Phenotypic Expression

1. Penetrance
2. Expressivity
3. Variable age of onset
4. Pleiotropy
5. Genetic heterogeneity
6. Sex-limited
7. Sex-influenced

Penetrance

* In a dominant disease, 1 mutant allele is enough to manifest clinical features.
* However, there are some diseases where NOT all individuals with that variant have the phenotype

* Imagine 100 individuals who have the same disease-causing variant/mutation, & ALL of them are affected with the disease.
  Since all the individuals who carry this variant are affected → 100% penetrance (fully penetrant)
* If 10 individuals out of those 100 do NOT manifest the clinical features & other 90 do. In this case, 90% of individuals manifest clinical features (not every person with the variant is affected) → 90% penetrance (reduced penetrance)

- **Penetrance** refers to the all or none expression of a mutant genotype. It usually refers to dominant traits in heterozygotes, and means that even though an individual has inherited the mutant allele, there may be no expression of the phenotype. If a condition is expressed in less than 100 % of persons who have one copy of the mutant allele, it is said to have reduced penetrance.
  If a condition/feature is expressed in less than 100% of individuals who carry the responsible allele, then it is said to have reduced penetrance

→ either there is a disease OR there is NOT (regardless of the disease severity)

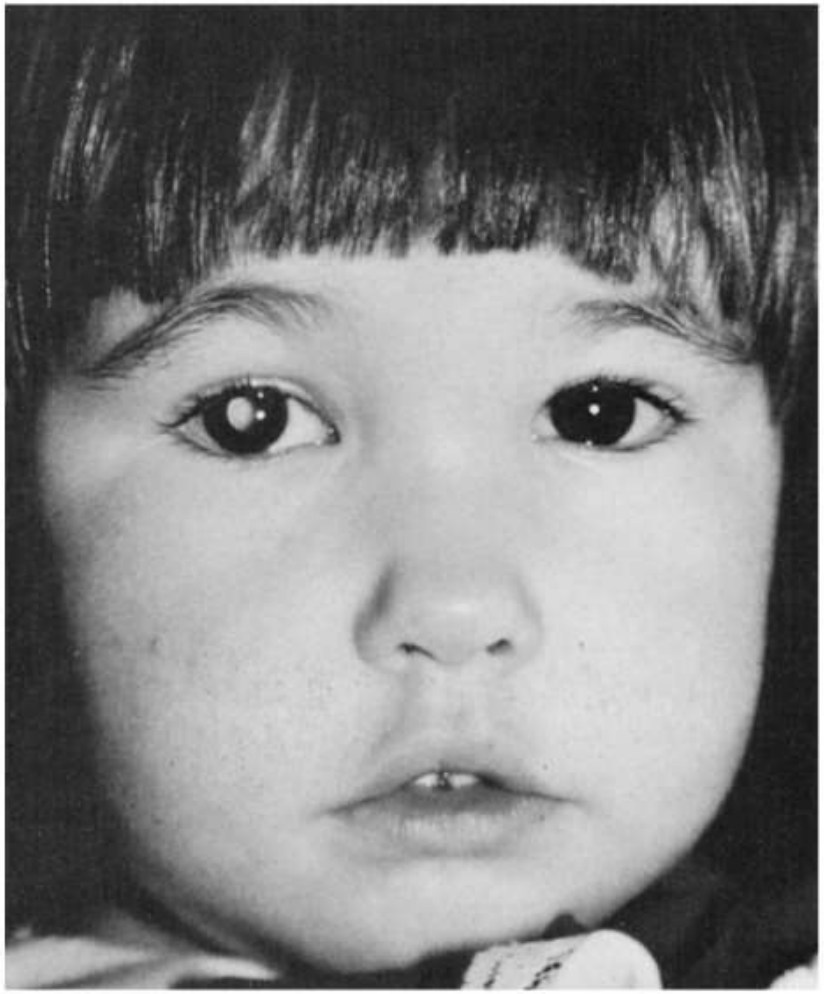
* reminder: the genotype of someone with a dominant disease is assumed to be heterozygous UNLESS proven otherwise

* In dominant diseases, the rule "mutation = disease" is ONLY true when the disease is fully penetrant
* Many dominant diseases have reduced penetrance (NOT all individuals with the mutation manifest the disease)

- The probability of expression of the phenotype given the genotype
- Term used for dominant conditions

Reduced Penetrance

Retinoblastoma, a malignant eye tumor. About 10% of individuals who transmit the mutant allele are unaffected. Therefore, the mutant allele is 90% penetrant.



Retinoblastoma

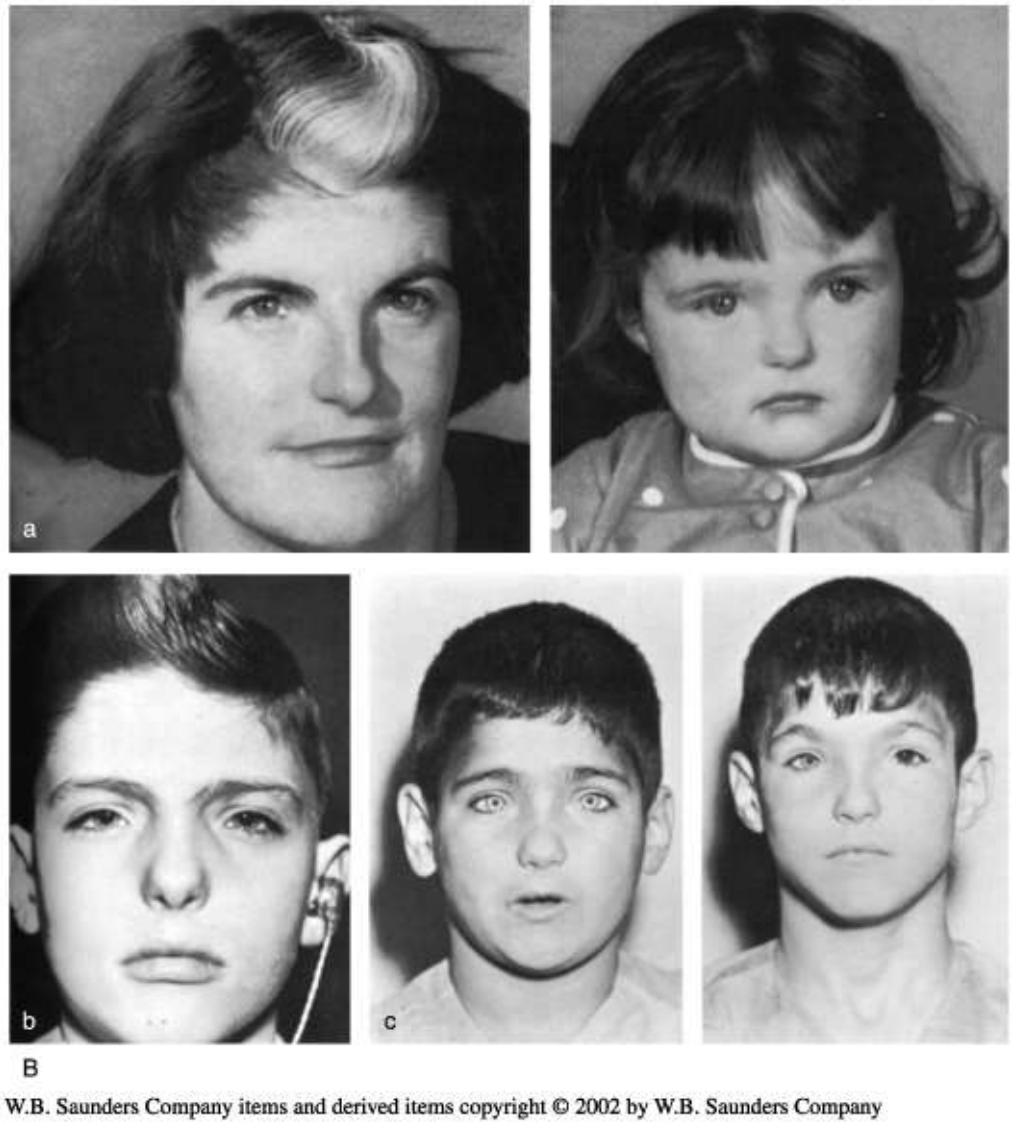
Reduced Penetrance

Waardenburg syndrome, a congenital sensorineural deafness, heterochromia, → each eye has a different color displacement of the inner canthi, white forelock, and other features. Since only about 20% of people with Waardenburg ⇒ 20% penetrance syndrome are deaf, this shows reduced penetrance of this feature of this syndrome

* Remember: a "syndromic" disease indicates different affected organs/tissues.
"Non-syndromic" refers to 1 clinical complication.
i.e.: Syndromic hearing loss = hearing loss + other clinical features.
Non-syndromic hearing loss = only hearing loss.

→ deafness in general could be

- conductive: related to the middle ear or outer ear
- sensorineural: related to damage in the inner ear (cochlea) (or damage to the nerve pathway of CN VIII)



Deafness in Waardenburg syndrome

Penetrance vs. Variable expressivity

either there is OR there is NOT a disease.

there is a disease BUT the severity varies among individuals.

Variable Expressivity

↳ Variable disease severity & clinical manifestations across different individuals with not only the same affected gene, but even with the same variant.

- The extent to which a trait is expressed
- If expression ranges from mild to severe then it is said to have variable expressivity
- However, it is never completely unexpressed
  - Eg. Neurofibromatosis & myotonic dystrophy

* check extra interesting example at minute 12:20 (conclusion: variable expressivity can be seen within the same family)

Variable age of onset & pleiotropy

Variable age of onset refers to the variation in the time to phenotypic expression of mutant gene (s). Example: the onset of Huntington disease is typically in the 40's, however, age of onset may range from the 20's to 60's.

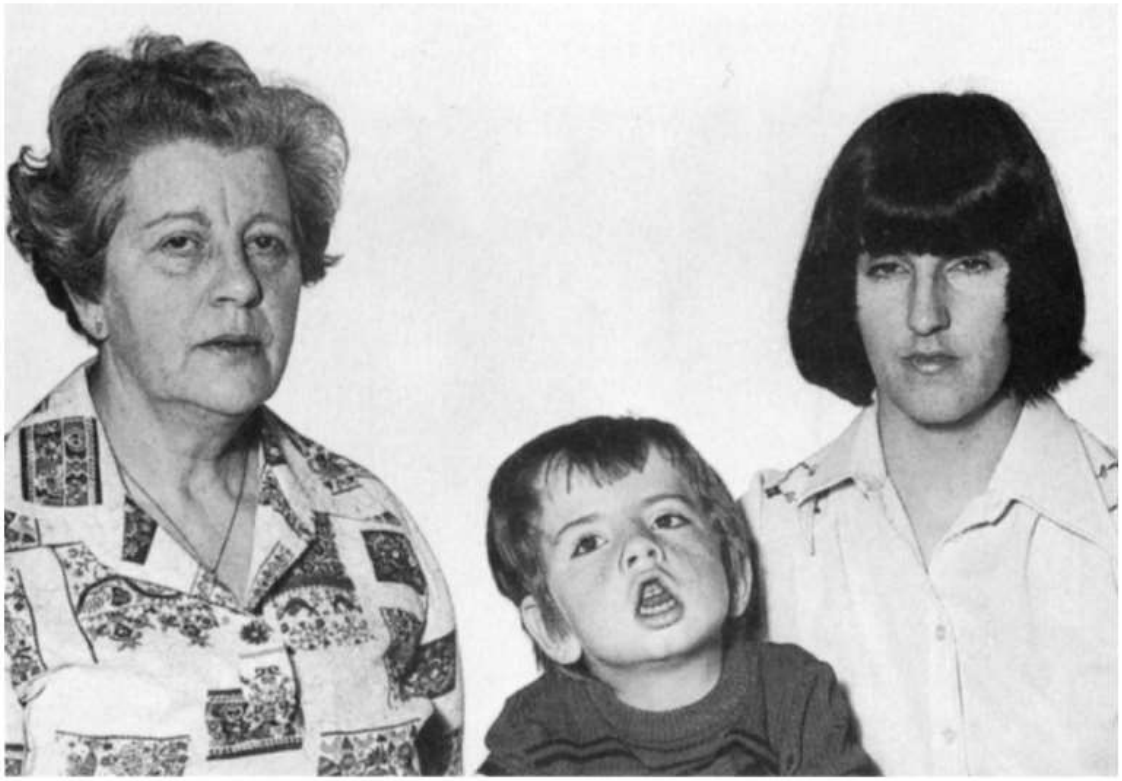
↳ 1 gene mutation causing multiple & different clinical manifestations. ⇒ i.e.: Cystic Fibrosis (CFTR gene mutation) which causes systemic manifestations.

A mutant gene is said to be **pleiotropic** when it produces a wide range of phenotypic effects. Example: Marfan syndrome involves the skeletal, cardiovascular, and ocular systems.

ex. Marfan Syndrome is a connective tissue disease. Marfan pts are tall, with hypermobility of the joints, also dislocation of the eye lens BUT the most impactful clinical presentations are cardiovascular, those pts are at risk of aortic rupture leading to death due to CT abnormalities.

→ Across generations within the same family, the severity of the disease increases & the age of onset becomes earlier.

Anticipation: Earlier Age of Onset & Increasing Severity



Example on anticipation:

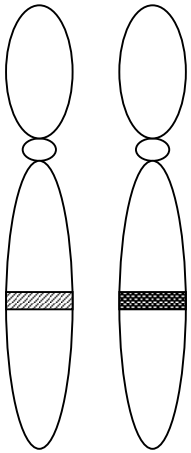
Myotonic dystrophy

Genetic heterogeneity

Allelic heterogeneity: different mutations in the same gene can cause the disease
i.e: there is a variation in mutant alleles of the CFTR gene among pts with CF.

Locus heterogeneity: different genes at different chromosomal locations cause the same disease.
i.e: Congenital Hearing Loss.

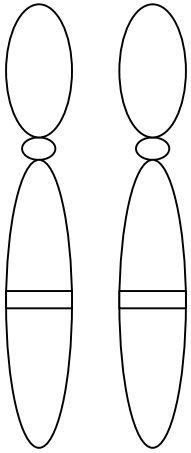
allelic heterogeneity



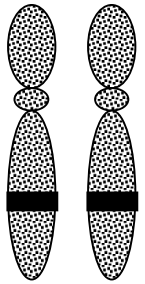
a1 a2

At the CF locus on 7q
a1 = ΔF508 allele
a2 = S549R allele

locus heterogeneity



PAX3 on 2q
Auto dom HL

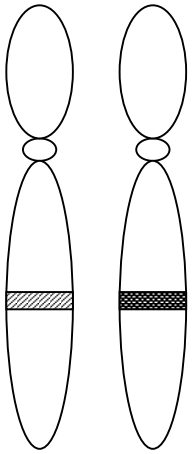


GJB2 on 13q
Auto rec HL

Genetic heterogeneity

Allelic heterogeneity refers to two or more different mutant alleles at the same genetic locus (Example: Duchenne and (the less severe) Becker muscular dystrophy; cystic fibrosis).

↳ on the individual level, each person has 2 alleles (autosomes) BUT in the population there are many alleles found for the same genes.



a1 a2

At the CF locus on 7q

a1 = ΔF508 allele

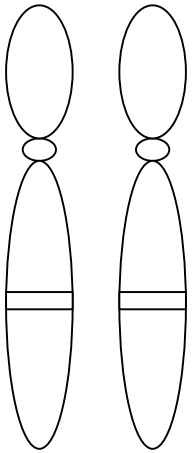
↳ most common mutation of the CFTR gene. (in-frame deletion of the a.a #508 phenylalanine)

a2 = S549R allele

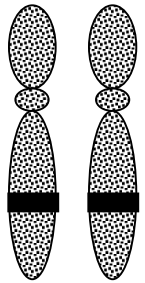
↳ example on another variant seen in the population → missense from Ser at a.a #549 to Arg.

Genetic heterogeneity

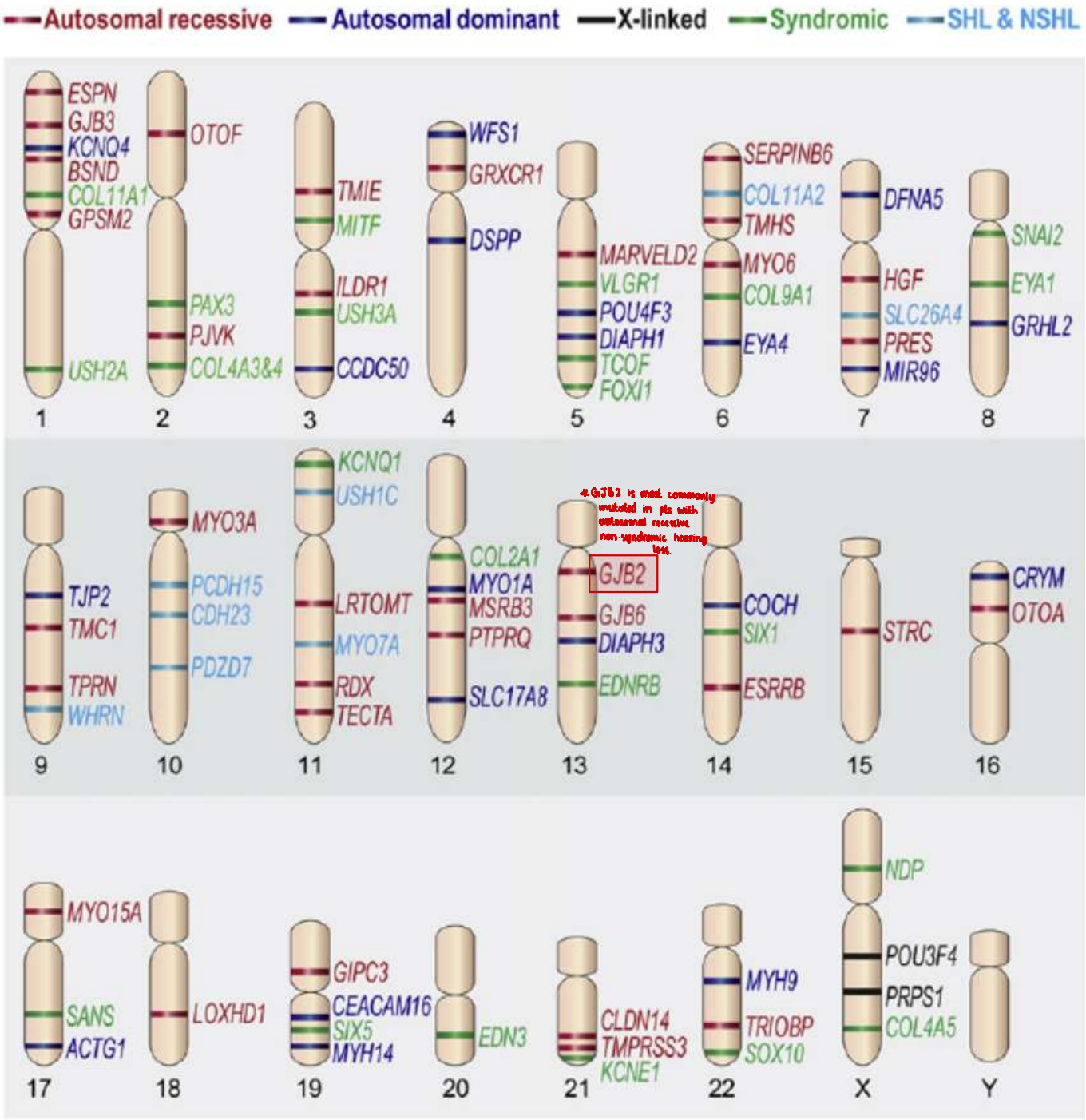
Locus heterogeneity is when mutations at two different genetic loci result in similar phenotypes (Example: congenital deafness). In some cases, the mode of inheritance of the disorders can vary



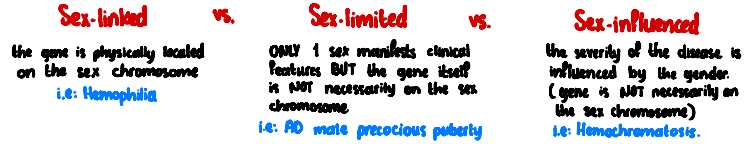
PAX3 on 2q
Auto dom HL



GJB2 on 13q
Auto rec HL


Autosomal recessive
Autosomal dominant
X-linked
Syndromic
SHL & NSHL
ESPN
GJB3
KCNQ4
BSND
COL11A1
GPSM2
USH2A
1
OTOF
PAX3
PJVK
COL4A3&4
2
TMIE
MITF
ILDR1
USH3A
CCDC50
3
WFS1
GRXCR1
DSPP
4
MARVELD2
VLGR1
POU4F3
DIAPH1
TCOF
FOXI1
5
SERPINB6
COL11A2
TMHS
MYO6
COL9A1
EYA4
6
DFNA5
HGF
SLC26A4
PRES
MIR96
7
SNAI2
EYA1
GRHL2
8
TJP2
TMC1
TPRN
WHRN
9
MYO3A
PCDH15
CDH23
PDZD7
10
KCNQ1
USH1C
LRTOMT
MYO7A
RDX
TECTA
11
COL2A1
MYO1A
MSRB3
PTPRQ
SLC17A8
12
GJB2 is most commonly mutated in pts with autosomal recessive non-syndromic hearing loss.
GJB2
GJB6
DIAPH3
EDNRB
13
COCH
SIX1
ESRRB
14
STRC
15
CRYM
OTOA
16
MYO15A
SANS
ACTG1
17
LOXHD1
18
GIPC3
CEACAM16
SIX5
MYH14
19
EDN3
20
CLDN14
TMPRSS3
KCNE1
21
MYH9
TRIOBP
SOX10
22
NDP
POU3F4
PRPS1
COL4A5
X
Y

Sex-limited & Sex-influenced



"Sex-limited"

– refers to a phenotype that is autosomally transmitted but expressed only in one sex. Example: Autosomal dominant male precocious puberty. → If a female has its disease-causing variant she will NOT develop the disease.

– **Sex-influenced** refers to autosomally inherited traits that are expressed differently, in either degree or frequency, in males and females. Example: hemochromatosis (autosomal recessive disorder of increased absorption of dietary iron → causes iron overload (>normal)) is more commonly found in males due to lower dietary intake and menstruation in females. * Males usually have higher dietary intake so there is more iron to absorb.

(the prof. mentioned in lec 8 of the mid material that Hemochromatosis was more severe in females & I wrote it but turns out it is wrong, sorry)

- *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***.

Trinucleotide Repeats

* there are diseases such as myotonic dystrophy & FMR have mutations that are considered to be "dynamic" bcz they have to do with 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.

↳ which parent has the premutation. (green note slide 16)

Anticipation and **parent of origin** effects are now known to be due to a novel type of **dynamic mutation** known as unstable trinucleotide repeats.

Trinucleotide Repeats

Tandemly repeated trinucleotides (i.e. CGG, CTG) within or adjacent to a gene that may increase or decrease in number during formation of egg or sperm cells and thus disrupt the functioning of the gene and lead to disease

Examples:

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

*FMR is a gene that is located on ch.X.
* Nowadays the term "intellectual disability" is more preferred.

Trinucleotide Repeat Expansion

Fragile X MR Syndrome

Anticipation & parent of origin:
In the case of FMR, if it was
- maternal: premutation will expand to full mutation during oogenesis (it will be passed as full mutation)
- paternal: spermatogenesis will result only in premutation (will be passed as premutation ONLY)

} that's why the parent of origin (which parent has the premutation) is related to these dynamic mutations.

CGG

NORMAL (CCG)$_{<50}$

this trinucleotide in normal individuals is repeated <60 times. (randomly repeated) (one after another)

$(CCG)_{<50}$

PREMUTATION (CCG)$_{50\text{-}200}$

if an individual has a premutation (>50 & <200), he will NOT display FMR clinical manifestations caused by a full mutation BUT since the repeats are above normal they might likely expand to >200 during gametogenesis, therefore it is considered an example on anticipation.

$(CCG)_{50\text{-}200}$

FULL MUTATION (CCG)$_{>200}$

an individual with >200 CGG repeats will be clinically affected.

that's why it's called "dynamic" bcz the # of repeats changes across generations (it's not gain or loss or substitution BUT it's an expansion due to increase repeats # across generations)

$(CCG)_{>200}$

* In the past, they used to test for the # of the repeats by cytogenetic analysis (karyotyping) bcz when karyotyping is performed on an individual with CGG repeats > normal ch. X will break, hence the name Fragile X Syndrome. (nowadays testing is PCR-based)

FX MR Clinical Features

1. Incidence of about 1 in 5000 males; presumed incidence in females is about one-half that of males.
2. Most common cause of inherited mental retardation in males.
3. 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.
4. Approximately 50% of female carriers of a full mutation have mental retardation that is usually less severe than in affected males.
5. 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.

About 20% of females who carry a premutation will develop premature ovarian failure (POF).

Genetic Features

A. Atypical X-linked inheritance showing parent of origin effect.

1st premutation expands to full mutation only during oogenesis & NOT spermatogenesis

B. 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.

if those repeats could be located on coding OR non-coding regions of the gene.

if in FMR, the repeats are on non-coding region (UTR), when these repeats are ↑↑ this will induce methylation & the gene becomes hypermethylated, therefore unexpressed

a Huntington's disease is different in which the repeats are found on a coding region (CAG trinucleotide which codes for a.a Gln) which results in extra a.as in the ptn & therefore an abnormal structure

C. 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.

Genetic Features

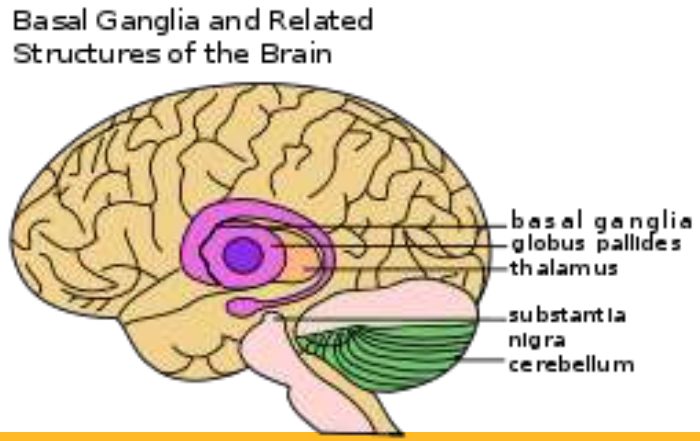
D. Allele sizes (these categories are not absolute):
   - Normal alleles: 5-54 repeats
   - Premutation alleles: **55-200 repeats** (not associated with MR but there is risk for FXTAS and POF; may expand to full mutation in female carrier)
   - Full mutation alleles: > 200 repeats (affected individuals)

E. Existence of transmitting males who are of normal intelligence but can transmit the Fragile X chromosome to their daughters. These daughters are of normal intelligence, however, their children are at risk for mental retardation.

F. The change from phenotypically normal to affected state (i.e. expansion of the trinucleotide repeats into the full mutation range) has only been observed following oogenesis.

Huntington's Disease: A Late-Onset Lethal Disease

- **Huntington's disease** is a degenerative disease of the nervous system
- The disease destroys cells in the **basal ganglia**, the part of the brain that controls movement, emotion, and cognitive ability
- The disease has no obvious phenotypic effects until the individual is about 35 to 40 years of age
- Once the deterioration of the nervous system begins the condition is irreversible and fatal



Genomic Imprinting

⇒ Methylation pattern impacts clin

- For a few mammalian traits, the phenotype depends on which parent passed along the alleles for those traits
- Such variation in phenotype is called **genomic imprinting**
- Genomic imprinting involves the silencing of certain genes that are "stamped" with an imprint during gamete production

Human genome contains around 20,000 ptn-coding genes. (even though we have 100,000 different ptns & some ptns have >1 subunit)

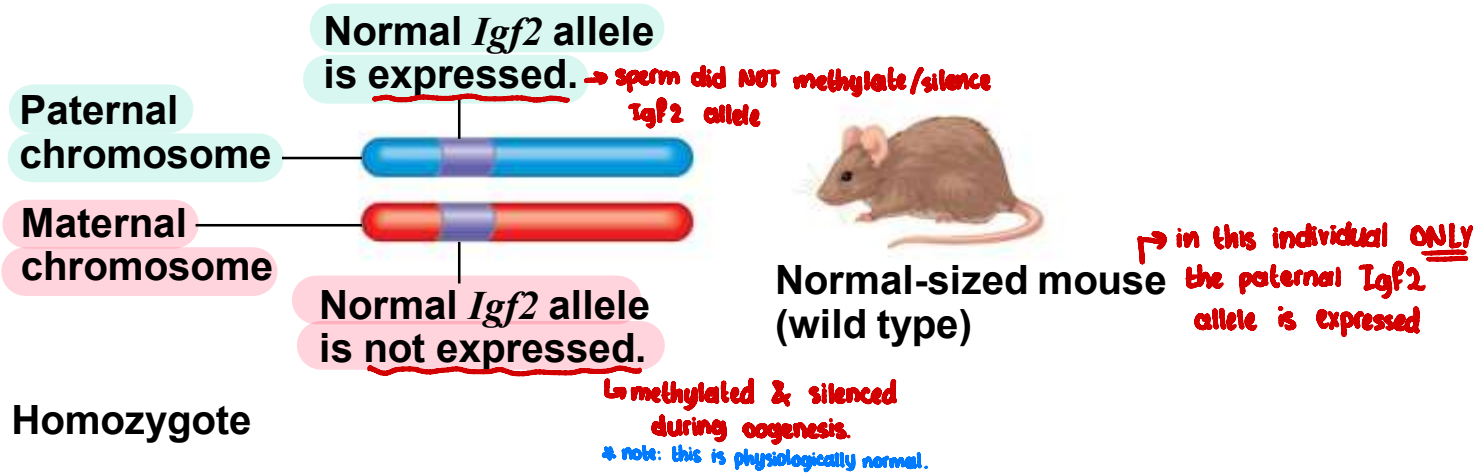
Q: How come 20,000 ptn-coding genes encode for 100,000 different ptns?
Ans: the main reason is Alternative Splicing.

Human genome contains 20,000+ non-coding genes (they are transcribed to RNA but NOT translated into ptn)

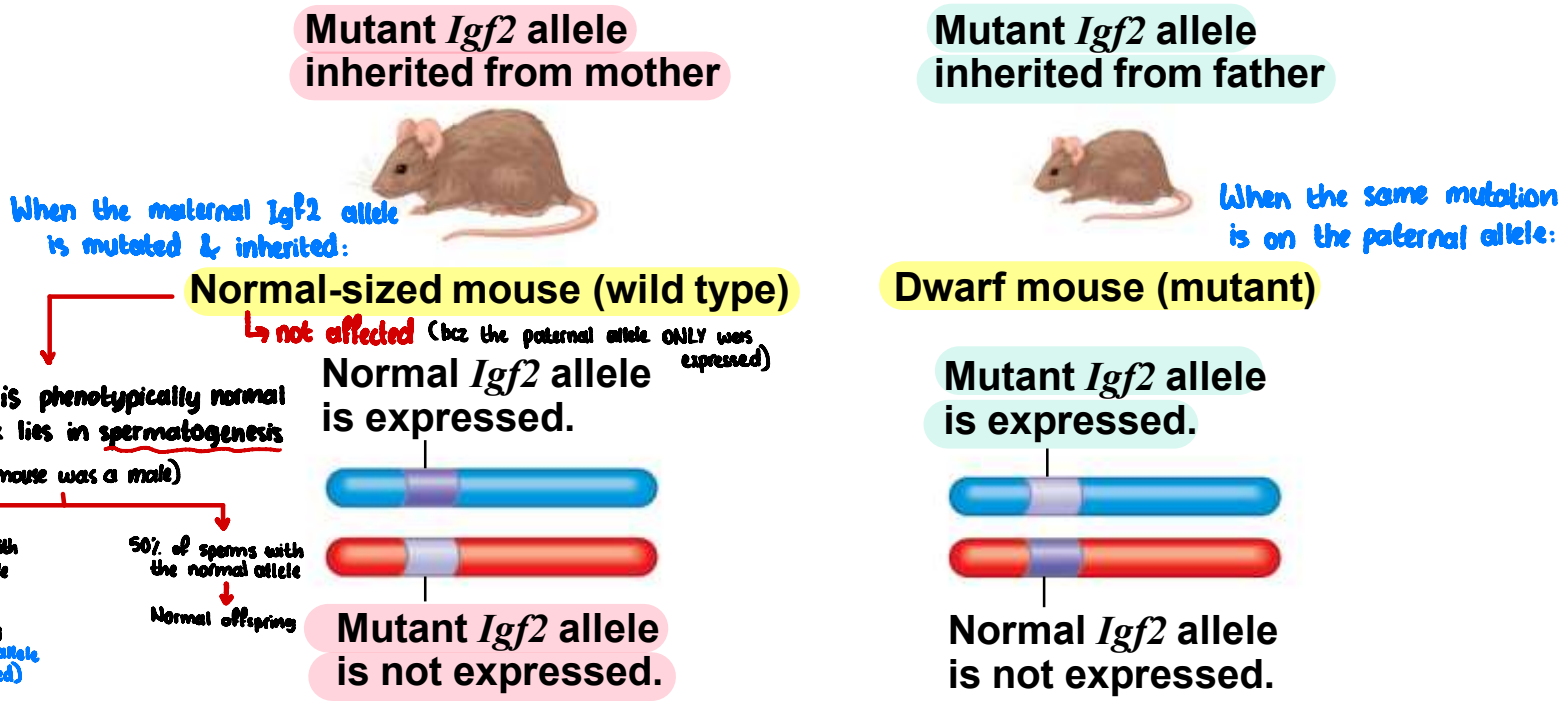
A few hundred of them undergo differential methylation during spermatogenesis & oogenesis ⇒
(methylated genes are NOT necessarily the same in the sperm & oocyte)

Figure 15.17

* In mice, genes are referred to using small letters while in humans using big letters.

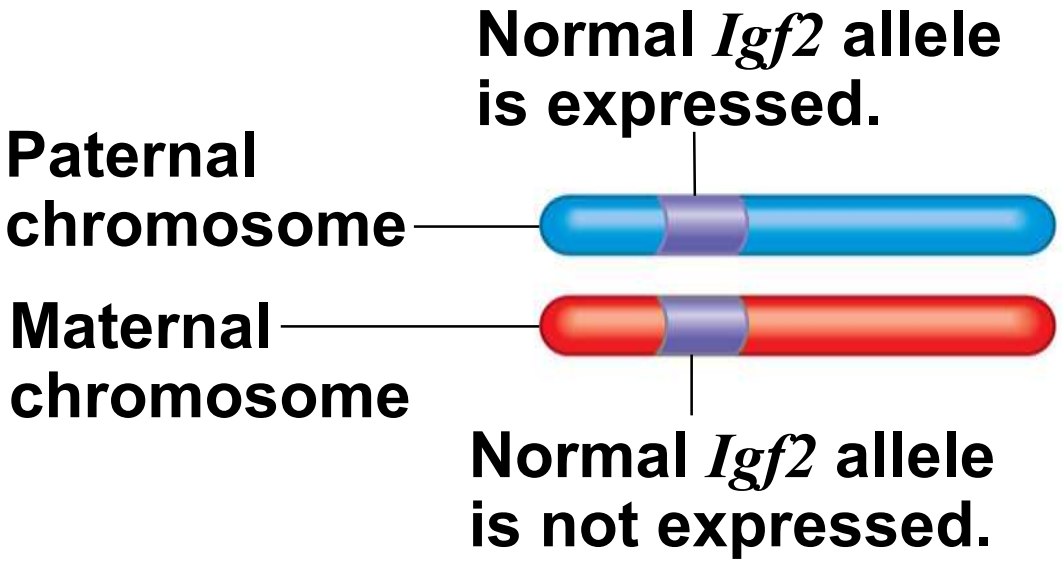


(a) Homozygote



(b) Heterozygotes

Figure 15.17a



Normal-sized mouse (wild type)

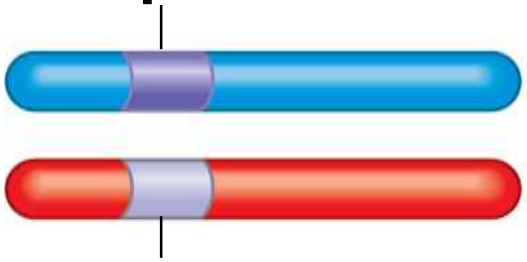
(a) Homozygote

Figure 15.17b

Mutant *Igf2* allele inherited from mother

Normal-sized mouse (wild type)

Normal *Igf2* allele is expressed.

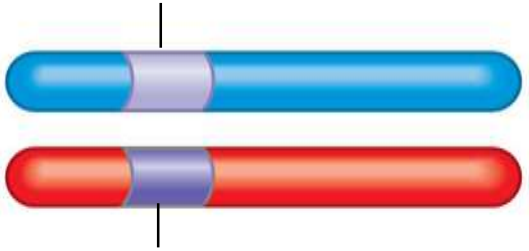


Mutant *Igf2* allele is not expressed.

Mutant *Igf2* allele inherited from father

Dwarf mouse (mutant)

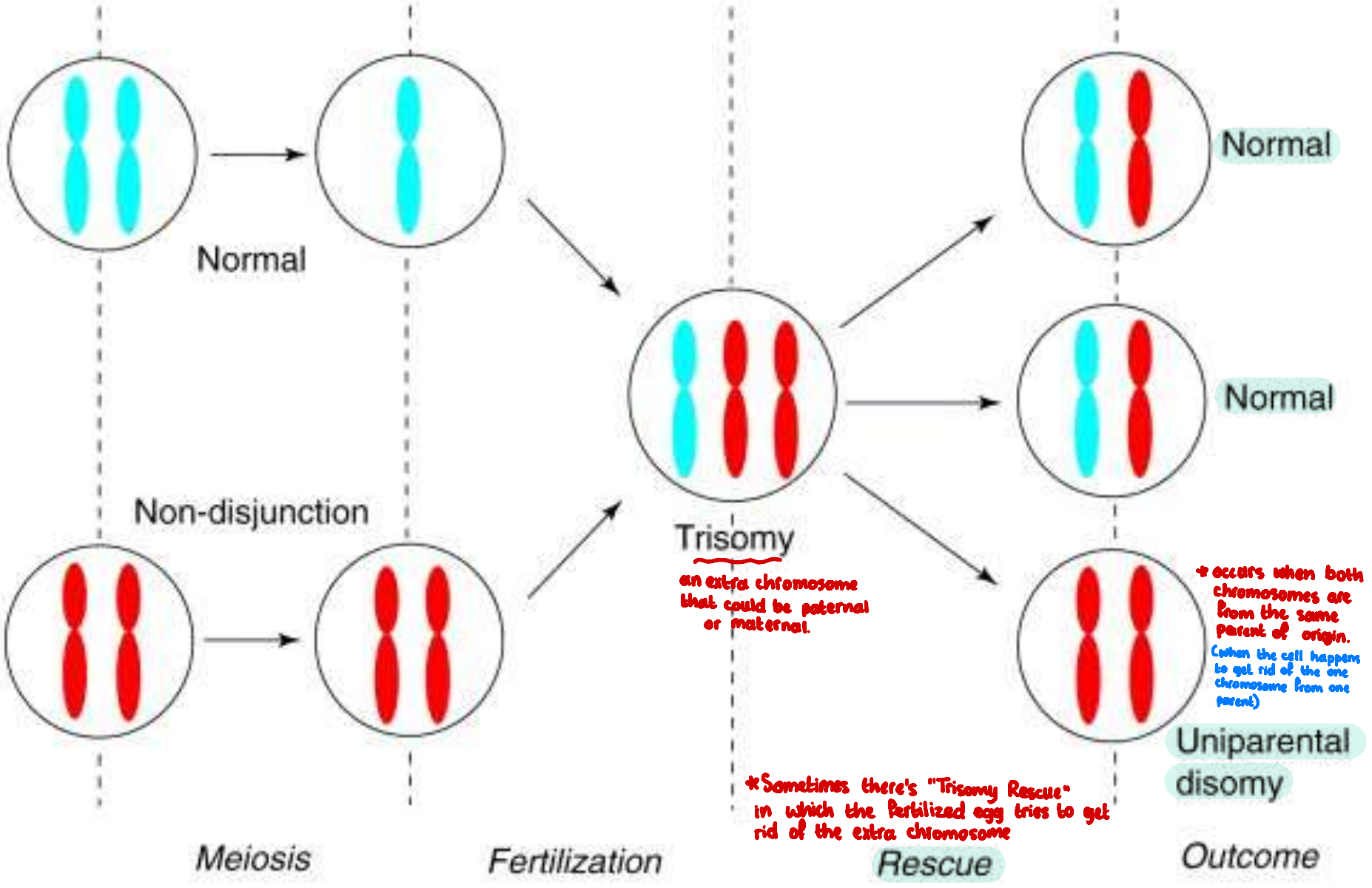
Mutant *Igf2* allele is expressed.



Normal *Igf2* allele is not expressed.

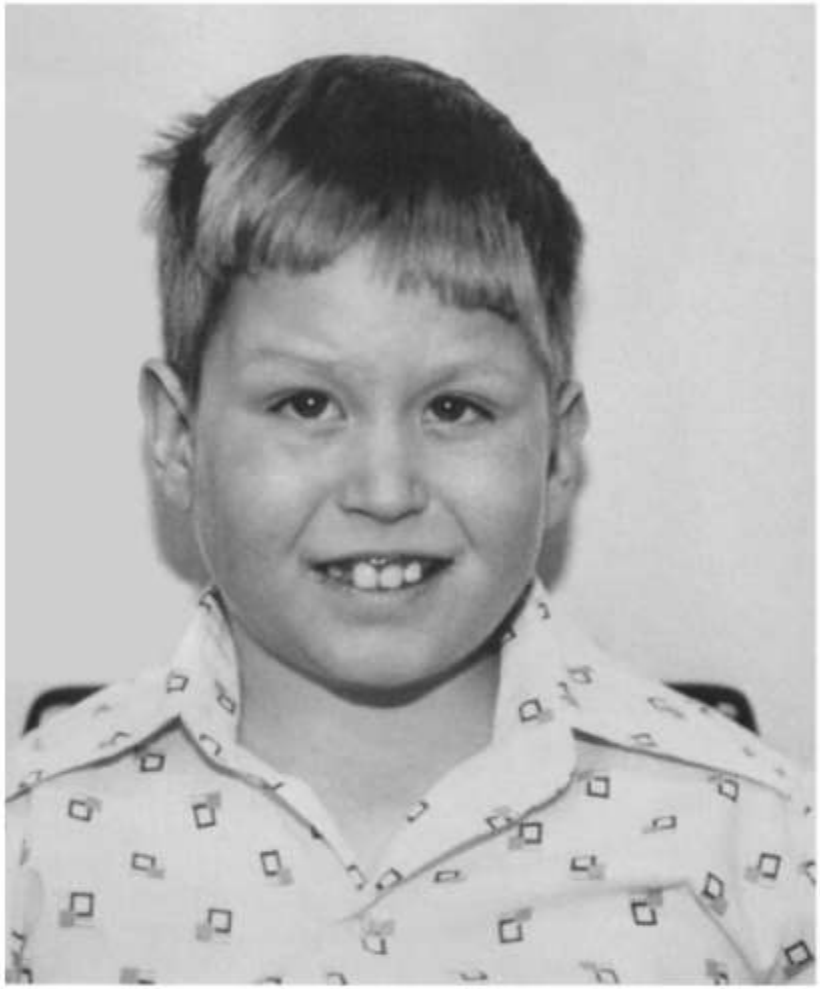
(b) Heterozygotes

- It appears that imprinting is the result of the methylation (addition of $-CH_3$) of cysteine nucleotides
- Genomic imprinting is thought to affect only a small fraction of mammalian genes
- Most imprinted genes are critical for embryonic development



trends in Endocrinology and Metabolism

Imprinting



Prader-Willi syndrome → they are 2 different diseases clinically ← **Angelman syndrome**

BUT genetically from the same region.

Imprinting

I.Definition: the differential expression of a gene depending on the sex of the parent from which it is inherited (i.e., the parental origin of the gene).

Implications:

A.Implies that there is a critical or sensitive period during development (i.e. during or before gametogenesis) during which the genetic information is marked or imprinted in order to permit differential expression based on parental origin.

B.The imprint must persist stably through DNA replication and cell division in the body cells.

C.The imprint must be capable of affecting gene expression (i.e. turning genes on or off).
D.Imprinting is not a permanent alteration since it must be erased in the germ cell line of every individual so that new imprinting may be introduced.

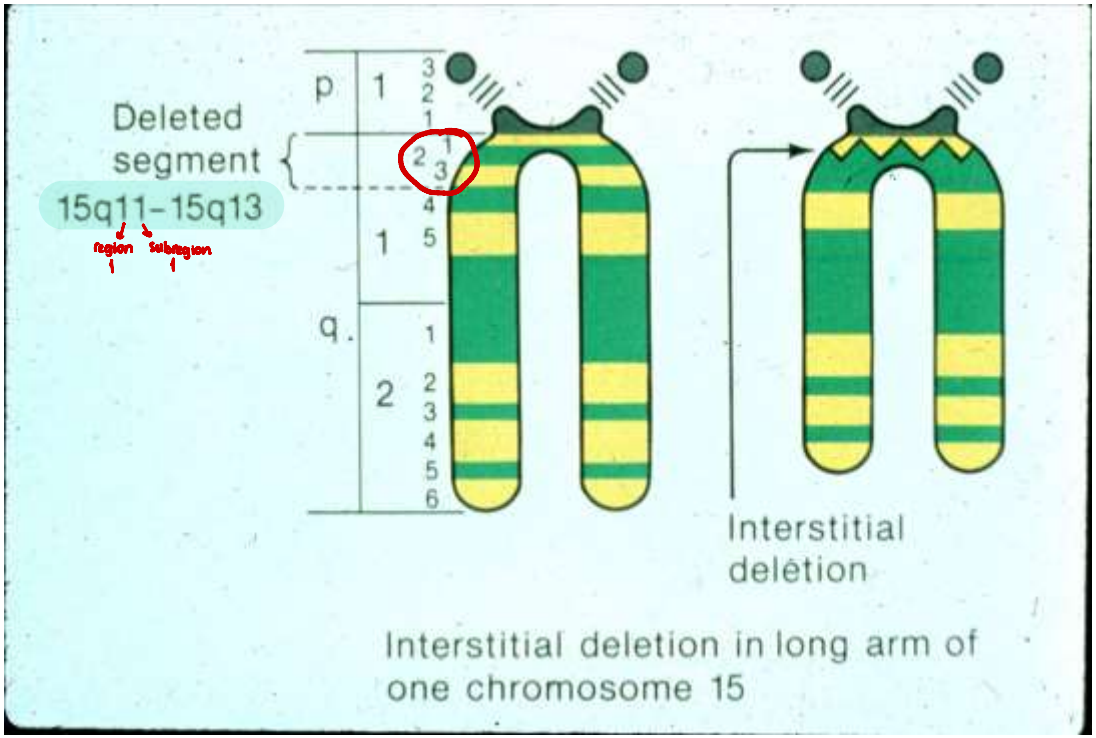
Example of Imprinting in Humans

Prader-Willi syndrome (PWS) and Angelman syndrome (AS)

(Another disease implicated by genomic imprinting is Silver-Russell Syndrome)

1. Both map to and may involve deletions of 15q11-13 but they have distinct phenotypes.
2. PWS is characterized by obesity, voracious appetite, and mental retardation, whereas, Angelman is characterized by gait ataxia, smiling facies and happy demeanor, and mental retardation.
   (described as "happy puppet")
3. Deletions are found in about 50-60% of cases of PWS and AS.
4. If the deletion is paternally derived (only maternal 15q11-13 present) then PWS.
5. If the deletion is maternally derived (only paternal 15q11-13 present) then AS.
6. Some cases of PWS (about 30%) have been attributed to maternal uniparental disomy and some cases of AS (about 5%) have been attributed to paternal uniparental disomy. About 10-15% of cases of AS are caused by a single gene mutation in the UBE3A gene. Other causes of PWS and AS include defects in the imprinting center, chromosomal translocation within the PWS/AS critical region, and unknown cause.

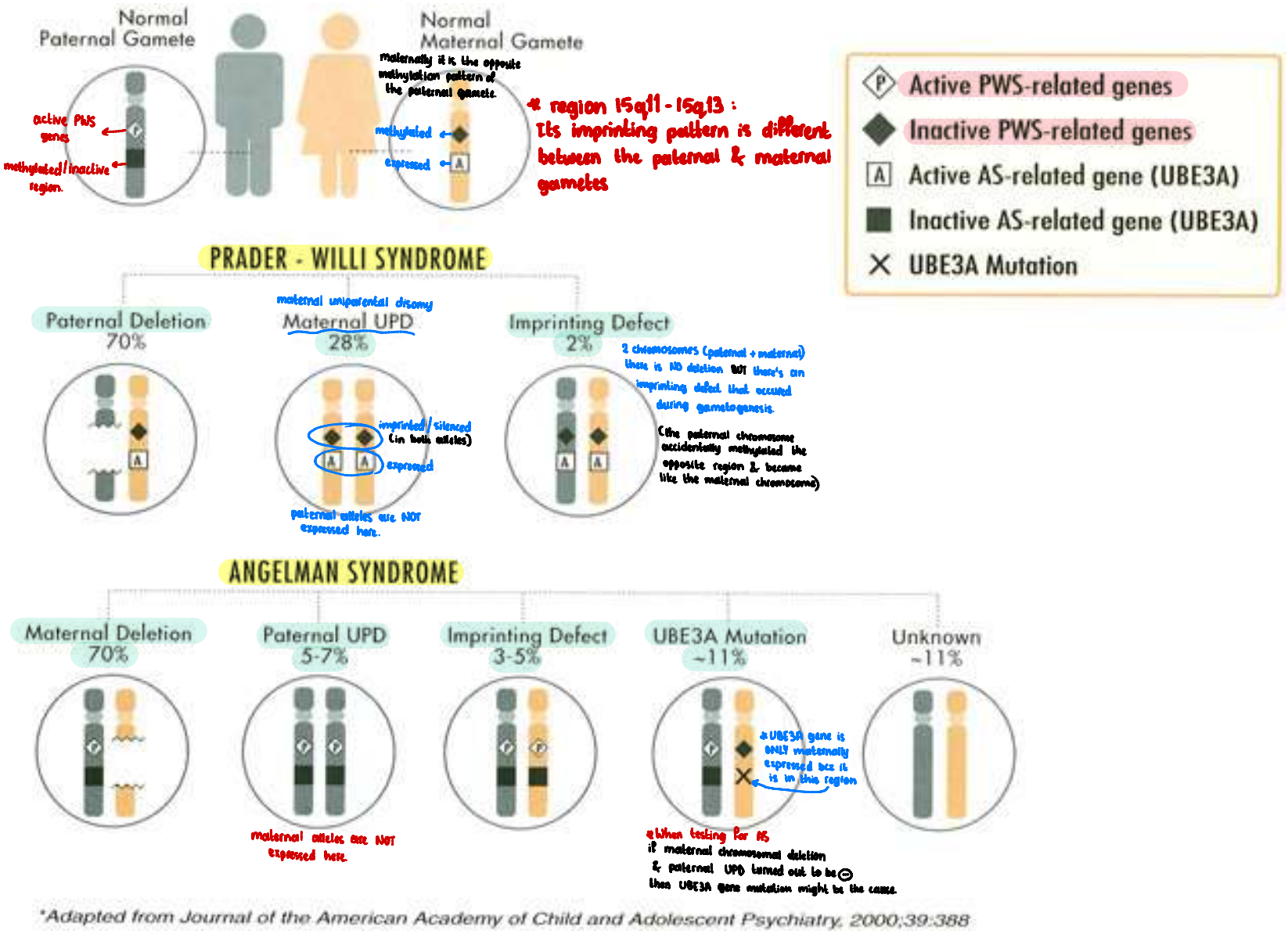
PWS & AS both involve chromo 15q11-13



Deletions account for ~ 70% cases of PWS & AS

- If paternal deletion of 15q11-13 → PWS
- If maternal deletion of 15q11-13 → AS

Causes of PWS and AS



*Adapted from Journal of the American Academy of Child and Adolescent Psychiatry, 2000;39:388

Inheritance of Organelle Genes

- Extranuclear genes (or cytoplasmic genes) are found in Mitochondria
- Extranuclear genes are inherited maternally because the zygote's cytoplasm comes from the egg

→ A male affected with a mitochondrial will never have affected children
(only maternally inherited)

- Some defects in mitochondrial genes prevent cells from making enough ATP and result in diseases that affect the muscular and nervous systems → most affected systems from insufficient ATP. (keep in mind that some mitochondrial pts are encoded by nuclear genes)
  - For example, mitochondrial myopathy (**myopathy** is a muscular disease) and Leber's hereditary optic neuropathy (damage to nerves)