2017 HFCT Annual Scientific Meeting
The Heart Failure Crosstalk

Genetic Cardiomyopathies

Teerapat Yingchoncharoen M.D.

Ramathibodi Hospital

Mahidol University

Cardiomyopathy

Group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilation

Circulation 2006; 113:1807-16

Primary Cardiomyopathies

Genetics
- HCM
- LVNC
- ARVC/D
- Mitochondrial myopathies
- Conduction defects (Lenegere disease)
- Ion channel disorders (Brugada, LQTS, etc)

Mixed
- DCM
- Restrictive

Acquired
- Myocarditis
- Stress-induced
- Peripartum
- Tachycardia-induced

Circulation 2006; 113:1807-16

Secondary Cardiomyopathies

Infiltrative
- Amyloid
- Gaucher
- Hurler
- Hunter

Storage
- Hemochromatosis
- Fabry
- Glycogen storage
- Niemann-Pick

Inflammation/Autoimmune
- Loeffler's endocarditis
- Endomyocardial fibrosis
- Sarcoidosis
- SLE, RA, Scleroderma, PAN, Dermatomyositis

Endocrine
- DM
- Hypo/perthyroid
- Hyperparathyroid
- Pheochromocytoma
- Acromegaly

Neuromuscular
- Freidreich
- Duchene/Becker
- Emery-Dreifuss
- Myotonic dystrophy
- NF, TS

Toxic/Nutrition
- Ethanol, Cocaine
- Chemotherapy
- Beriberi
- Selenium def
- Carnitine def, etc.

Circulation 2006; 113:1807-16

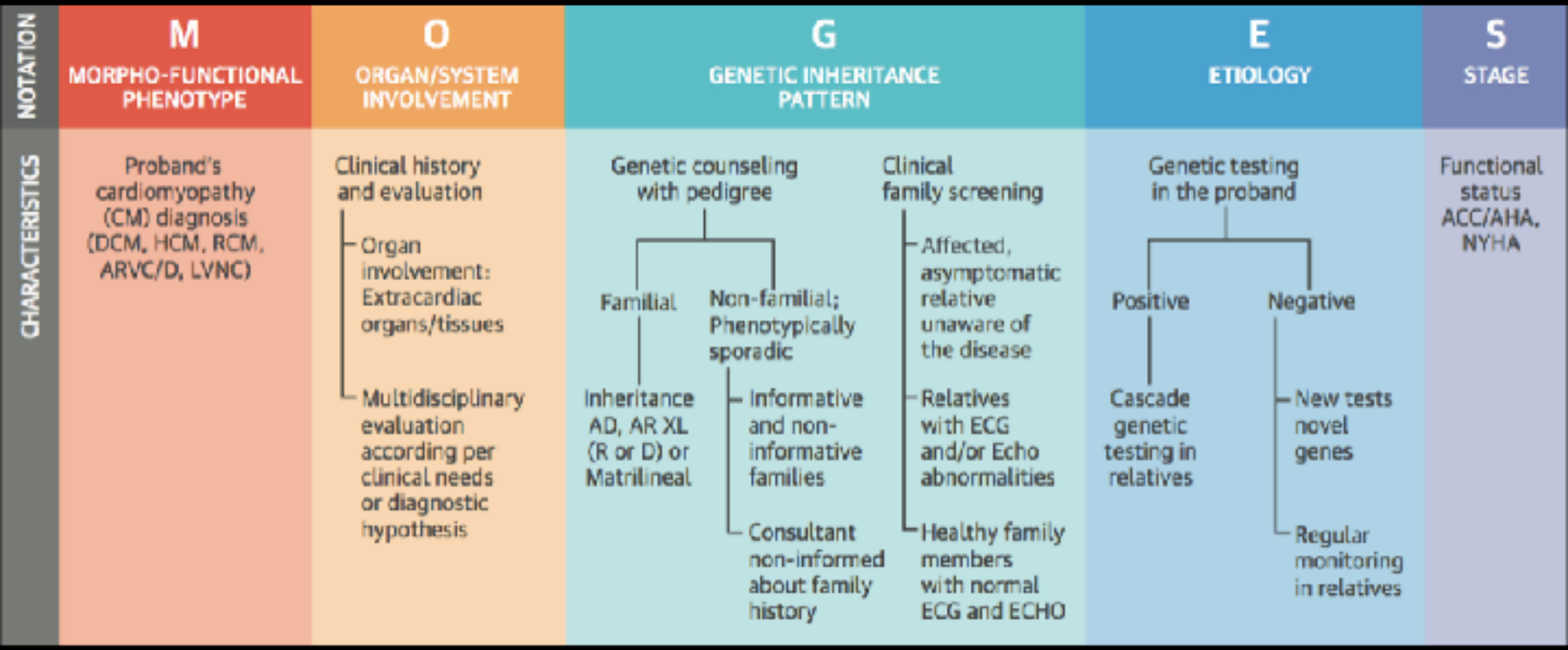
The MOGE(S) Classification for a Phenotype–Genotype Nomenclature of Cardiomyopathy

Endorsed by the World Heart Federation

- MOGE(S) Nomenclature
  - M - Morphofunctional characteristic
  - O - Organ involvement
  - G - Genetic or familial inheritance pattern
  - E - Explicit etiological annotation
  - S - Functional Status

J Am Coll Cardiol 2013;62:2046

MOGE(S) Classification



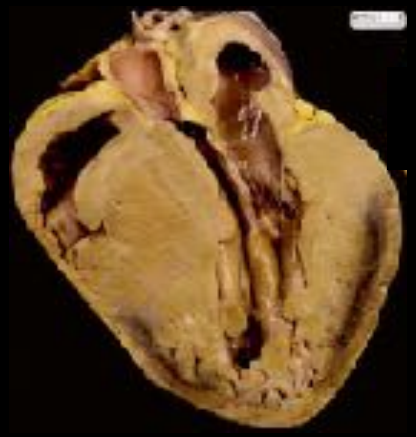
Artustini E. J Am Coll Cardiol. 2013;62:2046

MOGE(S) Classification

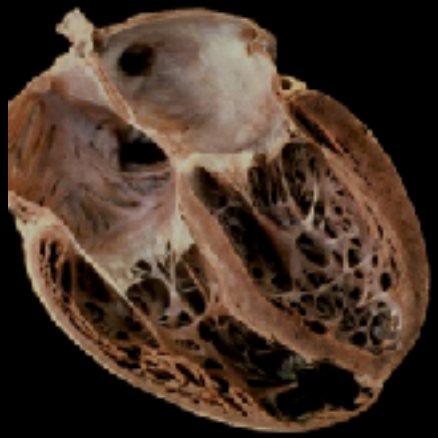
NOTATION	M MORPHO-FUNCTIONAL PHENOTYPE	O ORGAN/SYSTEM INVOLVEMENT	G GENETIC INHERITANCE PATTERN	E ETIOLOGY	S STAGE
SUBSCRIPT	D Dilated H Hypertrophic R Restrictive R EMF Endomyocardial fibrosis *LV=left ventricle RV=right ventricle RLV=biventricular* A ARVC *M=major m=minor c=category LV= left ventricle RV=right ventricle RLV=biventricular* NC LVNC E Early, with type in parentheses NS Nonspecific phenotype NA Information non available 0 Unaffected*	H Heart *LV=left ventricle RV=right ventricle RLV=biventricular* M Muscle (skeletal) N Nervous C Cutaneous E Eye, Ocular A Auditory K Kidney G Gastrointestinal Li Liver Lu Lung S Skeletal 0 Absence of organ/system involvement*, e.g. in family members who are healthy mutation carriers: the mutation is specified in E and inheritance in G	N Family history negative U Family history unknown AD Autosomal dominant AR Autosomal recessive XLD X-linked dominant XLR X-linked recessive XL X-linked M Matrilineal 0 Family history not investigated* Undet Inheritance still undetermined S Phenotypically Sporadic (apparent or real)	G Genetic cause OC Obligate carrier ONC Obligate non-carrier DN *De novo* Neg Genetic test negative for the known familial mutation N Genetic defect not identified 0 No genetic test, any reason* G-A-TTR Genetic amyloidosis G-HFE Hemochromatosis *Non-genetic etiologies:* M Myocarditis V Viral infection (add the virus identified in affected heart) AI Autoimmune/immune-mediate, suspected (AI-S), proven (AI-P) A Amyloidosis (add type: A-K, A-L, A-SAA) I Infectious, non viral (add the infectious agent) T Toxicity (add cause/drug) Eo Hypereosinophilic heart disease O Other	ACC-AHA stage represented as letter A, B, C, D NA not applicable NU not used *followed by* NYHA class represented as Roman numeral I, II, III, IV

Morphologic characteristics of cardiomyopathy

(H)
Hypertrophic cardiomyopathy

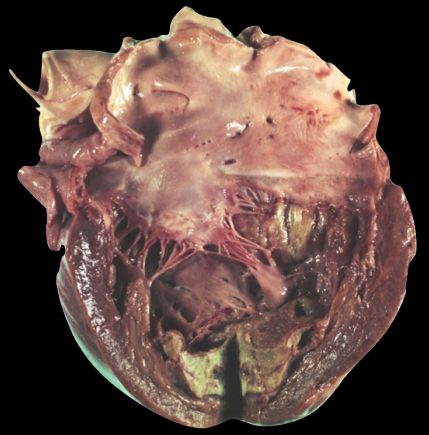


(D)
Dilated cardiomyopathy

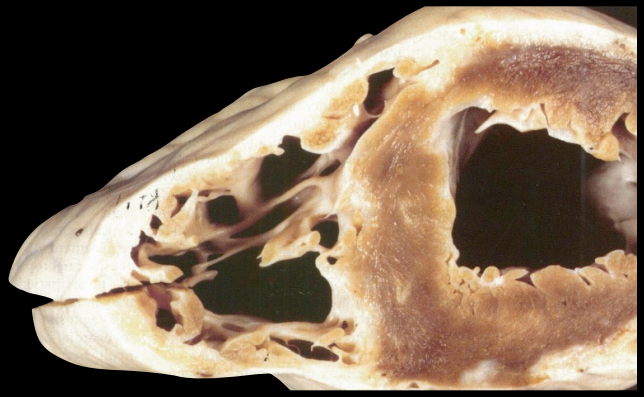


(R)
Restrictive cardiomyopathy

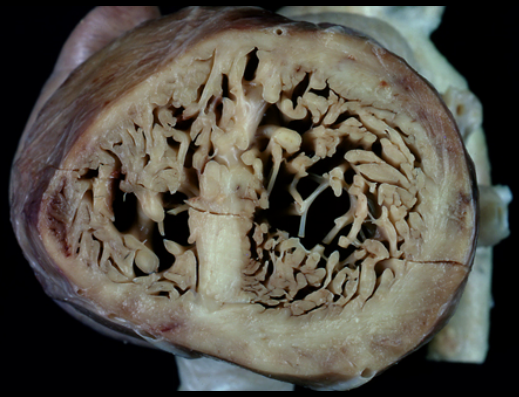
(R-EMF)
Endomyocardial fibrosis



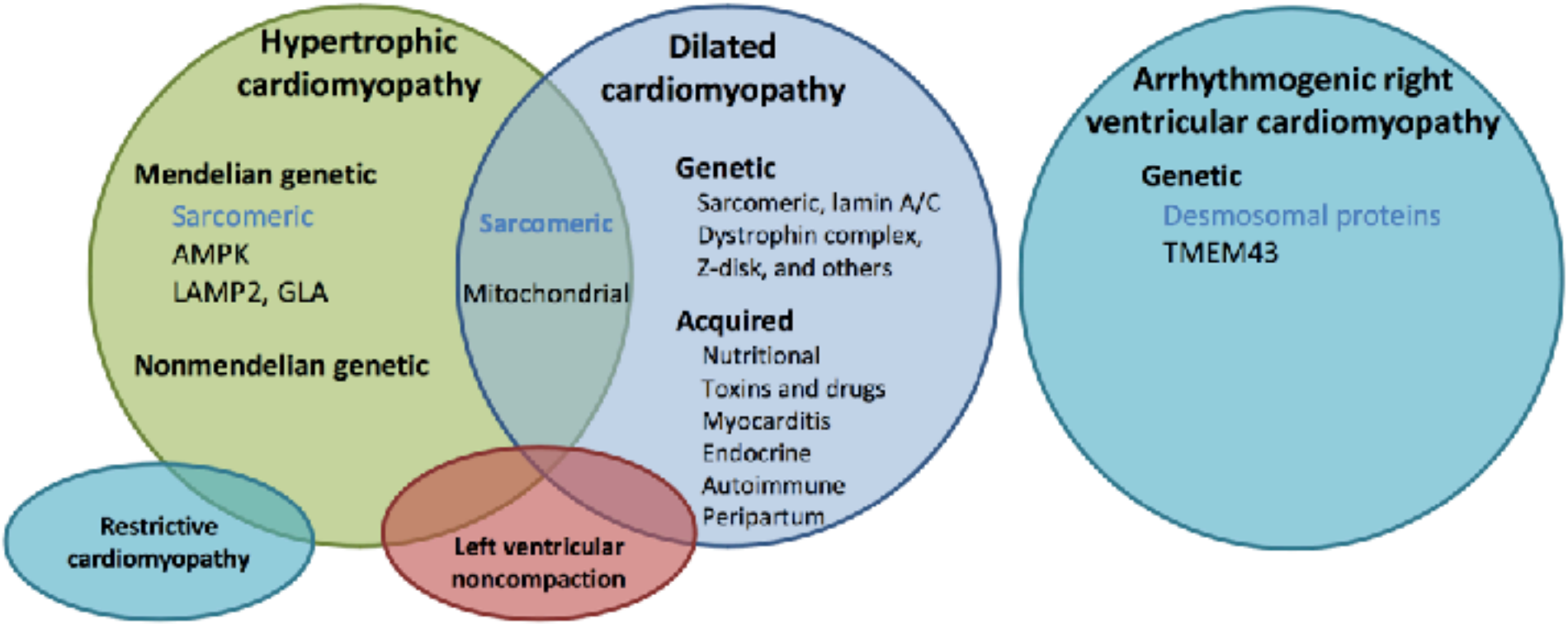
(A)
Arrhythmogenic RV cardiomyopathy



(NC)
Noncompaction



Inherited cardiomyopathies



N Eng J Med 2011;364:1643-56.

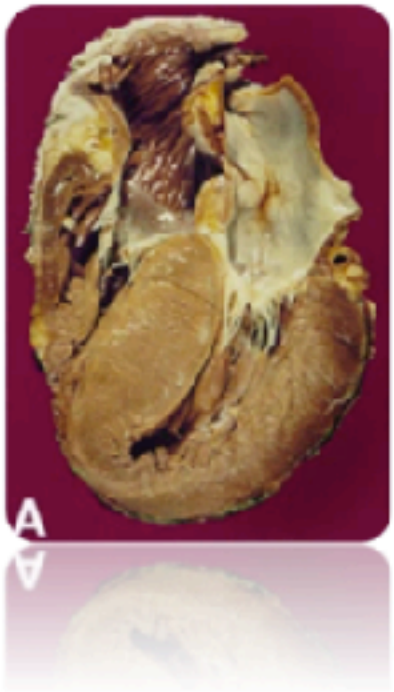
Hypertrophic Cardiomyopathy

- Most common genetic CV disease, incidence 1:500
- Caused by mutations in genes encoding sacromeric proteins
- Male ~Female
- Diverse pattern of phenotypic expression and clinical course
- Most common cause of sudden death in young athlete (<35y)

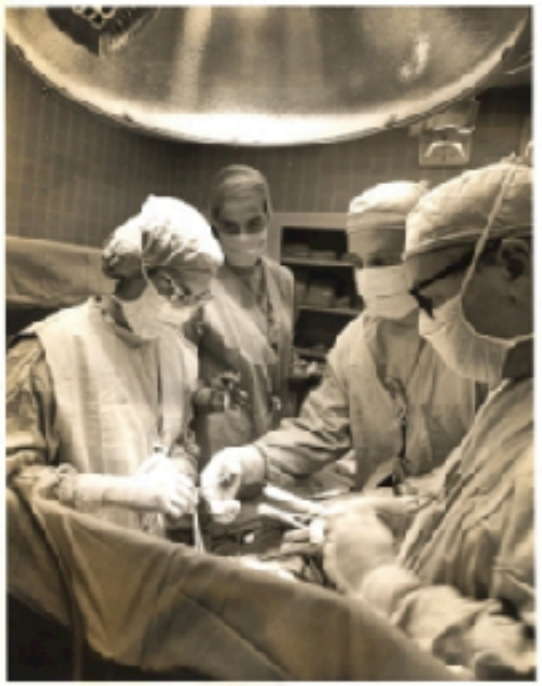
Asymmetrical hypertrophic cardiomyopathy
Asymmetrical hypertrophy of the heart
Asymmetric septal hypertrophy
Brock's disease
Diffuse muscular subaortic stenosis
Diffuse subvalvular aortic stenosis
Dynamic hypertrophic subaortic stenosis
Dynamic muscular subaortic stenosis
Familial hypertrophic subaortic stenosis
Familial hypertrophic cardiomyopathy
Familial muscular subaortic stenosis
Familial myocardial disease
Functional aortic stenosis
Functional hypertrophic subaortic stenosis
Functional obstructive cardiomyopathy
Functional obstruction of the left ventricle
Functional obstructive subvalvular aortic stenosis
Functional subaortic stenosis
Hereditary cardiovascular dysplasia
HYPERTROPHIC CARDIOMYOPATHY (HCM)
Hypertrophic constrictive cardiomyopathy
Hypertrophic hyperkinetic cardiomyopathy
Hypertrophic infundibular aortic stenosis
Hypertrophic nonobstructive cardiomyopathy
Hypertrophic obstructive cardiomyopathy (HOCM)
Hypertrophic stenosing cardiomyopathy
Hypertrophic subaortic stenosis
Idiopathic hypertrophic cardiomyopathy
Idiopathic hypertrophic obstructive cardiomyopathy
Idiopathic hypertrophic subaortic stenosis (IHSS)
Idiopathic hypertrophic subvalvular stenosis
Idiopathic muscular hypertrophic subaortic stenosis
Idiopathic muscular stenosis of the left ventricle
Idiopathic myocardial hypertrophy
Idiopathic stenosis of the flushing chamber of LV
Idiopathic ventricular septal hypertrophy
Irregular hypertrophic cardiomyopathy
Left ventricular muscular stenosis
Low subvalvular aortic stenosis
Muscular aortic stenosis
Muscular hypertrophic stenosis of LV
Muscular stenosis of the left ventricle
Muscular subaortic stenosis
Muscular subvalvular aortic stenosis
Non-dilated cardiomyopathy
Nonobstructive hypertrophic cardiomyopathy
Obstructive cardiomyopathy
Obstructive hypertrophic aortic stenosis
Obstructive hypertrophic cardiomyopathy
Obstructive hypertrophic myocardiopathy
Obstructive myocardiopathy
Pseudoaortic stenosis
Stenosing hypertrophy of the left ventricle
Stenosis of the ejection chamber of LV
Subaortic hypertrophic stenosis
Subaortic idiopathic stenosis
Subaortic muscular stenosis
Subvalvular aortic stenosis of the muscular type
Teare's disease

The first description of hypertrophic cardiomyopathy

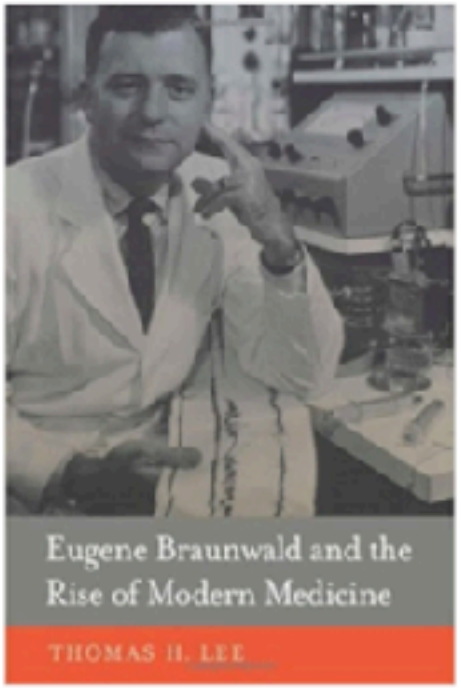
Hypertrophic Cardiomyopathy



Seidman & Seidman, *Cell* 2001



Andrew G. Morrow

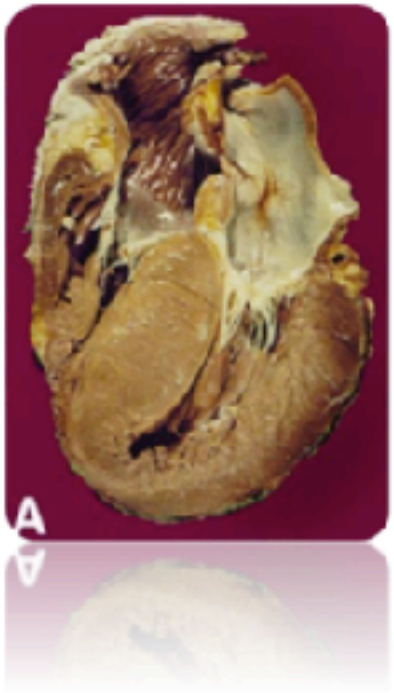


Eugene Braunwald

Am J Cardiol 2012;109:1539 –1547

The first description of hypertrophic cardiomyopathy

Hypertrophic Cardiomyopathy

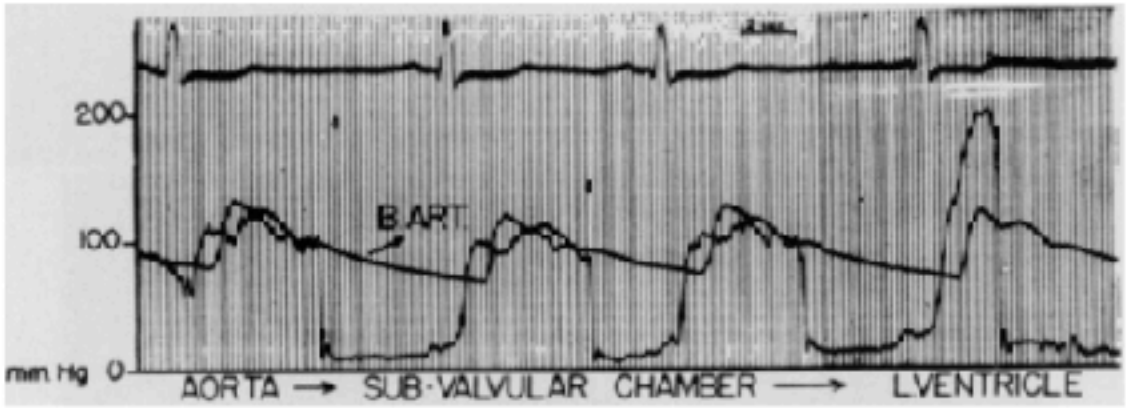


Seidman & Seidman, *Cell* 2001

Functional Aortic Stenosis

A Malformation Characterized by Resistance to Left Ventricular Outflow without Anatomic Obstruction

By Andrew G. Morrow, M.D., and Eugene Braunwald, M.D.

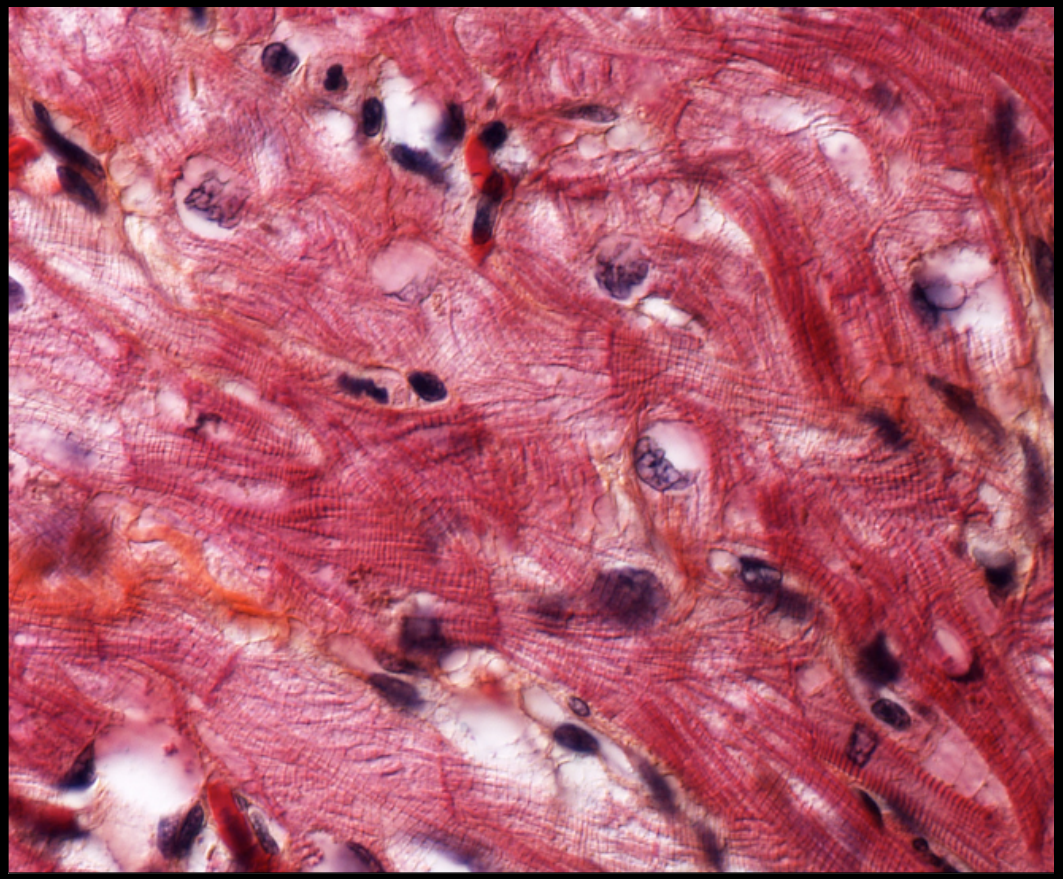


We have recently studied 2 patients in whom significant pressure gradients were demonstrated preoperatively but in whom no anatomic site of outflow obstruction could be detected at the time of open-heart operation.

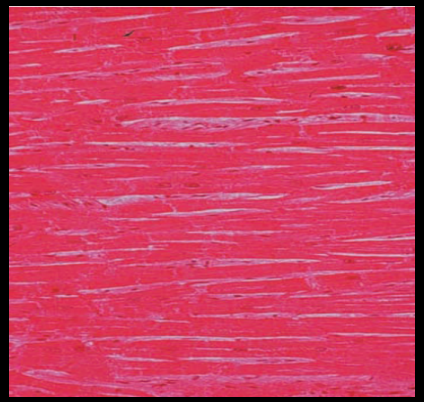
Circulation, Volume XX, August 1959

Pathological Hallmark
Cardiac myocyte disarray

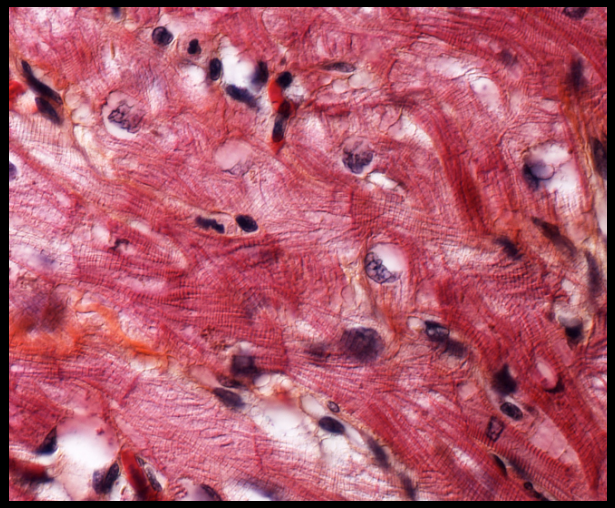
Haphazard alignment of adjacent myocyte
(perpendicular or oblique rather than parallel)



Normal myocardium



Cardiac myocyte disarray

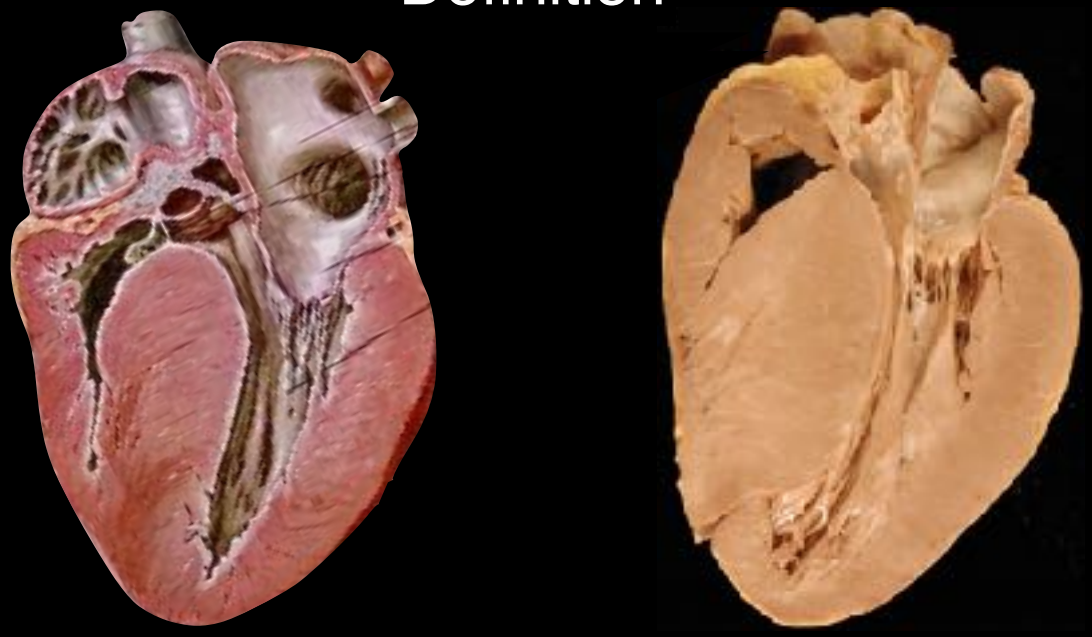


- Not specific for sarcomeric disease, significant if >10%
- Also been documented in genocopies
  - Anderson-Fabry disease
  - Noonan syndrome
  - Friedreich ataxia but not PRKAG2 mutation

Nat Review Cardiology 2016

Hypertrophic Cardiomyopathy

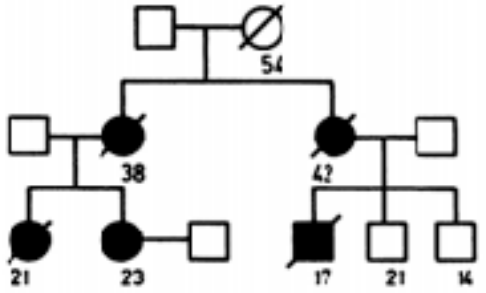
Definition

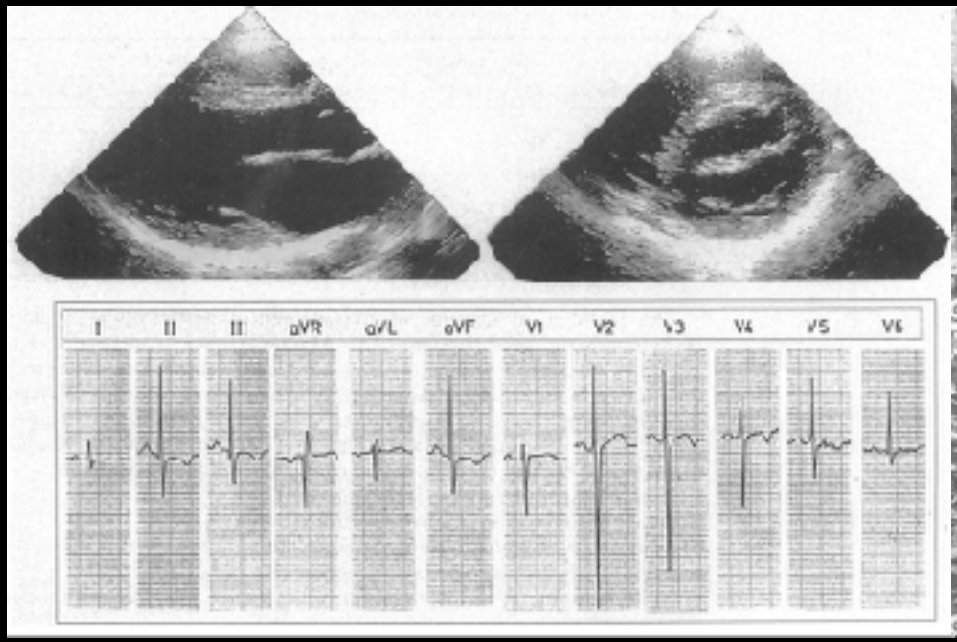


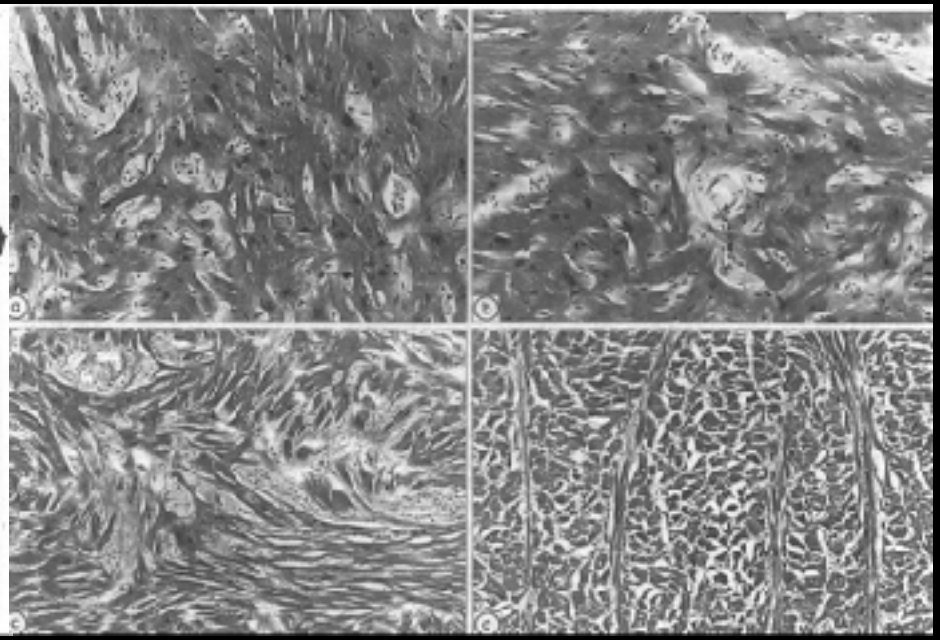
Increased LV wall thickness ≥15 mm in one or more LV segments in the absence of a hemodynamic pressure load to produce the hypertrophy

Limitation of LVH-based HCM definition

Hypertrophic cardiomyopathy without hypertrophy: two families with myocardial disarray in the absence of increased myocardial mass

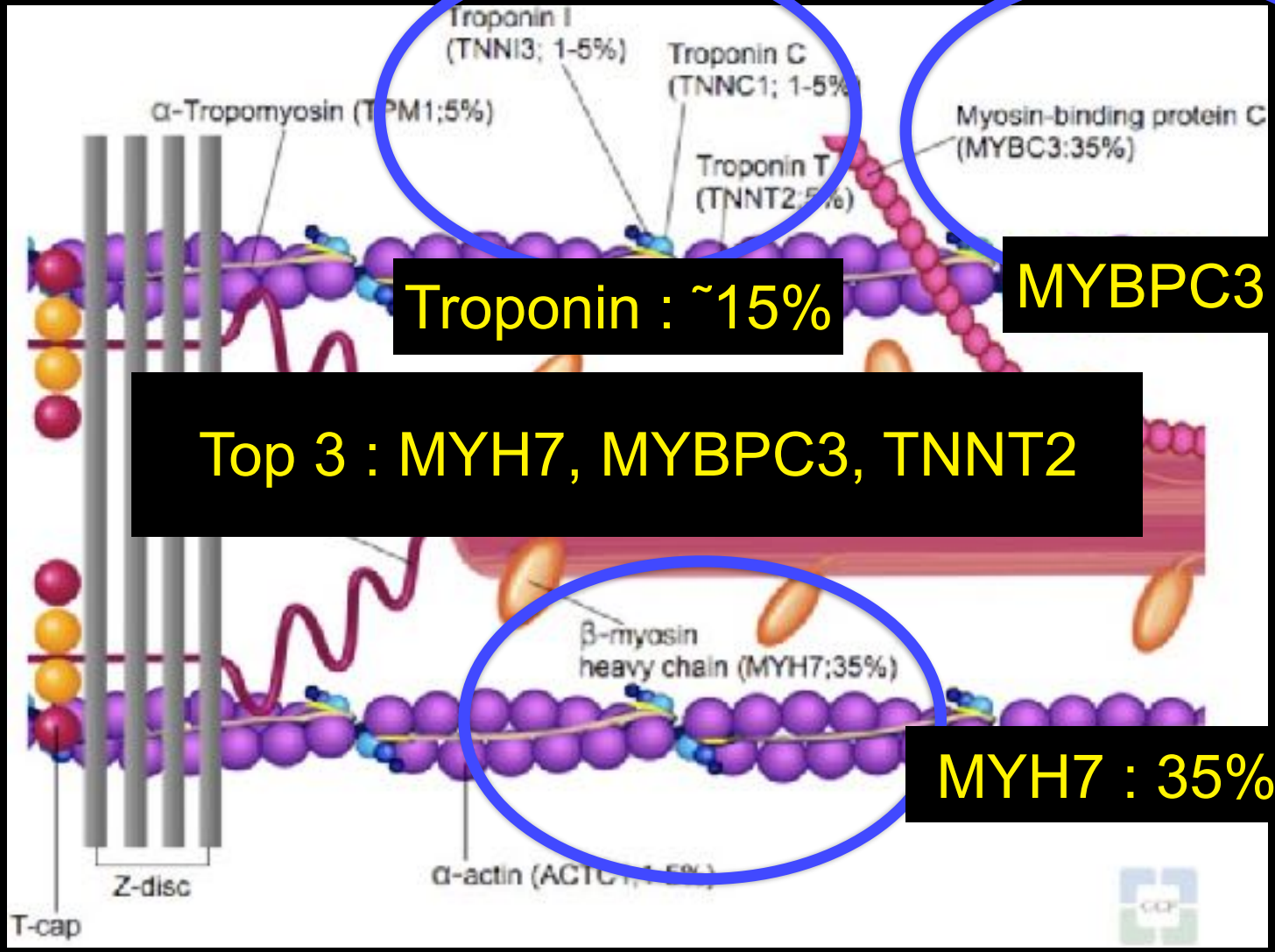


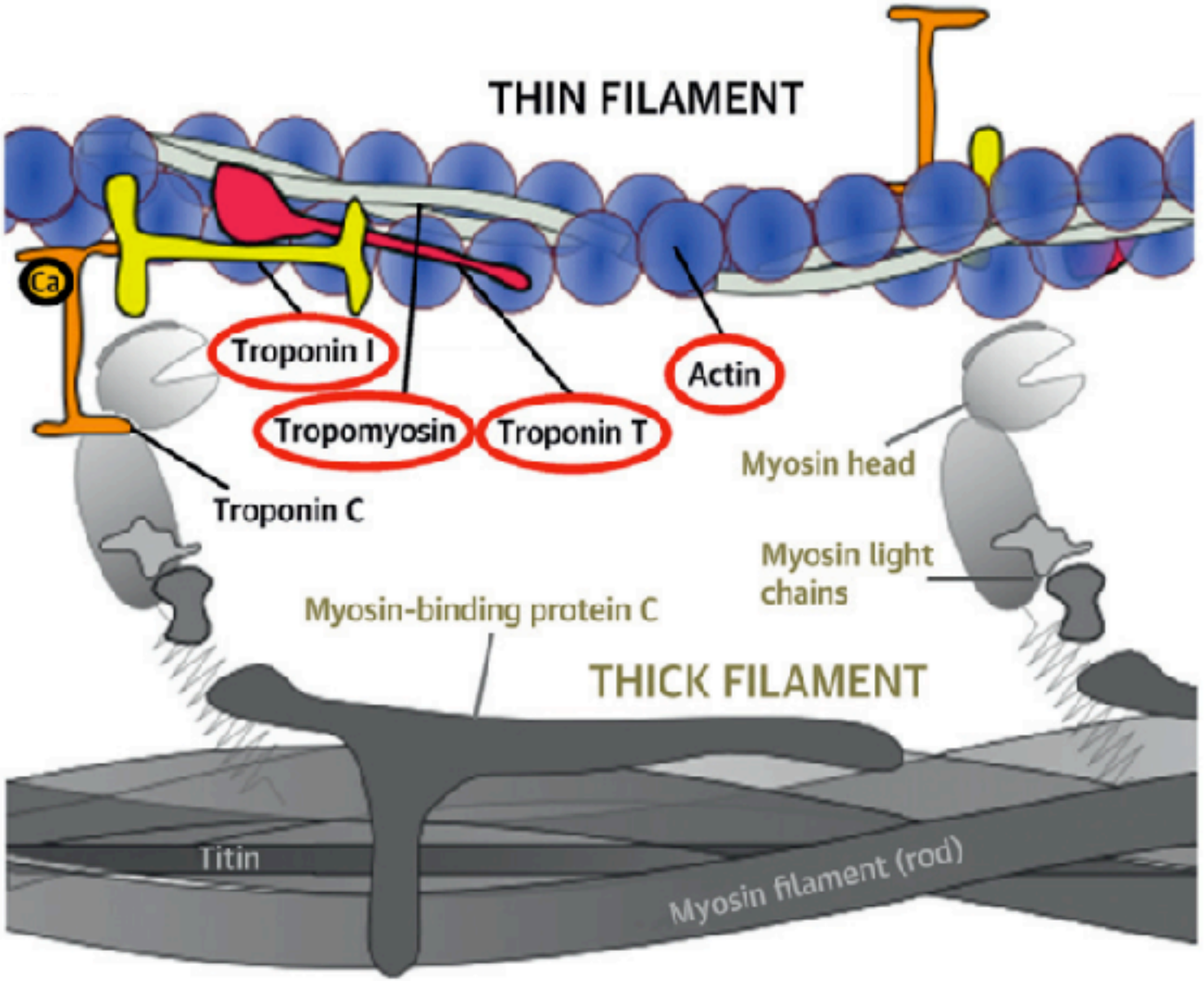




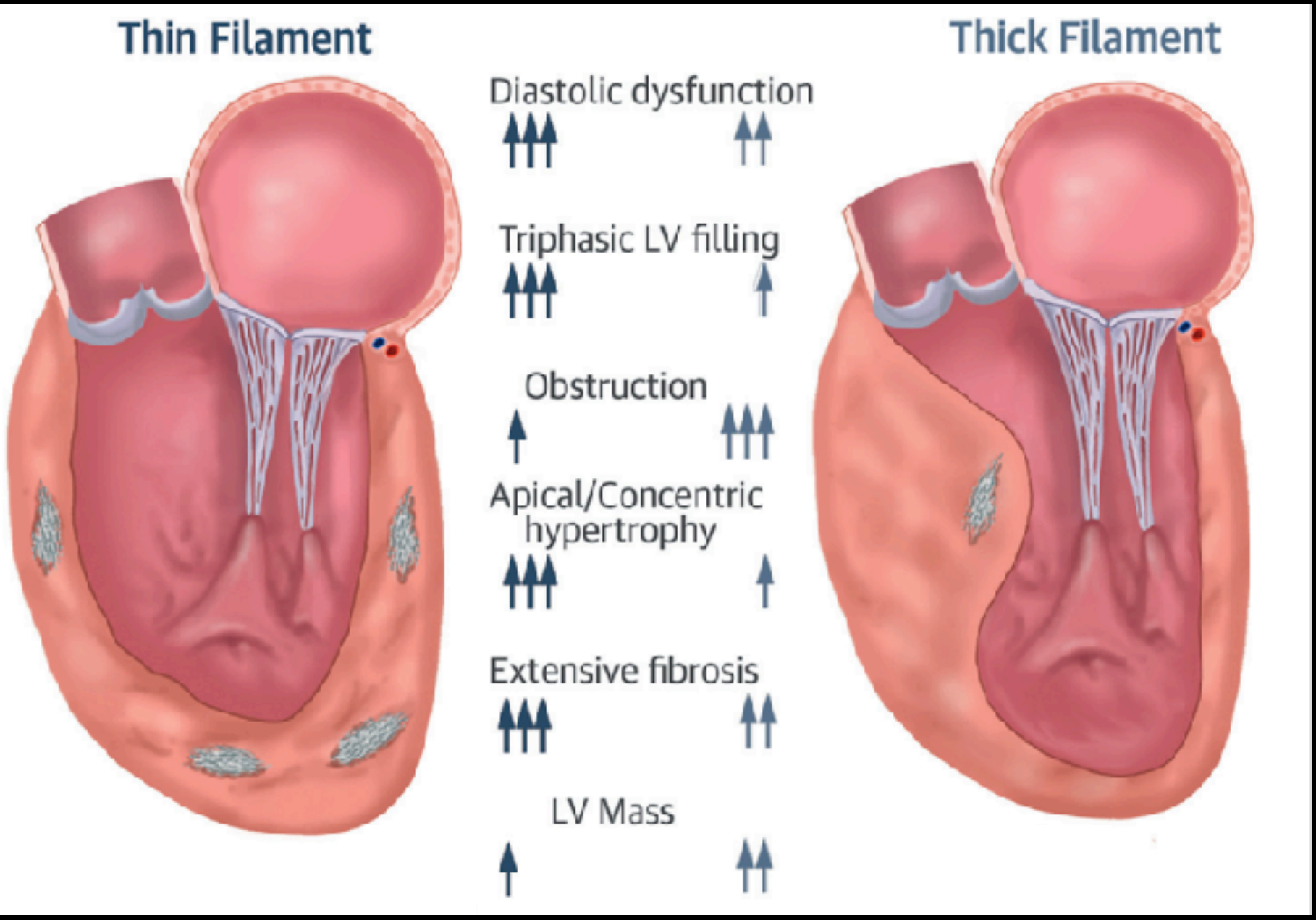
Br Heart J 1990;63:287-90

Mutation of sarcomeric protein

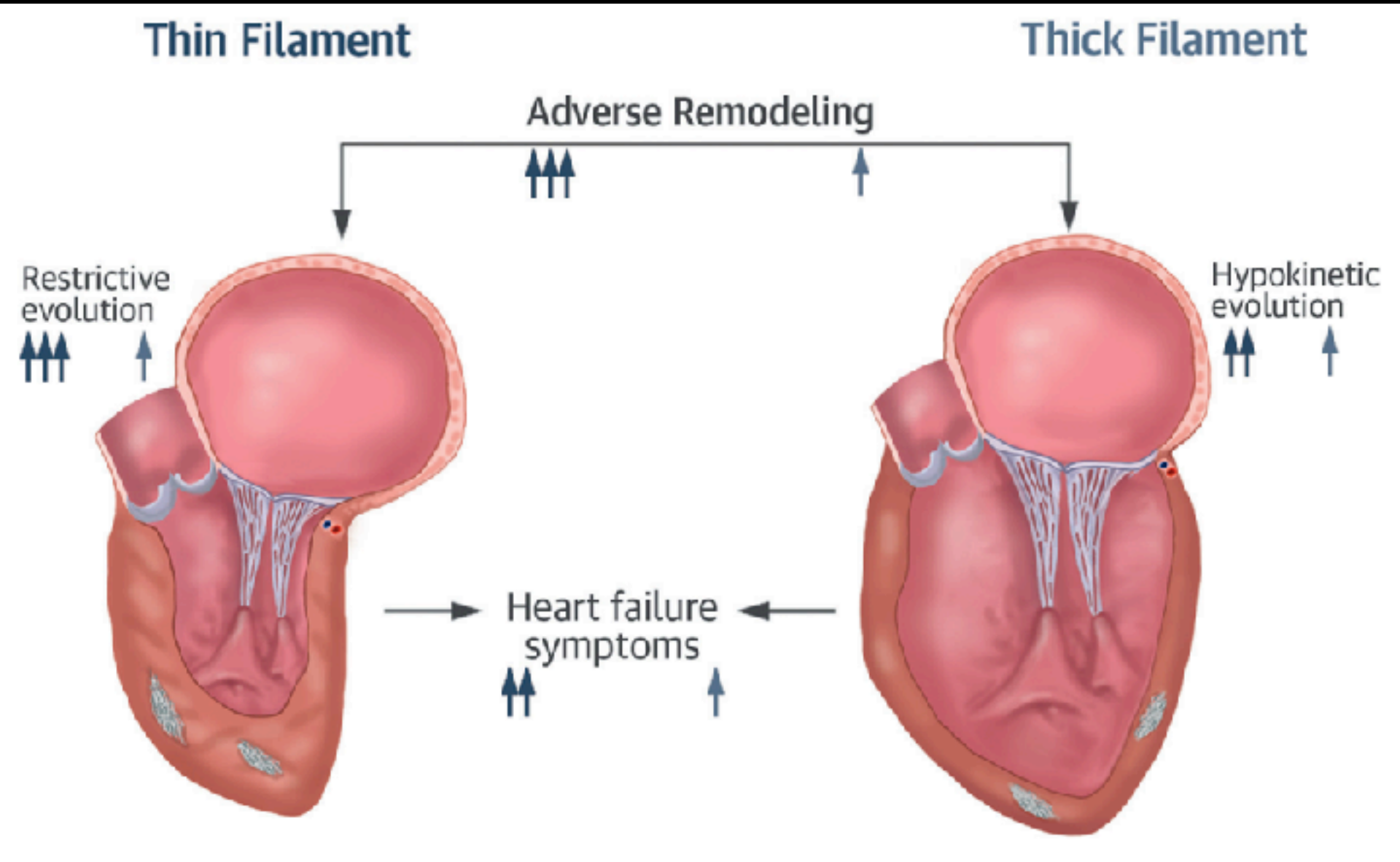




J Am Coll Cardiol. 2014 Dec 23;64(24):2589-600

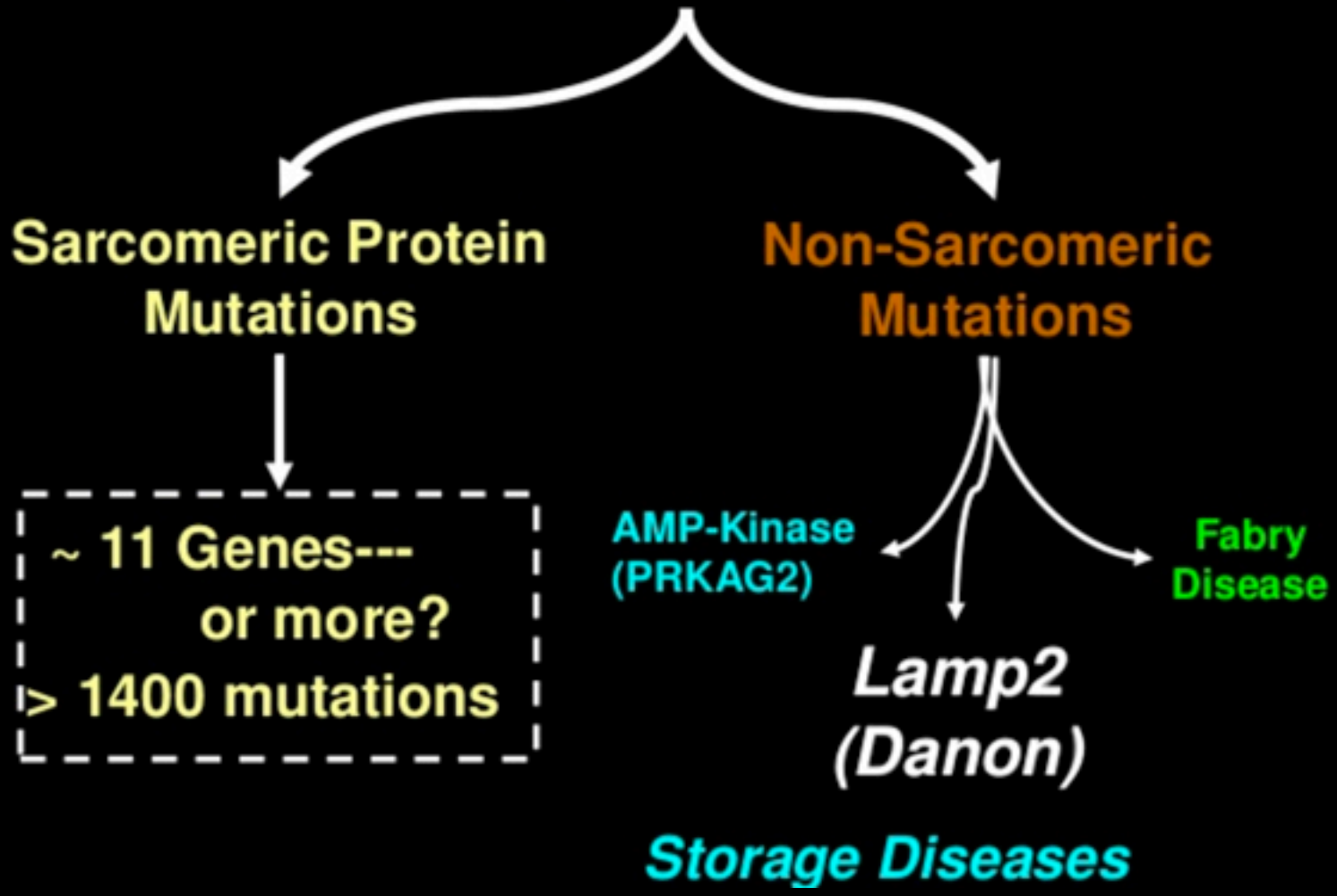


J Am Coll Cardiol. 2014 Dec 23;64(24):2589-600



J Am Coll Cardiol. 2014 Dec 23;64(24):2589-600

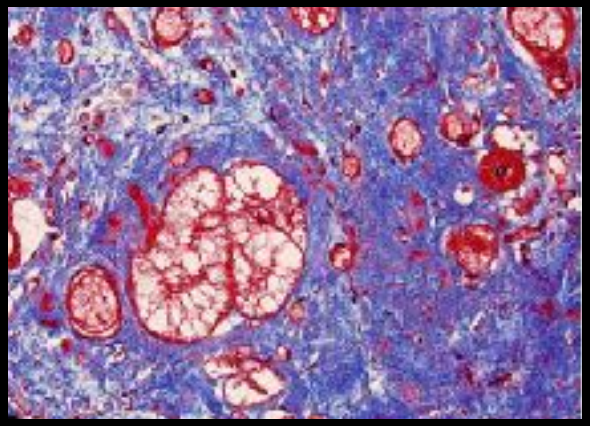
Unexplained LVH



Eur Heart J (2012) 33 (5): 649-656.

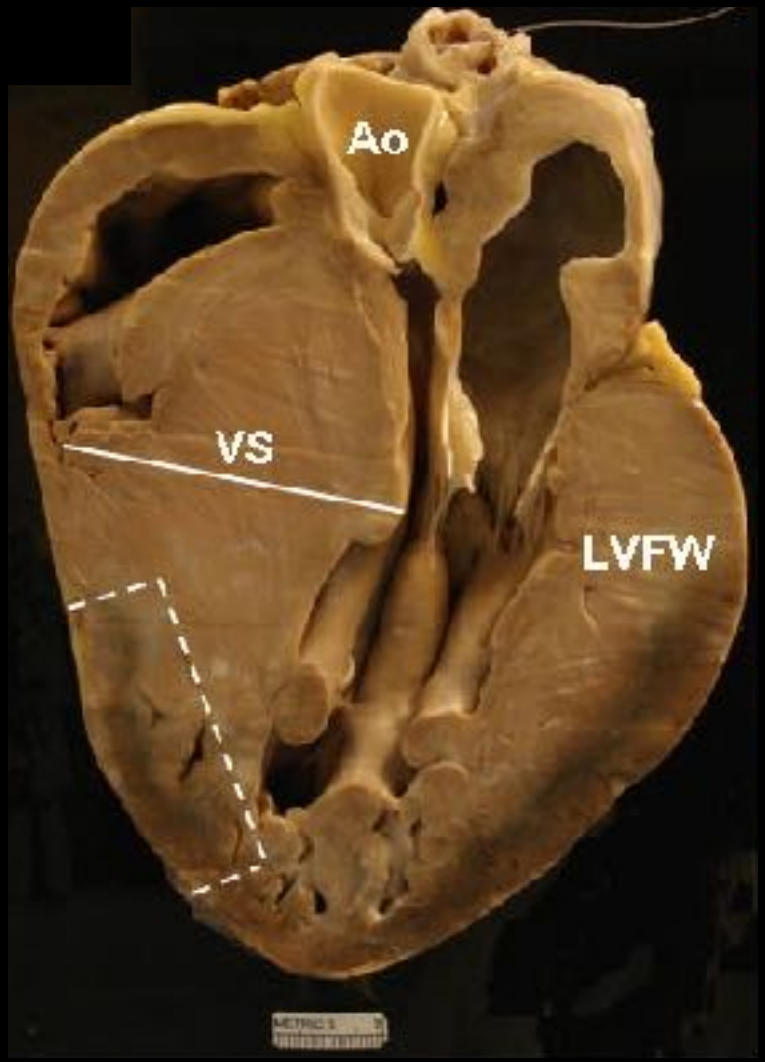
Danon Disease

- Rare X-linked dominant metabolic disorder
- Lysosome Associated Membrane Protein-2LAMP2 mutation
- Histology :Autophagic and vacuolated myocytes containing degraded lysosomal material
- Data from Danon registry
  - First symptoms 12 years
  - Transplant 18 years
  - Death without transplant 19 years
  - Survival beyond 25 years is uncommon



Genet Med , 2011, vol. 13 (pg. 563-568)

Danon Disease

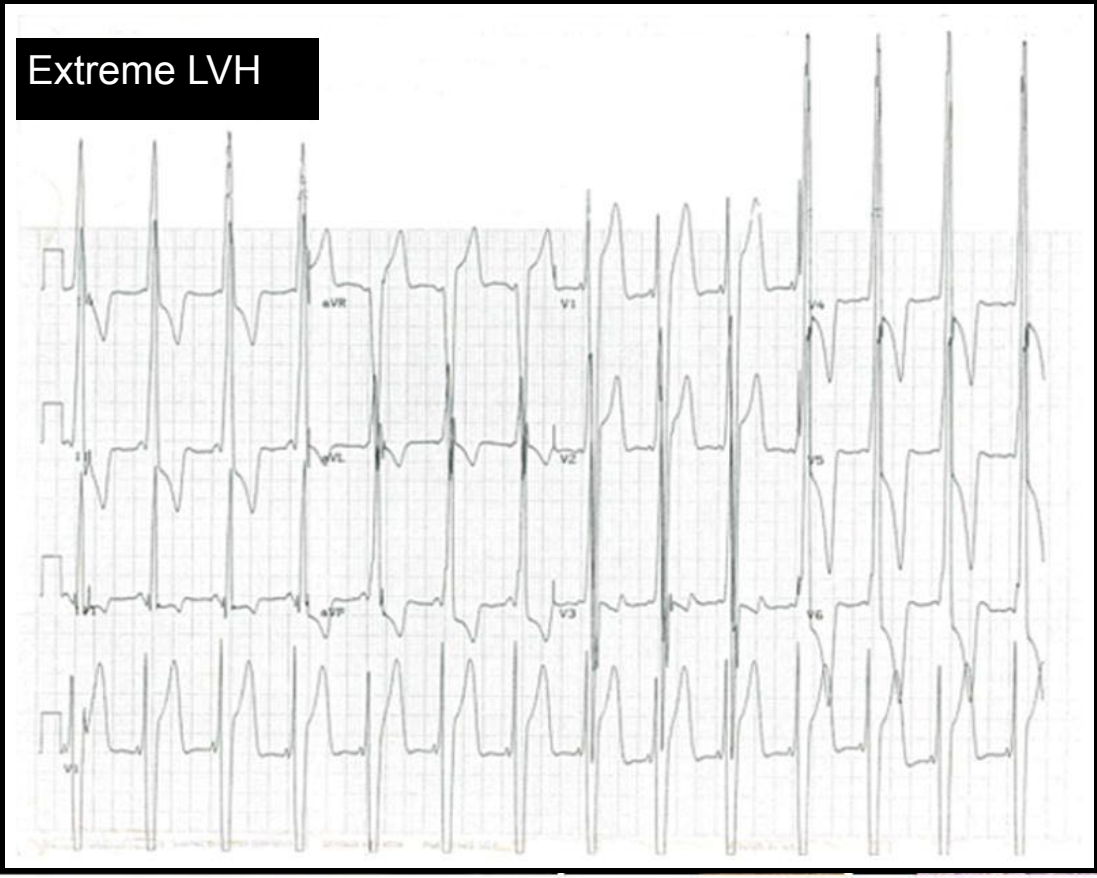


- Extreme concentric LVH (> 3cm)
- Followed by cavity dilation and systolic dysfunction with rapid deterioration to end-stage HF
- ECG: WPW, and/or extraordinary increases in pre-cordial voltages with T-wave inversion
- VA refractory to ICD shock
- Intellectual disability, skeletal myopathy

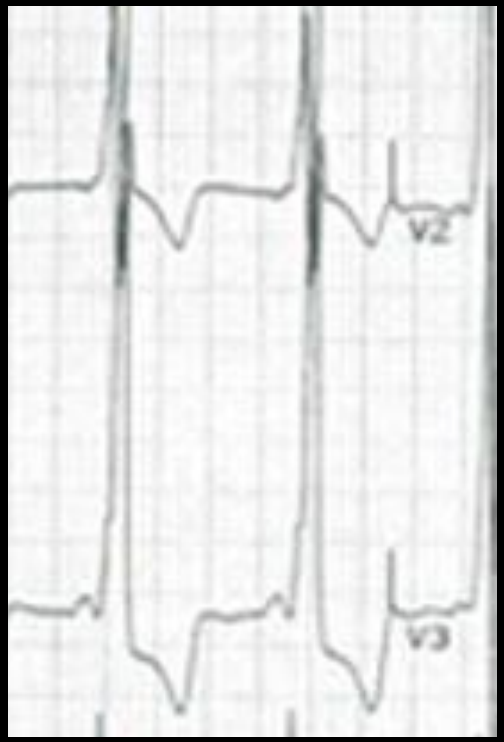
JAMA 2009;301(12):1253-1259

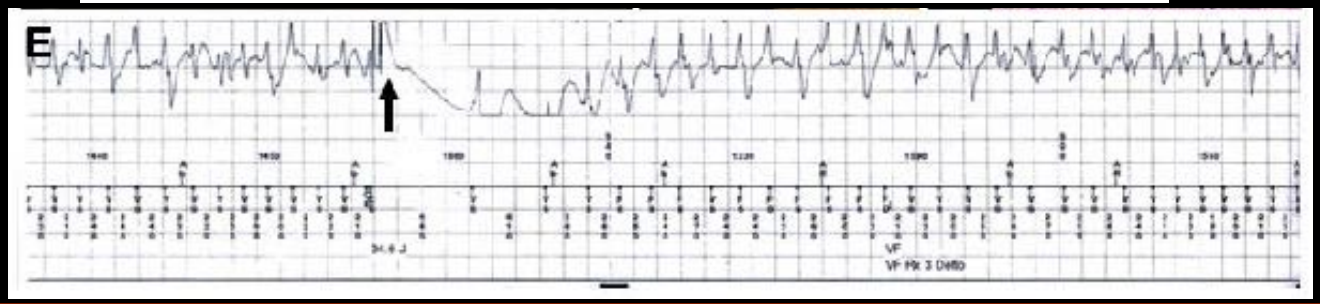
Danon Disease

Extreme LVH



with ventricular preexcitation





VA refractory
of ICD shock

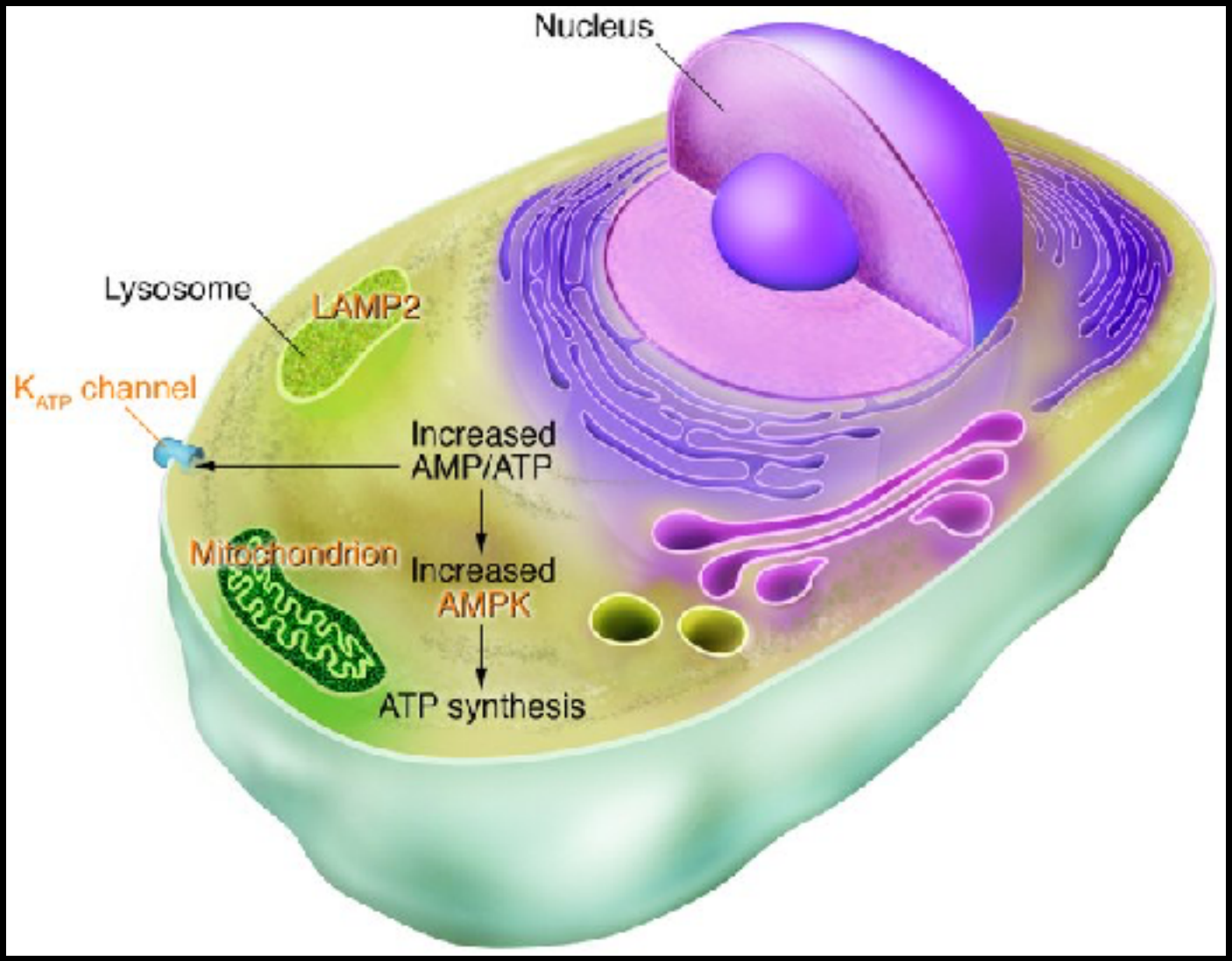
JAMA 2009;301(12):1253-1259

PRKAG2 Syndrome

- Autosomal dominant
- PRKAG2 gene encodes γ2 regulatory subunit of adenosine monophosphate (AMP)-activated protein kinase (AMPK)
- AMPK is a cardiac energy-sensing apparatus (regulating cellular glucose and fatty acid metabolic pathways)
- Mutation of AMPK subunit cause glycogen accumulation
- Produce phenocopy of HCM accompanied by WPW and progressive heart block

Genet Med , 2011, vol. 13 (pg. 563-568)

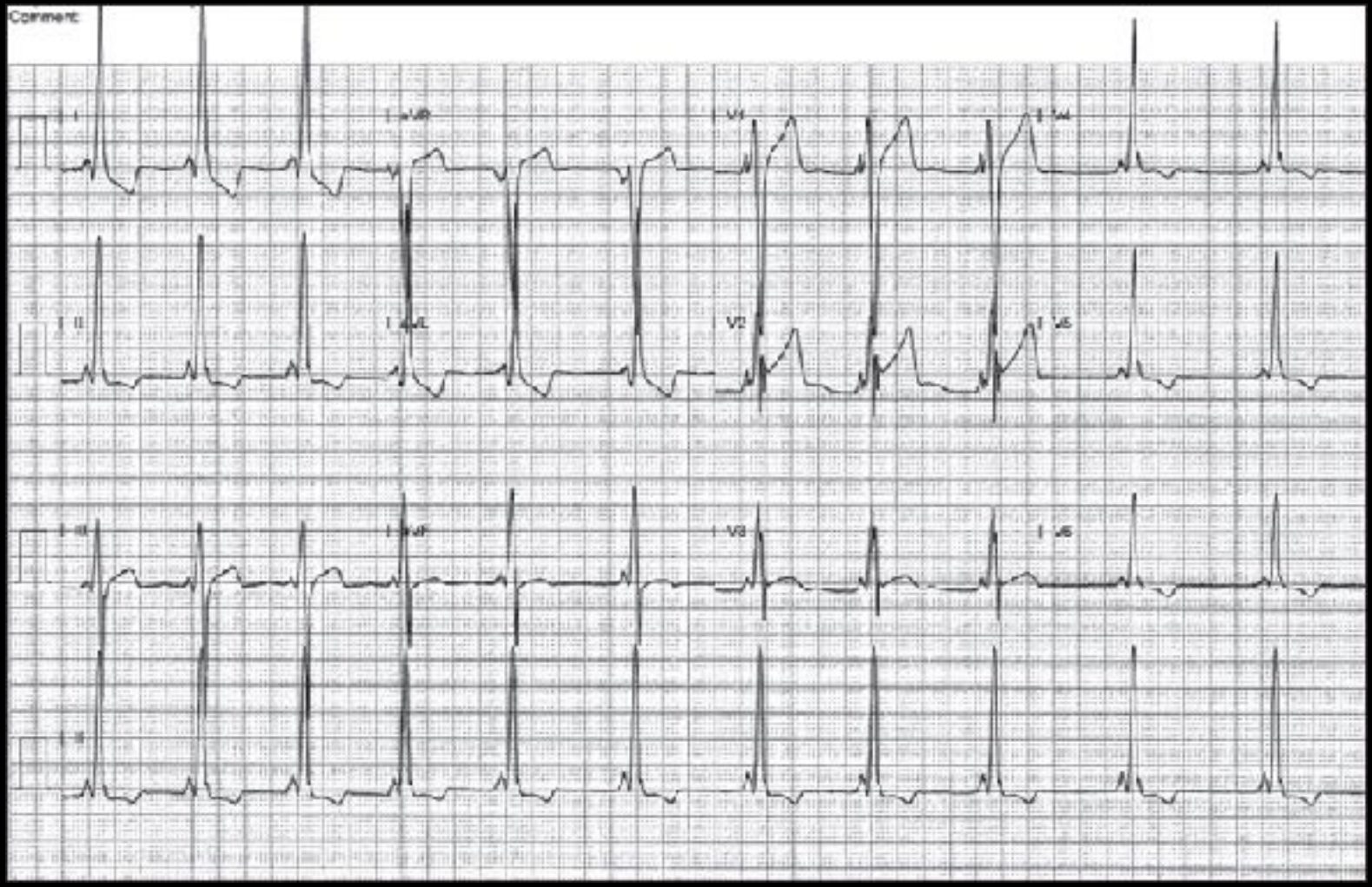
Human gene mutations affecting cardiac energetics and metabolism



Morita JCI. 2005;115: 518

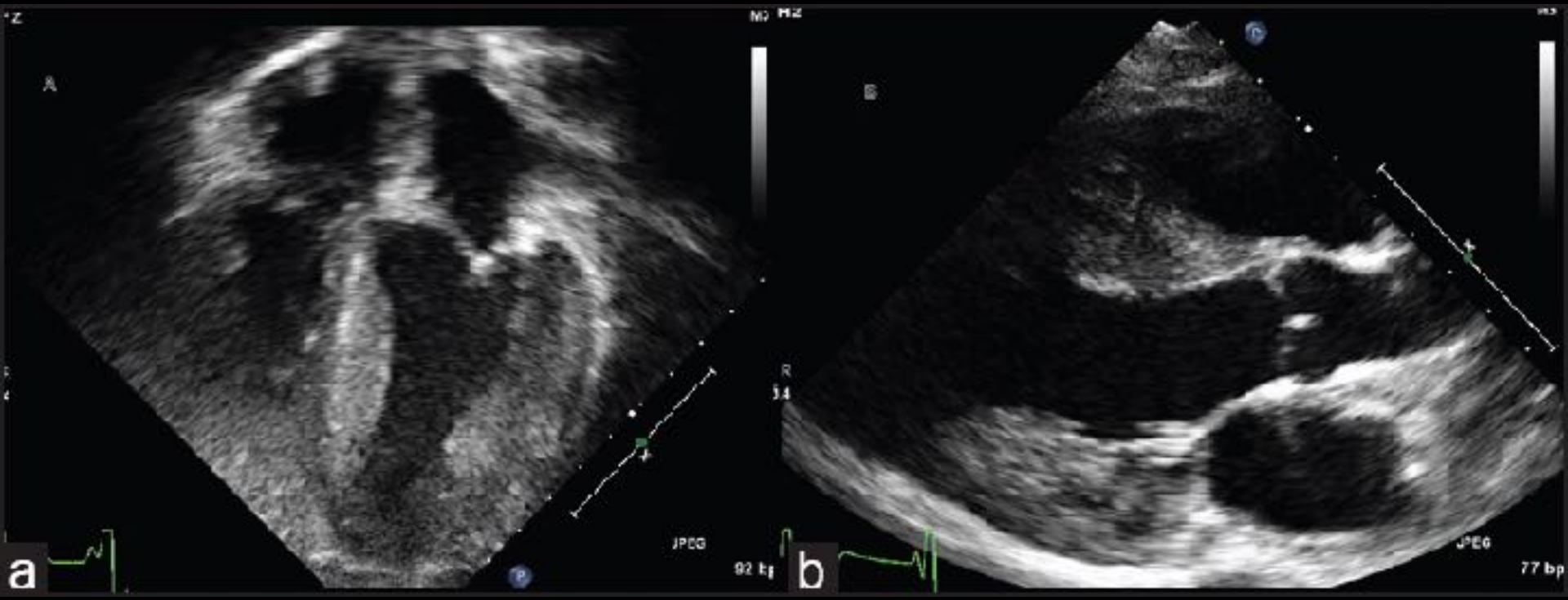
PRKAG2 Syndrome

LVH with ventricular pre-excitation



PRKAG2 Syndrome

Concentric LVH



PRKAG2 Syndrome

Post ablation day 1 showed persistent pre-excitation

The presence of ventricular pre-excitation is the result of cellular enlargement due to excessive glycogen content, resulting in the disruption of the normal development of the annulus fibrosus,