Types of gene mutations and Genetic Disorders

MUTATIONS

- **PERMANENT change in DNA** can be either inherited from a parent or acquired

  - **GENE MUTATION: (may, and often, result in a single base error)**
  - **CHROMOSOME MUTATION: (visible chromosome change)**

Many kinds of gene alternations
Gene mutations are classified in various ways

- **Single bp substitution, deletion and insertion.**
- **Changes in the number of copies of tri-nucleotides. e.g. (AGC)3 to (AGC)5.**
- **Insertion of transposable elements.**

- **1- Mutations can be spontaneous or induced.**
- **2- It can occur in somatic or germ cells.**
- **3- It can occur in coding genes or non-coding regions.**

Spontaneous and induced mutations

- **Spontaneous mutations have no known cause, it is accidental, it occurs in normal biological and chemical process; (e.g. DNA replication, free radicals in respiration, tautamers).**
- **Induced mutations results from external factors. Could be due to natural factors (e.g. UV from sun, radiations from cosmic and minerals), or artificial (e.g. X-ray) .**

Classification based on location of mutation " gametes or somatic cells"

Somatic mutations occur in somatic cells and only affect the individual in which the mutation arises.

It may be autosomal mutation or X-linked mutation. It could be dominant or recessive.

It have pronounced effect if happen early in development. Later it could be masked within the tissue containing thousands of normal cells

Germ-line mutations alter gametes and passed to the next generation.

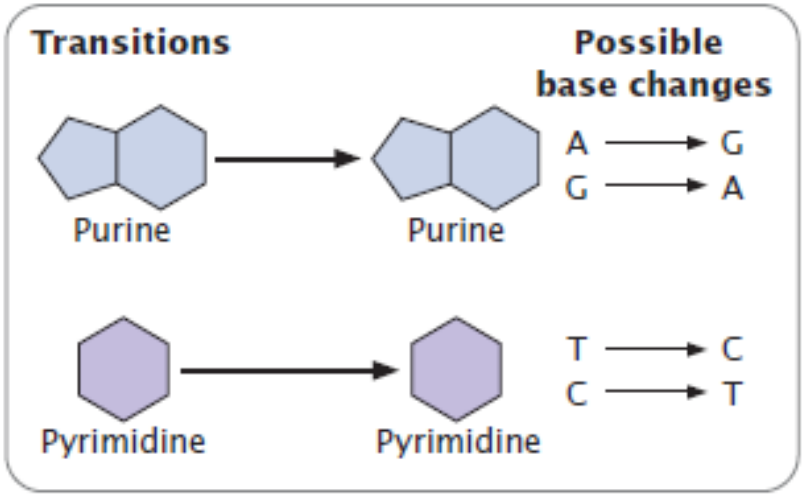
1- Mutations affecting single base pair of DNA (Point mutation)

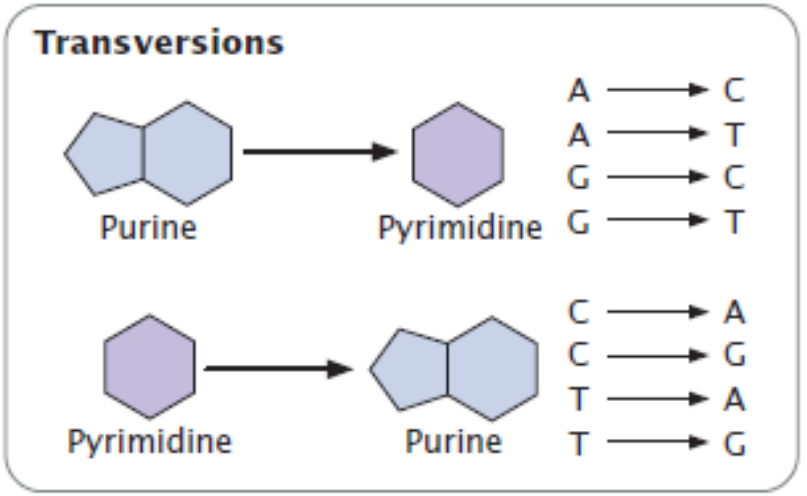
- This is the **minimum** change possible.
- It can reduce or eliminate gene function (**Loss-of-function**) mutation.
- Rarely, it can increase a gene activity (**Gain of function** mutation).
- Two types of point mutations:

1-Base pair substitutions.

2-Base pair insertion and deletion (Indel mutations)

Base substitution:Transitions Vs transversions





18.3 A transition is the substitution of a purine for a purine or of a pyrimidine for a pyrimidine; a transversion is the substitution of a pyrimidine for a purine or of a purine for a pyrimidine.

Consequences of point mutations

silent mutation

Base pair substitution results in the same amino acid (different codon).
(Never alters amino acid sequence)

missense mutation

Base pair substitution results in substitution of a different amino acid.

1- Conservative substitution: Replaces one amino acid with chemically similar amino acid. (Less likely to affect severely= Neutral mutation)

2- Non-conservative mutation. Replaces one amino acid with chemically different amino acid. Could result in severe change.

Nonsense mutation (The most dangerous)

Base pair substitution results in a stop codon (and shorter polypeptide).
The closer to 3'UTR, might still produce protein possessing some activity

2- Indel mutation

- **Frameshift mutations:**

Deletions or insertions (not divisible by 3) result in translation of incorrect amino acids, stops codons (shorter polypeptides), or read-through of stop codons (longer polypeptides).

This results in complete loss of structure and function.

In-frame deletion or insertion :Deletion or insertion of a multiple of three nucleotides that does not alter the reading frame

Forward Mutation and Reversion

- **Forward mutation**: converts a wild-type allele to a mutant allele

- **Reverse mutations** : convert mutant alleles back to original wild-type alleles

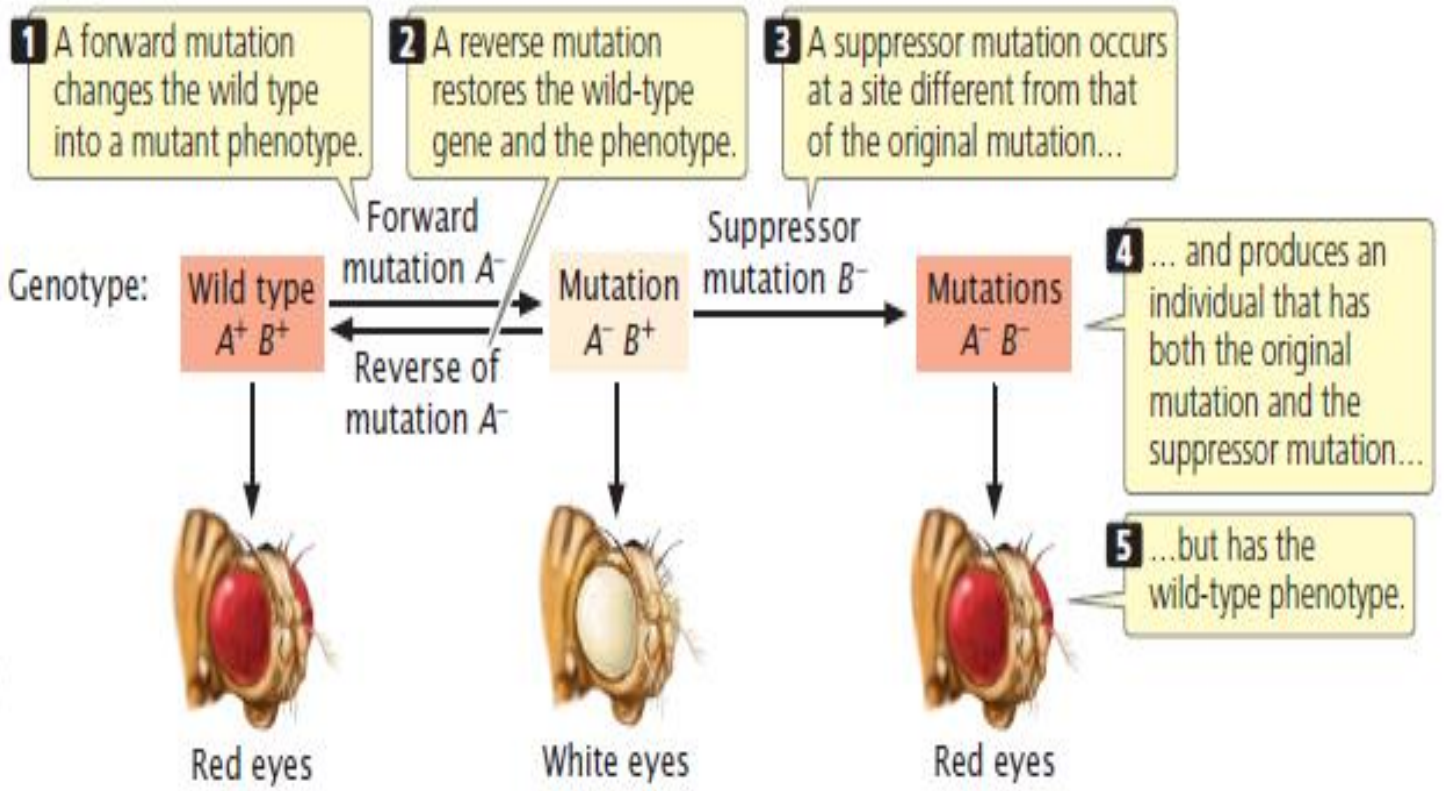
Suppressor mutation

- **Suppressor mutation**: a mutation of a second site hides or suppresses the original mutation

-- **Intragenic**: wild-type DNA sequence is restored by a second mutation within the same codon OR occurs through mutation elsewhere in the same gene

---**intergenic** : occurs by mutation in a different gene and together the two mutations restore the organism to wild-type

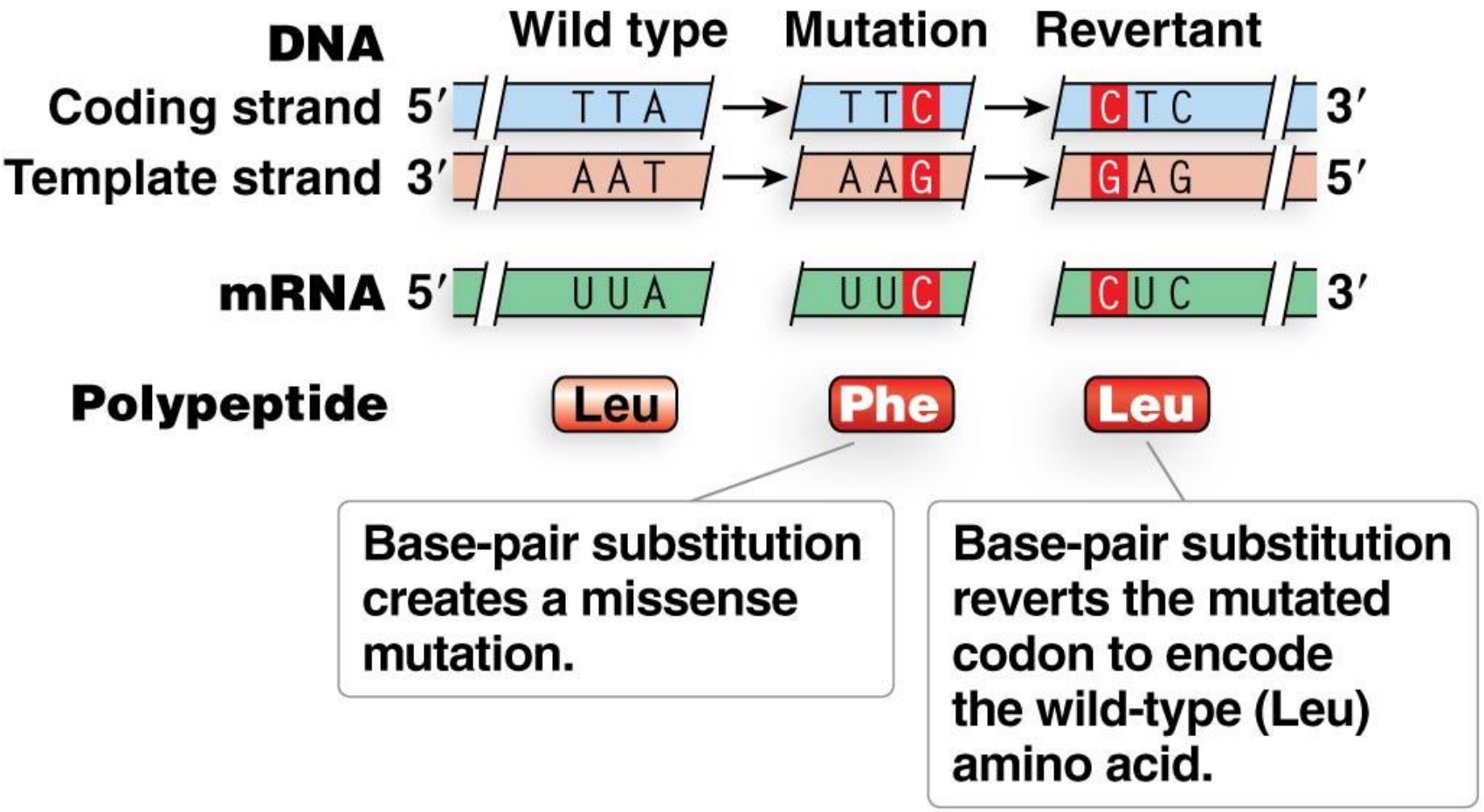
Suppressor Mutations

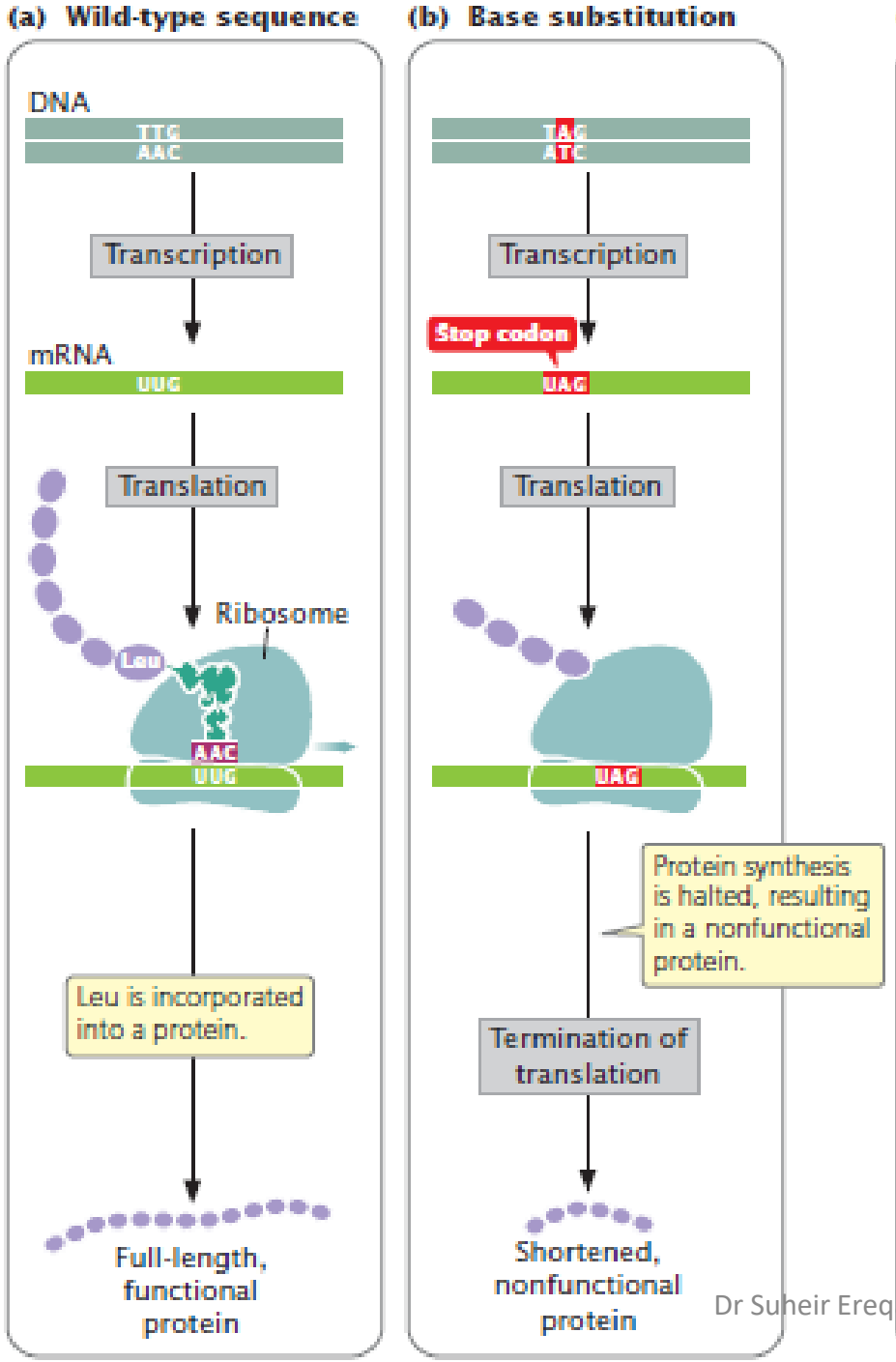


18.7 Relation of forward, reverse, and suppressor mutations.

Double mutant but exhibiting the phenotype of an unmutated wild type.

(a) Intragenic reversion




(a) Wild-type sequence
DNA
TTG
AAC
Transcription
mRNA
UUG
Translation
Ribosome
Leu
AAC
UUG
Leu is incorporated into a protein.
Full-length, functional protein
(b) Base substitution
TAG
ATC
Transcription
Stop codon
UAG
Translation
UAG
Protein synthesis is halted, resulting in a nonfunctional protein.
Termination of translation
Shortened, nonfunctional protein
(c) Base substitution at a second site
Site 1 (first mutation)
Site 2
TAG
ATC
ATA
TAT
At site 2 is a gene encoding tyrosine-tRNA.
tRNA
AUA
Second base-substitution mutation
Normal transcription produces a tRNA with an anticodon (AUA) which would pair with the tyrosine codon UAU in translation).
TAG
ATC
ATC
TAG
Transcription
Introduction of an incorrect base (G), results in a mutant tRNA that has anticodon AUC (instead of AUA),...
UAG
tRNA
AUC
Tyr
Translation
Tyr
AUC
UAG
...which can pair with the stop codon UAG.
Translation continues past the stop codon, and Tyr is incorporated into the protein.
Full-length, functional protein

Intergenic

Mutation in non-coding sequences

- 1- No phenotypes.
- 2- mutations in promoters or enhancers. (These affect quantity but not quality. e.g:

A- Binding site for transcription factor (No response to environmental cue).

B- Binding site for suppressor (Constitutively active gene).

C- Binding site for RNA polymerase. (Block gene expression).

Other mutations can occur at docking sites of RNA

- Ribosome binding sites.
- Splice sites (Exon-Intron) junction.
- Sites that regulate translation.
- Sites that regulate localization of mRNA.

Table 18.2 Characteristics of different types of mutations

Type of Mutation	Definition
Base substitution	Changes the base of a single DNA nucleotide
Transition	Base substitution in which a purine replaces a purine or a pyrimidine replaces a pyrimidine
Transversion	Base substitution in which a purine replaces a pyrimidine or a pyrimidine replaces a purine
Insertion	Addition of one or more nucleotides
Deletion	Deletion of one or more nucleotides
Frameshift mutation	Insertion or deletion that alters the reading frame of a gene
In-frame deletion or insertion	Deletion or insertion of a multiple of three nucleotides that does not alter the reading frame
Expanding nucleotide repeats	Repeated sequence of a set of nucleotides in which the number of copies of the sequence increases
Forward mutation	Changes the wild-type phenotype to a mutant phenotype
Reverse mutation	Changes a mutant phenotype back to the wild-type phenotype
Missense mutation	Changes a sense codon into a different sense codon, resulting in the incorporation of a different amino acid in the protein
Nonsense mutation	Changes a sense codon into a nonsense codon, causing premature termination of translation
Silent mutation	Changes a sense codon into a synonymous codon, leaving unchanged the amino acid sequence of the protein
Neutral mutation	Changes the amino acid sequence of a protein without altering its ability to function
Loss-of-function mutation	Causes a complete or partial loss of function
Gain-of-function mutation	Causes the appearance of a new trait or function or causes the appearance of a trait in inappropriate tissue or at an inappropriate time
Lethal mutation	Causes premature death
Suppressor mutation	Suppresses the effect of an earlier mutation at a different site
Intragenic suppressor mutation	Suppresses the effect of an earlier mutation within the same gene
Intergenic suppressor mutation	Suppresses the effect of an earlier mutation in another gene

Familial Mediterranean fever (FMF)

- FMF is inherited autosomal recessively; however, a significant proportion of heterozygotes also express the phenotype.
- It affects people of the Mediterranean basin, mainly Armenians, Sephardic Jews, Arabs and Turks but not restricted to these ethnic groups.
- About 100,000-150,000 patients are affected worldwide.

Clinical features

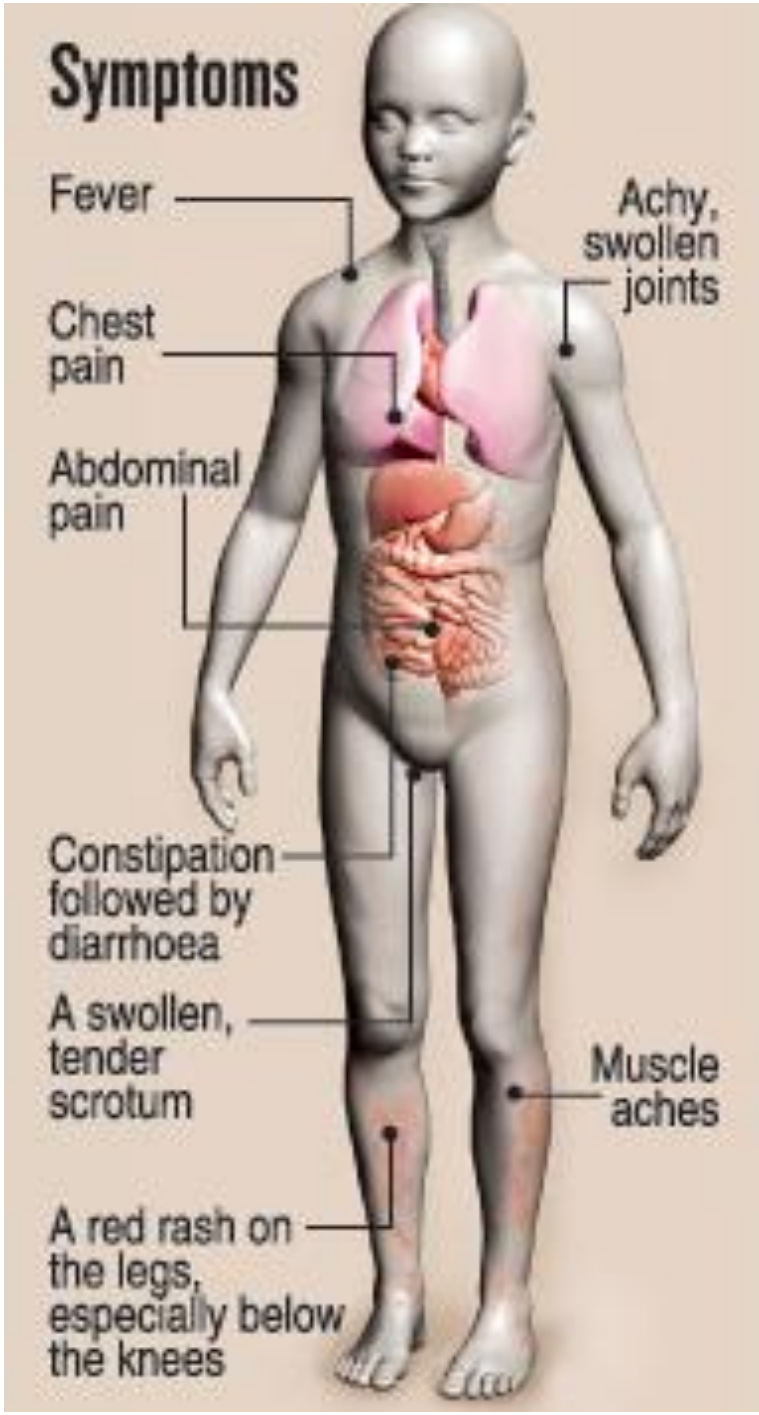
- **Age of onset:** childhood onset in about 50% of cases and most patients will develop the disease before the age of thirty

- **Symptoms**

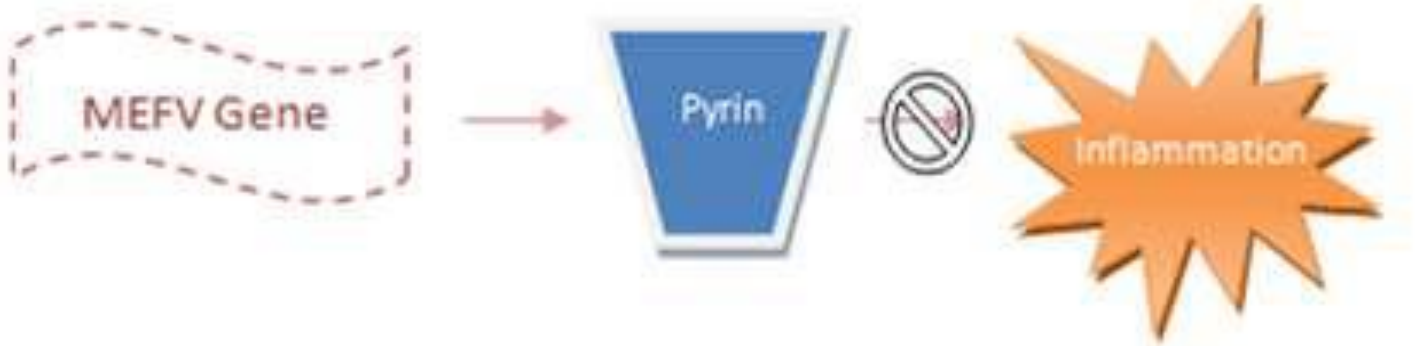
- Recurrent episodes of painful inflammation of the abdomen, chest or pericardium
- Acute mono- or oligo-arthritis
- Fever
- Rash

- **Duration of crisis:** from 1 to 3 days

- **Frequency of attacks:** from several times per week to once every few months or even years



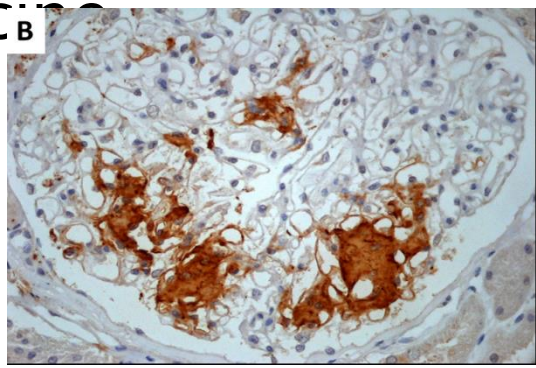
FMF is caused by mutations in the MEditerranean FeVer (*MEFV)* gene



- *MEFV* is located on the short arm of chromosome 16 and encodes a protein called **pyrin**
- Pyrin expressed mostly in neutrophils and monocytes and has a key role in apoptosis and inflammatory pathways.
- Mutated pyrin causes an exaggerated inflammatory response by uncontrolled interleukin-1B secretion
- **Sequence variants:** almost all single-nucleotide substitutions with the most frequent pathogenic ones:p.Met680Ile, p.Met694Val, p.Met694Ile and p.Val726Ala are clustered within exon 10 of *MEFV*

- **Treatment**:
- Colchicine is the first line of treatment for FMF patients.
- Its anti-inflammatory action is attributed to its capacity to inhibit microtubule polymerization and thus alter the adhesion and mobility of leukocytes.
- Colchicine prevents acute symptoms, reoccurrence of the episodes

- **Complications**: Serum amyloid A (SAA) amyloidosis, which can lead to renal failure and can be prophylactically treated with colchicine



Glomerular deposition of SAA in kidney biopsy of an FMF patient

Cystic Fibrosis (CF)

- Monogenic
- Cause: deletion of only 3 bases of CFTR gene on the long arm of chromosome 7
- Fluid in lungs, the mucus clogs the airways and traps bacteria leading to infections, potential respiratory failure
- the mucus prevents the release of digestive enzymes that allow the body to break down food and absorb vital nutrients.
- Common among Caucasians…1 in 20 are carriers
  - Therefore is it dominant or recessive?
  - One of the first disorders to be actively studied for gene therapy.

Expanding nucleotide repeats Mutations

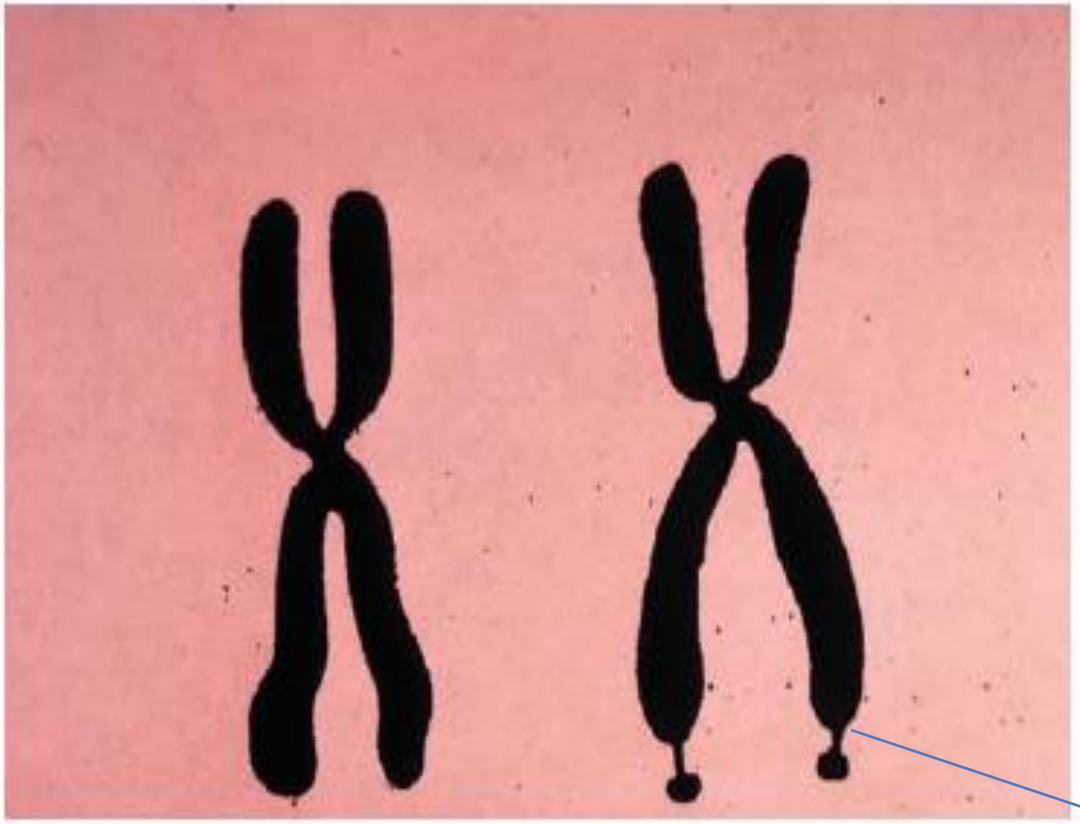
- in which the number of copies of a set of nucleotides increases in number
- Most of these diseases are caused by the expansion of a set of three nucleotides (called a trinucleotide), most often CNG, where N can be any nucleotide

- This type of mutation was first observed in 1991 in a gene called *FMR-1*, which causes fragile-X syndrome, the most common hereditary cause of mental retardation.
- FMR 1=development of brain

fragile-X syndrome

Repeated sequence: CGG

X-linked dominant, Spontaneous mutation



18.4 The fragile-X chromosome is associated with a characteristic constriction (fragile site) on the long arm.
[Visuals Unlimited.]

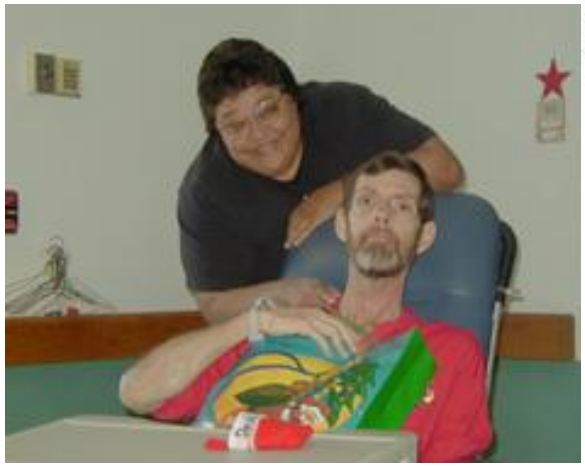
The number of copies of nucleotide repeats correlates to the severity of the disease and the probability of expansion=anticipation

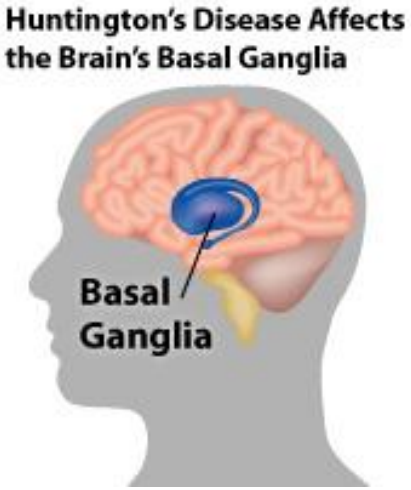
Methylation=turn off gene

Table 18.1 Examples of genetic diseases caused by expanding nucleotide repeats

Disease	Repeated Sequence	Number of Copies of Repeat	
		Normal Range	Disease Range
Spinal and bulbar muscular atrophy	CAG	11–33	40–62
Fragile-X syndrome	CGG	6–54	50–1500
Jacobsen syndrome	CGG	11	100–1000
Spinocerebellar ataxia (several types)	CAG	4–44	21–130
Autosomal dominant cerebellar ataxia	CAG	7–19	37–220
Myotonic dystrophy	CTG	5–37	44–3000
Huntington disease	CAG	9–37	37–121
Friedreich ataxia	GAA	6–29	200–900
Dentatorubral-pallidoluysian atrophy	CAG	7–25	49–75
Myoclonus epilepsy of the Unverricht–Lundborg type	CCCCGCCCCGCG	2–3	12–13

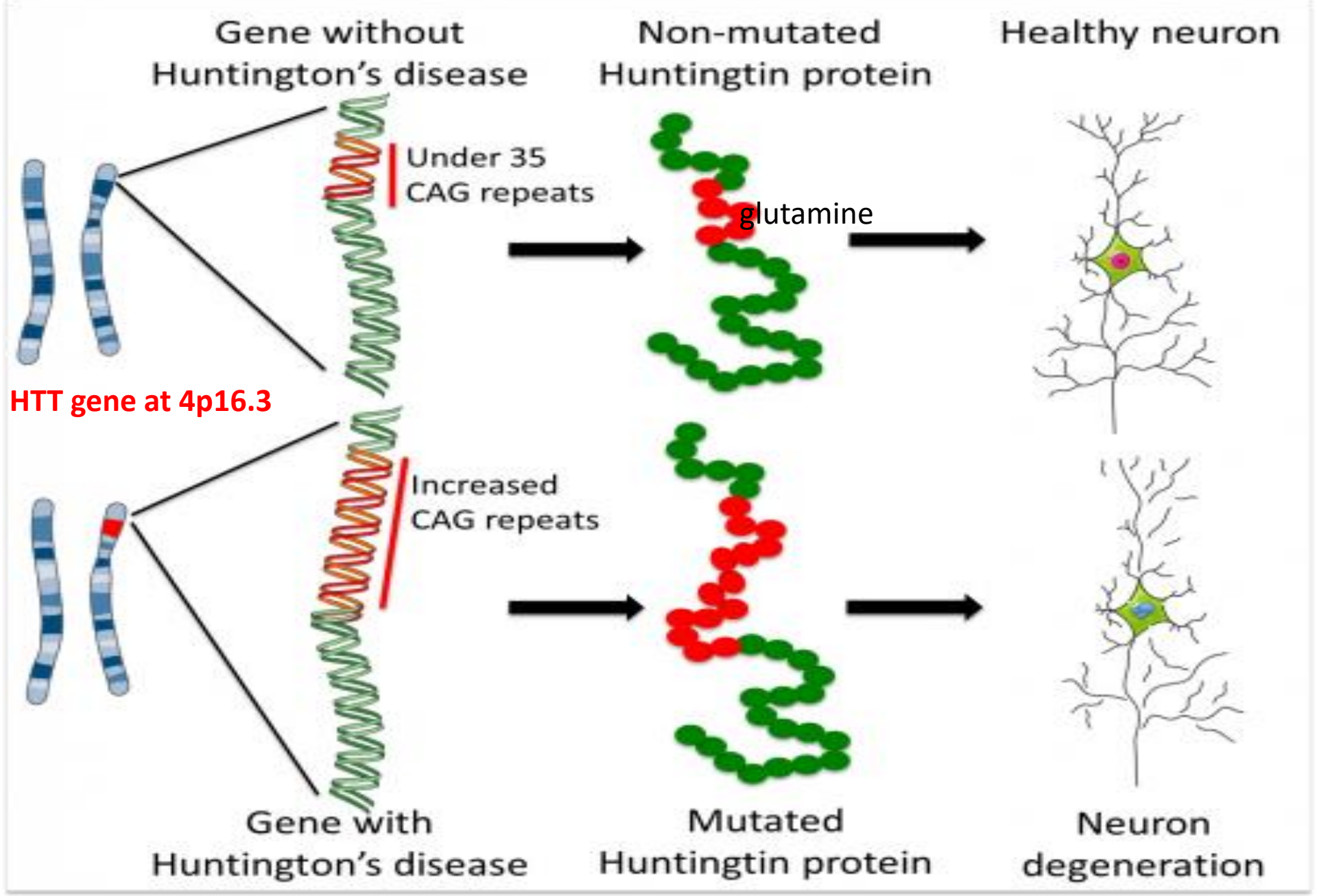
Huntington’s Disease





Caused by autosomal **dominant** allele

- Huntington's disease (HD) is an inherited, degenerative brain disorder which results in an eventual loss of both mental and physical control. The disease is also known as Huntington's chorea. Chorea means "dance-like movements" and refers to the uncontrolled motions often associated with the disease.


Gene without
Huntington's disease
Non-mutated
Huntingtin protein
Healthy neuron
Under 35
CAG repeats
glutamine
HTT gene at 4p16.3
Increased
CAG repeats
Gene with
Huntington's disease
Mutated
Huntingtin protein
Neuron
degeneration

Marfan syndrome

1- a genetic disorder that affects the body's connective tissue, the disease is **an autosomal dominant** disorder Caused by a mutation in the FBN1 gene that determines the structure of fibrillin-1 (a glycoprotein). this gene is localized to chromosome 15 on the long arm (q) at 15q21.1. .

2.- 25% of all Marfan cases are due to a spontaneous mutation at the time of conception

>1,300 *FBN1* gene mutations were identified

What is Fibrillin Protein

FBN1 Protein transported out of cells into the extracellular matrix,

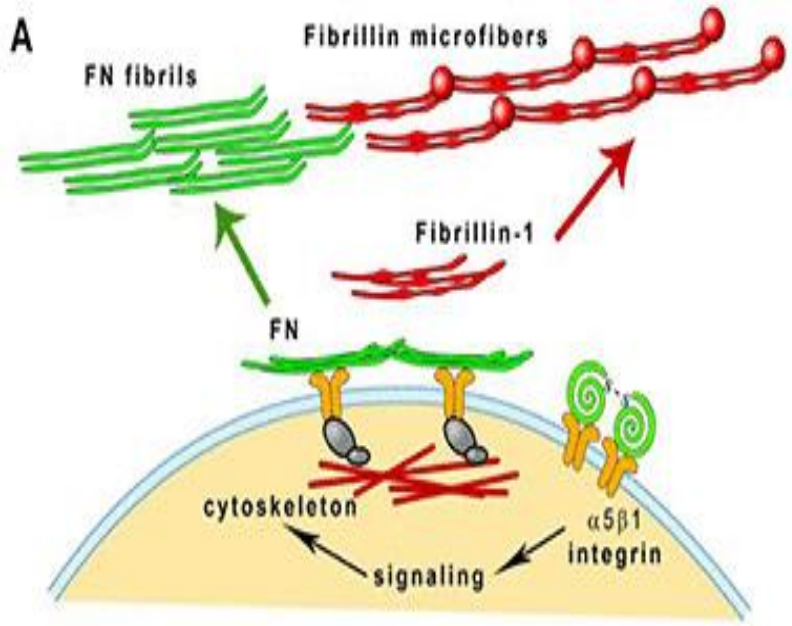
.

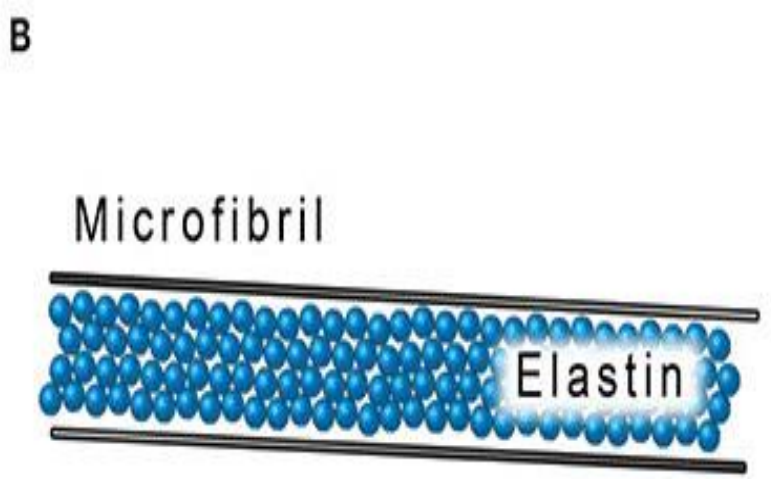
In the matrix, molecules of fibrillin-1 attach to each other and to other proteins to form threadlike filaments called microfibrils.

Microfibrils form elastic fibers, which enable the skin, ligaments, and blood vessels to stretch.

Microfibrils also provide support to more rigid tissues such as bones and the tissues that support the nerves, muscles, and lenses of the eyes.

What is fibrillin





principal clinical manifestations

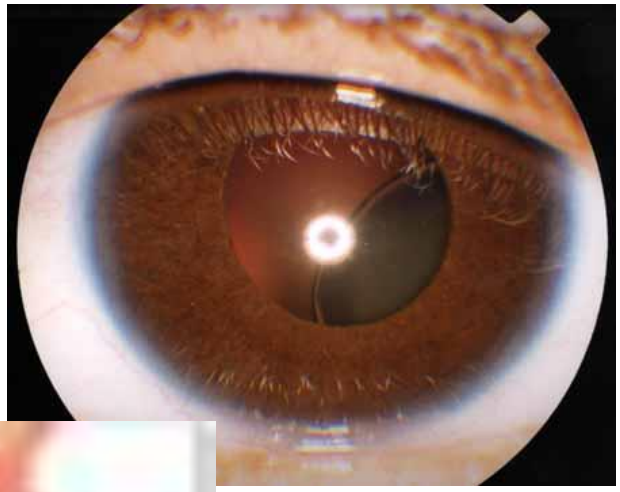
Skeleton: Long and skinny arms ands legs, Arachnodactyly, intruding chest bone, scoliosis

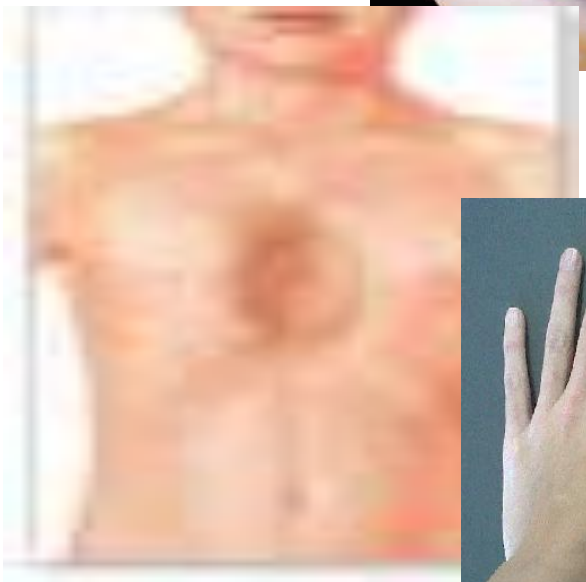
ocular changes

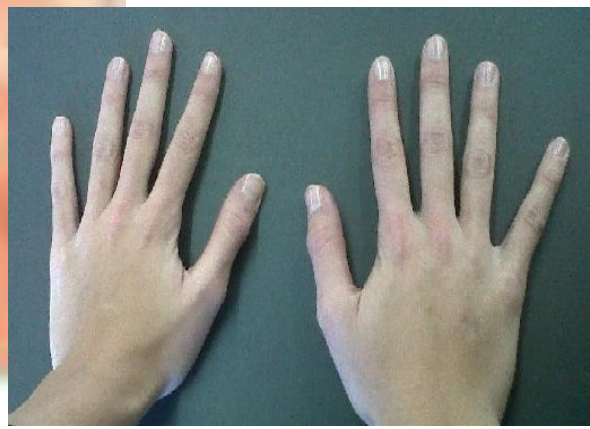
dislocation of one or both lenses

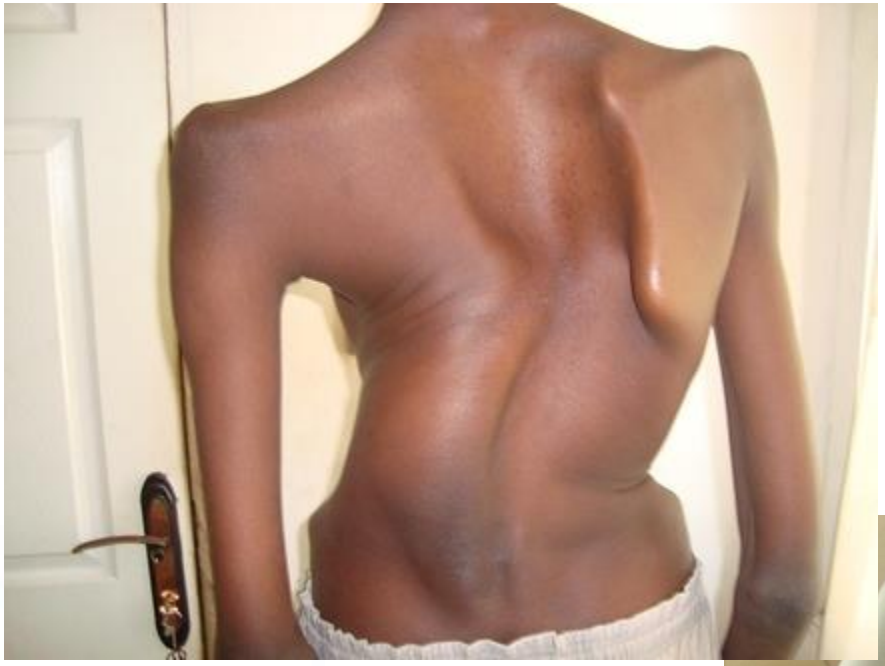
cardiovascular system:

defects of the heart valves and aorta**,**









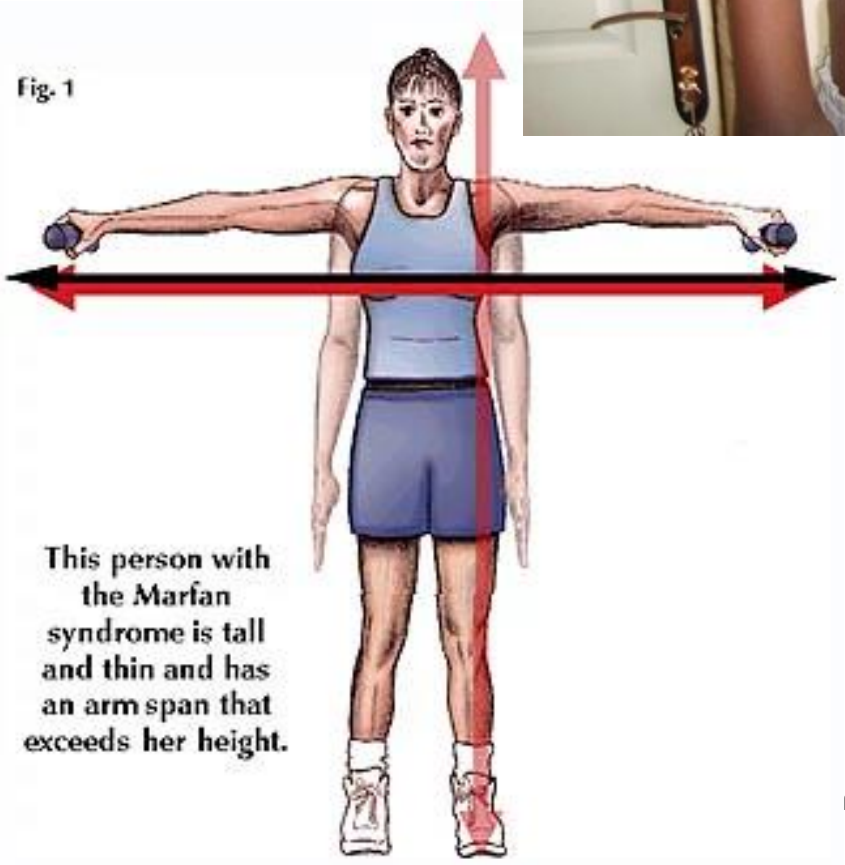
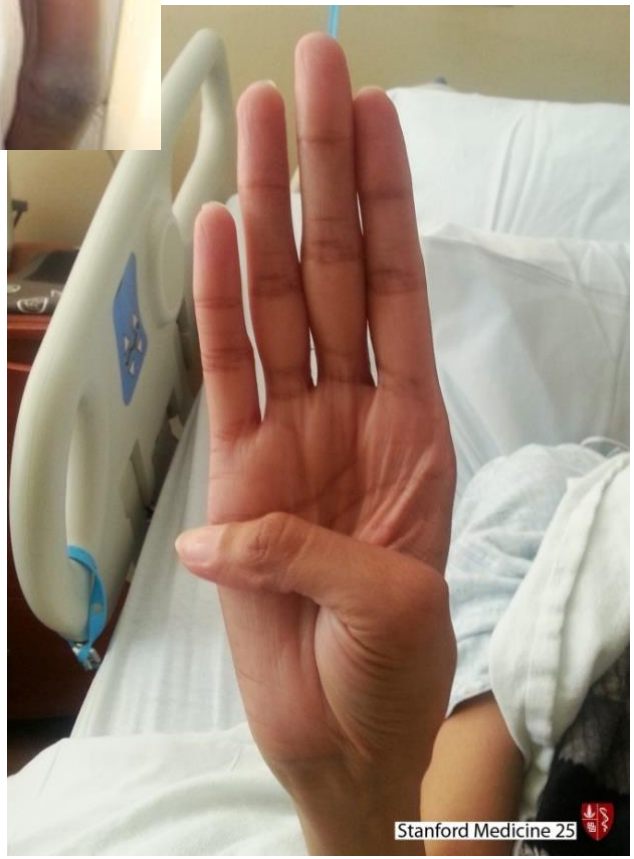


Fig. 1
This person with the Marfan syndrome is tall and thin and has an arm span that exceeds her height.

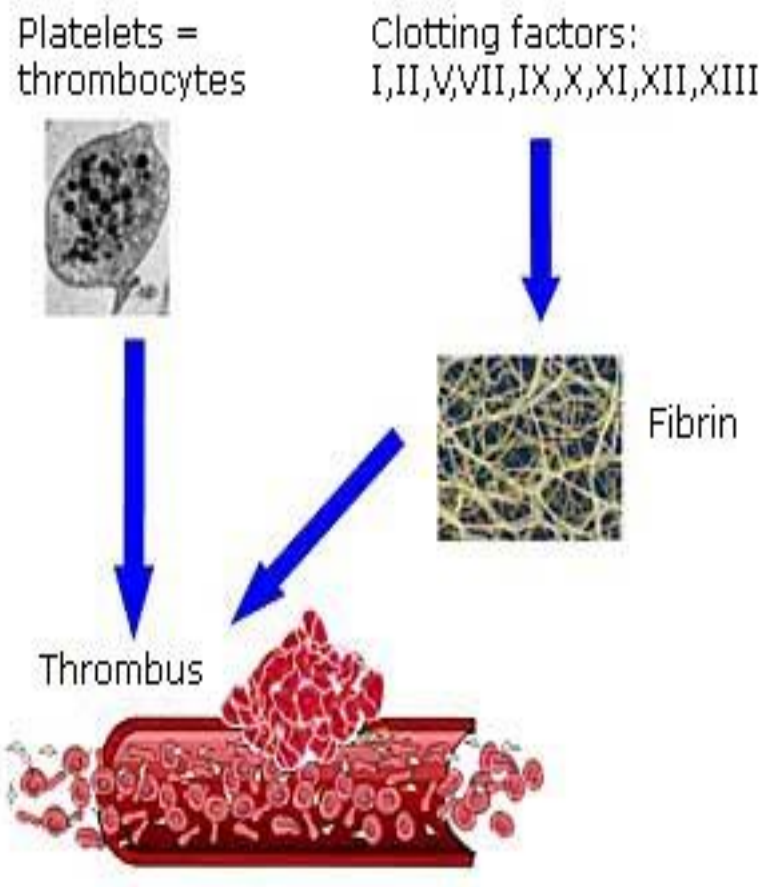

Stanford Medicine 25

Thrombophilia= hypercoagulable state

- is an abnormality of blood coagulation that increases the risk of thrombosis (blood clots in blood vessels).
- The most common types of congenital thrombophilia: Factor V Leiden mutation

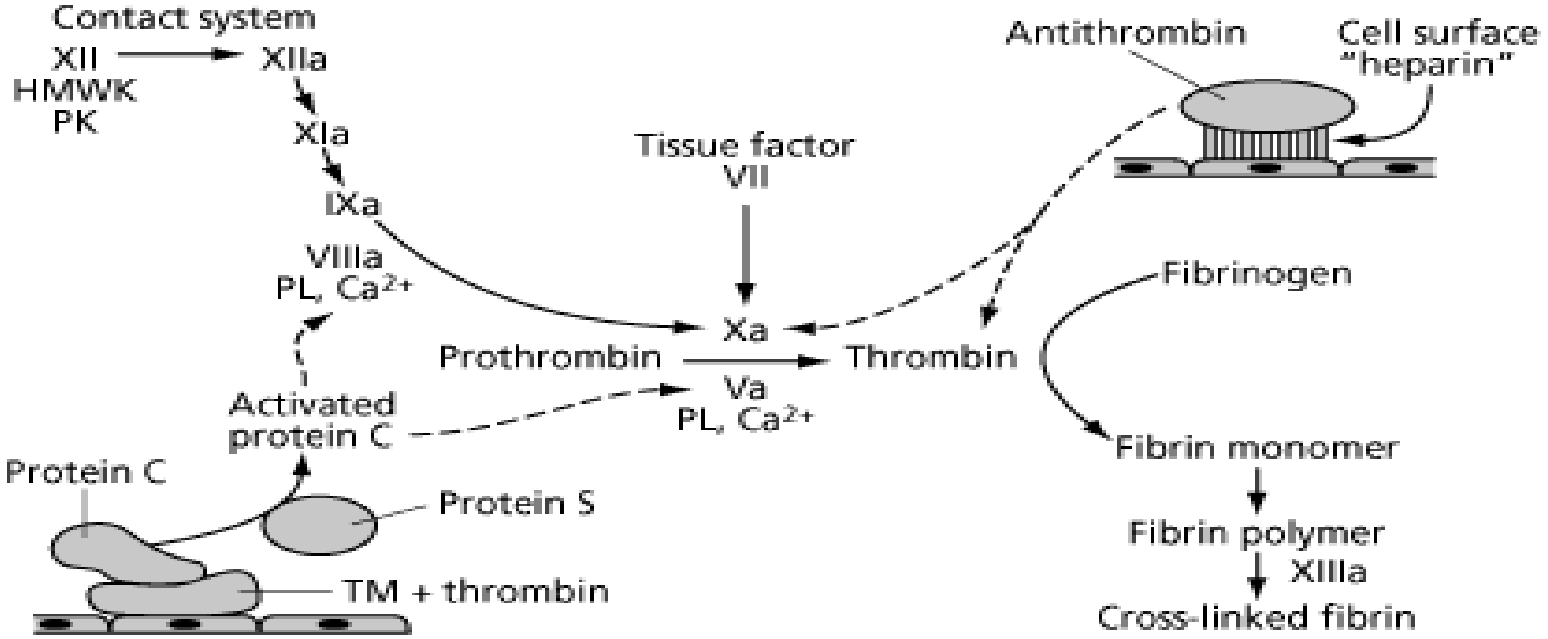
Factor V Leiden Mutation

- Autosomal Dominant Hypercoaguability Disorder (**incomplete penetrance**)
- Discovered in Leiden, Netherlands in 1994
- Most common genetic cause: G>A of F5 gene(chr 1)= arginine to glutamine=it facilitates overproduction of thrombin leading to generation of excess fibrin and excess clotting..



Mechanism of Hypercoaguability

- **Factor V** is a co-factor for the activation of thrombin
- **Protein C** is a natural anticoagulant and by cleaving Factor V arrests the clotting pathway because fibrin can no longer be formed
- The **Factor V Leiden** molecule has an abnormal shape making it resistant to APC resulting in a **hypercoaguable** state.



factor V remains active=overproduction of thrombin = excess fibrin and excess clotting=DVT

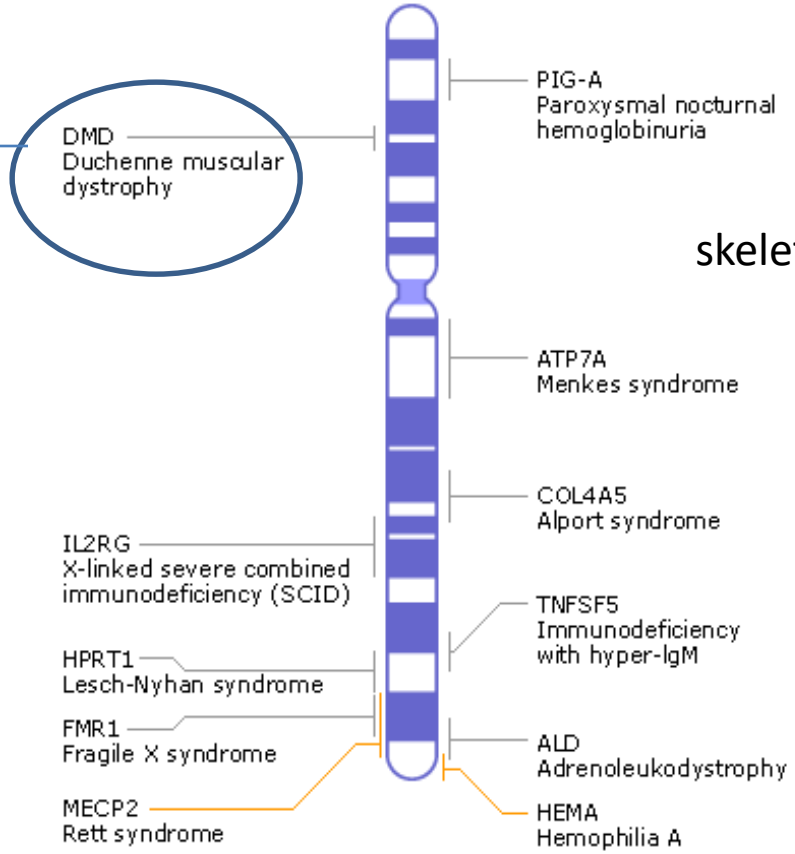
DVT=deep vein thrombosis

Duchenne muscular dystrophy (DMD)

is a recessive X-linked form of muscular dystrophy= muscle degeneration

The disorder is caused by a mutation/deletion in the gene dystrophin,

79 exons,>millions bp



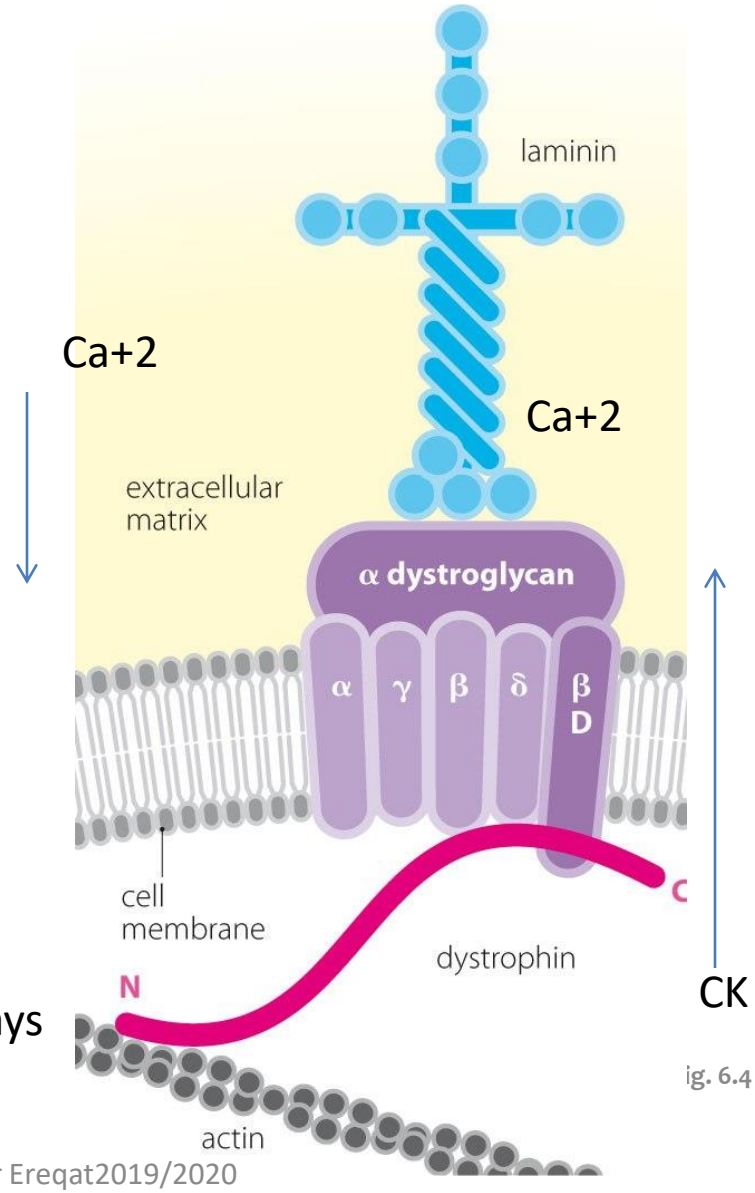
skeletal and cardiac muscle

Since the gene for DMD is carried on the X chromosome, it is usually the mother that passes the condition on to her children

Dystrophin

The dystrophin molecule anchors the cytoskeleton of muscle cells to the extracellular matrix, via the dystrophin glycoprotein complex.

.Muscle cells that lack dystrophin are mechanically fragile, and fail after a few years, hence progressive muscle weakness.



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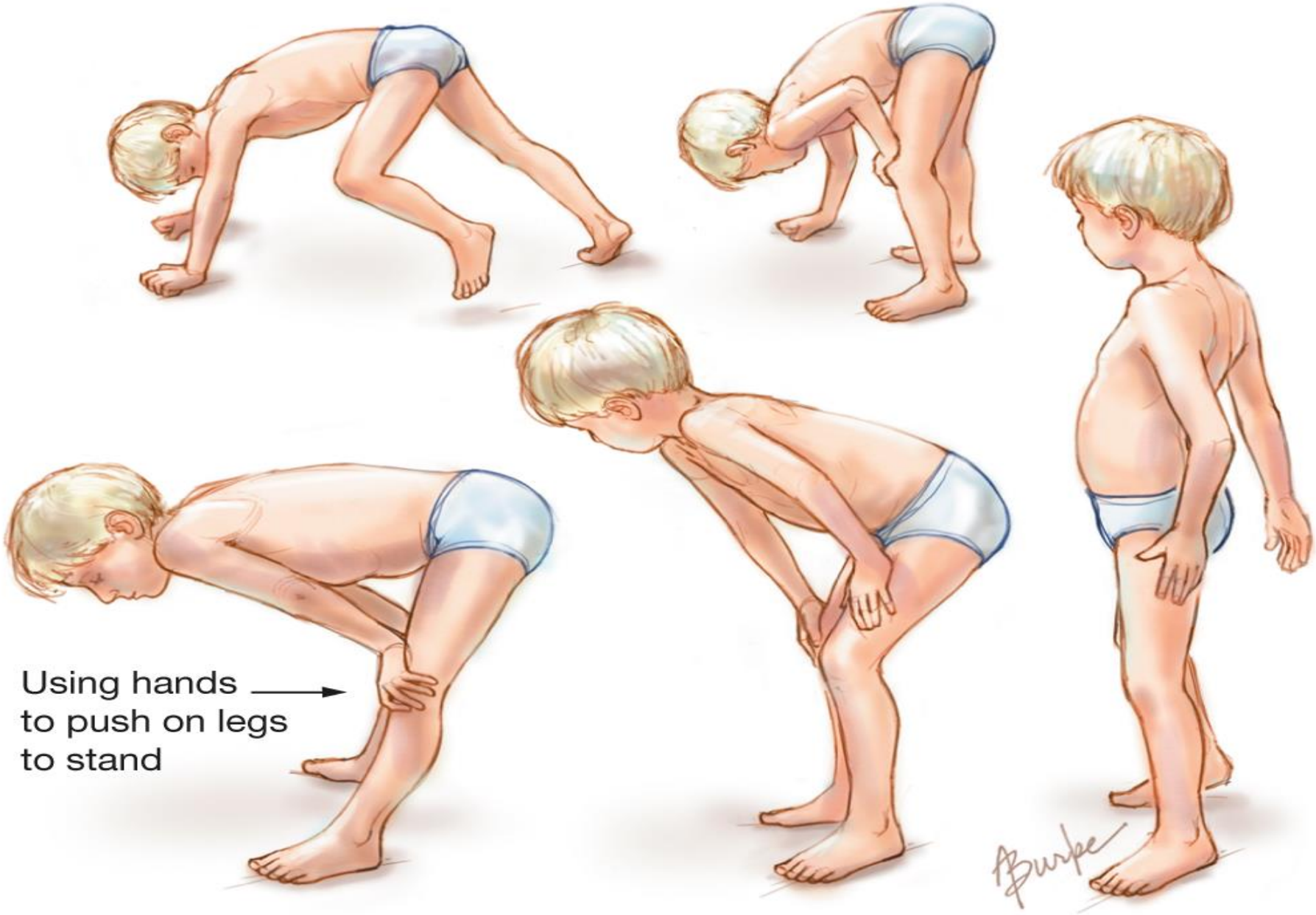
The absence of dystrophin permits excess calcium to penetrate the sarcolemma (the cell membrane) Alterations in calcium and signalling pathways cause water to enter into the mitochondria, which then burst=necrosis

Gowers Sign



Random X-Chromosome Inactivation

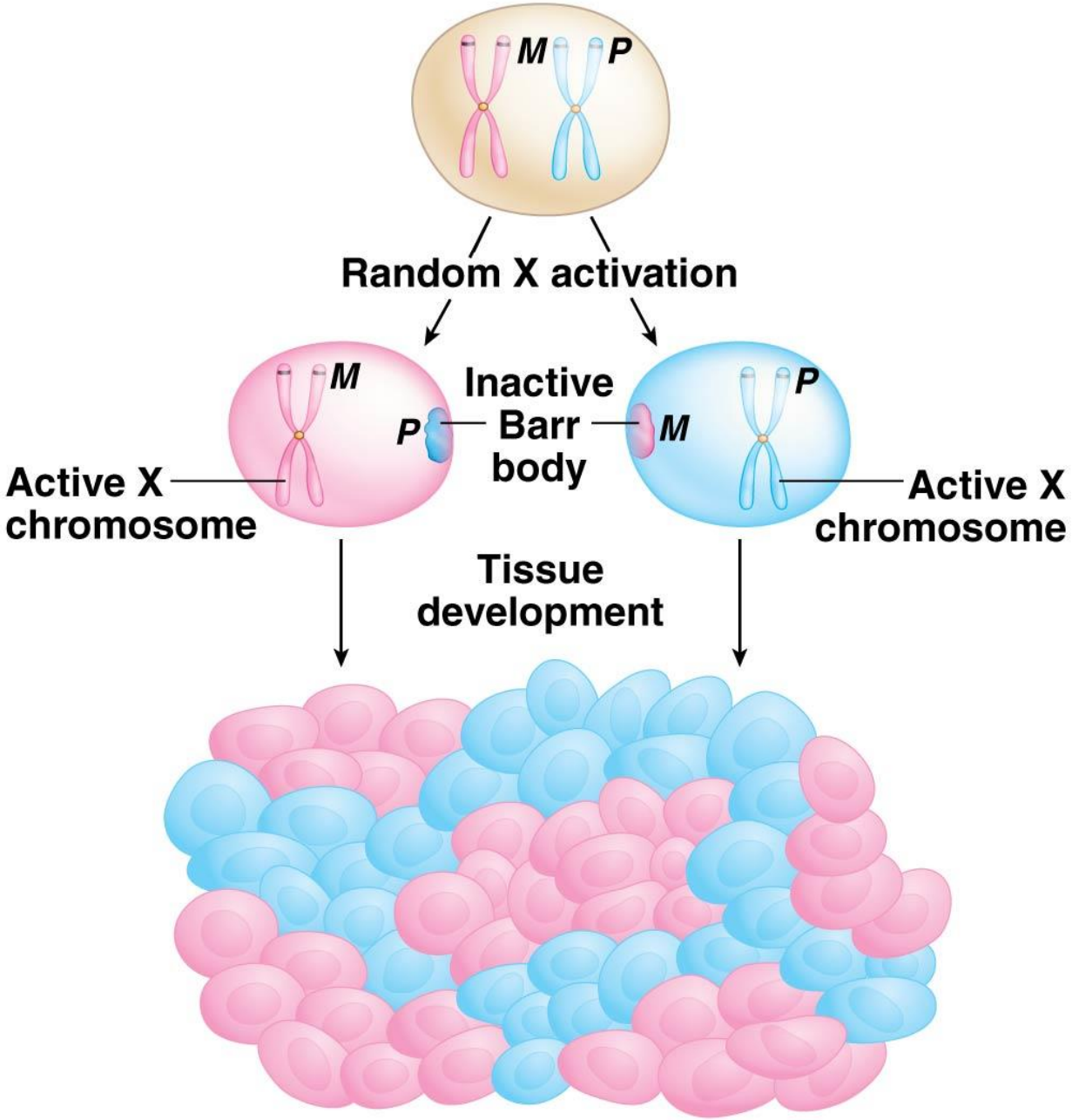
- Early in mammalian development, one of two X chromosomes in each female somatic cell is randomly inactivated

- The **random X inactivation hypothesis** is also called the **Lyon hypothesis**, after Mary Lyon, who first proposed it (1962)

- The inactive X chromosome is visible near the nuclear wall, as a condensed **Barr body**, first visualized by Murray Barr (1949)

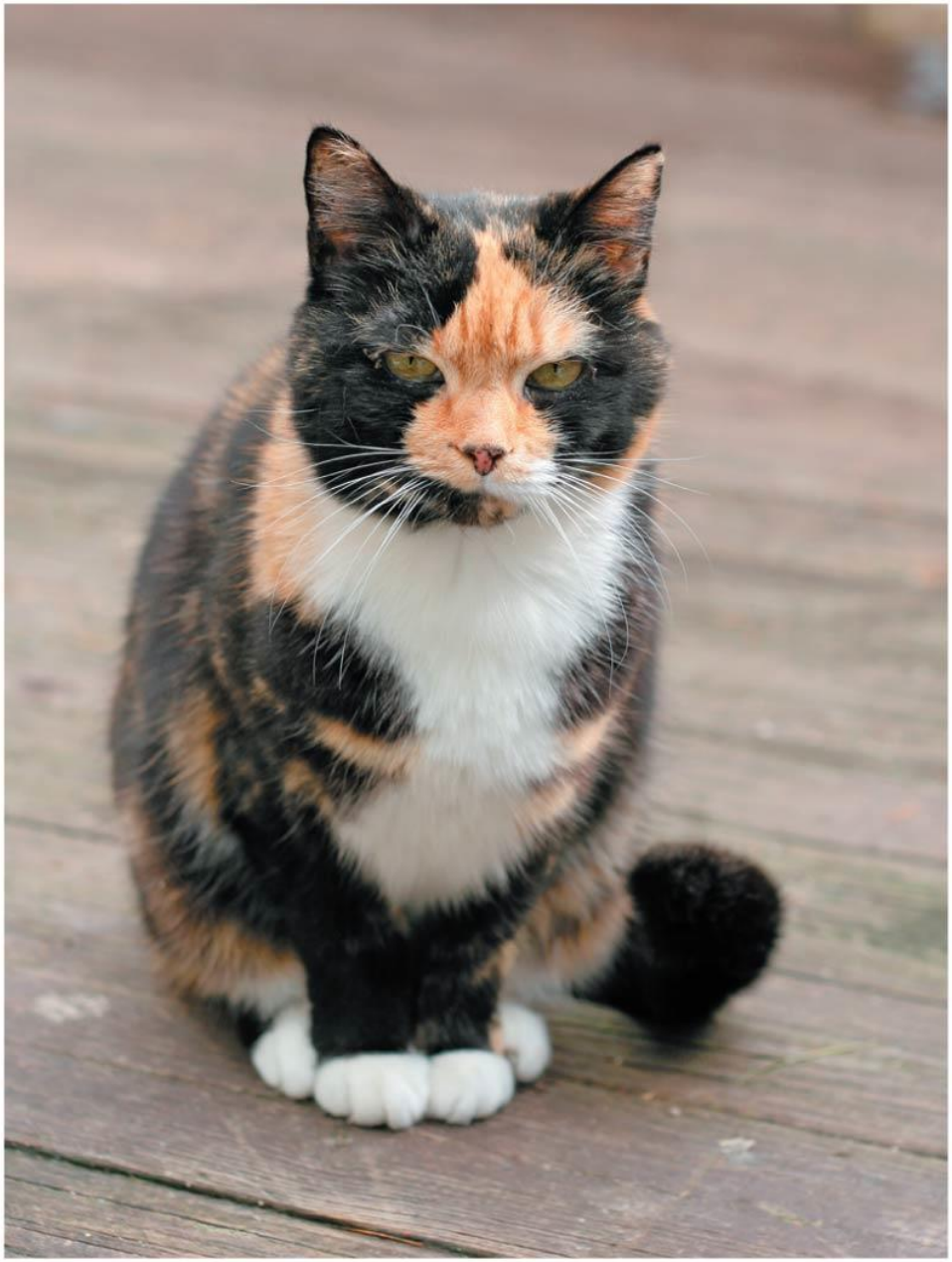
Female Mammals Are Mosaics

- Once X inactivation has occurred in a cell, it is permanent in all the descendants of that cell
- Female mammals are mosaics of two populations of cells; one expresses the maternal X and the other the paternal X
- Alleles of both chromosomes are expressed approximately equally over the whole organism


M
P
Random X activation
M
P
Inactive
Barr
body
M
P
Active X
chromosome
Active X
chromosome
Tissue
development

Calico Cats Are Visibly Mosaic

- In cats, the X chromosome carries a gene responsible for coat color
- One allele specifies a black color; the other a yellow color
- X inactivation in heterozygous females leads to a pattern of orange and black patches that is unique to each individual



Calico cat

Epistasis is a genetic condition in which certain alleles of one locus can alter the expression of alleles of a different locus