Adult Genetic Diseases

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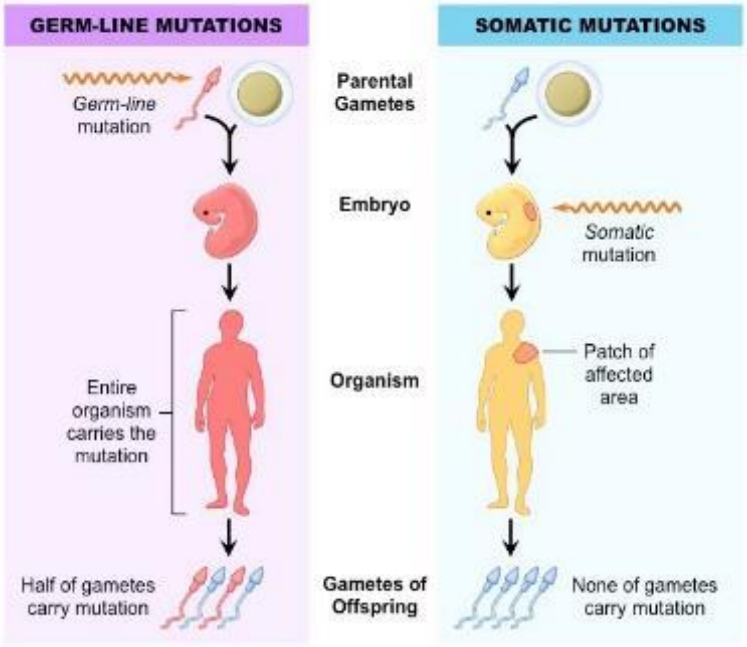
How common is genetic diseases?

- 20,000+ genes
- 6,000+ genetic diseases (MIM)
- mild mutation does not show phenotype
- very severe mutation does not survive
  - 1/6 spontaneous abort
  - 1/100 newborn with genetic disease
  - 1/100 adult has genetic affected health conditions eg. increases risk of cancer, hyperlipidemia, heart and metabolic diseases

Adult genetic disorders

- Principle of genetic transmission
  - Single gene diseases, polygenic, epigenetics, chromosomal, multifactorial
  - AD, AR, XR, mitochondrial
  - pedigree
- Phenotype of genetic diseases
- Type of mutation and genetic testing
  - Point mutation, in/del, CNV, trinucleotide repeat
- Genetic counseling
  - Inheritance risk

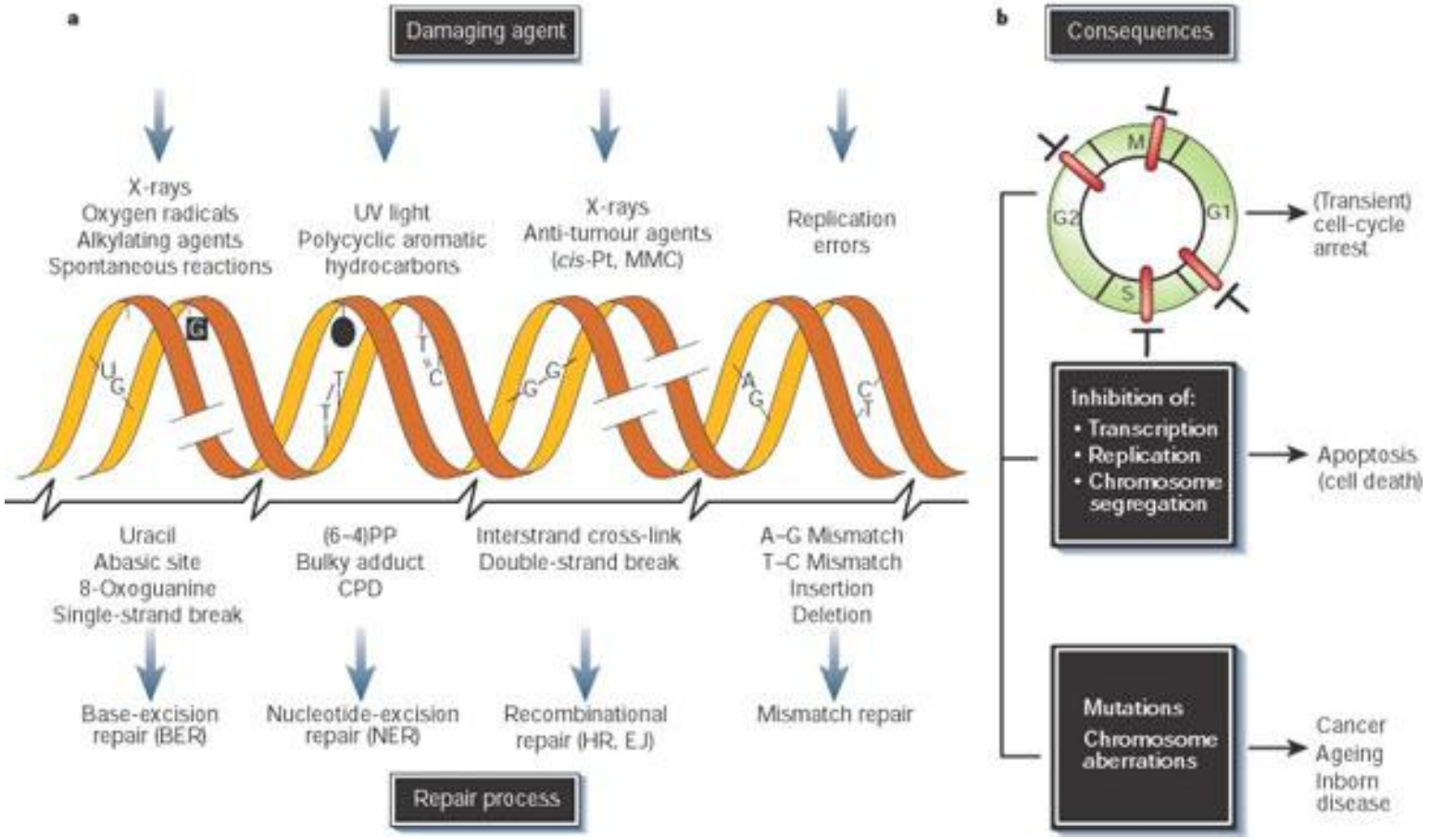
When do mutation occurs?



Germline & Somatic mutation

Source: http://ib.bioninja.com.au/standard-level/topic-3-genetics/33-meiosis/somatic-vs-germline-mutatio.html

How mutation occurs?



Hoeijmakers, 2001

Topics

Neuromuscular Disorders: Duchenne and other muscular dystrophies

Connective tissue disorders: Marfan syndrome

Neurocutaneous disorders: Neurofibromatosis

Neurodegenerative disorders: Spinocerebellar Ataxia

Hereditary Cancers: Breast and Ovarian Syndrome, Colorectal Cancer

Genetic of sudden cardiac death (SUDs) and other genetic diseases

Terminology

- **Penetrance** is the probability that a gene will have any phenotypic expression at all.
- **Expressivity** is the severity of expression of the phenotype.
- **Pleiotropy** is a gene that controls several functions or has more than one effect.

Penetrance → all or none expression of a genotype
Expressivity → severity of extent
Pleiotropy → one gene causes many effects

Topics

Neuromuscular Disorders: Duchenne and other muscular dystrophies

Connective tissue disorders: Marfan syndrome

Neurocutaneous disorders: Neurofibromatosis

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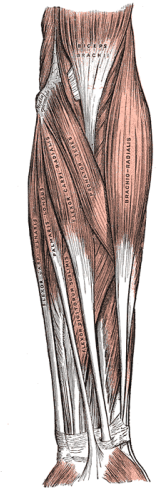
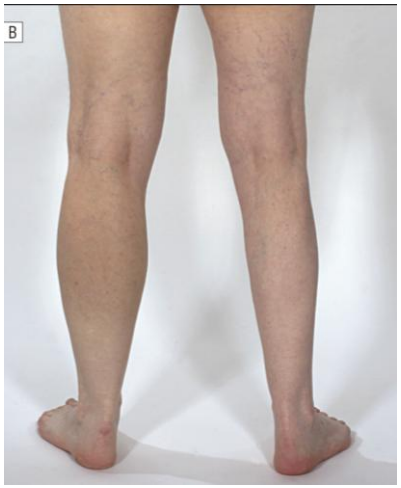
Genetic of sudden cardiac death (SUDs) and other genetic diseases

Genetic of neuromuscular disorders

- Neuromuscular disorders affect the peripheral nervous system and muscles
- Cause by defect of the voluntary muscle, or indirectly, being defect of nerves or neuromuscular junctions
- muscle weakness (twitching/fasciculation, cramps/spasms, aches and pains), muscle loss, movement issues, balance problems, numbness, painful sensations, droopy eyelids, double vision, trouble swallowing, trouble breathing

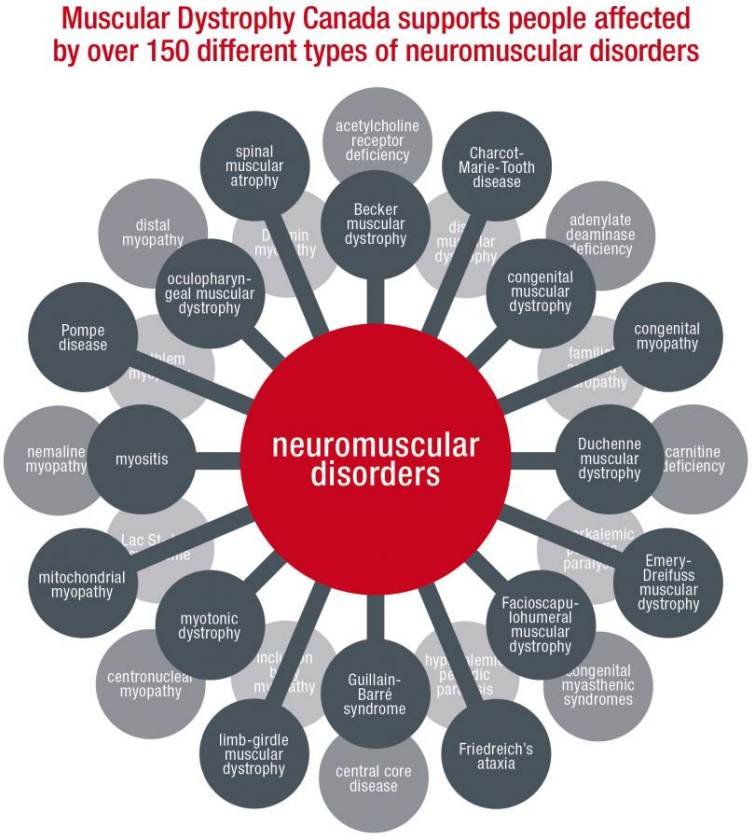




WikiCommon, JAMA Neurology

Genetic of neuromuscular disorders

- Genetic is the most common cause of neuromuscular disorders, other causes are autoimmune or still unknown

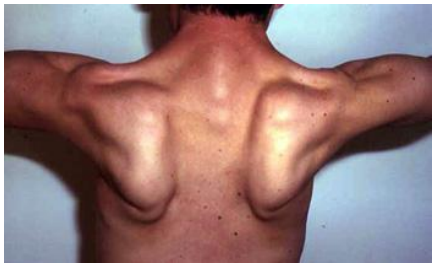


Muscular Dystrophy Canada

Muscular Dystrophies

- progressive skeletal muscle weakness
- muscle fibers are susceptible to damage
- Symptoms of the most common variety begin in childhood. Other types of muscular dystrophy don't surface until adulthood

Duchenne/Becker



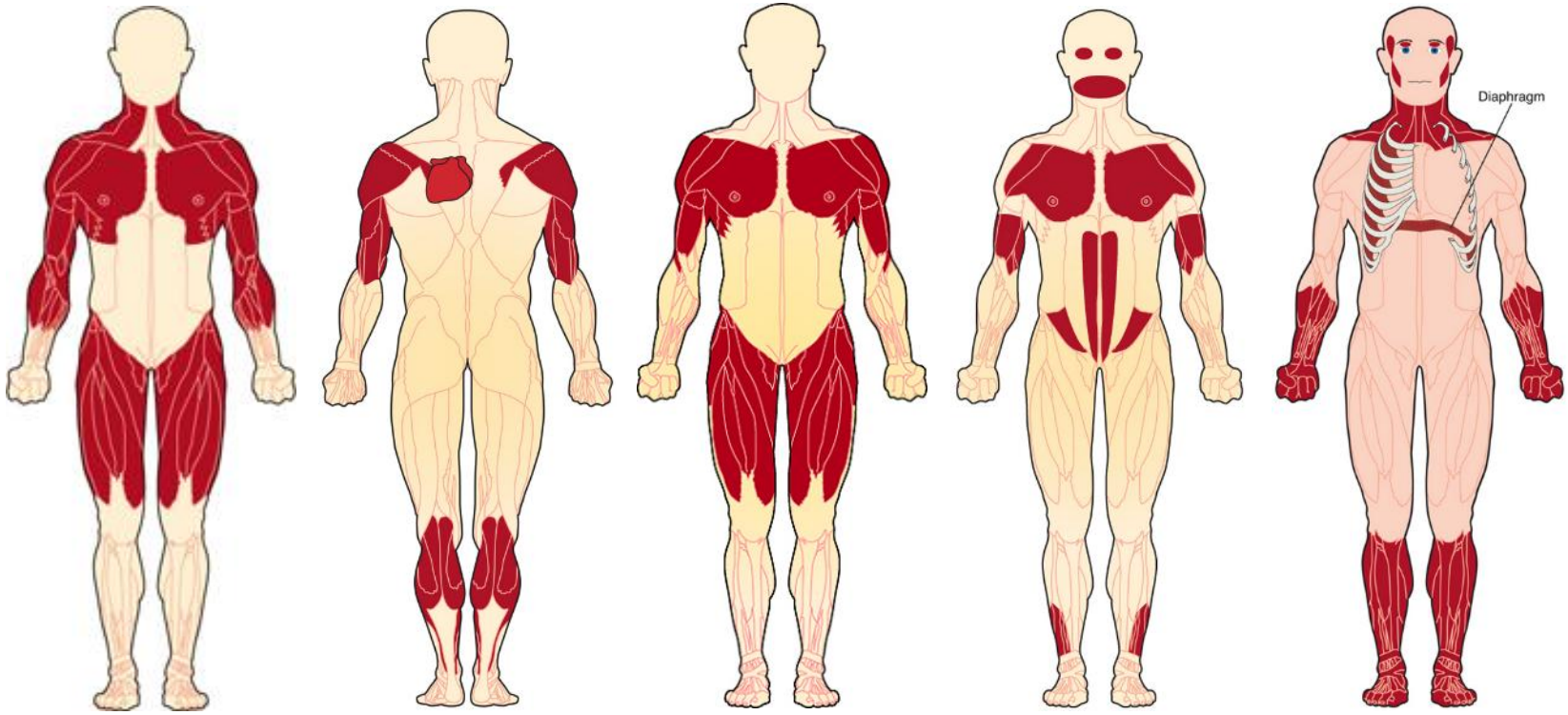
Limb-Girdle

Facioscapulohumeral

Myotonic Dystrophy

Muscular Dystrophy Association

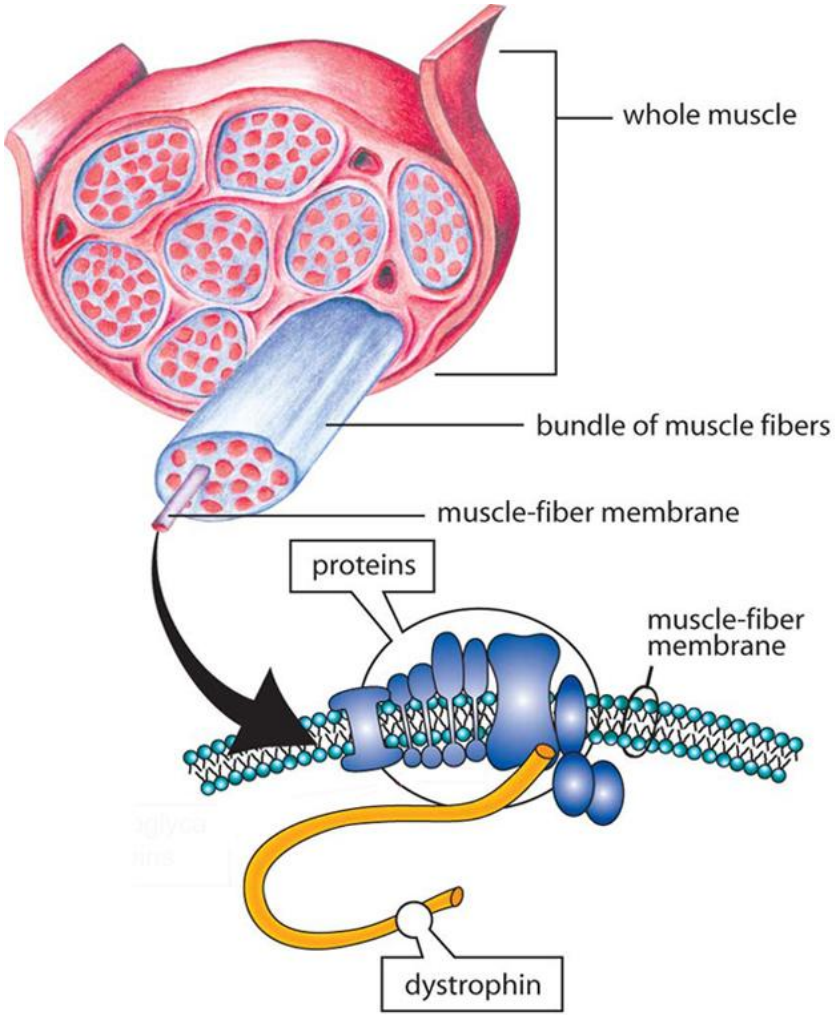
Affected group of muscles in MDs



Duchenne/Becker	Emery-Dreifuss	Limb-Girdle	Facioscapulohumeral	Myotonic
most common MD				*common in adult*

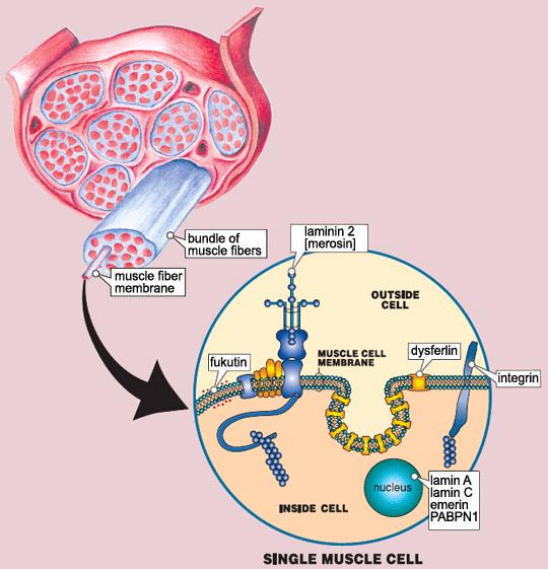
Muscular Dystrophy Association

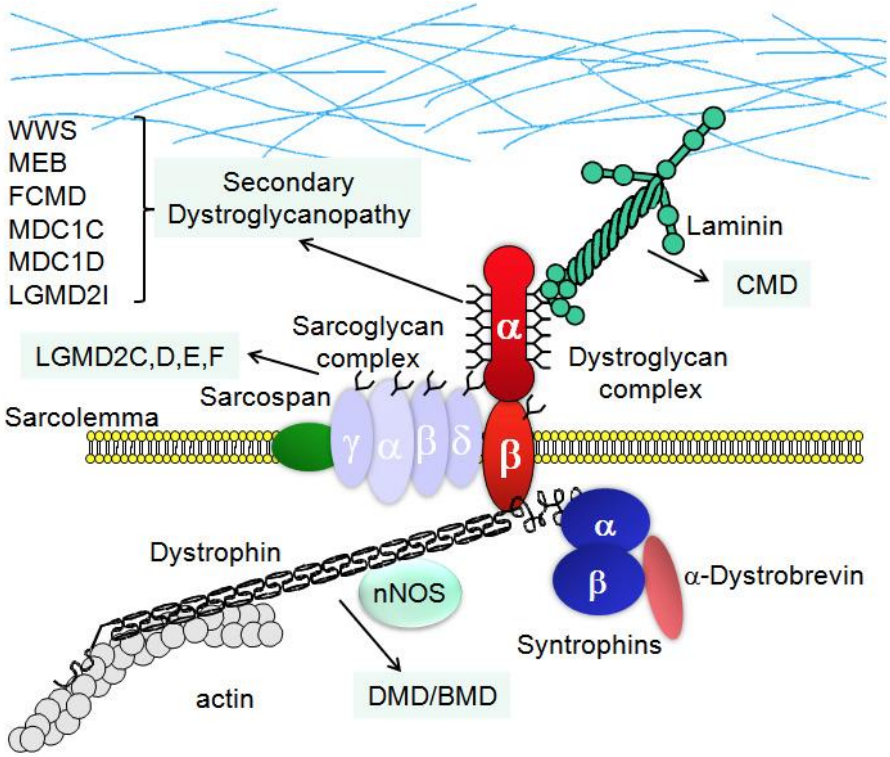
Defects at muscle cell membrane result in muscle fiber degeneration



Muscular Dystrophies

- Mutation in Cytoskeleton protein of muscle cell causes Muscular Dystrophies

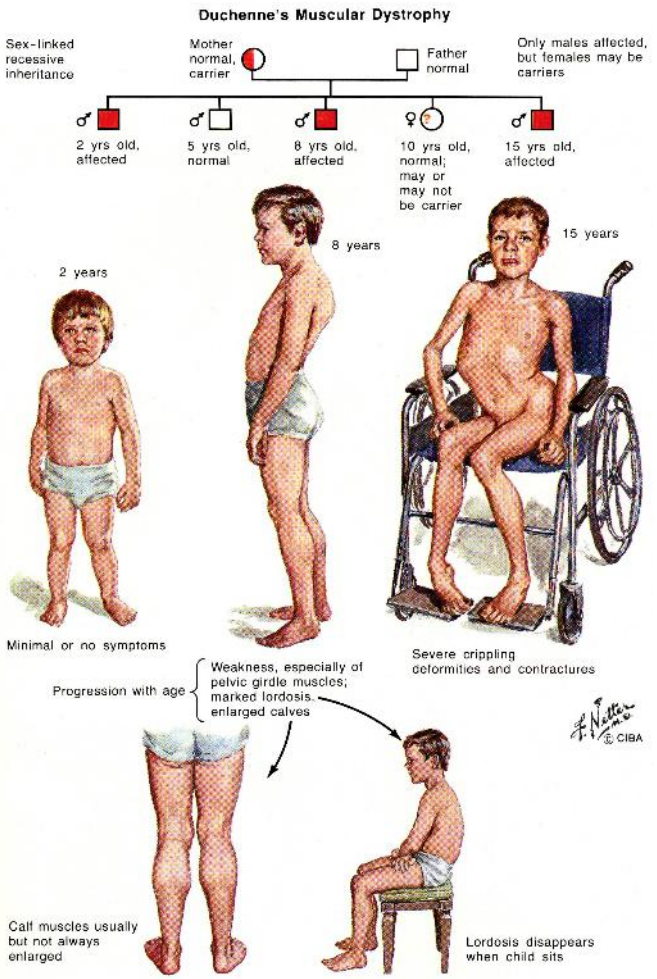




Muscular Dystrophy Association

Duchenne and Becker MD

- The most common form of muscular dystrophy in children (1:3,500)
- Symptoms start in early childhood with rapidly delayed gross motor development, including sitting, standing and walking
- muscle loss occurs first in the upper legs and pelvis followed by upper arms, heart, respiratory muscles
- Wheelchair bound at average of 12 year old
- Cardiomyopathy occurs around 18 year
- The life expectancy is <30 year (from respiratory complication and cardiomyopathy)

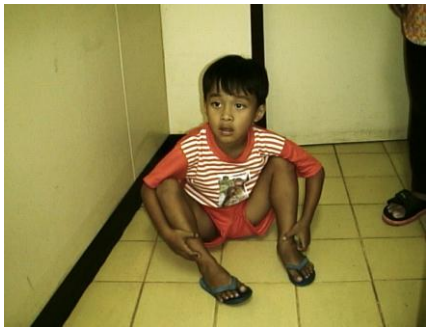


Waddling gait
Scoliosis
Joints contracture

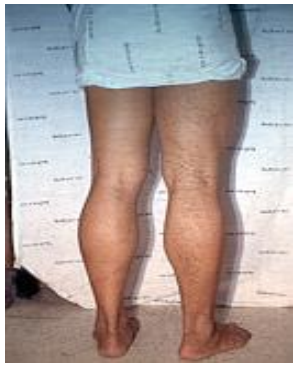
Duchenne and Becker MD

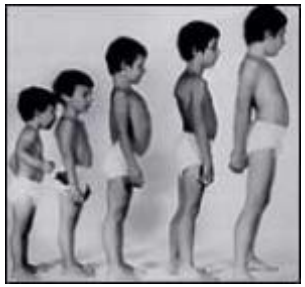
- In some cases, children with DMD may experience problems with learning and behavior
- DMD/BMD affect boys almost exclusively (x-link inheritance)
- Duchenne MD and Becker MD are similar and are caused by mutations in the same gene, but BMD is less severe than DMD

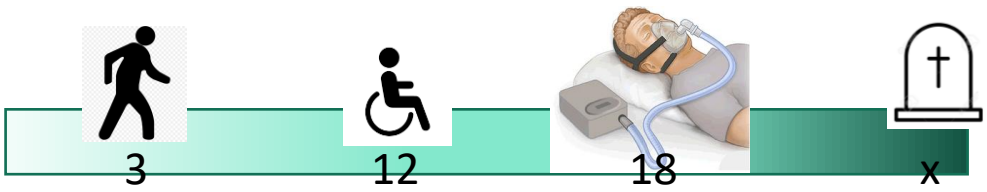
Gower sign



Calf pseudohypertrophy

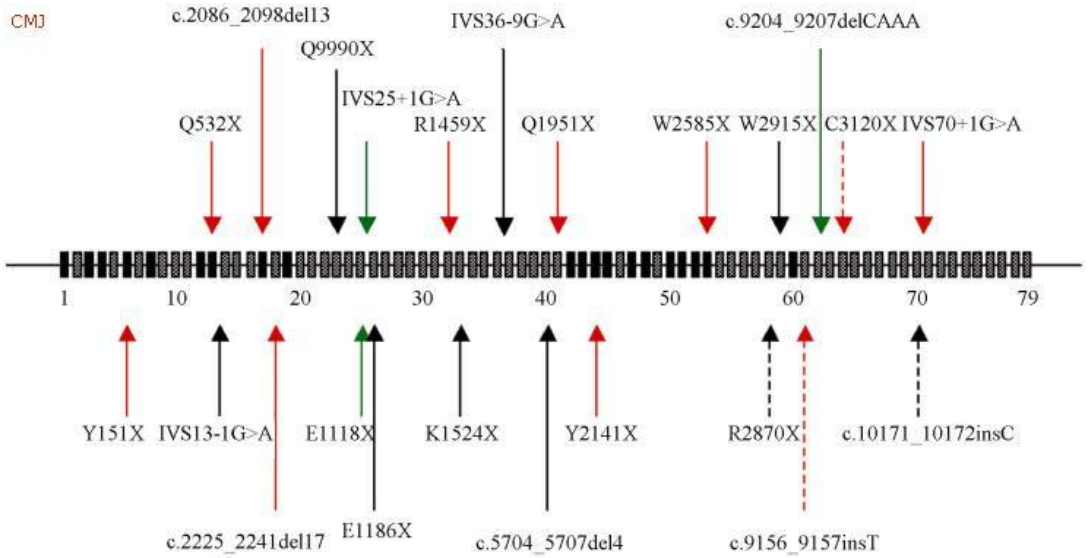




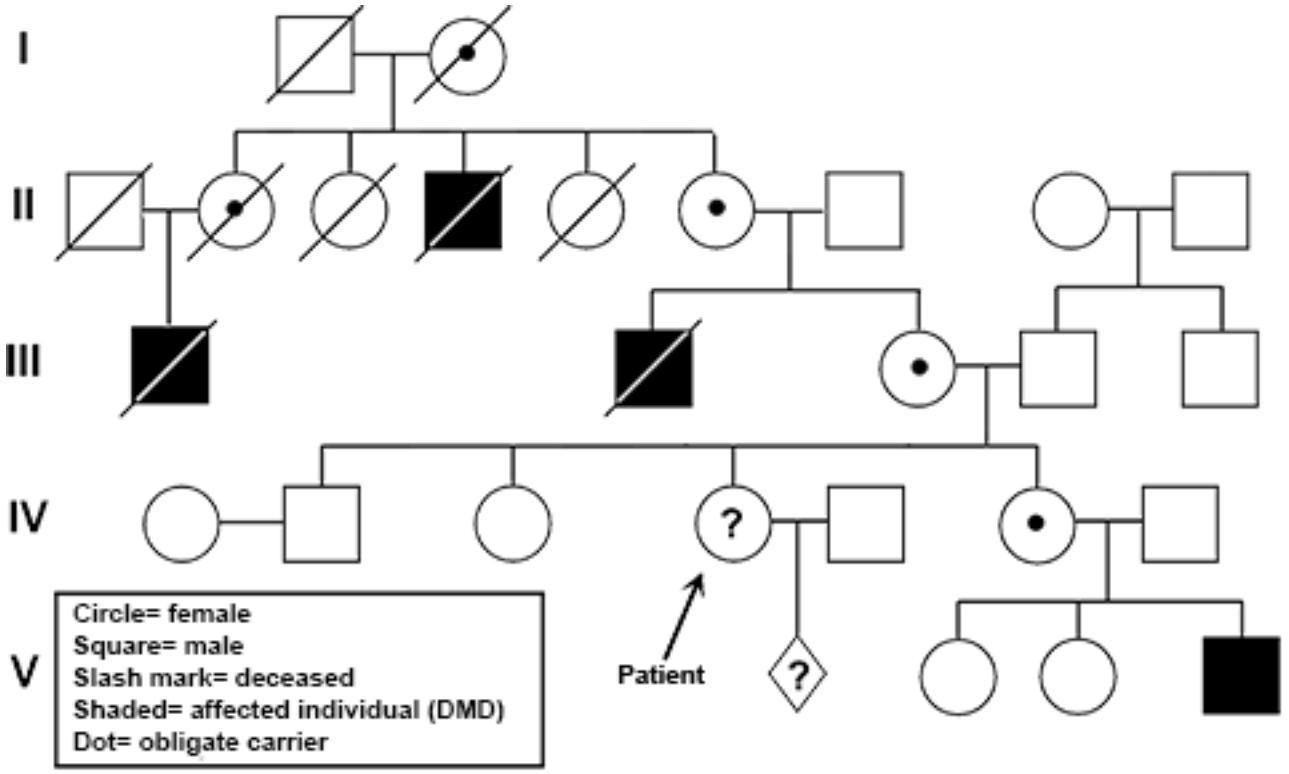


Dystrophin mutation in DMD/BMD

- *Dystrophin* gene located on X chromosome
- 79 exons, one of the largest known human gene
- mostly deletion type (65% deletion, 25% point mutation)
- 1/3 de novo
- Mutations with partial protein function cause Becker MD while mutation with loss of function results in Duchenne MD



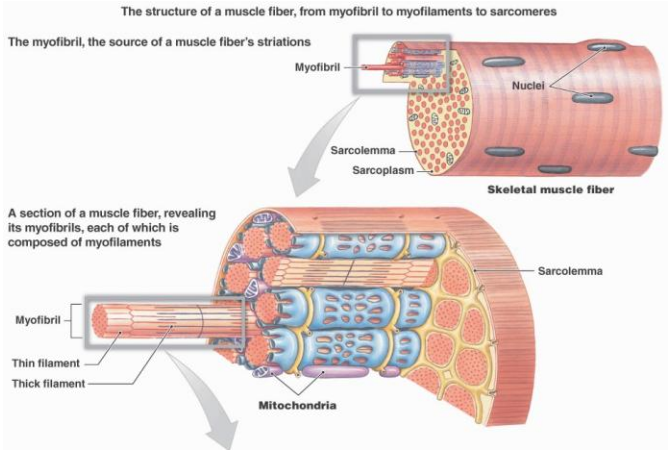
DMD Pedigree

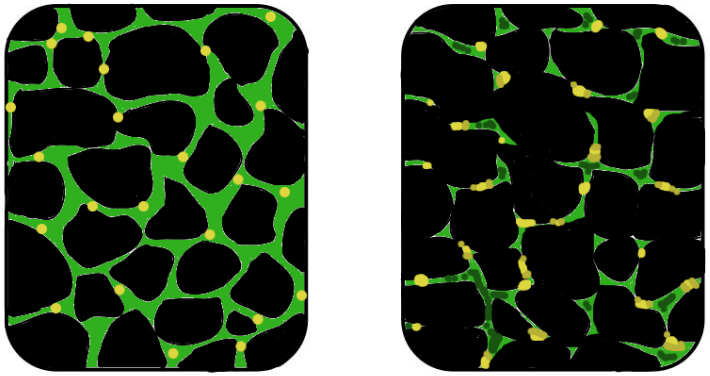


Girls with DMD?

Role of Creatine phosphokinase (CK) in DMD

- Elevated CK levels indicates muscle cell damage, myocardial infarction and kidney injury
- High CK levels represent leakage of the enzyme from the muscle cells, this change is not exactly correlated with the severity of the disease
- All MDs result in some CK elevation during the active phase of the disease
- CK level is typically normal in SMA





Staining of Dystrophin protein by immunofluorescent
Left-normal, Right-patient muscle fiber from biopsy

DMD Treatments

- Genetic testing and counselling
- Supportive treatment: physical therapy, braces, corrective surgery, assisted ventilation
- Corticosteroids: slowdown muscle degeneration and inflammation

  (independent ambulation, improve pulmonary function, delay the onset of cardiomyopathy and reduce the incidence of scoliosis)
- Eteplirsen: morpholino antisense (exon 51 skipping)
- Gene Therapy, increase muscle growth, enhance muscle repair

DMD Treatments

In-frame errors can occur when a deletion mutation takes out "three-letter" chunks without disrupting the "words" on either side. This allows a shorter — but still readable — sentence to be produced. In-frame mutations in the dystrophin gene allow shorter but still functional dystrophin to be made, as in BMD.

The mad cat ate the ~~fat rat and the~~ big bat.

deletion

The mad cat ate the big bat.

Out-of-frame errors occur when the deletion disrupts the "three-letter" reading pattern, creating "words" that don't make sense. This leads to an unreadable sentence, just as an out-of-frame mutation leads to nonfunctional dystrophin in DMD.

The mad cat ate the ~~fa~~t rat and the big bat.

deletion

The mad cat ate the tra tan dth ebi gba t.

Exon skipping converts an out-of-frame error into an in-frame error by causing the cell to skip not only the deleted section but also a nearby section (exon), restoring the reading frame and creating a readable sentence:

The mad cat ate the ~~tra tan dth e~~bi gba t.

skipped exon

The mad cat ate the big bat.

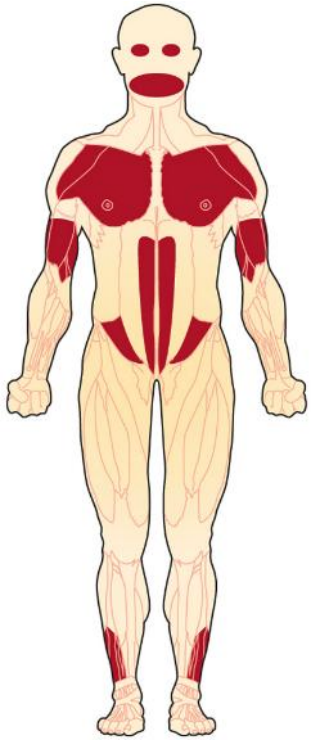
mda.org

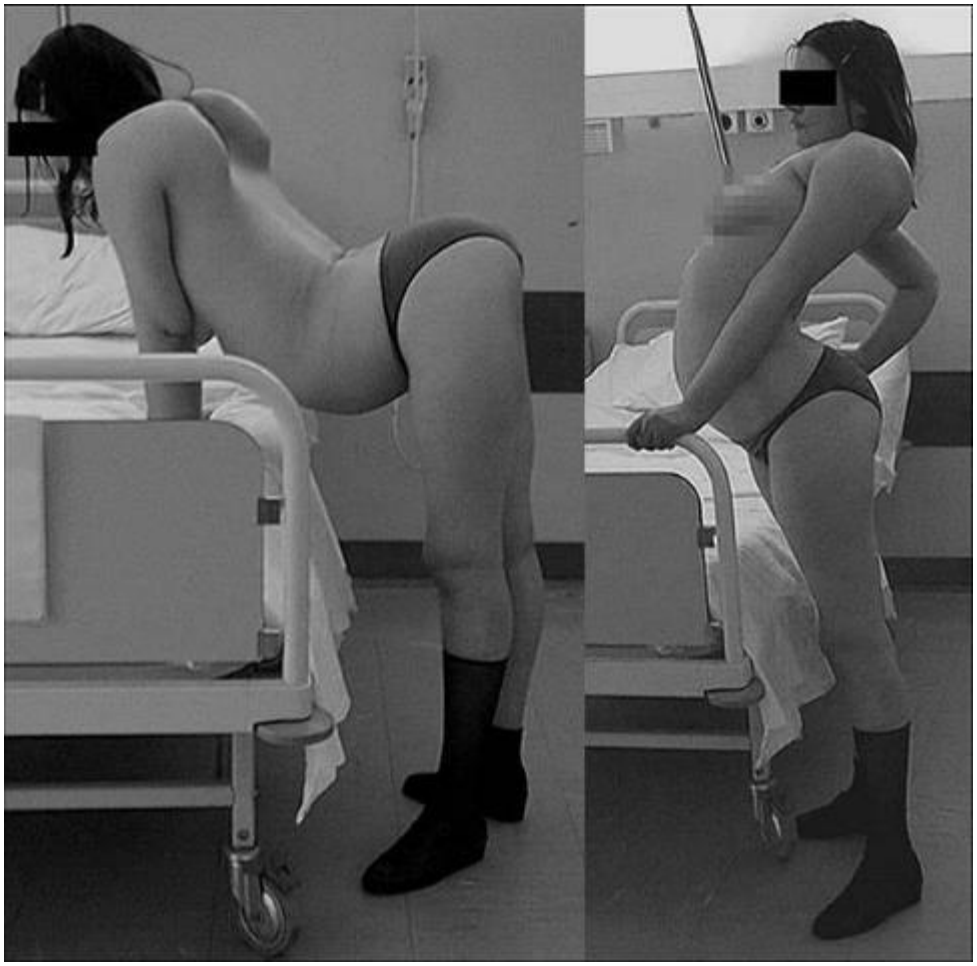
Facio-Scapulo-Humeral Muscular Dystrophy (FSHD)

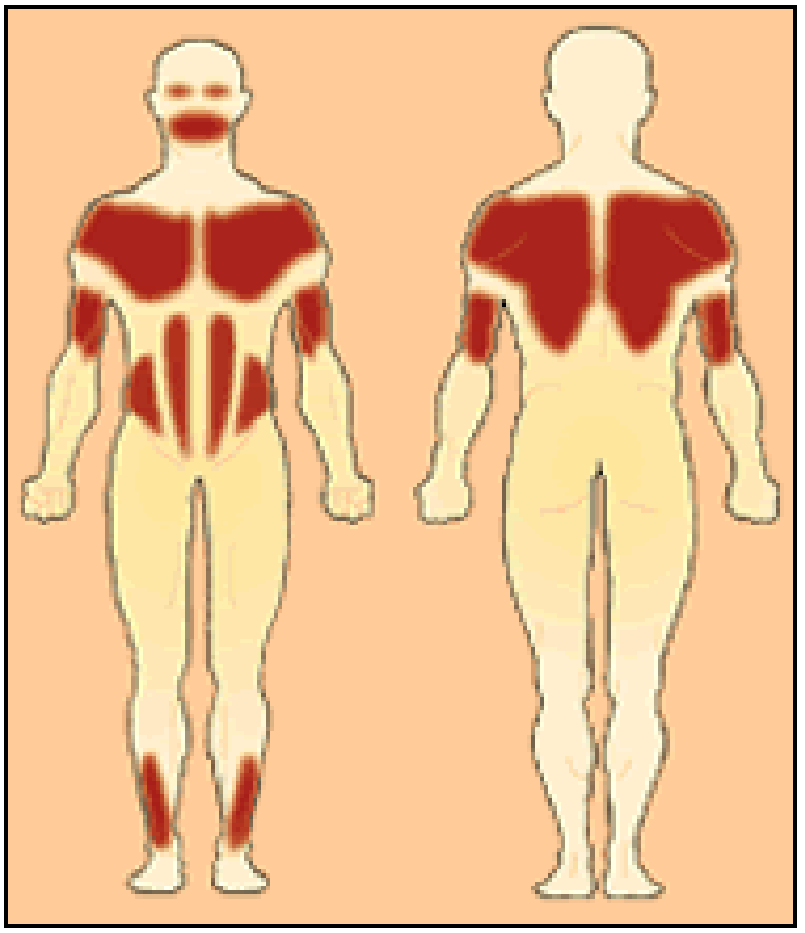
- FSHD affects about five in 100,000 people
- Affects muscle of face, scapula and upper arm
- Normal life expectancy
- progresses slowly and is generally mild, so it's usually not diagnosed until the late teens or in early adulthood
- FSHD is one of the few forms of MD that causes asymmetric weakness, defects in blowing and whistling

(i.e. weakness in the left arm but not the right)

- Mutation in *D4Z4* gene on chromosome 4
- autosomal dominant inheritance pattern (FSHD type I)







Limb-girdle Muscular Dystrophy

- Various clinical manifestation and onsets
  (variable expressivity)
- Proximal muscle atrophy of limbs and girdles
- Both autosomal dominant and recessive inheritance, rarely X-linked
- Mortality due to respiratory and cardiac failure

Limb-Girdle Muscular Dystrophy

- The hip and shoulder muscles are the first affected
- Some type has clinical similar to DMD/BMD, diagnosis by rule out DMD
- In some cases, it becomes difficult to lift the front part of the foot, so frequent tripping may occur.
- Signs and symptoms may begin from early childhood to adulthood

Locus heterogeneity of LGMD

Autosomal recessive LGMD

autosomal dominant LGMD

Table 1. Molecular Genetics of Autosomal Recessive Limb-Girdle Muscular Dystrophy (LGMD)

% of Individuals with AR LGMD	Disease Name (Synonym)	Populations with Founder Mutations	Gene Symbol	Locus [1]
Up to 68% of individuals with childhood onset and ~10% with adult onset [2]	Alpha-sarcoglycanopathy (LGMD2D)	None	*SGCA*	17q21.33
	Beta-sarcoglycanopathy (LGMD2E)	Amish	*SGCB*	4q12
	Gamma-sarcoglycanopathy (formerly SCARMD) (LGMD2C) [3]	North Africans; Gypsies [4]	*SGCG*	13q12.12
	Delta-sarcoglycanopathy (LGMD2F)	Brazilian [5]	*SGCD*	5q33.3
~10% [6]	Calpainopathy (LGMD2A)	Amish, La Reunion Island, Basque (Spain), Turkish	*CAPN3*	15q15.1
~5%	Dysferlinopathy (LGMD2B)	Libyan Jewish	*DYSF*	2p13.2
3%	LGMD2G	Italian (?)	*TCAP*	17q12

Table 3. Molecular Genetics of Autosomal Dominant LGMD

Disease Name	Gene Symbol (Locus Name [1])	Chromosom
LGMD1A (Myotilinopathy)	*MYOT*	5q31.2
LGMD1B	*LMNA*	1q22
LGMD1C (Caveolinopathy)	*CAV3*	3p25.3
LGMD1D	*DES*	2q35
LGMD1E	*DNAJB6*	7q36.3
LGMD1F	Unknown	7q32.1-q32.2
LGMD1G	Unknown	4q21
LGMD1H	Unknown	3p25.1-p23

Myotonic Dystrophy

- Most common MD in adult (1:8,000)
- Mostly adult onset slowly progressive muscle weakness with myotonia (muscle spasm with prolonged relaxation)
- Cataracts, cardiac conduction defects, impairment of gastrointestinal function, frontal balding, testicular atrophy
- Autosomal dominant inheritance, CTG repeats in *DMPK* gene with anticipation

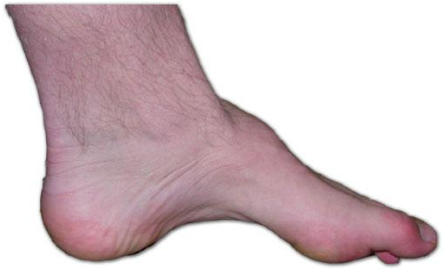
Muscular Dystrophy Association

Huntington Disease

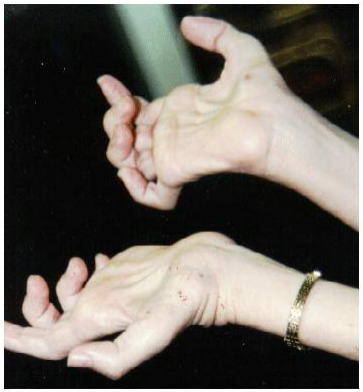
- progressive disorder of motor disability featuring chorea; voluntary movement, dyarthria and dysphagia
- cognitive, and mental disturbances, changes in personality, and/or depression
- mean age of onset is 35 to 44 years
- In late stages, motor disability becomes severe and patient will be totally dependent
- median survival time is 15 to 18 years after onset
- Autosomal dominant, 36 or more CAG repeats in HTT genes

Peripheral nerve degenerative diseases

- Spinal Muscular Atrophy
  - loss of function of neuronal cells in the anterior horn of the spinal cord
  - progressive muscle wasting and mobility impairment early in life, proximal muscles, arm and leg muscles and respiratory muscles are affected first
  - Deletion of *SMN1* (survival of motor neurons) gene, AR inheritance

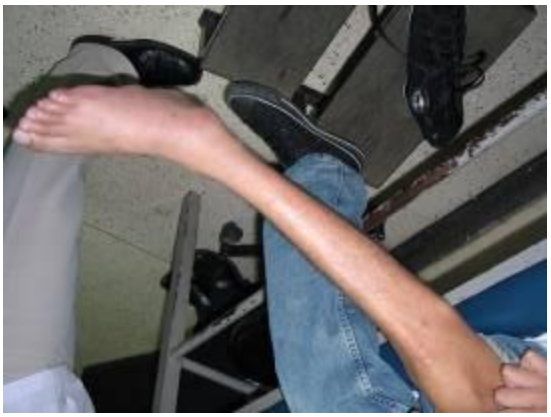


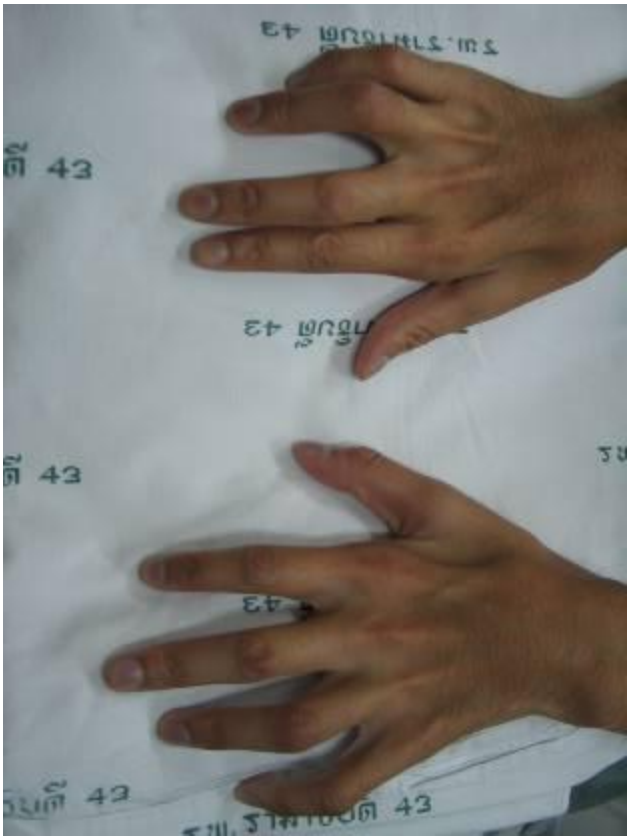
- Charcot-Marie-Tooth (CMT) /Hereditary Motor and Sensory Neuropathies(HMSN)
  - progressive *distal* muscle weakness, loss of touch sensation, gait impairment in adult
  - High-arched feet (pes cavus),
  - Most mutations in CMT affect the myelin sheath -> decrease nerve conduction, but some affect the axon

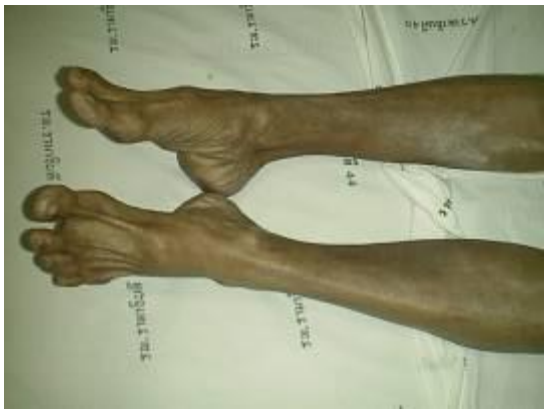


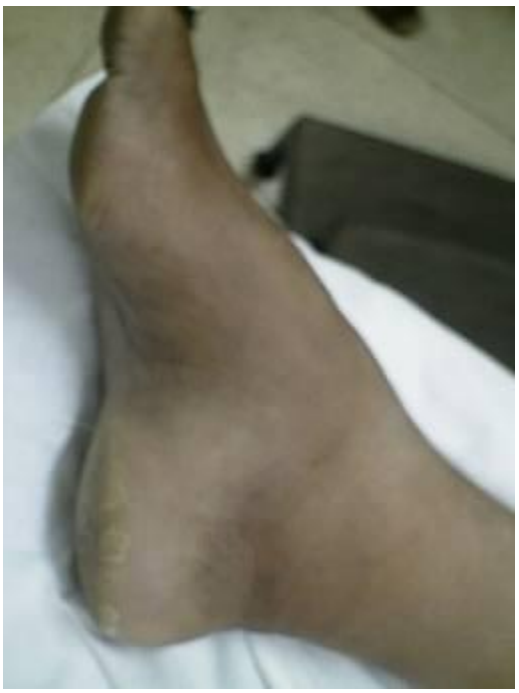
pes cavus and claw hand in Charcot-Marie-Tooth

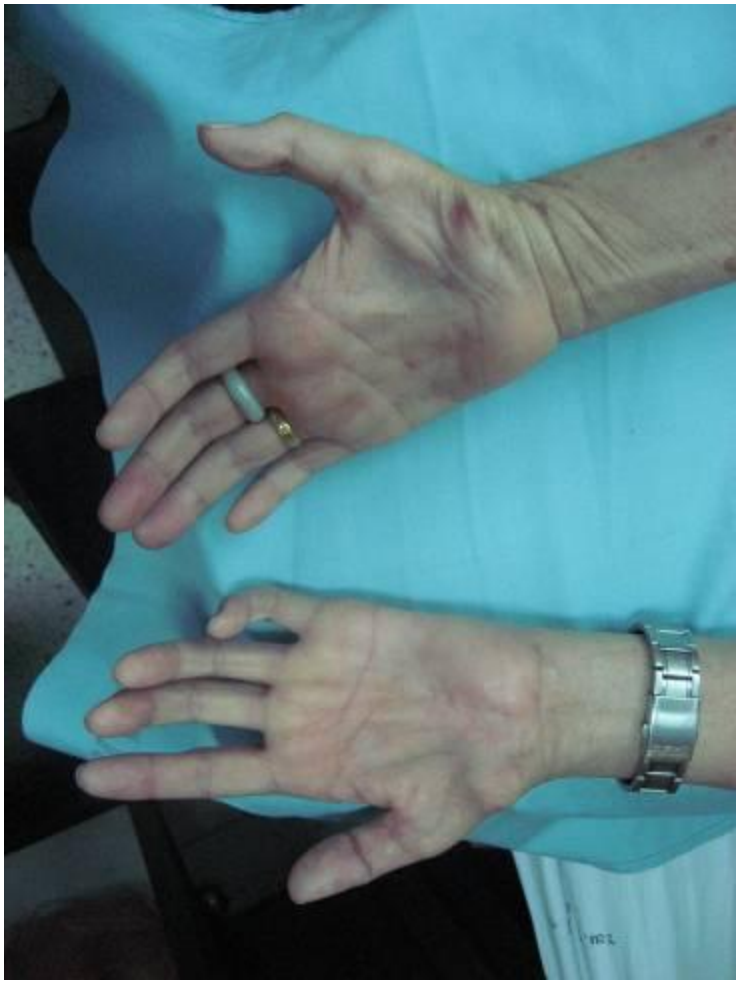
Muscular Dystrophy Association

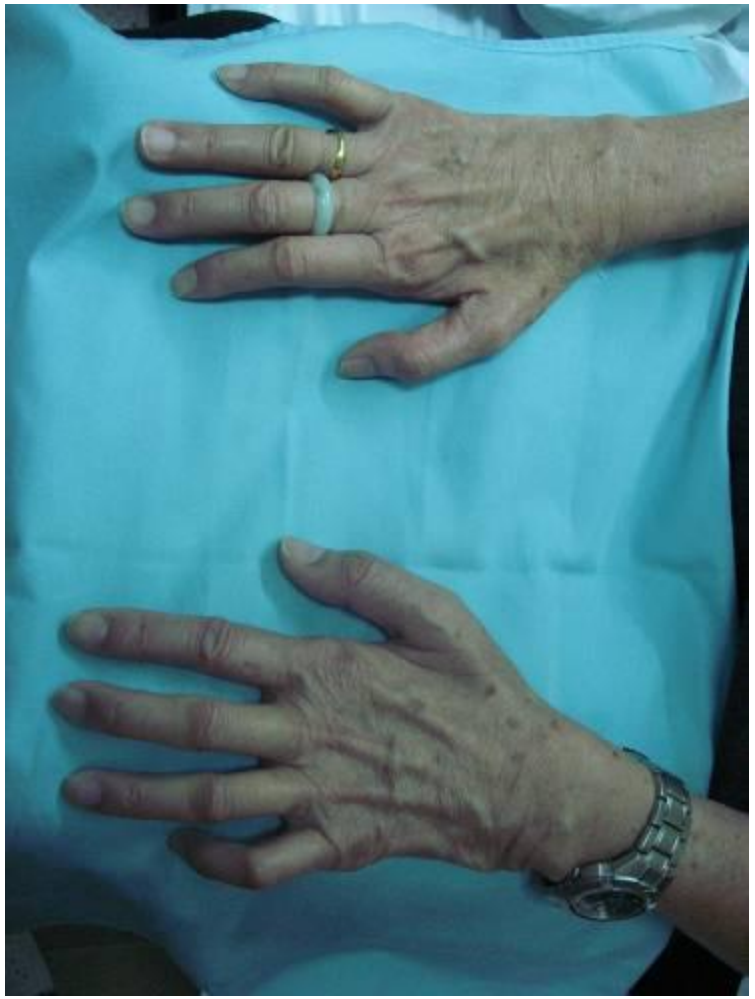


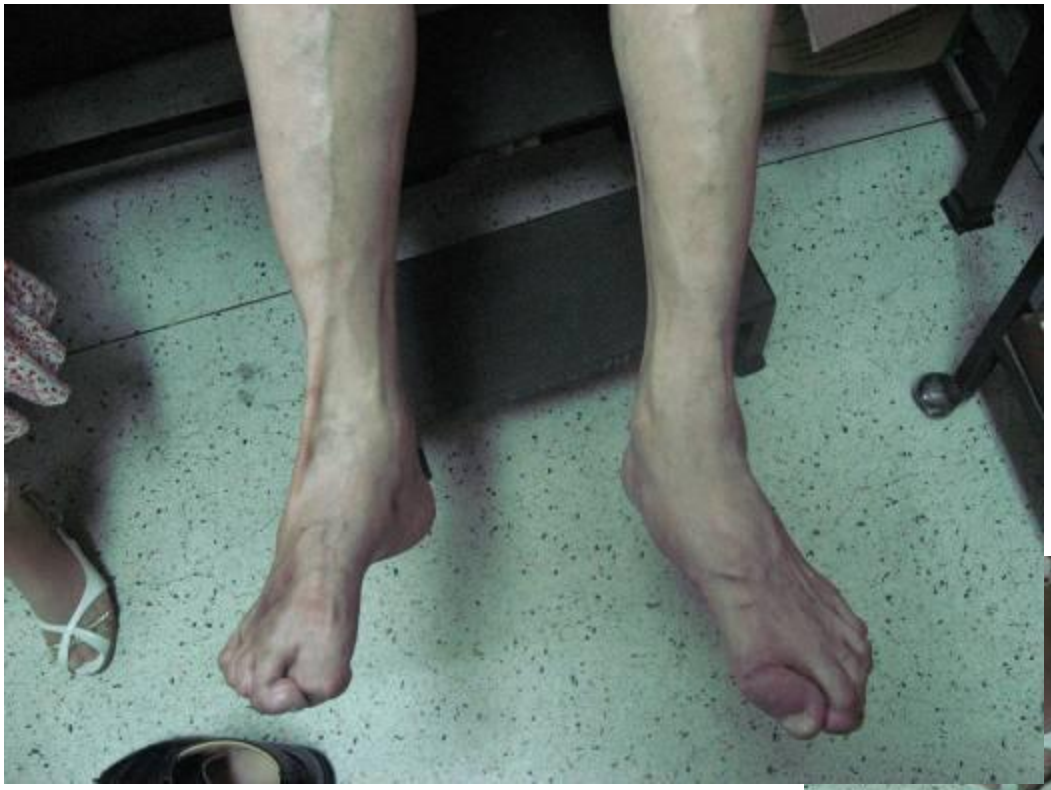


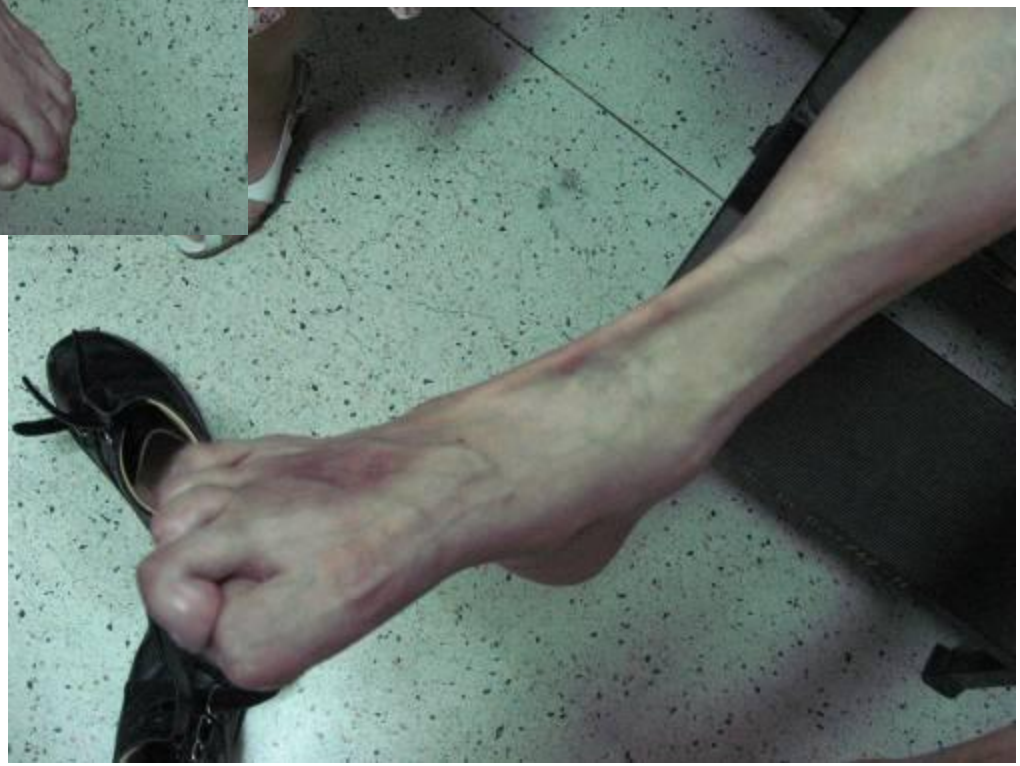












Genetic Heterogeneity of CMT

Genetic heterogeneity: (multiple genes cause similar phenotype)

CMT: Genes, Mode of Inheritance, Neuropathy Phenotype

Gene [1]	MOI	Neuropathy Type			Other Phenotypic Features / Comments	*GeneReview* / OMIM / Reference	Other Designations [2]
		Ax	De	In			
Most commonly involved genes [3]							
GDAP1	AR	•			Vocal cord paresis [4]	*GDAP1*-Related Hereditary Motor and Sensory Neuropathy	CMT2K
	AR	•	•	•			CMT4A CMT2H CMT2K CMTRIA
	AD, AR	•				OMIM 607831	
GJB1	XL	•			Family history may appear to be AD as females can be as severely affected as males.	CMT Neuropathy X Type 1	CMTX1
HINT1	AR	•			Neuromyotonia	OMIM 601314	
MFN2	AD, AR	•			Optic atrophy	CMT Neuropathy Type 2A	CMT2A2 CMT2I/2J
MPZ	AD	•	•	•		OMIM 118200	CMT1B CMT2I/J DI-CMTD
PMP22	AD		•			OMIM 601097	CMT1A CMT1E
SH3TC2	AR	•				CMT Neuropathy Type 4C	CMT4C

GeneReview

Topics

Neuromuscular Disorders: Duchenne and other muscular dystrophies

Connective tissue disorders: Marfan syndrome

Neurocutaneous disorders: Neurofibromatosis

Neurodegenerative disorders: Spinocerebellar Ataxia

Hereditary Cancers: Breast and Ovarian Syndrome, Colorectal Cancer

Genetic of sudden cardiac death (SUDs) and other genetic diseases

Connective Tissue Disorder

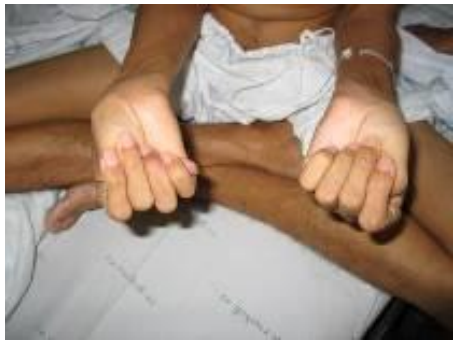
- connective tissues provide shape and support to many parts of the body e.g. heart and blood vessels, joints, eyes, lungs and skeletal system
- genetic disorder that causes connective tissues to weaken

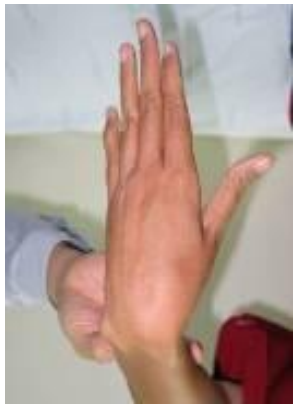

Marfan

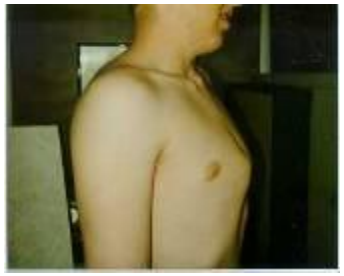
- *I Marfan Syndrome*
- *II Ehler-Danlos Syndrome*
- *III Osteogenesis Imperfecta*

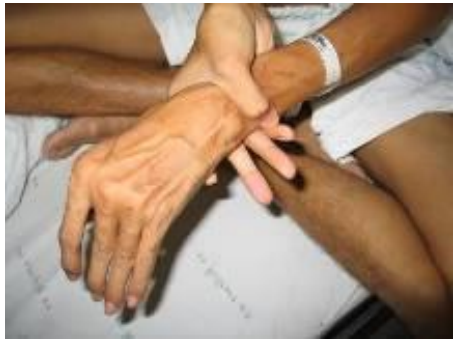

Osteogenesis Imperfecta

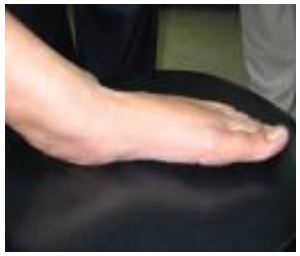
Marfan syndrome

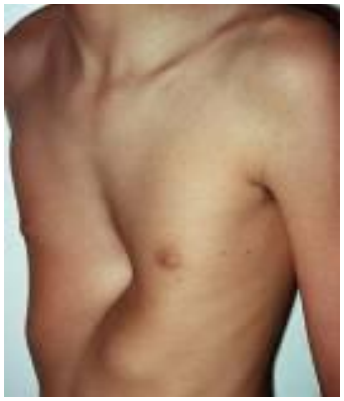




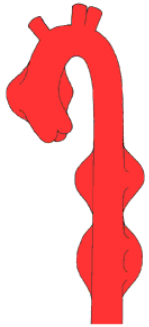


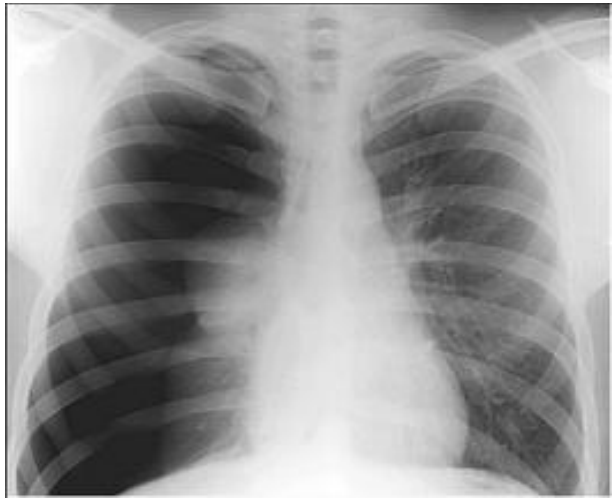


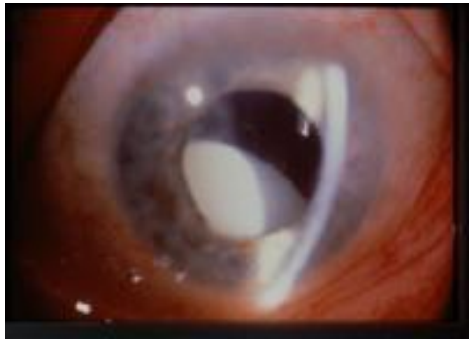


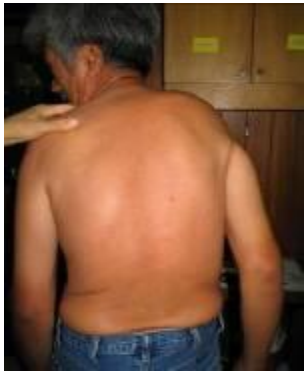


A defect in FBN1 gene which affected patient presented with multi organ disorders.





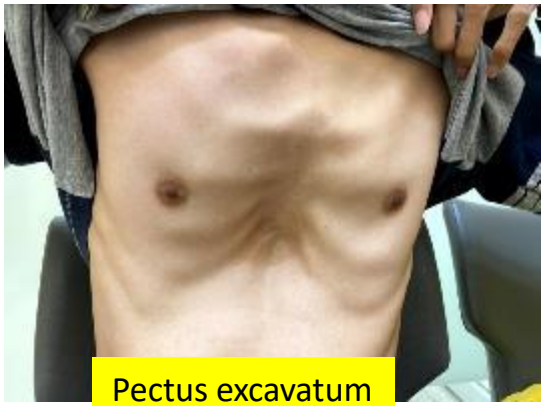




One gene

Many effects

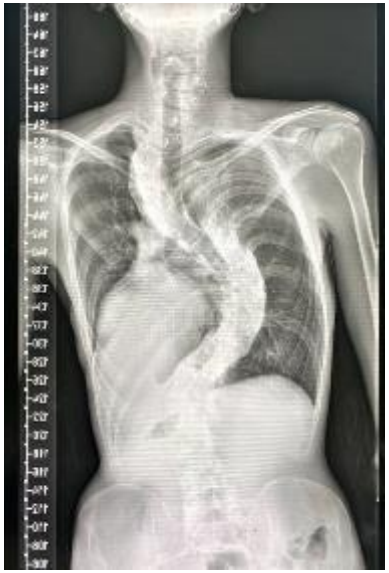
Pleiotropy


Pectus excavatum

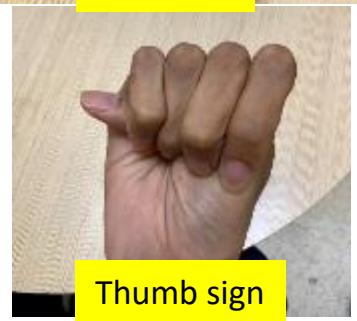

Arachnodactyly


Scoliosis

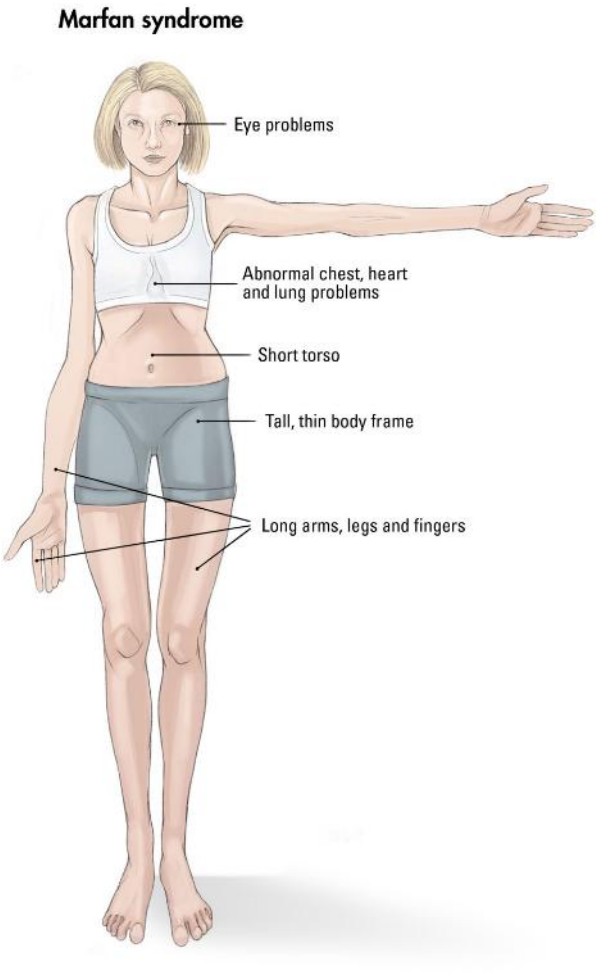
Striae atrophicae



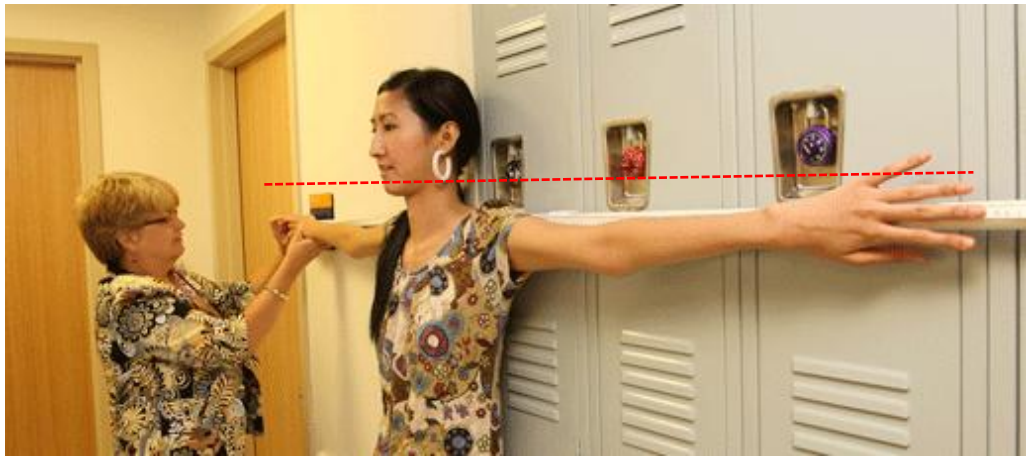

wrist sign


Thumb sign

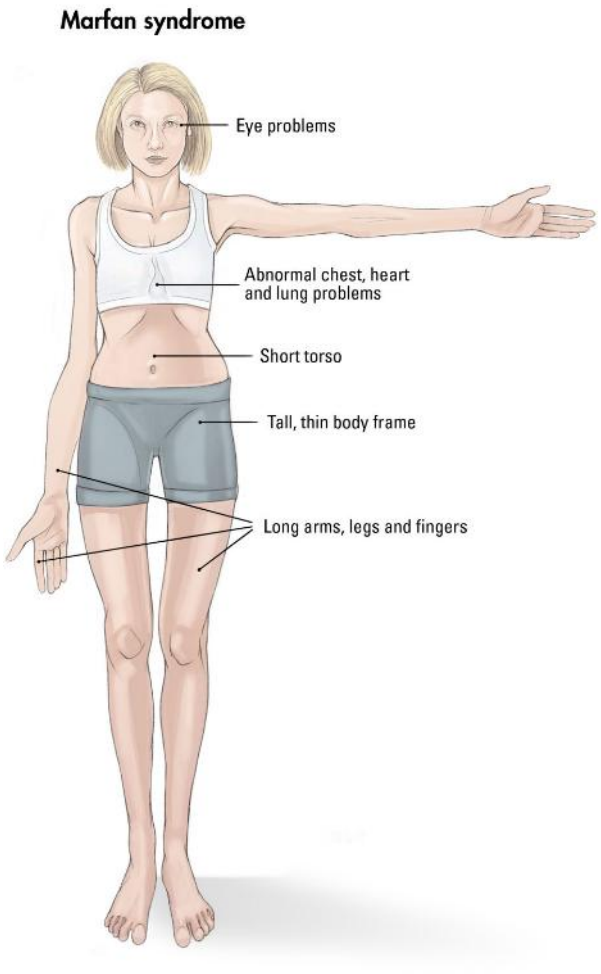
Marfan Syndrome



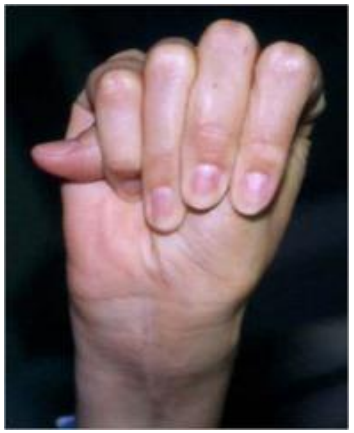
- Adolescent and adult onset
- Skeletal features
  - Tall stature, long armspan (dolichostenomelia)
  - Reduce upper:lower segment ratio
  - Arm span > height
  - Reduced elbow extension



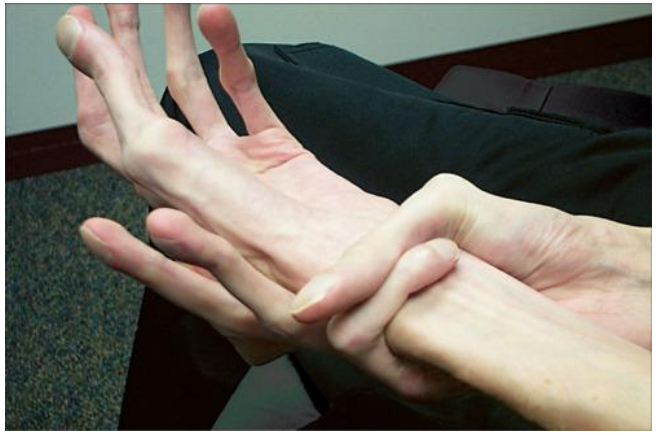
Marfan Syndrome



- Wrist and Thumb signs
- Marfanoid face
- Pes planus
- Protusio acetabulae
- Skin striae

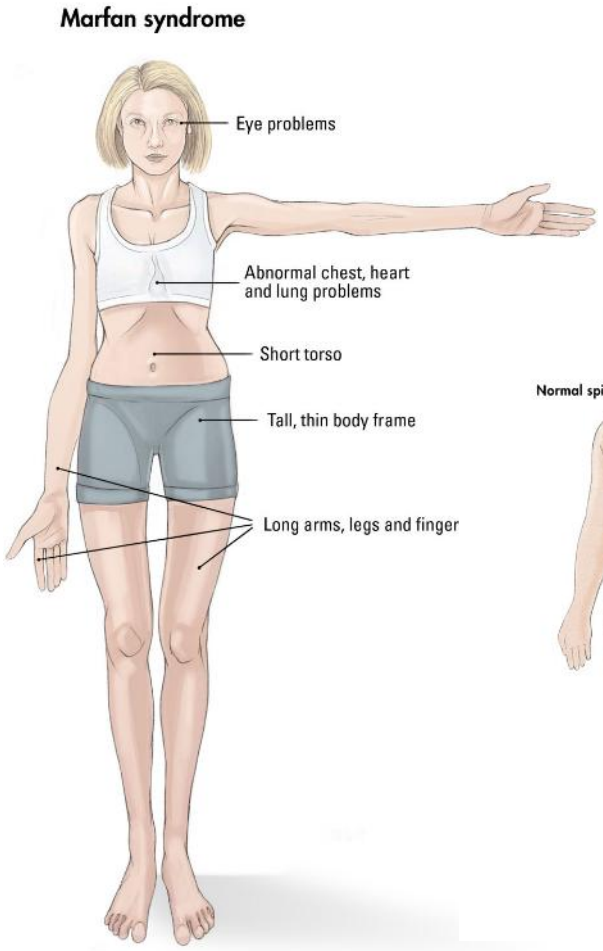


Thumb sign

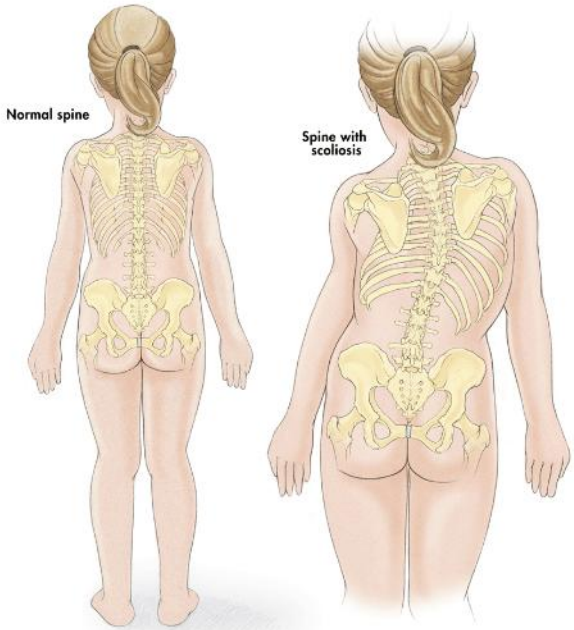


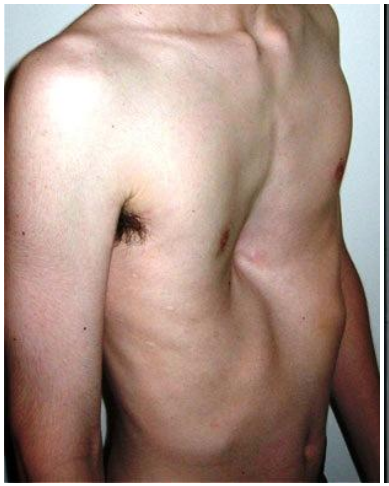
Wrist sign

Marfan Syndrome

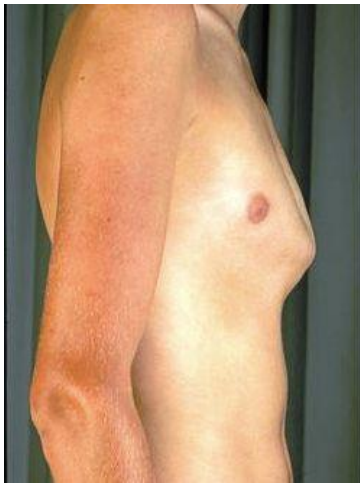


- Scoliosis, chest wall deformity
- Dural ectasia



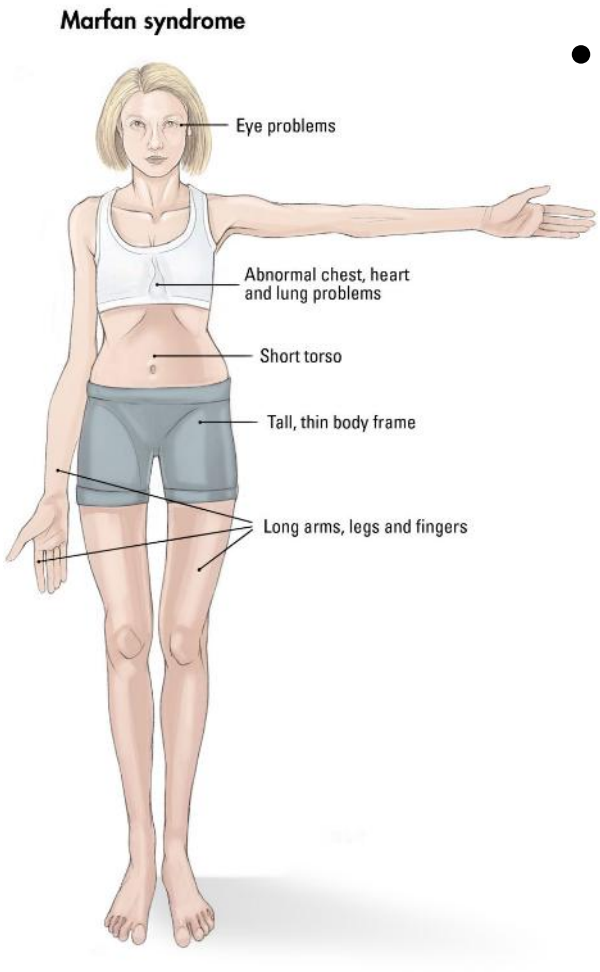


pectus excavatum

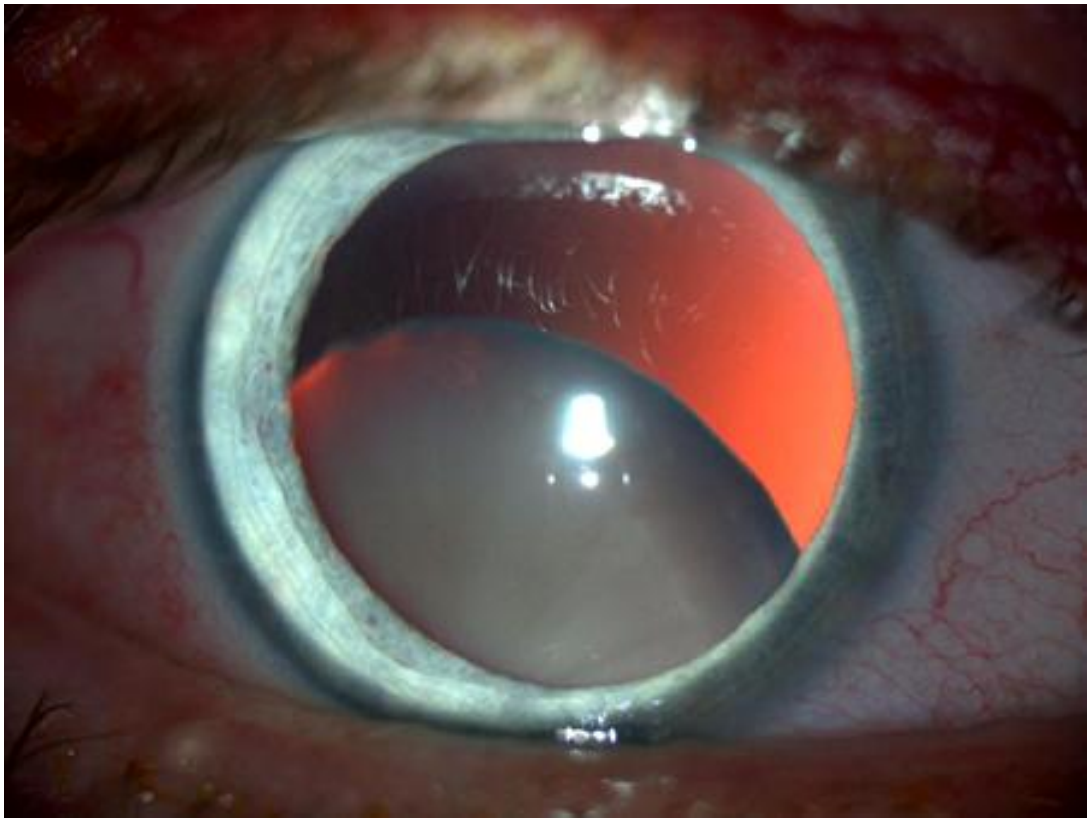


pectus carinatum

Marfan Syndrome



- Lens dislocation



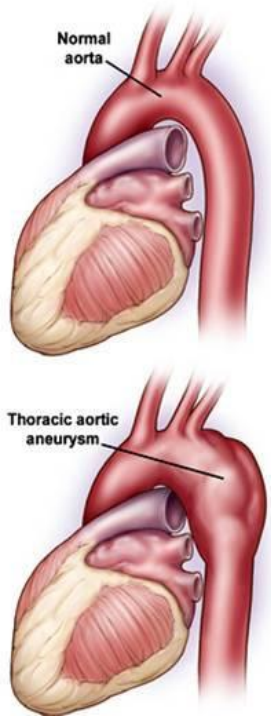
Marfan Syndrome

Pneumothorax

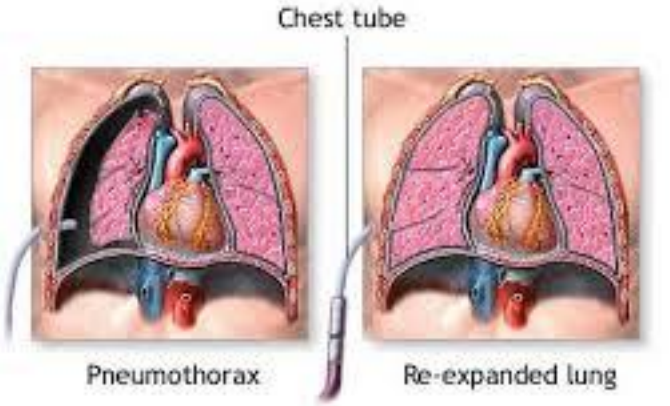
Valve Malformations (MVP)

Aortic root aneurysm/dissection*

*a major cause of death!!



Aortic root dilatation

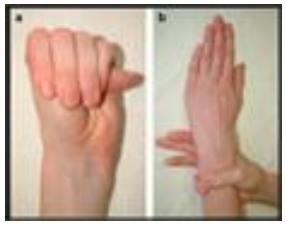
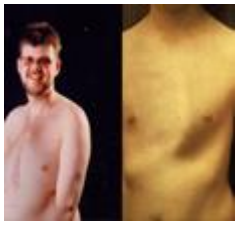
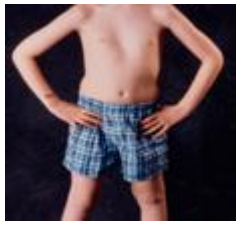
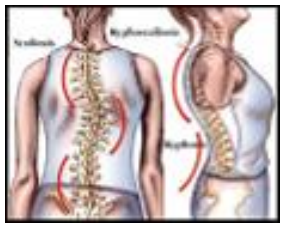


pneumothorax

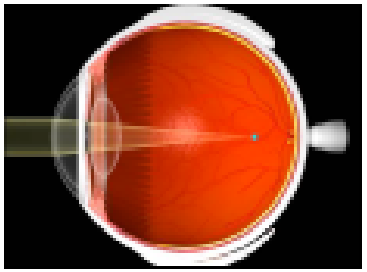
Marfan Syndrome

Cardinal signs

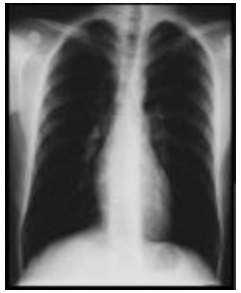
Skeletal

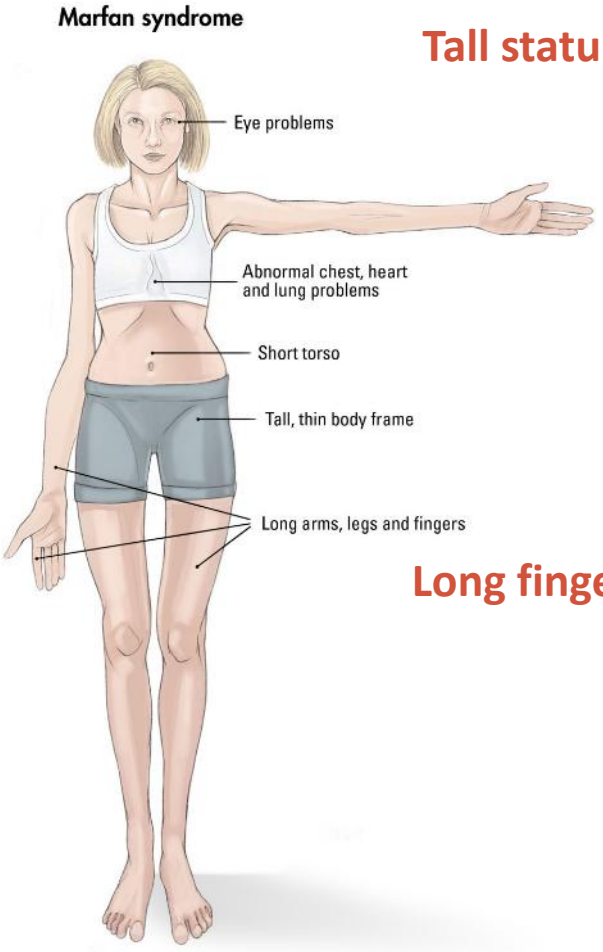
Ocular



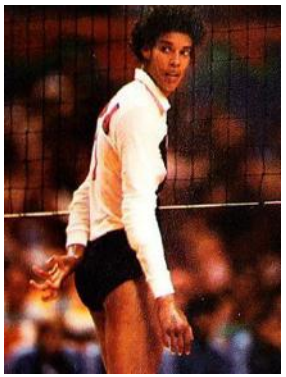
Cardiovascular+pulmonary




People suspected with Marfan Syndrome

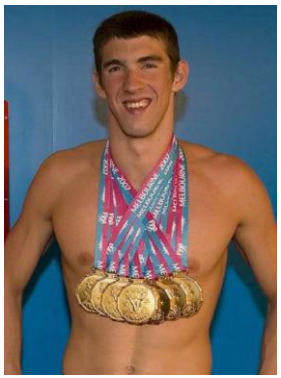


Tall stature



volleyball athlete

basketball athlete



Michael Phelps

Long fingers

Bradford Cox

(guitarist)

Nicolo Paganini

(violinist)

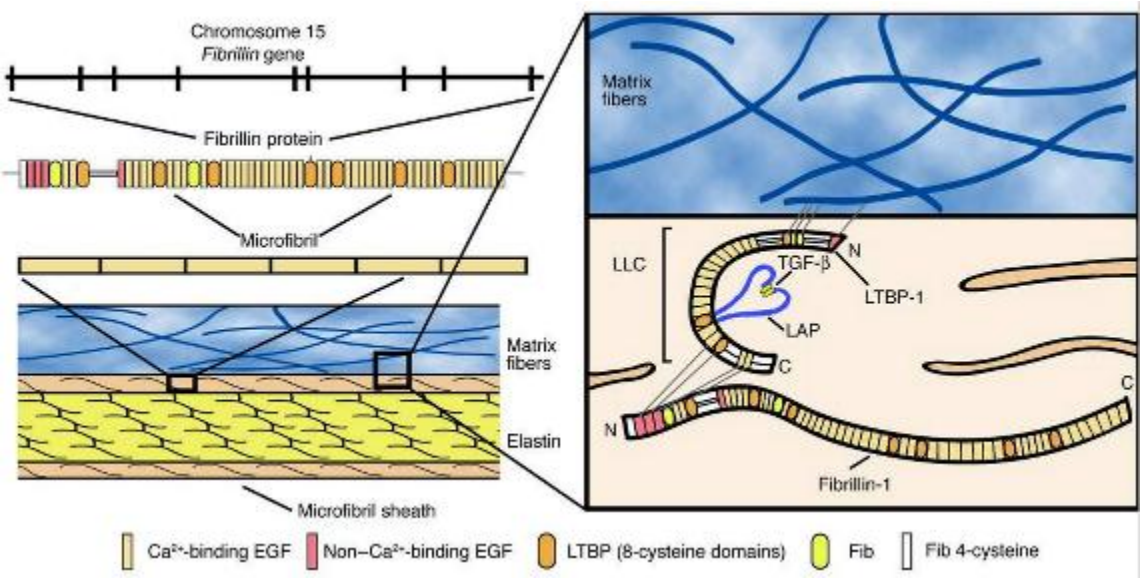
Sergei Rachmaninoff

(pianist)

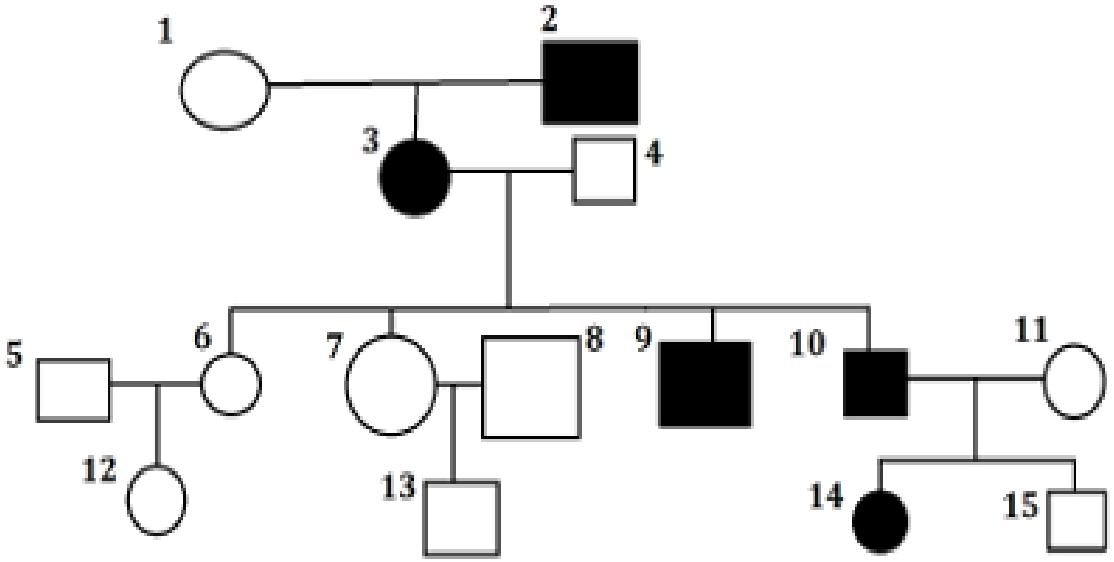
Marfan Syndrome: Fibrillin 1

- Fibrillin 1 (*FBN1*) gene on chromosome 15 (65 exons)
- Estimated gene length 200,000 bp

  (average human gene =3000 bp)
- Limited use of molecular testing => clinical diagnosis
- Autosomal dominant, 25% are de novo mutation



Marfan Syndrome Pedigree



Complete penetrance, Variable expressivity

- Variation in clinical features (type and severity) of a genetic disorder between affected individuals, even within the same family

Box 1 Revised Ghent criteria for diagnosis of Marfan syndrome and related conditions

In the absence of family history:
(1) Ao (Z ≥2) AND EL=MFS*
(2) Ao (Z ≥2) AND *FBN1*=MFS
(3) Ao (Z ≥2) AND Syst (≥7pts)=MFS*
(4) EL AND *FBN1* with known Ao=MFS

EL with or without Syst AND with an *FBN1* not known with Ao or no *FBN1*=ELS
Ao (Z < 2) AND Syst (≥5 with at least one skeletal feature) without EL=MASS
MVP AND Ao (Z <2) AND Syst (<5) without EL=MVPS

In the presence of family history:
(5) EL AND FH of MFS (as defined above)=MFS
(6) Syst (≥7 pts) AND FH of MFS (as defined above)=MFS*
(7) Ao (Z≥2 above 20 years old, ≥3 below 20 years) +FH of MFS (as defined above)=MFS*

* Caveat: without discriminating features of SGS, LDS or vEDS (as defined in table 1) AND after *TGFBR1/2*, collagen biochemistry, *COL3A1* testing if indicated. Other conditions/genes will emerge with time.
Ao, aortic diameter at the sinuses of Valsalva above indicated Z-score or aortic root dissection; EL, ectopia lentis; ELS, ectopia lentis syndrome; *FBN1*, fibrillin-1 mutation (as defined in box 3); *FBN1* not known with Ao, *FBN1* mutation that has not previously been associated aortic root aneurysm/dissection; *FBN1* with known Ao, *FBN1* mutation that has been identified in an individual with aortic aneurysm; MASS, myopia, mitral valve prolapse, borderline (Z<2) aortic root dilatation, striae, skeletal findings phenotype; MFS, Marfan syndrome; MVPS, mitral valve prolapse syndrome; Syst, systemic score (see box 2); and Z, Z-score.

Box 2 Scoring of systemic features

- Wrist AND thumb sign — 3 (wrist OR thumb sign — 1)
- Pectus carinatum deformity — 2 (pectus excavatum or chest asymmetry — 1)
- Hindfoot deformity — 2 (plain pes planus — 1)
- Pneumothorax — 2
- Dural ectasia — 2
- Protrusio acetabuli — 2
- Reduced US/LS AND increased arm/height AND no severe scoliosis — 1
- Scoliosis or thoracolumbar kyphosis — 1
- Reduced elbow extension — 1
- Facial features (3/5) — 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
- Skin striae — 1
- Myopia > 3 diopters - 1
- Mitral valve prolapse (all types) — 1

Maximum total: 20 points; score ≥7 indicates systemic involvement; US/LS, upper segment/lower segment ratio.

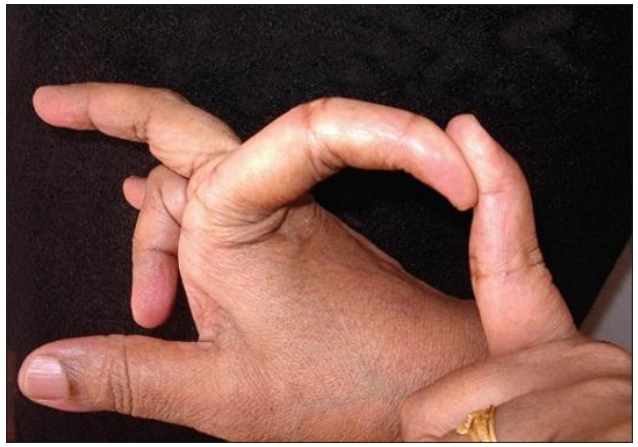
J Med Genet 2010;47:476-485.

Marfan Syndrome: Treatment

- Annual eye exam, eyeglasses for lens dislocation
- Stabilization of scoliosis and pectus deformity
- Avoid contact and competitive sports, non-pressurized aircraft
- Monitor the status of the ascending aorta
- Genetic counseling!!

Ehlers-Danlos Syndrome

- Genetic heterogeneity (type I-VII, different mutation), majority is classic type
- Classic type cause by mutation in *COL5A1* or *COL5A2* genes, AD inheritance)
- hypermobility in the hands, fingers and toes
- loose joints that are prone to sprains
- dislocations and double-jointedness flat feet
- a high narrow palate with dental crowding
- pale skin that bruises and stretches easily
- wounds that don't heal easily with scarring
- Ehlers-Danlos Type IV (vascular type) is the most severe with arterial rupture



Osteogenesis Imperfecta

- also known as brittle-bone disease
- characterized by fragile bones that break easily
- history of frequent fractures with minimal trauma
- four major types of OI
- Type I: the mildest and most common type
  - most fractures occur before puberty
  - blue or blue-gray sclera
  - hearing loss beginning in 20s
  - Mutation in procollagen genes *COL1A1* and *COL1A2*
  - Autosomal dominant

Villefranche classification of EDS (1997; taken from Beighton et al, (1998))

Classical (type I and II) AD; up to 50% are due to mutation in COL5A1 and COL5A2 soft, heperextensible skin with easy bruising and then atrophic scar; joint hypermobility; varicose veins; risk of prematurity in affected case

Hypermobility (type III) AD; common and usu. mild disorder; Soft skin with hypermobility of large and small joints

Vascular (type V) AD due to mutation in COL3A1 encoding type III collagen; uncommon but serious disorder; characteristic facies with prominent eyes due to decreased adipose tissue below the eyes and thin, slightly "pinched" nose, thin lips, and hollow cheeks. Thin translucent skin with visible veins, easy bruising. No significant large joint hypermobility. Risk of arterial, bowel, bladder and uterus rupture leads to reduce life expectancy.

Kyphoscoliosis (type VI) AR due to mutation in PLOD1 (lysyl hydroxylase deficiency) Soft, hyperextesible skin, joint hypermobility, muscle hypotonia, scoliosis, globe rupture

Arthrochalsia (type VIIA and B) AD due to exonic deletion in COL1A1 and COL1A2

Soft skin +/- normal scarring, severe jt. hypermobility and cong. hip dislocation

Dermatosporaxis (type VIIC) AR mutation in type 1 collagen N-peptidase (ADAMTS2) Severe skin fragility with sagging, redundent skin

Other variants

e.g. X-linked (type V) and AD Periodontal EDS (type VIII), AR Progeroid (XGPT1 mutation) and AR EDS without scarring (tenascin-X deficiency)

Topics

Neuromuscular Disorders: Duchenne and other muscular dystrophies

Connective tissue disorders: Marfan syndrome

Neurocutaneous disorders: Neurofibromatosis

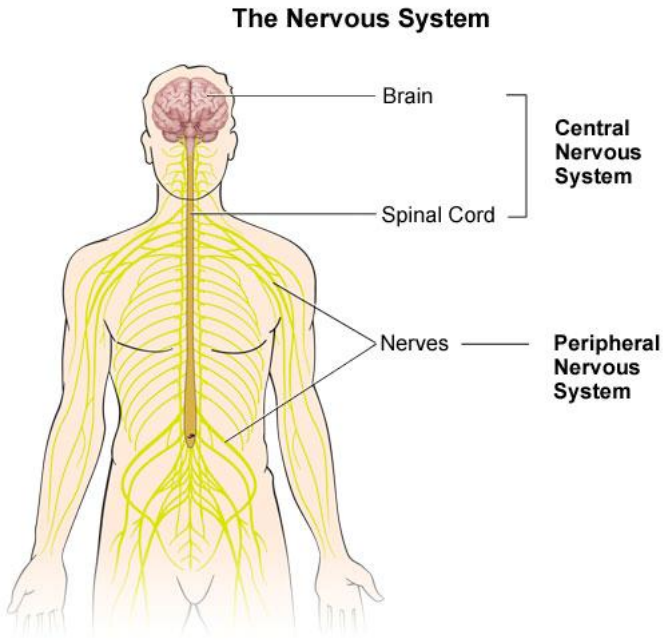
Neurodegenerative disorders: Spinocerebellar Ataxia

Hereditary Cancers: Breast and Ovarian Syndrome, Colorectal Cancer

Genetic of sudden cardiac death (SUDs) and other genetic diseases

Neurocutaneous Syndrome

- group of neurologic (brain, spine, and peripheral nerve) disorders
- progressive conditions
- can cause tumors to grow inside brain, spinal cord, organs, skin and bones



- Neurofibromatosis: Type I (~1:2,500)
- Neurofibromatosis: Type II (~1:25,000)
- Tuberous Sclerosis (~1:50,000)

Hopkins Medicine

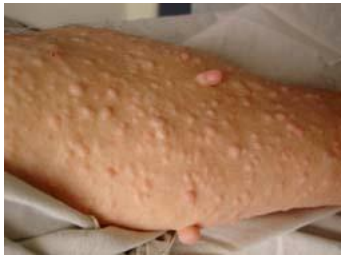
Neurofibromatosis type I
(von Recklinghausen disease)

- Cutaneous neurofibromas

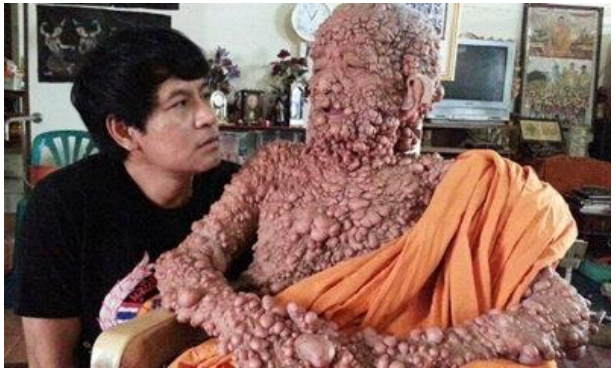
  Benign nerve sheath tumors

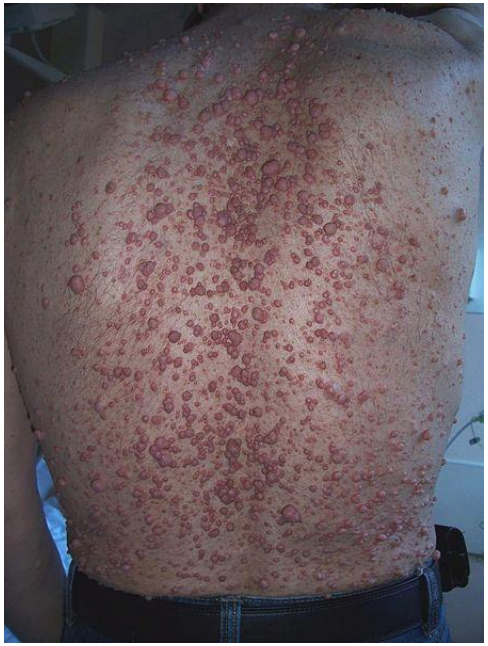
- plexiform neurofibromas

  tumors of large , often internal



Cutaneous neurofibroma

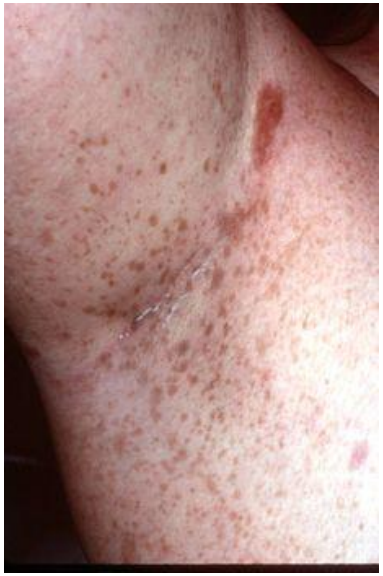




plexiform neurofibroma

Neurofibromatosis type I
(von Recklinghausen disease)

- multiple skin café au lait spots (light brown patches)
- axillary and inguinal freckling

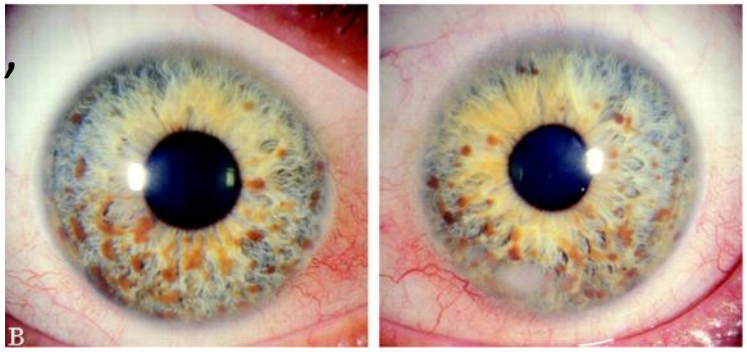


Axillary freckling

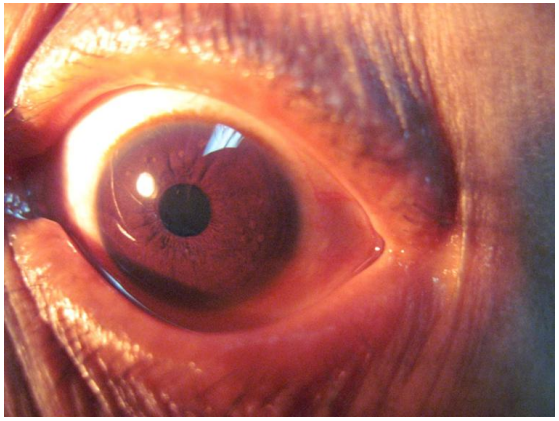
Neurofibromatosis type I
(von Recklinghausen disease)

- Lisch nodules (harmartoma of the iris),
- optic nerve and other central nervous system gliomas (glial cells tumor)
- learning disabilities
- features of NF1 increase with age

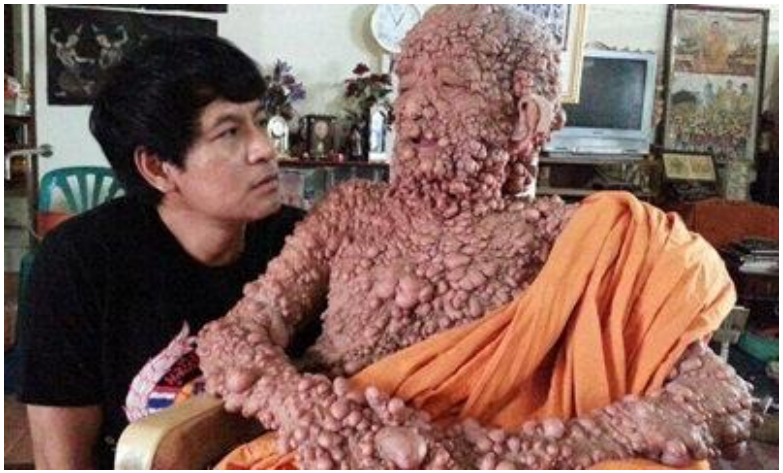
  (up to 8 years for all features to present)



Lisch nodules:
(hamartomatous nodule of dendritic melanocytes)

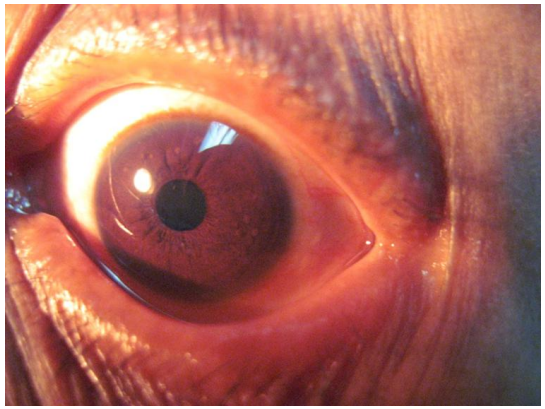


Cutaneous neurofibroma

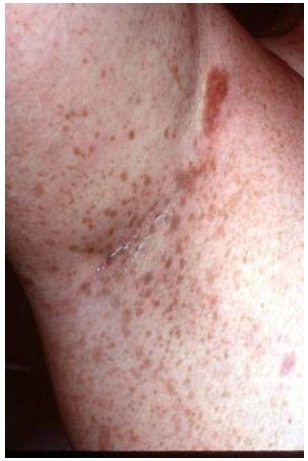


Café au lait spot

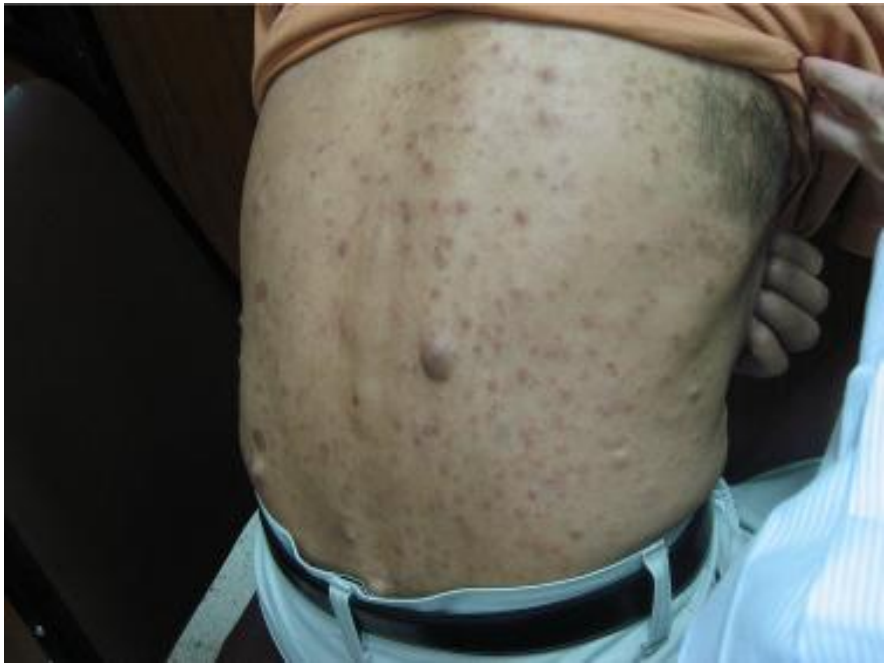
Plexiform neurofibroma



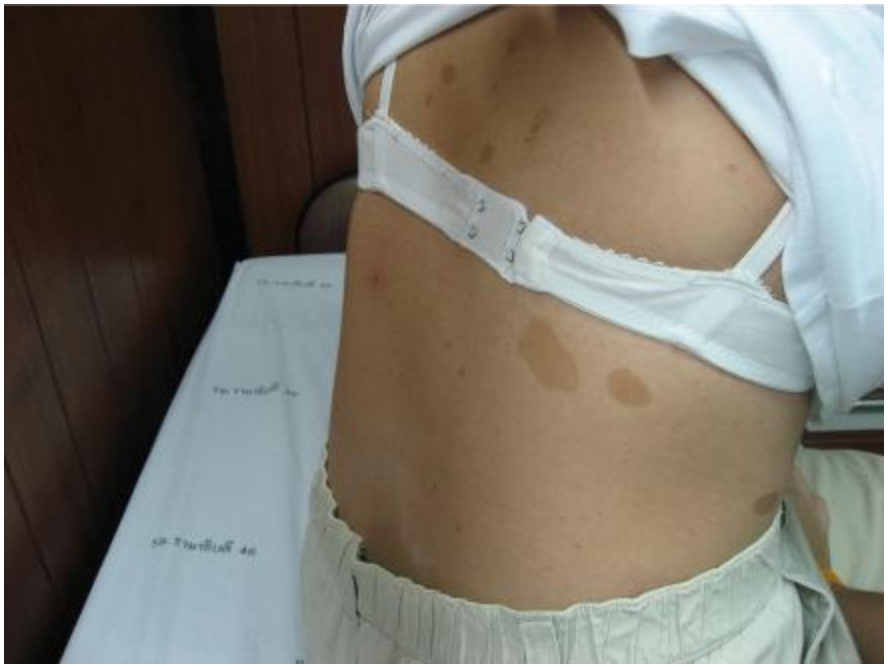
Lisch nodules
(hamartomatous nodule of dendritic melanocytes)

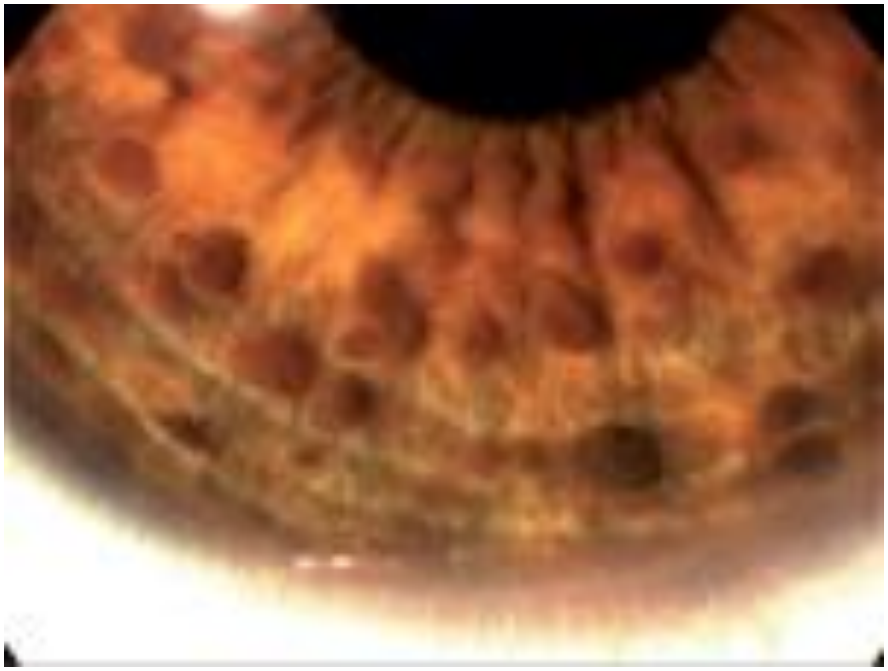


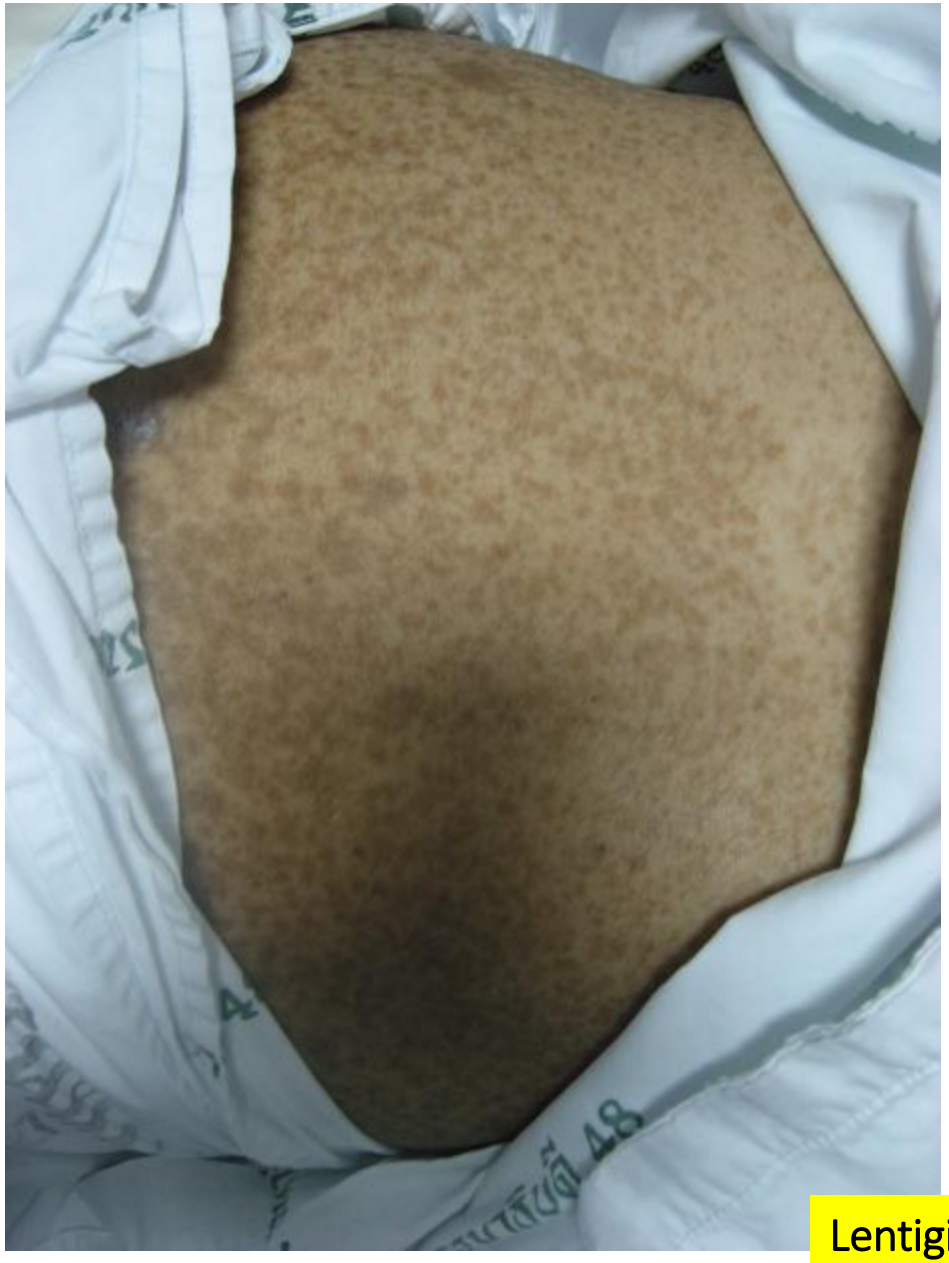
Axillary freckling

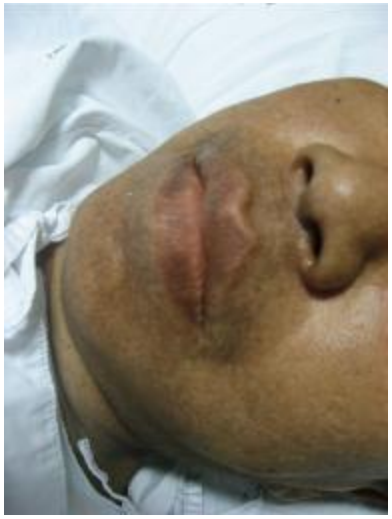


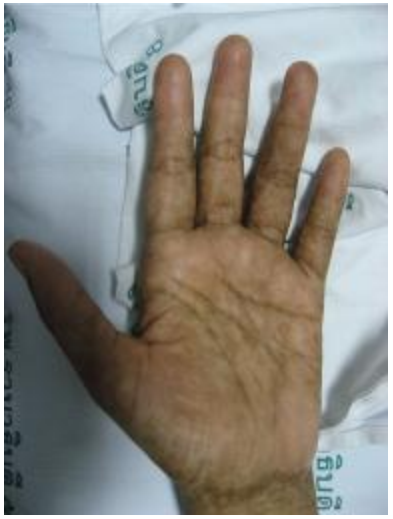
Neurofibromatosis type 1 is 100% penetrance but variable expressivity.

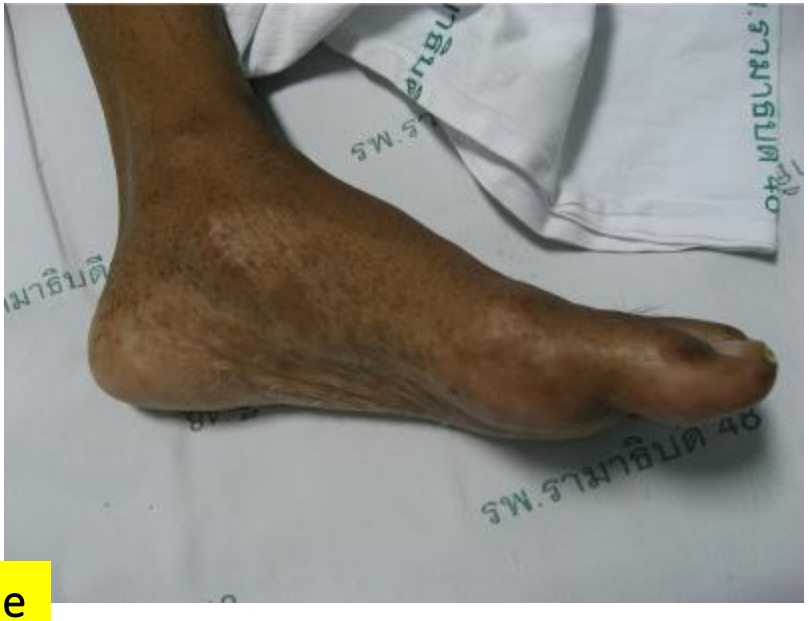




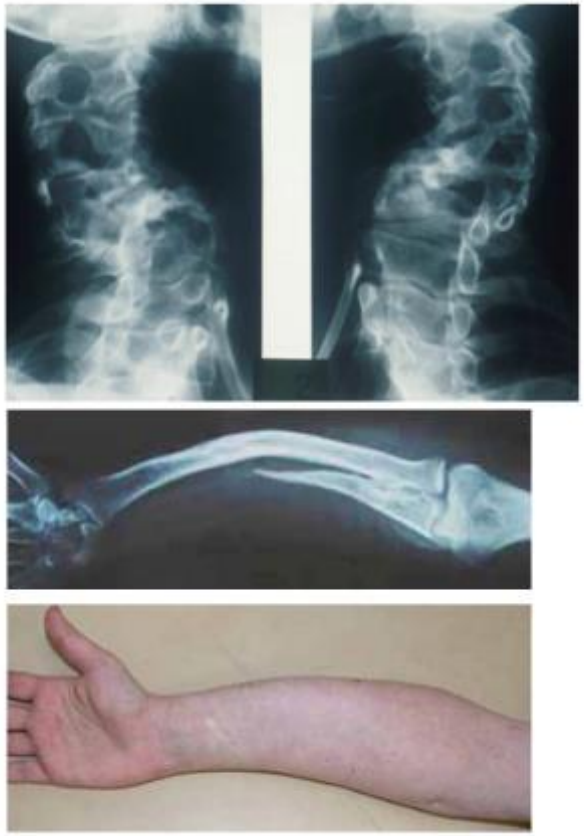


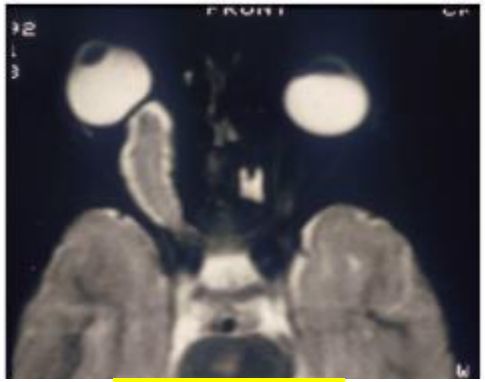




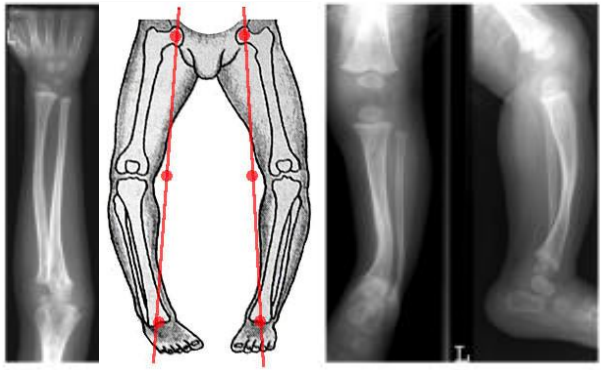


Lentigine





Optic glioma

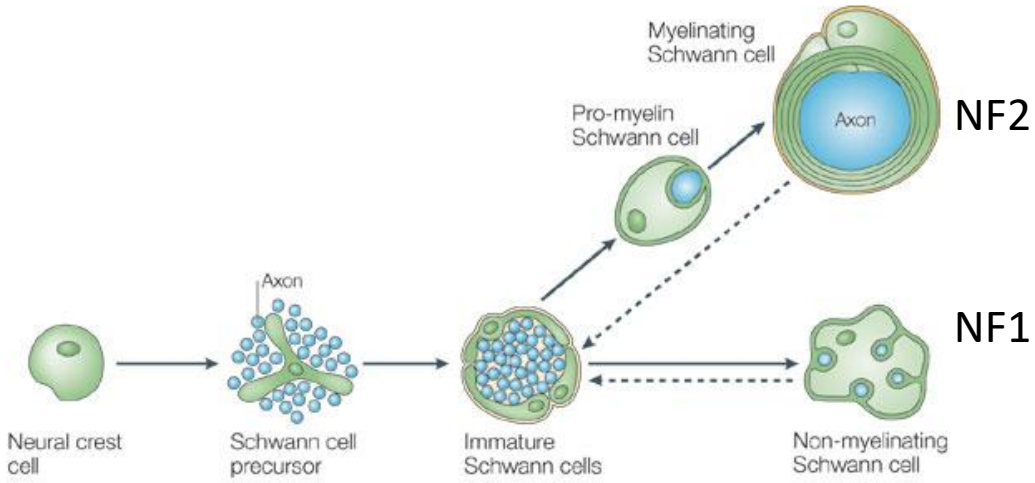


Pseudarthrosis, bowed legs

Neurofibromatosis type I

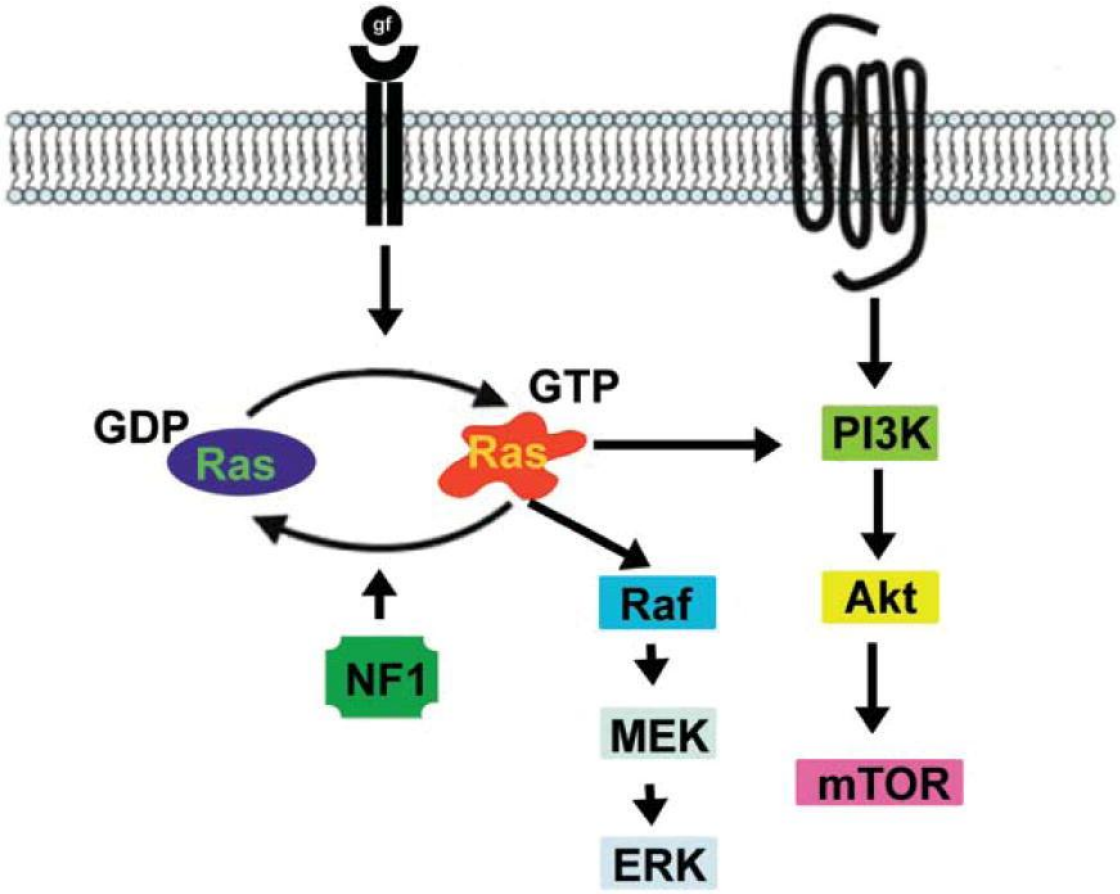
(von Recklinghausen disease)

- NF1 gene codes for the protein Neurofibromin
- responsible for regulating the RAS-mediated cell growth signaling pathway
- autosomal dominant, 50% de novo mutation



Neurofibromatosis type I

(von Recklinghausen disease)



Gottfried et.al., J Neurosurgery 2010

NF1: Treatment

- cutaneous or subcutaneous neurofibromas that are disfiguring or in inconvenient locations (e.g., at belt or collar lines) can be removed surgically
- Surgical treatment of plexiform neurofibromas is often unsatisfactory because of their intimate involvement with nerves and their tendency to grow back
- Annual physical examination for tumors associated with NF1 (brain tumors, optic pathway glioma, malignant peripheral nerve sheath tumors)

Neurofibromatosis type II
(Central neurofibromatosis)

- mutation of the merlin gene (NF2), autosomal dominant
- accounts for only 10% of all cases of NF
- bilateral acoustic neuromas (also known as Schwannoma)
- Hearing loss around age 20
- do not have the cognitive problems

- In NF2, benign tumors called schwannomas grow on nerves throughout the nervous system and often cause impaired hearing and vision
- In NF1, benign tumors called neurofibromas cover the peripheral nerve and, similarly, may cause pain or specific neurologic symptoms

Topics

Neuromuscular Disorders: Duchenne and other muscular dystrophies

Connective tissue disorders: Marfan syndrome

Neurocutaneous disorders: Neurofibromatosis

Neurodegenerative disorders: Spinocerebellar Ataxia

Hereditary Cancers: Breast and Ovarian Syndrome, Colorectal Cancer

Genetic of sudden cardiac death (SUDs) and other genetic diseases

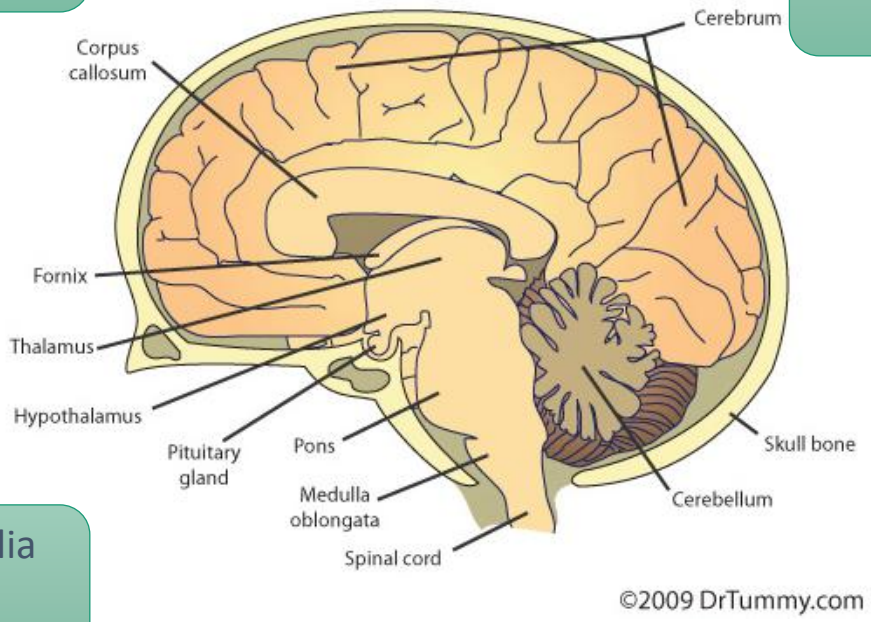
Neurodegenerative Disorder

Progressive loss of structure or function of neurons

Cerebral cortex
Alzheimer
(Protein misfolding)

multifactorial

Cerebellum
Spinocerebellar Ataxia
(CAG repeats)



Striatum
Huntington
(CAG repeats)

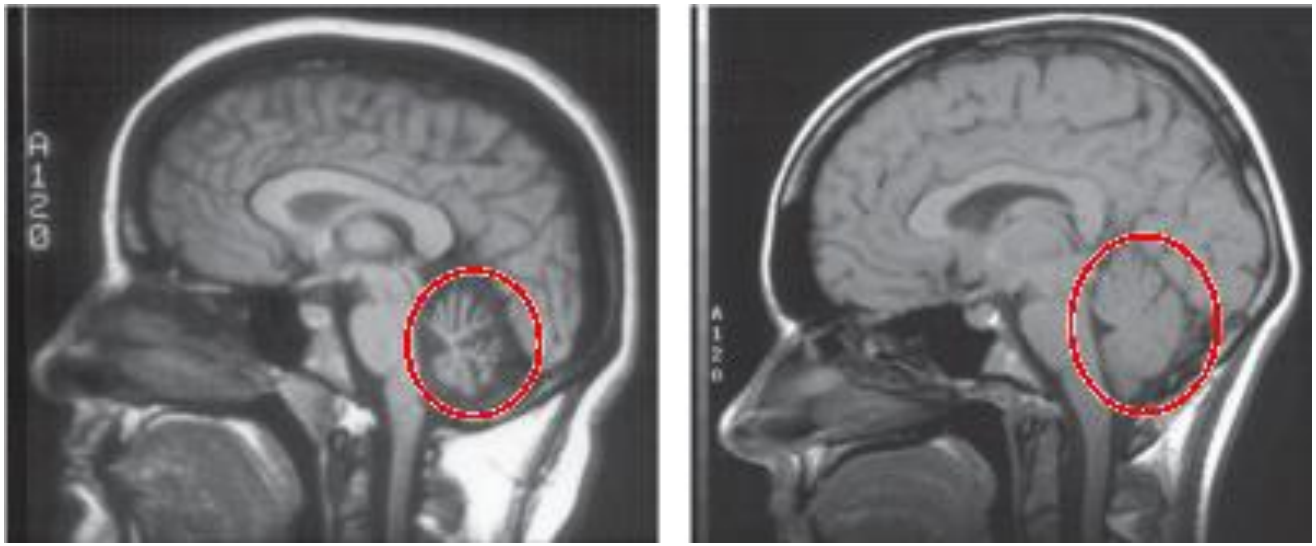
Striatum/Basal ganglia
Parkinson
(Protein misfolding)

Multifactorial (except early-onset)

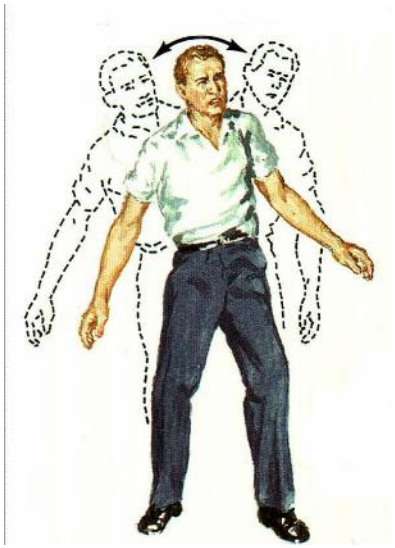
Spinocerebellar Ataxia

- Age of onset is variable, usually adult onset
- gait problems, speech difficulties, clumsiness
- Progressive ataxia, nystagmus, and dysarthria
- assistive devices (wheelchair) needed ~10 y after onset
- abnormal trinucleotide repeat (CAG) expansion
- In SCA type 3, normal repeats is <44, patients have 52-86 CAG repeats
- Autosomal dominant with anticipation

Spinocerebellar Ataxia



severe cerebellar atrophy



Spinocerebellar ataxia subtypes

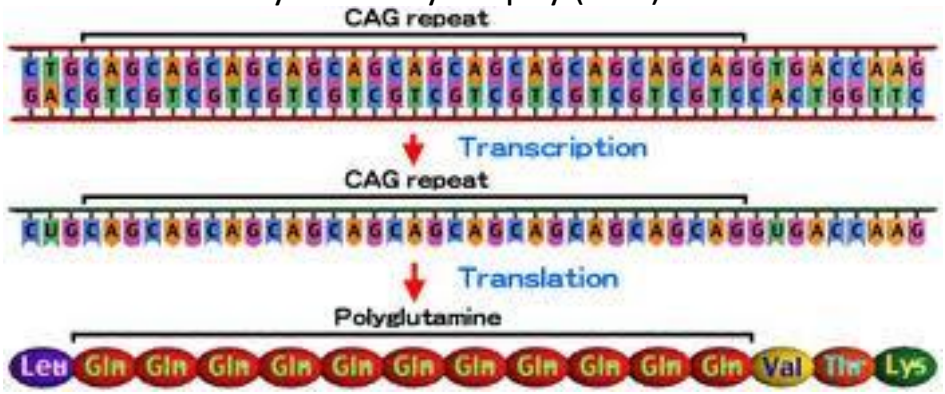
- More than 30 subtypes of SCAs
- SCA 1, 2 and 3 are the most common in Thailand

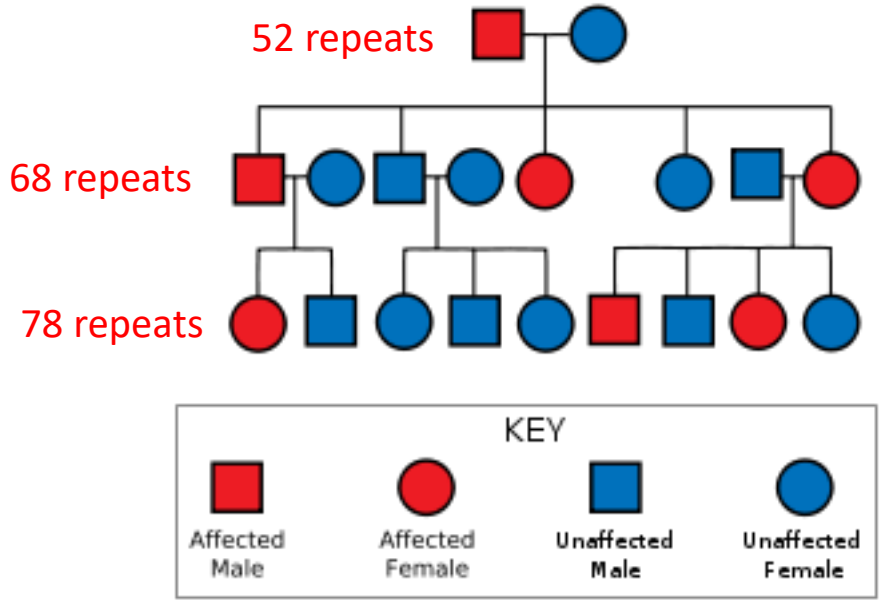
Table 1. Molecular Genetics of Autosomal Dominant Cerebellar **Ataxias**

Disease Name	Gene Symbol or Chromosomal Locus [1]	Type of Mutation	Reference
SCA1	*ATXN1*	CAG repeat	Subramony & Ashizawa [2011]
SCA2	*ATXN2*	CAG repeat	Pulst [2010]
SCA3	*ATXN3*	CAG repeat	Paulson [2011]
SCA4 [2]	16q22.1	---	Flanigan et al [1996], Hellenbroich et al [2003], Edener et al [2011]
SCA5	*SPTBN2*	Non-repeat mutations	Ikeda et al [2006], Lise et al [2012], Elsayed et al [2013]
SCA6	*CACNA1A*	CAG repeat	Gomez [2013]
SCA7	*ATXN7*	CAG repeat	Garden [2012]
SCA8	*ATXN8 / ATXN80S*	CAG·CTG	Ikeda et al [2007]
SCA9 [3]	—	---	
SCA10	*ATXN10*	ATTCT repeat	Matsuura & Ashizawa [2012]

Trinucleotide Repeat expansion and Anticipation

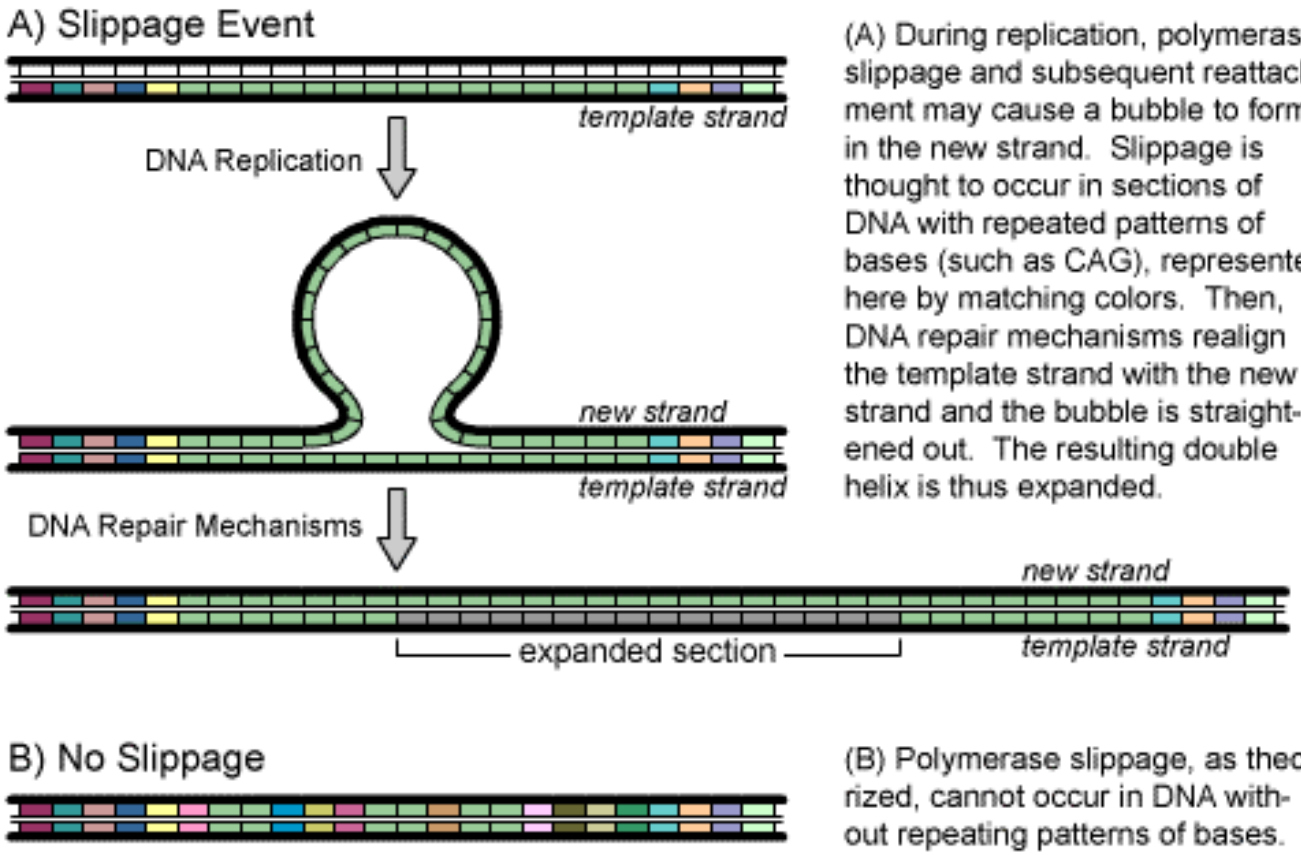
- caused by slippage during DNA replication
- One or two bases expansion is likely possible but lethal (frameshift)
- severity increases with each successive generation (anticipation)
- Longer expansion affects protein stability
- Other diseases with trinucleotide repeats
  - Spinocerebellar Ataxia (CAG)
  - Huntington Disease (CAG)
  - Myotonic Dystrophy (CTG)





Mechanism of Trinucleotide Repeat expansion

Figure Q-5: The Polymerase Slippage Model



(A) During replication, polymerase slippage and subsequent reattachment may cause a bubble to form in the new strand. Slippage is thought to occur in sections of DNA with repeated patterns of bases (such as CAG), represented here by matching colors. Then, DNA repair mechanisms realign the template strand with the new strand and the bubble is straightened out. The resulting double helix is thus expanded.

(B) Polymerase slippage, as theorized, cannot occur in DNA without repeating patterns of bases.

Topics

Neuromuscular Disorders: Duchenne and other muscular dystrophies

Connective tissue disorders: Marfan syndrome

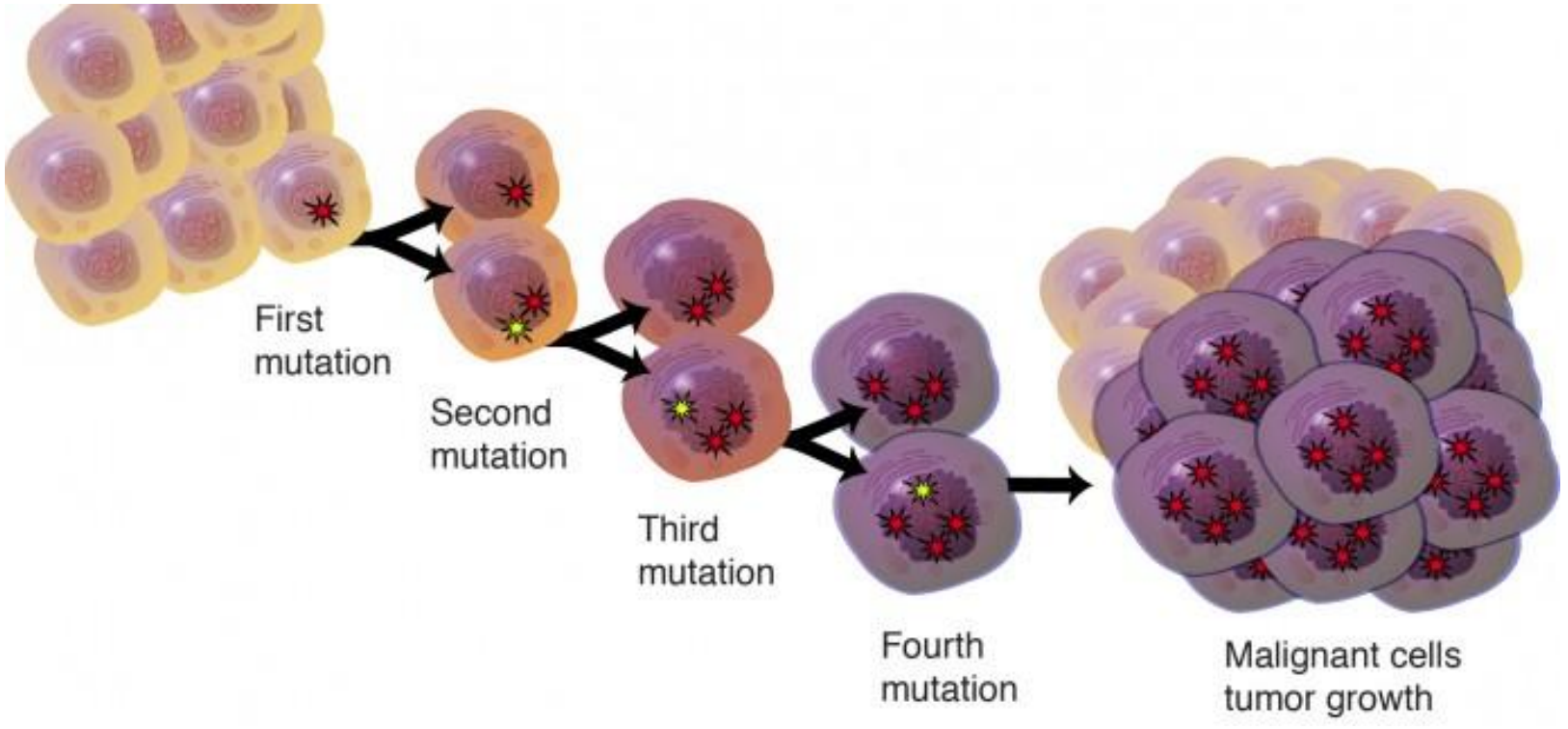
Neurocutaneous disorders: Neurofibromatosis

Neurodegenerative disorders: Spinocerebellar Ataxia

Hereditary Cancers: Breast and Ovarian Syndrome, Colorectal Cancer

Genetic of sudden cardiac death (SUDs) and other genetic diseases

Cancer arises from mutation in DNA



grow and divide in an uncontrolled manner,
invading normal tissues and organs

PLOS | BLOGS

Genetics and Cancers

- **Sporadic cancers**
  - *No known* genetic risk factor and family history
  - Somatic mutation
  - 60% of all cancers
- **Familial Cancers**
  - Multifactorial: genetic and environment e.g. lung, pancreas, prostate
  - Multiple genes involvement is possible
  - Each variation in the gene causes slight increase in risk
  - Do not follow rule of inheritance
- **Hereditary Cancers**

Genetics and Cancers

- **Hereditary Cancers**
  - Single gene disease
  - However, hereditary cancers account for small percentage of all cancers

Hereditary Breast and Ovarian Syndromes

:*BRCA1*, *BRCA2*, etc genes

Colorectal Cancers

Familial Adenomatous Polyposis (FAP): *APC* gene

Hereditary Non-Polyposis Colorectal Cancer (HNPCC): *MLH1*, *MSH2* genes

Genetic testing is available for HBOC and Colorectal cancers

Hereditary Breast and Ovarian Cancer (HBOC)

- Mutation in *BRCA1* and *BRCA2,* AD inheritance(tumor suppressor/DNA repair genes)
- Mutation in other genes also cause HBOCs:

  CHEK2, *PALB2*, *RAD51C*, etc
- Breast cancers
  - Inherited mutation in BRCA1/2 increase risk from 10% to 50%
- Ovarian cancers
  - Inherited mutation in BRCA1/2 increase risk from 1.4% to 10-40%
- Increase risk of pancreatic cancer
- Men with mutation have risk in prostate and male breast cancers
- BRCAs mutation account for 10% of all breast cancers

Hereditary Colorectal Cancer

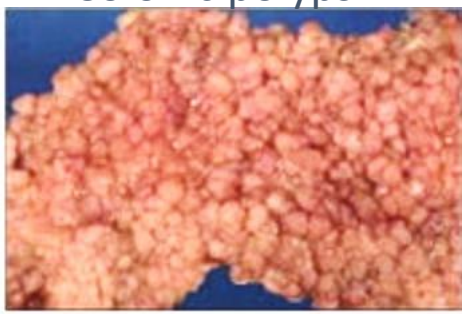
- Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women in the US
- 25% of patients have a family history of CRC that suggests a hereditary contribution
- Genetic mutations are estimated for 5% of CRC cases

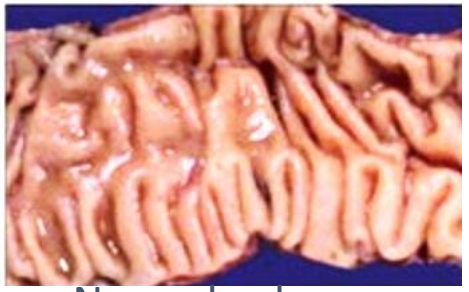
Hereditary Colorectal Cancer

Familial adenomatous polyposis (FAP)

- Patients with FAP develop hundreds to thousands of colon polyps starting in the teens
- untreated eventually develop colorectal cancer, often around age 40
- ~100% penetrance by age 50 year
- colon and rectum will be removed to prevent colon cancer
- Autosomal dominant, APC gene

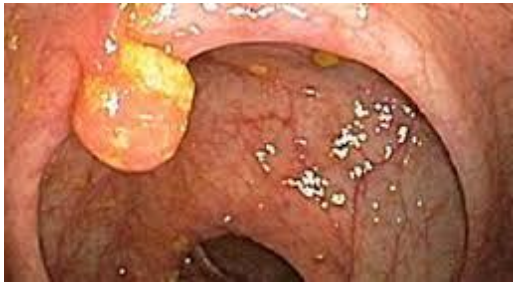
Colonic polyps





Normal colon

Hereditary Colorectal Cancer

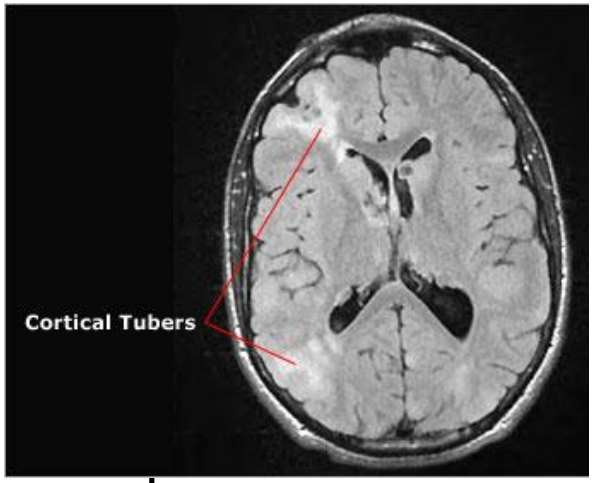


Hereditary Non-Polyposis Colon Cancer (HNPCC)

- Also known as Lynch Syndrome
- increased risk of life time colon cancer 50-80%
- Also increase risk for endometrium, ovary, stomach, small intestine cancers
- germline mutation in one of four mismatch repair (MMR) genes (*MLH1, MSH2, MSH6,* and *PMS2*), autosomal dominant
- Regular colonoscopy with removal of precancerous polyps
- prophylactic colectomy is generally not recommended

Tuberous Sclerosis Complex (TSC)

- Multiple benign tumors and other abnormal tissue in multiple organs
  - brain (cortical tuber and giant cell astrocytoma)
    => seizure and learning disability
  - Kidneys (angiomyolipoma and renal cysts)
  - lungs (multiple lung cysts)
  - skin (facial angiofibroma, Ashleaf spot))
  - heart (rhabdomyoma)
  - eyes (hamartomas)

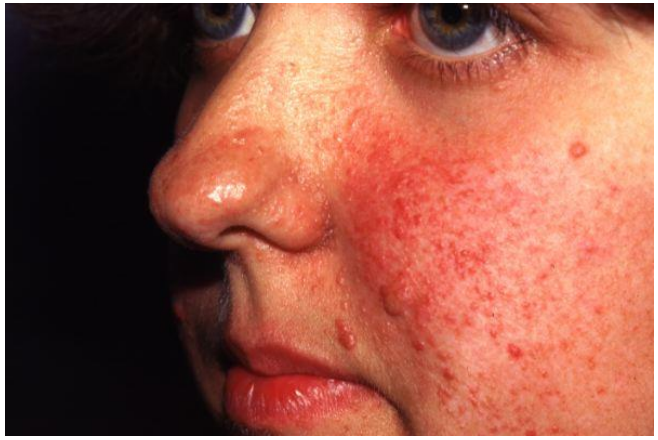


- often first recognized when a child has seizures or shows developmental delays
- symptoms varies greatly among kids, ranging from mild skin changes to learning disabilities, mental retardation, or kidney failure
- Treatment usually includes medication to control seizures, treatments to address skin problems, surgery to remove tumors

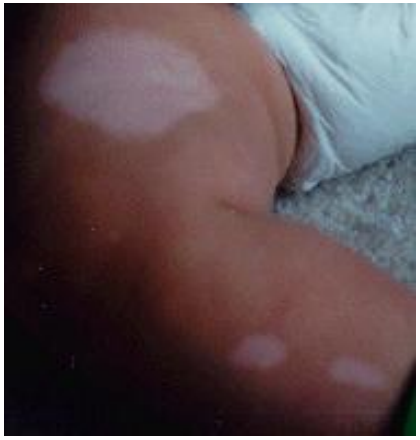
Tuberous Sclerosis Complex (TSC)

- Autosomal dominant with mutation in *TSC1* (Hamartin) or *TSC2* (Tuberin) genes
- TSC1 and TSC2 are both tumor suppressor genes involved in the control of cell growth and cell division

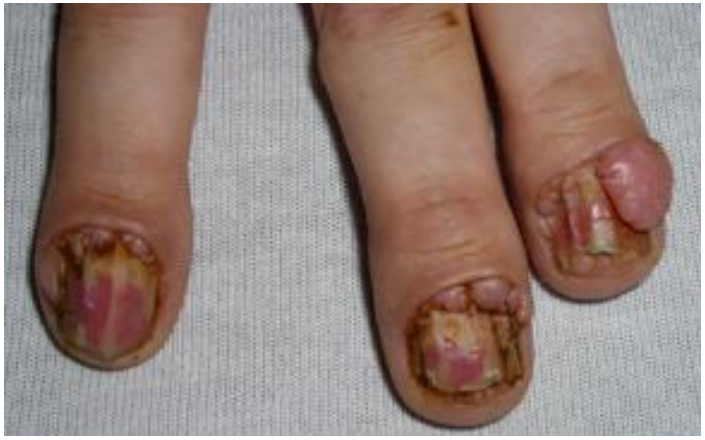
facial angiofibroma (adenoma sebaceum)

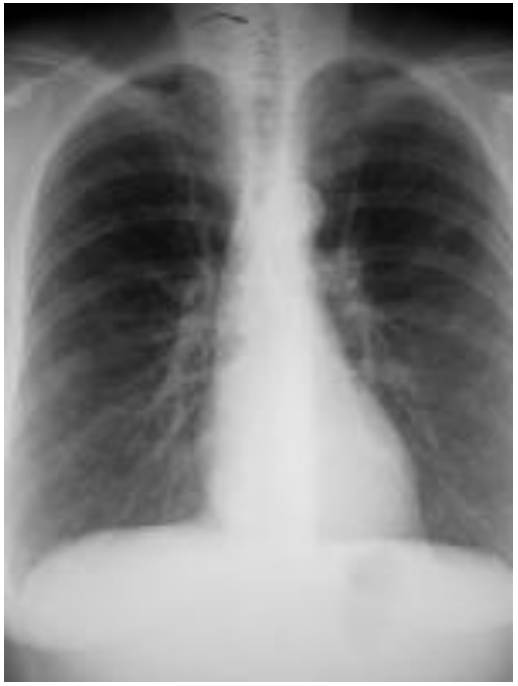


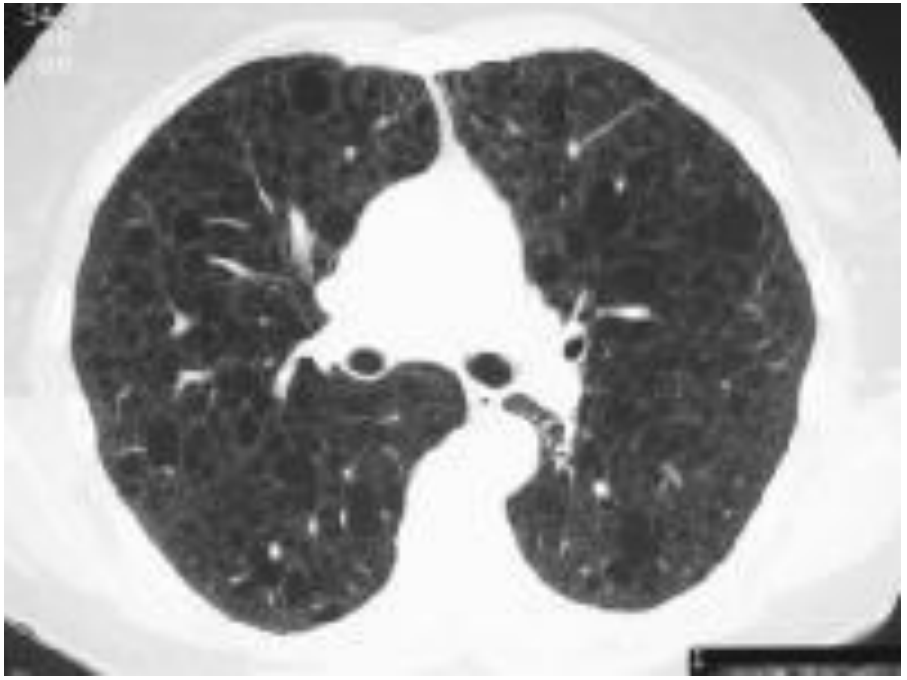
hypomelanotic macules (ashleaf spot)



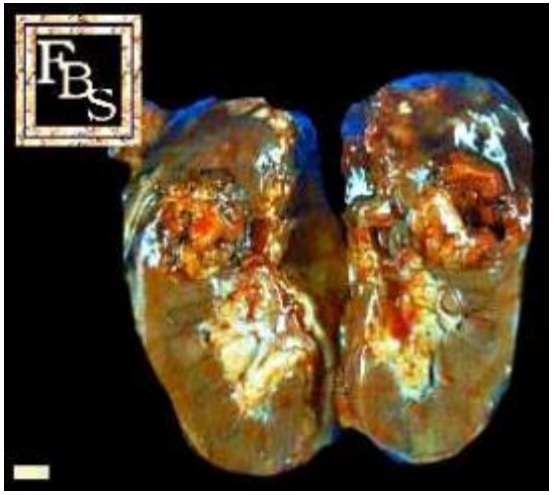
ungual fibroma

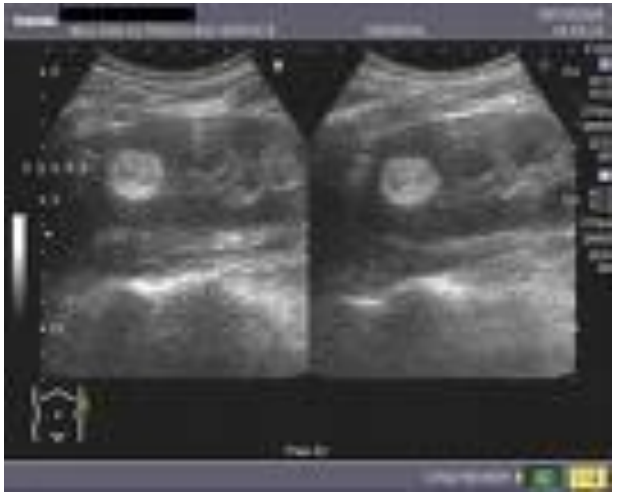






Lymphangioleiomyomatosis (LAM)





Angiomyolipoma (AML)

Topics

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Connective tissue disorders: Marfan syndrome

Neurocutaneous disorders: Neurofibromatosis

Neurodegenerative disorders: Spinocerebellar Ataxia

Hereditary Cancers: Breast and Ovarian Syndrome, Colorectal Cancer

Genetic of sudden cardiac death (SUDs) and other genetic diseases

Genetic in Sudden Cardiac Death

- Sudden cardiac death (SCD) is referred to as an unexpected natural death occurring within one hour of a cardiac event
- Annually, more than 300,000 cases of SCD occur in the US
- 80% related to underlying coronary artery disease
- In young, healthy adult, CAD is not common

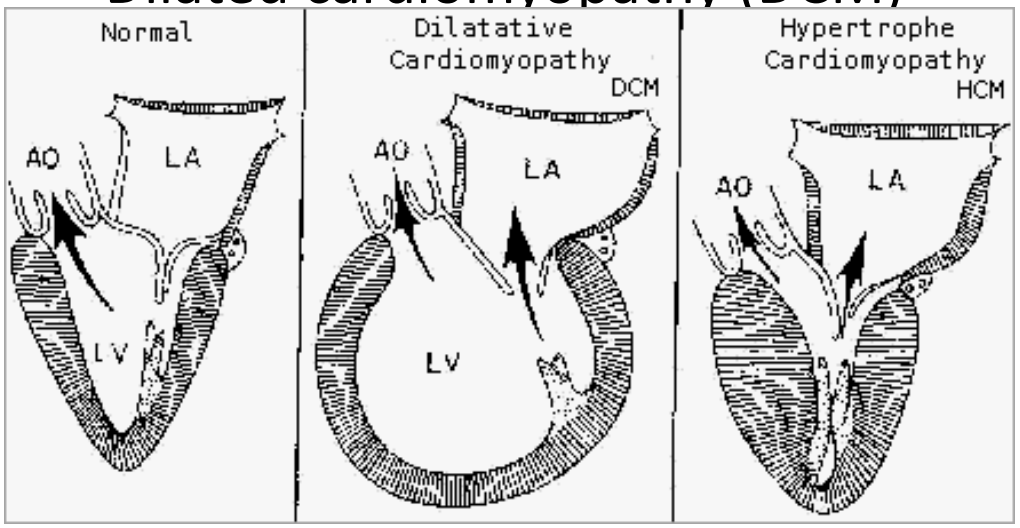
- 15% Cardiomyopathy
- 5% Defect of cardiac electrophysiology
- Ruptured aortic aneurysm (Marfan syndrome)

Monogenic diseases of SCD

- Cardiomyopathy
  - Hypertrophic Cardiomyopathy (HCM)

autosomal dominant, mutation in >10 genes involve in sarcomere proteins

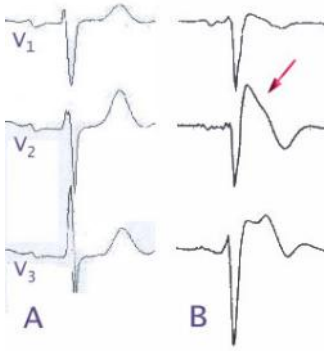
  - Dilated cardiomyopathy (DCM)



Marc-Vivien Foé *1975-2003*
Cameroon/Manchester City

Monogenic diseases of SCD

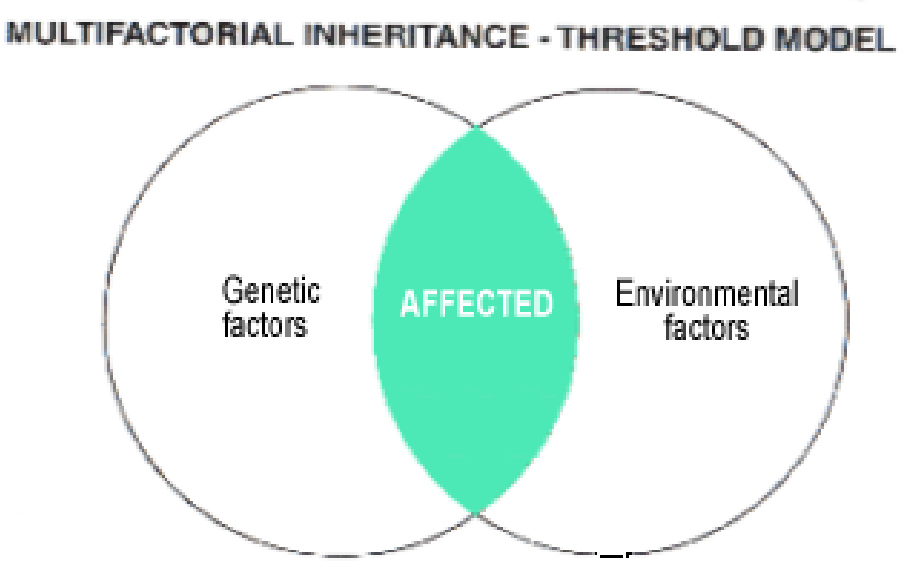
Defect of cardiac electrophysiology



- Brugada syndrome (ไหลตาย)
- abnormal electrocardiogram (ECG) findings
- sudden death by causing ventricular fibrillation
- mutation in genes that encodes for cardiac myocyte sodium ion channel
- incomplete penetrance, most of affected individuals are male
- Long QT syndrome

ผวาผีแม่ม่าย เอาชีวิตผู้ชายตายเพียบ

Multifactorial disorders



Multifactorial disorders

This type is caused by a combination of environmental factors and mutations in multiple genes. For example, different genes that influence **breast cancer** susceptibility have been found on chromosomes 6, 11, 13, 14, 15, 17, and 22. Its more complicated nature makes it much more difficult to analyze than single-gene or chromosomal disorders.

Some of the most common chronic disorders are multifactorial disorders. Examples include **heart disease**, **high blood pressure**, **Alzheimer's disease**, **arthritis**, **diabetes**, **cancer**, and **obesity**.

Multifactorial inheritance also is associated with heritable traits such as fingerprint patterns, height, eye color, and skin color.

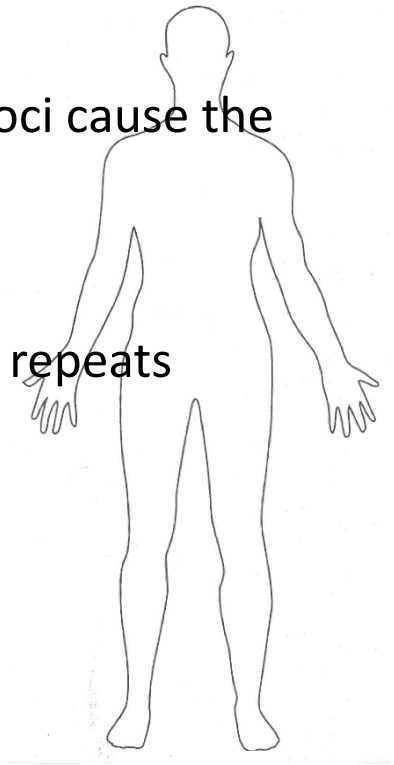
Summary

- Genetic disease by system
- Pattern of inheritance: AD, AR, X-linked
- Penetrance
- Genetic Heterogeneity
- Variable Expressivity
- Anticipation
- Clinical Diagnosis vs Molecular Testing

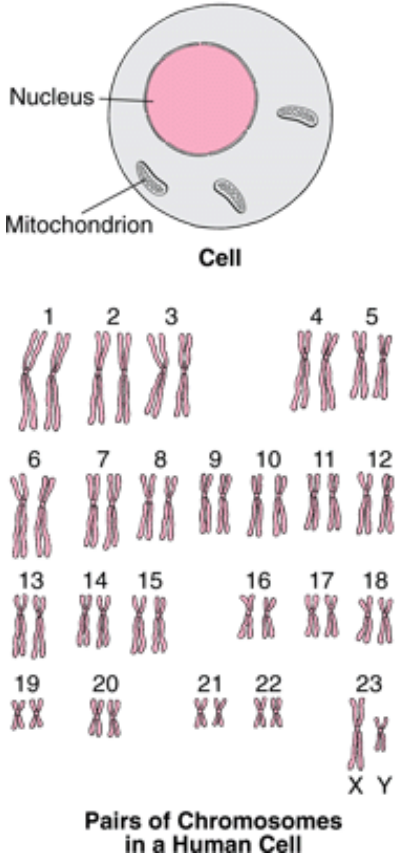
Recognize

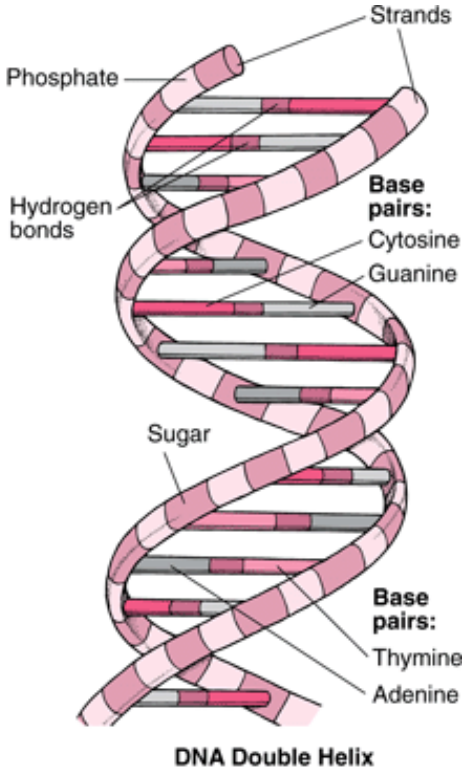
- Variable expressivity
  - Variation in clinical features (type and severity) of a genetic disorder between affected individuals, even within the same family
- Genetic heterogeneity

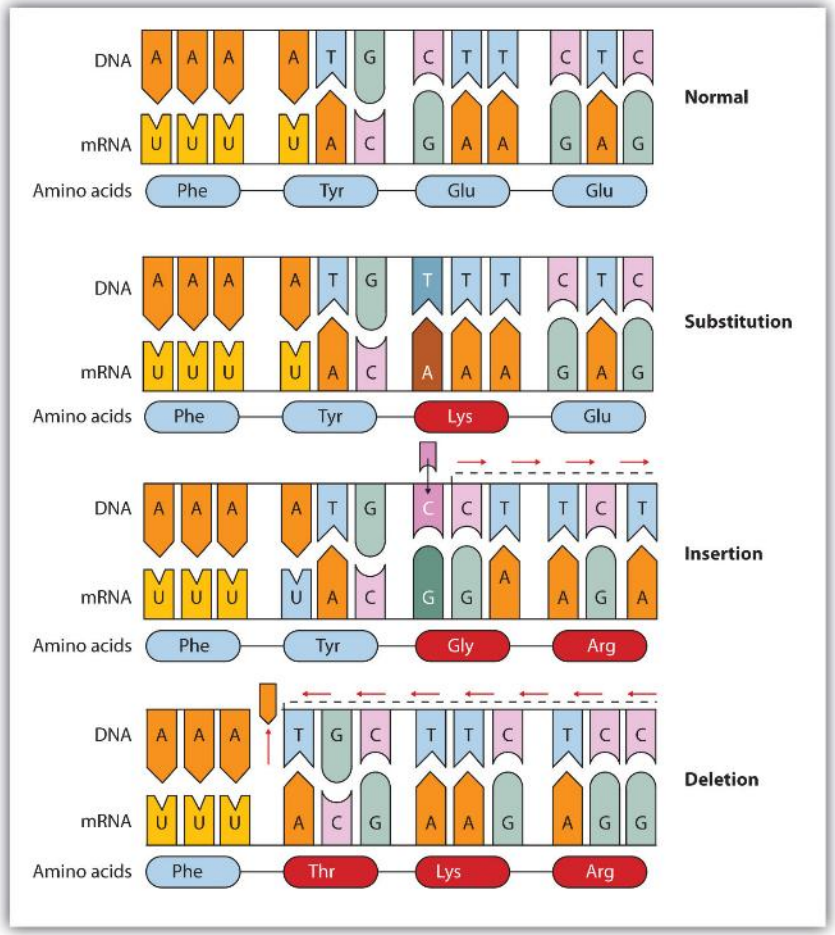
  (mutations in different genes at different chromosomal loci cause the same phenotype e.g. LGMD)
- Type of mutation
  - Point mutation, deleletion/duplication, trinucleotide repeats
- Penetrance
- Risk calculation



Type of mutation







Genetic Testing

- Phenotypic identification
- Biochemical diagnosis
- Enzyme assay
- Molecular diagnosis-gene, DNA analysis
- Cytogenetic diagnosis-chromosomal karyotype, FISH

THANK YOU