

Mestroni 2002 JACC

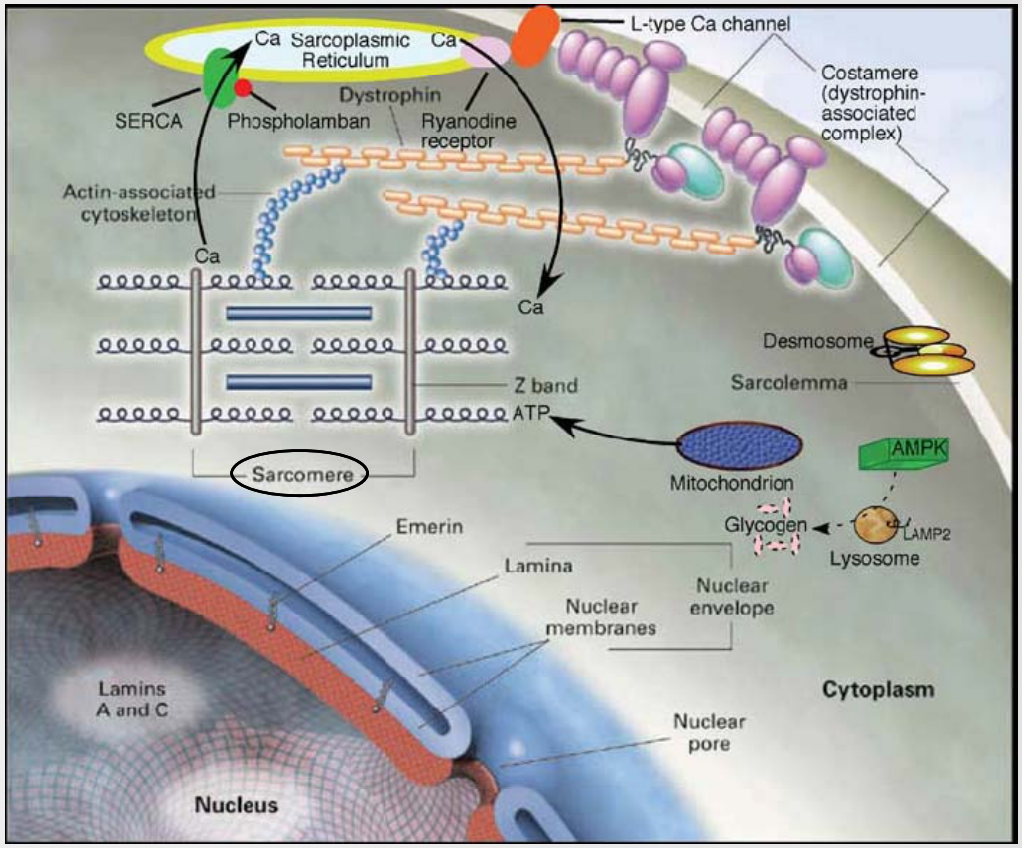
Lamin A/C mutation

- Emery-Dreifuss Muscular Dystrophy/ Skeletal myopathy
- Hutchinson-Gilford Progeria
- **DCM + Conduction Disease**
  - Fibrofatty degeneration of myocardium and conduction system
  - Progressive AV block and atrial arrhythmias (2^{nd}-4^{th} decades)
  - ~8% of DCM (5^{th}-7^{th} decades)
  - May have concomitant skeletal muscle involvement (CK)
  - Worse prognosis than in DCM w/o LMNA mutation

Chromosomal Locus	Gene	Protein	Inheritance	Phenotype/Associated Abnormality
DCM autosomal dominant inheritance				
1p1–q21	*LMNA*	Lamins A & C	AD	DCM + conduction system disease
1p1–q21	*LMNA*	Lamins A & C	AD	DCM + skeletal myopathy (AD Emery-Dreifuss or limb-girdle muscular dystrophies) ± conduction-system disease
1q32*	*TNNT2*	Cardiac troponin T	AD	Pure DCM
2q14–q22	?	?	AD	DCM + conduction system disease
2q31*	*TTN*	Titin	AD	Pure DCM
2q35	*DES*	Desmin	AD	Pure DCM
3p22–p25	?	?	AD	DCM + conduction system disease
5q33	*SGCD*	δ-sarcoglycan	AD	Pure DCM
6q12–q16	?	?	AD	Pure DCM
6q22	*PLN*	Phospholamban	AD	Pure DCM
6q23	?	?	AD	DCM + skeletal myopathy (limb-girdle muscular dystrophy) ± conduction-system disease
6q23–q24	*EYA4*	Eya4	AD	DCM + sensorineural deafness
9q13–q22	?	?	AD	Pure DCM
9q22–q31	?	?	AD	Pure DCM
10q22–q23	*VCL*	Metavinculin	AD	Pure DCM
11p11*	*MYBPC3*	Cardiac myosin-binding protein C	AD	Pure DCM
12p12.1	*ABCC9*	ATP-sensitive K channel	AD	Pure DCM
14q12*	*MYH7*	β-myosin heavy chain	AD	Pure DCM
15q14*	*ACTC*	α-cardiac actin	AD	Pure DCM
15q22*	*TPM1*	α-tropomyosin	AD	Pure DCM

DCM autosomal recessive inheritance				
4q12	*SCGB*	β-sarcoglycan	AR	Limb-girdle muscular dystrophy + severe DCM
6p24	*DSP*	Desmoplakin	AR	DCM + woolly hair and keratoderma
DCM X-linked inheritance				
Xp21	*DMD*	Dystrophin	X-linked	X-linked DCM, Duchenne & Becker muscular dystrophy
Xq28	*G4.5*	Tafazzin	X-linked	X-linked infantile DCM, Barth syndrome, hypertrophic DCM, endocardial fibroelastosis, and left ventricular noncompaction
Xq28	*EMD*	Emerin	X-linked	X-linked Emery-Dreifuss muscular dystrophy

Genetic Causes of Dilated Cardiomyopathy



Sarcomere Proteins

Cytoskeletal proteins

Channels

Other Categories

Phospholamban
Eya4
Tafazzin
LaminA/C

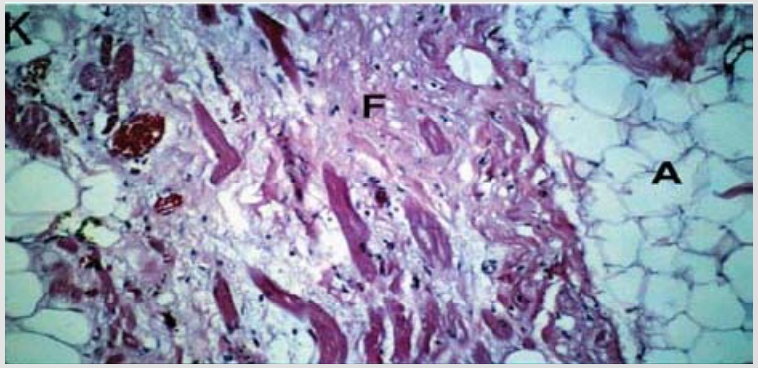
Arrhythmogenic Right Ventricular Cardiomyopathy

•Pathological Features
- •Adipose and fibrous tissue replacement of the RV myocardium

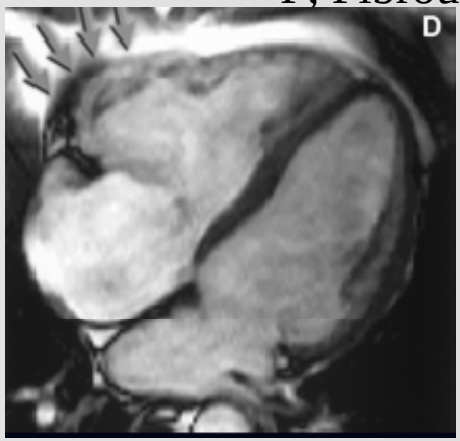
• Clinical Features
- •Electrical Instability: VT, syncope, SCD
- •Cardiomyopathy and Heart Failure
- •FH of SCD
- •EKG changes: epsilon waves, TWI V1-3
- •LV involvement in up to ~50%
- •Typically present between 13-50 years

•Prevalence: ~1:2000-5000
- •3:1 Male:Female
- •Familial disease in >50%
- •11% of SCD, 22% SCD in athletes (Italy)
- •Autosomal Dominant
- • Incomplete penetrance, variable expression

ARVC

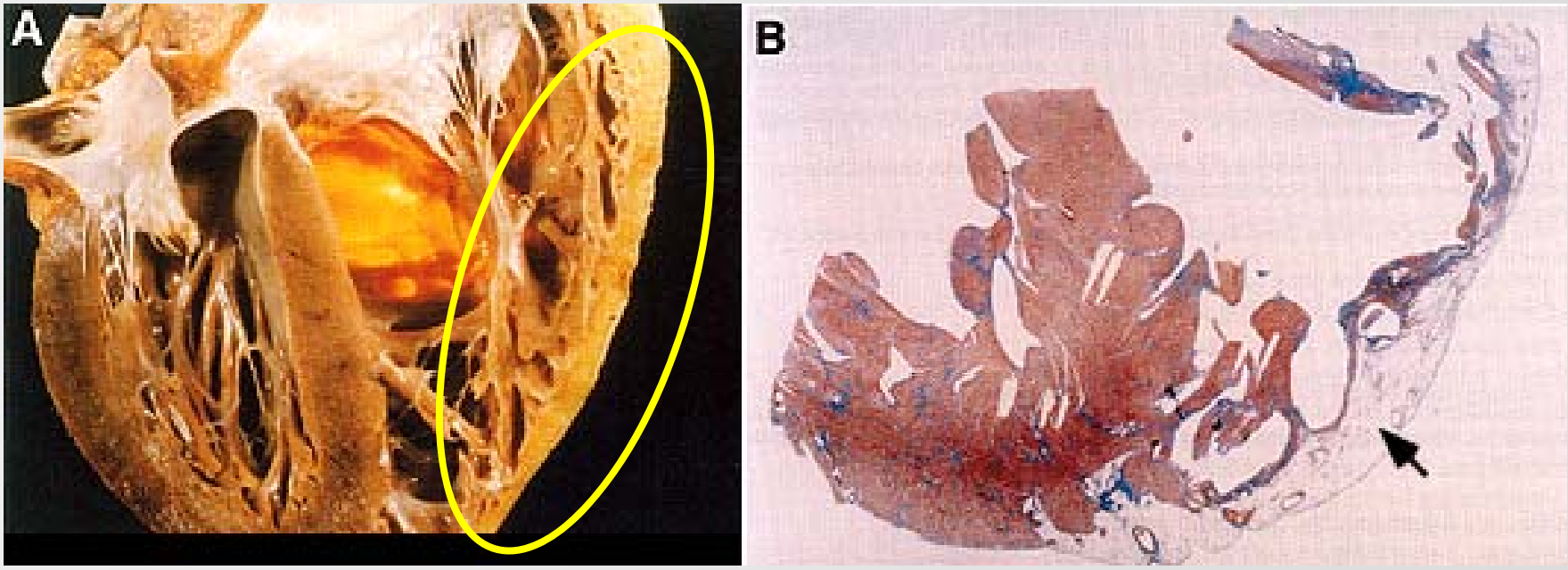


A; Adipose
F; Fibrous tissue



Sen-Chowdhry, et al. 2007 Circulation.

ARVC



- EM demostrates Desmosomal Abnormalities
  - plakoglobin, desmoplakin, and plakophilin-2
- Genetics
  - Sporadic
  - Autosomal Dominant
  - Autosomal Recessive (Naxos Disease)

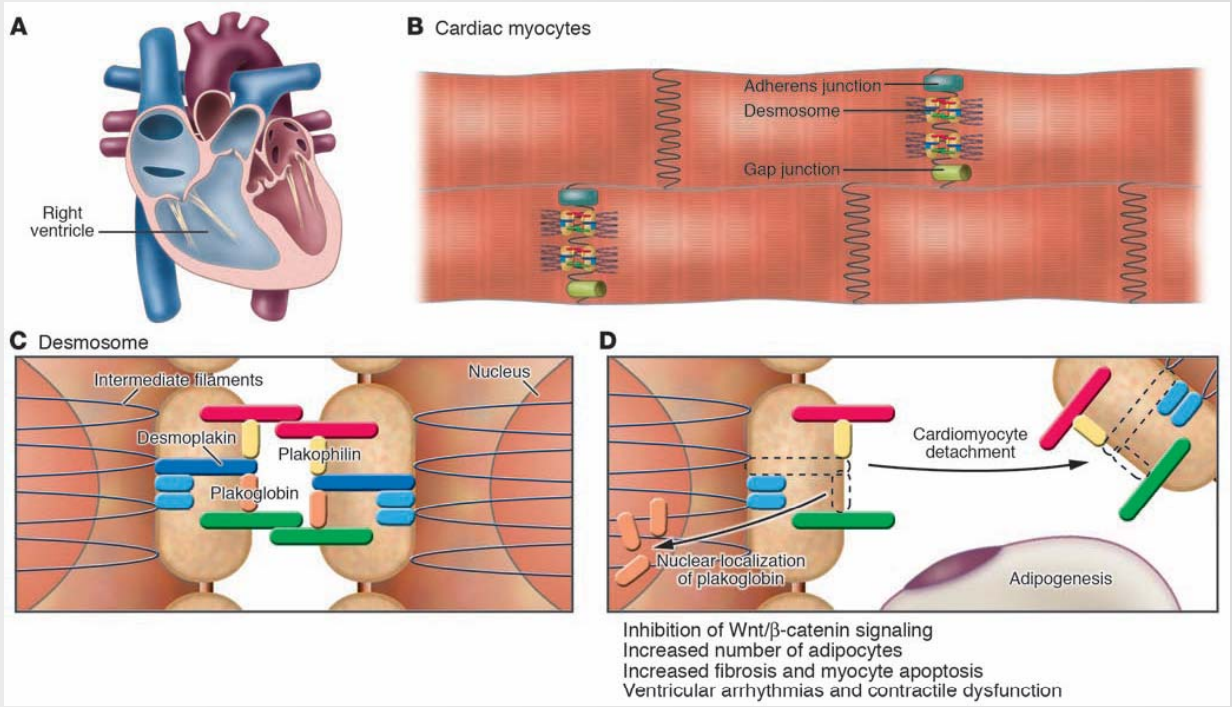
Genetic causes of ARVC

(A disease of the Desmosome)

ARVC autosomal dominant inheritance				
1q42–q43	*RyR2*	Cardiac ryanodine receptor	AD	ARVD2, catecholaminergic p ventricular tachycardia
2q32	?	?	AD	ARVD4
3p23	?	?	AD	ARVD5
6p24	*DSP*	Desmoplakin	AD	ARVD8
10p12-14	?	?	AD	ARVD6
10q22	?	?	AD	ARVD7, skeletal myopathy
12p11	*PkP2*	Plakophilin-2	AD	ARVD9
14q12-22	?	?	AD	ARVD3
14q23-24	?	?	AD	ARVD1
ARVC autosomal recessive inheritance				
17q21	*JUP*	Plakoglobin	AR	Naxos disease, palmoplantar woolly hair
18q12.1-12.2	*DSG2*	Desmoglein-2	AD	ARVD10
18q12.1	*DSC2*	Desmocollin-2	AD	ARVD11

Ashrafian & Watkins 2007 JACC

Pathway to ARVC



Intercellular Adhesion Molecules

Predisposition to cardiomyocyte detachment (cardiomyocyte loss by apoptosis)
→ Fibrofatty replacement
→ Perturbation of gap junctions
→ Electrical Instability

Restrictive Cardiomyopathy

- Non dilated Ventricle w/ normal wall thickness
  - Need to Exclude Constrictive Pericarditis
- Preserved LV systolic function (normal EF)
- Diastolic Dysfunction and restrictive filling
  - Abnormal Echo Doppler or Cardiac MRI
  - R/L cardiac cath to assess hemodynamics
- Rare form of cardiac remodeling: <5% of all cardiomyopathy
- Mutation found in some of the sarcomere gene, Troponin I.

Many pathways lead to a broken heart

Force transmission/ generation

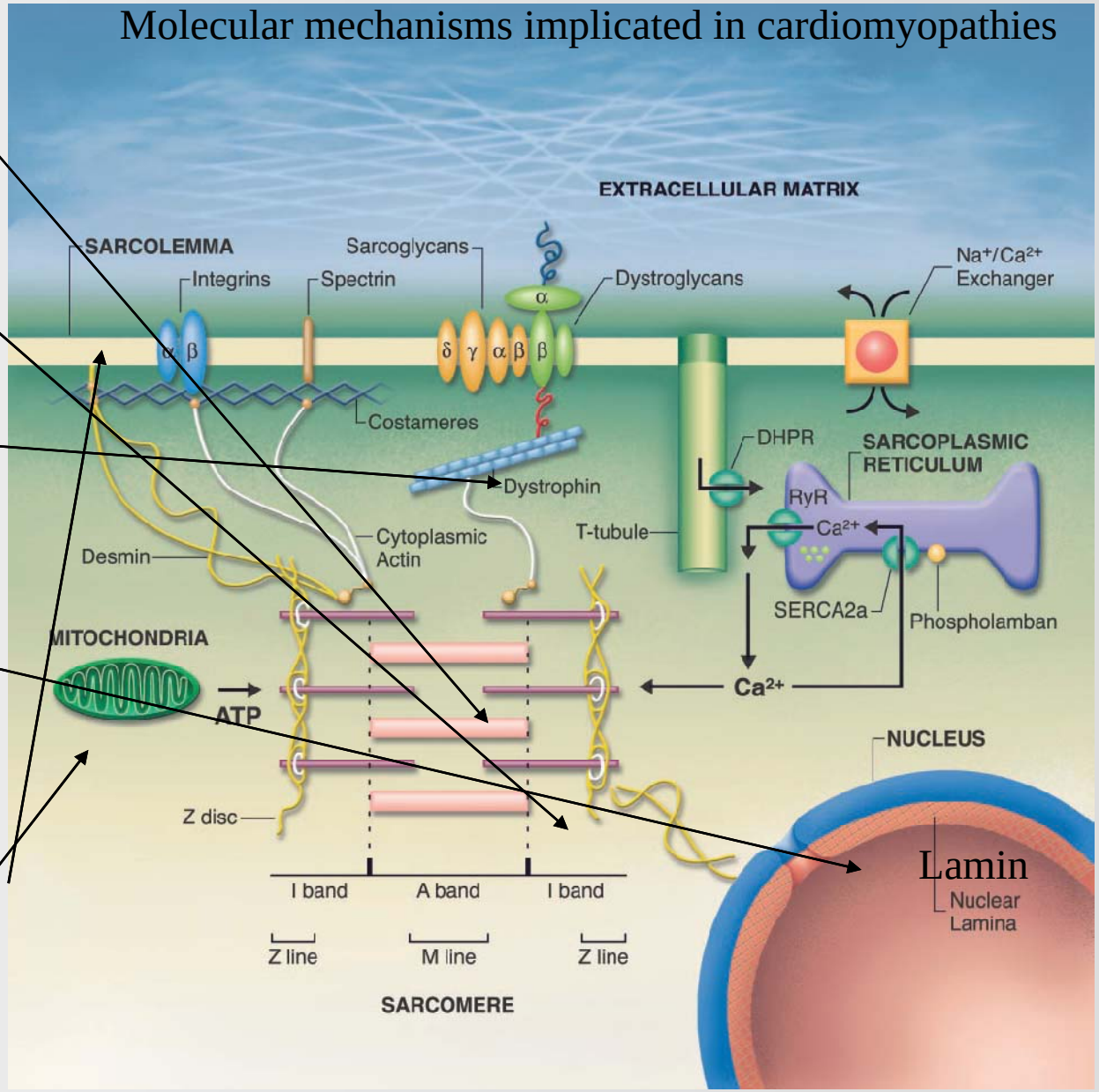
Intracellular Ca++ Handling

Cytoskeleton Cell membrane cytoplasm

Nuclear Membrane

Glycogen Metabolism/ Glucose Energetics

Intercellular Junctions



Fatkin and Graham 2002 Physiol Rev.

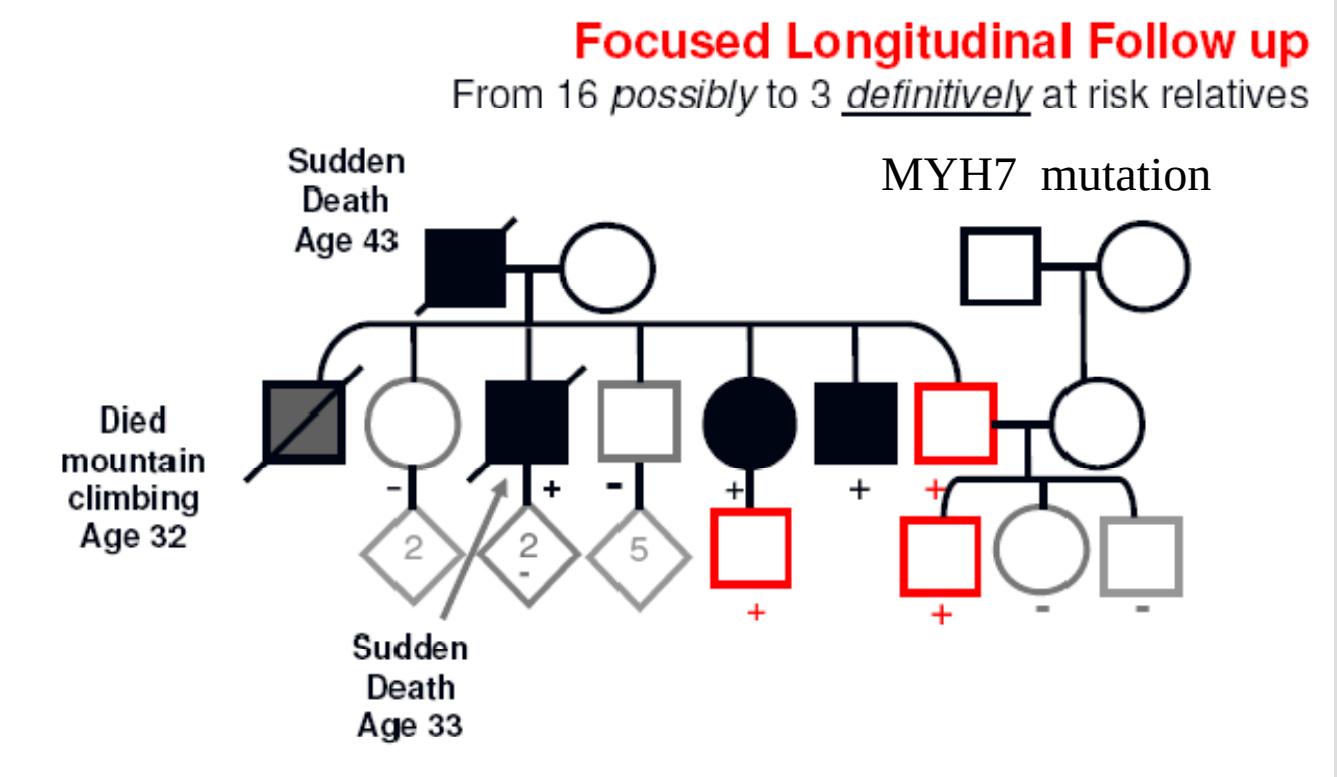
Genetics of Cardiomyopathies:
Implications for disease in the molecular era

- Improved accuracy in diagnosis and prognosis
  - Improved management of familial disease
  - Identification of causal gene mutations for HCM, DCM, ARVC
  - Definitive diagnosis, independently of age and clinical features
  - Preclinical identification of individuals at risk for disease development
- Molecular characterization of disease
  - Elucidation of important cellular pathways involved in cardiac remodeling
  - Identification of potential therapeutic targets
- Development of rational treatment strategies
  - Prevention or attenuation of phenotypic manifestations
  - Modification of natural history

Advantages of Genetic Testing

- Determination of the exact genetic etiology of HCM
- Clarification of diagnosis→ Implications for management
  - Other genetic causes of LVH
  - Athlete's heart
- Definitive genetic diagnosis in family members
  - **Mutation Present:** At risk for disease development
    - Genotype (+) ≠ Clinical Disease but penetrance is high
    - Identification of preclinical disease→ serial evaluation
    - 50% chance of transmission to offspring
  - **Mutation Absent:** Unaffected Family Members
    - Reassurance
    - No possibility for disease or transmission to offspring
    - No further clinical screening required
- Greater understanding of disease mechanisms
  - Insight into pathogenesis→ Novel preventive treatment strategies

After genetic testing



Clinical Genetic Testing for Cardiomyopathies

Harvard Partners Center for Genetics and Genomics (HPCGG)
Laboratory for Molecular Medicine www.hpcgg.org/lmm

- **HCM**
  - **Panel A** (106 exons): **Detection Rate 50-60%**
    - *MYH7* (14q12)
    - *MYBPC3* (11p11.2)
    - *TNNT2* (1q32)
    - *TNNI3* (19q13.4)
    - *TPM1* (15q22.1)
  - **Panel B** (19 exons): Detection Rate 5-10%
    - *ACTC* (15q14)
    - *MYL2* (12q23-q24.3)
    - *MYL3* (3p)
- **DCM** **Detection Rate ~10-20% of familial DCM**
  - HCM Panel A genes
  - Actin, Lamin, Phospholamban, Tafazzin, Cypher/ZASP
- **ARVC** **Detection Rate ~5-40% of clinical ARVC**
  - Desmosomes: PKP2, DSP, DSG2, DSC2