Genetic Causes of Cardiovascular Disease

February 25, 2008

Joe M. Moody, Jr, MD
UTHSCSA and STVAHCS

Topics

- Monogenetic disorders
- Chromosomal disorders
- Polygenic disorders
- Heart Failure
- Congenital malformations
- Arrhythmias
- Degenerative disorders
  - Connective tissue
  - Atherosclerotic risks

Topics – Phenotypic Approach

- Connective Tissue Disorders
- Genetic causes of cardiomyopathy
  - Hypertrophy
  - Dilation
  - Arrhythmogenic RV dysplasia
- Structural heart disease
  - Congenital heart disease
  - Genetic syndrome with heart defects
- Cardiac tumors

Connective Tissue Disorders

- Marfan's Syndrome – defect in fibrillin-1 gene which makes fibrils that surround elastin core – no specific genetic "hot spots" – most cases result from spontaneous mutation
- Ehlers-Danlos Syndrome – defect in type III collagen (EDS type IV, there are 10 types) – most die of arterial rupture, often before age 40
- Supravalvular AS (at sinotubular junction) – loss of one elastin allele – William's syndrome - deletion of 7q11.22
- Pseudoxanthoma elasticum – PXE – defect in ABCC6 /MRP6 cellular transport protein (ATP-binding cassette protein)
- Cutis laxa may be associated with pulmonary artery stenosis and fibromuscular dysplasia of the renal art

Milewicz DM "Inherited disorders of connective tissue" Ch 121 in Willerson CV medicine 3rd ed. 2007

Marfan's Syndrome

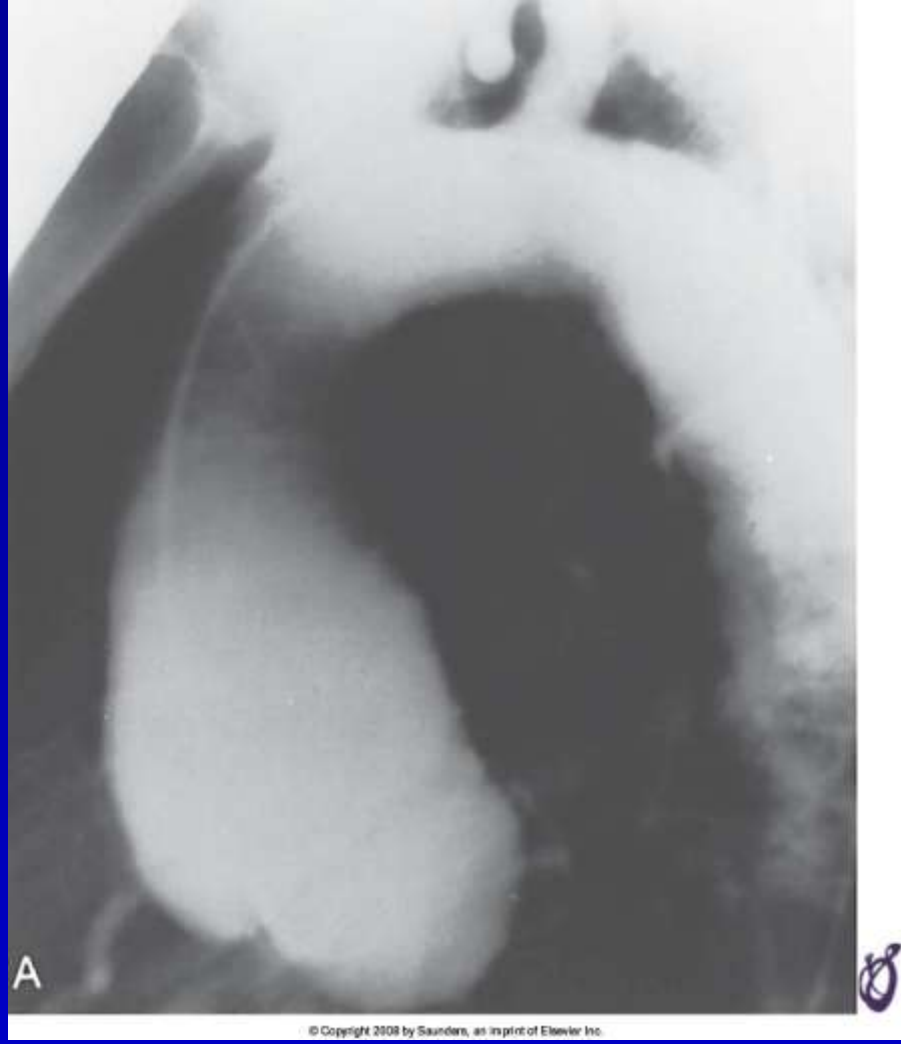
- External phenotype of patient with Marfan syndrome, showing long extremities and digits, tall stature, and pectus carinatum.

(Used with permission from Mediscan, Medical-On-Line-Ltd, London.)

Pyeritz RE et al. "Gen. principles of genetic factors in CV dz" BHD 8th ed. 2008

Marfan's Syndrome

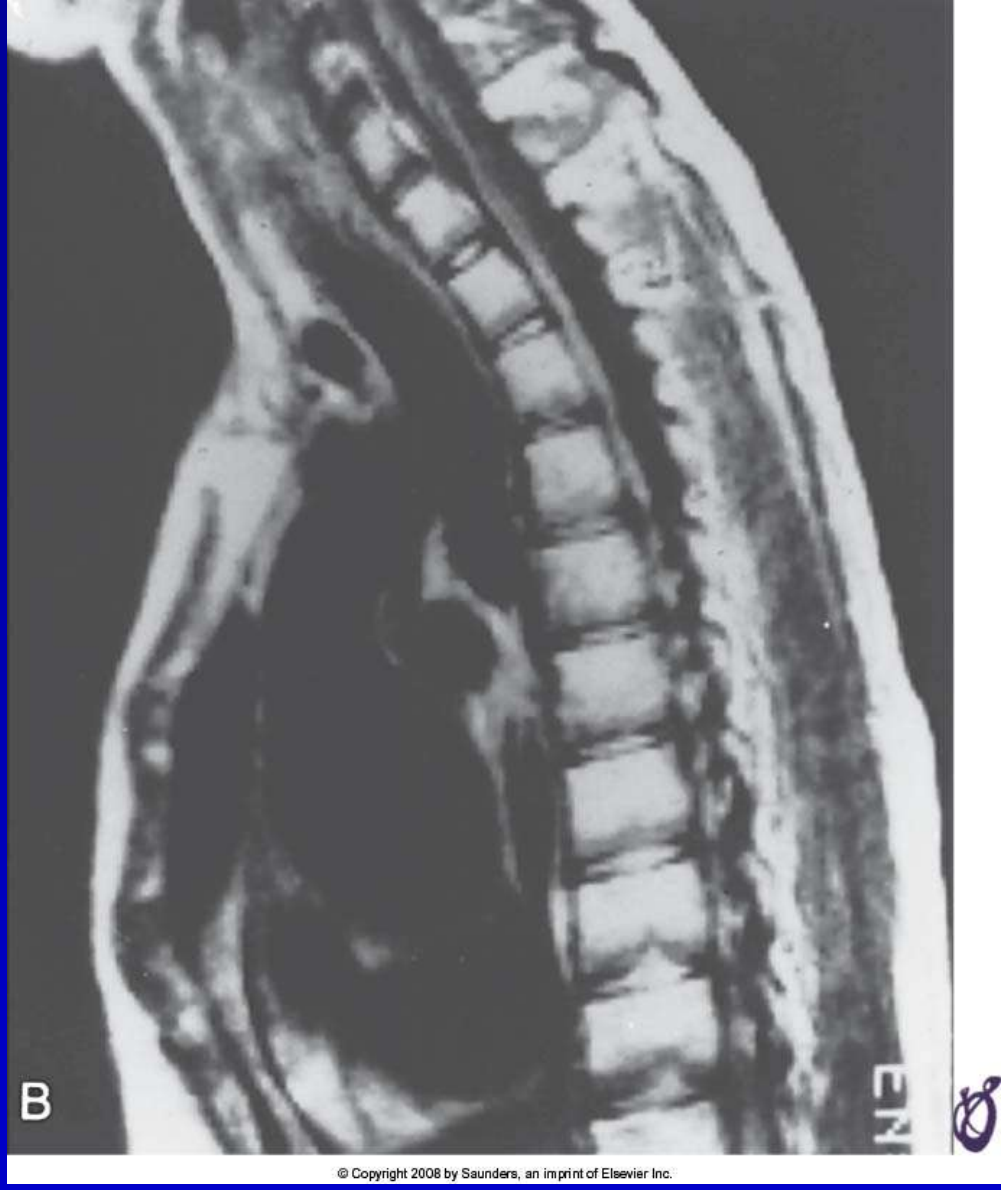
- Dilation of the aortic root in Marfan syndrome. Lateral angiogram of the ascending aorta showing dilation of the sinuses of Valsalva and proximal ascending aorta and relatively normal caliber of the ascending aorta.



Pyeritz RE et al. "Gen. principles of genetic factors in CV dz" BHD 8th ed. 2008

Marfan's Syndrome

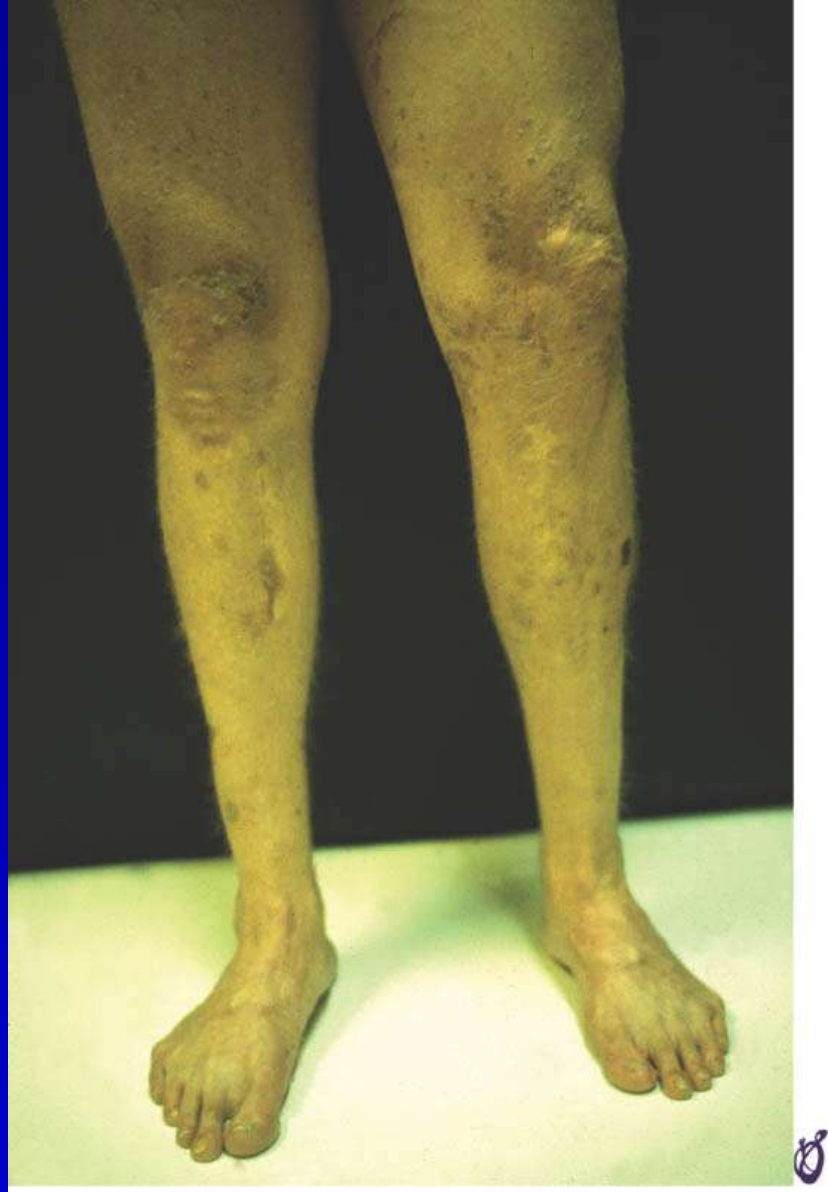
- Dilation of the aortic root in Marfan syndrome. Lateral magnetic resonance imaging scan of the same patient.



Pyeritz RE et al. "Gen. principles of genetic factors in CV dz" BHD 8th ed. 2008

Ehlers-Danlos Syndrome

- Defect in type III collagen (EDS type IV, there are 10 types) – most die of arterial rupture, often before age 40.
- Legs of a patient with Ehlers-Danlos syndrome type IV who died of rupture of the subclavian artery. Note the mild joint hypermobility and the striking dermal abnormalities—elastosis perforans serpiginosa and thin, atrophic scars over areas of recurrent trauma.



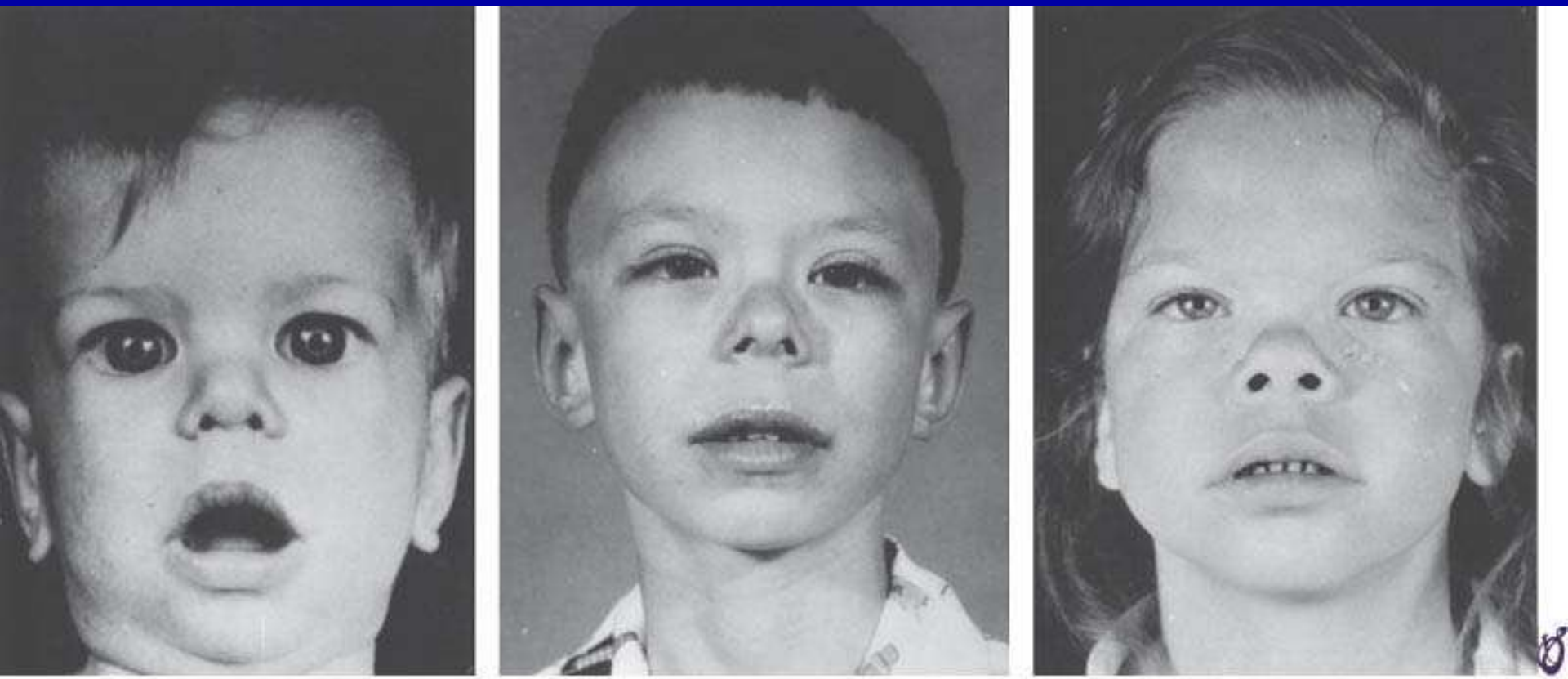
Pyeritz RE et al. “Gen. principles of genetic factors in CV dz” BHD 8th ed. 2008

Williams Syndrome

- Supravalvular AS (at sinotubular junction) and peripheral PS
- Williams-Beuren syndrome (WBS [MIM
- #194050]) is caused by hemizygous deletion of chromosome 7q11.23, which results in the haploinsufficiency of multiple genes. WBS is characterized by facial dysmorphia, microcephaly, growth retardation, and supravalvular aortic stenosis (SVAS [MIM #185500]). Hemizygous deletion or mutations in *ELN* (MIM *130160) alone, the gene encoding elastin, a structural component of arteries, cause SVAS.23 Patients with WBS, in contrast, have larger deletions encompassing replication factor C2 (*RFC2* [MIM*600404]), a subunit of replication factor C (RF-C)

O'Driscoll M et al. Am J Human Genet. 2007;81:77.

Williams Syndrome



(From Friedman WF, Kirkpatrick SE: Congenital aortic stenosis. In Adams FH, Emmanouilides GC, Riemenschneider TA, et al [eds]: Moss' Heart Disease in Infants, Children, and Adolescents. 4th ed. Baltimore, Williams & Wilkins, 1989.)

Webb GD et al. Ch. 61, "Congenital Heart Disease" BHD 8th ed. 2008

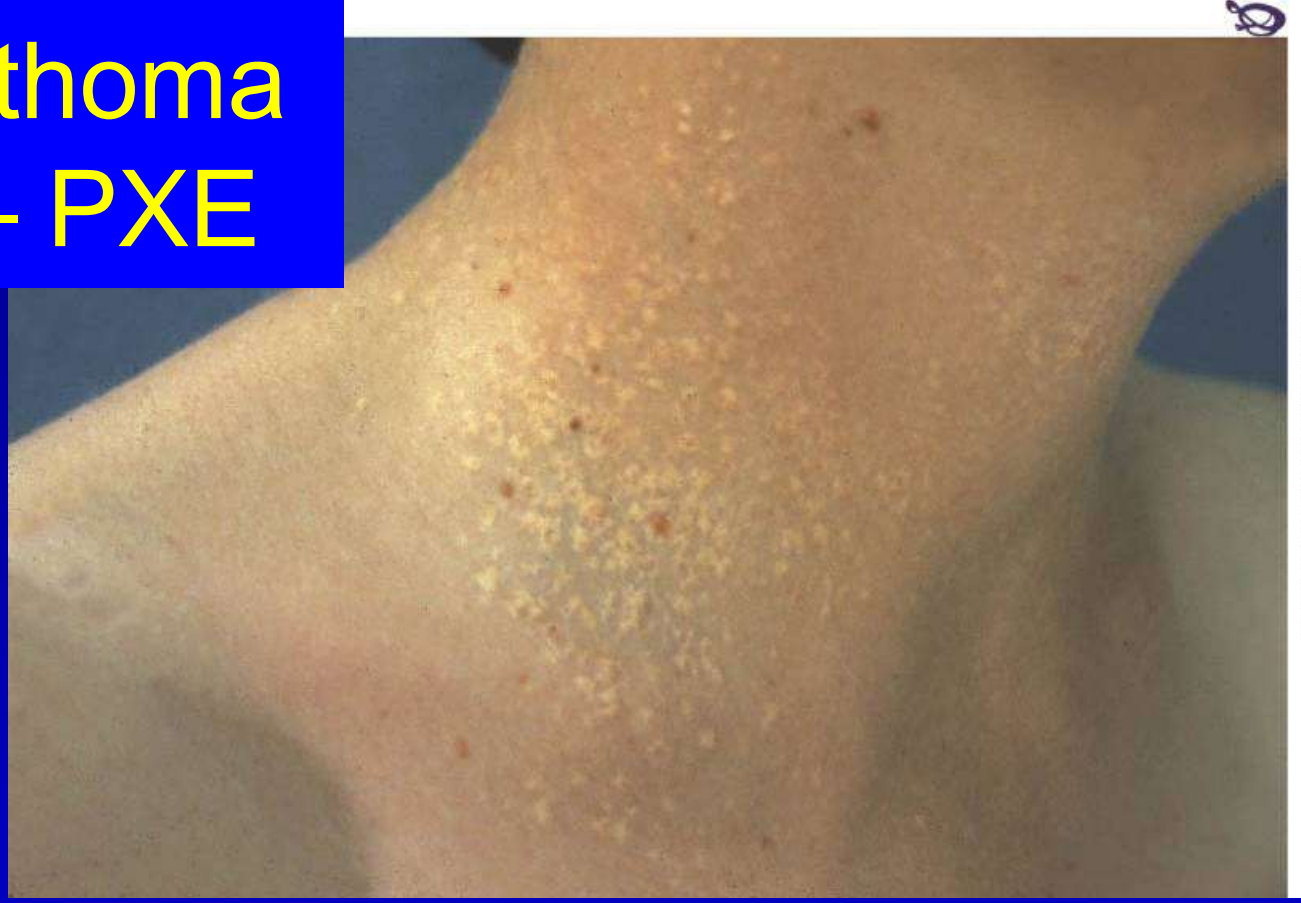
Williams Syndrome

- loss of one elastin allele – <u>William's syndrome</u> - deletion of 7q11.22
- loss of a gene called *LIMK1*
- LIMK1 is intimately involved in the regulation of the actin cytoskeleton

Pyeritz RE et al. "Gen. principles of genetic factors in CV dz" BHD 8th ed. 2008

Pseudoxanthoma elasticum – PXE

- Defect in ABCC6/MRP6 cellular transport protein (ATP-binding cassette protein)

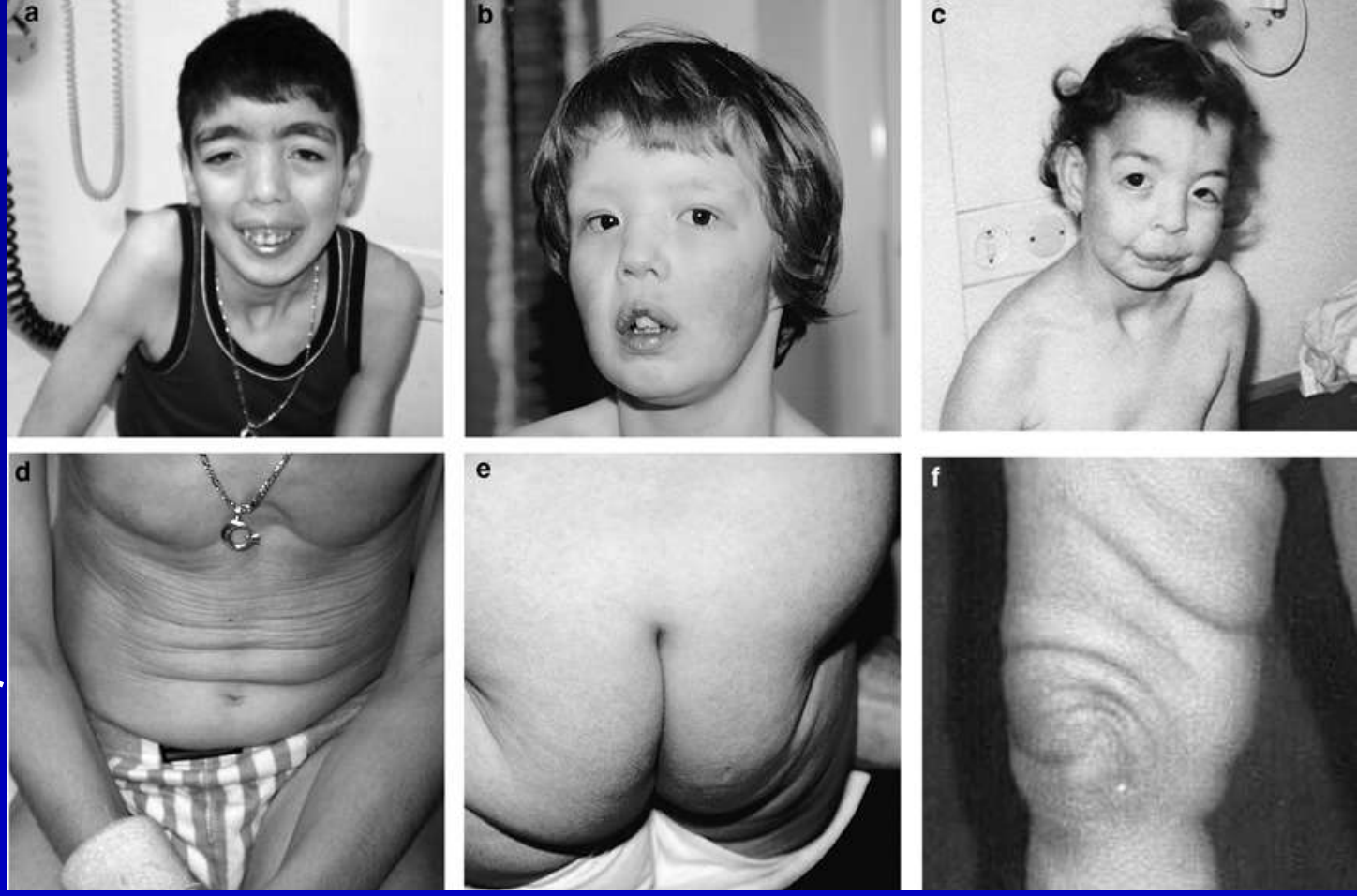


- Skin of a young man with pseudoxanthoma elasticum. The neck is a typical location to notice the raised, yellowish papules from which the name of the condition derives.

Pyeritz RE et al. “Gen. principles of genetic factors in CV dz” BHD 8th ed. 2008

Cutis Laxa

- May be associated with pulmonary artery stenosis and fibromuscular dysplasia of the renal artery

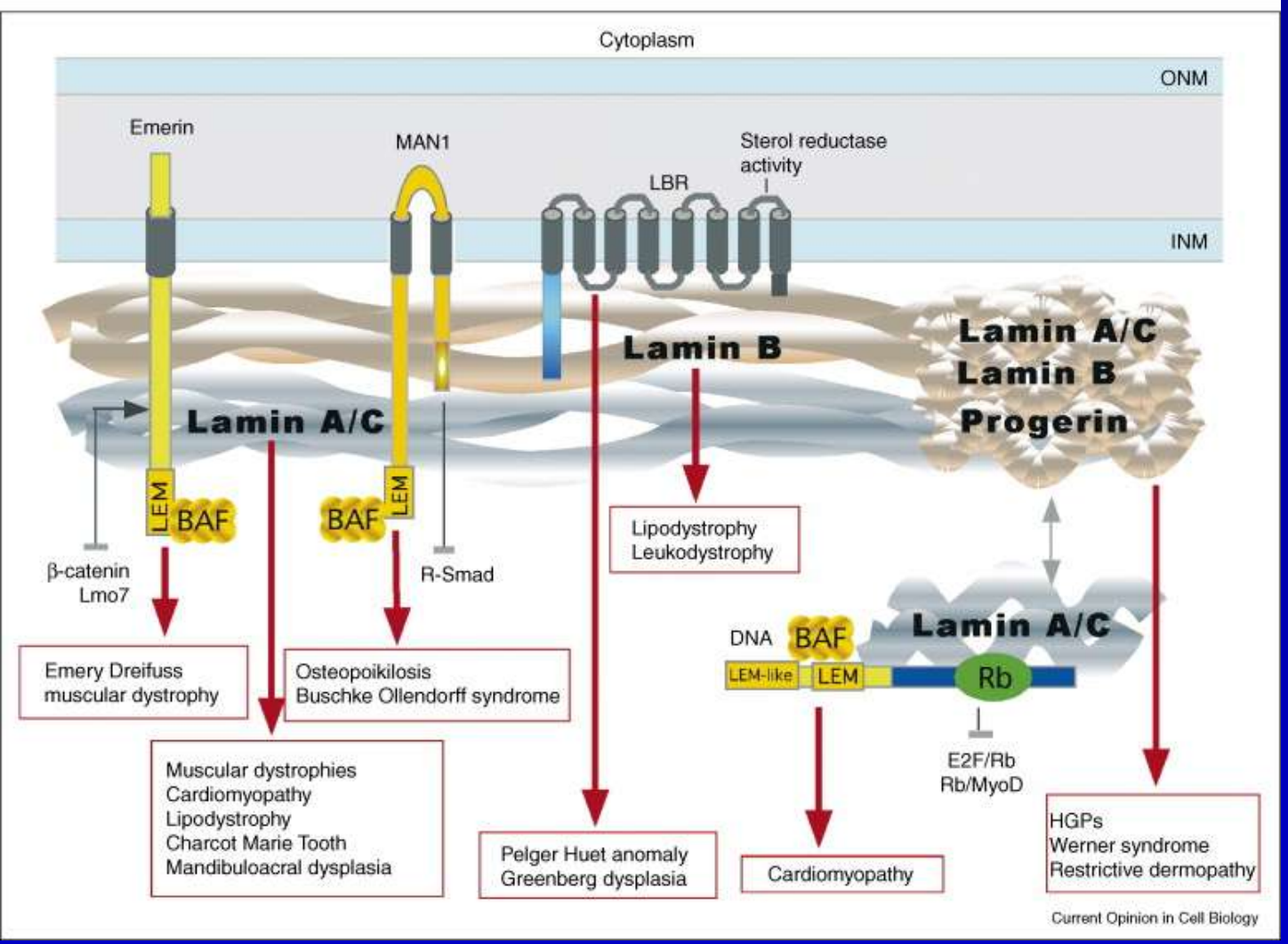


- *Patient 1*: facial features with down-slanting palpebral fissures, midfacial hypoplasia, long philtrum (**a**) and mild abdominal cutis laxa (**d**) at the age of 10 years. *Patient 2*: characteristic facial features with high forehead, down-slanting palpebral fissures, midfacial hypoplasia (**b**) and gluteal fat-pads (**e**) at the age of 7 years. *Patient 3*: facial features with down-slanting palpebral fissures, midfacial hypoplasia and facial cutis laxa at the age of 3 years (**c**), and cutis laxa on the extremities at the age of 3.5 years (**f**).

Morava E et al. European Journal of Human Genetics. 2005;13:414–421.

Muscular Dystrophies Affecting the Heart

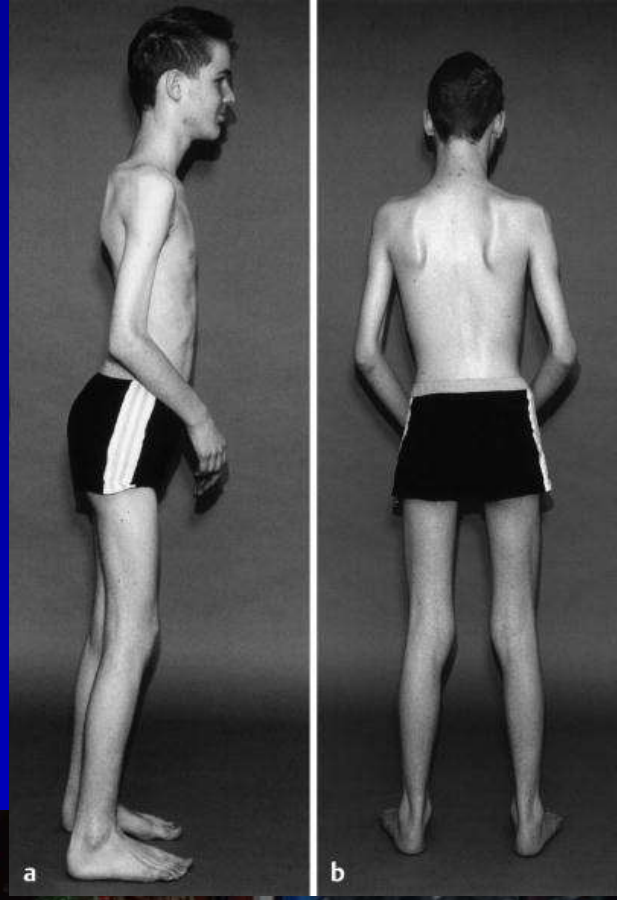
- Emery-Dreifuss Muscular Dystrophy
- Hypertrophic Cardiomyopathy
- Hypertrophy from metabolic defect

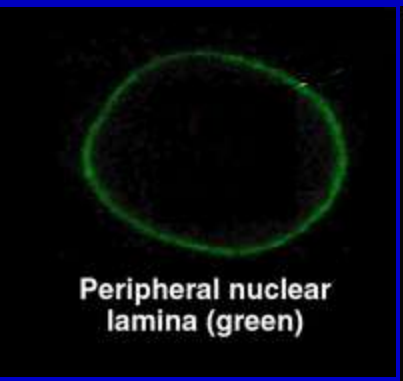


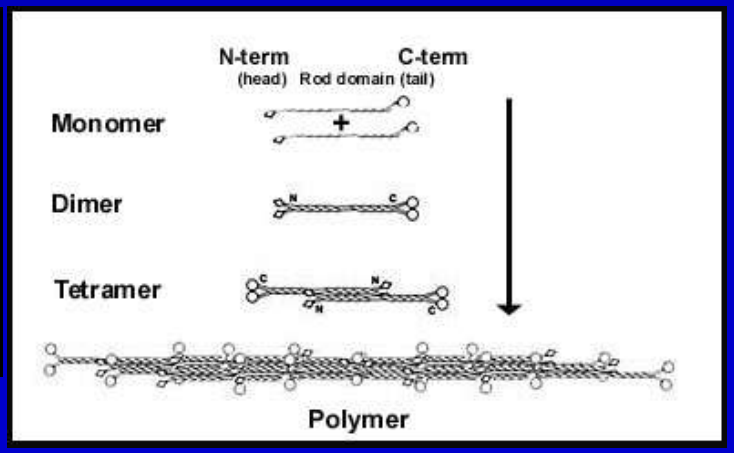
Schematic representation of the localization and relevant interactions of lamins and lamin-associated proteins involved in disease. A-and B-type lamins are depicted as homo-polymers. This segregation may be lost upon progerin expression (outermost right). The involvement of lamin-associated proteins in signaling pathways, potentially relevant for the laminopathic diseases, is indicated. Diseases linked to the respective proteins are depicted in the boxes. Vlcek S et al. Curr Opin Cell Biol. 2007;19:298.

Emery-Dreifuss Muscular Dystrophy

- Usually X-linked and with defect in emerin (in membrane of nucleus) or defect in lamin A/C (also in membrane of nucleus, A and C are alternate splices of the protein – autosomal dominant) – are intermediate filament proteins – heart failure and arrhythmias are important features



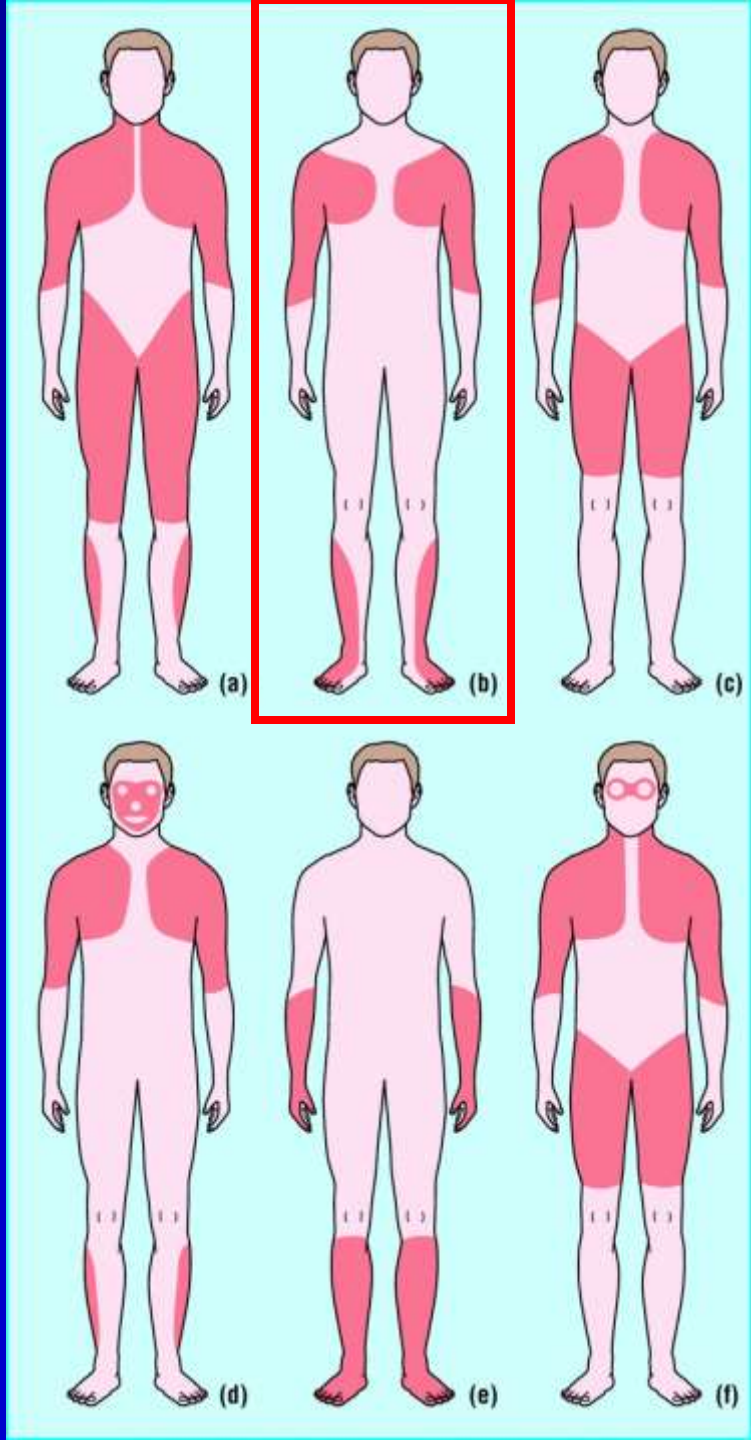




http://npd.hgu.mrc.ac.uk/compartments/lamina.html

Phenotypes of Muscular Dystrophy

- Distribution of predominant muscle weakness
- A – Duchenne and Becker
- B – Emery-Dreifuss
- C – Limb-girdle
- D – Facioscapulohumeral
- E – Distal
- F - Oculopharyngeal



Mayer, Karl C from the internet:
www.neuro24.de/emea1381.f1.gif

Hypertrophic Cardiomyopathy

Disarray and fibrosis are prominent features
Conduction disease uncommon

- Genetically heterogeneous (300+ mutations)
- Sarcomere defects – 11 proteins implicated
  - *B-myosin heavy chain (40% of cases)
  - Cardiac myosin binding protein C (40% of cases)
  - Cardiac troponin T (5% of cases)
  - Cardiac troponin I, troponin C, α-myosin heavy chain
  - Others
    - A-tropomyosin (<5% of cases)
    - A-cardiac actin - rare
    - Regulatory myosin light chain (<5% including essential)
    - Essential myosin light chain
    - Titin
- Metabolic defects

Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Genetic Causes of Hypertrophy

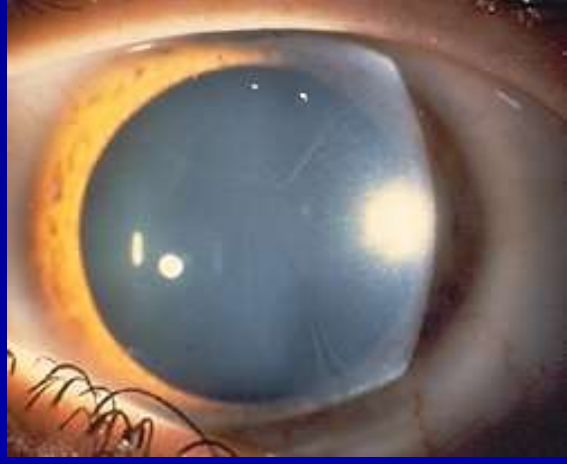
Disarray and fibrosis not prominent features
Conduction disease common

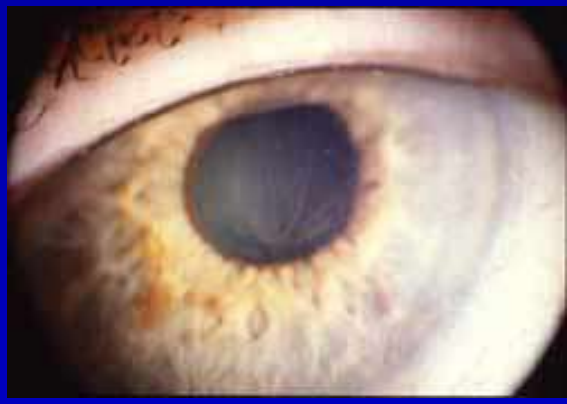
- Lysosomal protein mutations
  - Fabry Disease, a mutation of lysosomal hydrolase alpha-galactosidase A protein; increase in globotriaosylceramide (GL-3) levels – treat with alpha galactosidase A administration to reduce hypertrophy and improve ECG
  - Danon Disease, a mutation of lysosome-associated membrane protein (LAMP2) – accumulation of autophagic vacuoles – massive hypertropy, consider transplant if hepatic involvement not severe
- Glycogen storage - Mutation in gamma2 regulatory subunit of adenosine monophosphate-activated protein kinase (PRKAG2), (AMPK) – glycogen accumulates in vacuoles

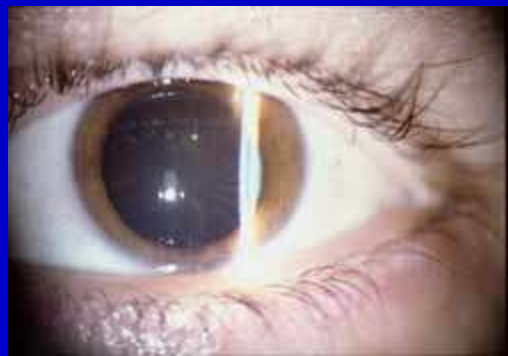
Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Fabry Disease

- A "starburst" pattern on the cornea is almost always present in people with Fabry disease. This pattern is sometimes called corneal whorling, and it is caused by GL-3 accumulation in the blood vessels of the eye. It does not affect vision and does not require any treatment. This symptom can only be seen during a special type of eye exam (slit-lamp) done by an ophthalmologist (eye doctor). Corneal whorling is found in almost all males with Fabry disease and in 70%-90% of female carriers.
- A galsidase beta (Fabrazyme) seems to be a highly effective therapeutic intervention. It is administered IV every two weeks for life.

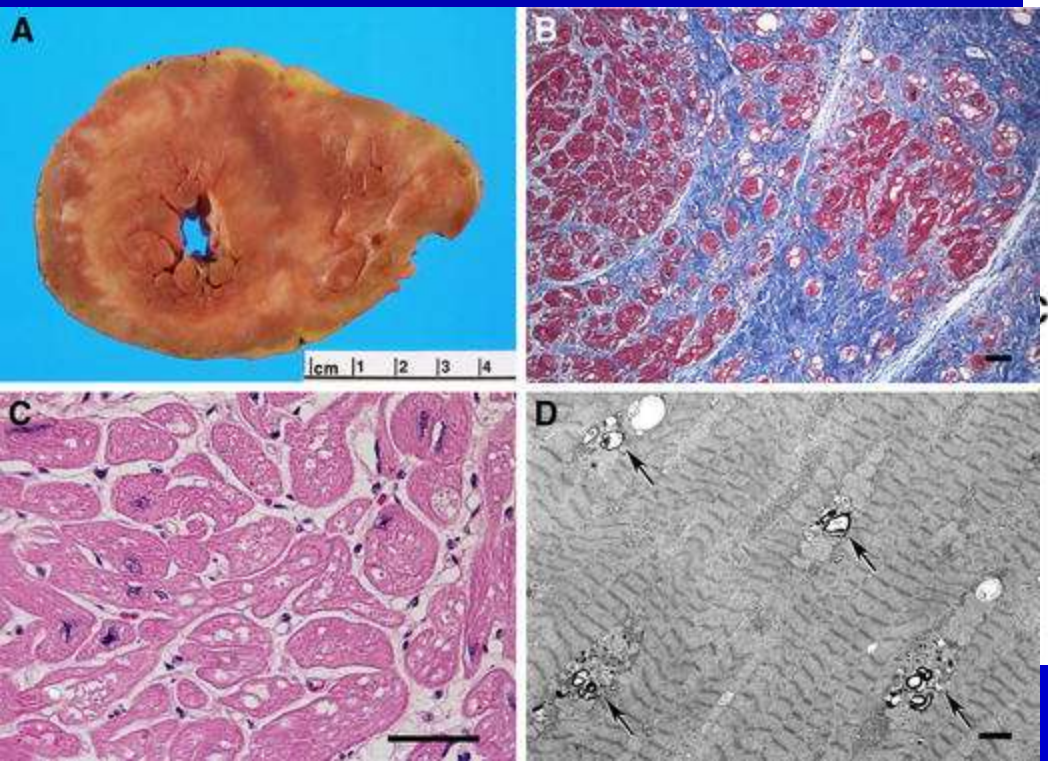


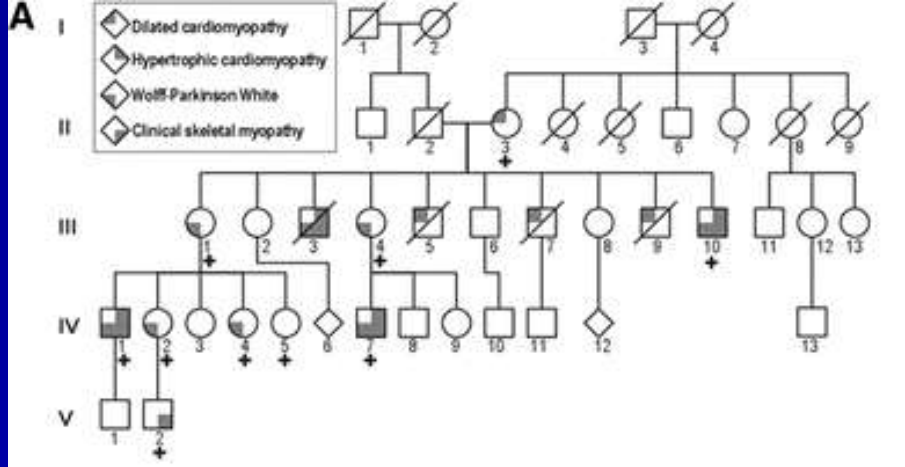


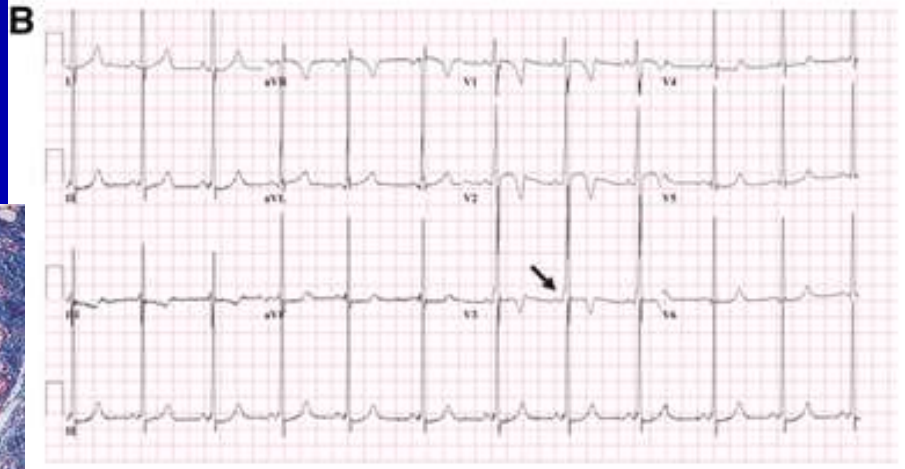


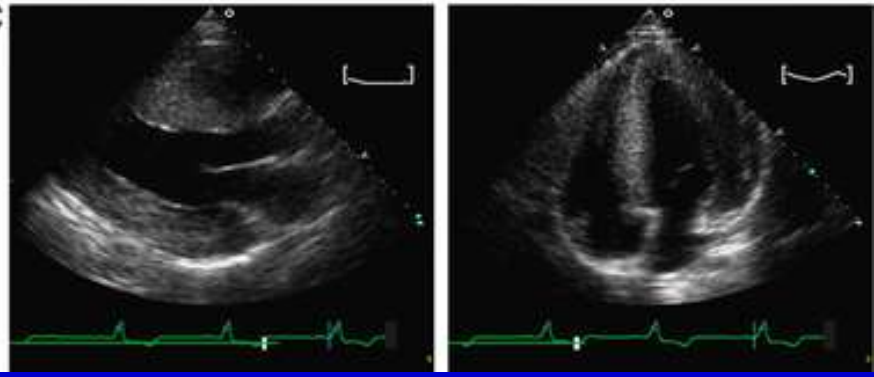
Danon Disease

- 14-yo explanted heart









Cardiac Dilation

- Many patients (30-50%) with “idiopathic dilated cardiomyopathy” have a familial component
- DCM mutations show wide diversity
- Classification
  - Isolated cardiac dilation without conduction system disease
  - Isolated cardiac dilation with conduction system disease
  - Cardiac dilation with extracardiac manifestations

Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Isolated Cardiac Dilation without Conduction System Disease

- Sarcomere mutations – same proteins as HCM, often early presentation
- In contrast to HCM, functional studies of the sarcomere show reduced force generation

Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Isolated Cardiac Dilation with Conduction System Disease

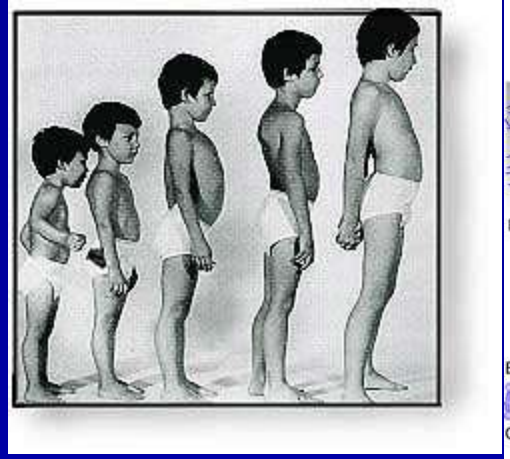
- Nuclear envelope protein lamin A/C is the most common cause of DCM with progressive conduction system abnormalities
- Onset usually third or fourth decade
- EP abnormalities usually precede systolic dysfunction

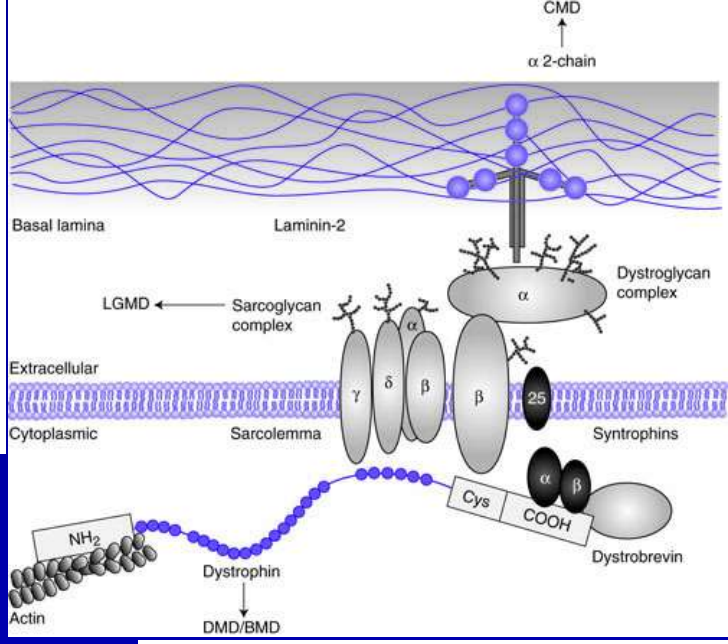
Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Cardiac Dilation with Extracardiac Manifestations

- Dystrophin-associated complex
  - Delta sarcoglycan
  - Dystrophin (Duchenne muscular dystrophy – X-linked)
- Tafazzin (Barth Syndrome – X-linked)
  - Probably involved in cardiolipin metabolism of the mitochondria with impaired mitochondrial function

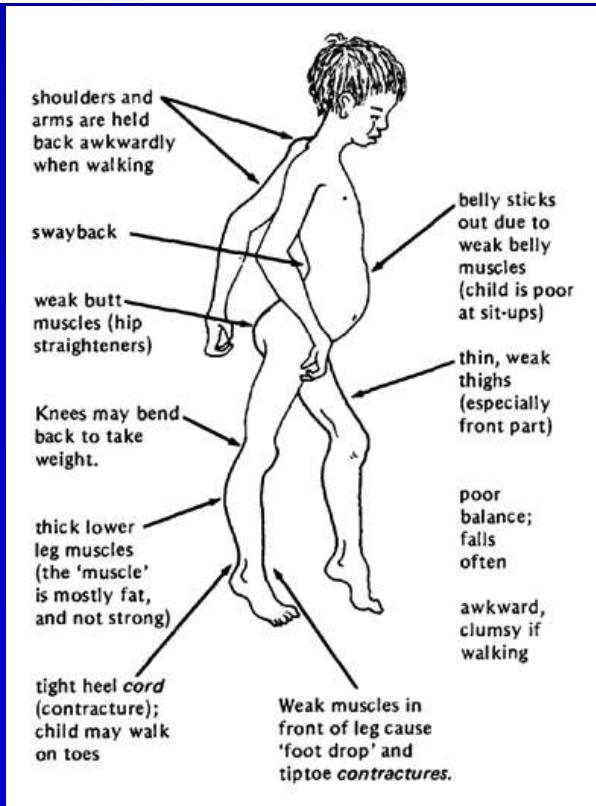
Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008



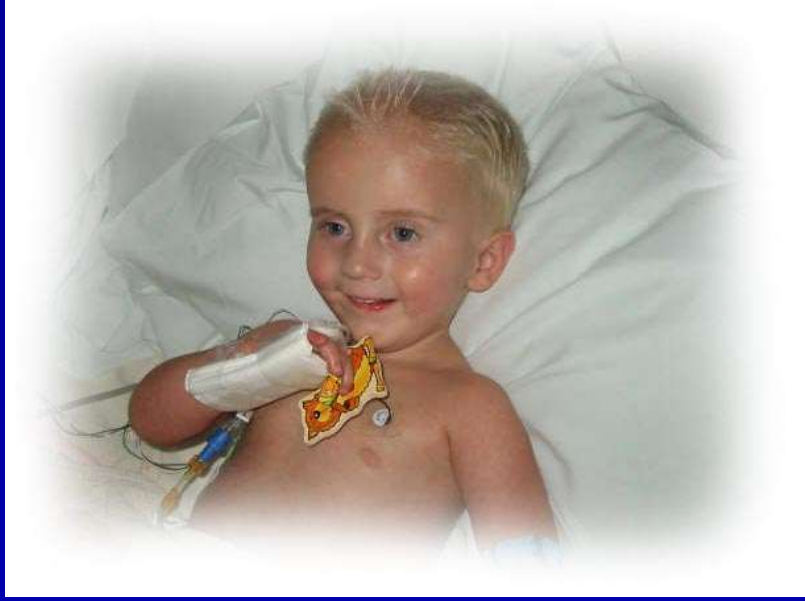


Duchenne Muscular Dystrophy

- Diagram of muscle cell membrane (sarcolemma), dystrophin, and the dystrophin-associated protein complex. Dystrophin is located inside the cell and binds actin at its N-terminus and the syntrophins, sarcoglycans, and dystrobrevin at the C-terminus. Mutations in dystrophin are responsible for Duchenne muscular dystrophy/ Becker muscular dystrophy (DMD/BMD). Mutations in the various sarcoglycans give rise to limb-girdle muscular dystrophy (LGMD), and laminin mutations result in congenital muscular dystrophy (CMD).



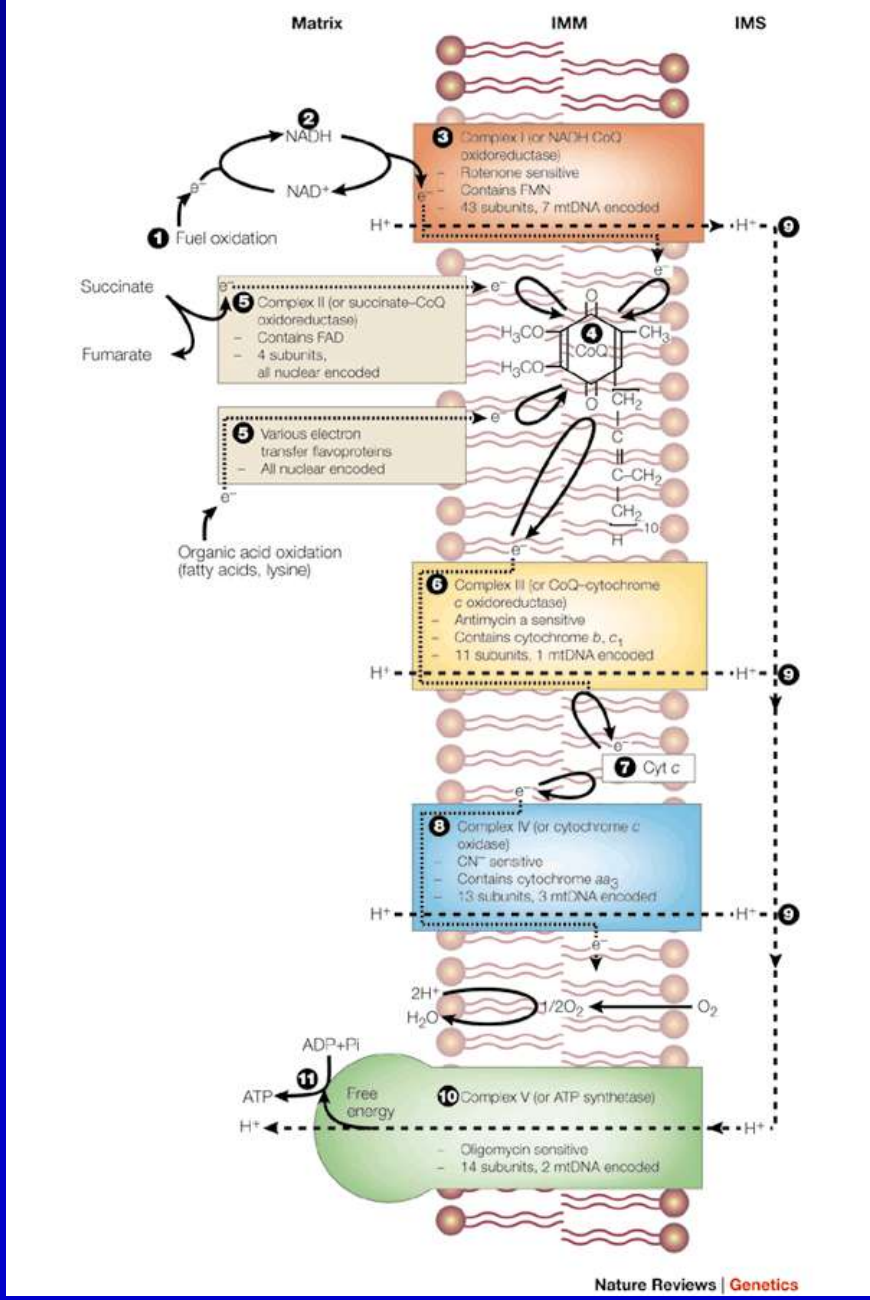
Barth Syndrome



- Cardiomyopathy
- Neutropenia
- Muscle Weakness and General Fatigue
- Growth Delay –can be substantial until late teenage years

Characteristics of Mitochondrial Syndromes

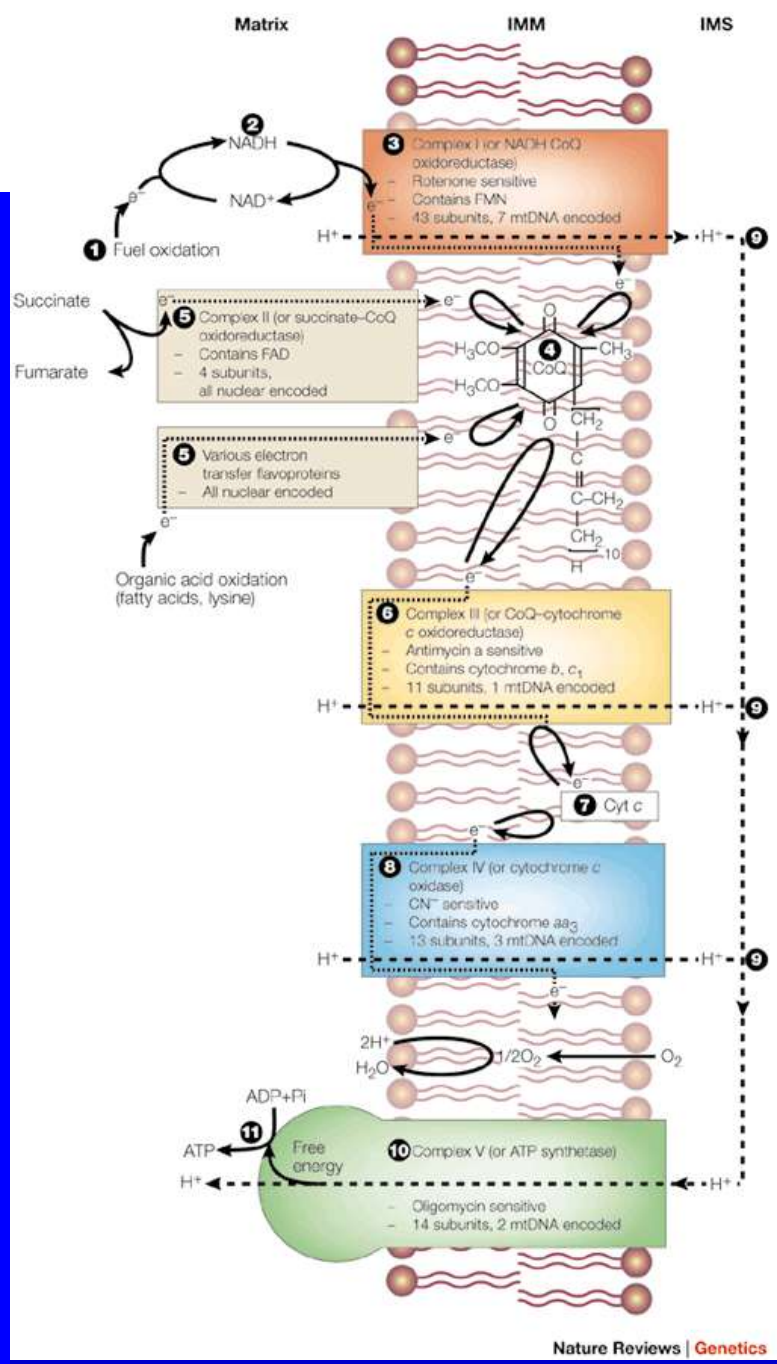
- Thirteen genes of oxidative phosphorylation are in the mitochondrial genome
- Matrilineal inheritance
- Mitochondrial mutations are often heteroplasmic (some mitochondria are affected, some not)



Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008
Smeitink J et al. Nature Reviews Genetics. 2001;2:342-352.

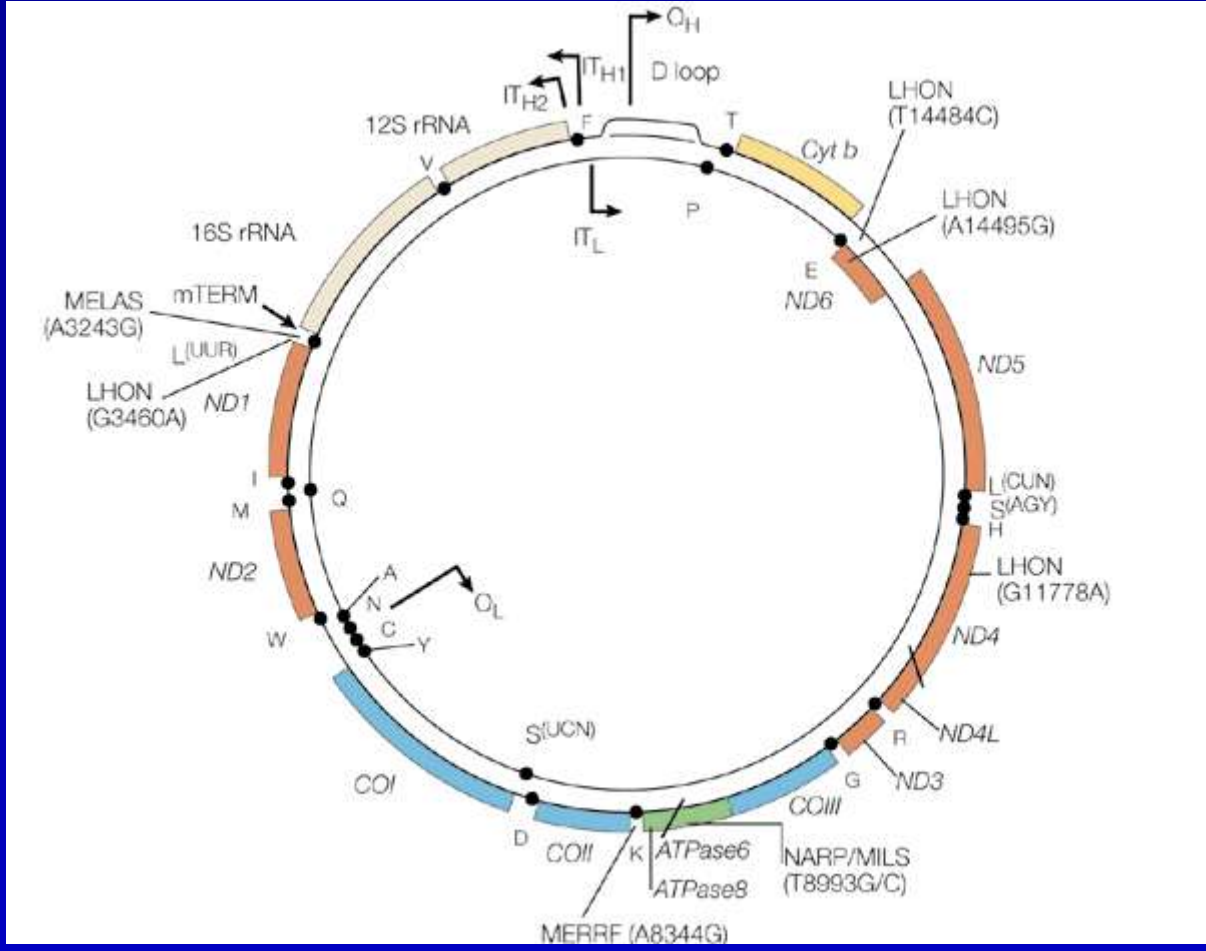
Mitochondrial Action

- Electrons (e-) from carbon oxidations (step 1 and dotted lines) are transferred via NADH (step 2) into OXPHOS complex I (step 3), which is embedded in the lipid bilayer of the inner mitochondrial membrane (IMM), then transported to coenzyme Q (CoQ) (step 4). Some electrons from organic-acid oxidations are transferred, via other flavin-containing enzyme complexes (step 5), directly to CoQ. CoQ delivers electrons via complex III (step 6) and cytochrome *c* (Cyt *c*) (step 7) to the final electron acceptor complex IV (step 8). Here, oxygen is reduced to water. The electrons lose free energy at each transfer step, and in complexes I, III and IV, the energy is harnessed and coupled to the movement of H+ (step 9 and dashed lines) from the mitochondrial matrix to the intermembrane space (IMS). The proton gradient thus generated is used for the production of ATP by complex V (step 10). Except for complex II, all complexes contain some proteins encoded by the mitochondrial genome and others encoded by the nuclear genome. The number of subunits for each complex is indicated.



Mitochondrial Genome

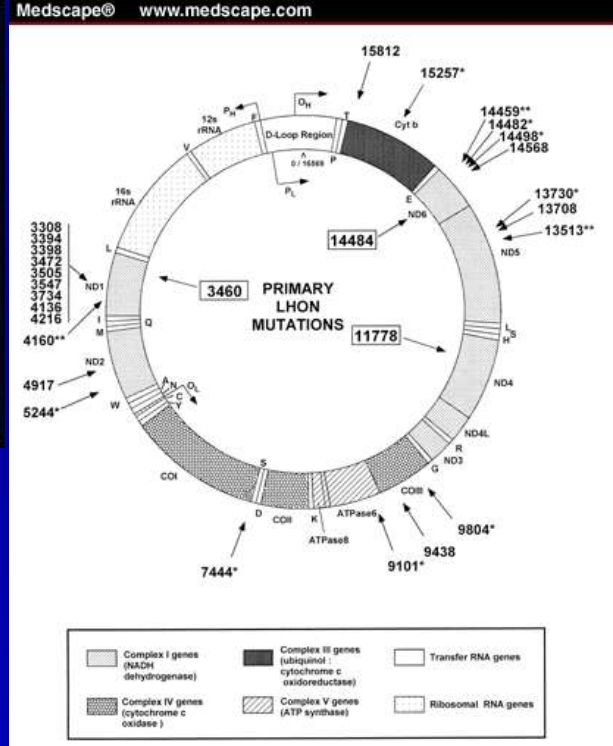
- The outer and inner circles represent the heavy (H) and light (L) strand, respectively. The D loop is shown as a three-stranded structure. The replication origins of the H strand (OH) and L strand (OL) and the direction of DNA synthesis are indicated by long bent arrows. The transcription initiation sites (ITL, ITH1 and ITH2) and the direction of RNA synthesis are indicated by short bent arrows.

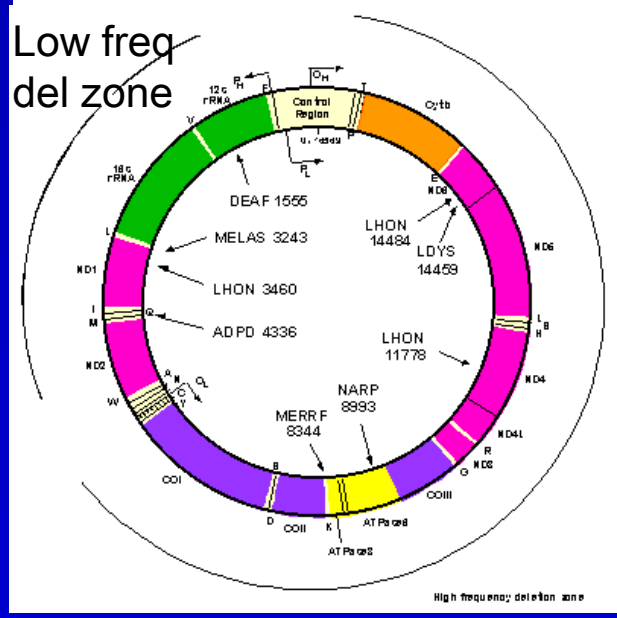


- mTERM is the binding site for the mitochondrial termination factor mTERF. The 22 tRNA genes are depicted by dots and the single-letter code of the amino acid (isoacceptors for serine and leucine are distinguished by their codon sequence). Depicted by shaded boxes are the genes that encode the 12S and 16S rRNA species and the 13 protein-coding genes. ND, *Cyt b*, CO and ATPase refer to genes that encode the subunits of OXPHOS complexes I, III, IV and V, respectively. The positions of the most commonly encountered point mutations, A3243G (in myopathy, encephalopathy, lactic acidosis, stroke-like episodes — MELAS), A8344G (in myoclonic epilepsy with ragged red fibres — MERRF), T8993G/C (in neurogenic weakness, ataxia, retinitis pigmentosa/maternally inherited Leigh syndrome — NARP/MILS), and G3460A, G11778A, T14484C and A14495G (in Leber's hereditary optic neuropathy — LHON) are indicated

Mitochondrial Syndromes with Dilated Cardiomyopathy

- Kearns-Sayre
- Ocular Myopathy
- MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes)
- MERRF (myoclonus epilepsy with ragged red fibers)

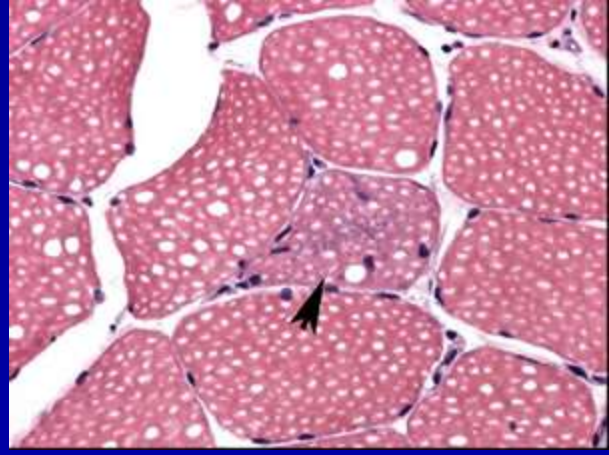




Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Kearns-Sayre Syndrome

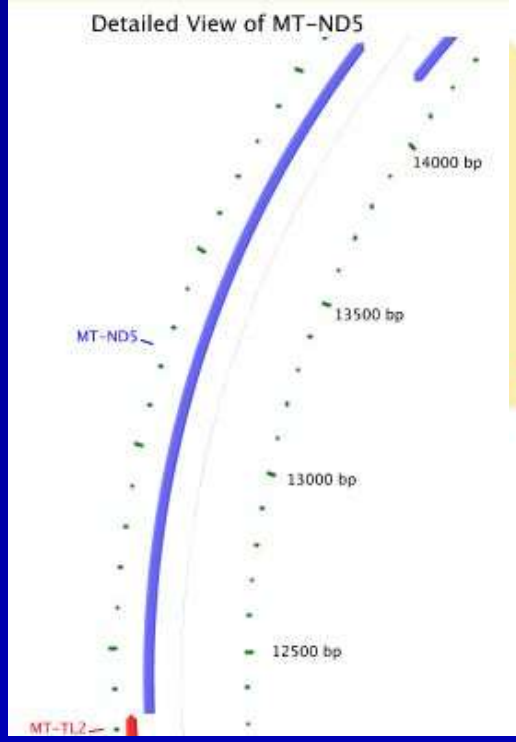
- "ragged red fibers," a marker for dysfunction of mitochondrial DNA. Ragged red fibers denote the absence of cytochrome oxidase staining in a proportion of muscle fibers in the biopsy. The affected muscle tissue appears as blue muscle fibers with H&E stain (arrowhead). The name is derived from bright red irregular (moth eaten) subsarcolemmal depositions with Gomori trichrome on frozen sections (not shown).

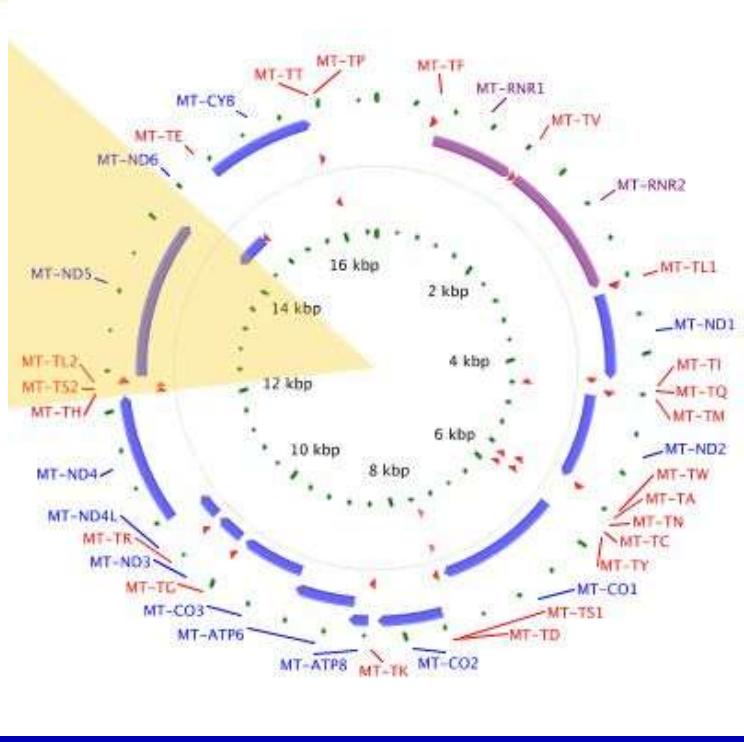


- Chronic Progressive external ophthalmoplegia, ptosis

- Single large deletion in mtDNA

MELAS syndrome





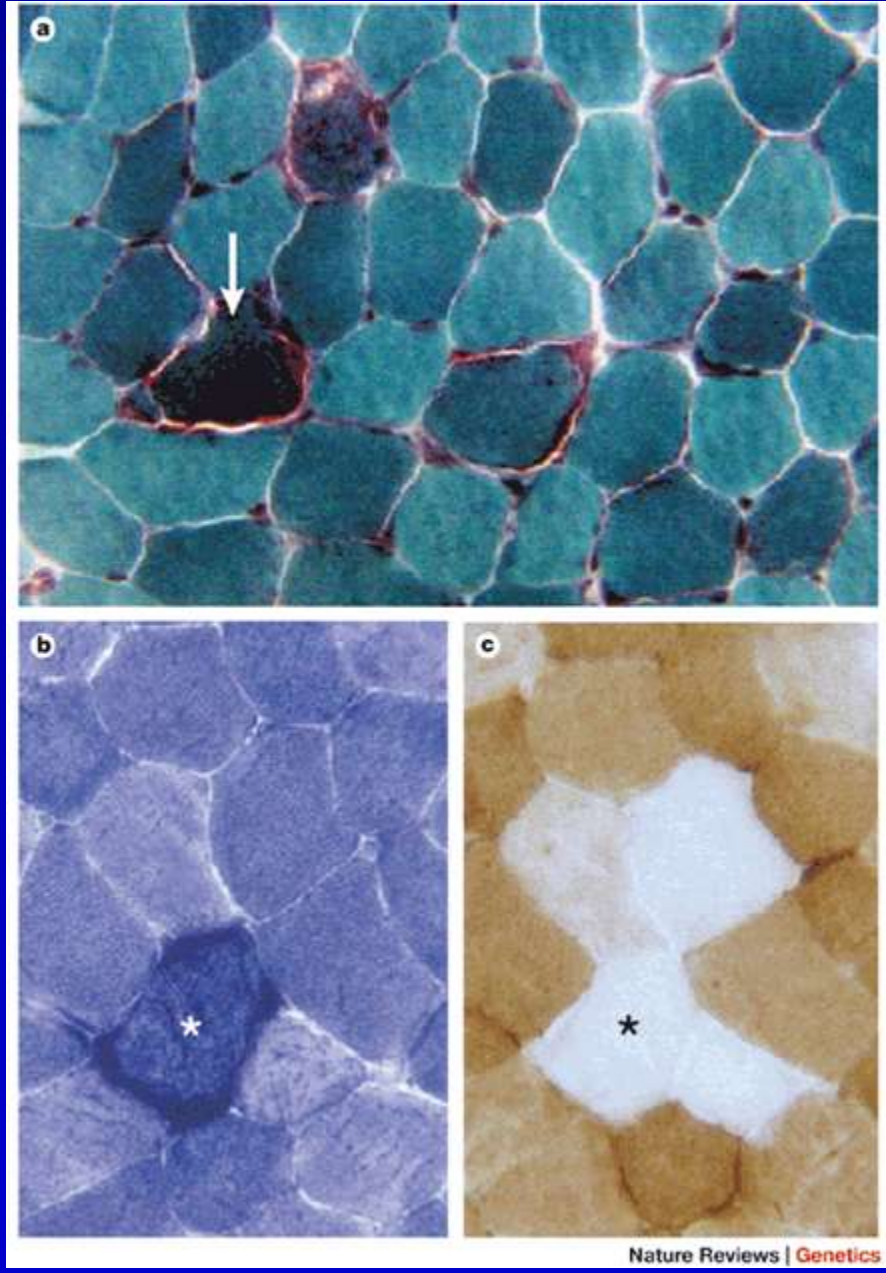
- MELAS = mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
- MT-ND5 is the gene's official symbol. (mitochondrially encoded NADH dehydrogenase 5)
- protein is part of a large enzyme complex known as complex I
- base pairs 12,337 to 14,148

Complex I Deficiency

- usually a progressive neuro-degenerative disorder, a variety of clinical symptoms, particularly in tissues that require high energy levels, such as brain, heart, liver, and skeletal muscles. A number of specific mitochondrial disorders have been associated with Complex I deficiency including: Leber's hereditary optic neuropathy (LHON), MELAS, MERRF, and Leigh Syndrome (LS).
  Fatal infantile multisystem disorder – characterized by poor muscle tone, developmental delay, heart disease, lactic acidosis, and respiratory failure.
  Myopathy (muscle disease) – starting in childhood or adulthood, and characterized by weakness or exercise intolerance.
  Mitochondrial encephalomyopathy (brain and muscle disease) – beginning in childhood or adulthood and involving variable symptom combinations which may include: eye muscle paralysis, pigmentary retinopathy (retinal color changes with loss of vision), hearing loss, sensory neuropathy (nerve damage involving the sense organs), seizures, dementia, ataxia (abnormal muscle coordination), and involuntary movements. This form of Complex I deficiency may cause Leigh Syndrome and MELAS.

Ragged-red fibres (RRFs)

- A - Ragged-red fibres (RRFs) revealed by the modified Gomori trichrome stain. Abnormal deposits of mitochondria appear as reddish blotches in the subsarcolemmal or intermyofibrillar space (arrow).
- B, C -Serial sections of a muscle biopsy from a patient with a mitochondrial DNA (mtDNA) single deletion.
- In **b**, the RRF (white asterisk) is highlighted by the histochemical stain for succinate dehydrogenase, an enzyme entirely encoded by nuclear DNA.
- In **c**, the same fibre shows no activity for cytochrome ***c*** oxidase, an enzyme containing ten subunits encoded by nuclear DNA and three encoded by mtDNA



Arrhythmogenic RV Dysplasia

- Progressive fibrofatty degeneration of myocardium and dysfunction and arrhythmia and SCD
- Junctional plakoglobin mutation (recessive)
  - Naxos syndrome (RV)
  - Carvajal syndrome (LV)
- Desmosomal proteins maintain structural and functional contacts between cells
- Desmoplakin
- Plakophilin-2
- Desmoglein-2
- Desmocollin-2
- Cardiac ryanodine receptor (RyR2) – less common

Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

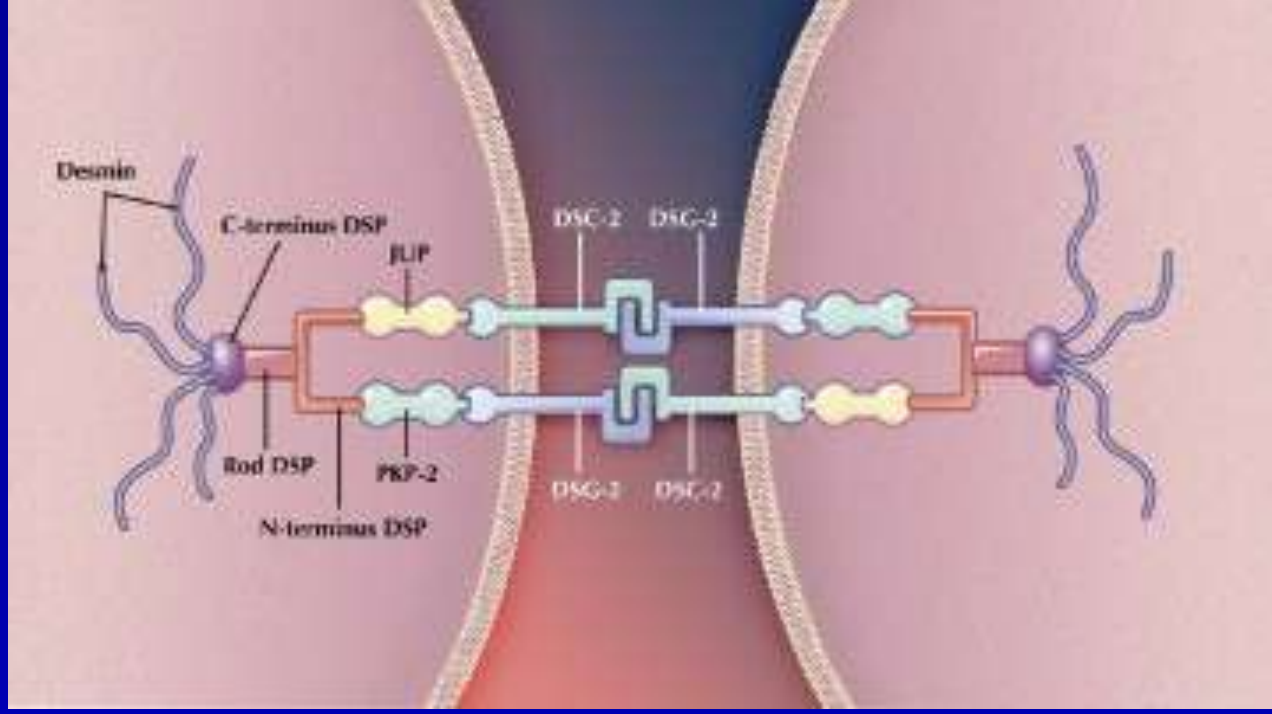
ARVD Genetics

Table 1 Summary of genes associated with ARVD

Locus	Chromosome location	Gene	Disease	References
ARVD1	14q23-q24	TGFB3	ARVD 1	Rampazzo *et al.*[2,3]
ARVD2	1q42.1-q43	RYR2	ARVD 2; ventricular tachycardia, stress-induced polymorphic	Rampazzo *et al.*[5]; Marx *et al*[26]
ARVD3	14q12-q22	Unknown	ARVD 3	Severini *et al.*[6]
ARVD4	2q32.1-q32.3	Unknown	ARVD 4	Rampazzo *et al.*[7]
ARVD5	3p21.3, 3p23	LAMR1	ARVD 5	Ahmad *et al.*[8]; Asano *et al.*[17]
ARVD6	10p14-p12; 10p13-14	PTPLA	ARVD 6	Li *et al.*[9,31]
ARVD7	2q35	DES	Desmin-related myopathies	Melberg *et al.*[10]; Ferreiro *et al.*[33]
	10q22.2-23.3	ZASP	Myopathy, myofibrillar, ZASP-related, cardiomyopathy,dilated; cardiomyopathy, dilated, with left ventricular non-compaction	
	10q22.3		ARVD 7	
ARVD8	6p24	DSP	Keratosis palmoplantaris striata ii; dilated cardiomyopathywith woolly hair and keratoderma; ARVD 8; skin fragility-woolly hair syndrome; epidermolysis bullosa, lethal acantholytic	Olavesen *et al.*[11]; Rampazzo *et al.*[18]
ARVD9	12p11	PKP2	ARVD 9	Bonne *et al.*[12]; Grossmann *et al.*[19]; Gerull *et al.*[20]; Mertens *et al.*[40]
ARVD10	18q12.1-q12.2	DSG2	ARVD 10	Arnemann *et al.*[13]; Syrris *et al.*[22]; Pilichou *et al.*[43]
ARVD11	18q21	DSC2	ARVD 11	Greenwood *et al.*[14]; Buxton *et al.*[44]

Moric-Janiszewska E et al. Europace. 2007;9:259.

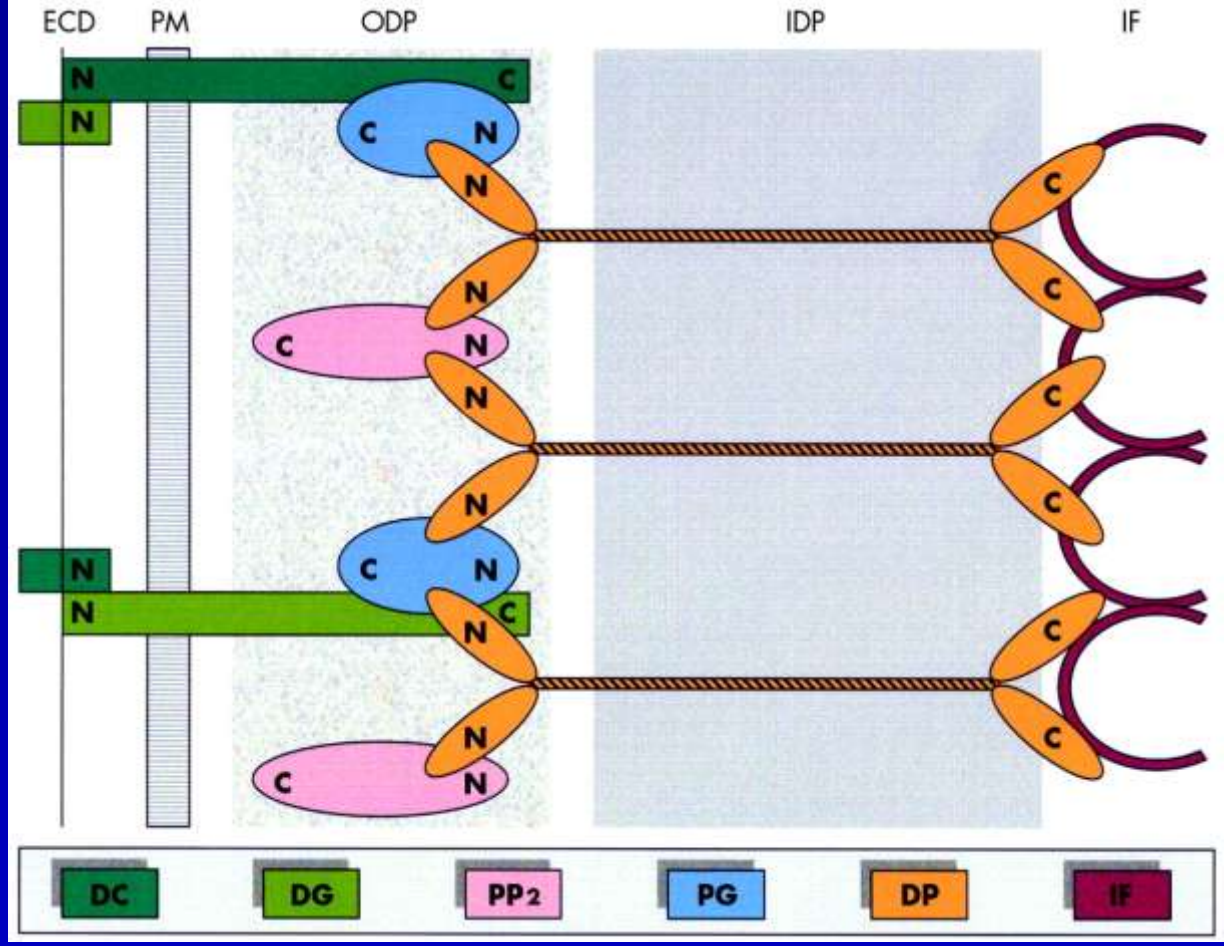
Arrhythmogenic RV Cardiomyopathy



- The desmosomal cadherins, desmoglein (DSG)-2 and desmocollin (DSC)-2 comprise the transmembrane component of the desmosomal complex. Their extracellular domains interface directly with their counterparts on neighboring cells. The intracellular portions of the desmosomal cadherins interact with proteins of the armadillo family: junctional plakoglobin (JUP) and plakophilin (PKP)-2, which in turn bind to the N-terminal domain of desmoplakin (DSP). At its C-terminal, DSP anchors desmin intermediate filaments to the cell surface

ARVD

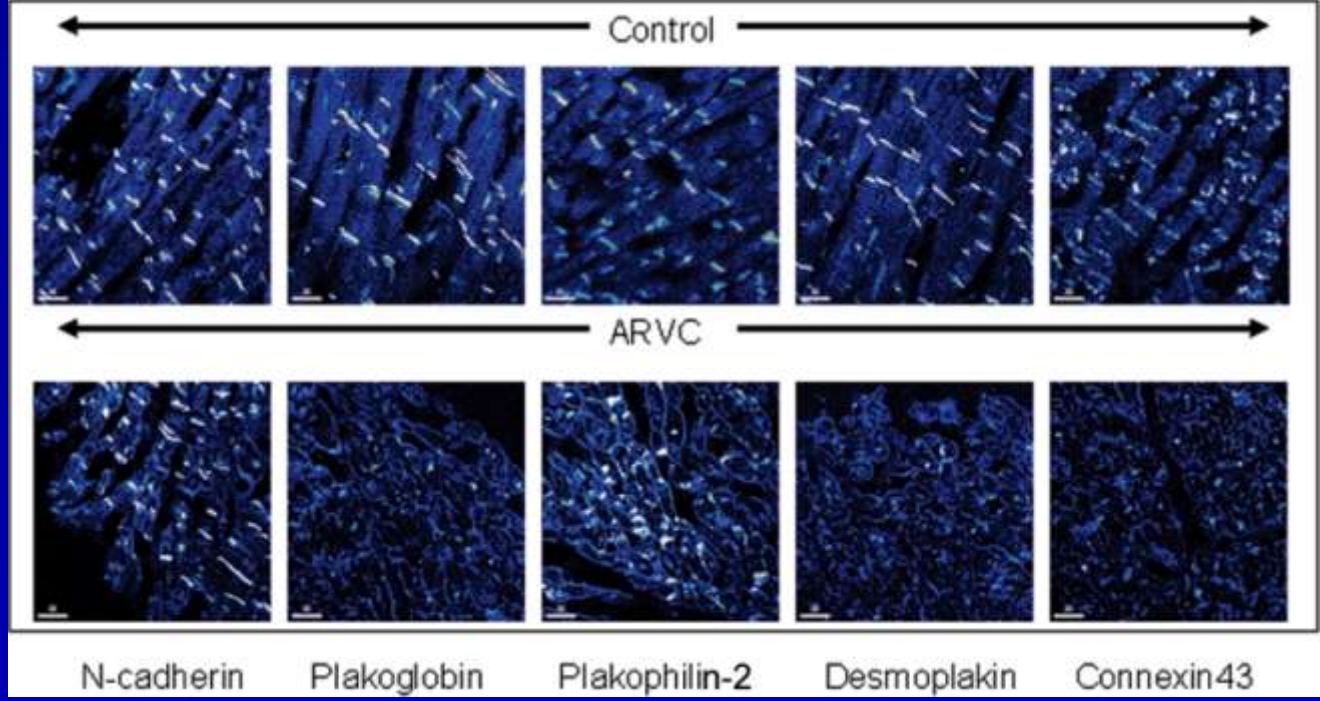
- DP, desmoplakin;
- DC, desmocollin;
- DG, desmoglein;
- ECD, extracellular core domain;
- IDP, inner dense plaque;
- IF, intermediate filaments;
- ODP, outer dense plaque;
- PG, plakoglobin;
- PP2, plakophilin2;
- PM; plasma membrane



- A model of desmosomal plaque demonstrating the position of the major adhesive components.

Tsatsopoulou AA et al. Heart. 2006;92:1720.

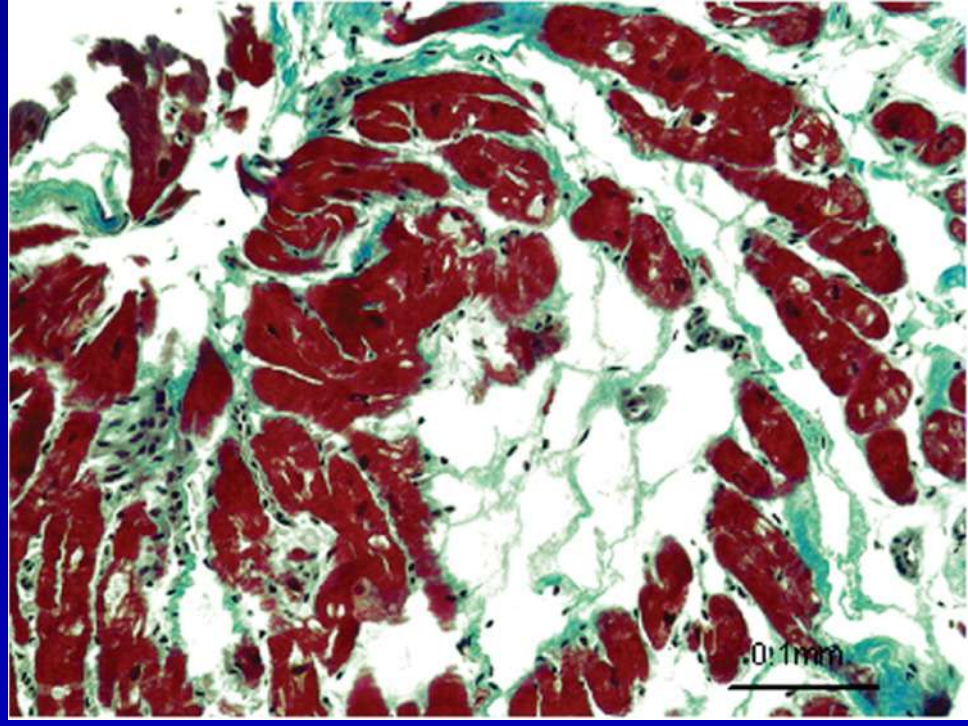
Arrhythmogenic RV Cardiomyopathy



- Confocal immunofluorescence microscopy analysis of control and proband left ventricular myocardium, showing the amount of immunoreactive signal for selected junctional proteins at intercalated disks
- The ARVC and control myocardium showed comparable levels of expression of N-cadherin (MIM *114020) and plakophilin-2, but there was a marked decrease in the amount of immunoreactive signal at intercalated discs for plakoglobin, desmoplakin, and the gap-junction protein Cx43 (MIM *121014)

Asimaki A et al. Am J Human Genet. 2007;81:964.

Arrhythmogenic RV Cardiomyopathy

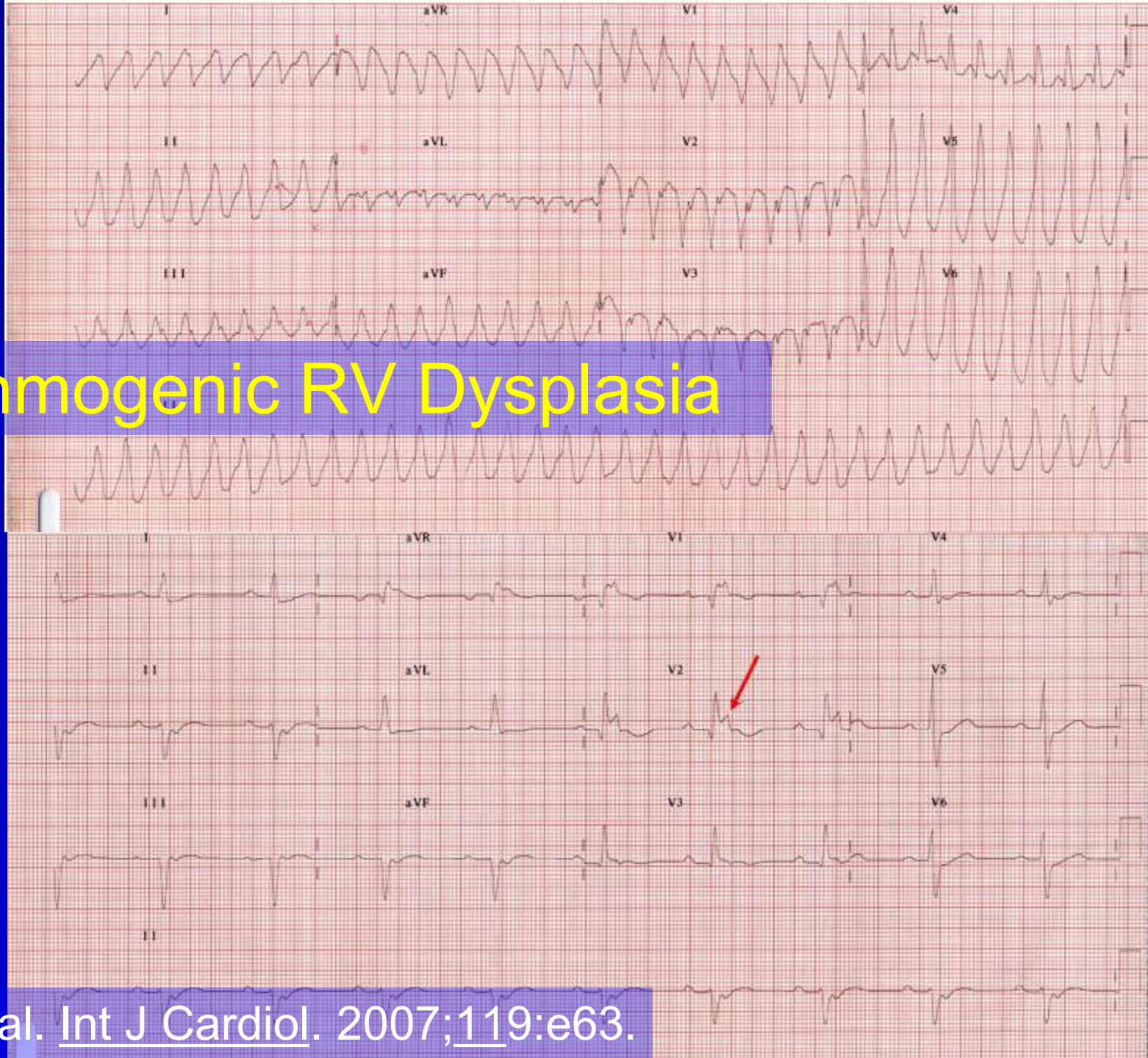


- Endomyocardial biopsy showing extensive fibrofatty replacement of right ventricular muscle and patchy mononuclear inflammatory infiltrate

Asimaki A et al. Am J Human Genet. 2007;81:964.

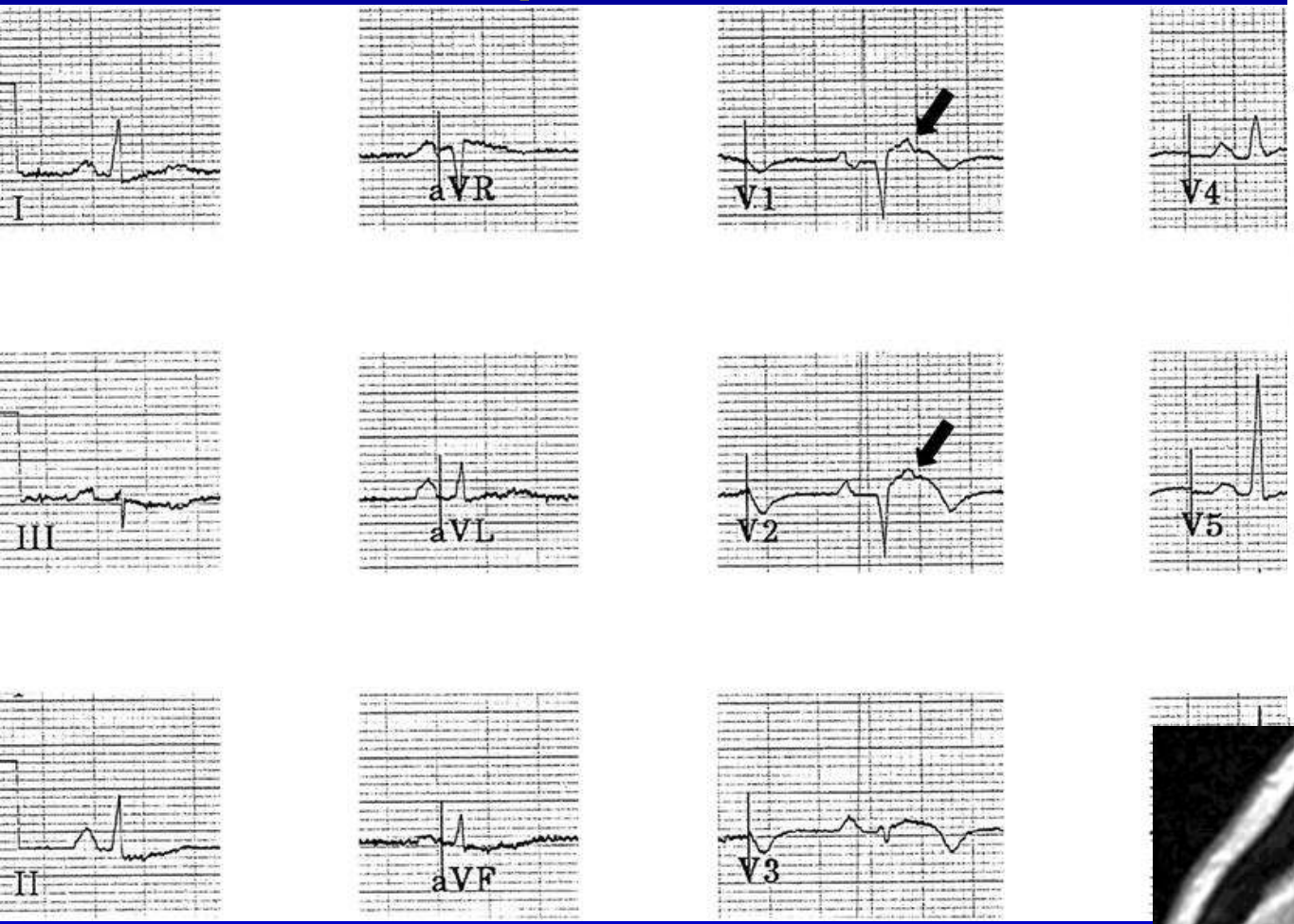
Arrhythmogenic RV Dysplasia

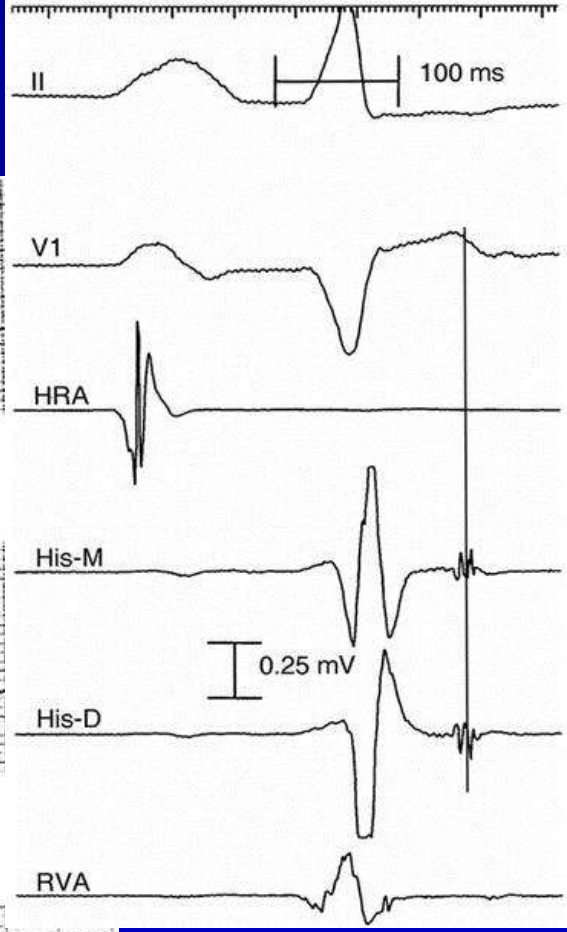
Epsilon wave

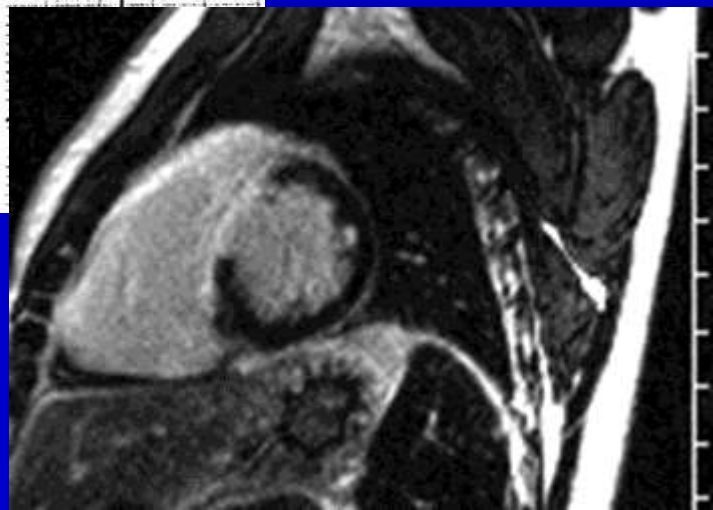


You C-C et al. Int J Cardiol. 2007;119:e63.

ARVD – Epsilon Wave







- Hyperenhancement of RV and IVS

Kenigsberg DN et al. Circulation. 2007;115:e538.

Genetic Causes of Structural Disase

- Transcription factors and signalling molecules that direct and integrate cardiac development
- Remarkably few structural protein genes
- Usually defects are quantitative and incomplete
- Categories of Mendelian Congenital heart disease
  - Isolated CV malformations
  - Pleiotropic syndromes that frequently affect the heart
  - Syndromes that only occasionally affect the CV system

Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Isolated Congenital Heart Disease

- ASD (GATA4 and myosin heavy chain) and VSD (NKX2-5 more general incl ASD and Wenck and SSS and AF)
- Bicuspid Aortic Valve mainly a sporadic problem (NOTCH1 transcription regulator – also ToF and HLHS)
- Mitral Valve Prolapse (under investigation)

Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Genetic Syndromes with Congenital Heart Disease

- Holt-Oram Syndrome
- Noonan Syndrome
- Trisomy 21 (Down's Syndrome)
- Turner Syndrome

Seidman JG et al. "Genetic factors in myocardial disease" in BHD 8th ed. 2008

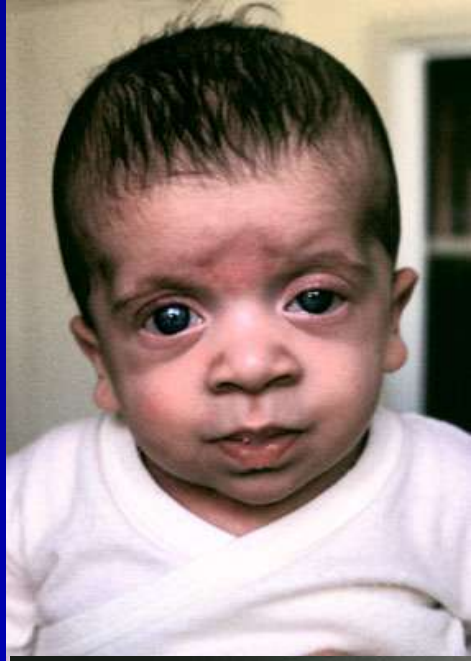
Genetic Syndromes with Congenital Heart Disease

- Holt-Oram Syndrome – (TBX5 mutation; hand-heart disorder) – 85% have heart probs – usually ASD, also VSD and PDA also EP probs AVblock and BBB – autosomal dominant – look for subtle UE defects

Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Genetic Syndromes with Congenital Heart Disease

- Noonan Syndrome – phenotype similar to Turner's Syndrome – a cardiofacial syndrome – mainly pulmonary valve stenosis (40%), also ASD (30%), also hypertrophy either LV or RV, also VSD and PDA (10%)
- Facial features: hypertelorism, flat nasal bridge, palpebral ptosis, thick lips, and low-set rotated ears with thick helix
- 2 mutations – PTPN11 tyrosine phosphatase participating in transcription, and KRAS



Seidman JG et al. "Genetic factors in myocardial disease" in BHD 8th ed. 2008

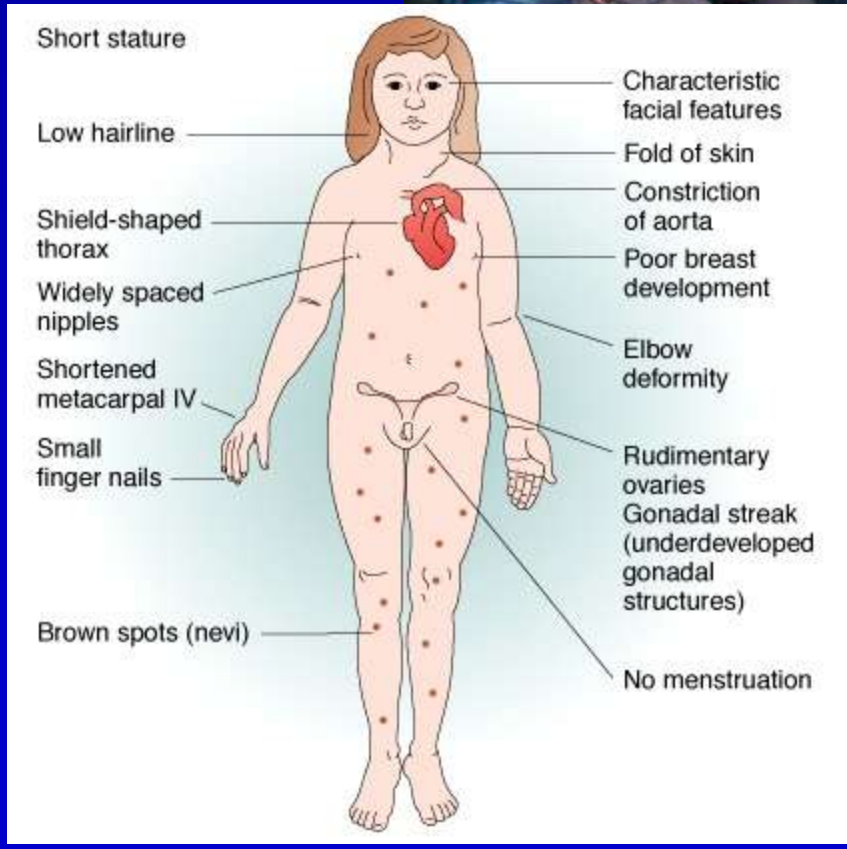
Genetic Syndromes with Congenital Heart Disease

- Trisomy 21 – (Down's Syndrome)
- Heart disease in 50%
  - Prototype is AV Canal defect
  - Complex disease present in 33%
  - Mitral prolapse
  - Semilunar valve fenestrations in older
- Specific genetic mechanisms obscure

Seidman JG et al. "Genetic factors in myocardial disease" in BHD 8th ed. 2008

Turner Syndrome

- Turner Syndrome – Partial or complete loss of 1 copy of chromosome 46 with 45-X or 46-XX or 46-XY mosaic; Short stature, web neck, bowed arms
- Cardiac defects in 20-50% of patients
  - Postductal coarctation in 50-70% of these
  - Bicuspid AoV, HLHS, PAPVR and no ASD
  - Conduction system dz and Long QT
  - Hypertension and ascending aortic dilation even without coarctation or after repair – aggressive rx



Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Contiguous Gene Syndromes with Congenital Heart Disease

- Arteriohepatic dysplasia – peripheral PS, hypoplasia
- Cat-eye syndrome – (gene dupl) TAPVR
- DiGeorge sequence – Truncus arteriosus, right aortic arch, ToF, PDA
- Miller-Dieker syndrome – PDA, complex anomalies
- Prader-Willi syndrome – cor pulmonale (from obesity and central apnea)
- WAGR syndrome – hypertension (from Wilms tumor)

Pyeritz RE et al. “Gen. principles of genetic factors in CV dz” BHD 8th ed. 2008

Cardiac Tumors

- Carney complex – dominant inheritance
- Extracardiac: mycomas, lentiginosis, hyperpigmentatin, endocrine dysfunction
- Mutation: PRKAR1α – regulatory subunit of cyclic adenosine monophosphate-dependent protein kinase A
- Cardiac myxomas – multiple, recurrent, in ventricles

Seidman JG et al. “Genetic factors in myocardial disease” in BHD 8th ed. 2008

Genetic Causes of Arrhythmias

- Long QT (10 types)
- Brugada (2 types)
- Catecholaminergic VT (2 types)
- Short QT (3 types)
- Cardiac conduction defect and SSS (3 types)
- Atrial fibrillation (3 types)
- Of the 23 types listed above, 18 are overlapping channelopathies and 5 are structural proteins
- Contrast to RV Cardiomyopathy – connecting proteins

Priori SG et al. “Genetics of cardiac arrhythmias” in BHD 8th ed. 2008