Lecture 11

- *Some disorders do not follow Mendelian patterns of inheritance.*
- *These disorders are clearly genetic (inherited) and their inheritance is classified as non-Mendelian.*
- *We now understand why some of these disorders do not follow Mendelian patterns and examples include:* ***mitochondrial inheritance***, ***unstable trinucleotide repeats***, *and* ***imprinting***.

MITOCHONDRIAL DNA (MTDNA)

- Mitochondria are double-membrane-bound organelles that are present in all nucleated eukaryotic cells and are responsible for the production of cellular energy required for the body to function through metabolic processes, in particular, oxidative phosphorylation
- The mitochondrion has been called the ‘powerhouse’ of the cell, as produce most of the energy.
- The most energy dependent organs are the brain, heart, skeletal muscle, kidney, endocrine glands and bone marrow and these are the organ systems commonly affected in mitochondrial diseases

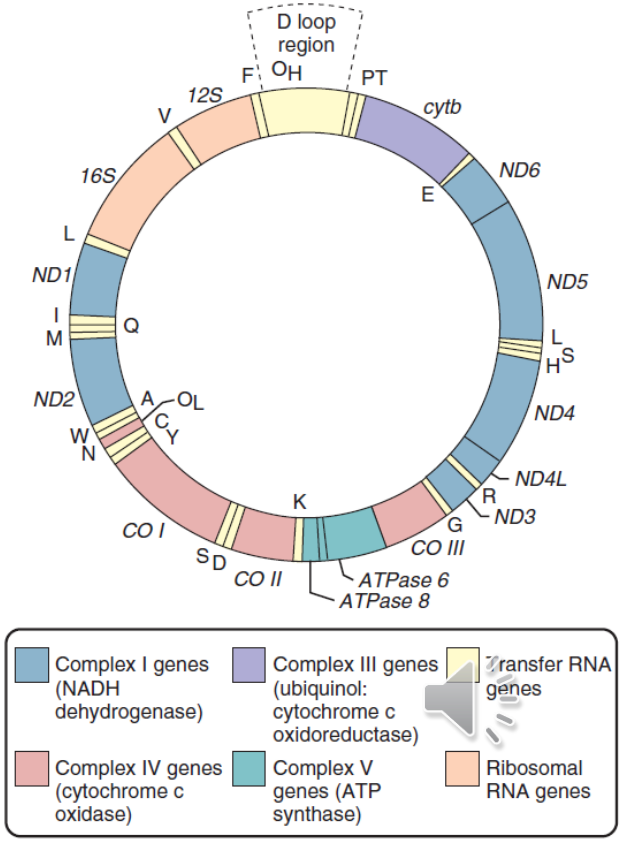
MITOCHONDRIAL INHERITANCE :

- Multiple copies of mtDNA exist within each cell and the total amount can vary between a few hundred and many tens of thousands of copies, depending on the cell type.
- mtDNA is usually a circular, double-stranded DNA molecule that is:
- Does not contain histones
- Is very compact, containing little repetitive DNA, and codes for essential enzymes involved in ATP production
- There are a few exceptions where mtDNA is linear, generally in lower eukaryotes such as yeast and some other fungi.
- mtDNA differs greatly in size among organisms.
- In animals, it is typically 16–18 kb (around 0.3% of total genome),
- Mutations in either the mtDNA or the nuclear genome underlie the largest collection of inborn errors of metabolism, and there is growing evidence that a gradual decline in mitochondrial activity is associated with aging and age-associated disorders.

MITOCHONDRIAL DNA (MTDNA)

- It carries relatively 37 genes
  - 2 rRNA and 22 tRNA genes
  - mRNA: Mammalian mitochondria contain their own genome (mtDNA), which encodes a total of 13 proteins that are all core components of oxidative phosphorylation.

- Nuclear genes: around 1300 (>99%) proteins are nuclear encoded and imported into the organelle mitochondria.

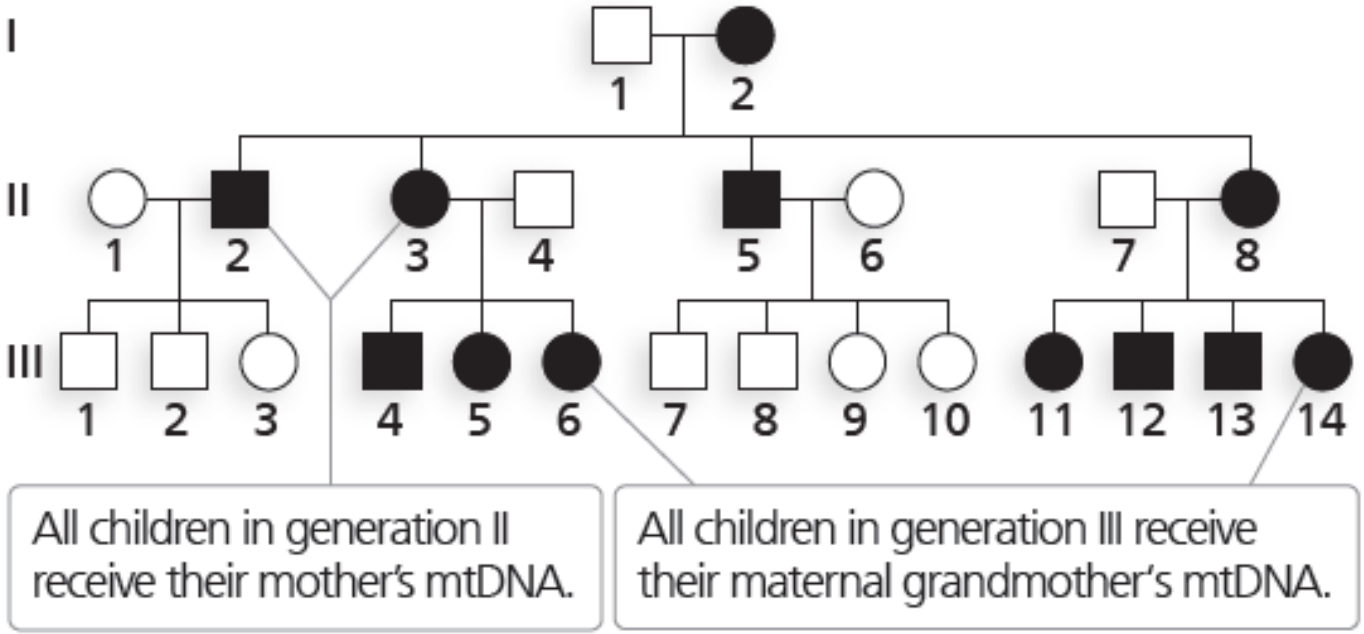


Mitochondrial Inheritance

- In humans, at fertilization, the ovum contributes significantly more cytoplasm to the zygote than does the sperm.
- The sperm mitochondria degenerate upon penetration of the ovum.
- Mitochondria in offspring are exclusively maternal in origin.

THE PATTERN OF INHERITANCE OF ORGANELLES

- Mutations in mitochondrial genes are also the cause of several single gene disorders.
- Mutation rate in mt is 10 times more than in nuclear DNA due to?



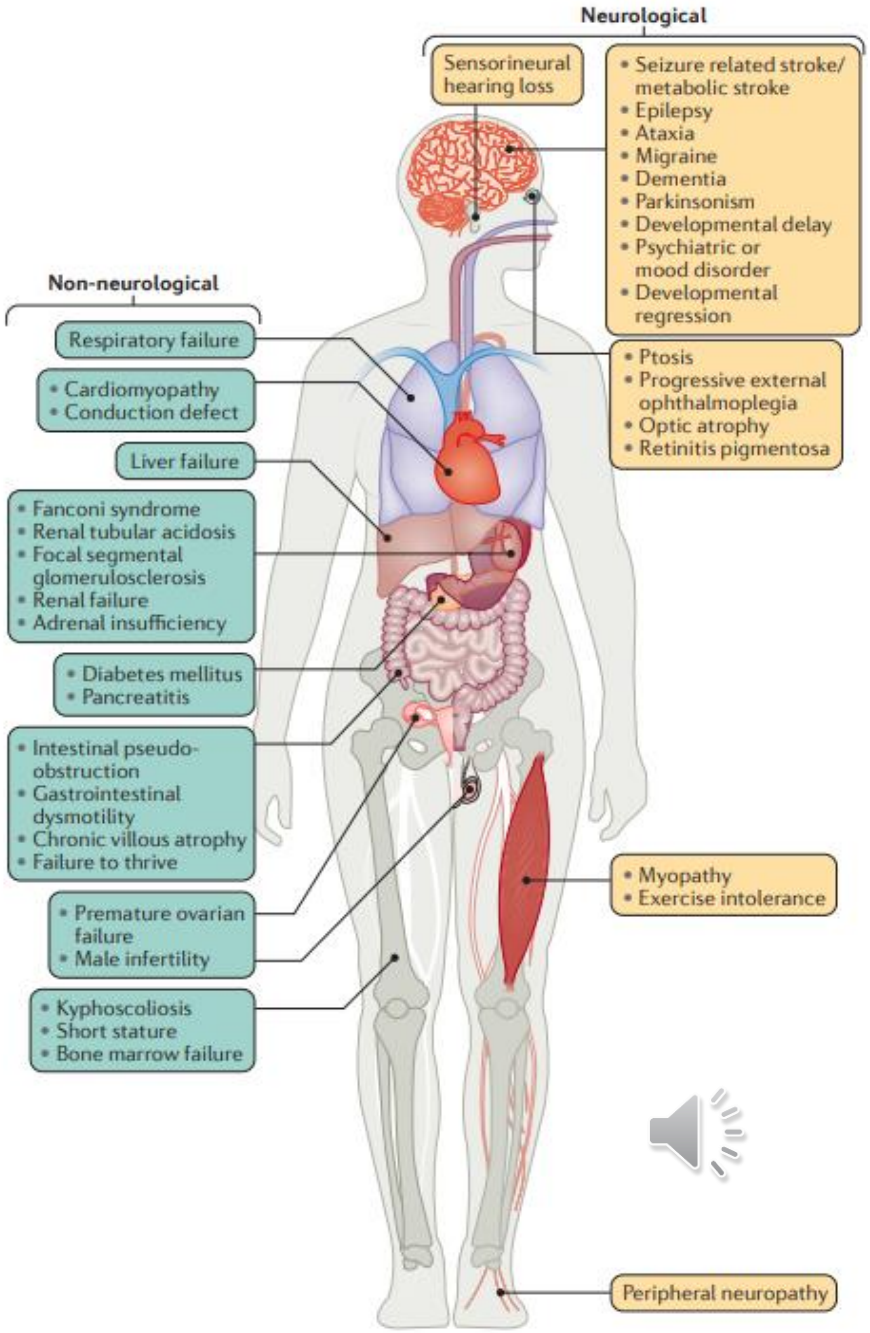
- Mother's children all inherit the trait.
- Father's children never inherit the trait!

The types of mitochondrial disease inheritance

- The pathophysiology of mitochondrial diseases is complex and involves genetic mutations in mitochondrial DNA (mtDNA) and nuclear DNA (nDNA).
- Autosomal and X-linked inheritance for nDNA
- Maternal inheritance for mtDNA mutations.
- de novo mutations

Mitochondrial diseases

- Mitochondria are under the dual control of mitochondrial DNA and nuclear DNA.
- More than 40 known types
- Mitochondrial disease is a difficult disorder to identify because it can take many forms and range from mild to severe.
- Such disorders are heterogeneous, genetically inherited and can affect an individual at any age and in any body organ, including nerves, the brain and other major organs.
- Mitochondrial disease is a chronic, genetic disorder that occurs when the mitochondria of the cell fails to produce enough energy for cell or organ function.



How Common is Adult Mitochondrial Disease?

Mitochondrial dysfunction can arise because of defects in either mitochondrial DNA or nuclear mitochondrial genes, and can present in childhood or adulthood in association with vast clinical heterogeneity, with symptoms affecting a single organ or tissue, or multisystem involvement.

These include

- Type II Diabetes Mellitus,
- Parkinson Disease,
- Atherosclerotic Heart Disease,
- Stroke,
- Alzheimer Dementia, and
- Cancer.

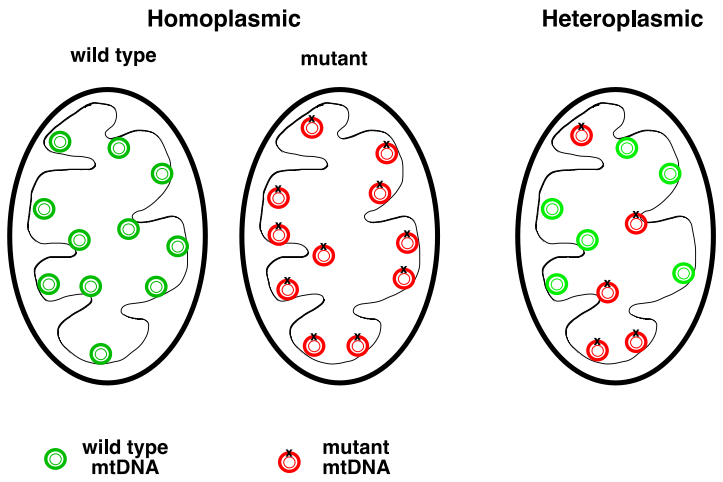
it is clear that mitochondria are involved because their function is measurably disturbed. Even autoimmune diseases such as Multiple Sclerosis, Systemic Lupus Erythematosus, and Rheumatoid Arthritis appear to have mitochondrial components.

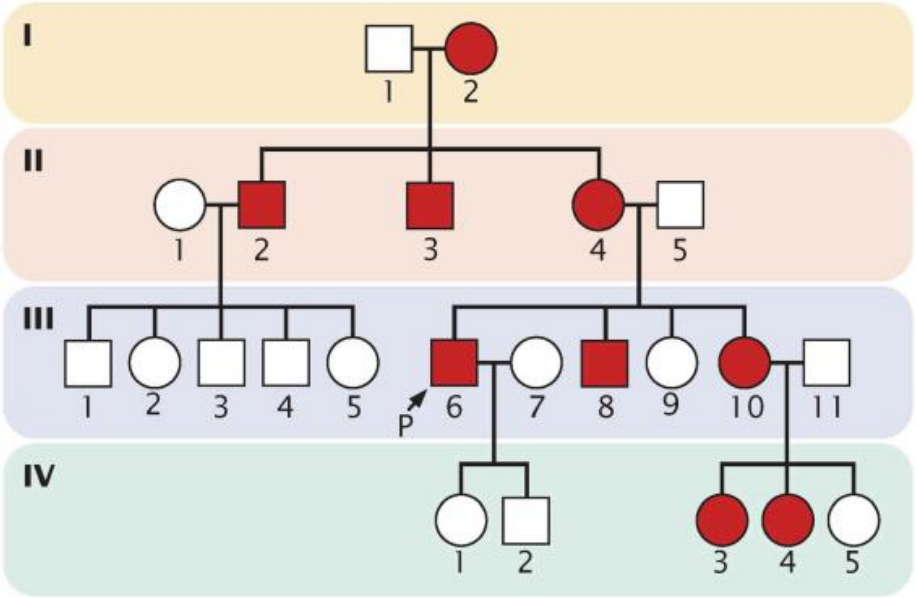
Examples of Diseases Due to Mutations and Deletions in Mitochondrial DNA

Abbreviation	MIM No.	Designation
LHON	535000	Leber's hereditary optical neuropathy (Missence M)
MELAS	540000	Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
	540050	Lactic acidosis with stroke-like signs (Single base M)
MERRF	545030	Myoclonic epilepsy and ragged red fibers (Single base M)
MMC	590050	Maternally inherited myopathy and cardiomyopathy
NARP	551500	Neurogenic muscular weakness with ataxia and retinitis pigmentosa
CEOP	258470	Progressive external ophthalmoplegia
KSS	530000	Kearns-Sayre syndrome (ophthalmoplegia, pigmental degeneration of the retina, and cardiomyopathy)
PEAR	557000	Pearson syndrome (bone marrow and pancreatic failure)
ADMIMY	157640	Autosomal dominant inherited mitochondrial myopathy with mitochondrial deletion in the D loop (type Zeviani)

- A typical human cell — including the egg cell — contains only **one nucleus but hundreds to thousands of mitochondria**. A single cell can contain both mutant mitochondria and normal mitochondria, and the balance between the two will determine the cell's health.
- This helps explain why the symptoms of mitochondrial disease can vary so much from person to person, even within the same family.
- Imagine that a woman's egg cells (and other cells in her body) contain both normal and mutant mitochondria, and that some have just a few mutant mitochondria, while others have many. A child conceived from a "mostly healthy" egg cell probably won't develop disease, and a child conceived from a "mostly mutant" egg cell probably will.
- Also, the woman may or may not have symptoms of mitochondrial disease herself.
- **These diseases also can arise in a *sporadic* fashion, meaning they may occur with no family history.**

Heteroplasmy vs. Homoplasmy





•***Heteroplasmy:*** A cell that has some mitochondria that have a mutation in the mtDNA and some that do not.

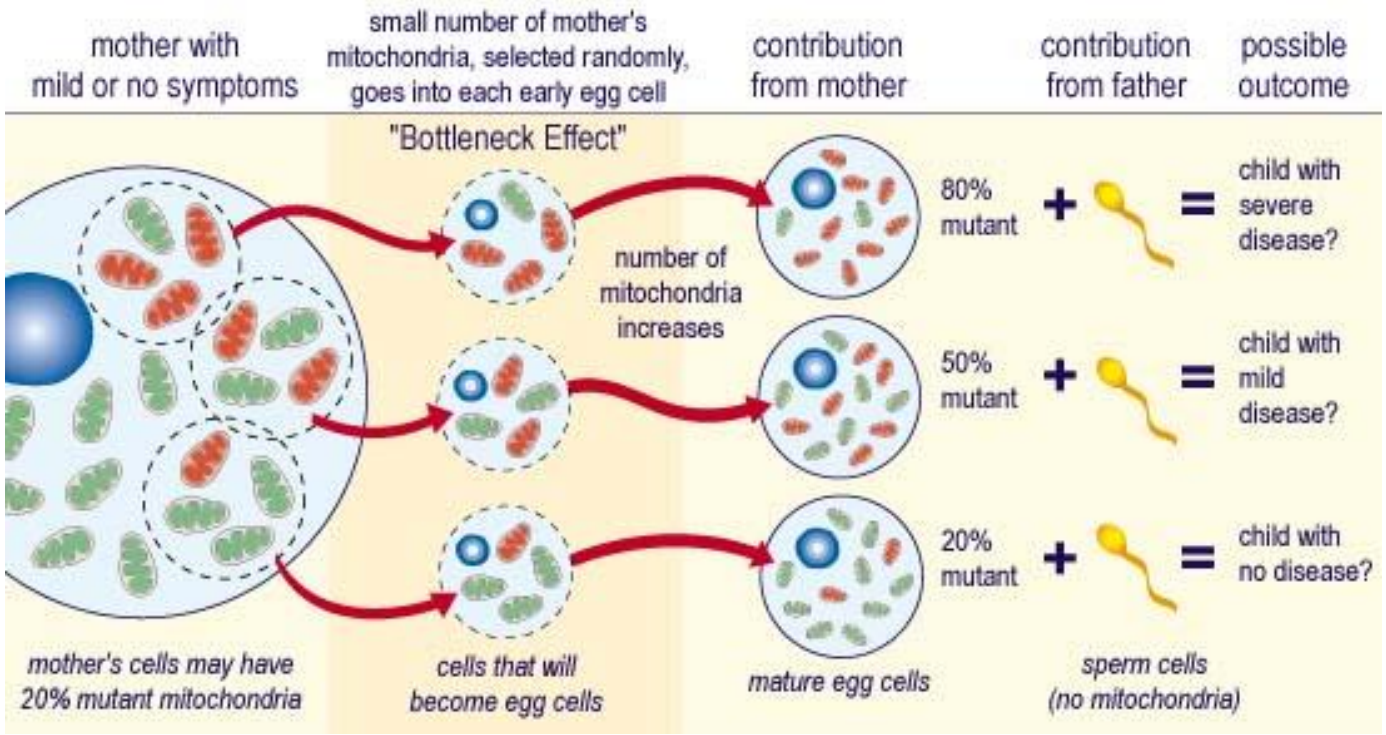
•The proportion of mutant mtDNA molecules determines both the penetrance and severity of expression of some diseases.

•***Homoplasmy***: A cell that has a uniform collection of mtDNA: either completely normal mtDNA or completely mutant mtDNA.

•A unique feature of mtDNA is that, at cell division, the mtDNA replicates and sorts randomly among mitochondria. In turn, the mitochondria sort randomly among daughter cells. Therefore, in cells where heteroplasmy is present, each daughter cell may receive different proportions of mitochondria carrying normal and mutant mtDNA.

MATERNAL INHERITANCE OF MITOCHONDRIAL DNA MUTATIONS

red mitos are mutant, green are normal



- The severity of the condition is dependent on the number of disabled mitochondria present in the egg.
- An egg with **a large** number of disabled mitochondria would result in a child with severe abnormalities
- An egg with only **a few** disabled mitochondria would result in an individual only mildly affected.

Trinucleotide Repeats

- Some disorders were observed to increase in severity from one generation to another,
- and/or the age of onset of symptoms became earlier in successive generations.
- This was termed **anticipation** and the mechanism was a mystery since mutations were presumed to be inherited in a stable manner from one generation to another.
- Furthermore, in some disorders the sex of the parent who passed on the disorder seemed to influence the severity or age of onset of symptoms.
- This too was a puzzle because in Mendelian traits maternal and paternal DNA was assumed to be equivalent.
- Anticipation and **parent of origin** effects are now known to be due to a novel type of **dynamic mutation** known as unstable trinucleotide repeats.

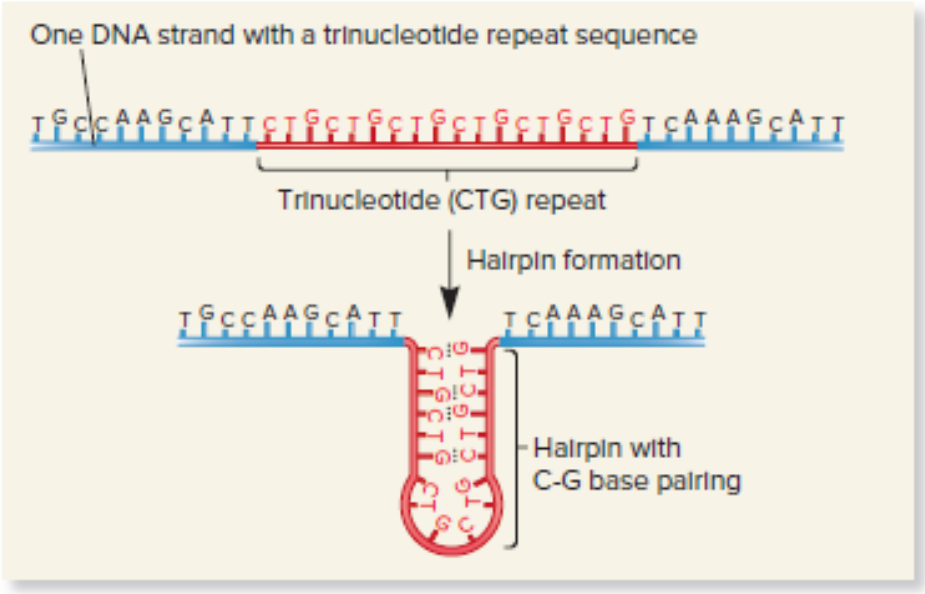
TABLE 19.5

TNRE Disorders

Disease*	SBMA	HD	SCA1	FRAXA	FRAXE	DM
Repeated Triplet	CAG	CAG	CAG	CGG	GCC	CTG
Location of Repeat	Coding sequence	Coding sequence	Coding sequence	5′-UTR	5′-UTR	3′-UTR
Number of Repeats in Unaffected Individuals	11–33	6–37	6–44	6–53	6–35	5–37
Number of Repeats in Affected Individuals	36–62	27–121	43–81	>200	>200	>200
Pattern of Inheritance	X-linked	Autosomal dominant	Autosomal dominant	X-linked	X-linked	Autosomal dominant
Disease Symptoms	Neuro-degenerative	Neuro-degenerative	Neuro-degenerative	Mental impairment	Mental impairment	Muscle disease
Anticipation†	None	Male	Male	Female	None	Female

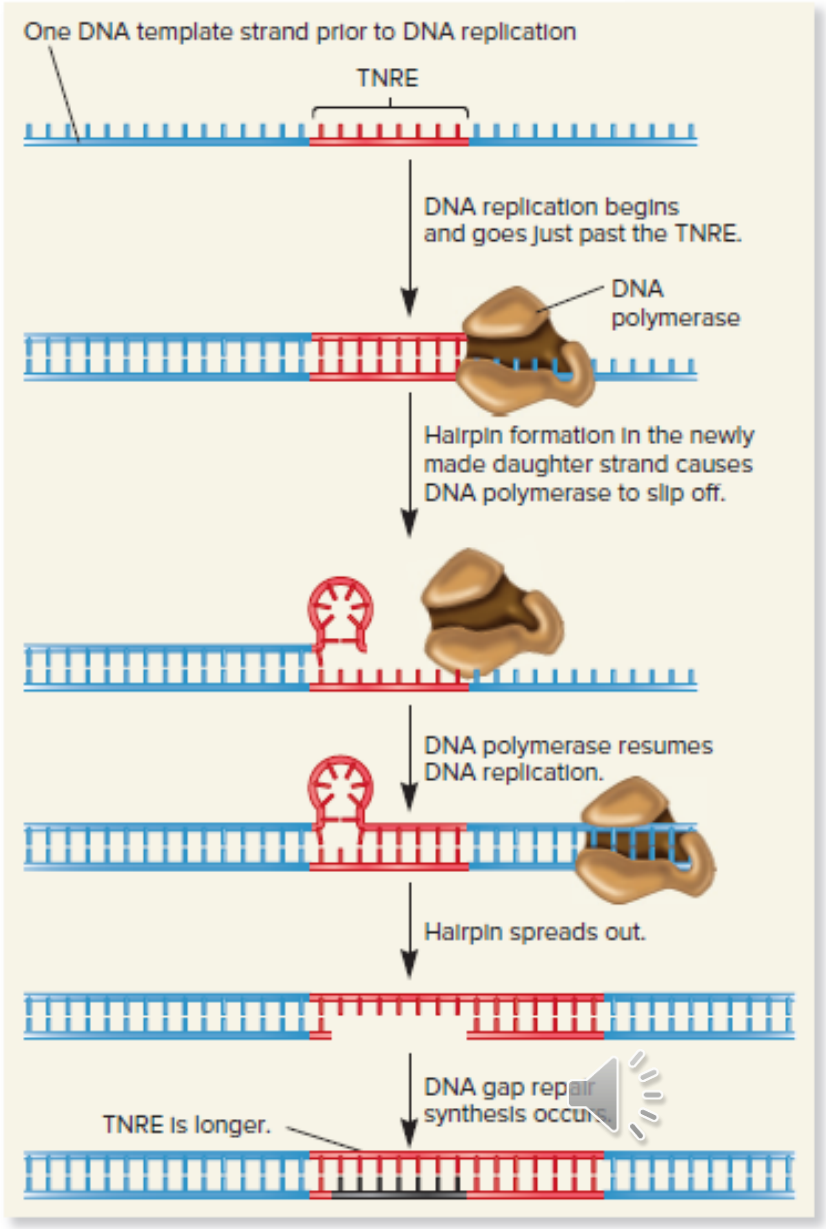
*SBMA, spinal and bulbar muscular atrophy; HD, Huntington disease; SCA1, spinocerebellar ataxia; FRAXA and FRAXE, fragile X syndromes; DM, *dystrophia myotonica* (myotonic muscular dystrophy).
†Indicates the sex of the parent from whom the disease is usually inherited when anticipation occurs.

- Anticipation usually depends on whether the disease is inherited from the mother or father.



(a) Formation of a hairpin with a trinucleotide (CTG) repeat sequence

- A triplet repeat can form a hairpin, also called a stem-loop
- During DNA replication can lead to an increase in the length of a DNA region if it occurs in the newly made daughter strand.
- DNA polymerase may temporarily slip off the template strand.
- Next, DNA polymerase back onto the template strand and resumes DNA replication from the end of the hairpin.
- When this occurs, DNA polymerase is synthesizing most of the hairpin region twice.



(b) Mechanism of trinucleotide repeat expansion

Trinucleotide Repeats

Examples:

- Fragile X Mental Retardation syndrome
- Huntington disease
- myotonic dystrophy
- spinocerebellar ataxia
- Kennedy disease
- Joseph disease
- Friedreich Ataxia

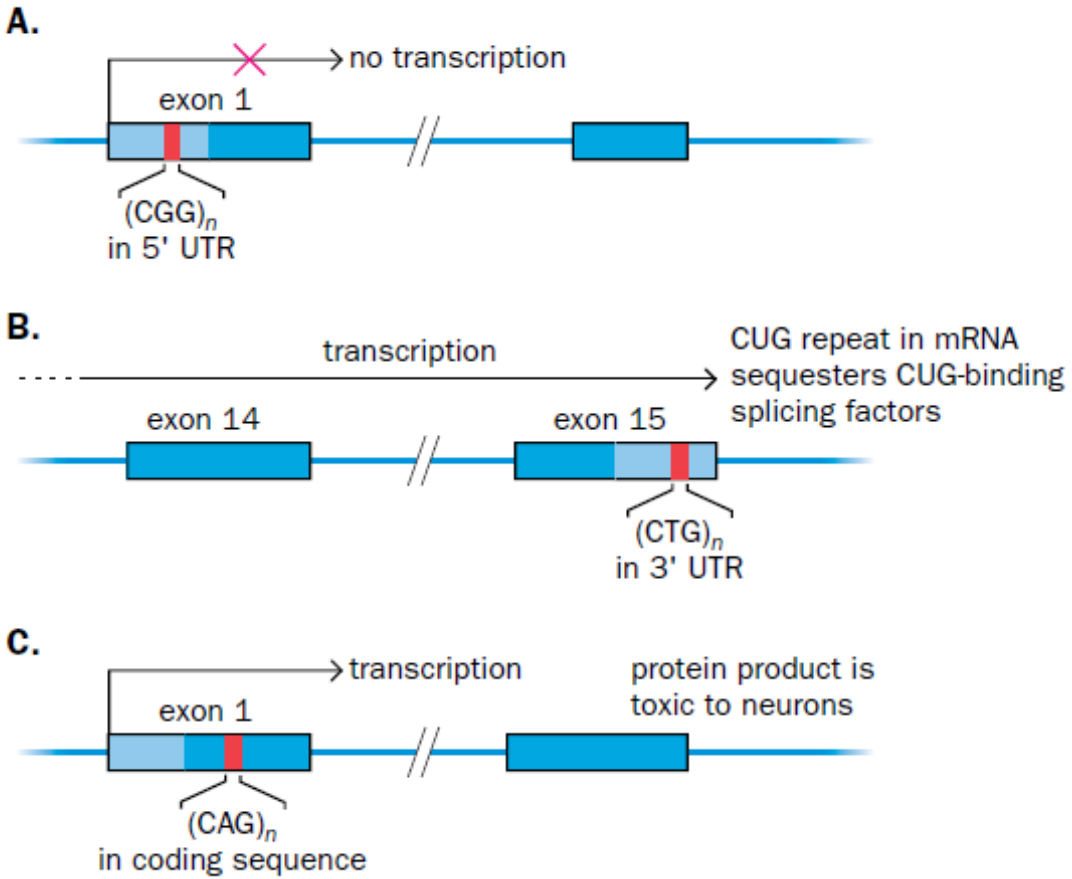


Figure 16.13 Three mechanisms by which dynamic mutations may be pathogenic.

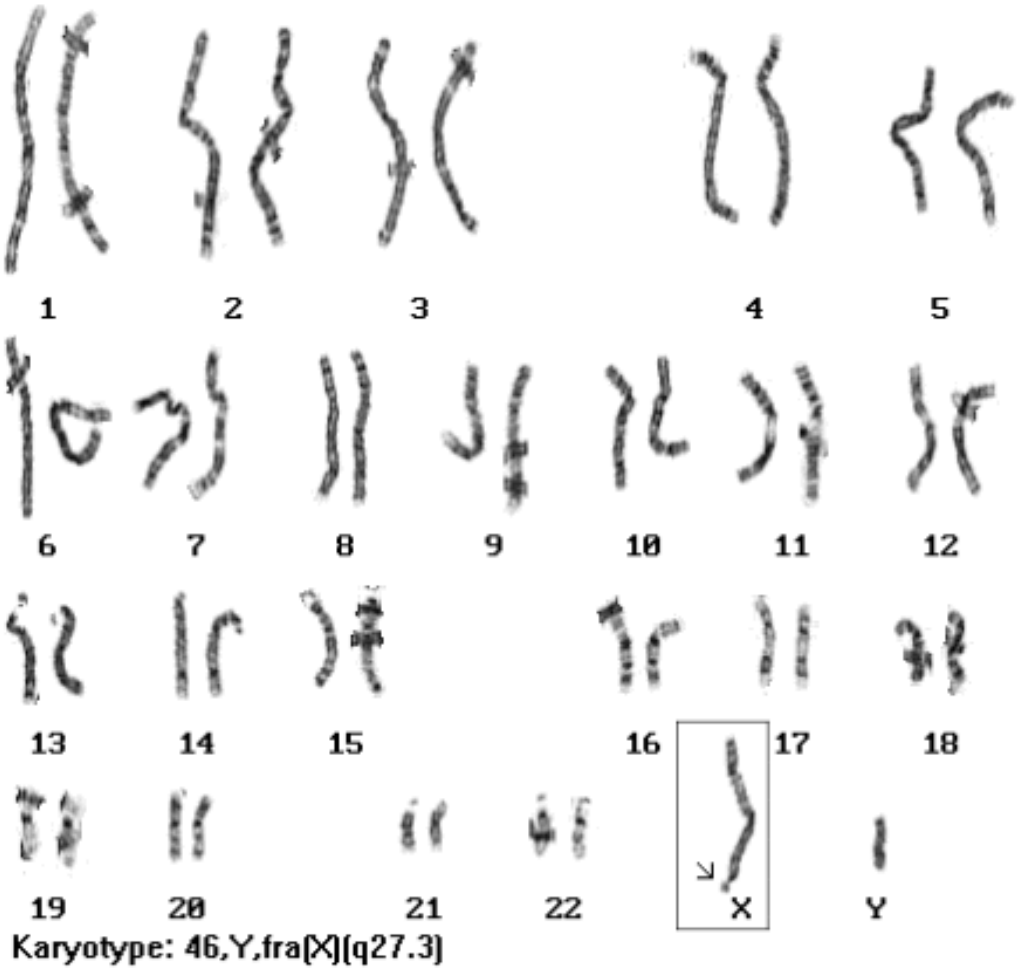
(A) In fragile X syndrome, the expanded repeat in the 5′ UTR of the gene triggers methylation of the promoter and prevents transcription.

(B) In myotonic dystrophy, the expanded repeat in the 3′ UTR causes the mRNA transcript to prevent the correct splicing of several unrelated genes.

(C) In Huntington disease, the gene containing the expanded repeat is transcribed and translated as normal, but the protein product has an expanded polyglutamine tract that renders it toxic.

Fragile X Syndrome

A fragile site close to the telomere at the end of the long arm at Xq27.3



Fragile X MR Syndrome

FX MR Clinical Features

Most common cause of inherited mental retardation in males.

Phenotype in males includes moderate mental retardation, large head, long face, prominent forehead and chin, protruding and larger ears, large testes after puberty, speech delay, and loose joints. Behavior abnormalities include hyperactivity, hand flapping, hand biting, temper tantrums and sometimes autism spectrum disorder.

1. Approximately 50% of female carriers of a full mutation have mental retardation that is usually less severe than in affected males.
2. About 30% of males who carry a premutation will develop Fragile X-associated tremor/ataxia syndrome (FXTAS) which is characterized by late-onset, progressive cerebellar ataxia and intention tremor.
3. About 20% of females who carry a premutation will develop premature ovarian failure (POF).

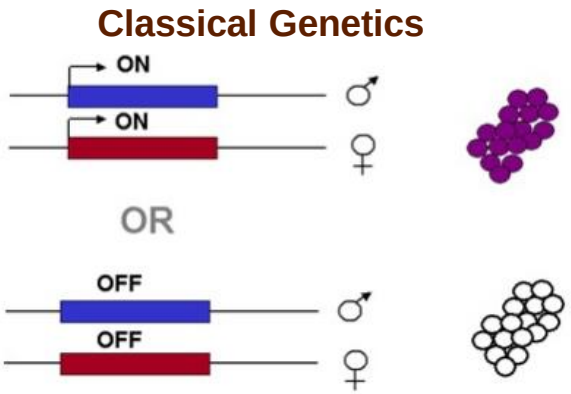
Number of Triplet Repeats (Normal Range 5–44)
Males
45–54 (intermediate alleles)
55–200 (premutation)
200–2000 (full mutation)
Females
45–54 (intermediate alleles)
55–200 (premutation)
200–2000 (full mutation)

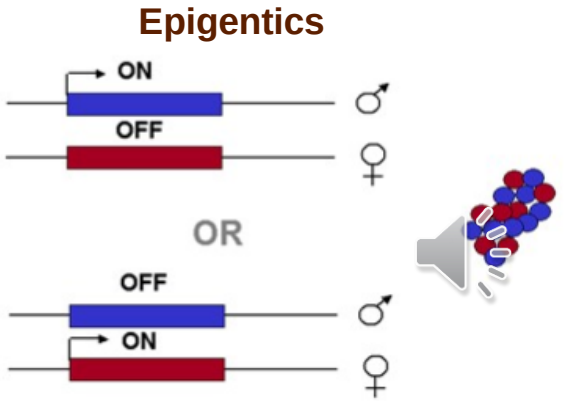
Genetic Features

- Atypical X-linked inheritance showing parent of origin effect.
- In affected males associated with a fragile site at Xq27.3 in 10-40% of metaphase spreads, however, this cytogenetic testing is no longer used for diagnostic testing.
- Amplified ‘CGG’ trinucleotide repeat as well as abnormal methylation (hypermethylation) of the FMR-1 gene. The normal protein product, FMRP, is an RNA-binding protein that seems to function as a nucleocytoplasmic shuttling protein and it binds several mRNAs including its own. It also seems to affect cytoskeletal structure, synaptic transmission and neuronal maturation.
- The FMR-1 gene mutation results in gene silencing and the loss of function results in suppression of translation of proteins from its RNA targets.

Epigentics

- Cells normally have two copies (alleles) of autosomal genes on chromosomes other than the X and Y.
- One allele is inherited from the mother (maternal allele) and one is inherited from the father (paternal allele).
- For most genes, both copies are expressed by the cell. However, a small class of genes is “monoallelically” expressed.





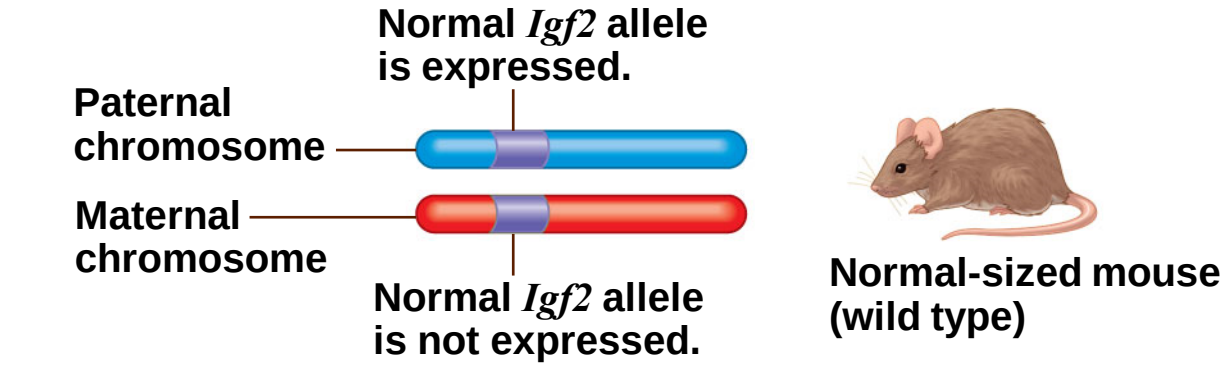
Epigentics

- Genomic imprinting: A small class of genes shows monoallelic expression, where a single allele in a cell is preferentially expressed
- Offspring expresses either the maternally-inherited or the paternally-inherited allele but not both (parent-of-origin expression)
- Imprinted genes - functionally haploid
- In most cases of genomic imprinting, the copy of a gene inherited from one parent is transcriptionally inactive in all or most of the tissues in which the copy from the other parent is active.
- The term “imprinting” signifies that whatever silences the maternal or paternal copy of an imprinted gene is not encoded in its DNA sequence but due to epigenetic alteration

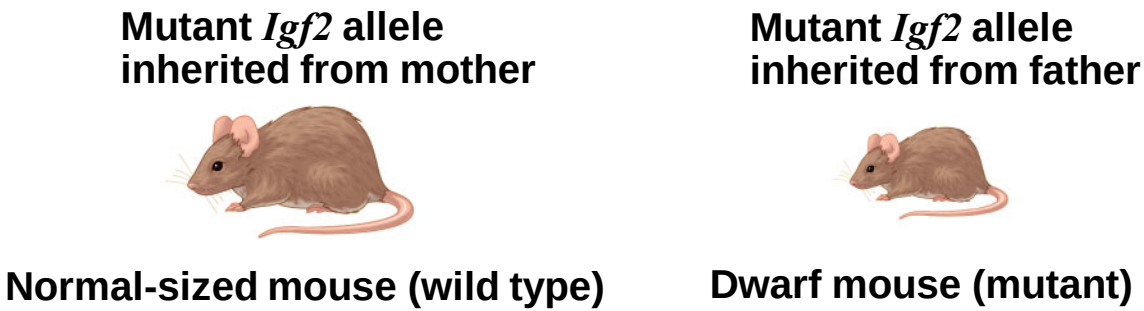
GENOMIC IMPRINTING

- genomic imprinting involves the transmission of epigenetic information, in the form of DNA methylation marks, from gametes to offspring, with the result that a set of genes (both protein coding genes and non-coding RNA genes) are expressed from only one of the two chromosomes in cells.
  - At present, over 100 genes have been confirmed to be imprinted in humans.
  - These genes tend to have important roles in development and the loss of imprinting is implicated in a number of genetic diseases and types of cancer in humans.

Figure 15.17



(a) Homozygote



(b) Heterozygotes

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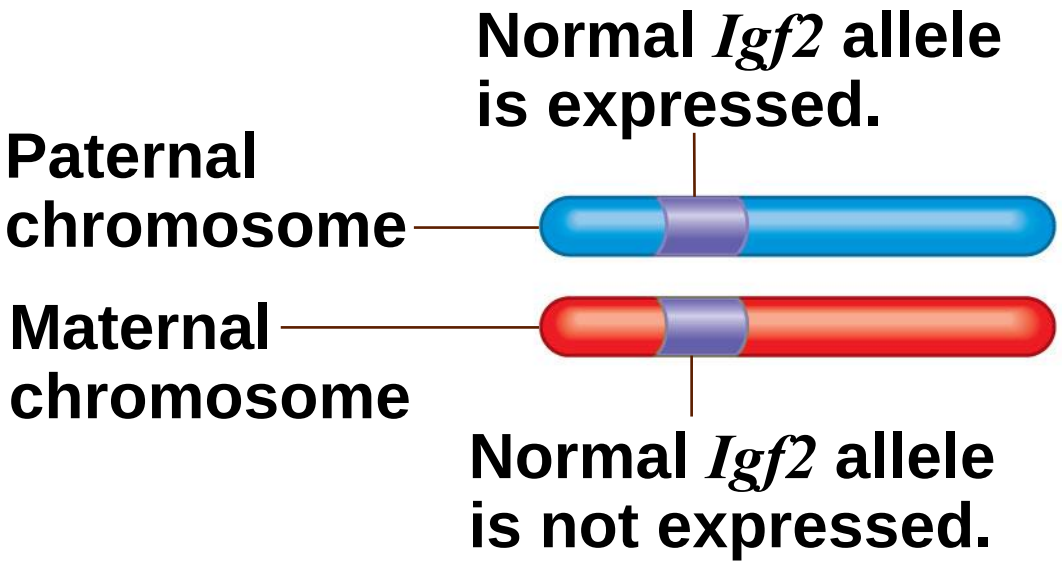
Figure 15.17a



(a) Homozygote

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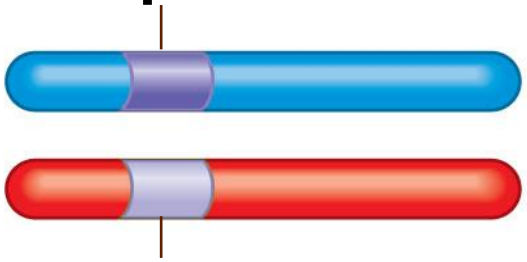
Normal-sized mouse (wild type)

Figure 15.17b

Mutant *Igf2* allele inherited from mother

Normal-sized mouse (wild type)

Normal *Igf2* allele is expressed.

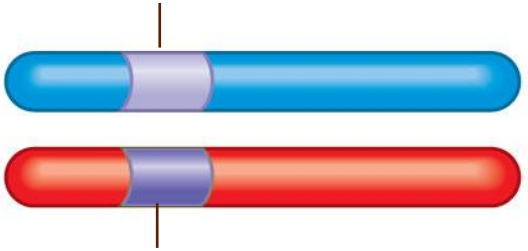


Mutant *Igf2* allele is not expressed.

Mutant *Igf2* allele inherited from father

Dwarf mouse (mutant)

Mutant *Igf2* allele is expressed.



Normal *Igf2* allele is not expressed.

(b) Heterozygotes

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Genomic imprinting is essential for normal development

- Many common cancers

  Paternally-expressed imprinted genes enhance growth/proliferation; some are 'oncogenes'

  ❑ Hypomethylation (20-60% less)=> chromosome instability + oncogene activation

  - IGF2 (Insulin-like Growth Factor 2)

    Function: IGF2 promotes fetal growth and development by stimulating cell proliferation and inhibiting apoptosis. It plays a vital role in prenatal growth by acting as a mitogen.

    Consequences of Dysregulation:

    - Beckwith-Wiedemann Syndrome (BWS): a disorder characterized by overgrowth, increased risk of embryonal tumors such as Wilms' tumor, and other developmental abnormalities.
    - Overexpression of IGF2 is associated with BWS, leading to overgrowth and an increased risk of childhood tumors.
    - Cancer: Aberrant IGF2 expression is linked to several cancers, including colorectal, liver, and breast cancers. Elevated IGF2 levels can promote tumor growth and survival.

Genomic imprinting is essential for normal development

- Maternally-expressed Imprinted genes constrain growth/proliferation; some are ‘tumor suppressors’
  - Hypermethylation => tumor suppressor genes silenced

E.g. CDKN1C

- **Function**: CDKN1C encodes a cyclin-dependent kinase inhibitor that controls cell cycle progression by inhibiting cyclin/CDK complexes.
  - **Consequences of Dysregulation**:
    - **Beckwith-Wiedemann Syndrome (BWS)**: Loss of function or reduced expression of CDKN1C is associated with BWS, a disorder characterized by overgrowth, increased risk of embryonal tumors such as Wilms' tumor, and other developmental abnormalities.
    - **Cancer**: As a tumor suppressor, reduced expression or mutations in CDKN1C can lead to uncontrolled cell proliferation and contribute to cancer development.

Genomic imprinting and neurodevelopmental disorders

Three disorders that are the result of either direct or indirect deregulation of imprinted genes.

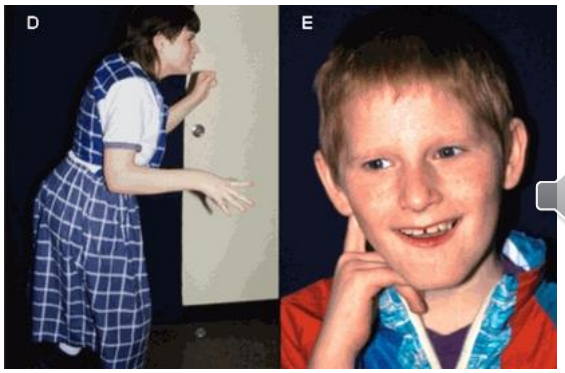
- Prader-Willi syndrome
- Angelman syndrome
- Rett syndrome

- Genes associated with both Prader–Willi syndrome and Angelman syndrome map to the long (q) arm of chromosome 15 (15q11-13).
- Prader-Willi Syndrome - obesity, mental retardation, short stature. (abbreviated PWS)
- Angelman Syndrome - uncontrollable laughter, jerky movements, and other motor and mental symptoms. (abbreviated AS) Syndrome

Defects in genomic imprinting lead to Prader-Willi syndrome (PWS) and Angelman syndrome (AS)

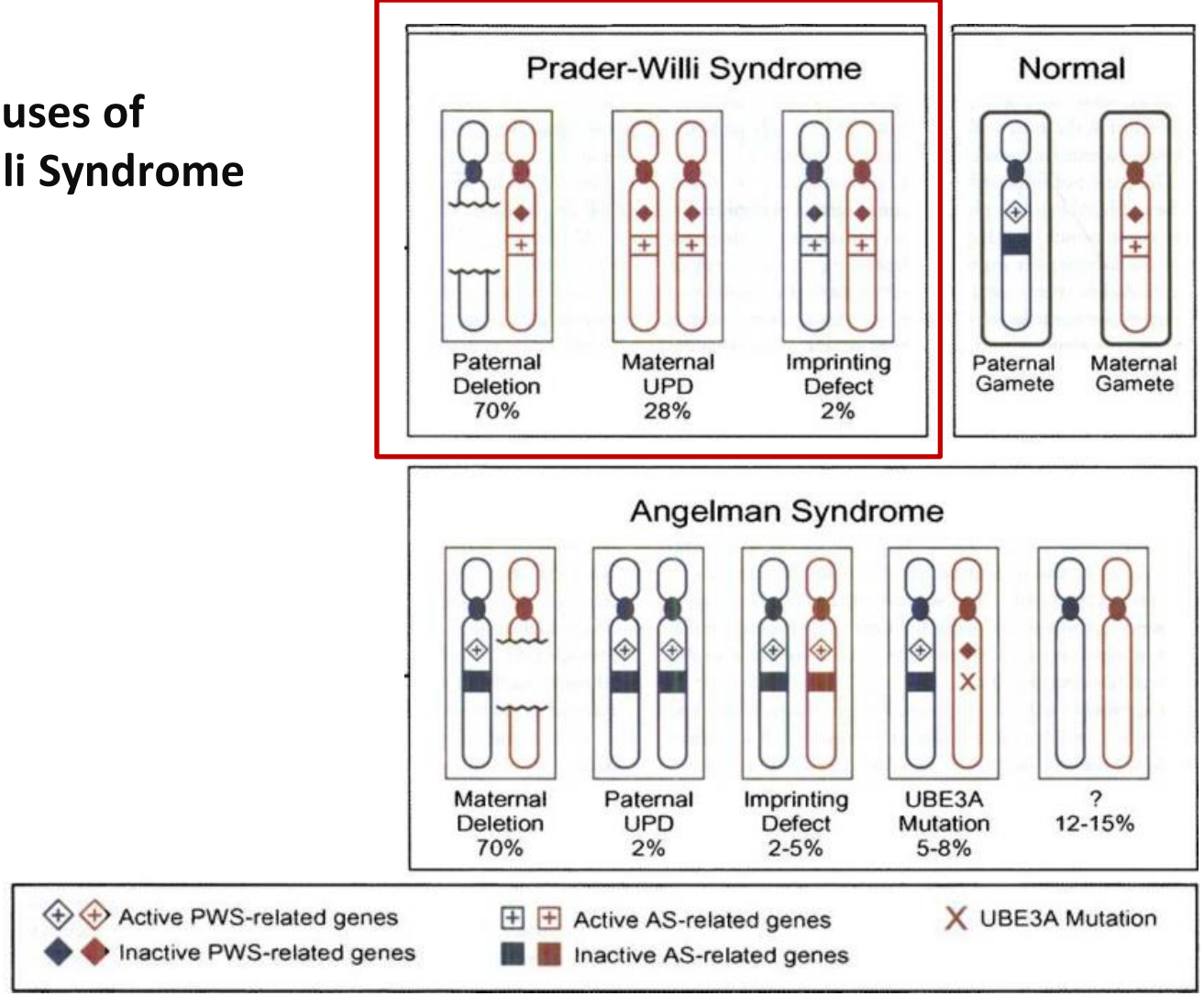
- Prader-Willi syndrome occurs when the paternal allele(s) that would normally be expressed are “missing.”
  - In a normal child the PWS allele(s) are only expressed from the paternal chromosome 15, and the PWS allele(s) on the maternal chromosome 15 are inactive.
- Angelman syndrome occurs when the maternal alleles that would normally be expressed are “missing.”
  - In a normal child the AS allele(s) are only expressed from maternal chromosome 15, and the AS allele(s) on the paternal chromosome 15 are inactive.

http://www.pwsausa.org



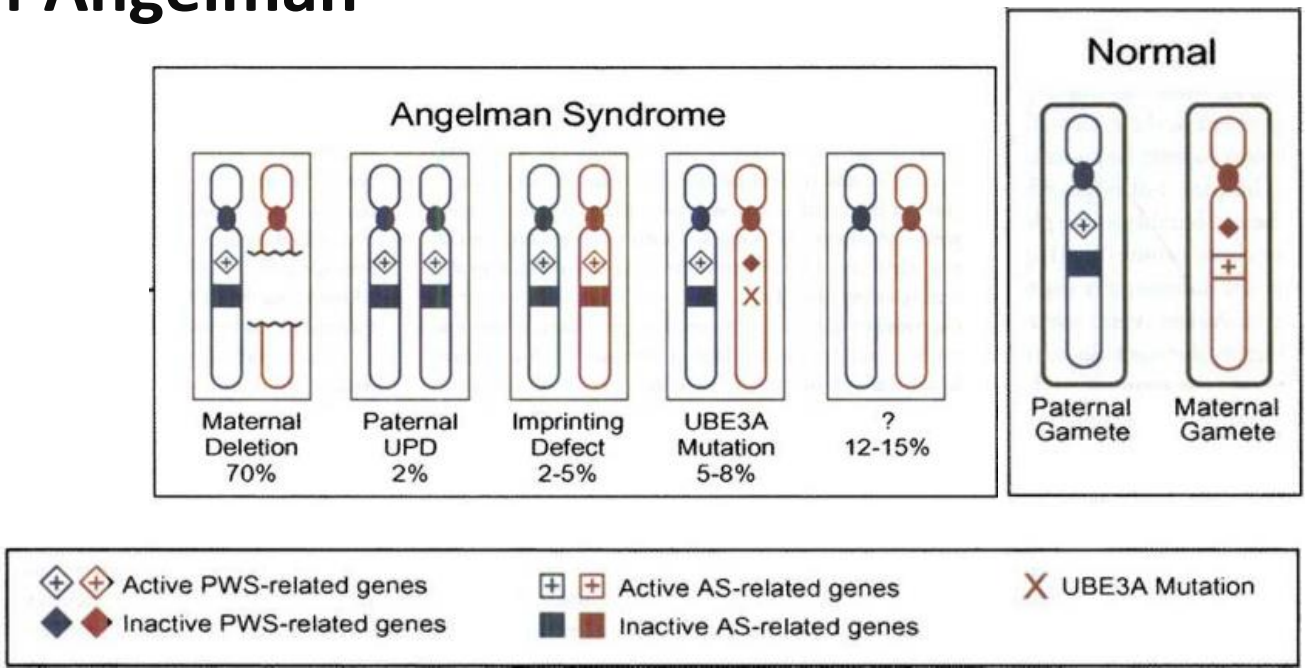
http://www.genereviews.org

Genetic Causes of Prader-Willi Syndrome



- **Paternal Deletion (70-75% of cases):**: Loss of a segment of the father's chromosome 15.
- **Maternal UPD (20-25% of cases)**: Inheritance of two maternal chromosome 15s with no paternal contribution.
- **Imprinting Defects (1-3% of cases)**: Errors in the expression of paternal genes due to imprinting control mutations or epigenetic changes.

Genetic Causes of Angelman Syndrome



- **Maternal Deletion (about 70% of cases):** Loss of a segment of the mother's chromosome 15, including the UBE3A gene.
- **Paternal UPD (1-3% of cases):** Inheritance of two paternal chromosome 15s with no maternal contribution, leading to absence of maternal UBE3A expression.
- **Imprinting Defects (about 3% of cases):** Errors in the expression of maternal genes due to imprinting control mutations or epigenetic changes.
- **UBE3A Mutations (about 10% of cases):** Direct mutations in the UBE3A gene inherited from the mother.