Cardiomyopathy: Etiology and Diagnosis

December 2010

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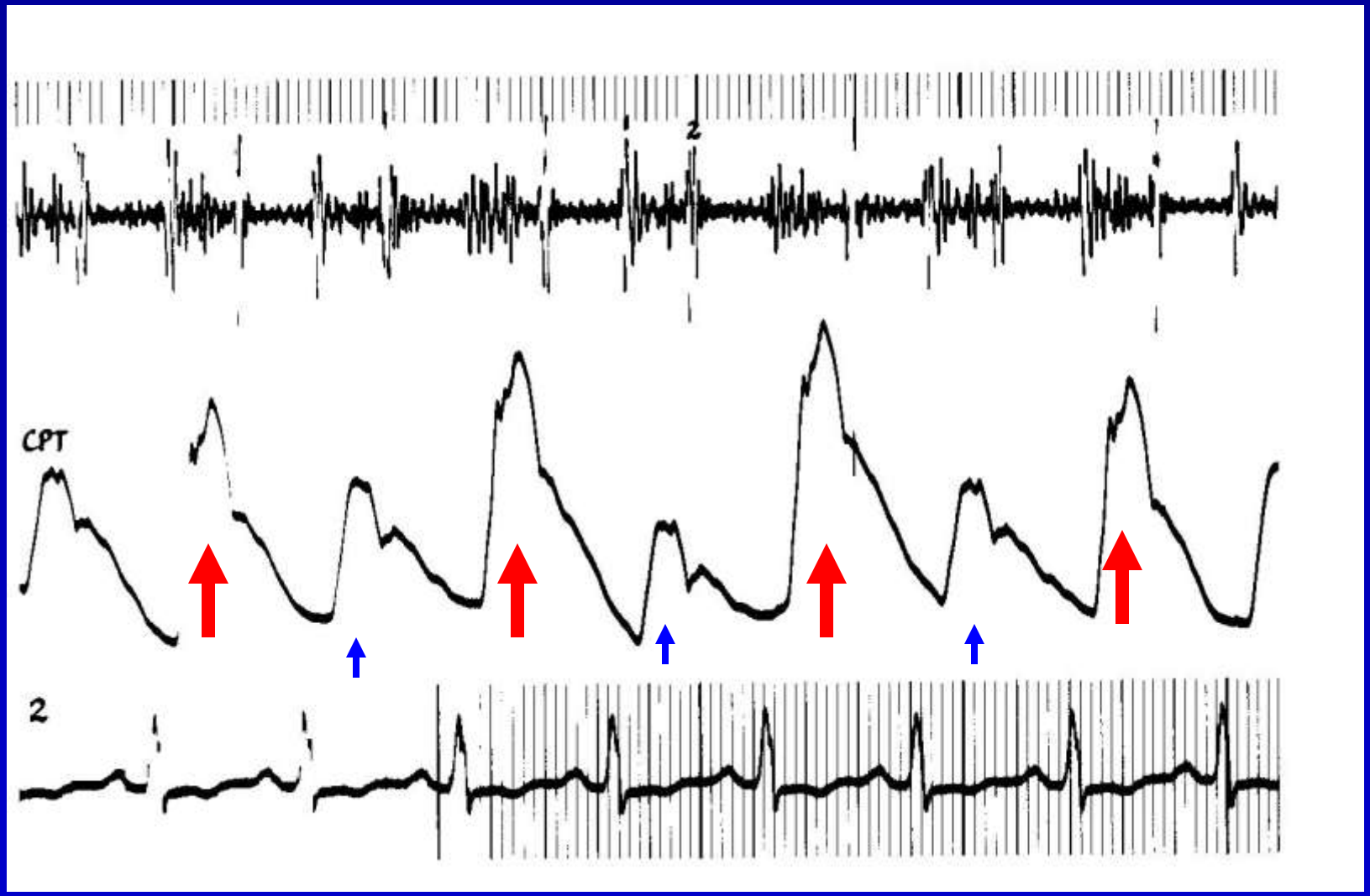
UTHSCSA and STVHCS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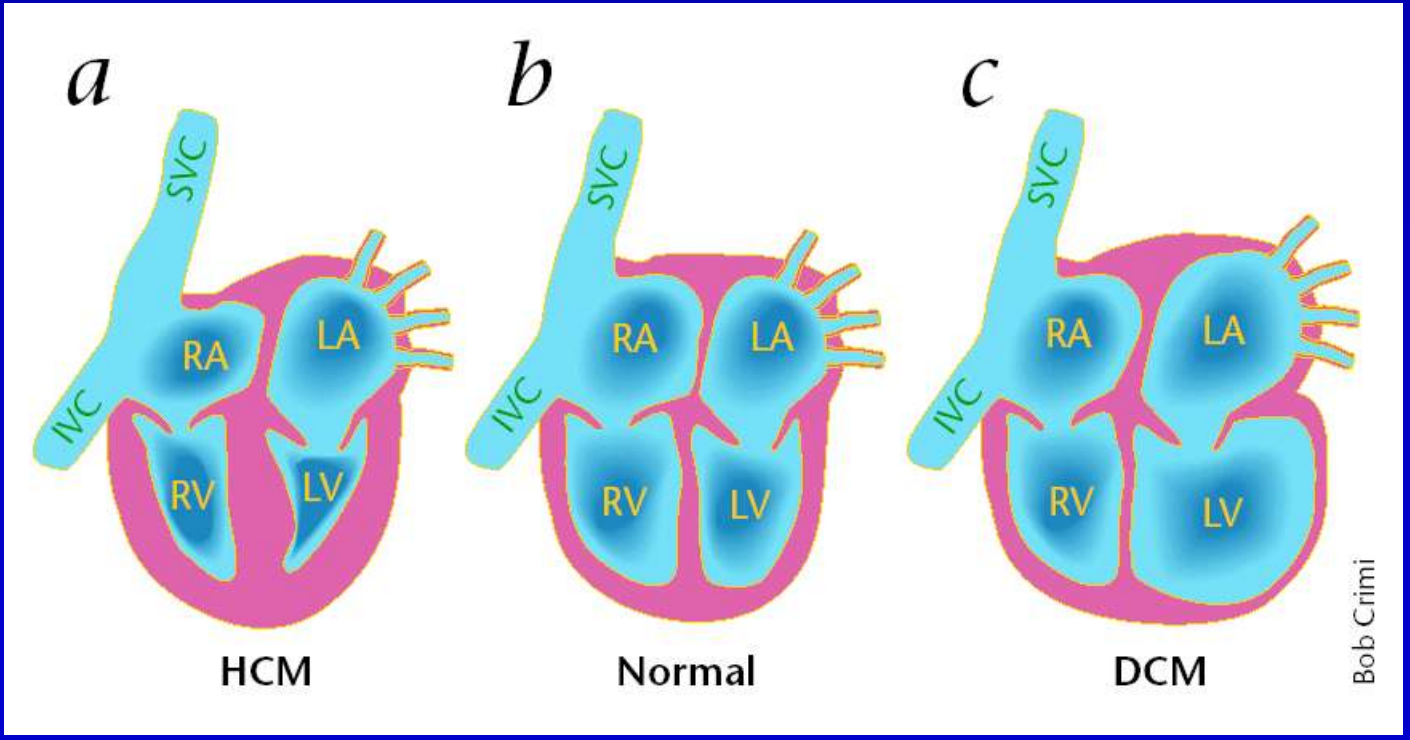
Cardiomyopathy –Morphologic Categories

- Dilated
- Hypertrophic
- Restrictive

Braunwald's Heart Dz, 8th ed, 2008; p. 1739.

Response of the Heart to Genetic Disorders

- Physiologic response:
  - Hypertrophy (FHCM)
  - Dilation (familial DCM, diffuse loss of myocytes and fibrosis)
  - Both
- Clinical disorders:
  - HCM
  - DCM
  - Restr CM



Nature Med 1999;5:266.

Dilated Cardiomyopathies

- Familial/genetic
- Viral/immune
- Alcohol/toxic
- Unknown

Braunwald's Heart Dz, 8th ed, 2008; p. 1740.

Restrictive Cardiomyopathies

- Idiopathic
- Infiltrative

Braunwald's Heart Dz, 8th ed, 2008; p. 1740.

Cardiomyopathy Etiologic Categories

Specific Cardio-myopathies

- Ischemic
- Valvular
- Hypertensive
- Inflammatory - myocarditis
- Metabolic
- General systemic disease
- Muscular Dystrophies
- Neuromuscular disorders
- Sensitivity and Toxic reactions
- Peripartum cardiomyopathy

Braunwald's Heart Dz, 8th ed, 2008; p. 1740.

Metabolic Cardio-myopathies

- Endocrine Abnormalities
- Glycogen storage disease
- Deficiencies (hypokalemia)
- Nutritional disorders

Braunwald's Heart Dz, 8th ed, 2008; p. 1740.

General Systemic Cardio-myopathies

- Connective tissue diseases
- Infiltrative diseases
  - Sarcoidosis
  - Leukemia

Muscular Dystrophies

- Duchenne/Becker muscular dystrophy
- Myotonic dystrophy
- Emery-Dreifuss muscular dystrophy

Braunwald's Heart Dz, 8th ed, 2008; p. 1740, 2142.

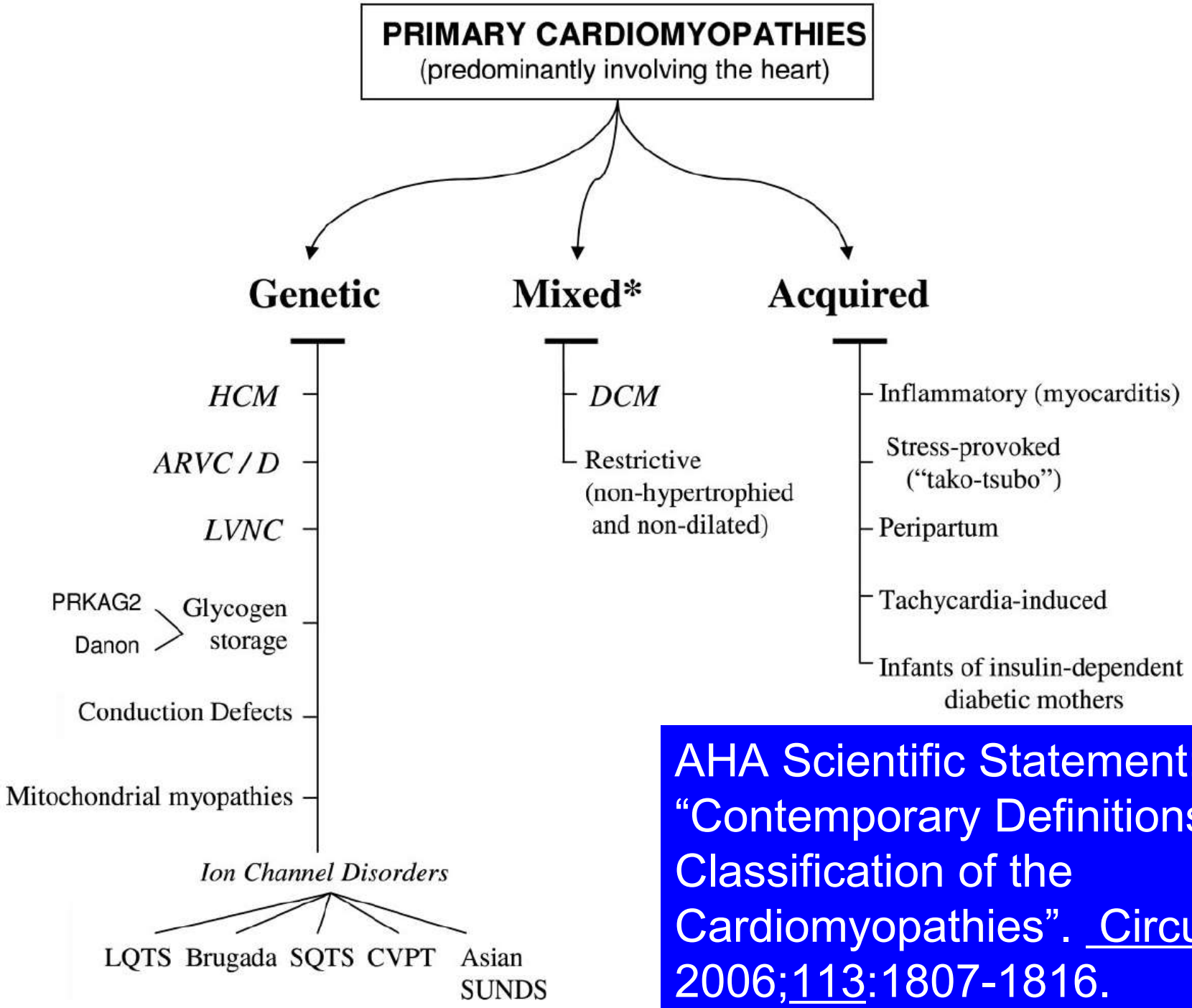
Neuro-muscular Disorders

- Friedreich's ataxia
- Noonan syndrome
- Lentiginosis

Sensitivity and Toxic Reactions

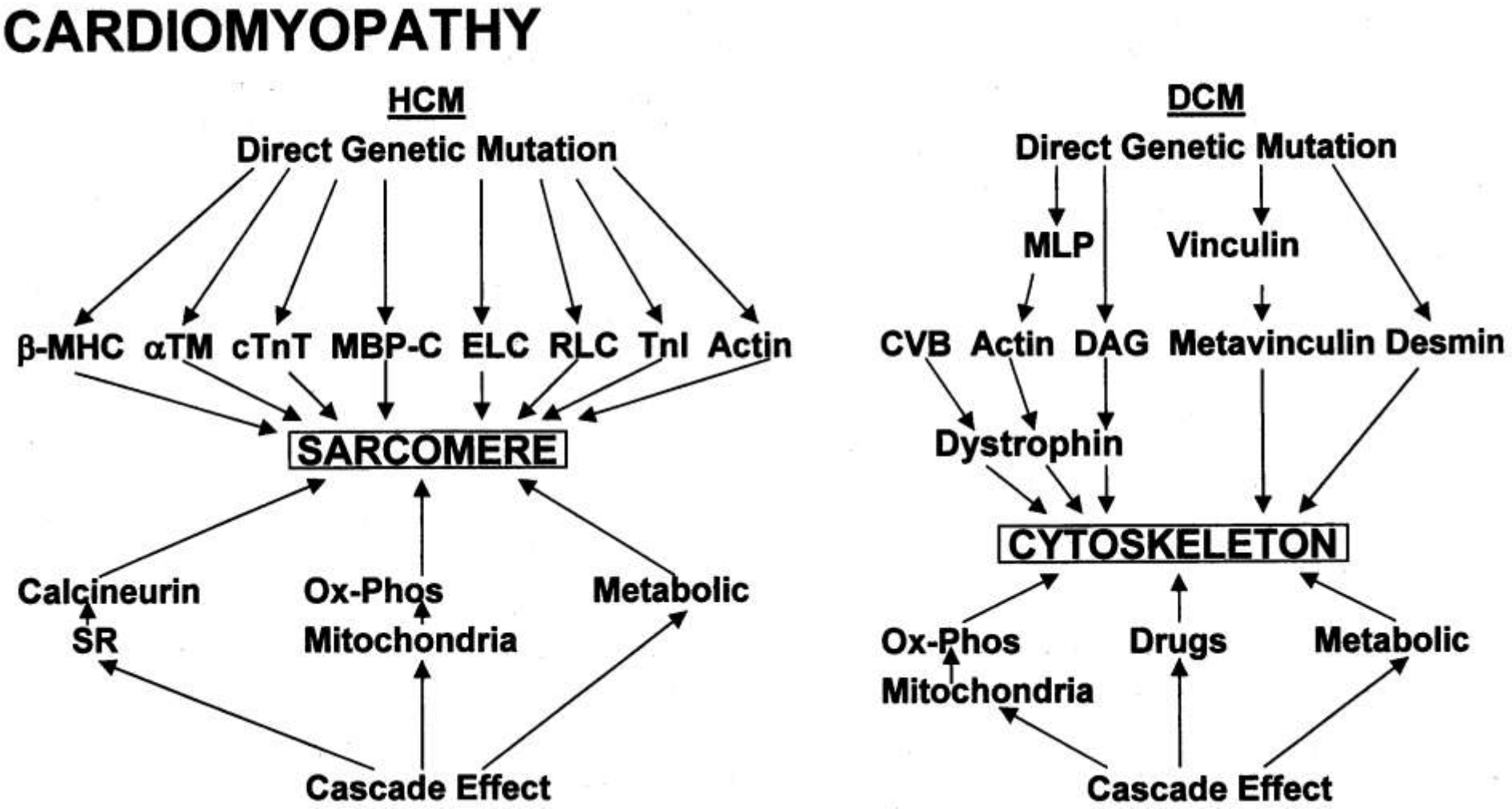
- Alcohol
- Catecholamine
- Anthracyclines
- Irradiation
- Others

Braunwald's Heart Dz, 8th ed, 2008; p. 1740.



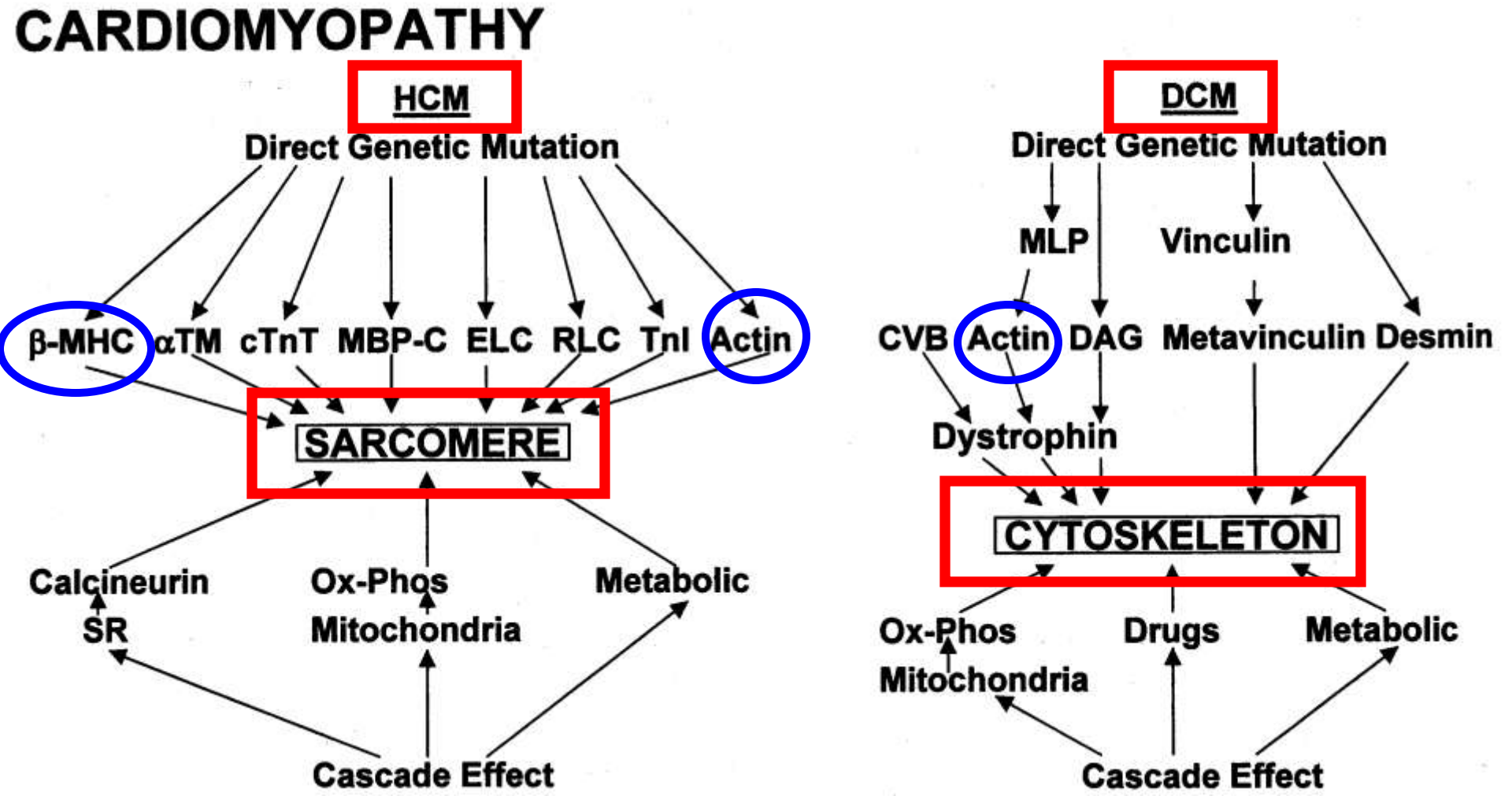
AHA Scientific Statement: "Contemporary Definitions and Classification of the Cardiomyopathies". Circulation. 2006;113:1807-1816.

Cardiomyopathy: Unifying Hypothesis



Hurst, 10th Ed, 2001, p. 1800

Cardiomyopathy: Unifying Hypothesis

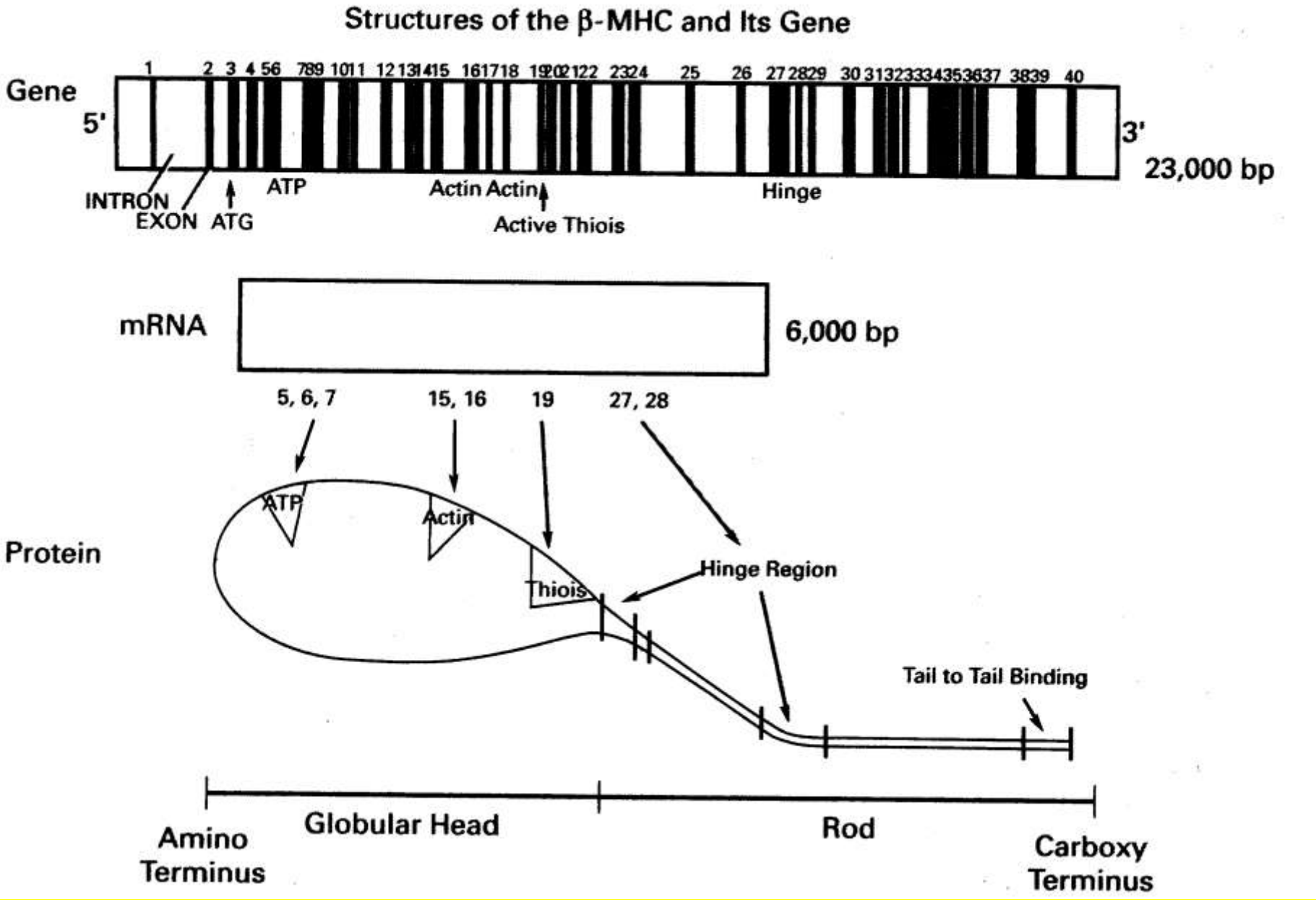


Hurst, 10th Ed, 2001, p. 1800

This hypothesis breaks down many places.

Update: Familial HCM

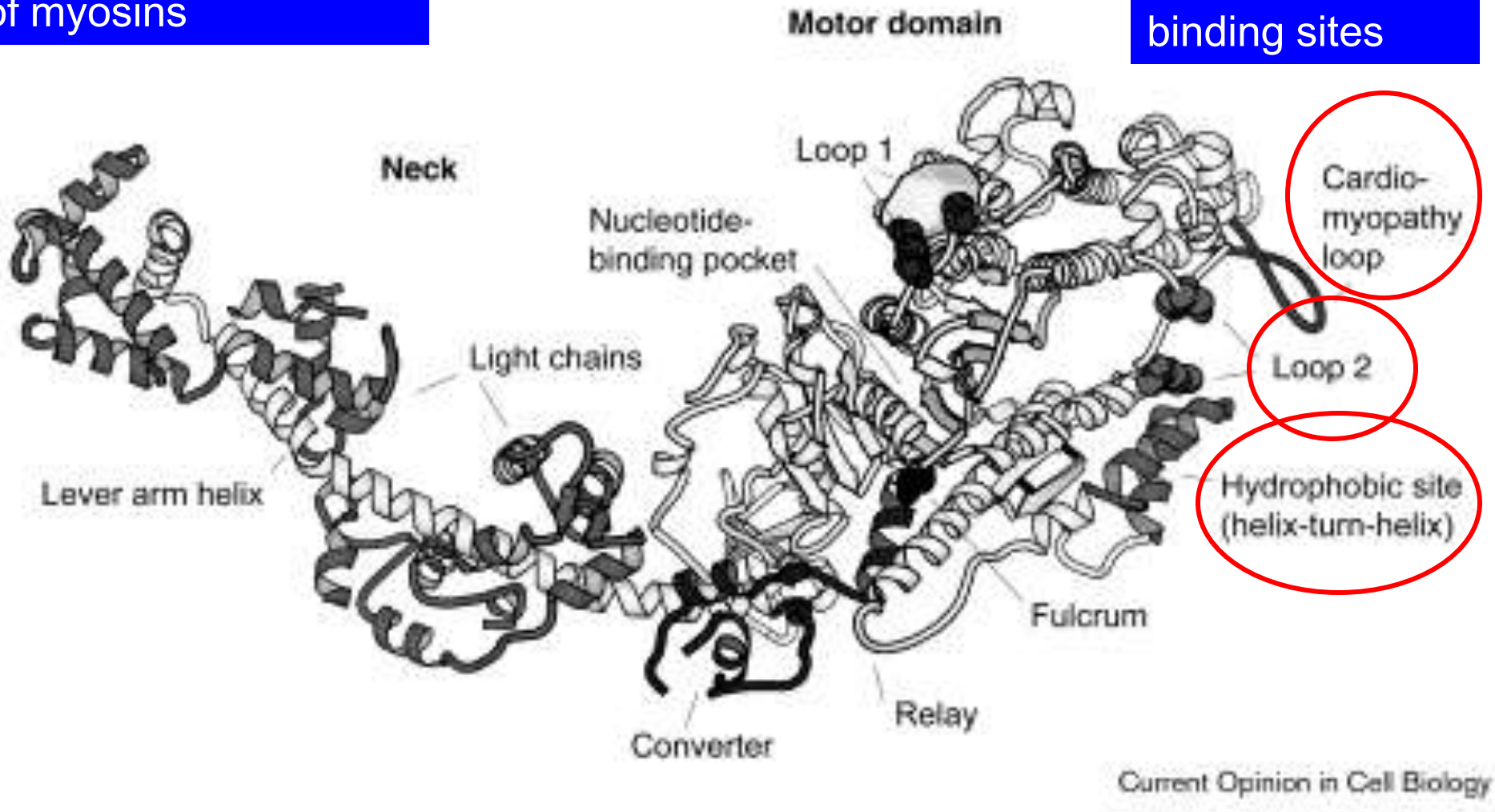
- Cause: always genetic in adults
- Some inherited, some *de novo* mutation
- Single-gene disorder
- Autosomal-dominant
- 11 genes, each for a sarcomeric protein
- Over 600 mutations, most single-point missense mutation



Hurst, 10th Ed, 2001, p. 1794

There are 15 classes of myosins

Tentative Actin-binding sites

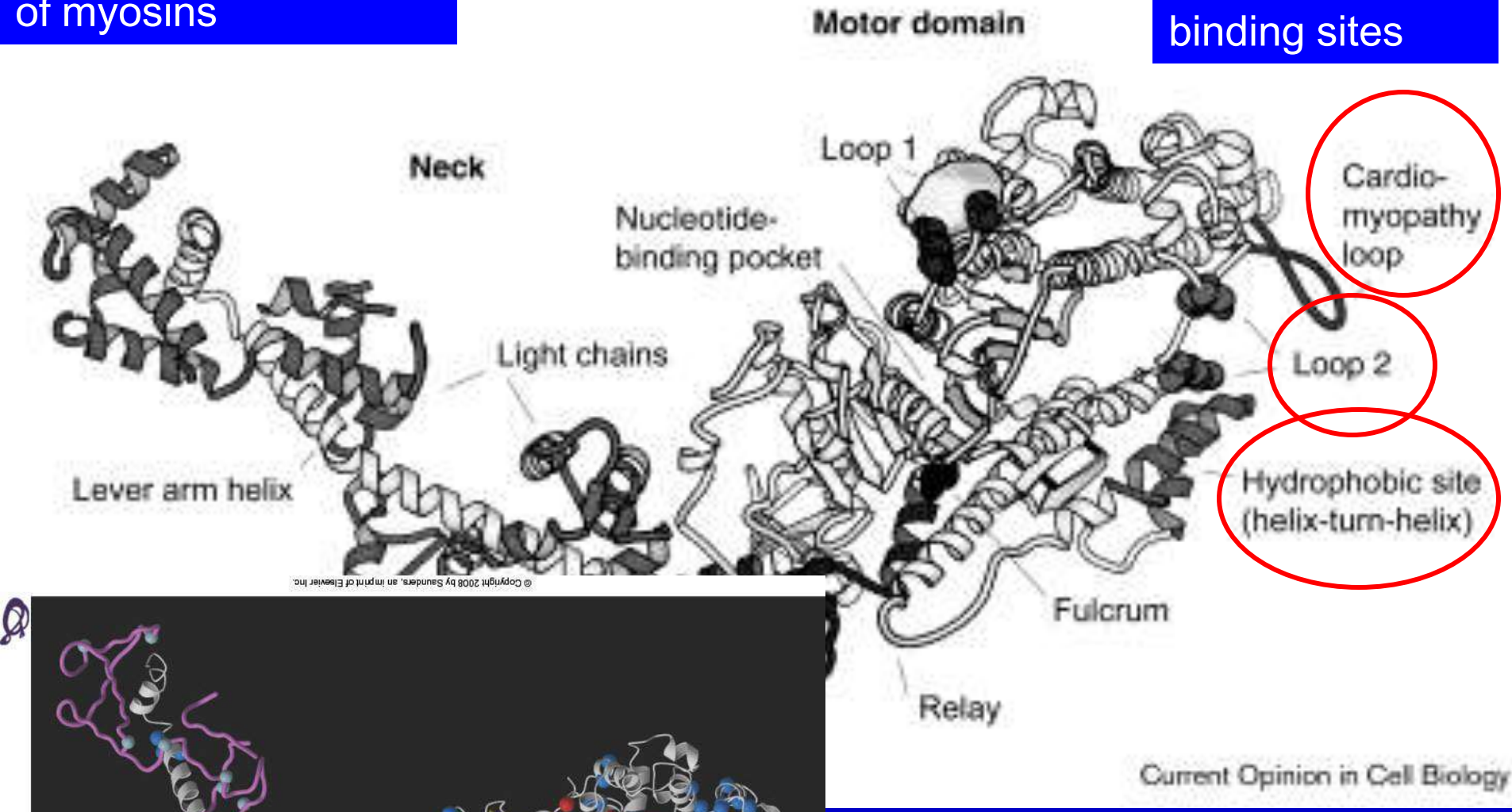


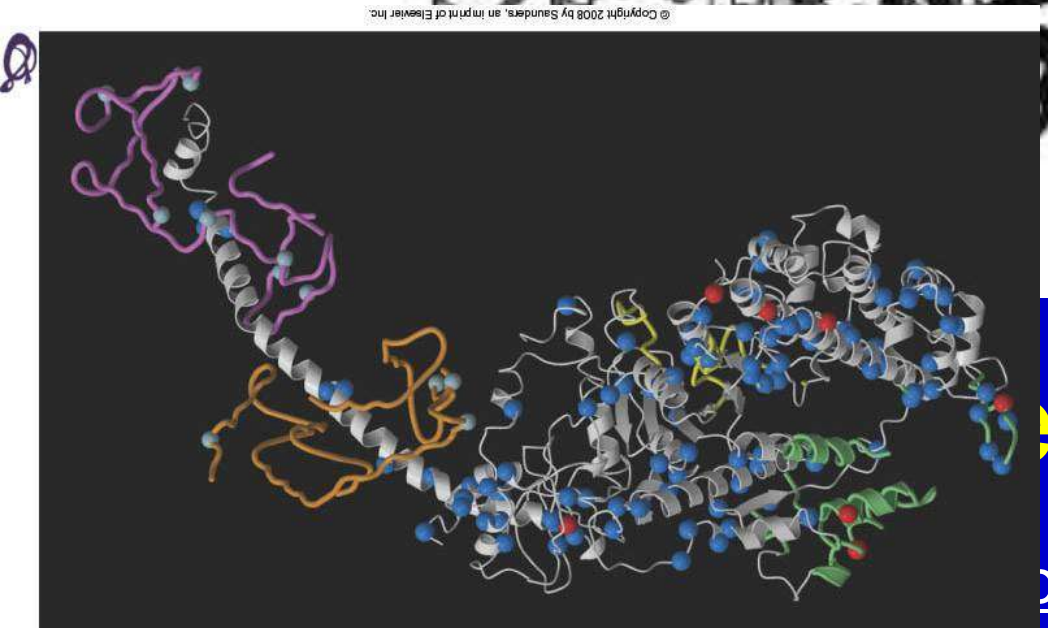
Chicken Skeletal Myosin

Volkmann N et al. Curr Opin Cell Biol 2000;12:26

There are 15 classes of myosins

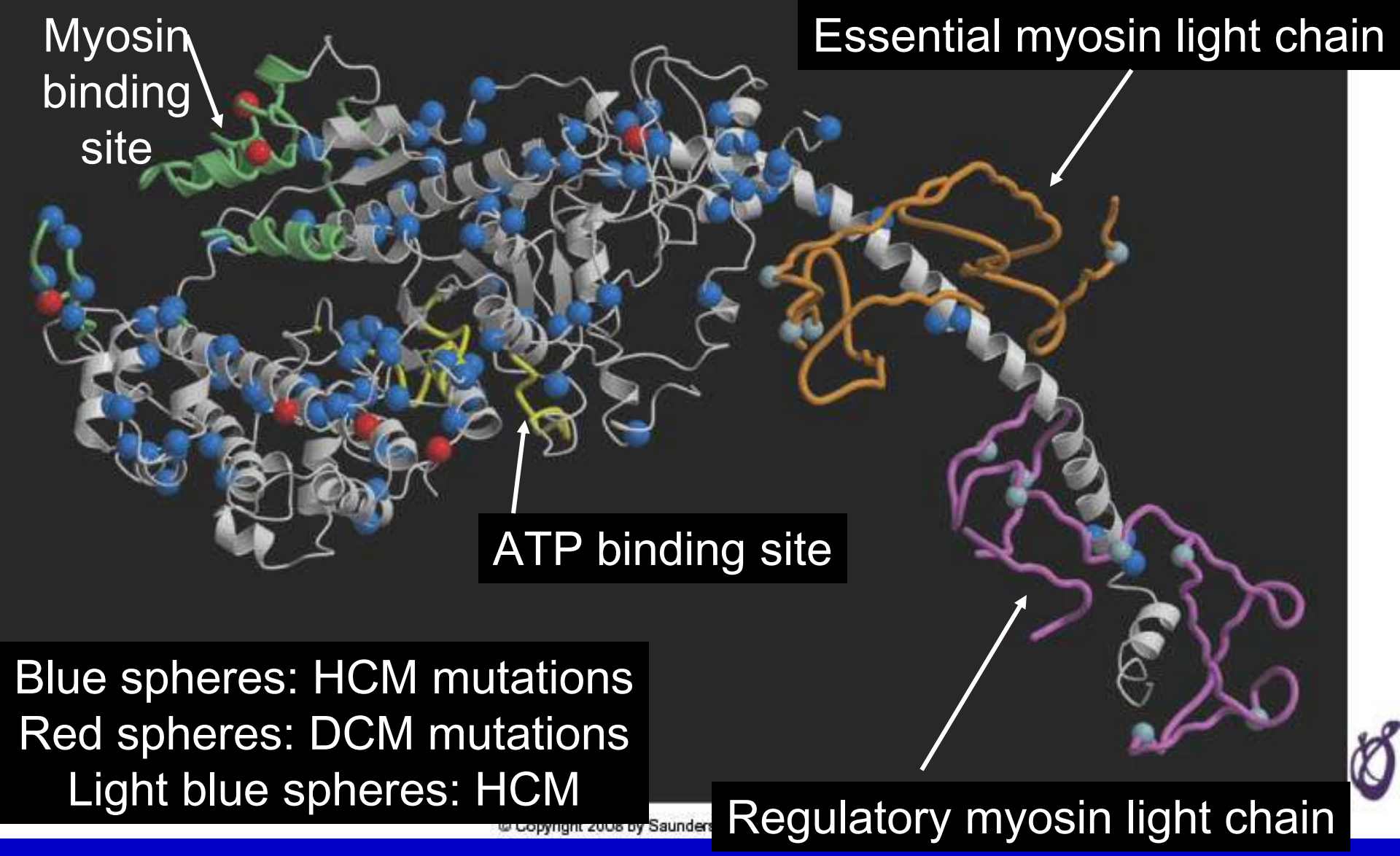
Tentative Actin-binding sites





etal Myosin

ol 2000;12:26



Myosin

Braunwald's Heart Disease, 8th ed, p. 116, 2008.

Update: Familial HCM - 2

- HCM is the most common cause of SCD in the young
- Prevalence: 1 in 500
- Symptoms: dyspnea, then chest pain, then syncope/presyncope/SCD
- Murmurs: midsystolic LV ejection murmur and mitral regurgitation, characteristic response to maneuvers
- ECG often with LVH
- Echocardiography is confirmatory IVS >1.3cm without other cause

Roberts R, Sigwart U. Circulation 2001;104:2113

Update: Familial HCM - 3

- Dominant mode of inheritance indicates that the abnormal protein poisons the effect of the normal protein
- Basic science studies: mutations in the contractile apparatus impair contractility and induce release of growth factors and stimulate hypertrophy and fibrosis, with sarcomere disarray as the hallmark of the phenotype

Roberts R, Sigwart U. Circulation 2001;104:2113

Update: Familial HCM - 4

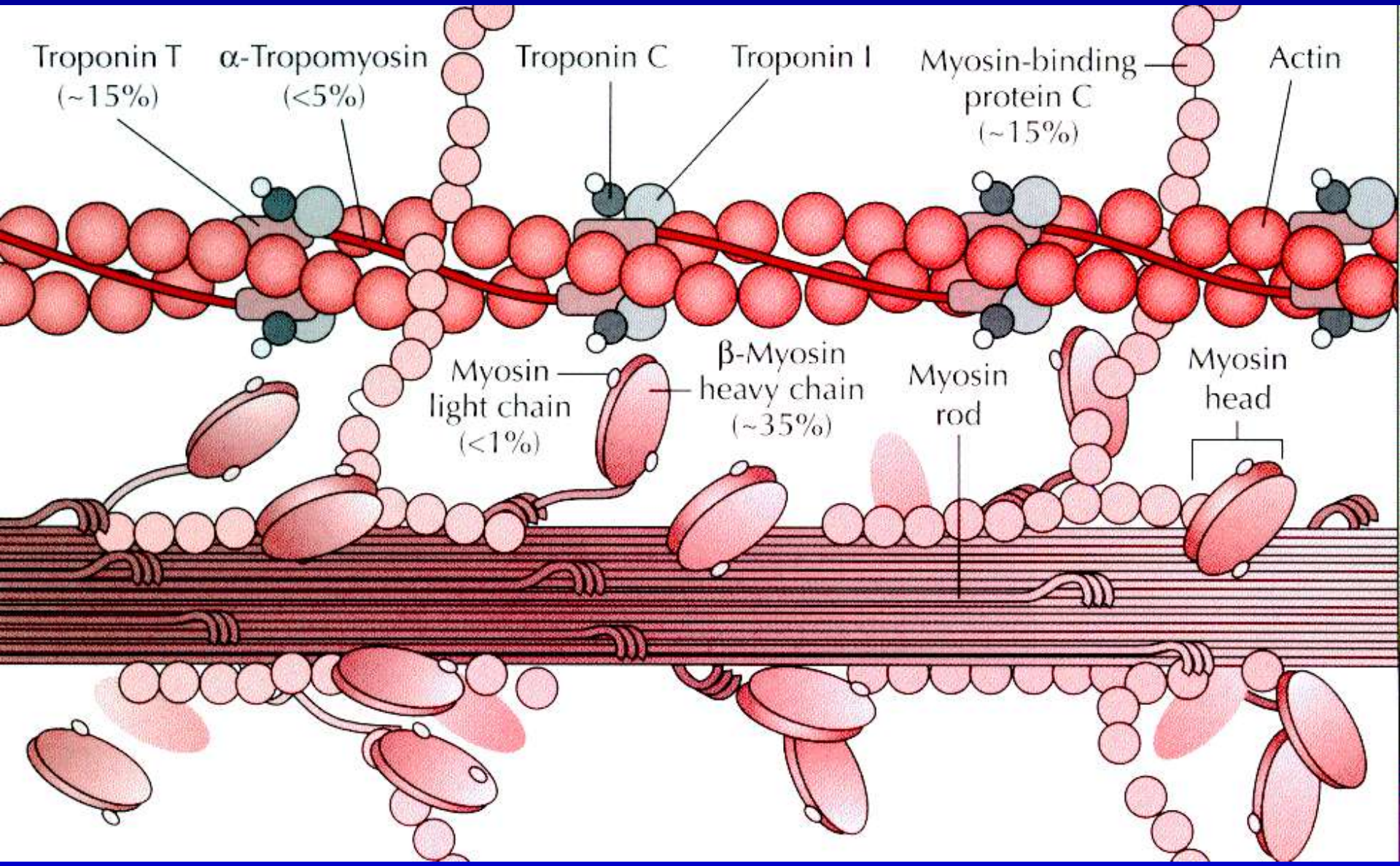
TABLE 10–1 Gene Mutations in Cardiac Hypertrophy

Locus	Symbol	Name	Function
1q32	*TNNT2*	Cardiac troponin T	Sarcomere
2q31	*TTN*	Titin	Sarcomere
3p21	*MYL3*	Essential myosin light chain	Sarcomere
3p21-p14	*TNNC1*	Cardiac troponin C	Sarcomere
11p11.2	*MYBPC3*	Cardiac myosin binding protein C	Sarcomere
12q23-q24	*MYL2*	Regulatory myosin light chain	Sarcomere
14q12	*MYH7*	Beta-myosin heavy chain	Sarcomere
14q12	*MYH6*	Alpha-myosin heavy chain	Sarcomere
15q14	*ACTC*	Cardiac actin	Sarcomere
15q22	*TPM1*	Alpha-tropomyosin	Sarcomere
19p13.2	*TNNI3*	Cardiac troponin I	Sarcomere
7q36	*PRKAG2*	Protein kinase, AMP-activated, noncatalytic, gamma-2	Metabolism
Xq22	*GLA*	Alpha-galactosidase A	Lysosome, metabolism
Xq24	*LAMP2*	Lysosome-associated membrane protein B	Lysosome, metabolism

AMP = adenosine monophosphate.

Braunwald's Heart Disease, 8th ed, p. 116, 2008.

Genetics of HCM

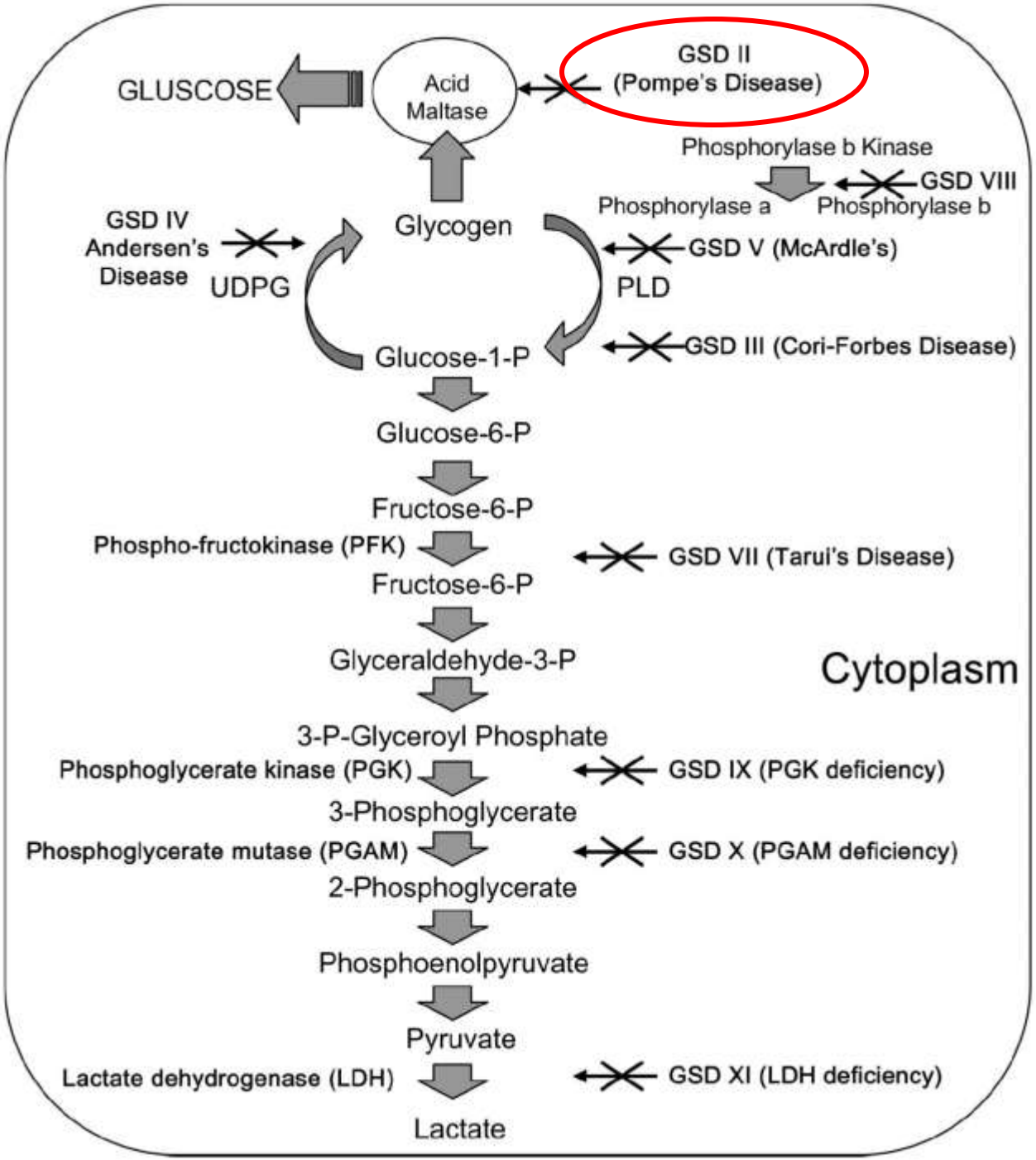


Colucci WS et al. Atlas of Heart Failure 2nd ed. 1999

Endocrinopathies

- Acromegaly – LVH and DCM
- Cushing – LVH and DCM
  - Carney complex: LA myxoma and pigmented skin lesions, genetic 17Q2
- Hyperthyroidism – afib beta blocker
- Hypothyroidism – effusion
- Pheo – HF

Glycogen Storage Diseases



Van Adel BA et al. "Metabolic Myopathies", J Clin Neuromusc Dis. 2009;10:97-121.

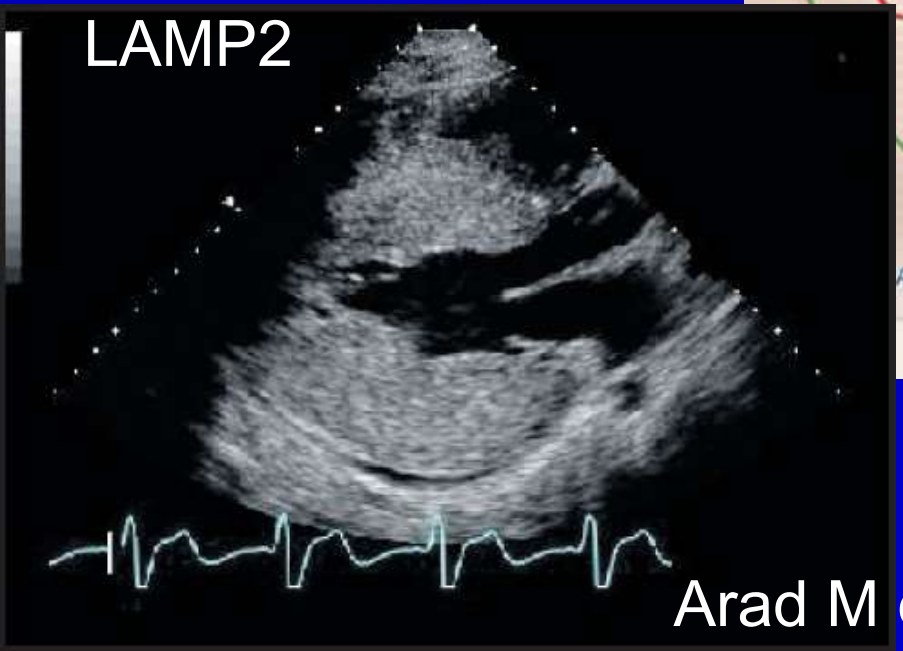
Metabolic Disorders Producing HCM - 1

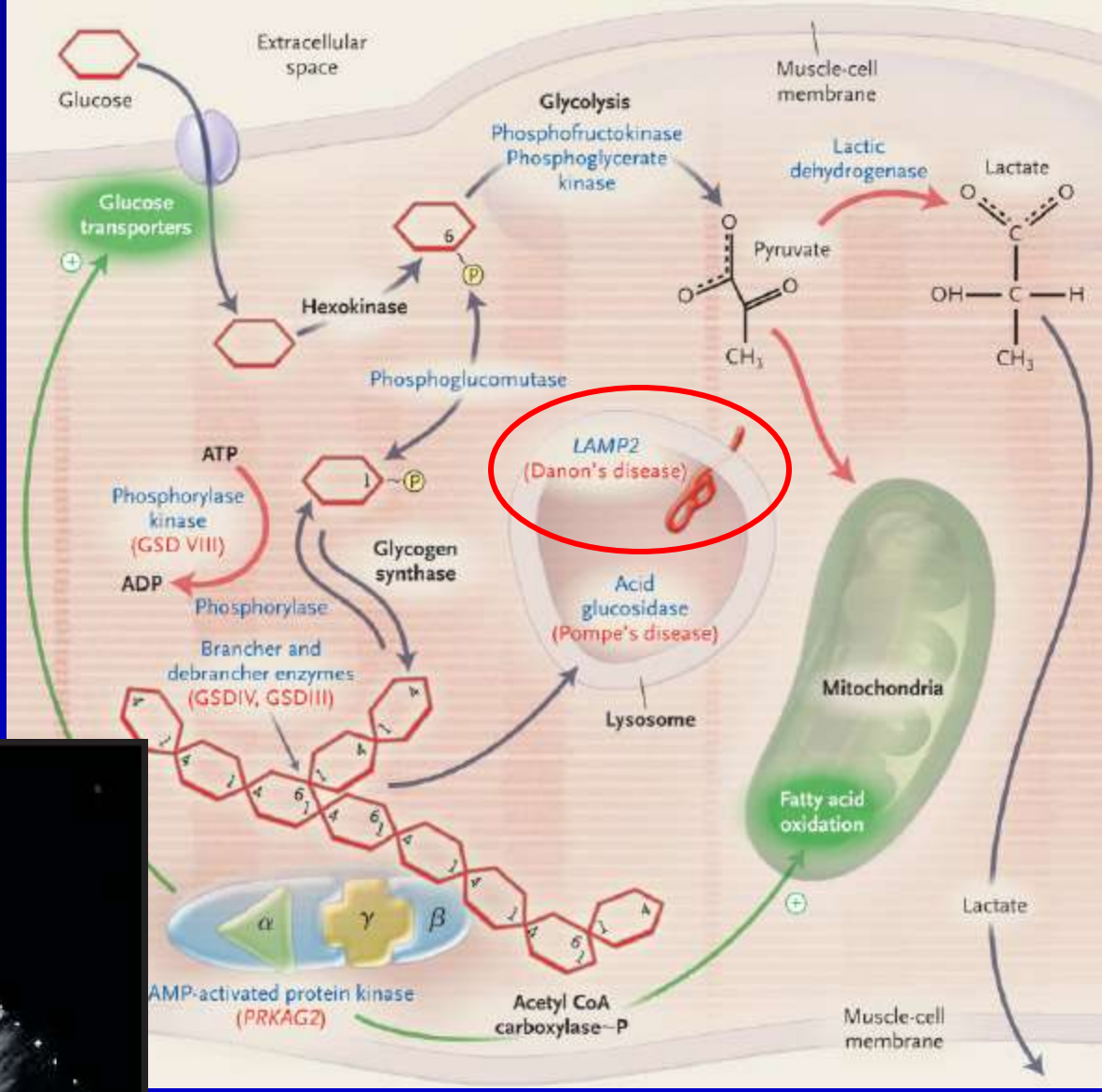
- **Pompe's disease** (glycogenosis type 2 = GSDII = acid maltase deficiency = MIM 232300; chromosome 17q23-25, the GAA gene): acid alpha-1,4 glucosidase deficiency, recessive, HCM phenotype, usually die by age 2, striking LVH voltage and CHF, lysosomal-associated membrane protein-1 (LAMP-1) levels elevated … Enzyme replacement therapy with human recombinant alglucosidase alpha is possible.

Danon's Disease

These have pre-excitation

X-linked lysosome-associated membrane protein





PRKAG2 mutations can also produce HCM

Arad M et al. N Engl J Med. 2005;352:362.

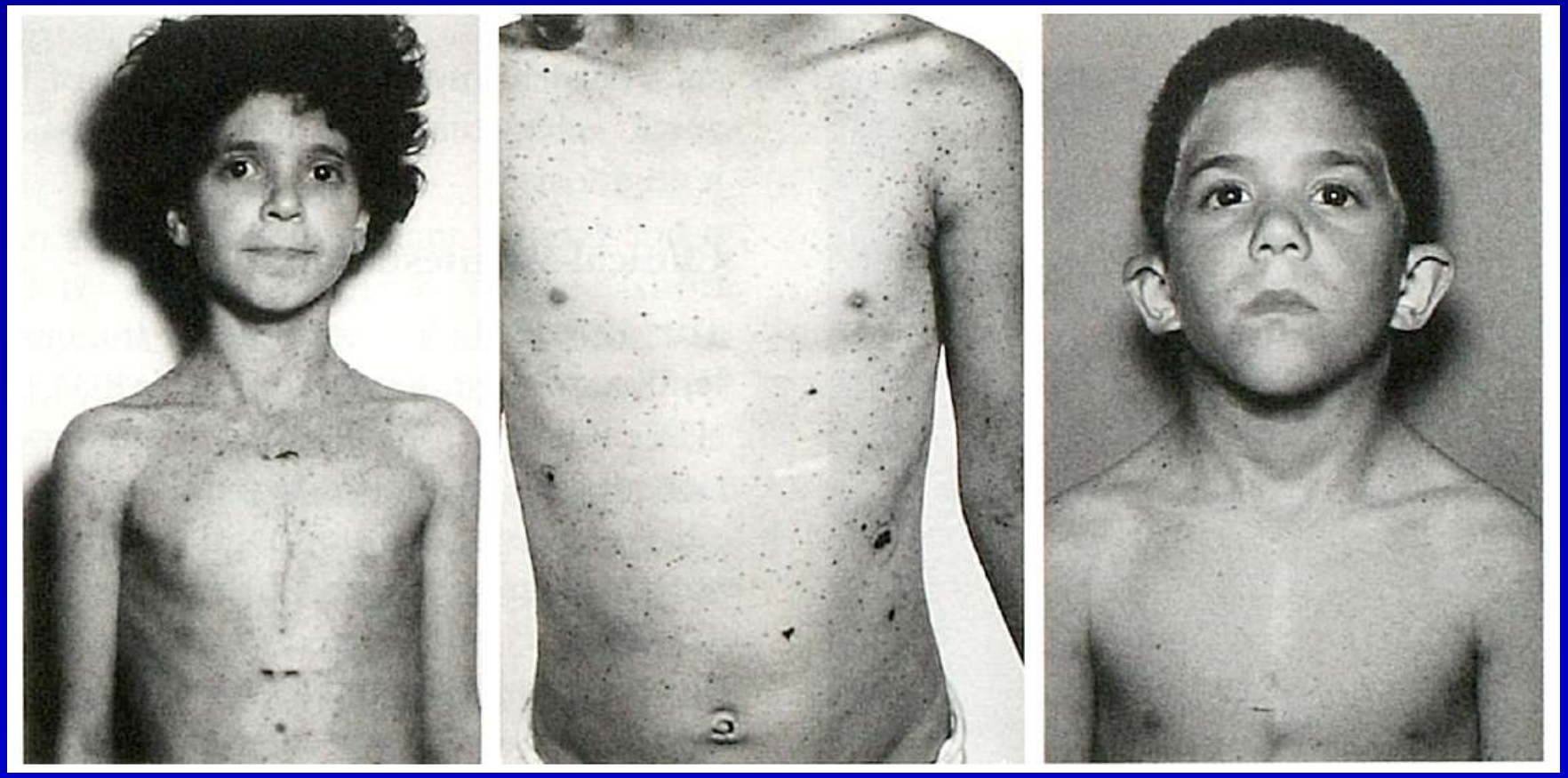
Metabolic Disorders Producing HCM - 2

- Beckwith-Wiedermann Syndrome: often dominant, error on Chromosome 11, multiple anomalies, hemihypertrophy or hemihyperplasia and macroglossia and susceptibility to tumors, esp Wilms, and HCM (not usually a prominent part of the syndrome)

Metabolic Disorders Producing HCM - 3

- **Leopard Syndrome**: lentigenes, ECG conduction defects, ocular hypertelorism, pulmonic valve stenosis, abnormality of genitalia, retardation of growth, deafness, sensorineural (HCM and endocardial fibroelastosis), molecular and genetic abnormality unknown
- Rarely, cardiomyopathy or complex CHD may be present (Braunwald's 8th ed, p. 1571).

Leopard Syndrome



Truncal or mucosal pigmented spots or larger café-au-lait spots; hypertelorism; deafness (low set ears) – each of these 3 had HCM

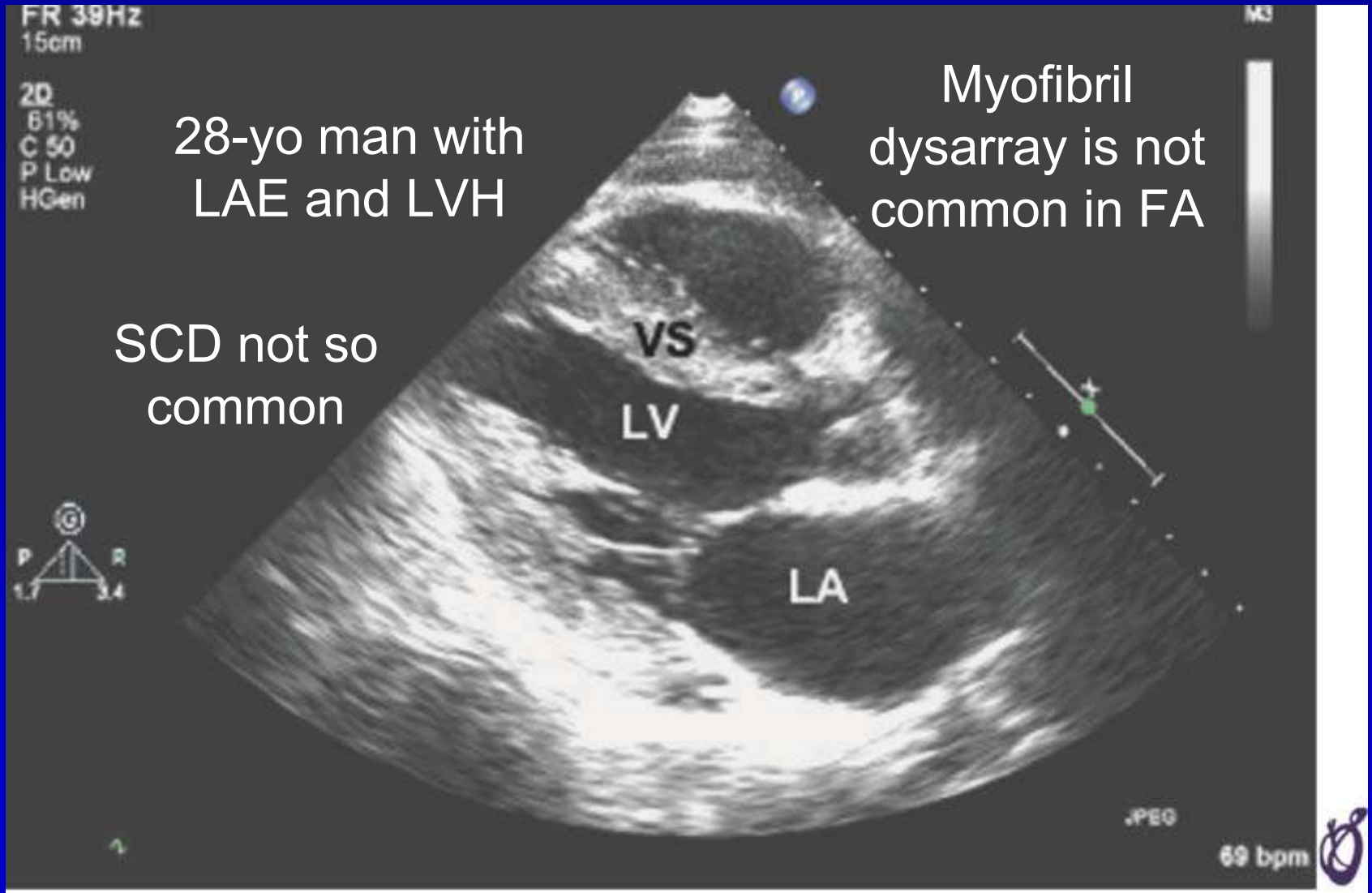
Alizad, A et al. J Am Soc Echocardiogr. 2000;13:73.

Metabolic Disorders Producing HCM - 4

- **Friedrich's Ataxia**: most common (1:50,000) hereditary spinal cerebellar degeneration; recessive, 50-90% have cardiac disease, HCM, rarely DCM, arrhythmias, 90% with inverted or biphasic T in inferior and left chest leads, AFL or AF common, concentric LVH, reduced protein – frataxin in mitochondrial membranes for iron homeostasis and respiratory function leading to mitochondrial dysfunction, poor oxidative stress response and apoptosis (9q13-31.1) Gene has too many GAA repeats in intron 1 (66-500)

Braunwald's Heart Disease, 8th ed. 2008. p. 2145.

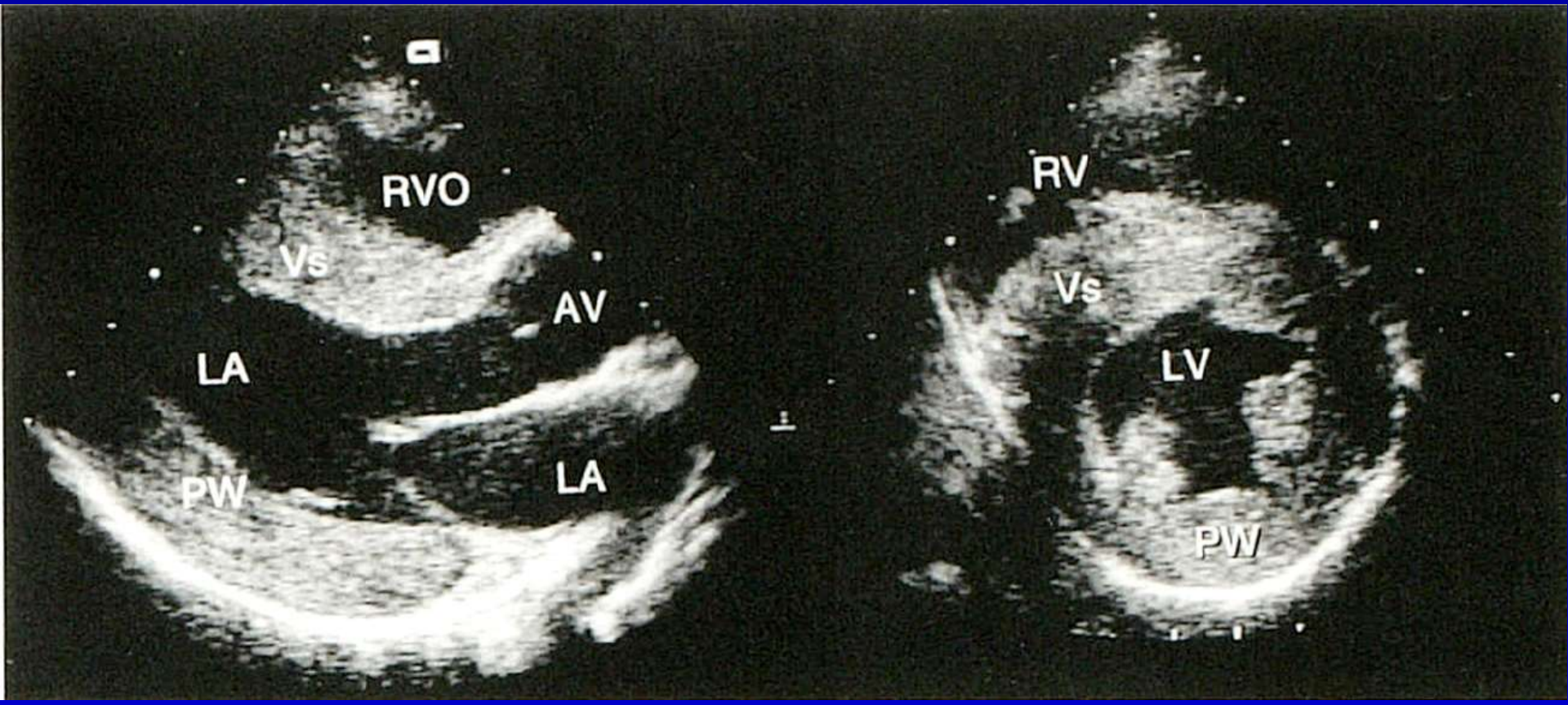
Friedrich's Ataxia



Braunwald's Heart Disease, 8th ed. 2008. p. 2145.

Friedrich's Ataxia

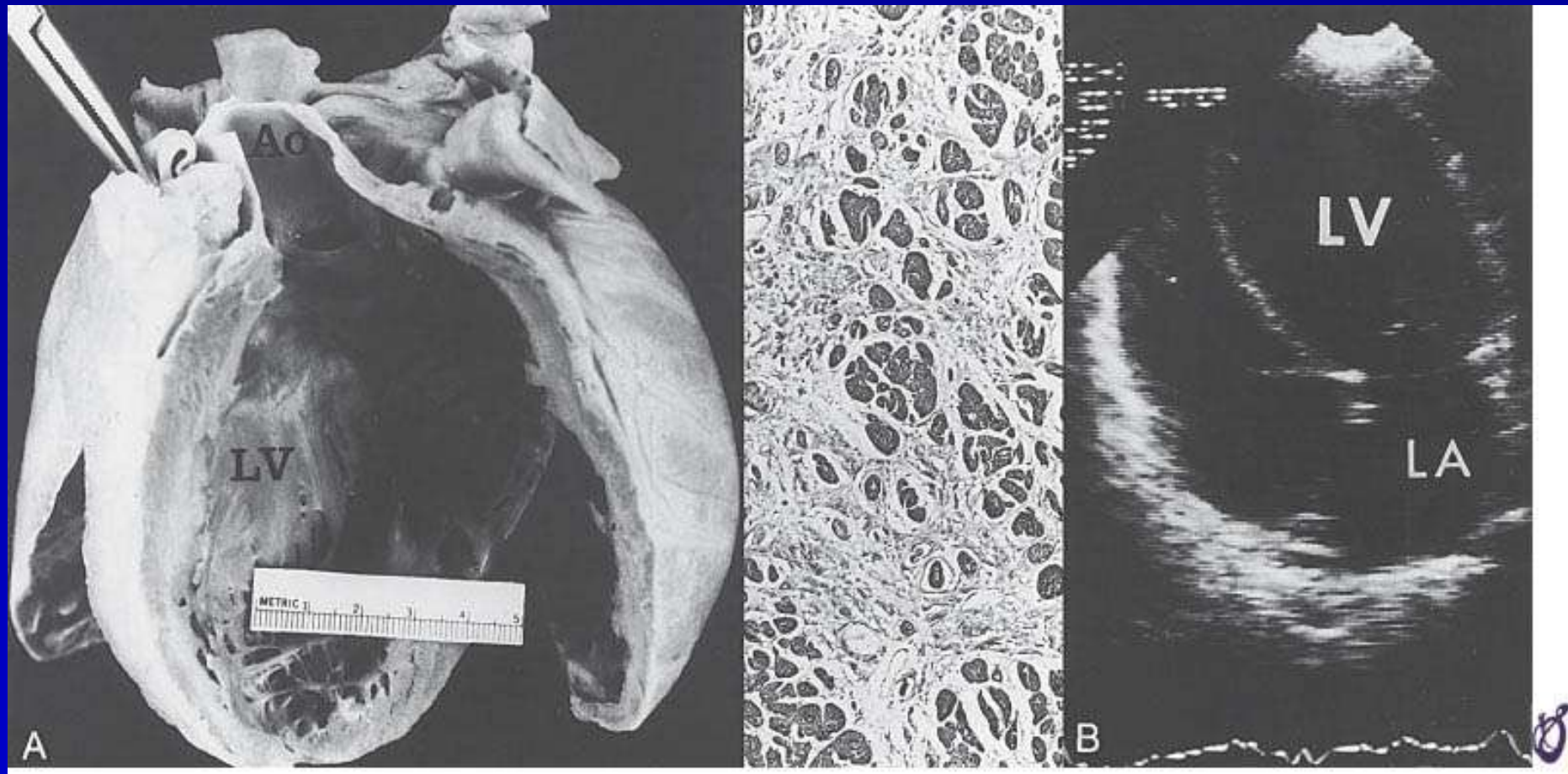
12-yo boy with severe ataxia,
systolic function is normal



Alizad, A et al. J Am Soc Echocardiogr. 2000;13:73.

Friedrich's Ataxia

AFlutt and AFib seen with dilated LV

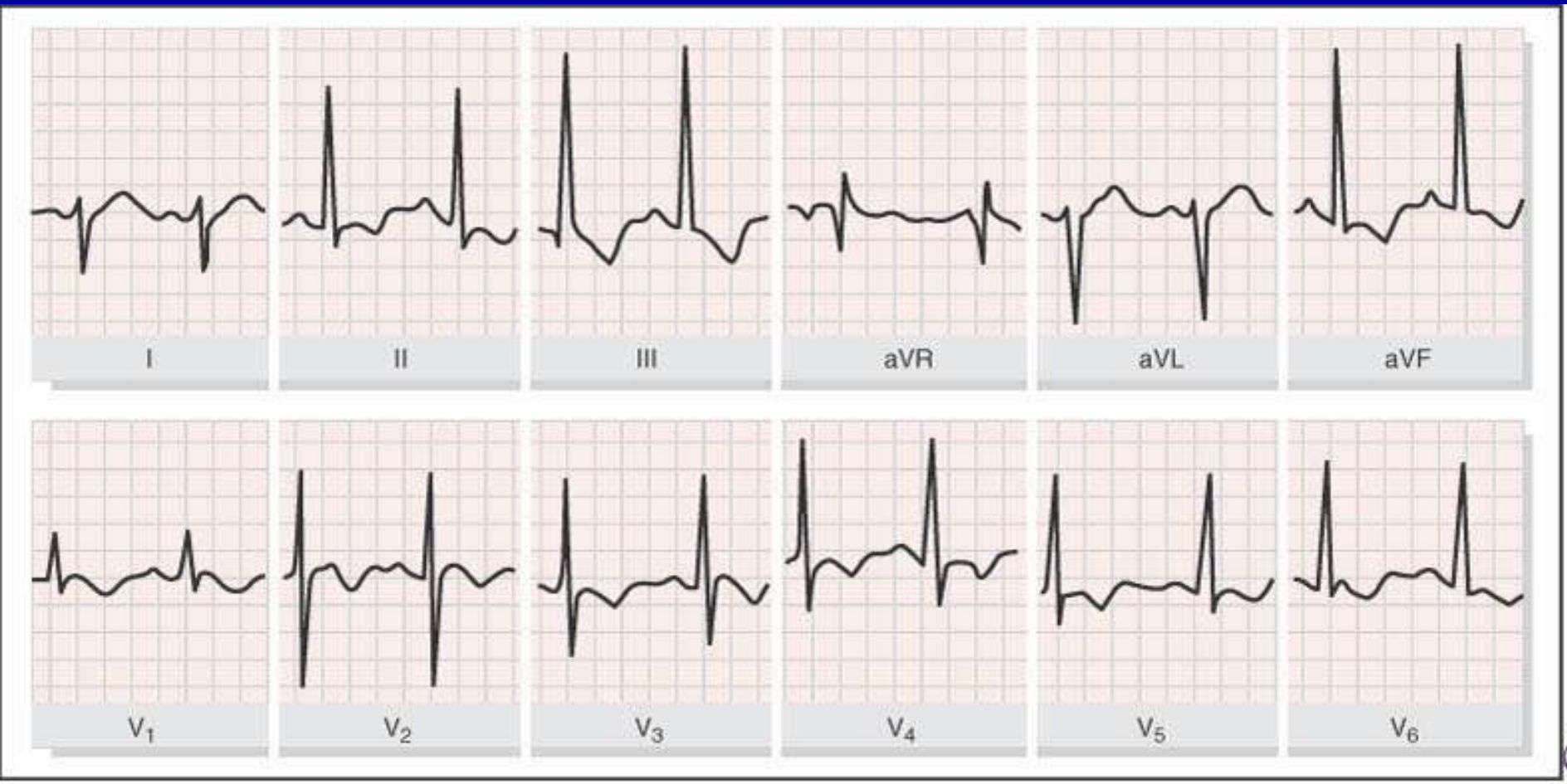


(From Child JS, Perloff JK, Bach PM, et al: Cardiac involvement in Friedreich ataxia. J Am Coll Cardiol 7:1370, 1986.)

17 yo who progressed from normal to DCM – marked connective tissue replacement

Braunwald's Heart Disease, 8th ed. 2008. p. 2146.

Friedrich's Ataxia



(Courtesy of Charles Fisch, M.D., Indiana University School of Medicine, Indianapolis.)

34 yo man with widespread ST-T changes

Braunwald's Heart Disease, 8th ed. 2008. p. 2146.

Friedrich's Ataxia

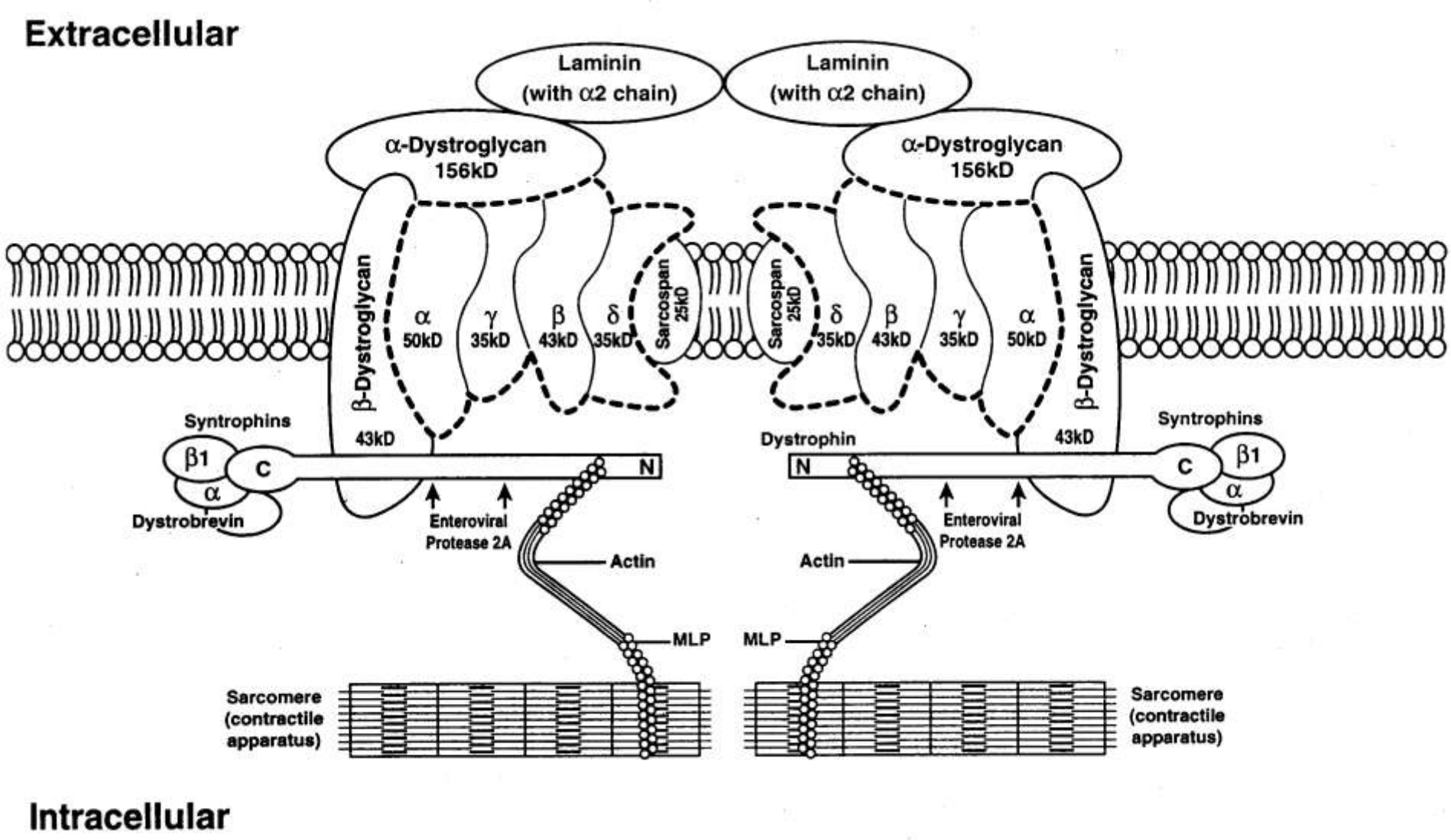
- Treatment: idebenone therapy (a free radical scavenger) may be helpful, may decrease wall thickness, and may improve EF if depressed, does not appear to improve neurological outcomes
- Death usually from neurologic respiratory failure or infection in 30s or 40s.

Braunwald's Heart Disease, 8th ed. 2008. p. 2147.

Dilated Cardiomyopathies

- Idiopathic dilated cardiomyopathy
- X-Linked dilated cardiomyopathy
- X-Linked cardioskeletal myopathy (Barth Syndrome)
- Familial arrhythmogenic RV dysplasia

Cytoskeletal Proteins Involved in DCM



Hurst, 10th Ed, 2001, p. 1799

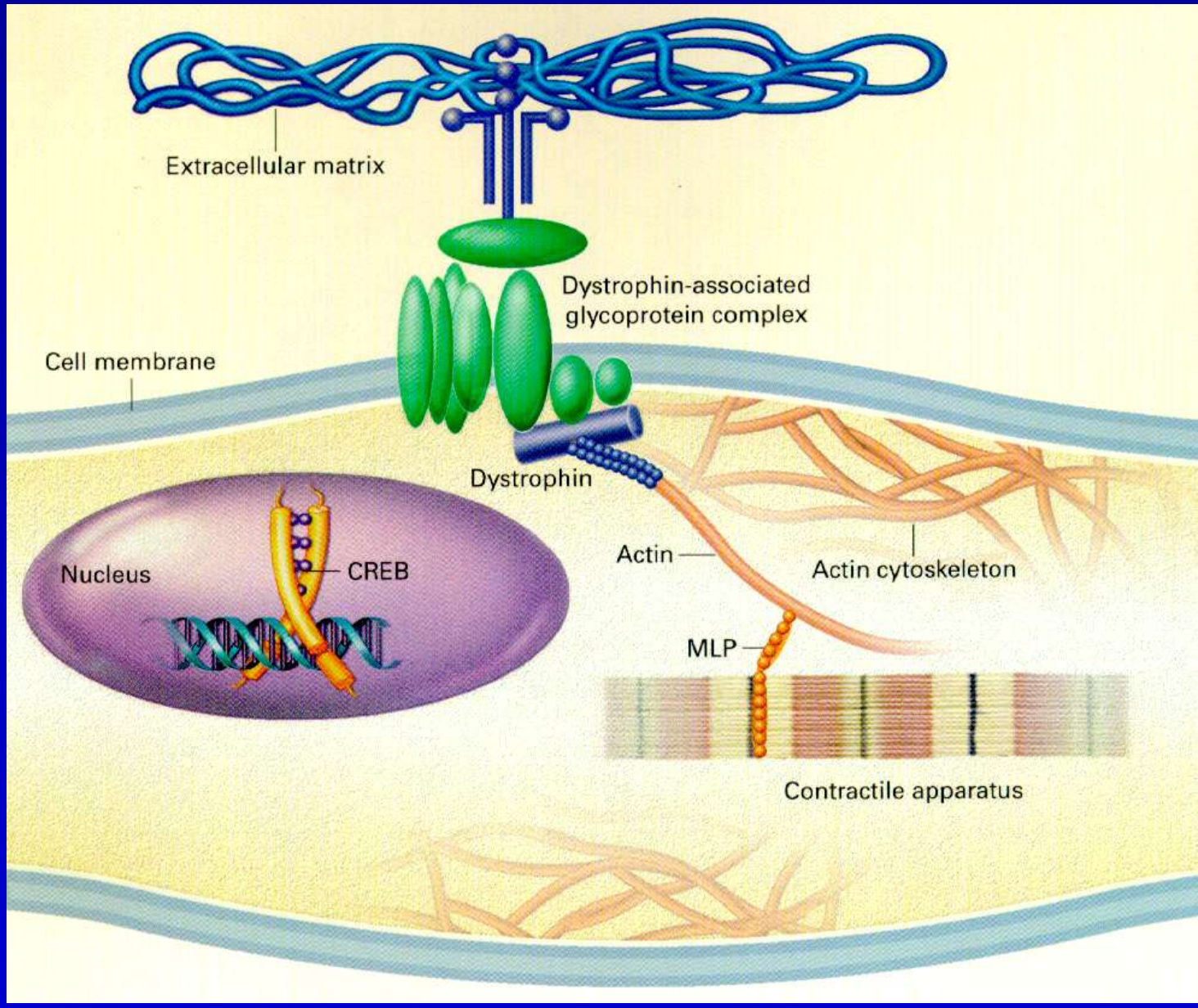
Cytoskeletal Proteins Involved in DCM

MLP(CRP-3): muscle LIM protein, regulates muscle differentiation. 2 adjacent Zinc fingers, dimerize, serve both mechanical and signaling functions

Lin-11, Isl-1, Mec-3, insulin binding protein and regulatory protein

CREB:

Cyclic AMP response element binding protein, a nuclear transcription factor



Leiden JM. NEJM 1997; 337:1080

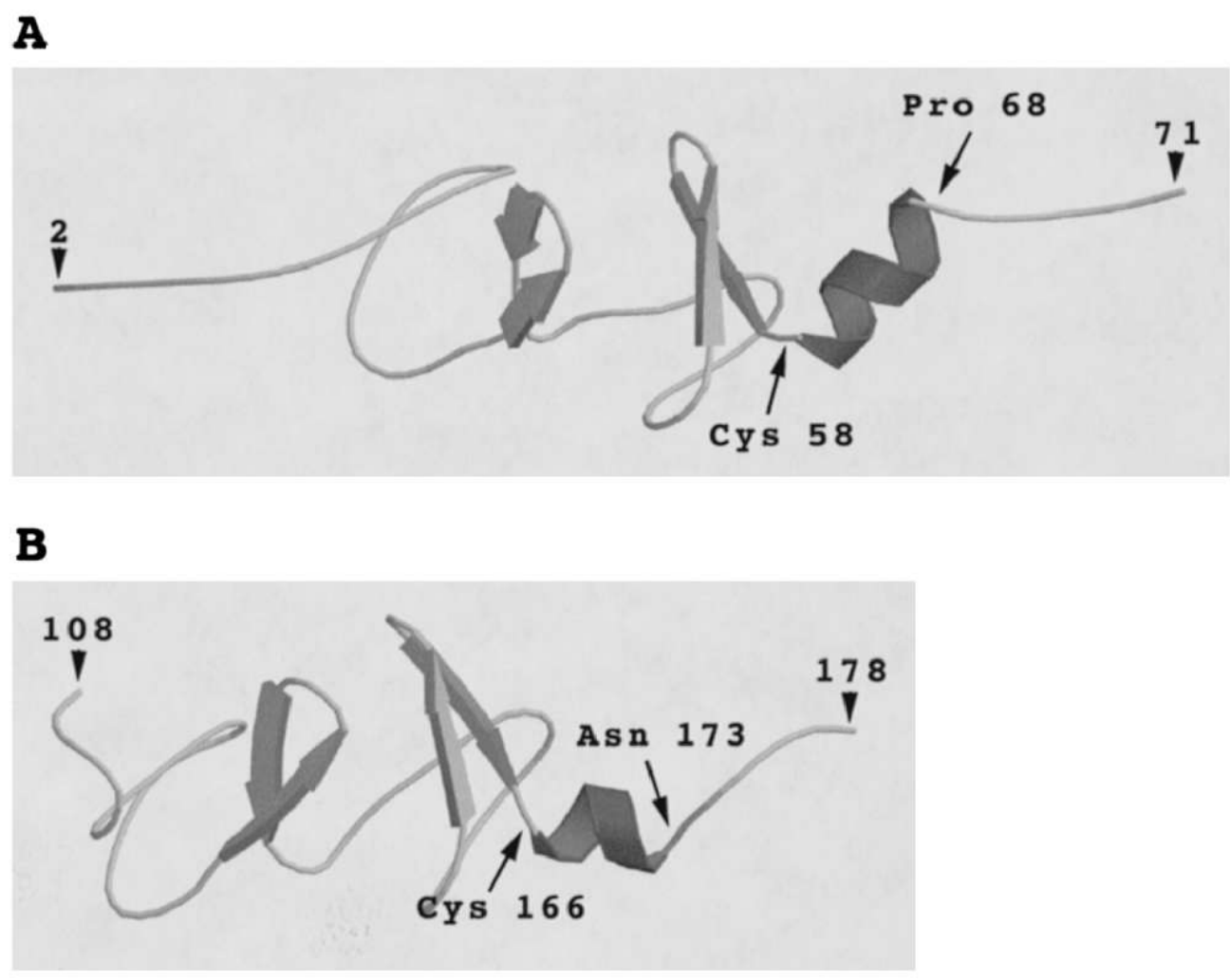
Cysteine-Rich Protein (CRP1)

A: N terminal

B: C terminal

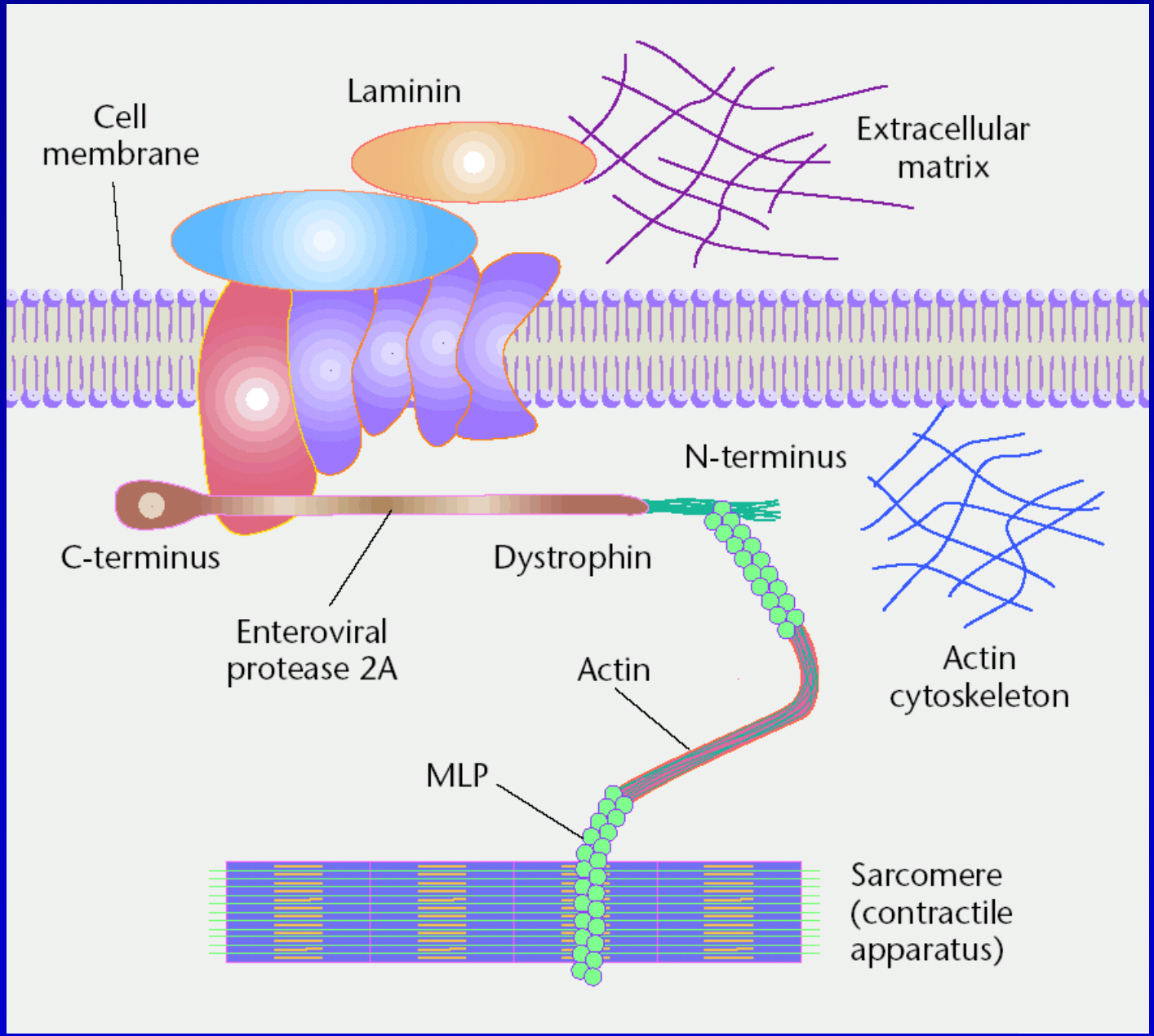
Residue 65 is largely responsible for alpha-actinin binding, and alpha-actinin is a cross-linker of cytoskeletal actin

Harper BD et al. Biochemical J. 2000; 350:269.



Cytoskeletal Proteins Involved in DCM

MLP – muscle LIM protein



Nature Med 1999;5:267

Dystrophin

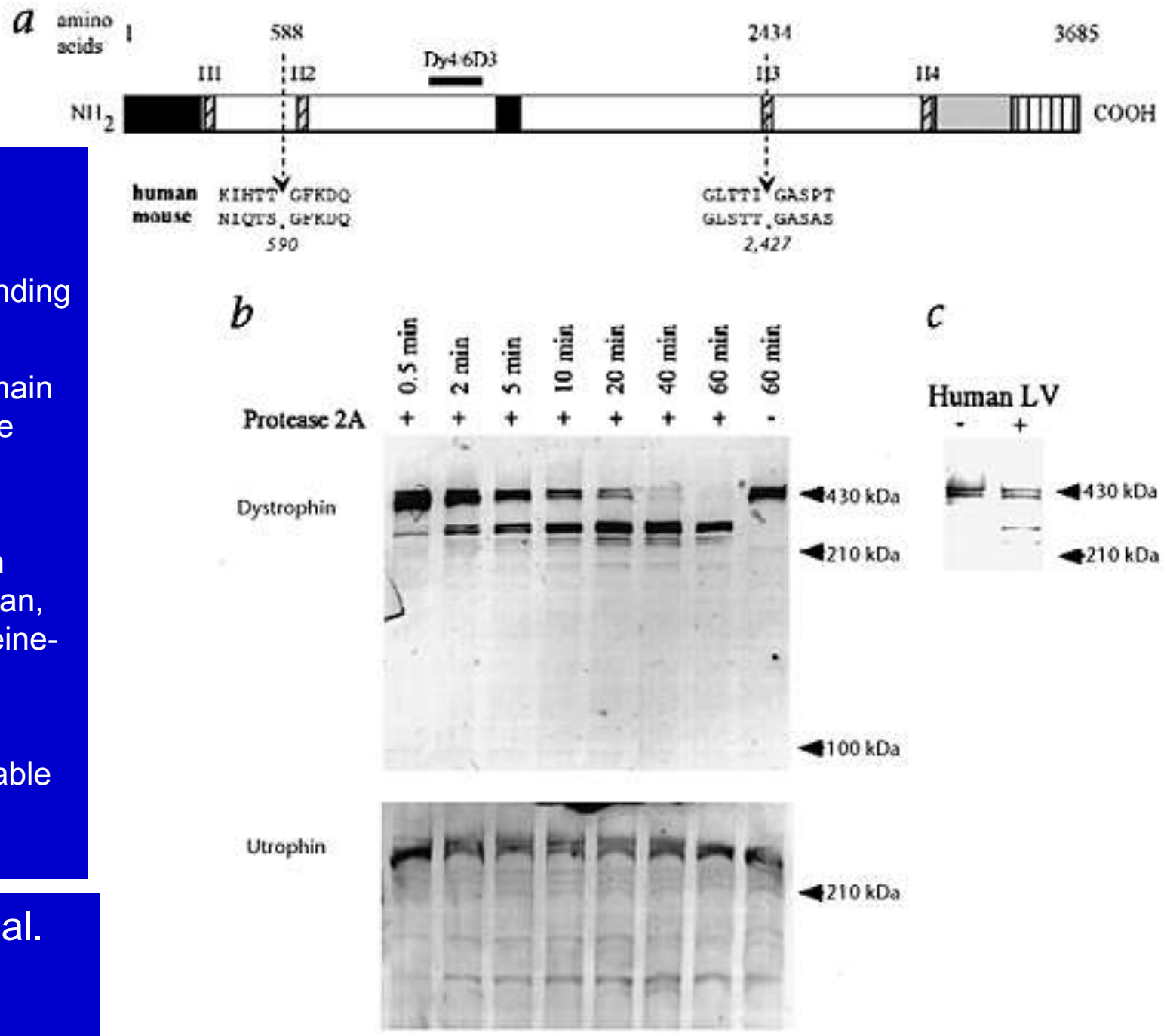
427 kDa

Black – actin-binding domains

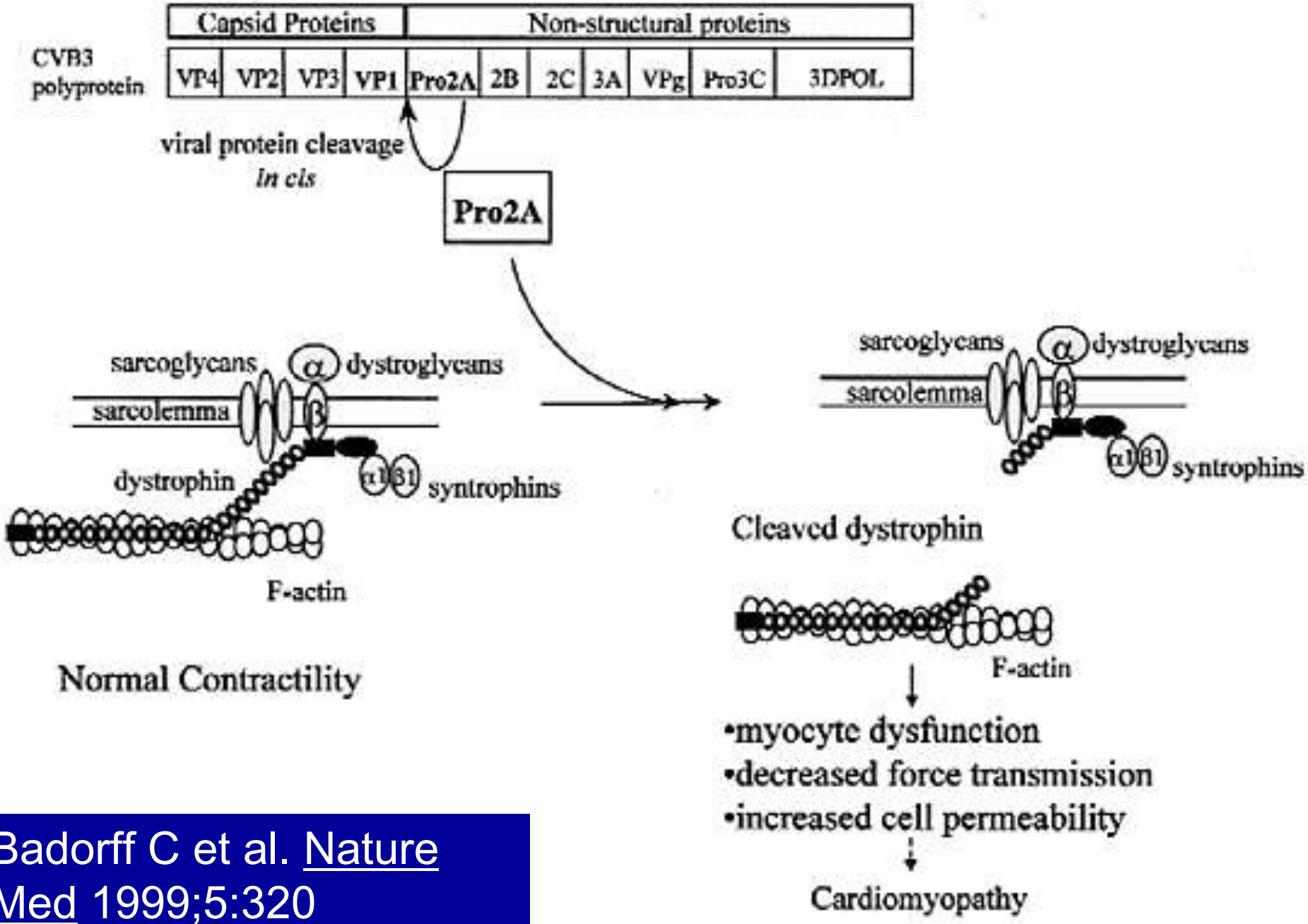
White – rod domain with spectrin-like repeats

Gray – Carboxy terminal domain bind dysgroglycan, along with cysteine-rich

H1-H4 – hinge segments available to proteolytic cleavage

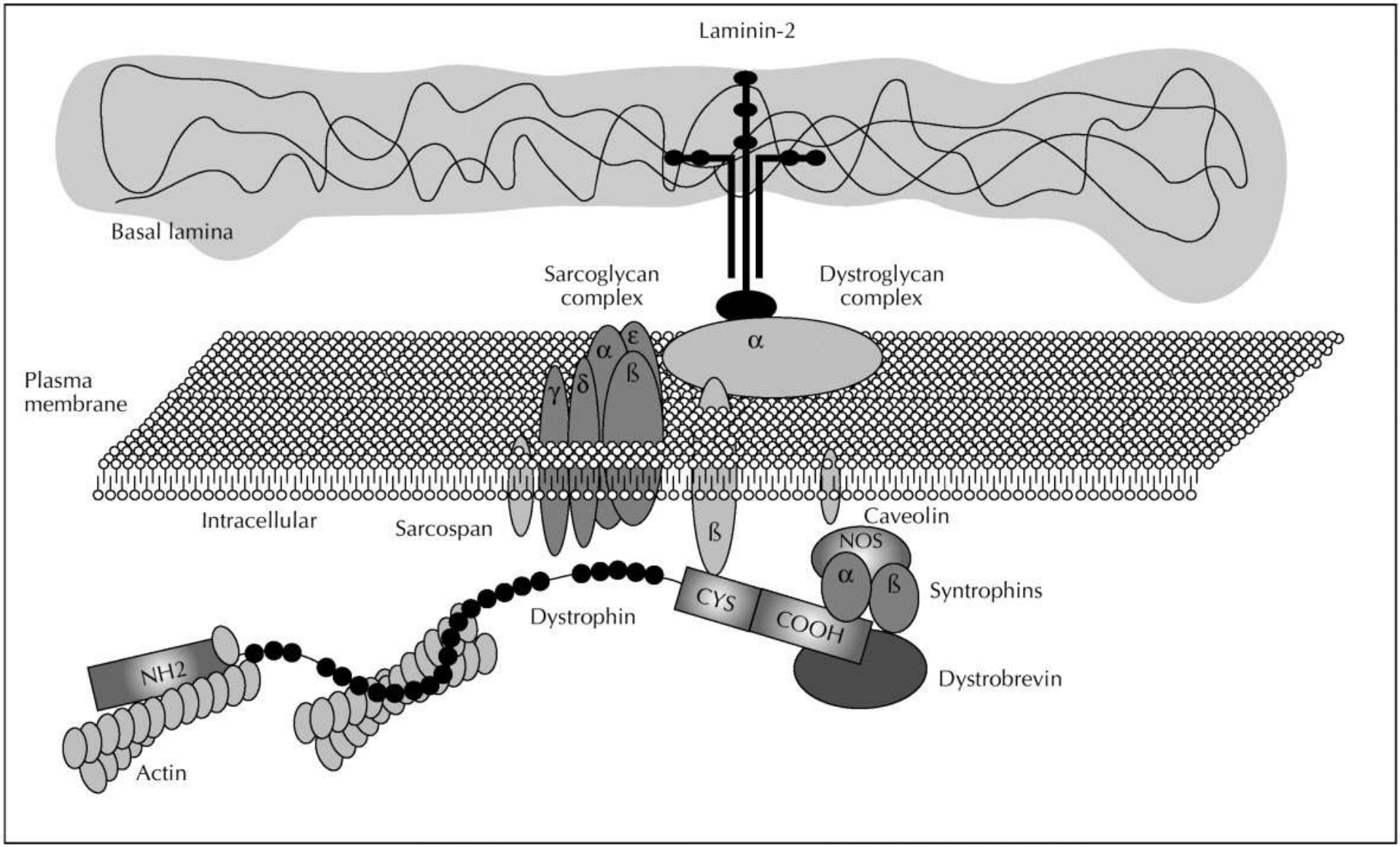


Badorff C et al. Nature Med 1999;5:320



Badorff C et al. Nature Med 1999;5:320

Dystrophin Glycoprotein Complex



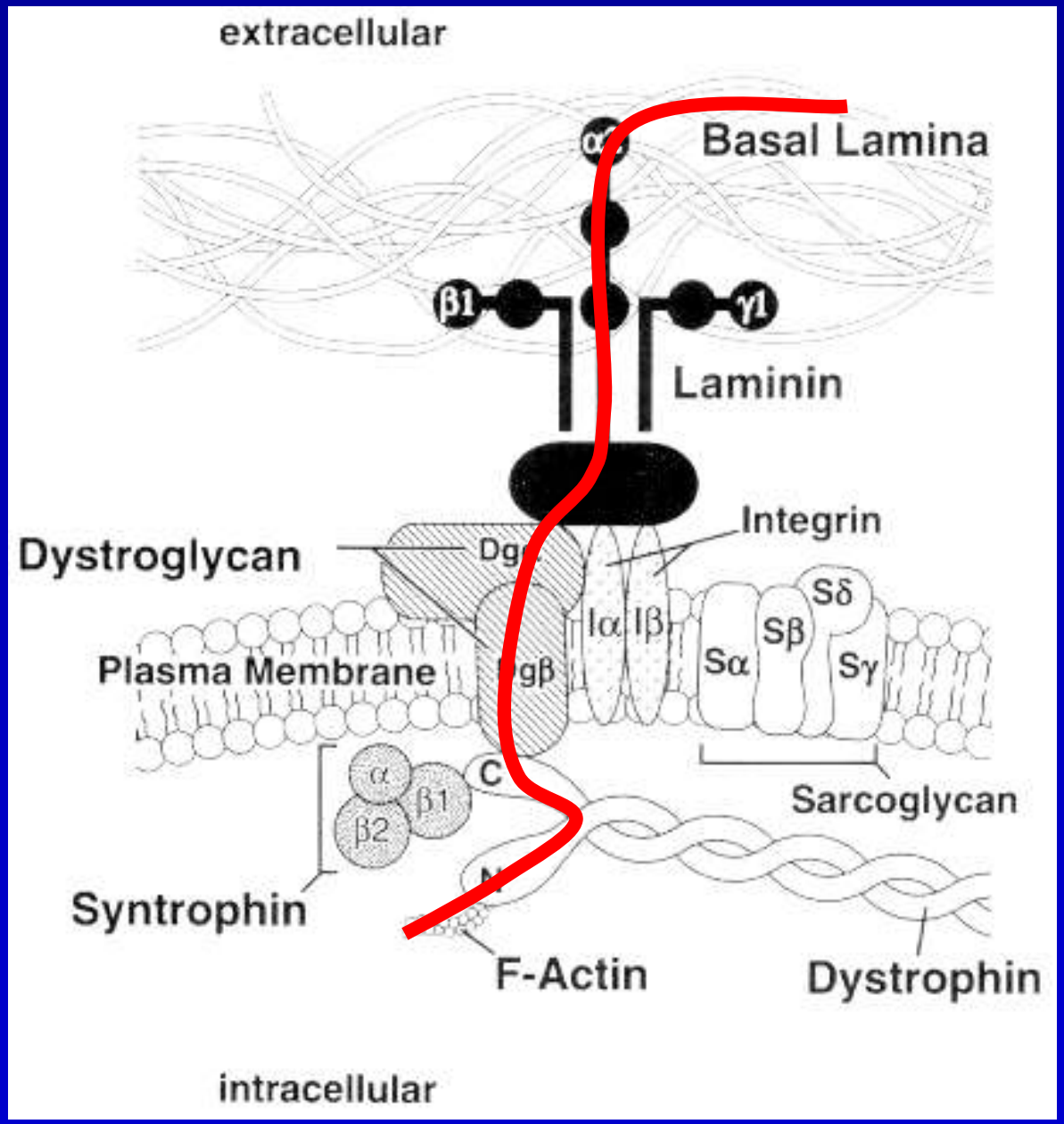
Curr Opin Cardiol. May 2001;16:211-17

Dystrophin Glycoprotein Complex

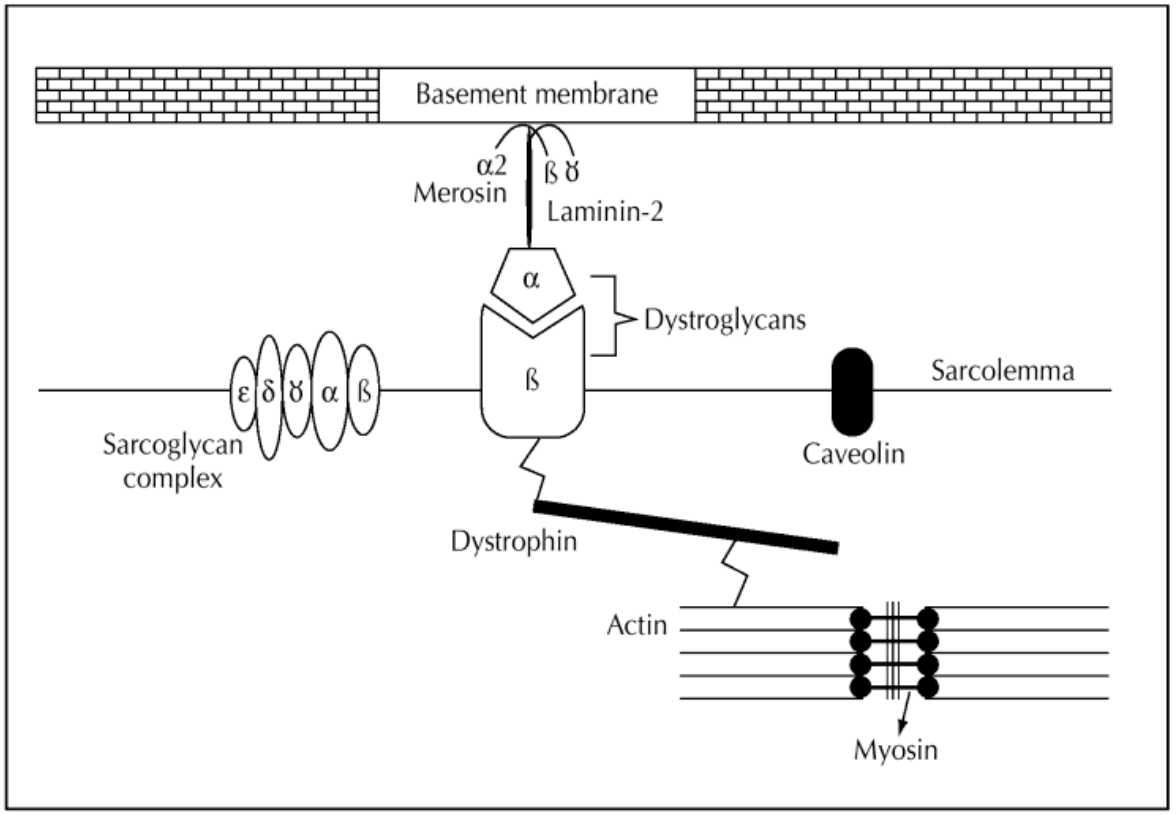
Basal Lamina:

collagen types I and IV, heparin sulfate proteoglycan, entactin, fibronectin, and laminin. *Laminin* is a heterotrimer composed of alpha, beta, and gamma chains held together by disulfide bonds. *Merosin* is the collective name for laminins that share a common alpha2 chain. alpha-Dystroglycan binds to laminin

Cecil Textbook of Medicine 2000, fig 505-1



Dystrophin Glycoprotein Complex



Curr Opin Pediat. Dec 2000;12:549

Familial DCM

- Accounts for 30% of idiopathic DCM
- Gene defects
  - Lamin A/C, esp A, on Chromosome 1 (like Emery-Dreyfuss muscular dystrophy), structural protein of nuclear membrane
  - Actin (located in domain that is immobilized and attached to the Z-band or intercalated disc, transmitting, not generating force)
  - Desmin (protein transmits force and other signals to the cytoplasm and nucleus from the sarcomere – it spans from Z-band to nuclear membrane and elsewhere)
  - Dystrophin (in Duchenne muscular dystrophy, intracellular)
  - Alpha dystroglycan on the extracellular surface
  - Alpha-sarcoglycan in the membrane

Hereditary DCM

TABLE 64–5 List of Molecular Defects in Familial Dilated Cardiomyopathy (FDC)

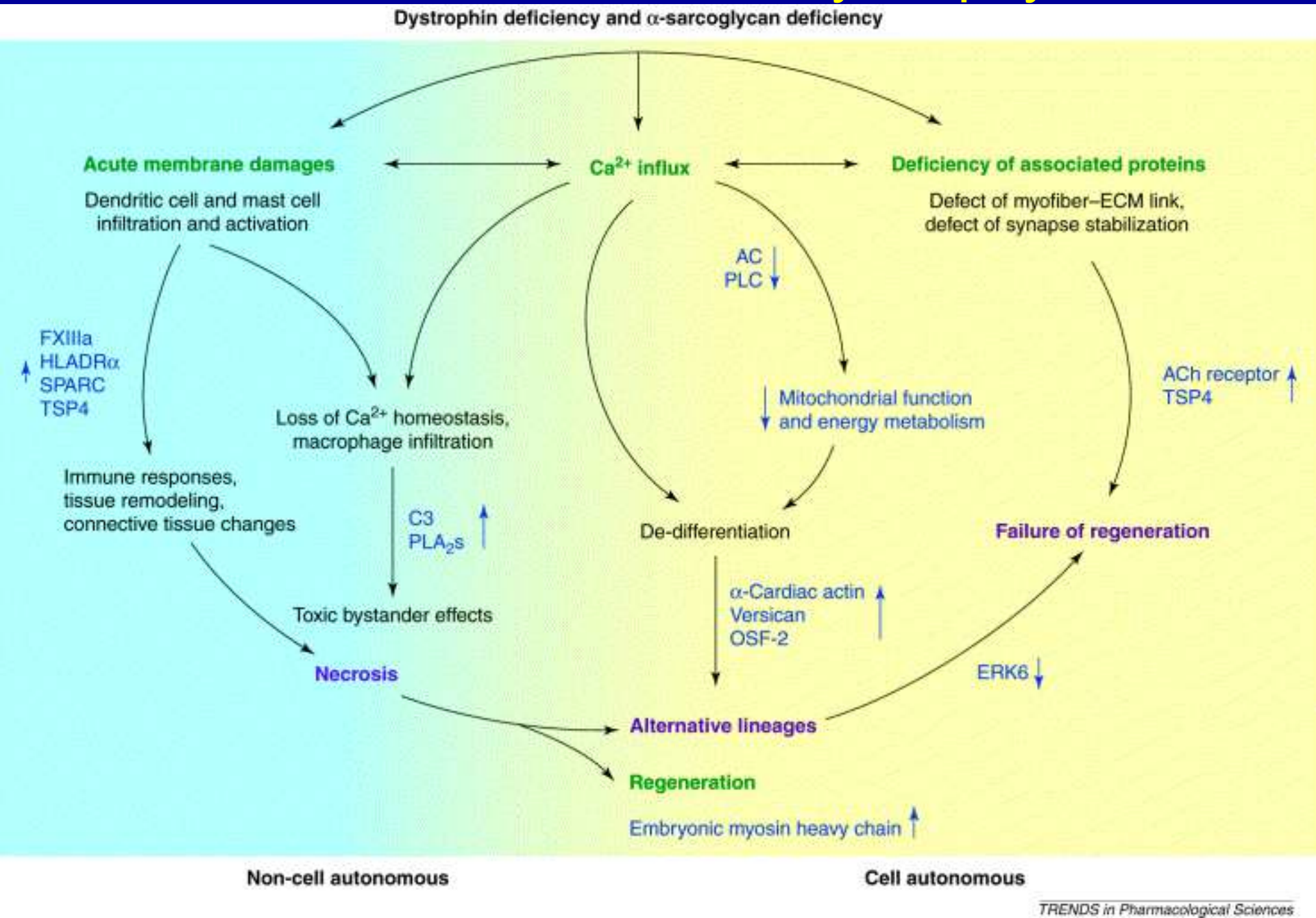
Gene	Protein	Function
Autosomal Dominant FDC Phenotype		
ACTC	Cardiac action	sarcomeric protein; muscle contraction
DES	Desmin	dystrophin-associated glycoprotein complex; transduces contractile forces
SGCD	δ-Sarcoglycan	dystrophin-associated glycoprotein complex; transduces contractile forces
MYH7	β-Myosin heavy chain	sarcomeric protein; muscle contraction
TNNT2	Cardiac troponin T	sarcomeric protein; muscle contraction
TPM1	α-Tropomyosin	sarcomeric protein; muscle contraction
TTN	Titin	sarcomere structure/extensible scaffold for other proteins
VCL	Metavinculin	sarcomere structure; intercalated discs
MYBPC	Myosin-binding protein C	sarcomeric protein; muscle contraction
MLP/CSRP3	Muscle LIM protein	sacromere stretch; sensor/Z discs
ACTN2	α-Actinin-2	sarcomere structure; anchor for myofibrillar actin
PLN	Phospholamban	sarcoplasmic reticulum Ca^{2+} regulator; inhibits SERCA2 pump
ZASP/LBD3	Cypher/LIM binding domain 3	cytoskeletal assembley; involved in targeting and clustering of membrane proteins
MYH6	α-Myosin heavy chain	sarcomeric protein; muscle contraction
ABCC	SUR2A	regulatory subunit of Kir6.2, an inwardly rectifying cardiac K_{ATP} channel
LMNA	Lamin A/C	inner leaflet, nuclear membrane protein; confers stability to nuclear membrane; gene expression
X-linked FDC		
DMD	Dystrophin	primary component of dystrophin-associated glycoprotein complex; transduces contractile force
TAZ/G4.5	Tafazzin	unknown
Recessive FDC		
TNNI3	cardiac troponin I	sarcomeric protein, muscle contraction

Derived from Burkett EL, Hershberger RE: Clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol 45:969, 2005. Copyright 2005, American College of Cardiology.

(Derived from Burkett EL, Hershberger RE: Clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol 45:969, 2005. Copyright 2005, American College of Cardiology.)

Braunwald's Heart Disease, 8th ed. 2008. p. 1747.

Effects of Muscular Dystrophy Sep 2001



TRENDS in Pharmacological Sciences

Limb-Girdle Dystrophies

Type	Protein product	Genetic loci	Age at onset	Unique features
IA	Myotilin	5q31	18–35 *y*	Dysarthria
IB	?	1q11–21	4–38 *y*	Cardiac involvement
IC	Caveolin 3	3q25	~ 5 *y*	Cramping, calf hypertrophy
IIA	Calpain-3	15q15.1–15.3	2nd decade	Shoulder girdle atrophy
IIB	Dysferlin	2p13	Late teens	Markedly elevated CPK
IIC	γ-Sarcoglycan	13q13	3–15 *y*	Asymptomatic scapular winging, calf hypertrophy
IID	a-Sarcoglycan	17q12–21.33	3–15 *y*	Same as γ-sarcoglycan
IIE	b-Sarcoglycan	4q12	Mean, 7.6 *y*	Early loss of ambulation
IIF	d-Sarcoglycan	5q33–34	4–10 *y*	Cardiomyopathy
IIG	Telethonin	17q11–12	2nd decade	Proximal upper extremities more involved, rimmed vacuoles
IIH	?	9q31–33	8–27 *y*	Facial muscle weakness

CPK, creatine phosphokinase.

Curr Opin Pediat. Dec 2000;12:549

X-Linked DCM (XLCM)

- Worse in men, fibrosis worst in posterior wall
- Dystrophin locus at Xp21 (same gene as for Duchenne and Becker muscular dystrophy), with defect at N-terminal end and rod portion, and also alpha dystroglycan was reduced
- Destabilization of muscle membrane
- CHF, ventricular arrhythmias, transplant

X-Linked Cardioskeletal Myopathy

- Barth syndrome
- Recessive: DCM with endocardial fibroelastosis, neutropenia, skeletal myopathy
- Males die in infancy, females unaffected
- Mitochondrial problems, locus Xq28, gene G4.5, protein tafazzin (function unclear), also causes isolated LV noncompaction and dilated HCM

Familial Arrhythmogenic RV Dysplasia (ARVD)

- Often the first symptom is SCD
- There is no definitive diagnostic standard, RV biopsy often false negative (abnormality moves from epicardium to endocardium)
- No common gene (chromosomes 1, 2, 14, 17, 3, 10 implicated in different families)
- MRI and Echo and ECG (T inversion in V1-3, late potentials, ventricular arrhythmia with LBBB pattern) helpful in diagnosis

Restrictive Cardiomyopathies

- Most common is amyloid, mutations in the transthyretin gene and protein
- Mucopolysaccharidoses
  - 7 types
    - Hurler's Syndrome
    - Hunter's Syndrome
    - Morquio's Disease
    - Maroteaux-Lamy Disease

  } Subsequent slides

  - deficient in lysosomal enzymes that degrade glycosaminoglycans, leading to their accumulation
  - Multiple system involvement
  - Diagnose by culturing skin fibroblasts or leukocytes and assessing enzyme activity

Amyloid Heart Disease

- An infiltrative disease, along with sarcoid and Gaucher's
- Group of diseases with beta-pleated sheet extracellular protein deposit (insoluble, impervious to proteolytic digetstion)
  - Primary systemic (AL): monoclonal immunoglobulin spike in 80% (MM light chain)
  - Secondary (AA): nonimmunoglobulin (TB, Rheum Arth)
  - Senile
  - Familial (transthyretin, >50-80 mutants), homotetramer 55kDa,

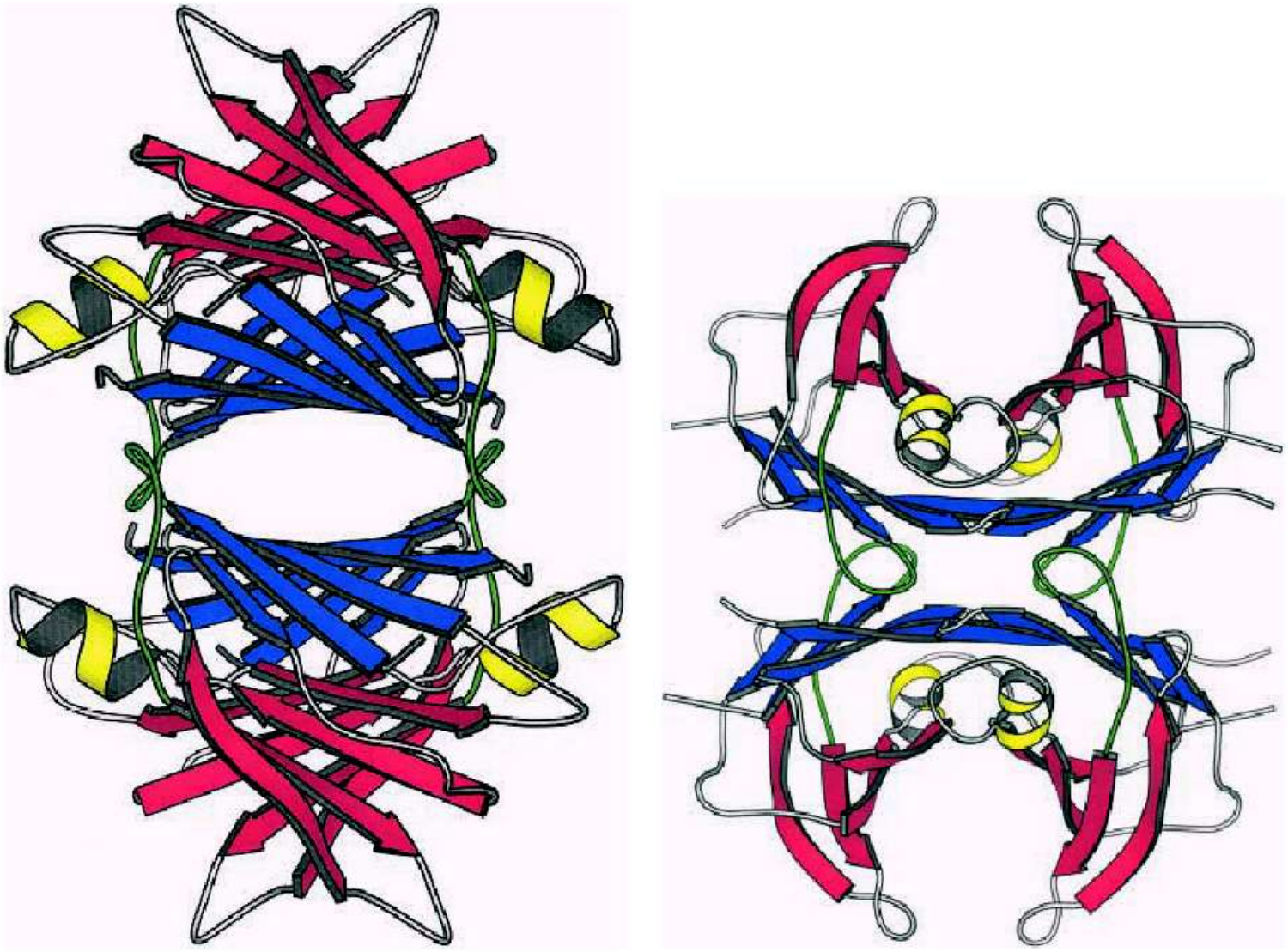
Human Transthyretin Tetramer

Blue – extended inner beta sheet

Red – outer beta sheet

Yellow – lone helix

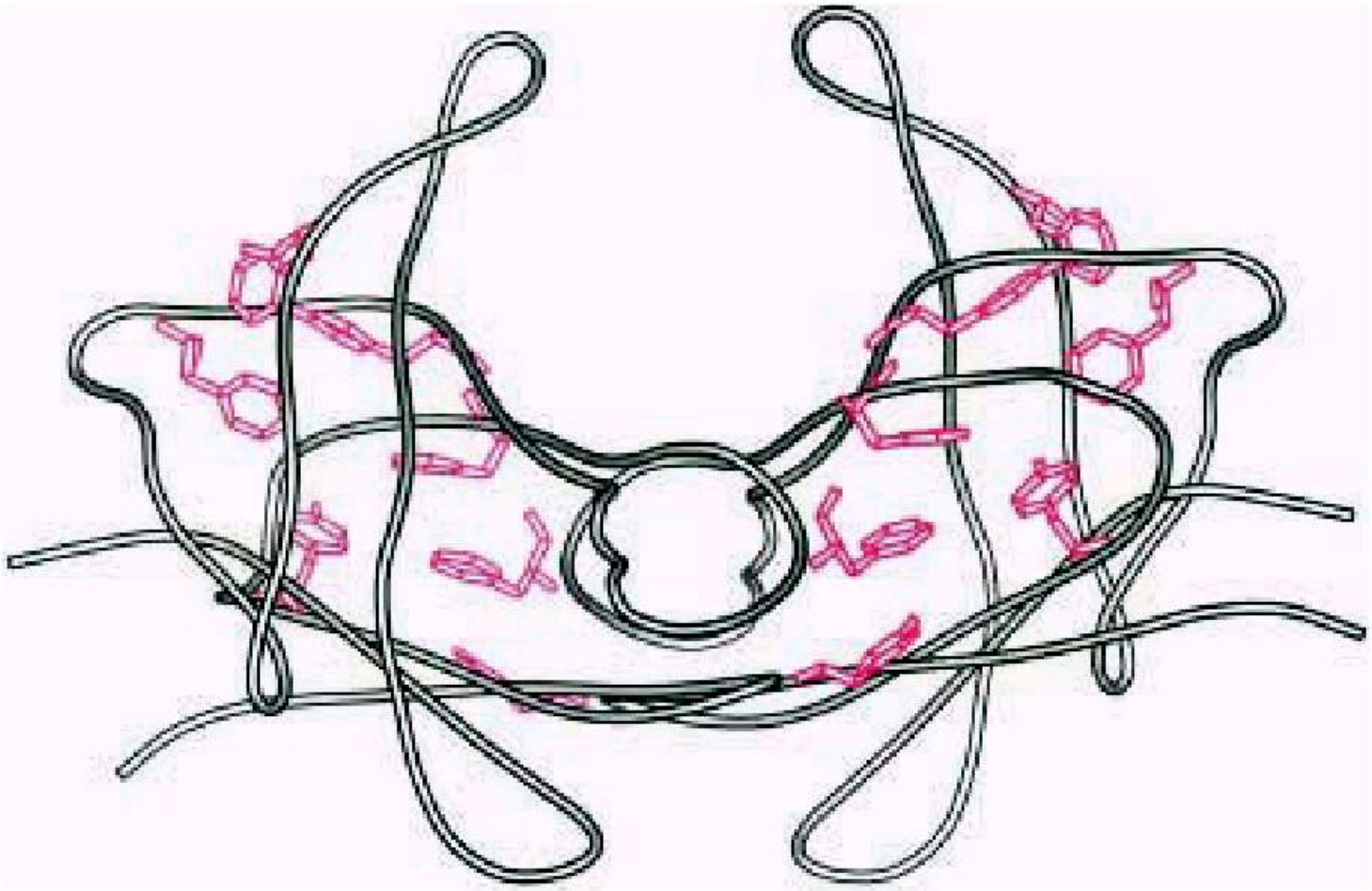
Green – loops, that contribute to the tetramer formation



Hamilton JA et al. Cellular and Molecular Life Sciences 2001;58:1491

Transthyretin Dimer

Red – aromatic residues between the extended beta-sheets



Hamilton JA et al. Cellular and Molecular Life Sciences 2001;58:1491

Hurler's Syndrome

- MPS-I, autosomal recessive, 22q11, 1:40,000, alpha-iduronidase (IDUA) deficiency – degrades heparan and dermatan sulfate, so these are elevated in urine (mucopolysaccharidiuria)
- Clinical subtypes:
  - severe (MPS-IH, Hurler, CAD, AS, MR/MS, HCM, EFE, death usually <10yo),
  - intermediate (MPS-IH-S, Hurler-Scheie, onset in teens),
  - mild (MPS-IS, Scheie, AR, nl lifespan)
- Treatment: allogeneic bone marrow transplant

Hunter's Syndrome

- Xq26-Xq28, 1:30,000, iduronate sulfatase, excess dermatan and heparan sulfate in urine
- MI in childhood, most die before 20yo
- Wide clinical variability, depending on type of genetic mutation

Morquio's Disease

- MPS-IVA, recessive, 16q24, deficient N-acetyl-galactosamine-6-sulfatase , excess urinary keratan sulfate and chondroitin 6-sulfate
- Prototypical chondroosteodystrophy, spondyloepiphyseal dysplasia, short-trunk dwarfism, normal intelligence
- Cardiac disease in 2nd decade, aortic valve disease, regurgitation

Maroteaux-Lamy Disease

- Syndrome, 5q13-q14, deficient arylsulfatase B, degrades dermatan sulfate and chondroitin 4-sulfate
- DCM and aortic or mitral stenosis or insufficiency
- Variable manifestations, and cardiac manifestations are usually after neurologic problems, usually by adolescence
- Treatment: Bone marrow transplantation

Muscular Dystrophies with Cardiac Involvement

- Duchenne Muscular Dystrophy (DMD)
- Becker's Muscular Dystrophy (BMD)
- Emery-Dreifuss Muscular Dystrophy (EDMD)
- Myotonic Dystrophy (Steinert's disease)
- Limb-girdle muscular dystrophy (DAG's)
- Fascioscapulohumeral Dystrophy
- Nemaline Myopathy
- Endocardial Fibroelastosis (EFE)

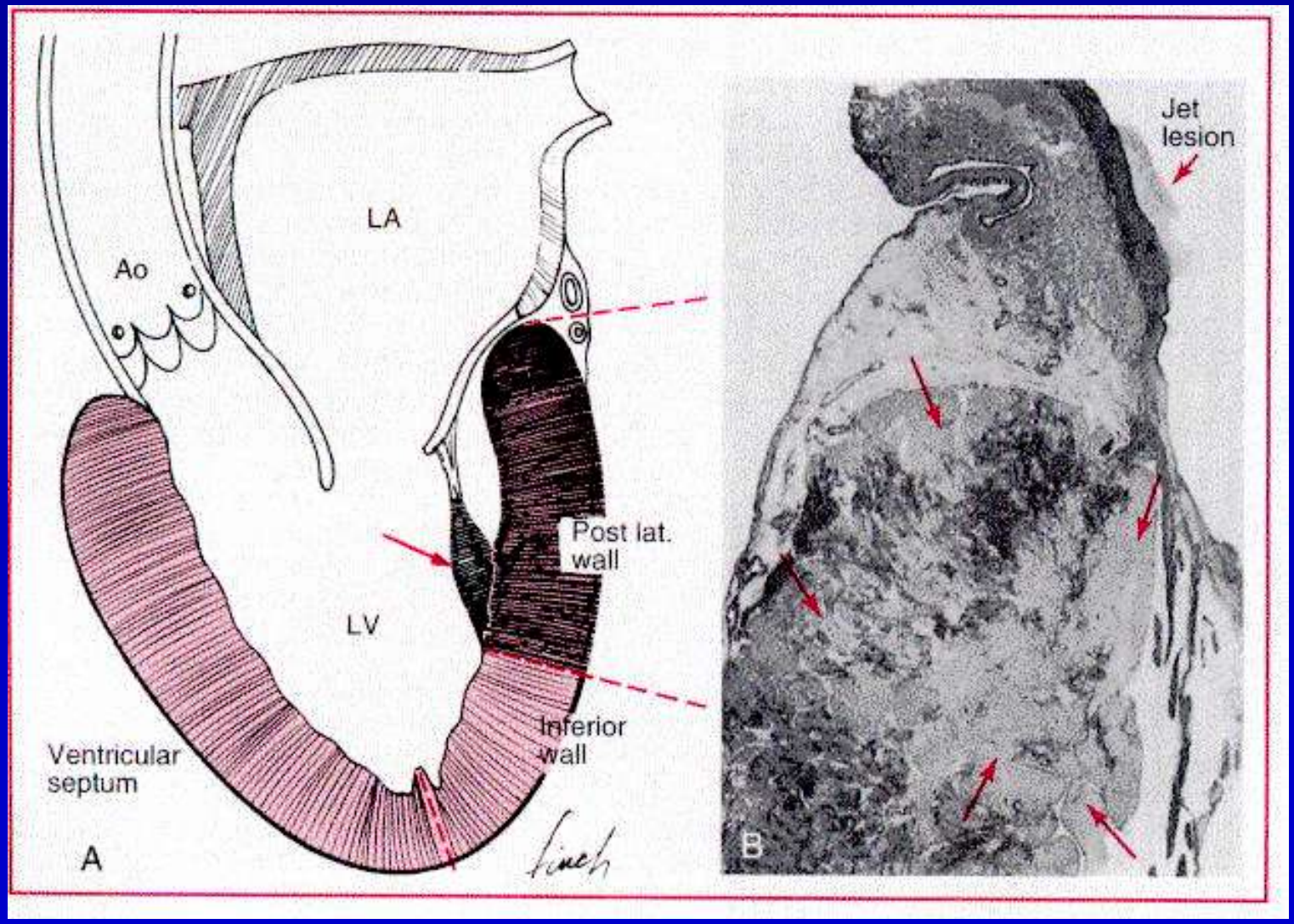
Duchenne Muscular Dystrophy (DMD) - 1

- 1:3,300 male births, 1/3 are spontaneous mutations, pseudohypertrophy calves
- Female carriers may (~8%) have mild or moderate slowly progressive myopathy

Duchenne Muscular Dystrophy (DMD) - 2

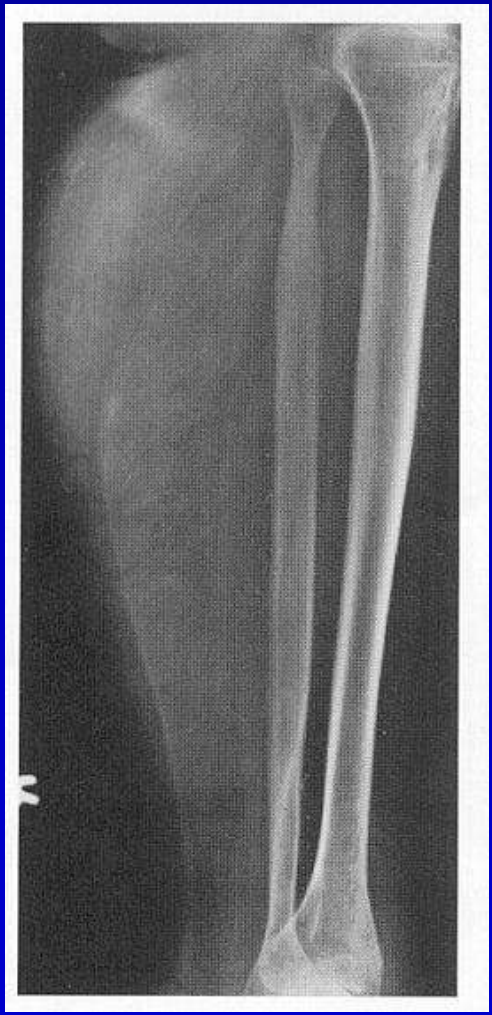
- Heart commonly involved: 25% of deaths are cardiac
  - DCM with fibrosis mainly in posterobasal and lateral walls, mitral prolapse (post-med pap musc dysfunction), and conduction abnormality, large R and R/S in V1, deep narrow Q in lateral leads
  - LAE on ECG may be conduction problem
  - AFB, PFB, atrial flutter, IVCD, pacing not usually necessary

Duchenne Muscular Dystrophy



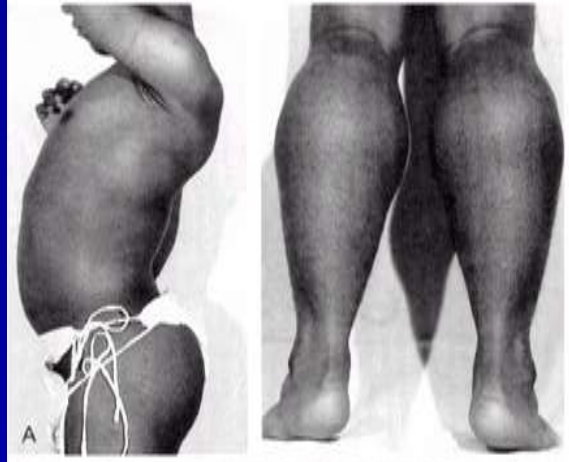
Braunwald fig 71-3, from Perloff. Posterobasal necrosis/fibrosis

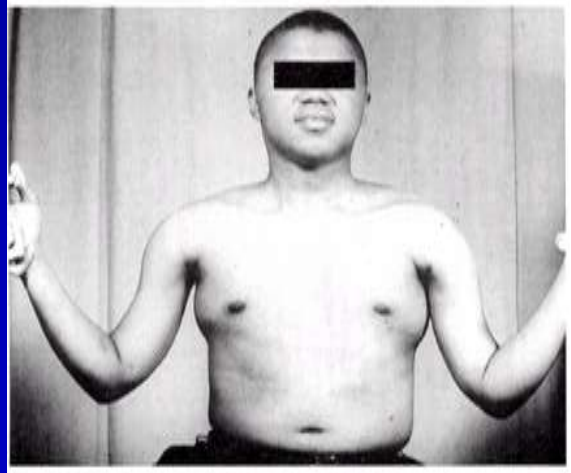
X-linked Duchenne Muscular Dystrophy



- Exaggerated lumbar lordosis
- Calf pseudohypertrophy (fat accum streaky Xray)
- Shortened Achilles tendon

- Hypertrophy/pseudohypertrophy of deltoid and pectoralis major
- Also trapezius





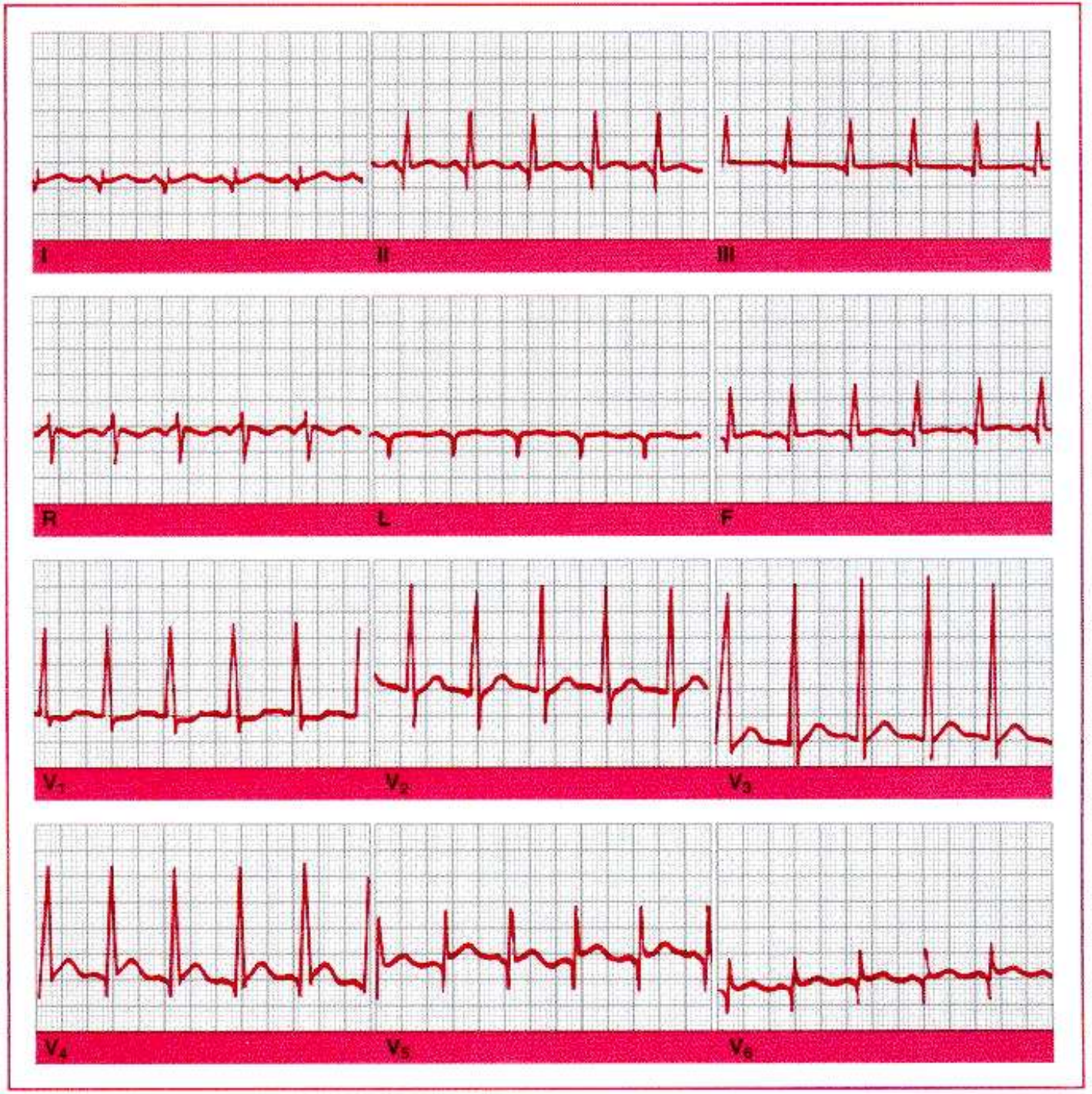
Paul and Juhl, 1998 Fig 10-8

Braunwald 2001, Fig 71-1. From Perloff JK

ECG in DMD

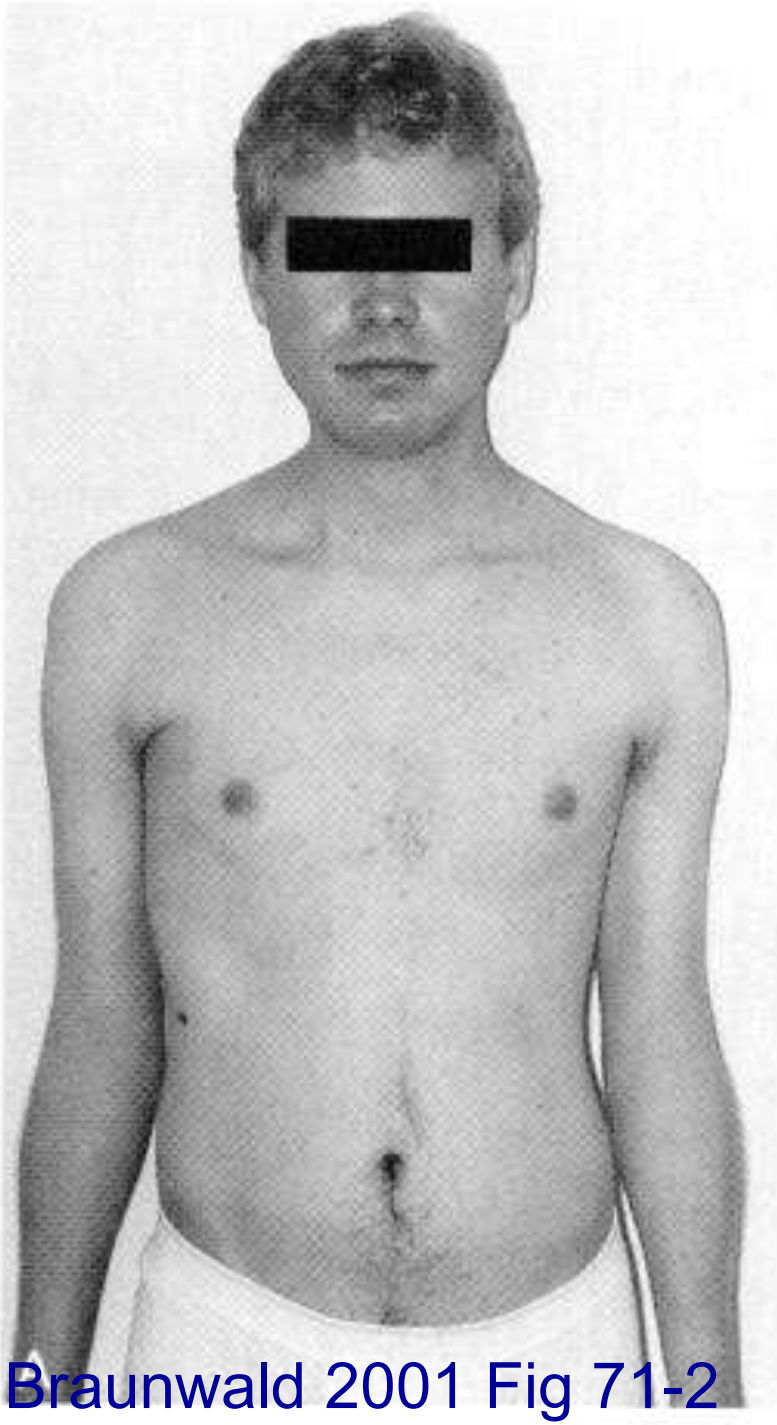
Half of the cardiac deaths are sudden

Braunwald 2001, fig 71-4 from Fisch C

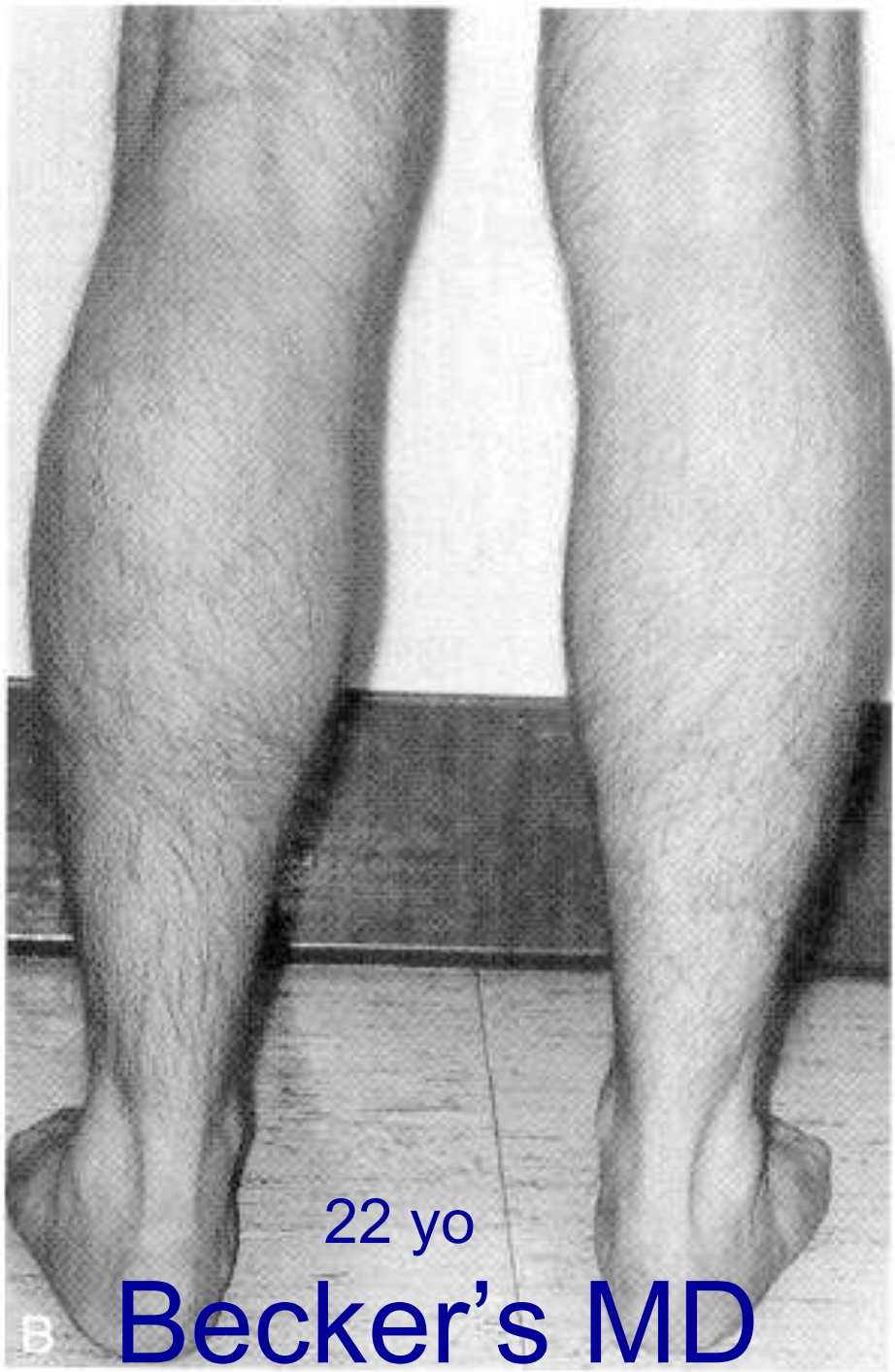


Becker's Muscular Dystrophy (BMD)

- 1:25,000, Dystrophin abnormality like DMD but less severe and later onset, with survival to middle age, muscle abnormality identical pattern to DMD
- Heart involved in 80%, DCM, CHF, conduction abnormalities, MR from annular dilation



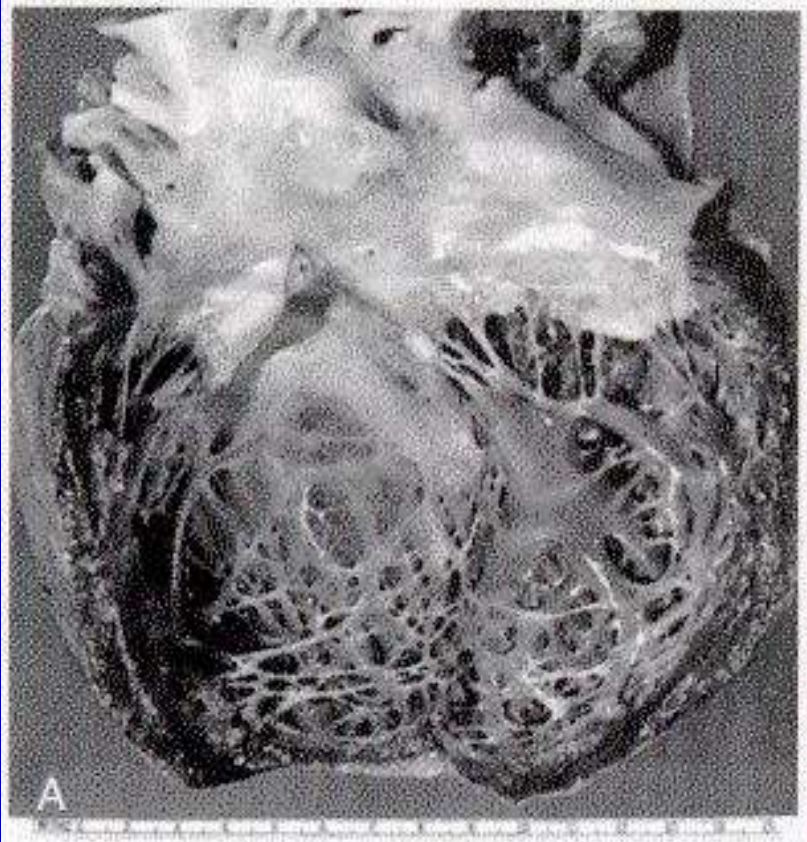
Braunwald 2001 Fig 71-2

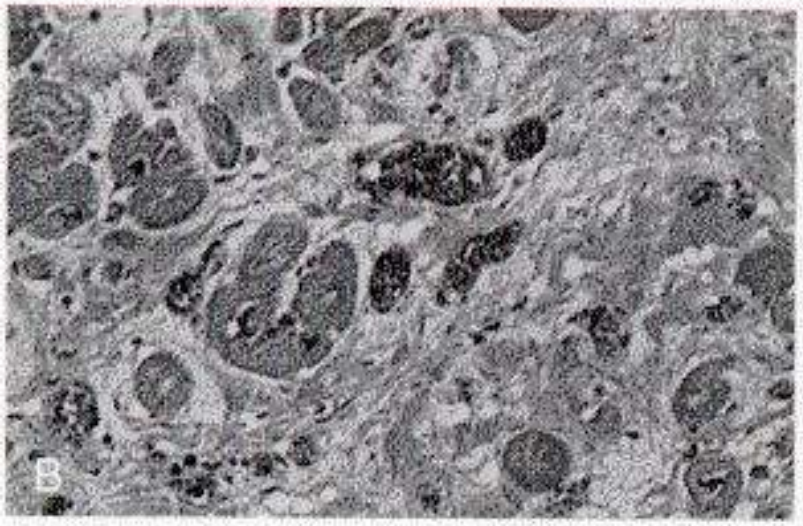


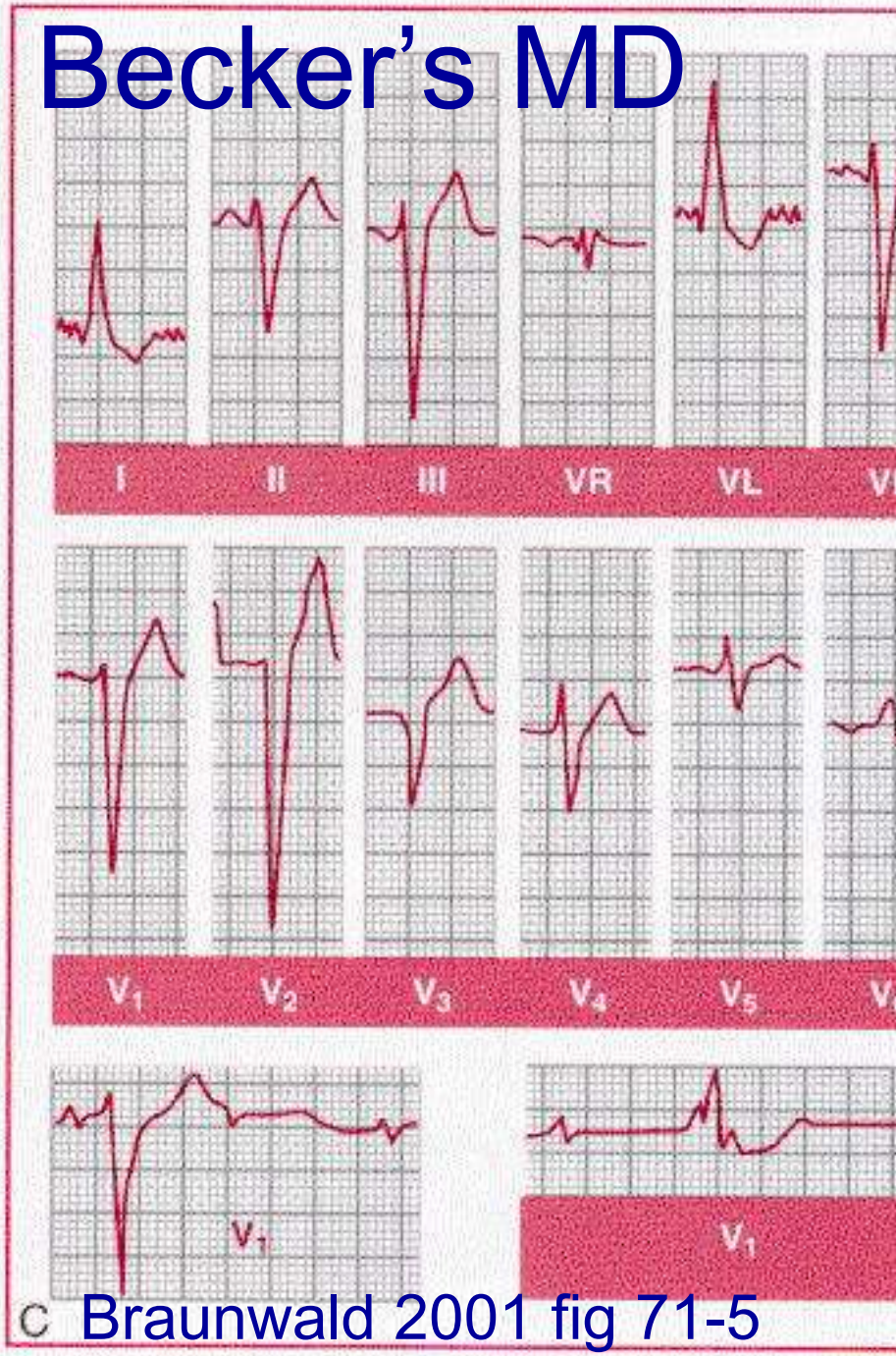
22 yo

Becker's MD

Becker's MD







Braunwald 2001 fig 71-5

Emery-Dreifuss Muscular Dystrophy (EDMD)

- Xq28 gene that makes emerin, Chromosome 1 defect in lamin A/C; Relatively rare, no pseurohypertrophy, DCM is common, variable severity, AV block, commonly need pacemaker
- Some have DCM and no peripheral disease

Myotonic Dystrophy (Steinert's Disease, DM) - 1

- 19q13.3 encoding myotonin protein kinase (DMPK), a serine-threonine protein kinase, excessive triplet repeats in the gene of CTG, usually with >100 repeats (CTG expansion size, nl <37) to produce disease
- Most common form of inherited muscular dystrophy in adults (1:8000, more in French Canadians, less in African blacks), autosomal dominant, ties up a CUG-binding protein (CUG-BP), has "anticipation"

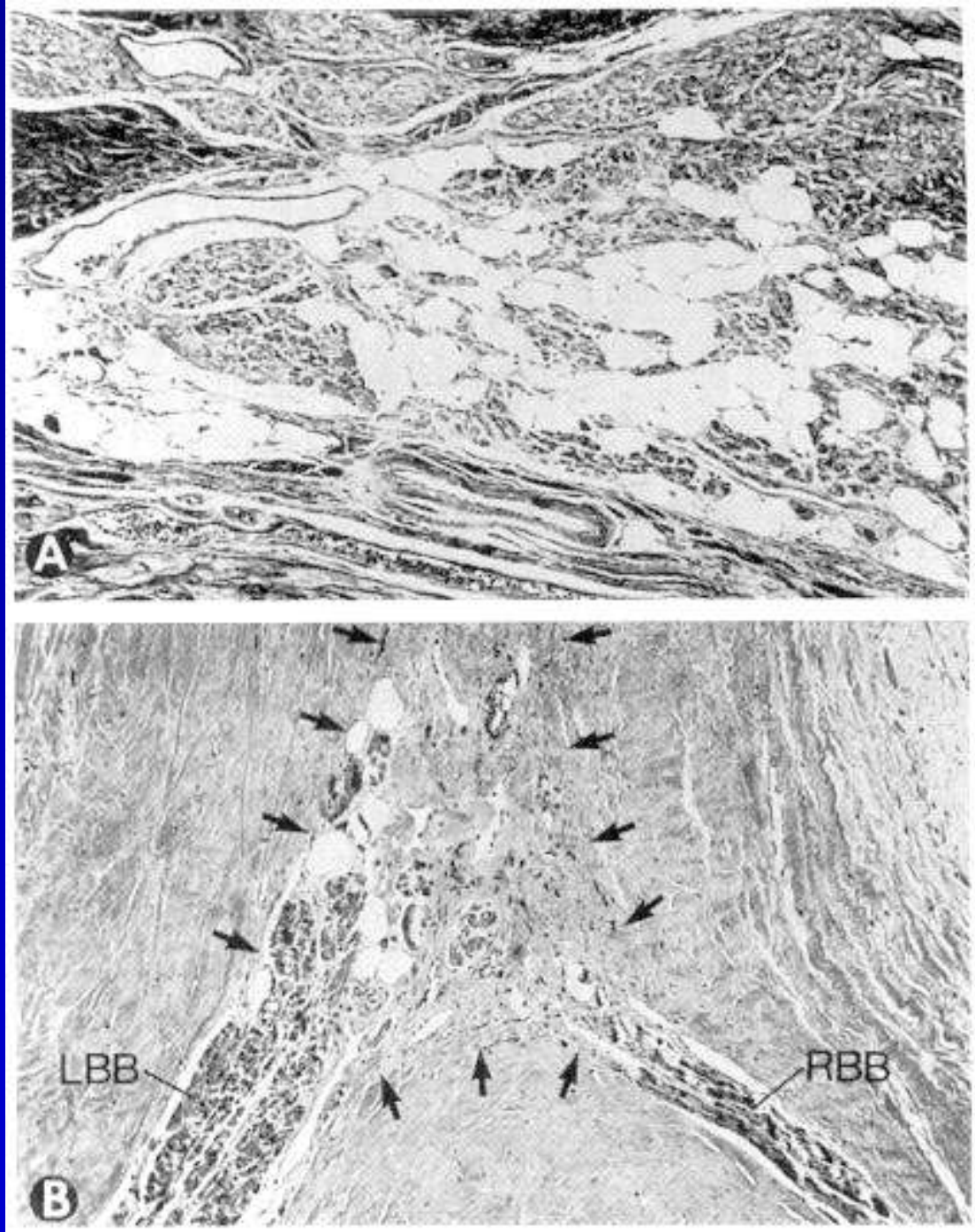
Myotonic Dystrophy (Steinert's Disease, DM) - 1

- Serious cardiac complications: fibrosis and fatty infiltration, common conduction abnormalities, SCD, bradycardia, prolonged PR and progression to CHB, VD, DCM may occur, less than diastolic dysfunction

Myotonic Dystrophy: Histology

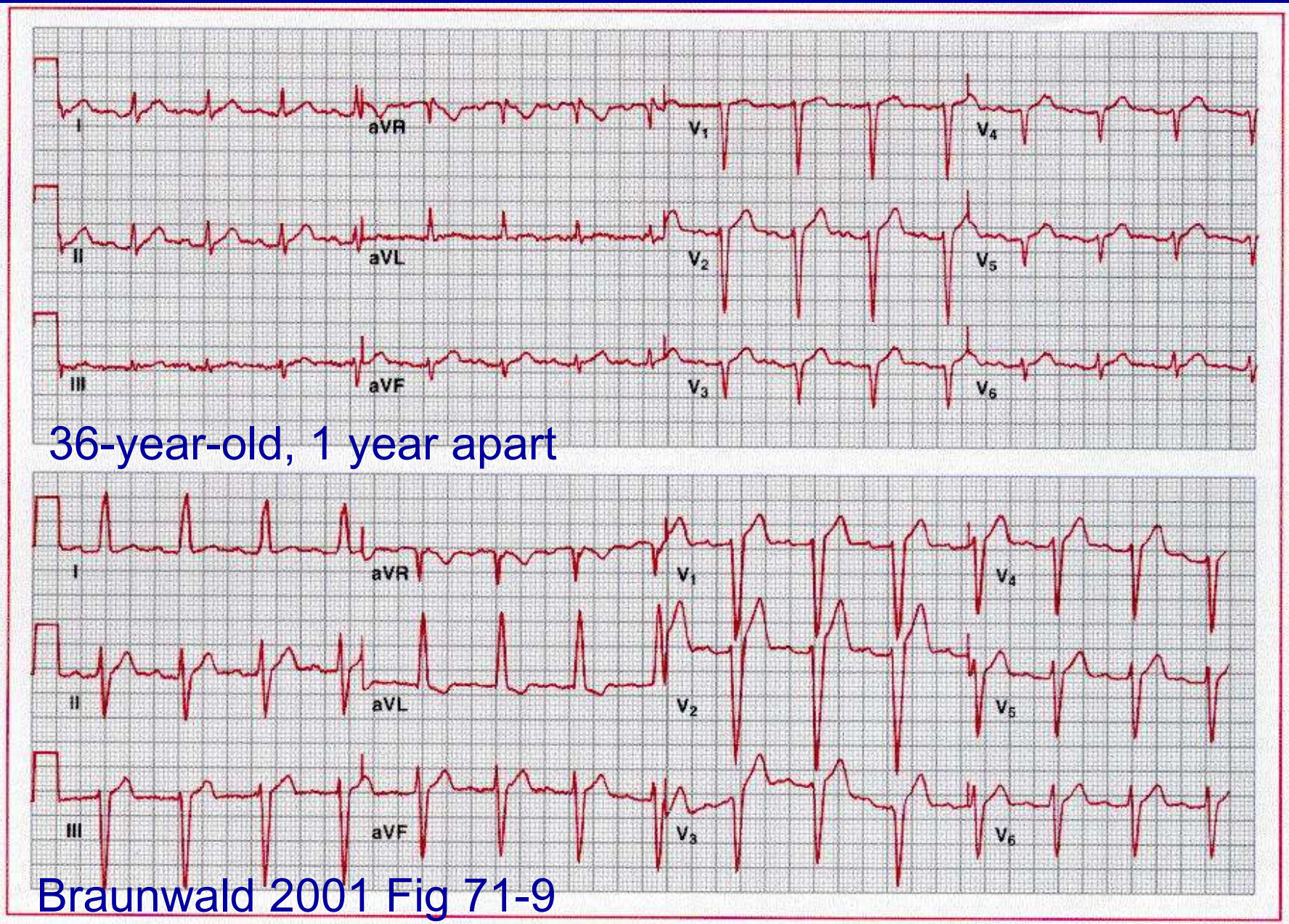
- Fatty infiltration of AVN in 57 yo man
- Focal replacement fibrosis and atrophy in 48 yo woman

- Risk of progression of AV block with anesthesia is significant



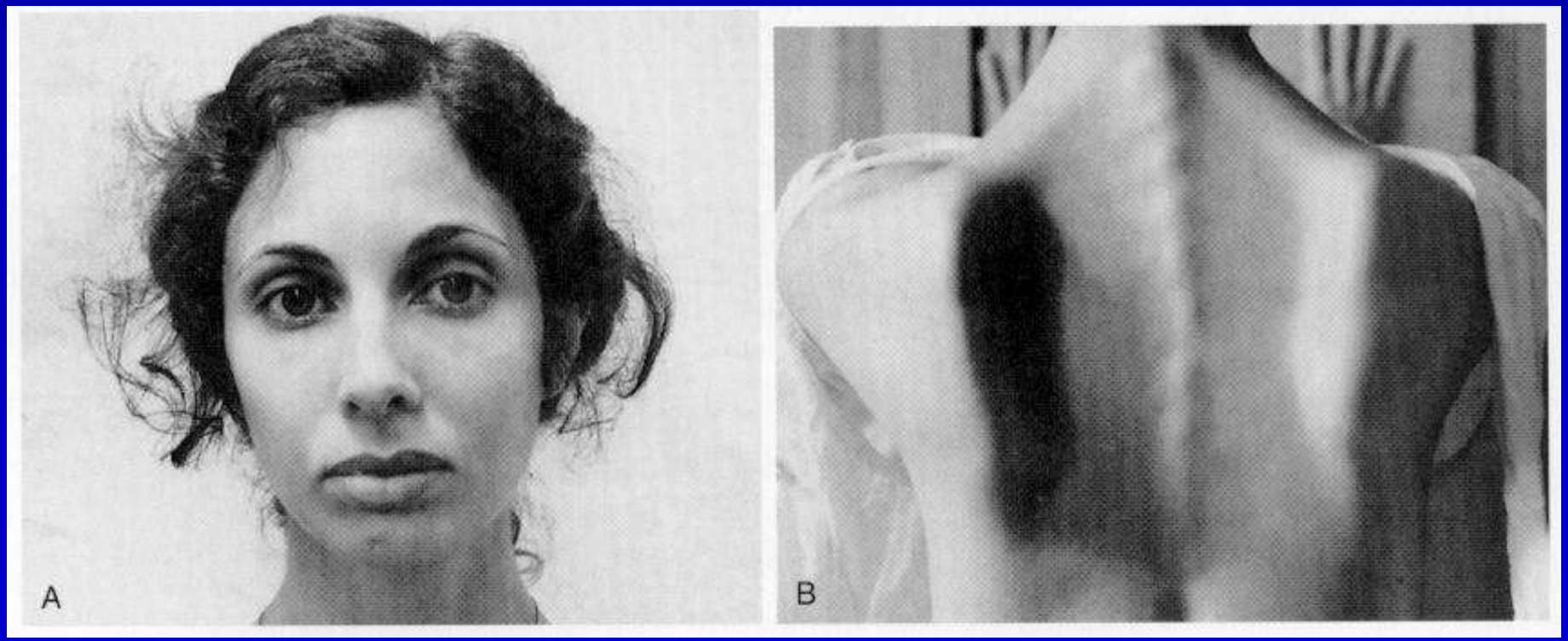
Braunwald 2001 Fig 71-8
From Nguyen HH. JACC 1988

Myotonic Dystrophy ECG



Fascioscapulohumeral Dystrophy

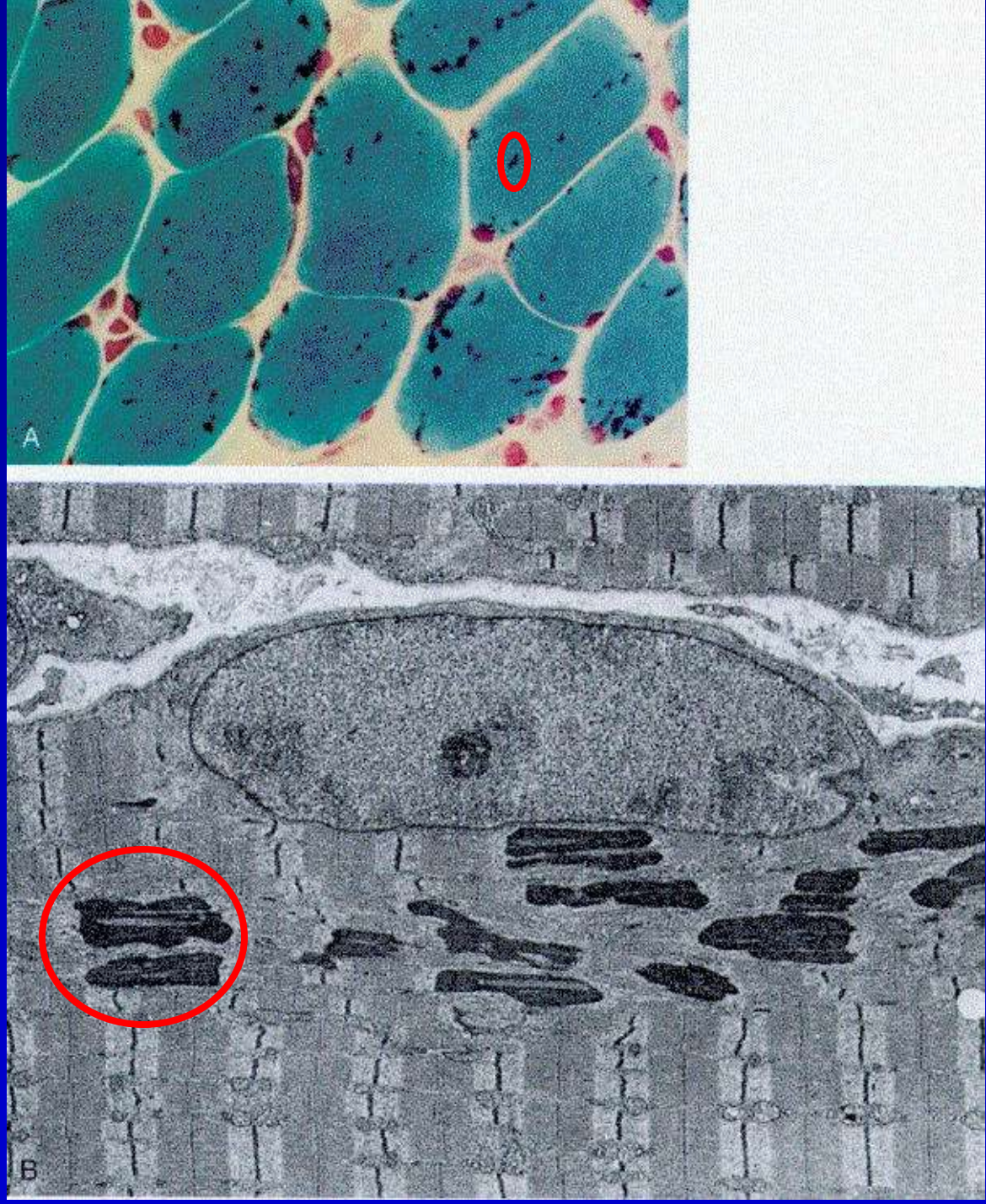
- 4q35, gene unknown, eponym Landouzy-Dejerine MD, 2 clinical types, one autosomal dominant around 10 yo, one is infantile
- Cardiac problems are generally mild. Progressive atrial dysfunction with atrial paralysis (?EDMD), sinus bradycardia, junctional escape rhythm, AV block, and atrium is unresponsive to electrical stimulation, also may have atrial flutter or atrial tachycardia



Braunwald 2001 Fig 71-10 From Perloff JK

Nemaline Myopathy

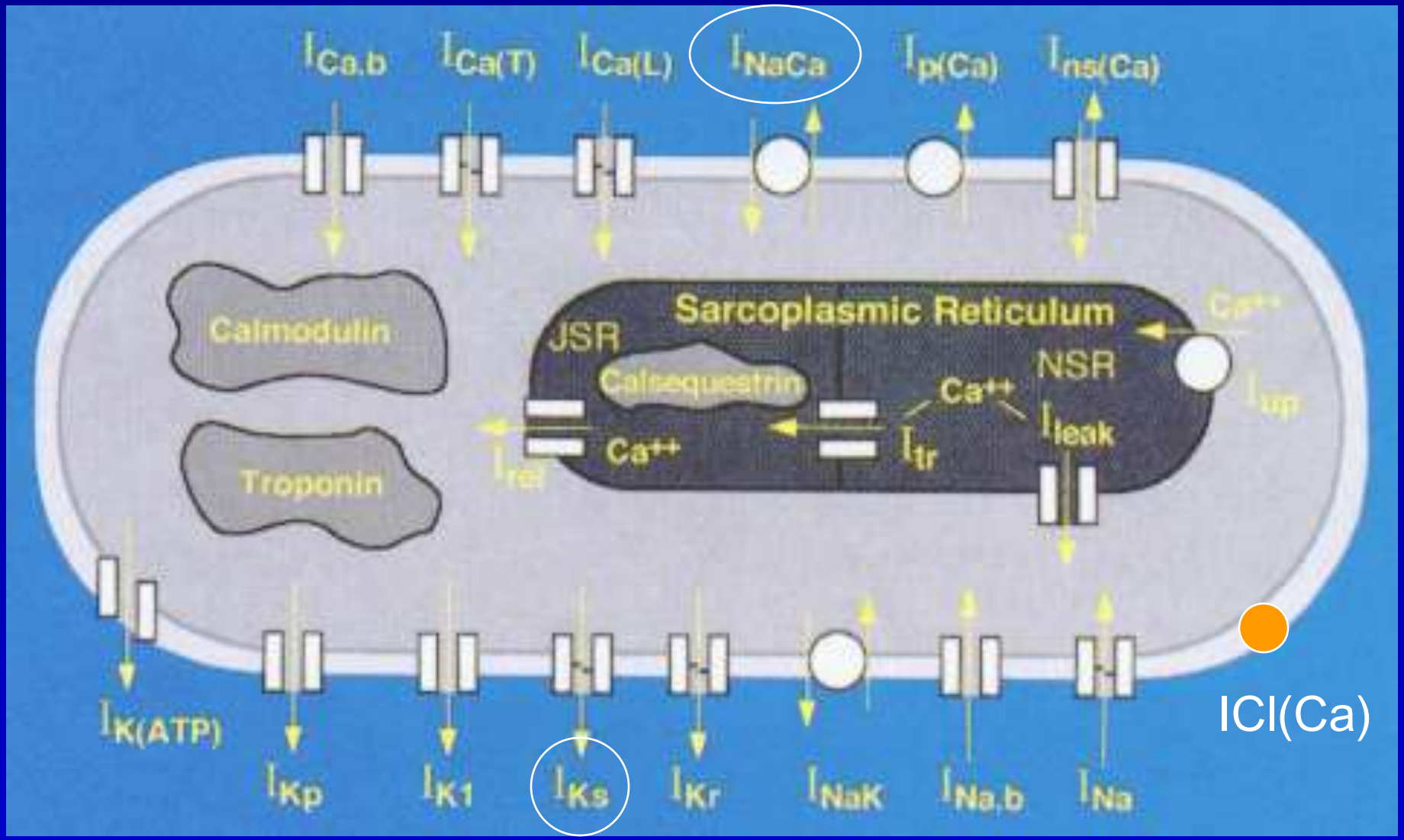
- Probably autosomal dominant, mutation in alpha-actin gene (ACTA1), or TPM3 encoding alpha-tropomyosin slow, or NEB encoding nebulin
- ACTA1 also causes actin myopathy with excessive thin filaments
- Conduction abnormalities and cardiac dilatation are unusual, with nemaline rods in the myocardium
- Z-band material – alpha actinin



Robbins, 1998, fig 29-12

Endocardial Fibroelastosis

- Autosomal dominant or recessive or X-linked, now a rare disease, since MMR vaccination, may have been due to mumps intrauterine



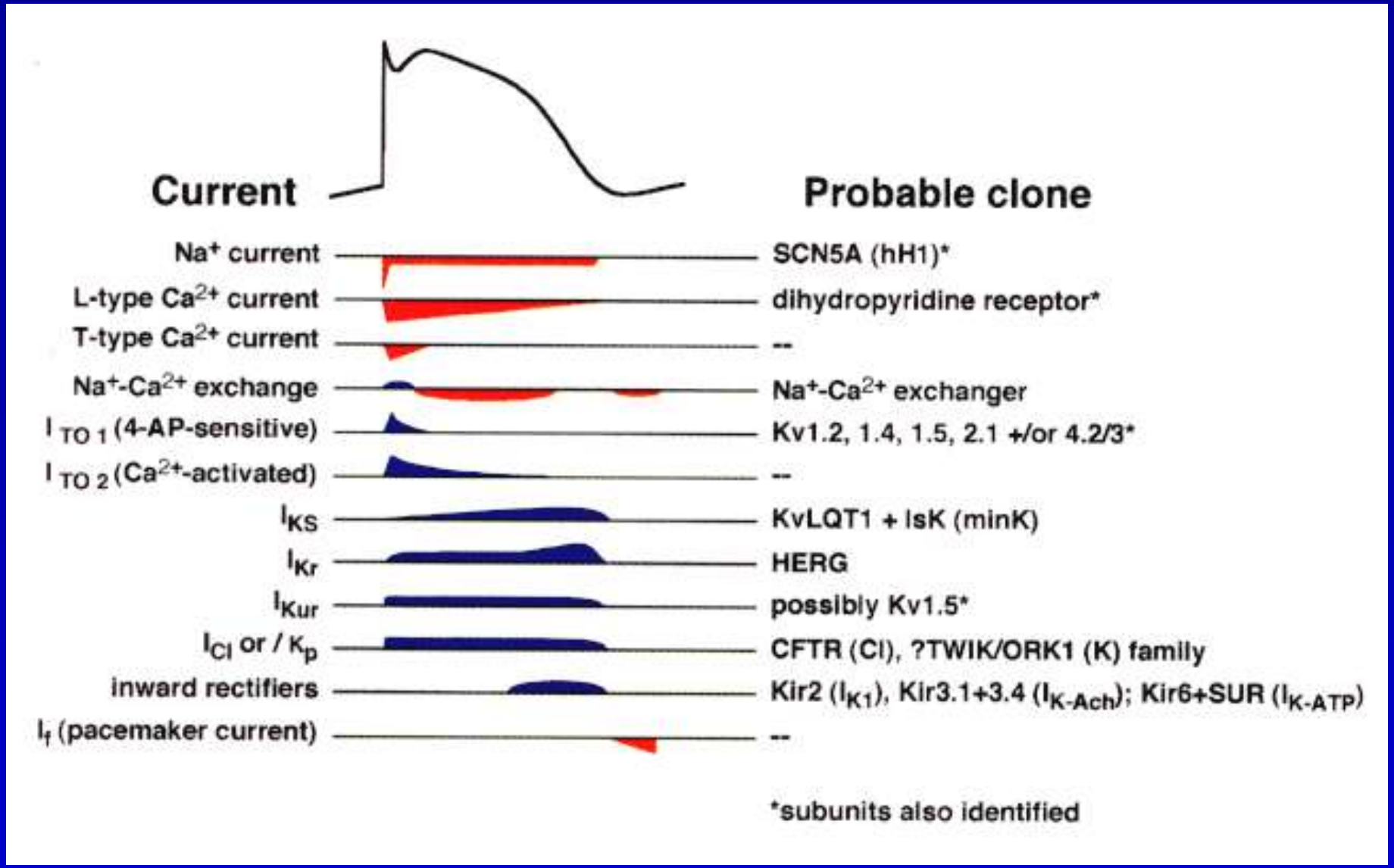
Model of Cardiac Ventricular Cell, with Ion Channels and Pumps
Circles indicate beta adrenergic augmentation

Priori SG, et al. Circulation 1999;99:674-81.

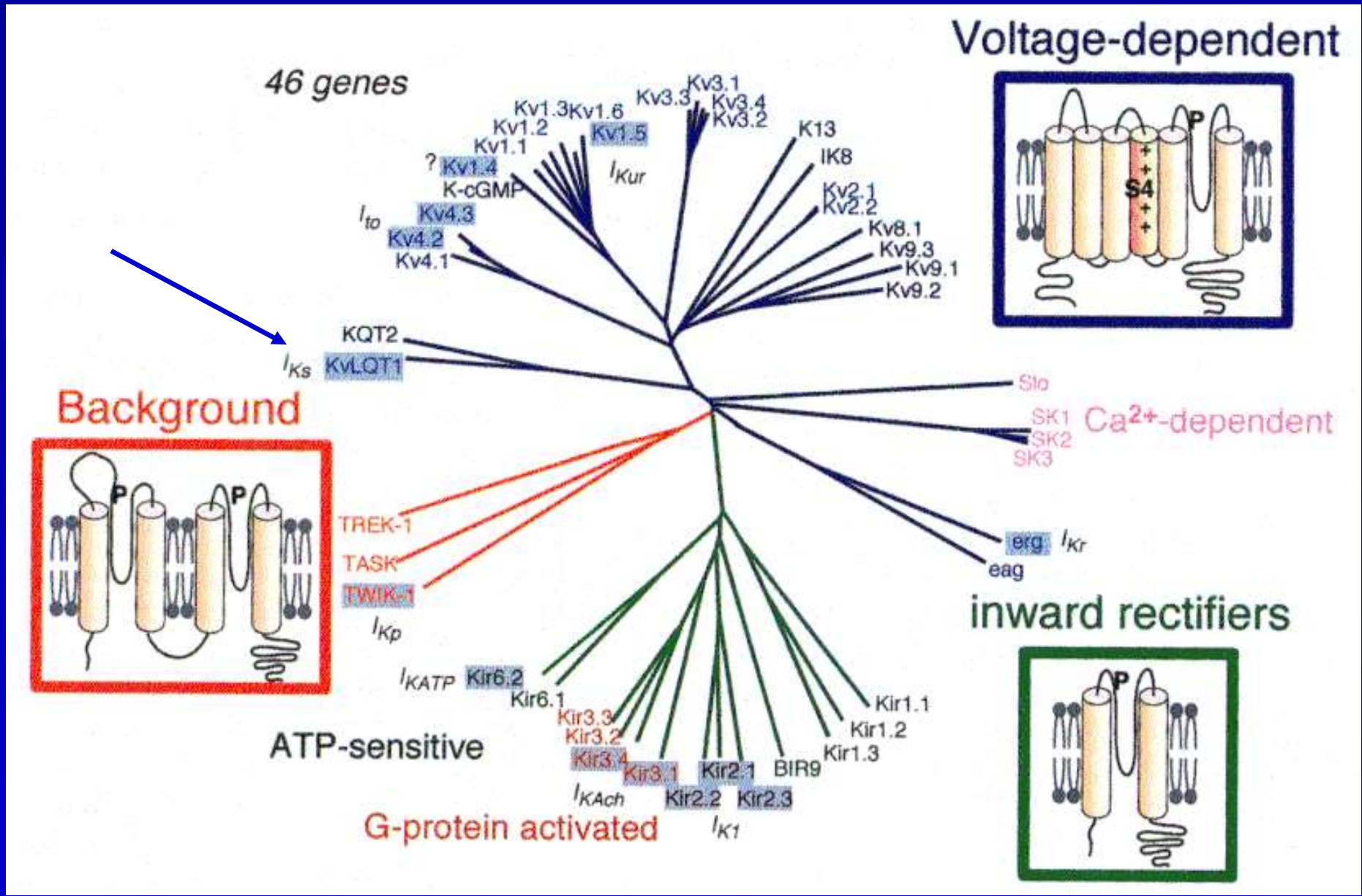
18 Currents in a Cardiac Ventricular Cell:

INa indicates fast sodium current;
ICa(L), calcium current through L-type calcium channels;
ICa(T) calcium current through T-type calcium channels;
IKr, fast component of delayed rectifier potassium current;
IKs, slow component of delayed rectifier potassium current;
IK1, inward rectifier potassium current;
IKp, plateau potassium current;
IK(ATP), ATP-sensitive potassium current;
INaK, sodium-potassium pump current;
INaCa, sodium-calcium exchange current;
Ip(Ca), calcium pump in sarcolemma;
INa,b, sodium background current;
ICa,b, calcium background current;
Ins(Ca), nonspecific calcium-activated current;
Iup, calcium uptake from myoplasm to network sarcoplasmic reticulum (NSR);
Irel, calcium release from junctional sarcoplasmic reticulum (JSR);
Ileak, calcium leakage from NSR to myoplasm; and
Itr, calcium translocation from NSR to JSR.
Calmodulin, troponin, and calsequestrin are calcium buffers.

Priori SG, et al.
Circulation
1999;99:674-81.



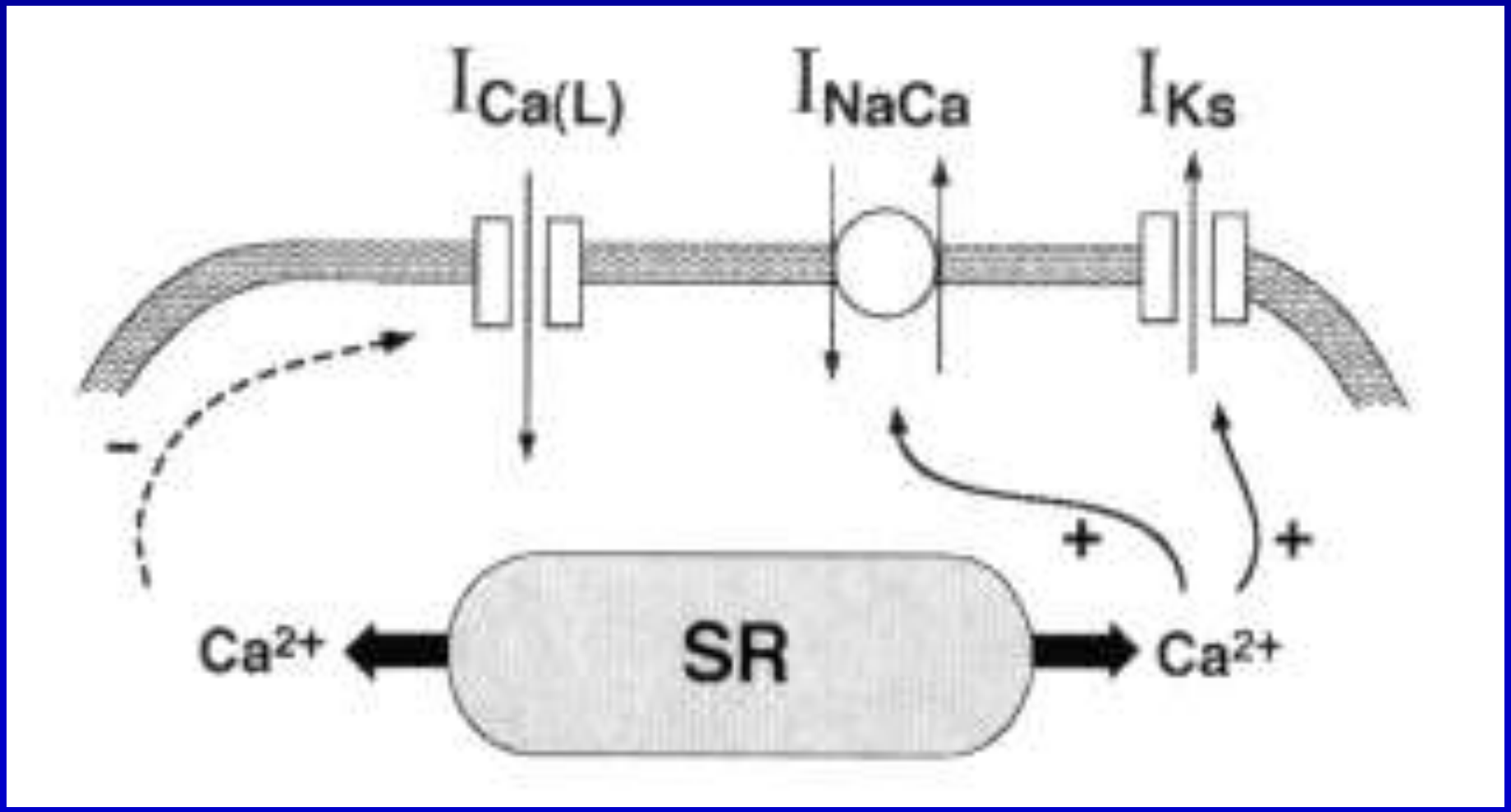
Priori SG, et al. Circulation 1999;99:674-81.



Pore-forming K+ channel subunits in man and rodent. grey box=hea

Priori SG, et al. Circulation 1999;99:674-81.

Interactive Processes in a Cell



Priori SG, et al. Circulation 1999;99:674-81.

Congenital QT Prolongation

- Diagnostic Criteria:
  - Asymptomatic patient, QTc>470msec
  - OR: Male with QTc>440 or female with QTc>460 PLUS:
    - Stress-related syncope
    - Torsade de pointes
    - Family history of early (<35yo) SCD
  - These criteria are neither totally sensitive or specific

Priori SG et al. Circulation 1999;99:529-33

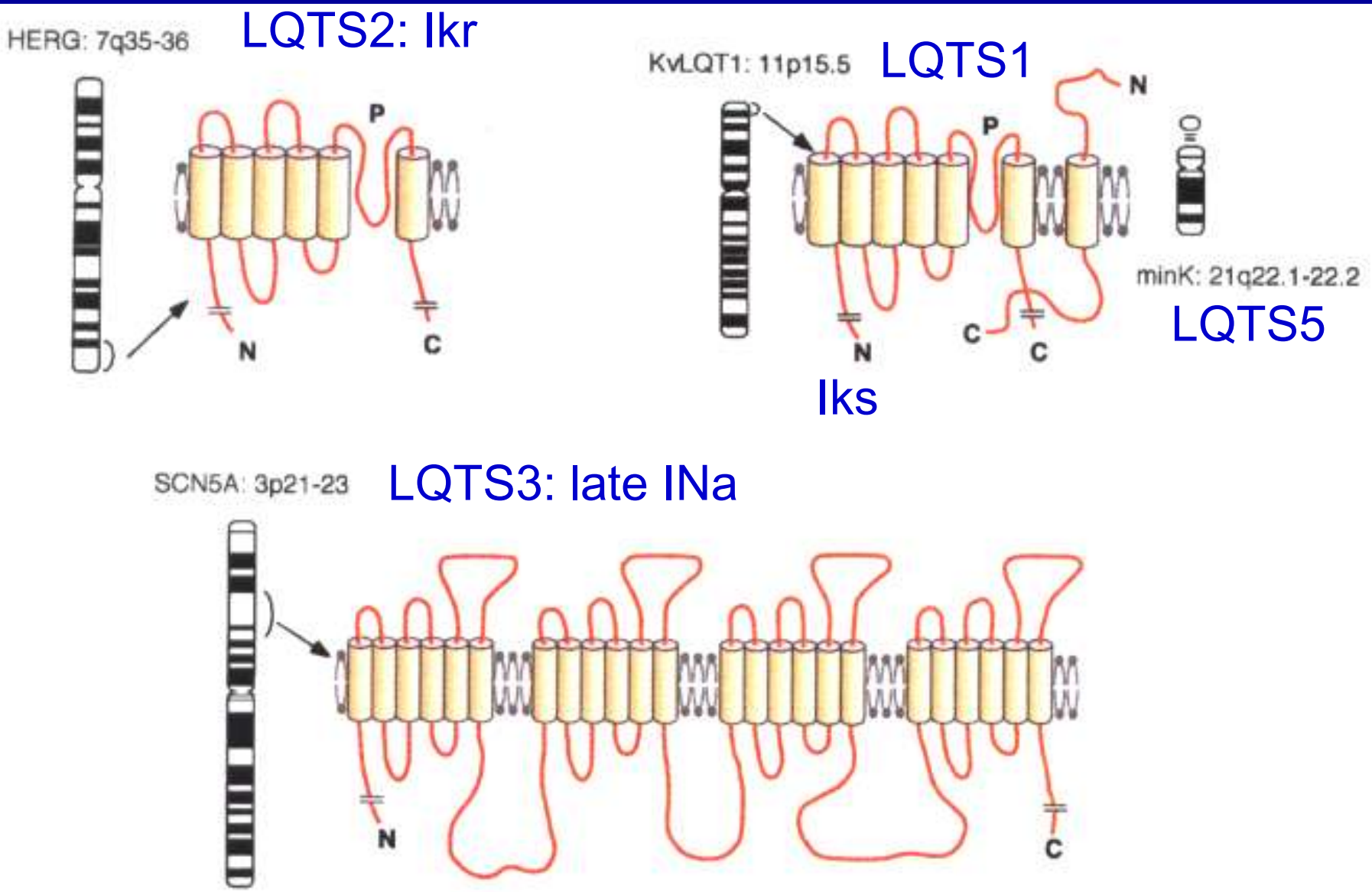
Congenital QT Prolongation

- Romano-Ward: autosomal dominant, no deafness
- Jervell and Lange-Nielson: autosomal recessive, with deafness (KVLQT1 and minK also control inner ear endolymph homeostasis)
- These 2 syndromes are disturbances in the same genes and channels, except Jervell and Lange-Nielson patients are homozygous, and the Romano-Ward patients are heterozygous with variable penetrance

Types of Congenital Prolonged QT interval

Syndrome	Gene	Chromosome	Current
LQTS1 (most common)*	KvLQT1	11p15.5	↓Iks (alpha subunit)
LQTS2	HERG	7q35-q36	↓Ikr
LQTS3 (rare)	SCN5A	3p21-p23	↑late INa
LQTS4	?	4q25-q27	?
LQTS5 (rare)*	minK (KCNE1)	21q22.1-q22	↓Iks (ancillary subunit)
LQTS6	MiRP1 (KCNE2)	21q22.1-q22	↓Ikr

* Jervell and Lange-Nielson as well as Romano-Ward



Priori SG, et al. Circulation 1999;99:518-528.

Adrenergic Effects in Congenital Prolonged QT interval

Syndrome	Pharm Mimic	↑QT/ ↑TDR	Isoproterenol, +Propranolol	Current
LQTS1	chromanol 293B	+/-	↑/↑, n/n	↓Iks
LQTS2	dofetalide, E-4031, d-sotalol	+/+	↑/↑↓, n/n	↓Ikr
LQTS3	anthopleurin A, ATX-II	++/++	↓/↓, n/n	↑late INa

Experimentally: beta-blockade totally suppresses Tdp in LQT1, partially suppresses TdP in LQT2, and may provoke TdP in LQT3

Shimizu, J Am Coll Cardiol 2000;35:778-86

Mutations in LQTS Genes

- Each gene has multiple types of abnormalities, some are hot spots
- Modifier genes?: identical gene defects have variability in clinical features
- Modification of channel function:
  - Related to specific amino acid defect
  - KvLQT1, KCNE1 and HERG lose function
  - SCN5A gains function (defective inactivation)

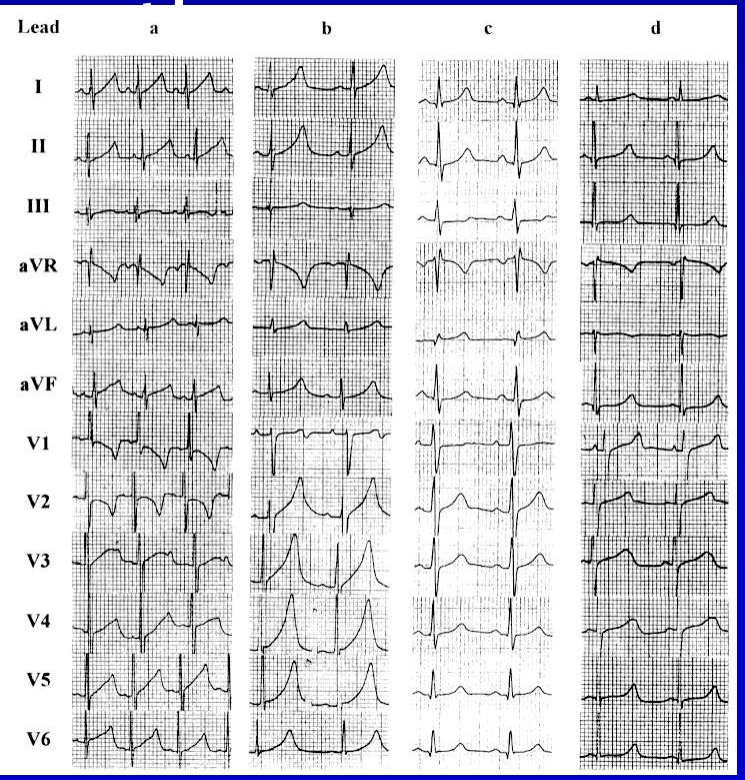
Clinical Correlation in Congenital LQTS

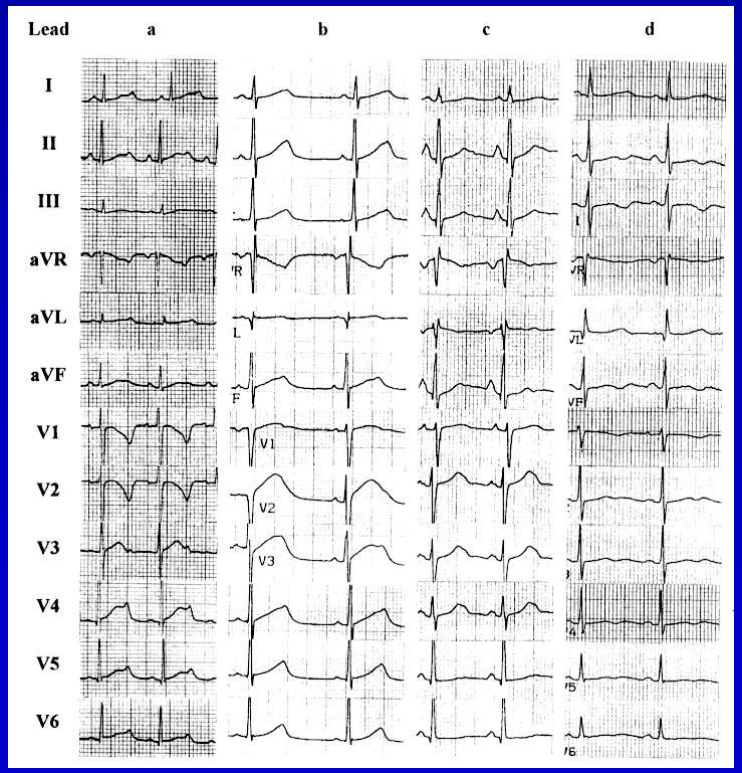
- Manifestations
  - LQTS1: trigger of exercise
  - LQTS3: trigger with sleep or rest, shorten QT with exercise
  - LQTS2: both rest and exercise
- Management
  - Beta-blocker is first choice therapy
  - LQT3 usually improve with mexiletine
  - LQT2 may improve with mexiletine

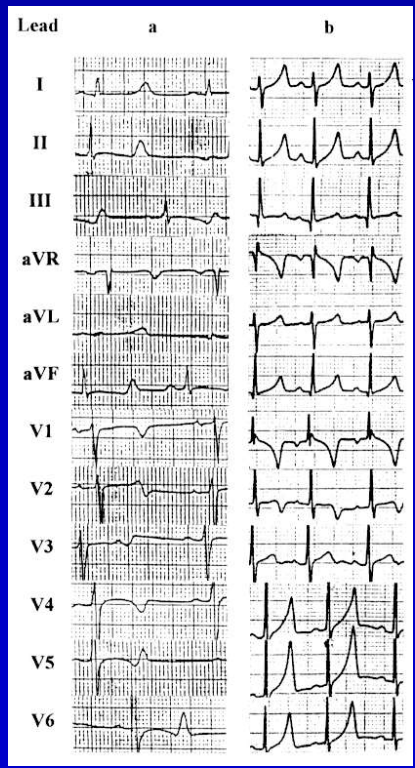
ECG manifestations of LQTS

- Vary with genotype

Type 1 Type 2 Type 3



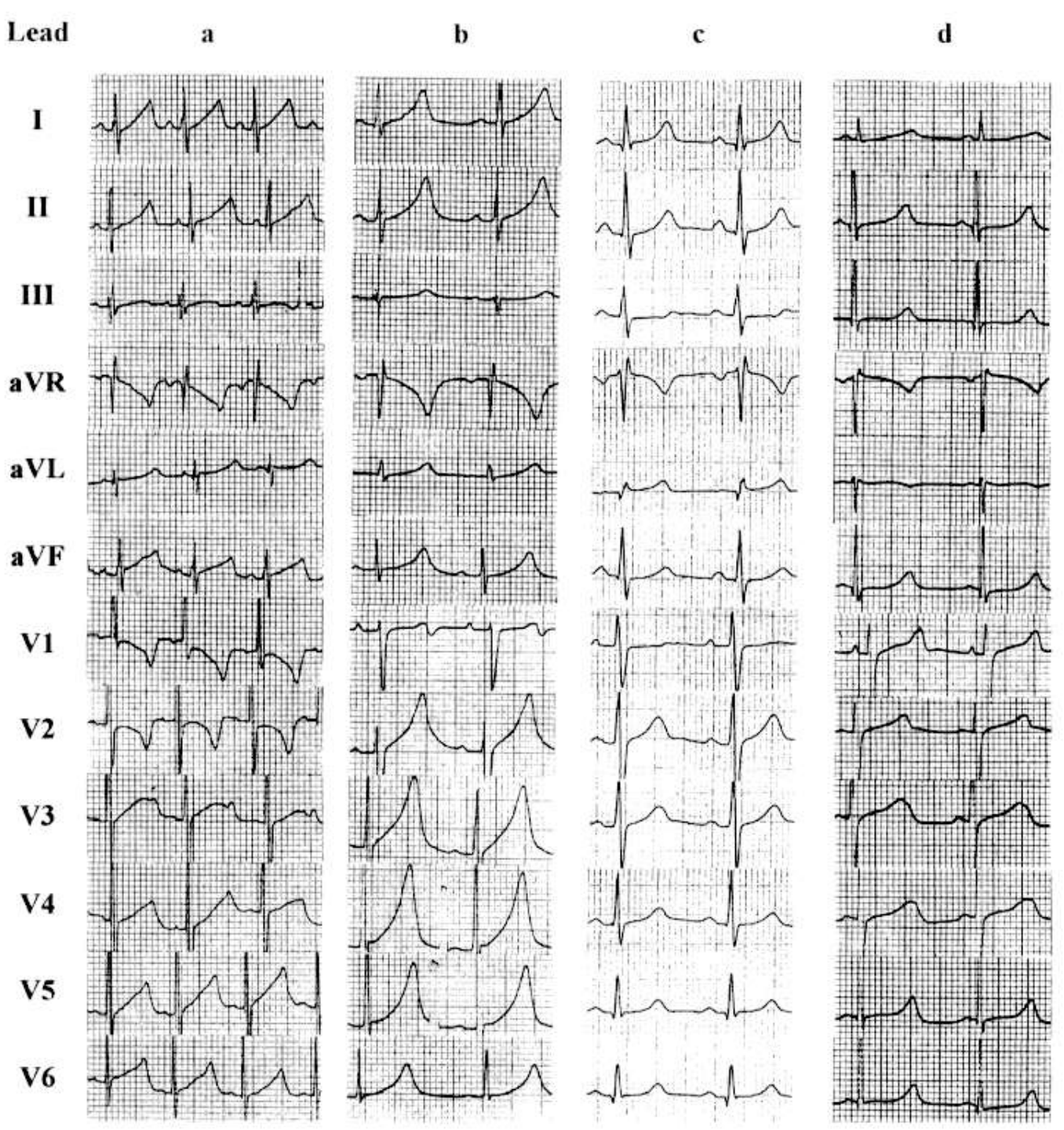




Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849

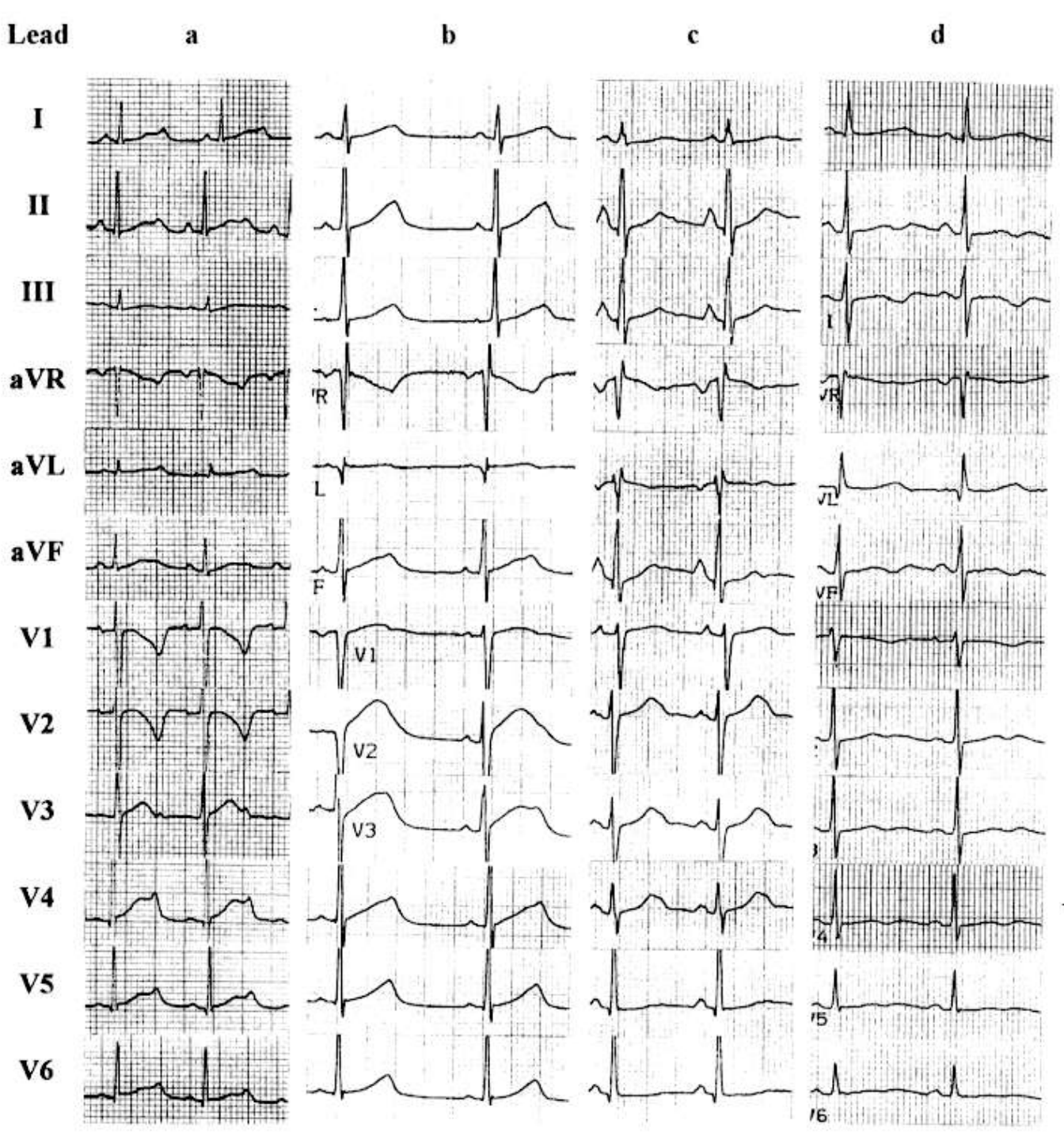
Type 1

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849



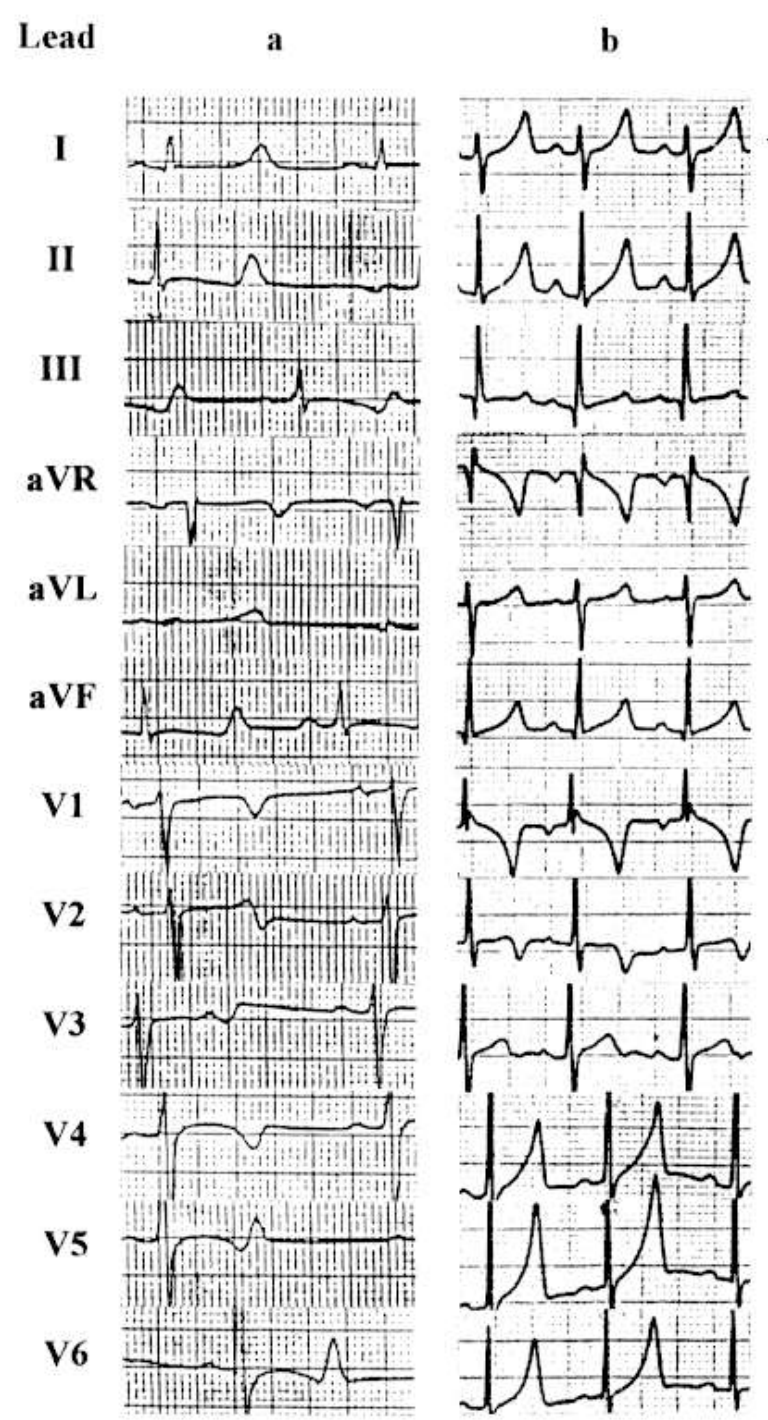
Type 2

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849



Type 3

Circ, Dec 5, 2000… Wilde and Roden p 2797, Zhang et al, p.2849



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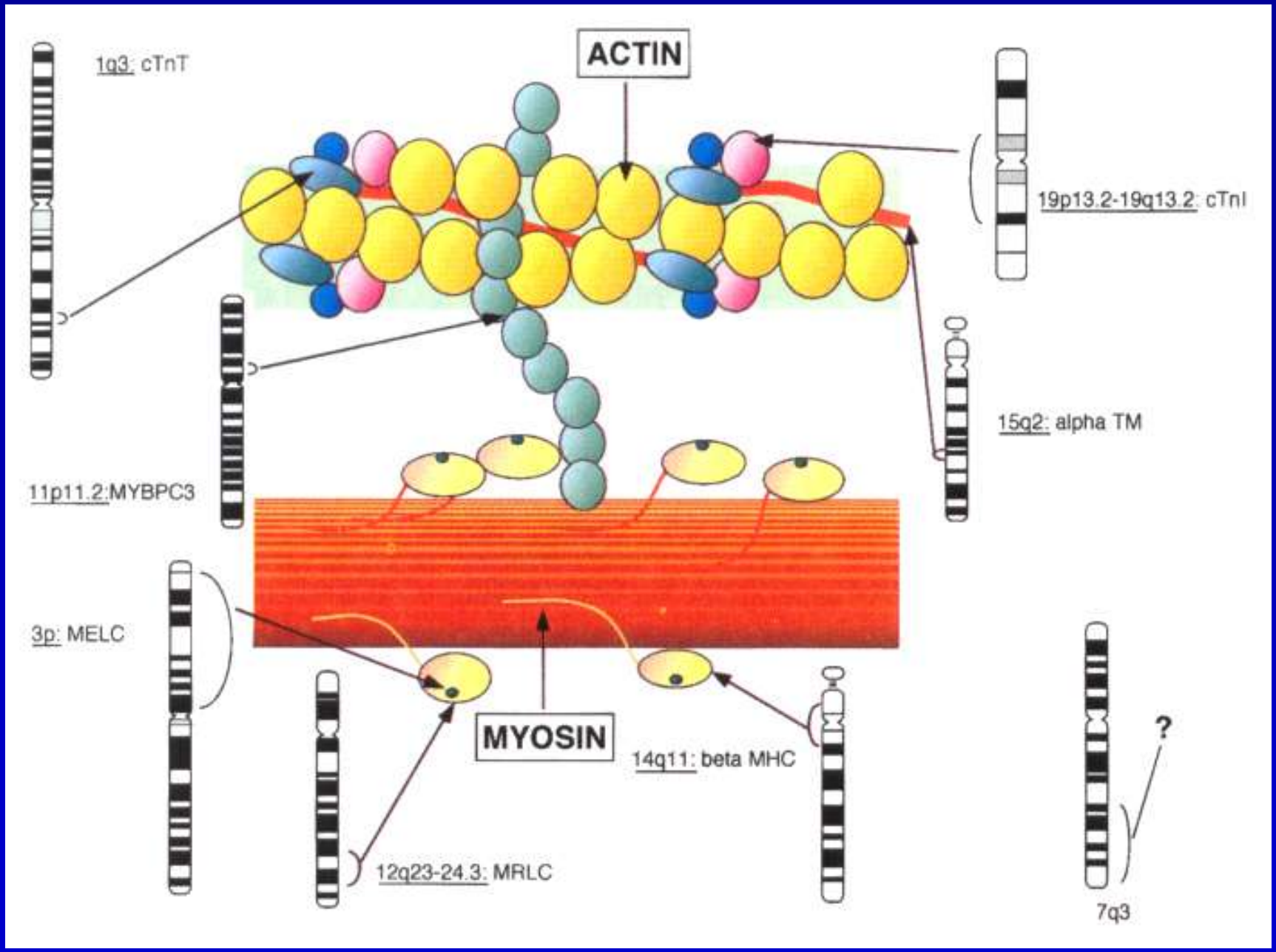
- Zhang et al. Circulation 2000;102:2849-55
- Wilde et al. Circulation 2000;102:2799-2801



Priori SG, et al. Circulation 1999;99:518-528.

Defects of Metabolism Causing Cardiomyopathy

- Carnitine deficiency
- Medium chain Acyl-CoA Dehydrogenase (MCAD) deficiency
- Long/Very long chain Acyl-CoA Dehydrogenase (LCAD/VLCAD) deficiency
- Fabry's disease
- Homocysteinuria
- Mitochondrial cardiomyopathies
- Connective tissue disorders
- Primary rhythm/conduction disorders
- Congenital heart disease c/s genetic syndromes

Homocystinuria

- Autosomal Recessive, 1:75,000, 21q22.3, cystathionine beta-synthase (CBS) deficient, elevated serum methionine and elevated urine homocystine
- Homozygous: marfanoid habitus, arterial and venous thrombosis (activation of factor V, inhibition of protein C and decreased AT-III), medial degeneration of the aorta and intimal hyperplasia and fibrosis
- 13-47% respond to pyridoxine
- May occur from Vit B6 or B12 or folate deficiency
- Mechanism: induction of cyclin A gene, inducing VSMC proliferation

Note: article on post PCI improved outcomes in folate admin; NEJM Nov 29, 200

Mitochondrial DNA

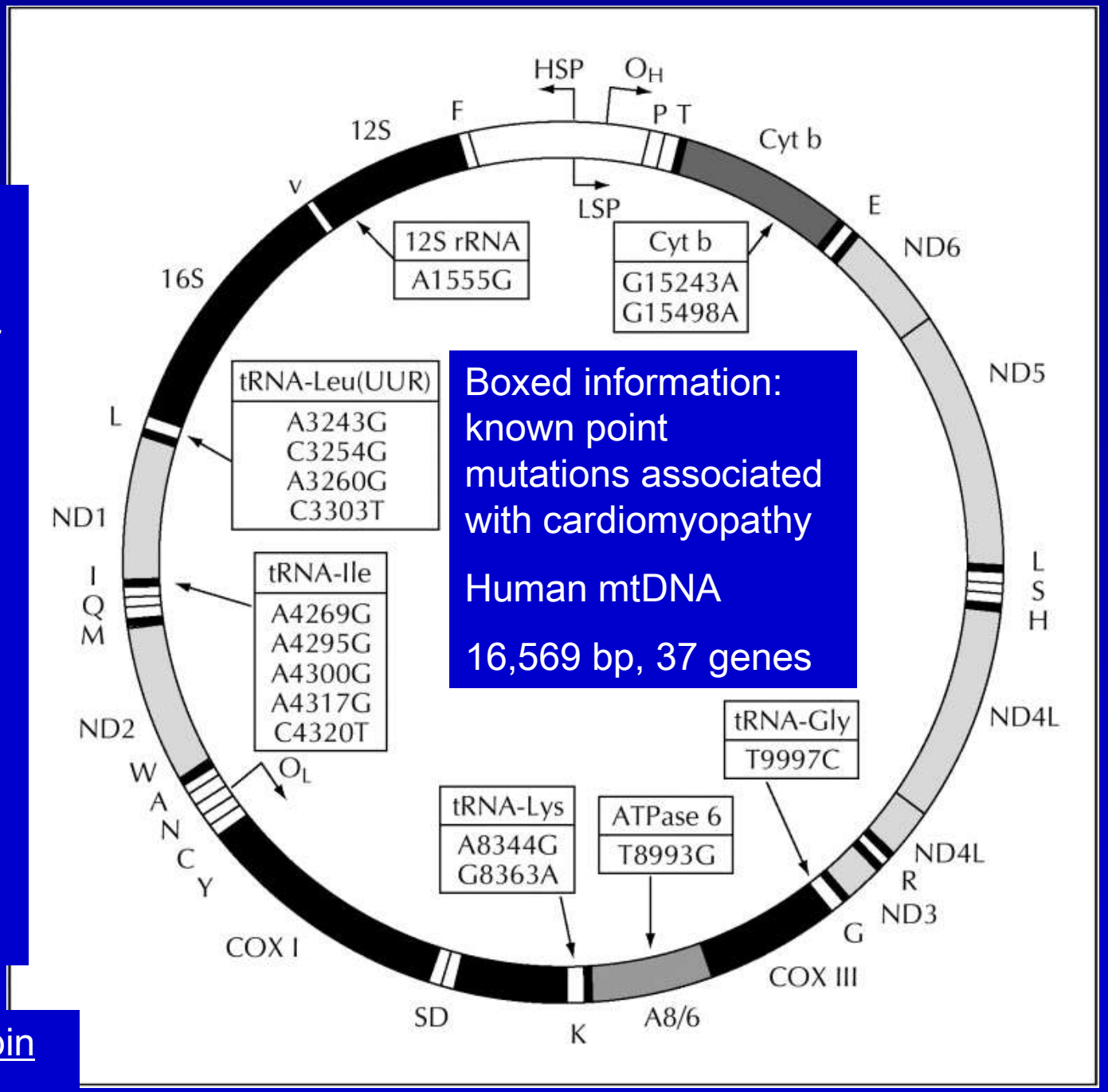
Gray – 7 subunits of complex I (ND)

Black – 3 subunits of cytochrome c oxidase (COX), 12S and 16S ribosomal RNA (rRNA)

Dark gray – Cytochrome b

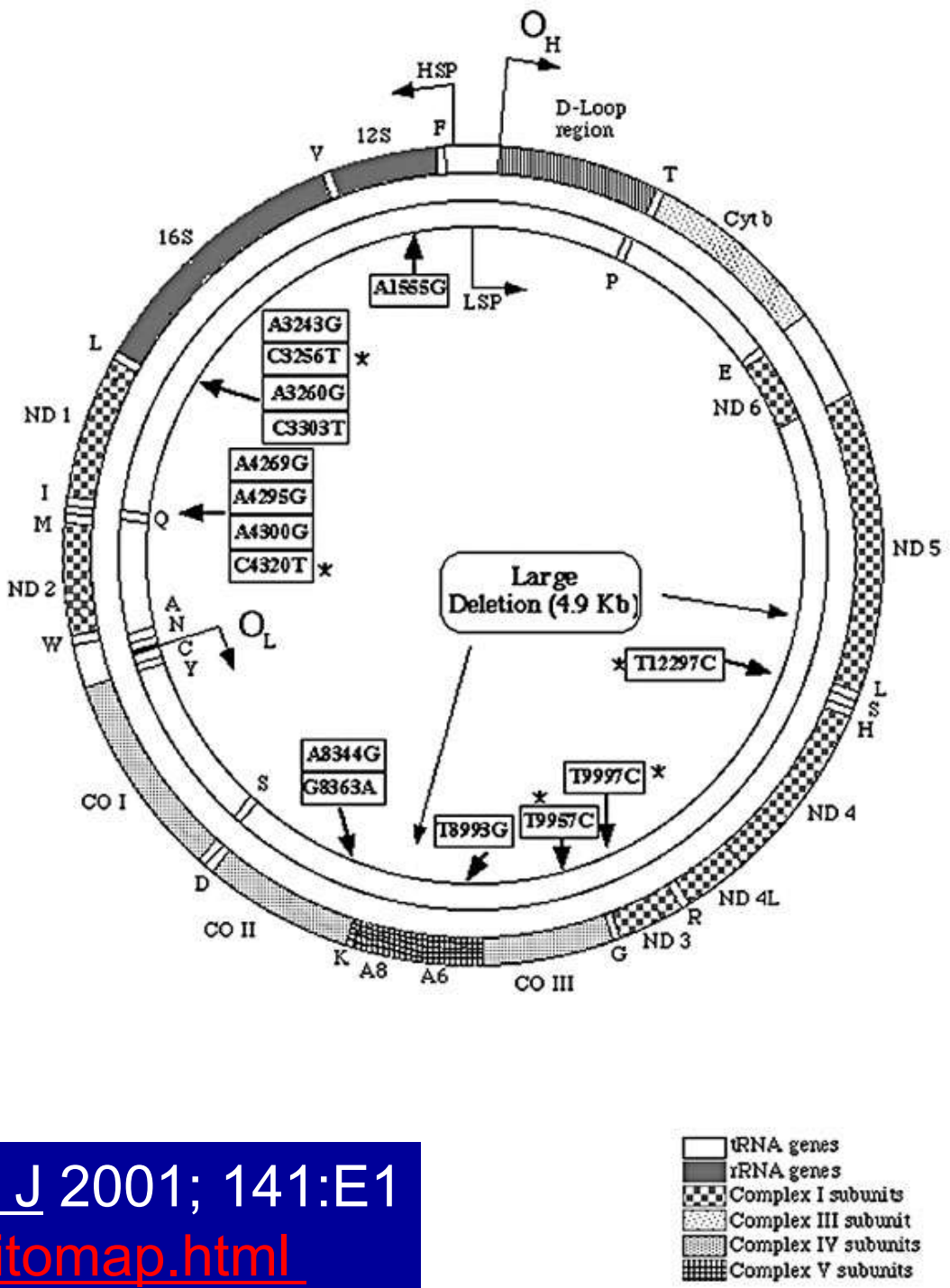
Gray – 2 subunits of ATP synthetase (ATPase 6 and 8)

White – 22 tRNA's



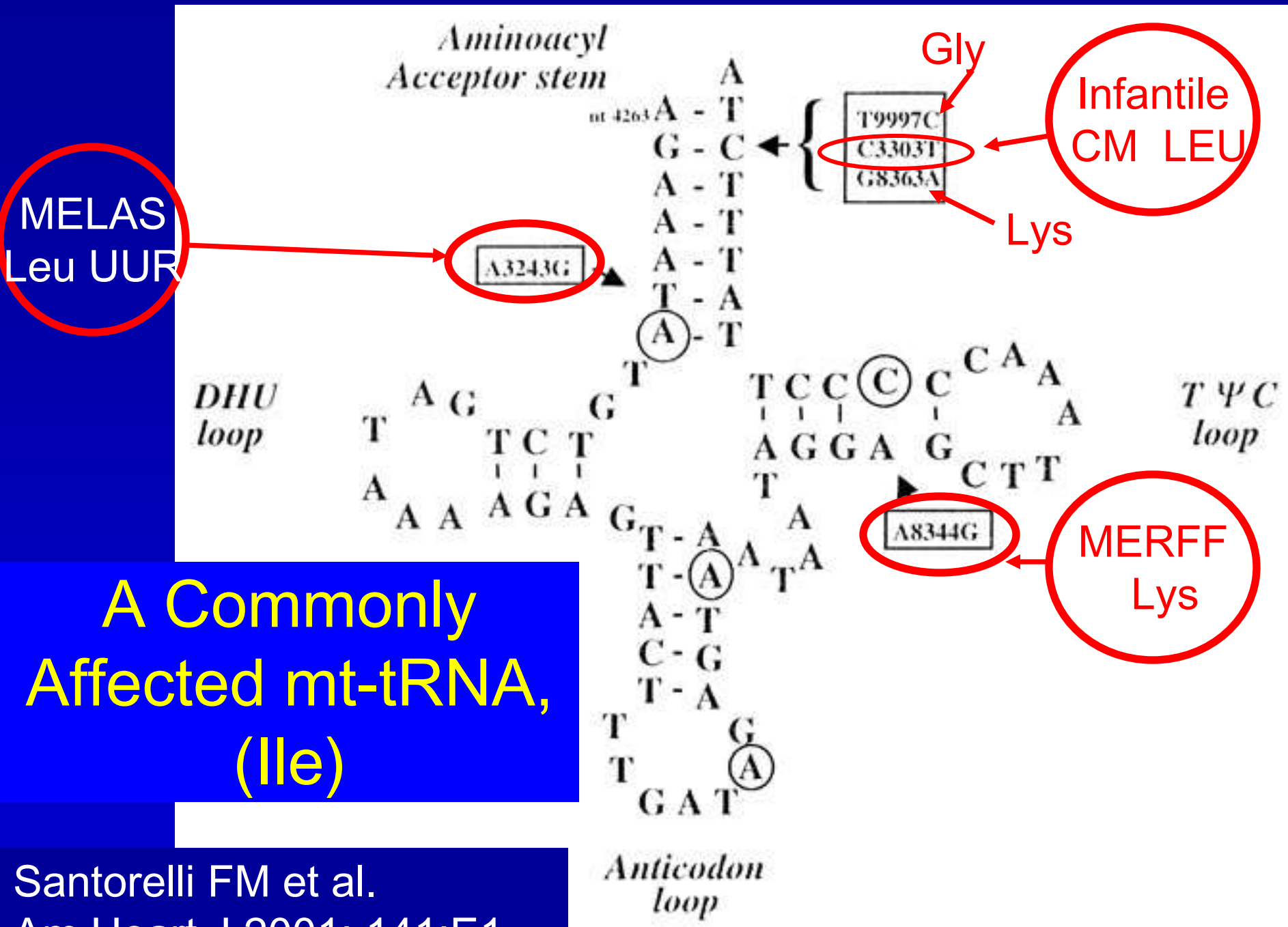
Hirano M et al. Curr Opin Cardiol 2001; 16:201

Mitochondrial DNA



Santorelli FM et al. Am Heart J 2001; 141:E1

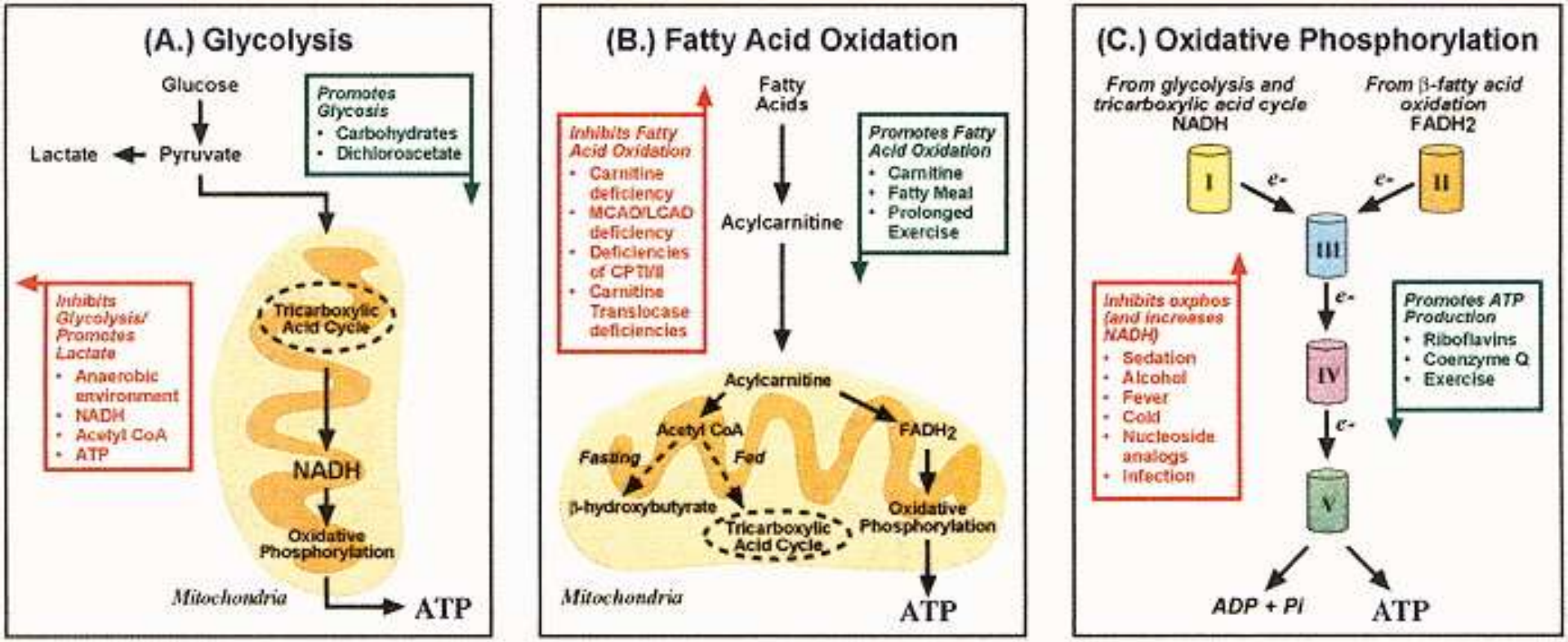
http://www.gen.emory.edu/mitomap.html



A Commonly Affected mt-tRNA, (Ile)

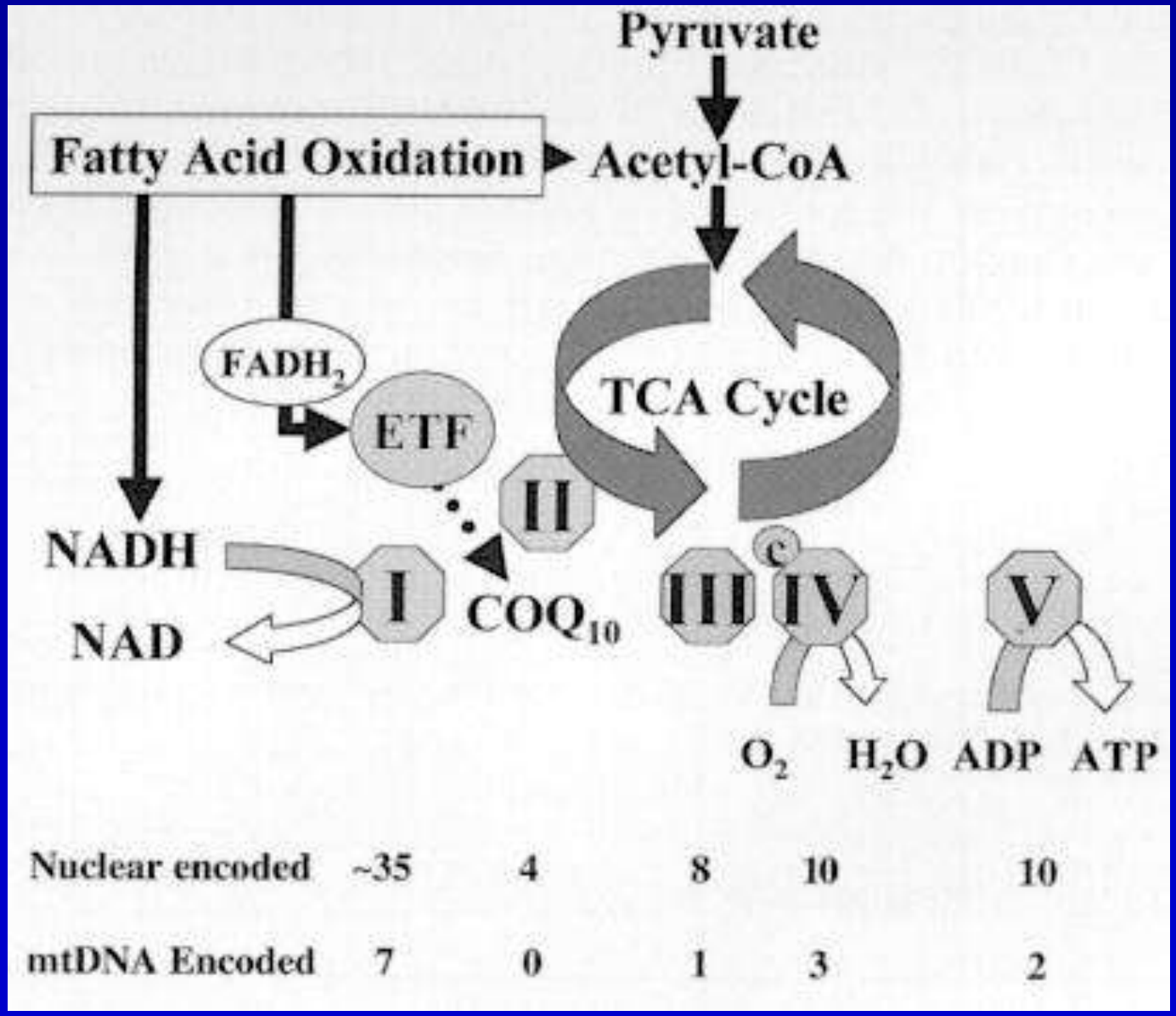
Santorelli FM et al.
Am Heart J 2001; 141:E1

Generation of ATP



Clay AS et al. Chest 2001;120:634

Oxidative Metabolism

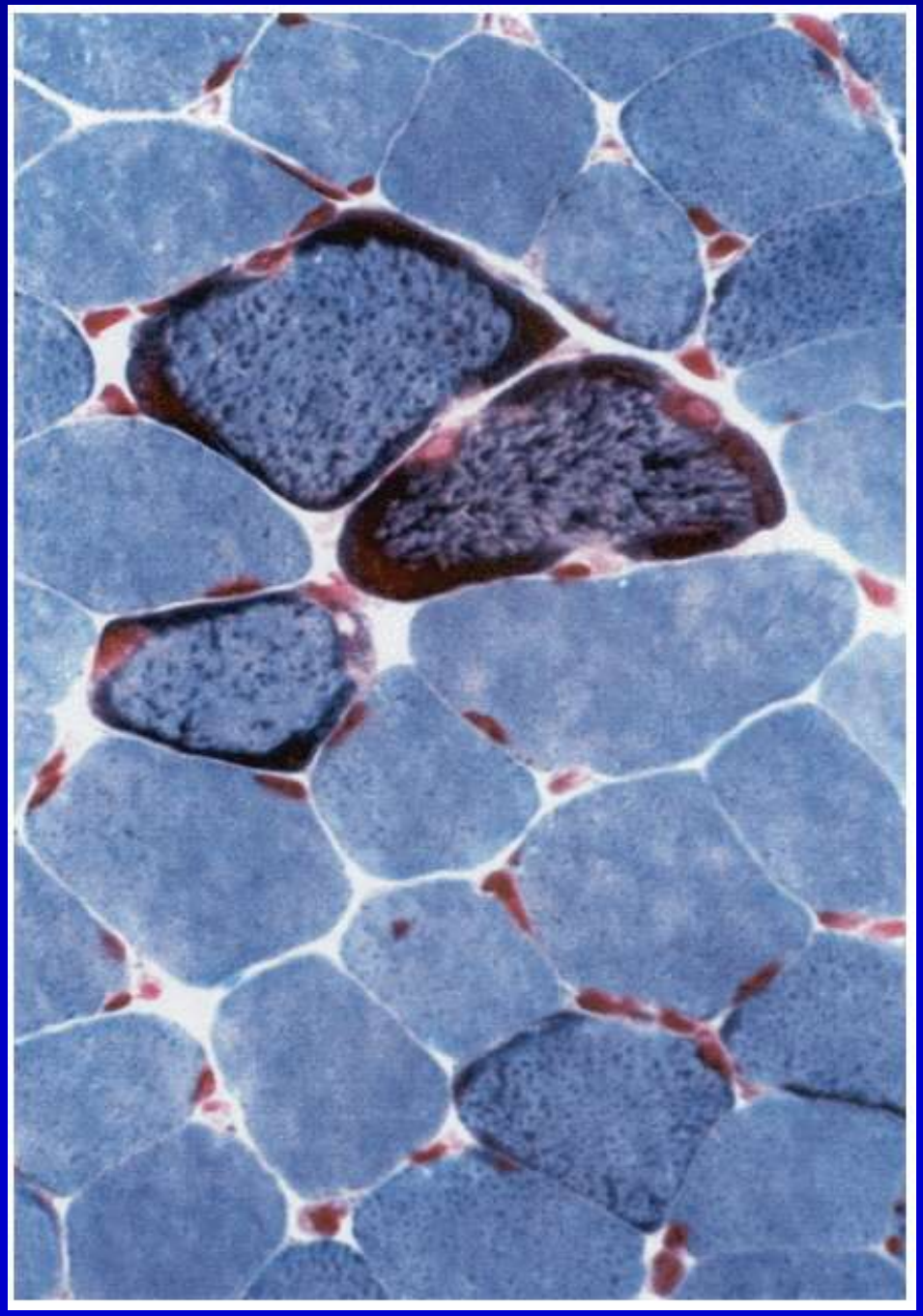


Shoffner JM Neurology Clinics Feb 2000;18:105

Ragged Red Fibers in Mitochondrial Disease

Gomori's trichrome

Abnormal mitochondria give a blotchy red appearance to the fiber, initially subsarcolemmal, then throughout fiber



Clay AS et al. Chest 2001;120:634

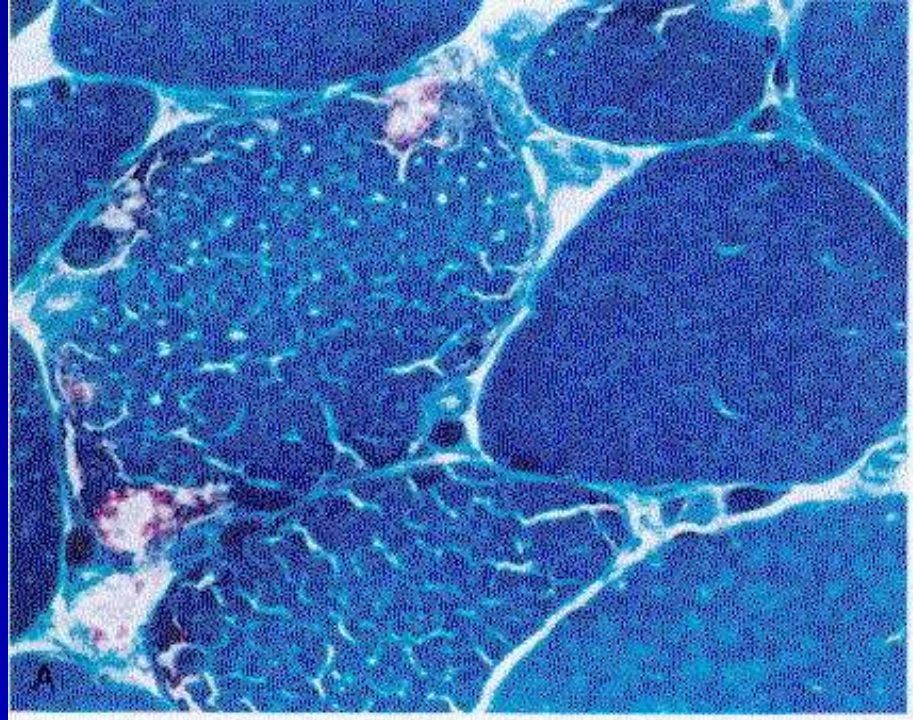
Ragged Red Fibers in Mitochondrial Disease

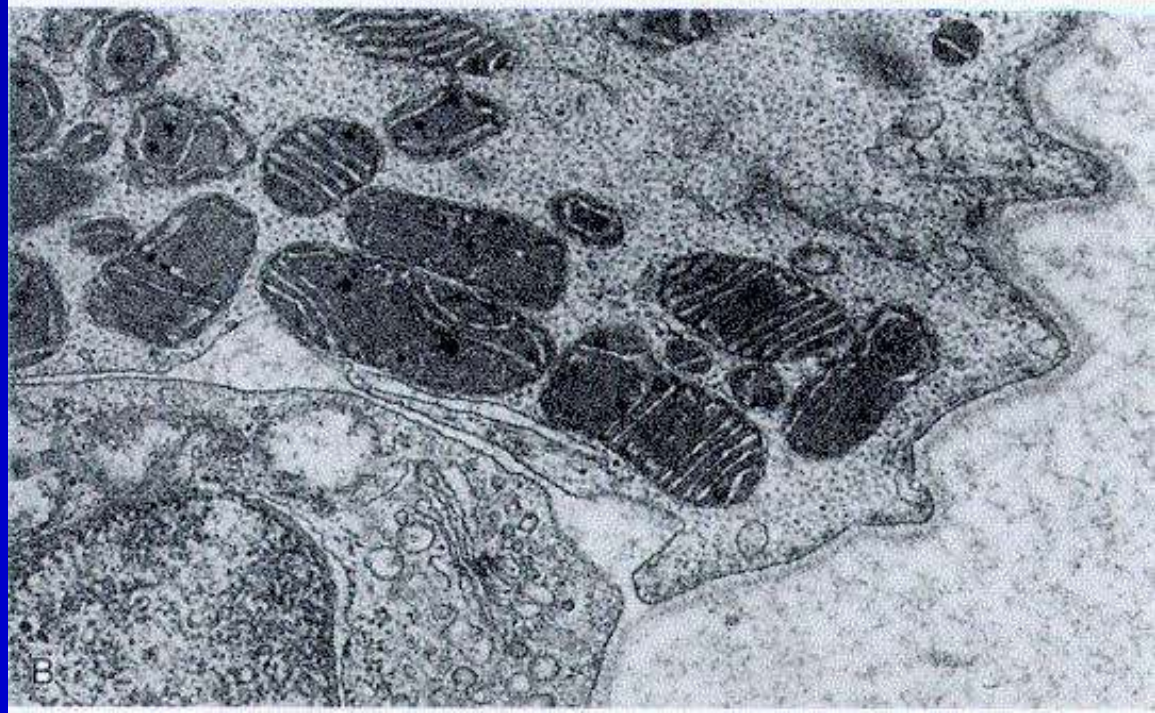
Gomori's trichrome

Abnormal mitochondria give a blotchy red appearance to the fiber, initially subsarcolemmal, then throughout fiber

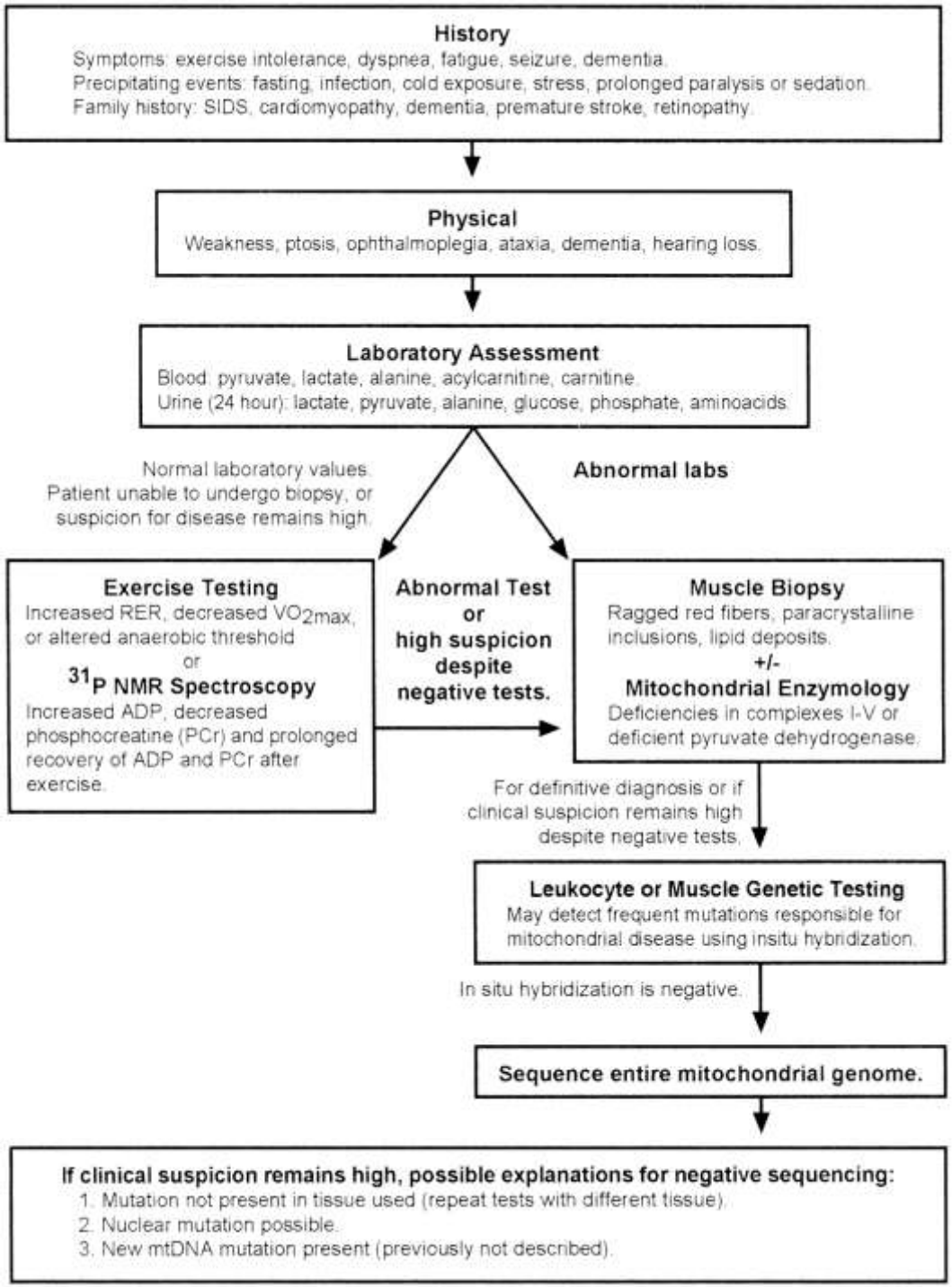
EM: mitochondria show "parking lot" inclusions

Robbins 1998, fig 29-13





Diagnostic Workup in Suspected Mitochondrial Disease



Clay AS et al. Chest 2001;120:634

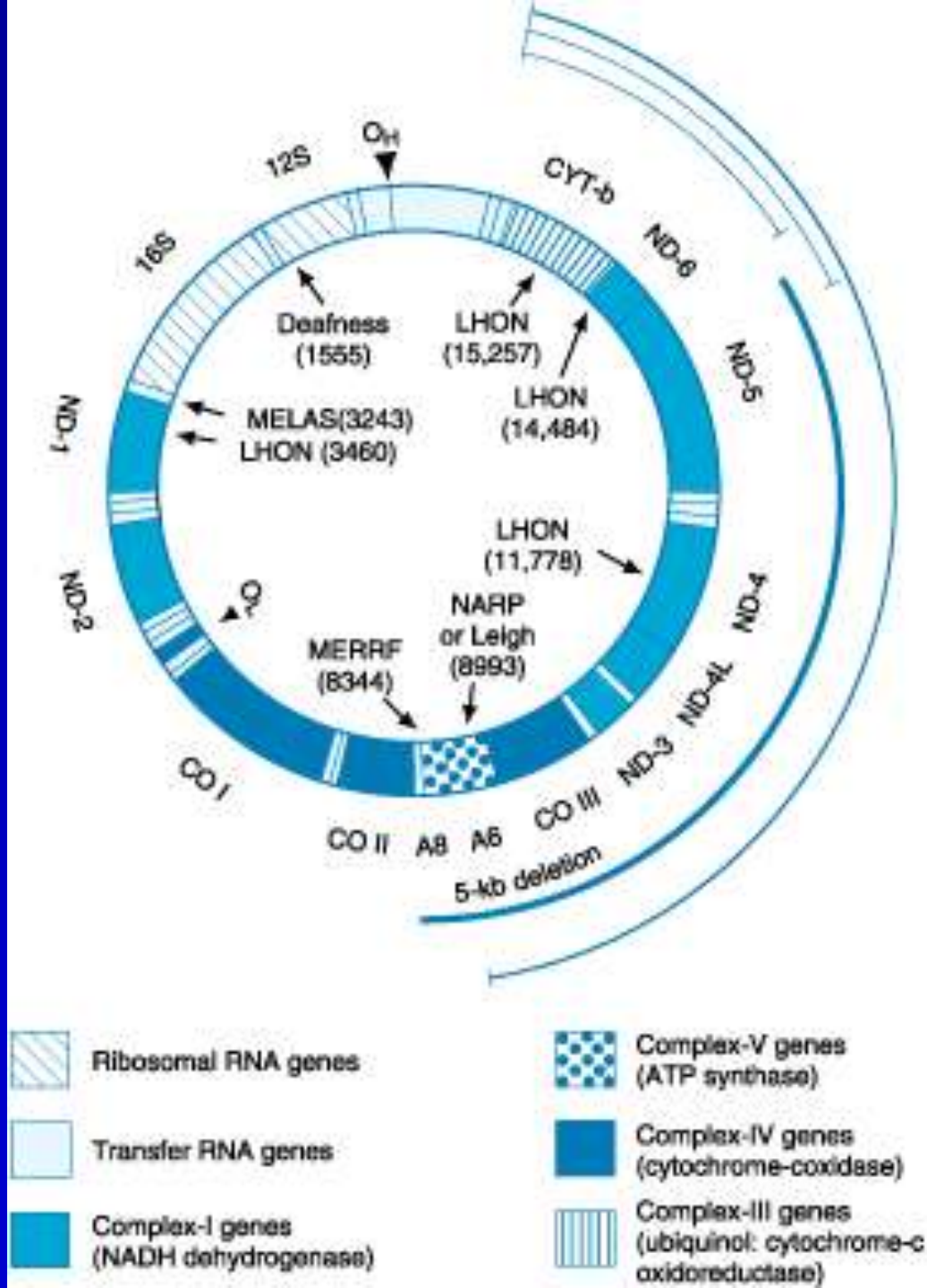
Mitochondrial DNA Defects

- mtDNA is in 2-10 copies/organelle, and multiple organelles/cell, 200 mutations identified so far, maternal transmission
- Tissues with high oxidative phosphorylation demand are more affected by problems: kidney, retina, brain, muscle, heart
- Most have heteroplasmy, mix of mutant and normal mitochondria correlation with severity of phenotype, often brain and muscle disturbances
- Cardiac problems more with respiratory chain defects

Mitochondrial DNA

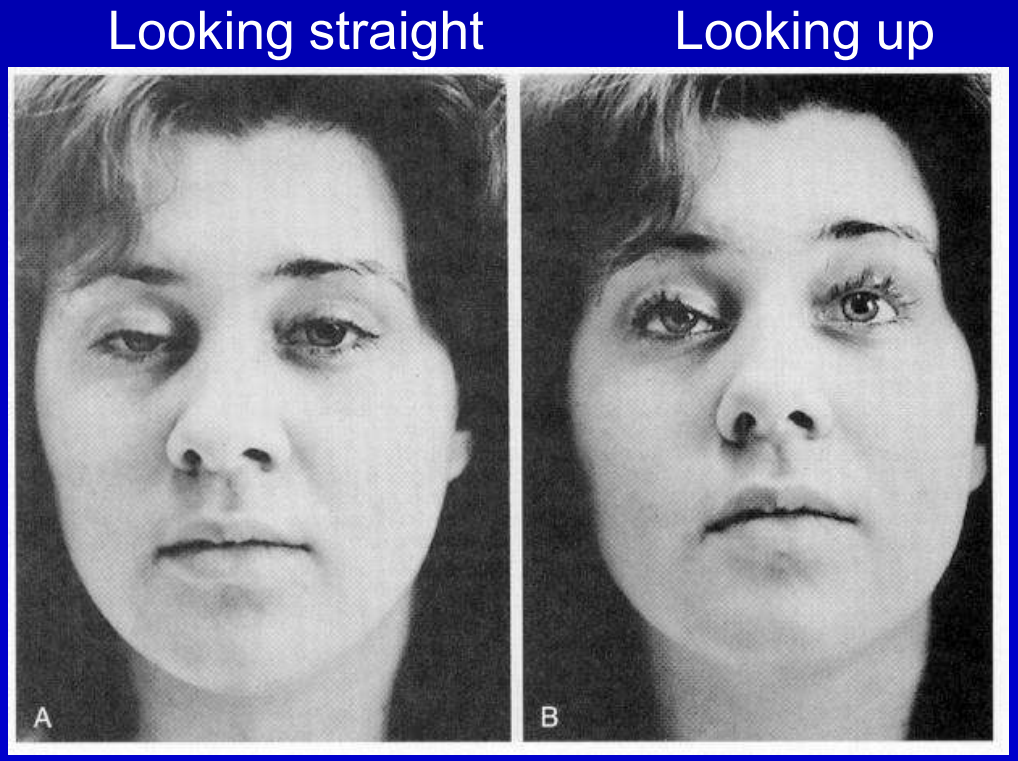
Point mutations in structural and protein-coding genes are indicated inside the circle, with the clinical phenotype and the nucleotide position of the mutation. The thick arc indicates the position of the most common single deletion, which is 5 kb in length, and the thin arcs outside the circle indicate the multiple deletions. MERRF, myoclonic epilepsy with ragged red fibers; MELAS, the syndrome of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; LHON, Leber's hereditary optic neuropathy; NARP, neuropathy, ataxia, and retinitis pigmentosa; Leigh, maternally inherited Leigh's disease.

Harrison's Principles of Internal Medicine, fig 67-1



Kearns-Sayre Syndrome (KSS)

- Ptosis, chronic progressive external ophthalmoplegia, retinal pigmentation, cardiac conduction defects (20% pts have cardiac involvement, prolonged H-V), DCM, hearing loss, limb weakness, DM, hypoparathyroid
- Deletion esp tRNA leu in mtDNA



Braunwald 2001, fig 71-15

MERRF Syndrome

- MERRF: myoclonic epilepsy with ragged-red muscle fibers, tRNA-Lys: seizures, ataxia, HCM, complex I and IV abnormality

MELAS Syndrome

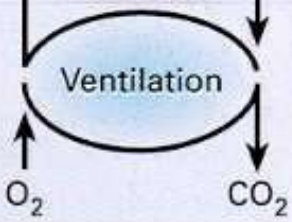
- MELAS: mitochondrial encephalopathy, lactic acidosis, stroke-like episodes, can have ragged-red fibers, exercise intolerance, HCM, DCM, usually complex I abnormality, tRNA-Leu

CONTIGUOUS GENE SYNDROMES

	REGION	LOCUS	CARDIOVASCULAR ABNORMALITIES
Syndromes with Cardiovascular Involvement			
Arteriohepatic dysplasia	AHD	del 20p11.23-p12.2	Peripheral pulmonic stenosis/hypoplasia
Cat-eye syndrome	CES	dup22q11	Total anomalous pulmonary venous return
DiGeorge sequence	DGS	del 22q11	Truncus arteriosus, right aortic arch, TOF, PDA
Miller-Dieker syndrome	MDS	del 17p13	PDA ± complex anomalies
Prader-Willi syndrome and	PWS/AS	del 15q12(pat)	Cor pulmonale (secondary to obesity central apnea)
WAGR syndrome		del 11p13	Hypertension (secondary to Wilms tumor)
Syndromes Without Frequent Cardiovascular Involvement			
Angelman syndrome		del 15q12 (mat)	
Smith-Magenis syndrome		del 17p11.2	

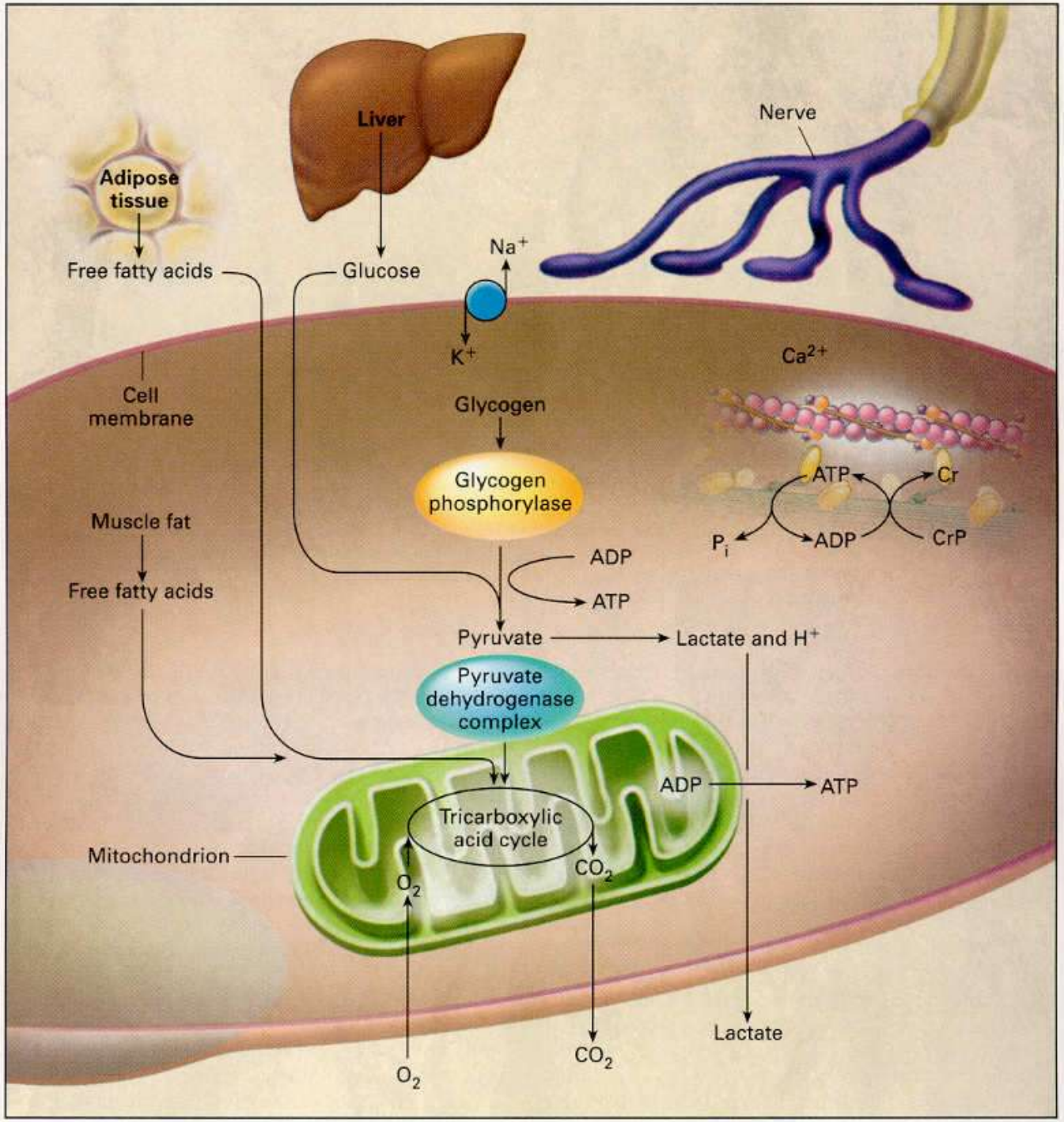
Braunwald 2001 Table 56-

Physiology of Sensation During Exercise

System	Process	Sensation
Brain	Motor command	Effort
Nerve	↓ Excitation–contraction (Na^+–K^+)	Weakness
Muscle	↓ Cross-bridge formation (Ca^{2+}) ↓ Power output (ATP → ADP)	Tension
Metabolism	↓ $Glycogen + ADP \longrightarrow ATP + Lactate + H^+$ $Glycogen + ADP + O_2 \longrightarrow ATP + CO_2$ $FFA + ADP + O_2 \longrightarrow ATP + CO_2$	Fatigue
Circulation		
Lungs		

Jones NL et al.
NEJM 2000; 343:632.

Major Metabolic Pathways During Exercise



Jones NL et al.
NEJM 2000; 343:632