Phenotypic Expression

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

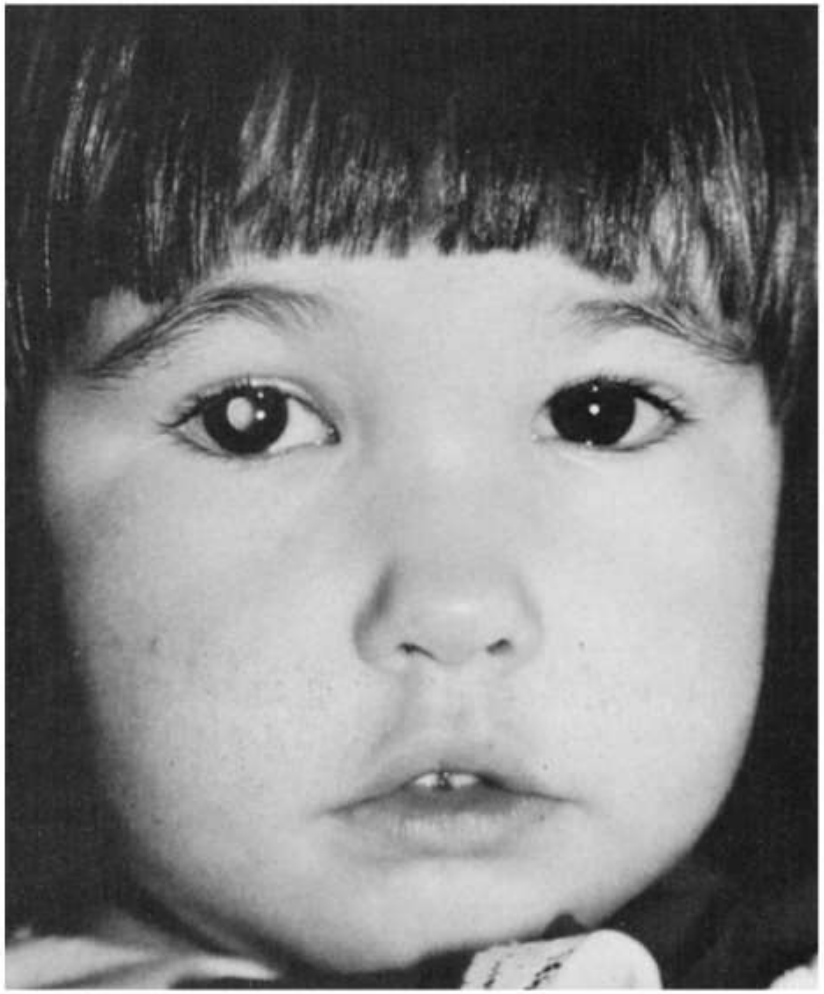
Penetrance

- **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

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

Reduced Penetrance

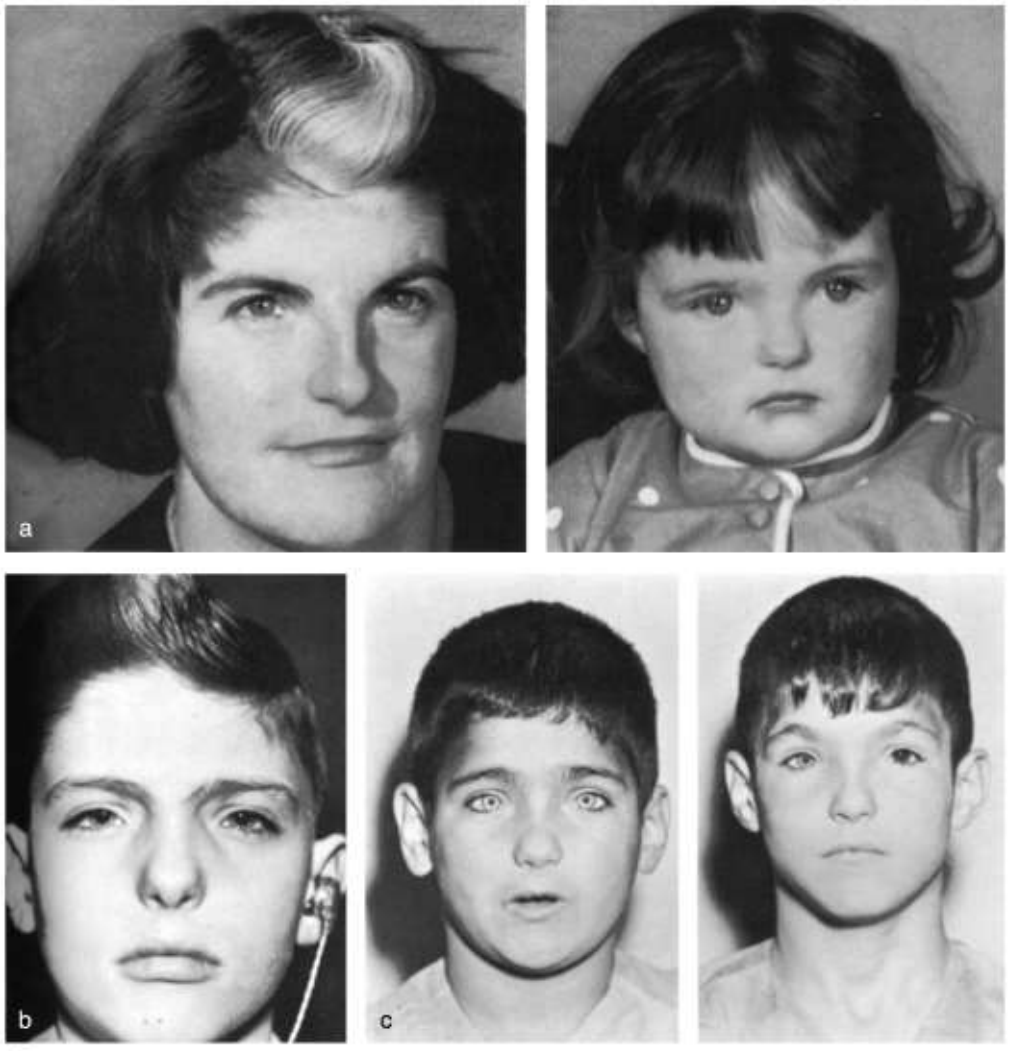
Retinoblastoma, a malignant eye tumor. About 10% of individuals who transmit the mutant allele are unaffected. Therefore, the mutant allele is 90% penetrant.



Retinoblastoma

Reduced Penetrance

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



Deafness in Waardenburg syndrome

Variable Expressivity

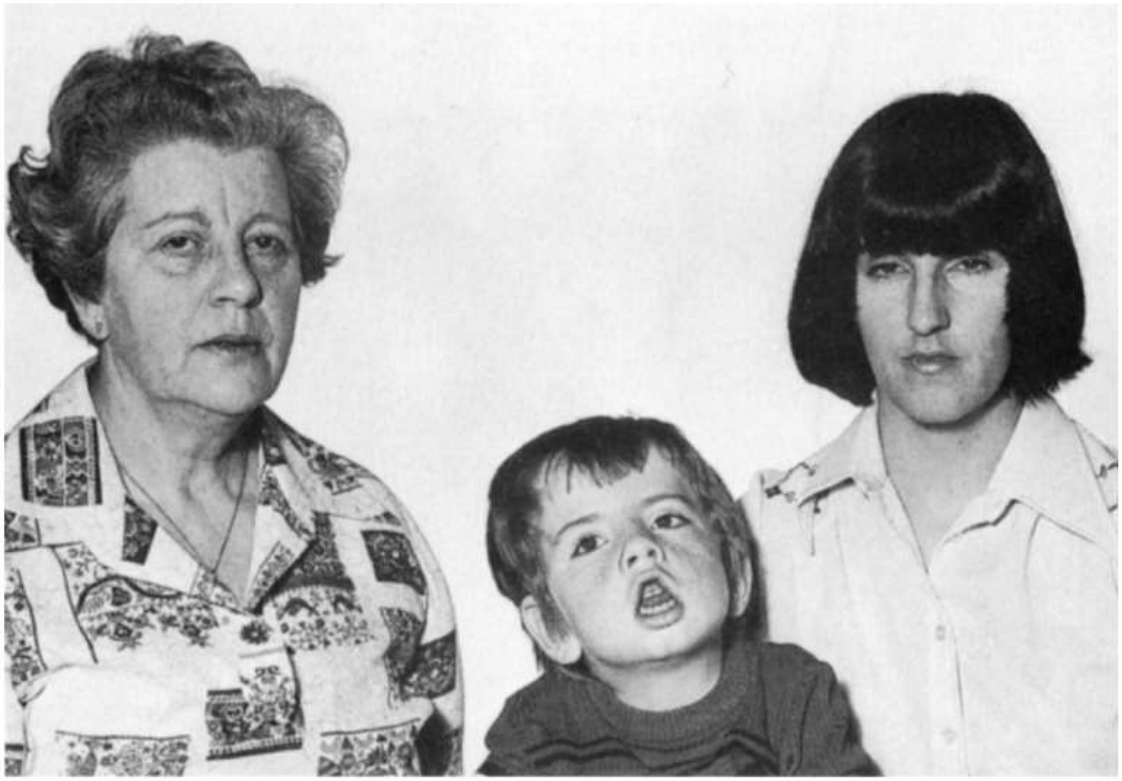
- The extent to which a trait is expressed
- If expression ranges from mild to severe then it is said to have variable expressivity
- However, it is never completely unexpressed
  - Eg. Neurofibromatosis & myotonic dystrophy

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.

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.

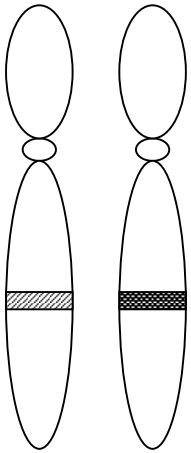
Anticipation: Earlier Age of Onset & Increasing Severity



Myotonic dystrophy

Genetic heterogeneity

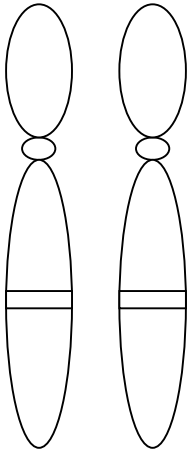
allelic heterogeneity



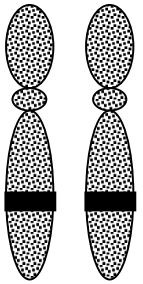
a1 a2

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

locus heterogeneity



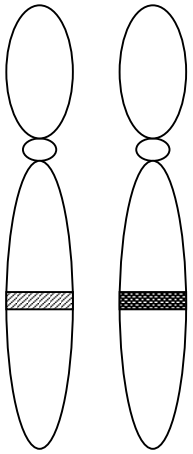
PAX3 on 2q
Auto dom HL



GJB2 on 13q
Auto rec HL

Genetic heterogeneity

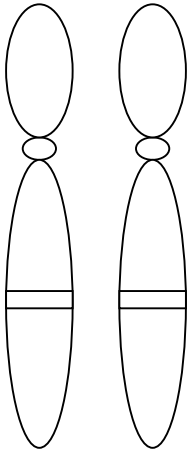
Allelic heterogeneity refers to two or more different mutant alleles at the same genetic locus (Example: Duchenne and (the less severe) Becker muscular dystrophy; cystic fibrosis).



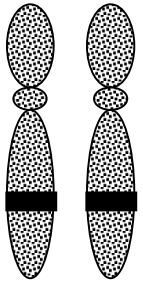
At the CF locus on 7q
a1 = ΔF508 allele
a2 = S549R allele

Genetic heterogeneity

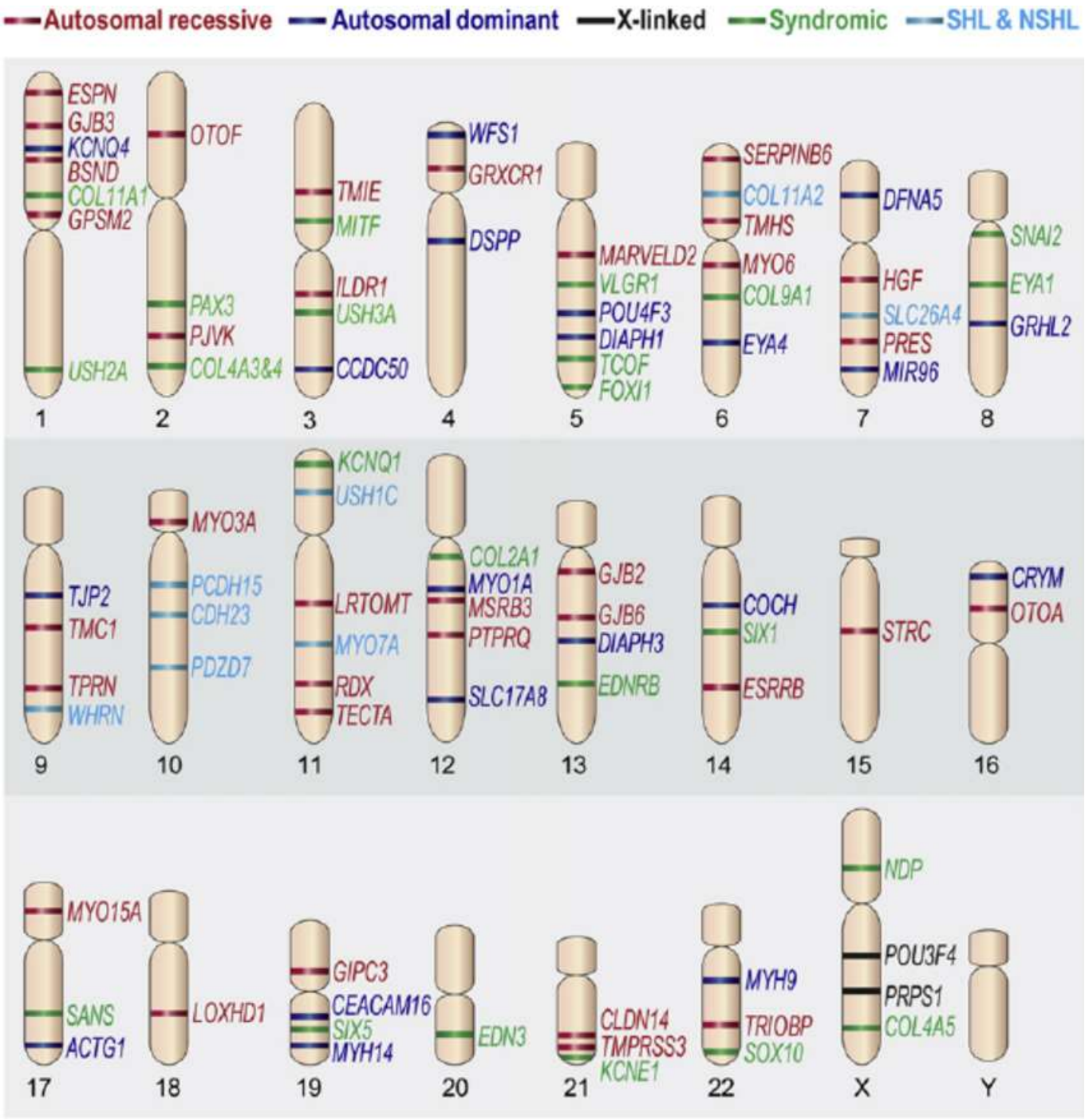
Locus heterogeneity is when mutations at two different genetic loci result in similar phenotypes (Example: congenital deafness). In some cases, the mode of inheritance of the disorders can vary



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
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

- refers to a phenotype that is autosomally transmitted but expressed only in one sex. Example: Autosomal dominant male precocious puberty.

- **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) is more commonly found in males due to lower dietary intake and menstruation in females.

- *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

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.

Trinucleotide Repeats

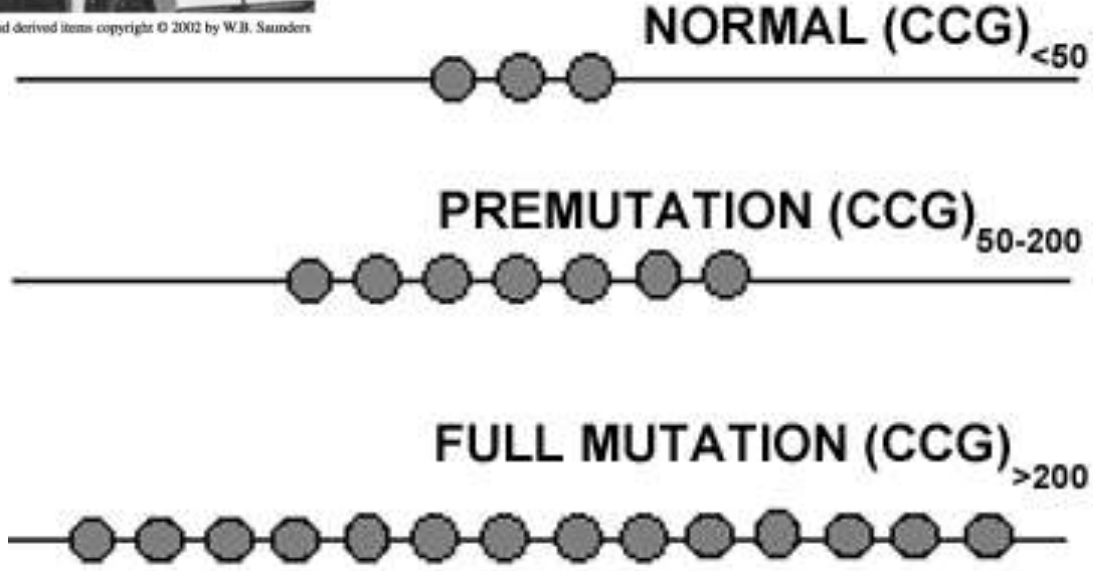
Tandemly repeated trinucleotides (i.e. CGG, CTG) within or adjacent to a gene that may increase or decrease in number during formation of egg or sperm cells and thus disrupt the functioning of the gene and lead to disease

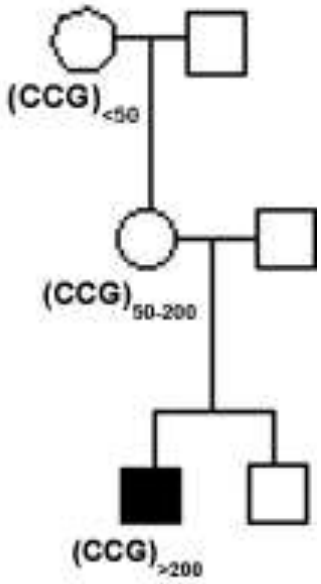
Examples:

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

Trinucleotide Repeat Expansion

Fragile X MR Syndrome





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.

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.

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

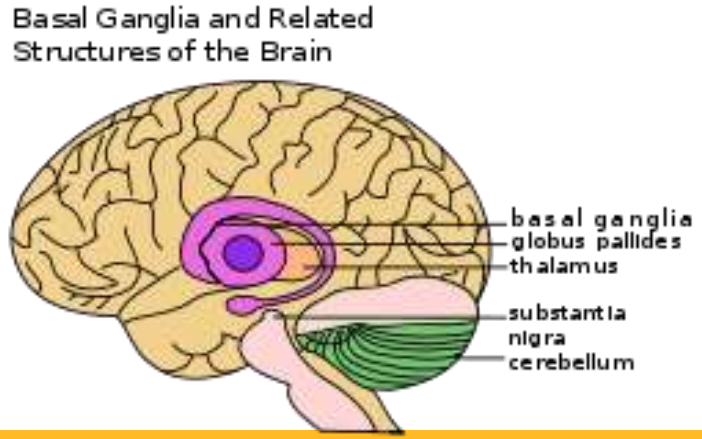
D. Allele sizes (these categories are not absolute):
   - Normal alleles: 5-54 repeats
   - Premutation alleles: **55-200 repeats** (not associated with MR but there is risk for FXTAS and POF; may expand to full mutation in female carrier)
   - Full mutation alleles: > 200 repeats (affected individuals)

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

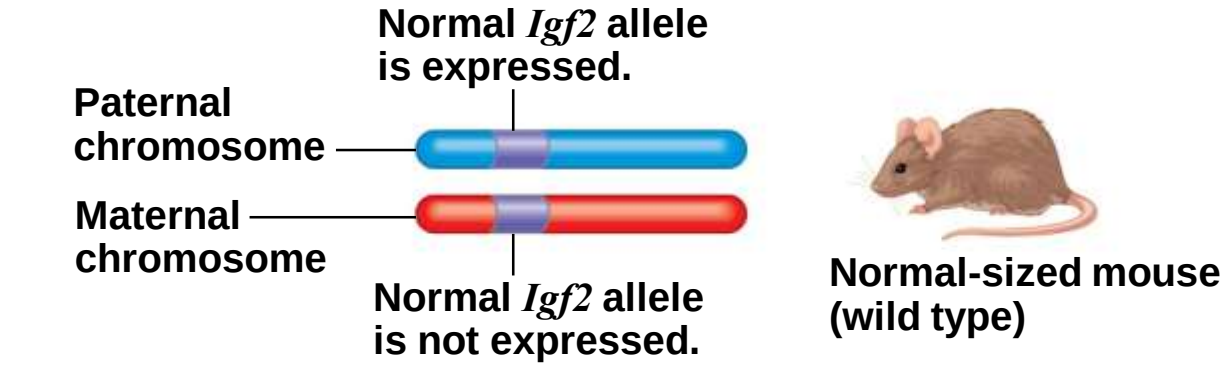
- **Huntington's disease** is a degenerative disease of the nervous system
- The disease destroys cells in the **basal ganglia**, the part of the brain that controls movement, emotion, and cognitive ability
- The disease has no obvious phenotypic effects until the individual is about 35 to 40 years of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



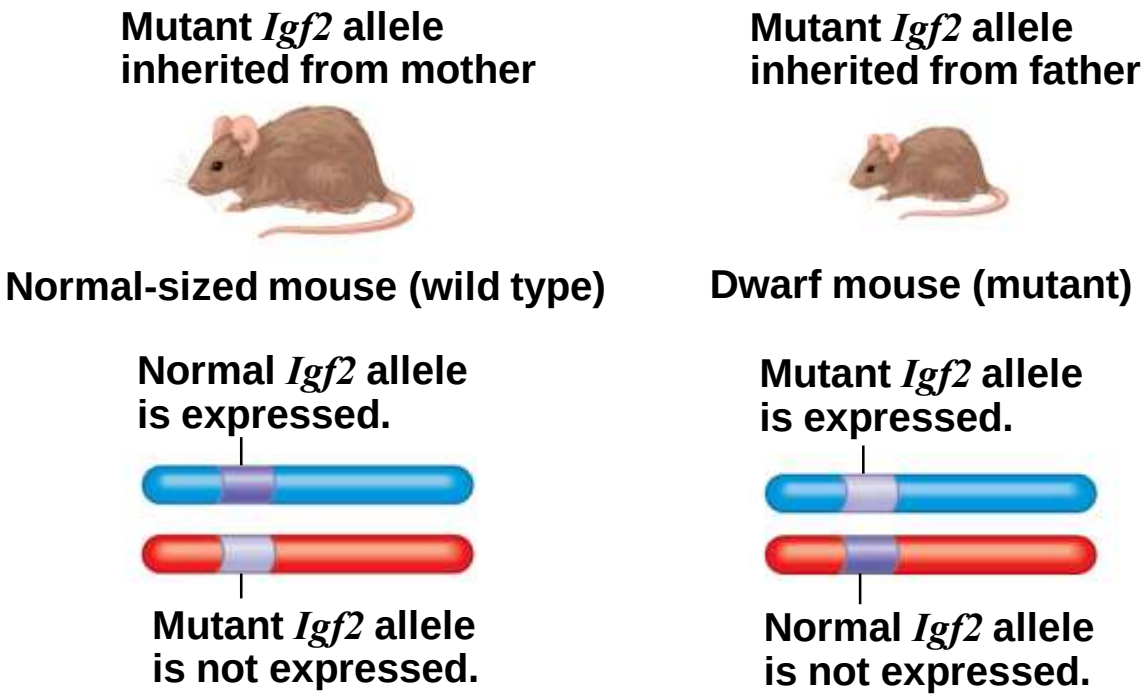
Genomic Imprinting

- 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

Figure 15.17

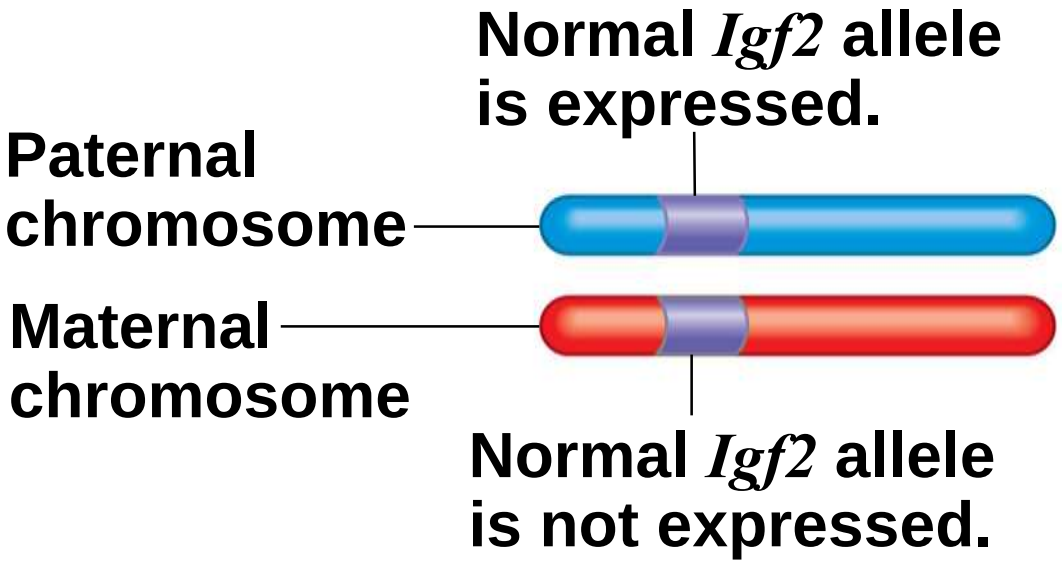


(a) Homozygote



(b) Heterozygotes

Figure 15.17a



Normal-sized mouse (wild type)

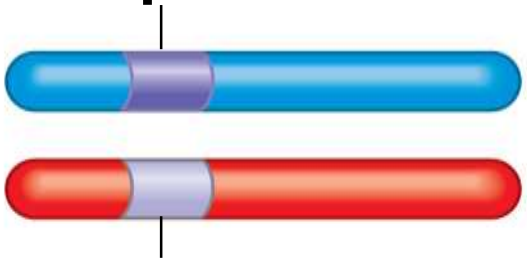
(a) Homozygote

Figure 15.17b

Mutant *Igf2* allele inherited from mother

Normal-sized mouse (wild type)

Normal *Igf2* allele is expressed.

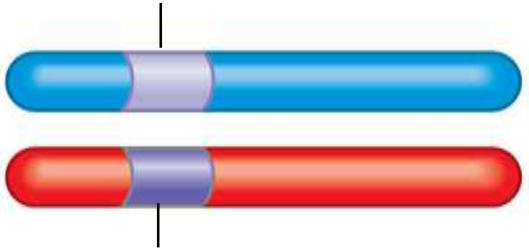


Mutant *Igf2* allele is not expressed.

Mutant *Igf2* allele inherited from father

Dwarf mouse (mutant)

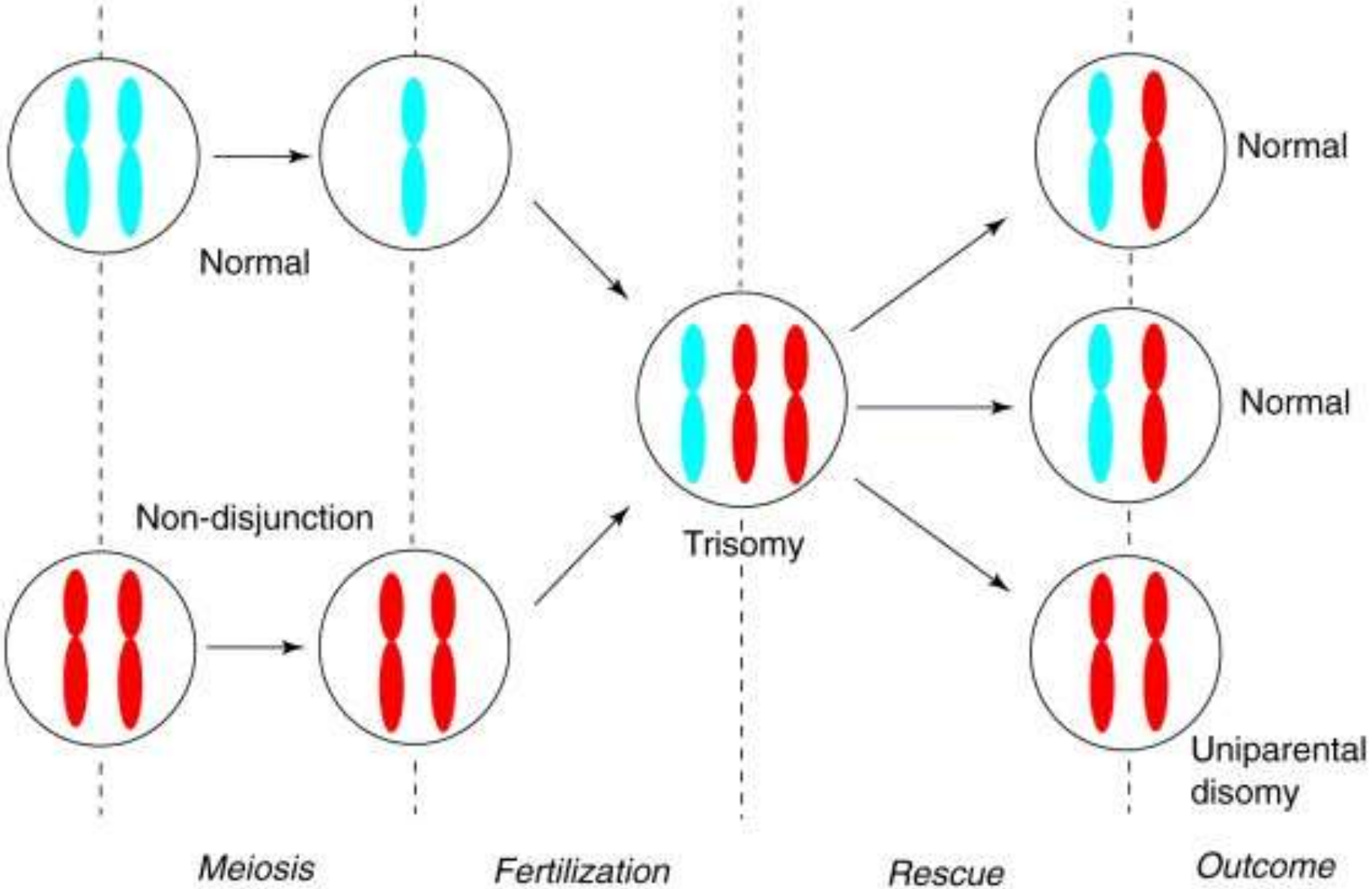
Mutant *Igf2* allele is expressed.



Normal *Igf2* allele is not expressed.

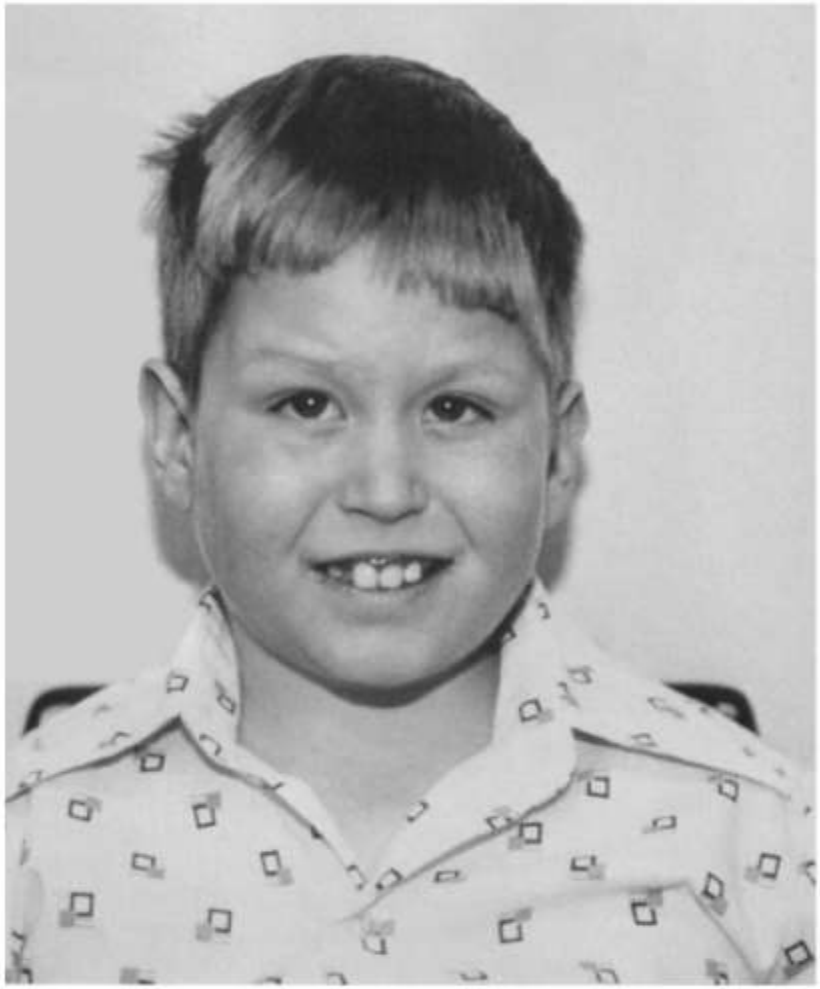
(b) Heterozygotes

- 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

Angelman syndrome

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.

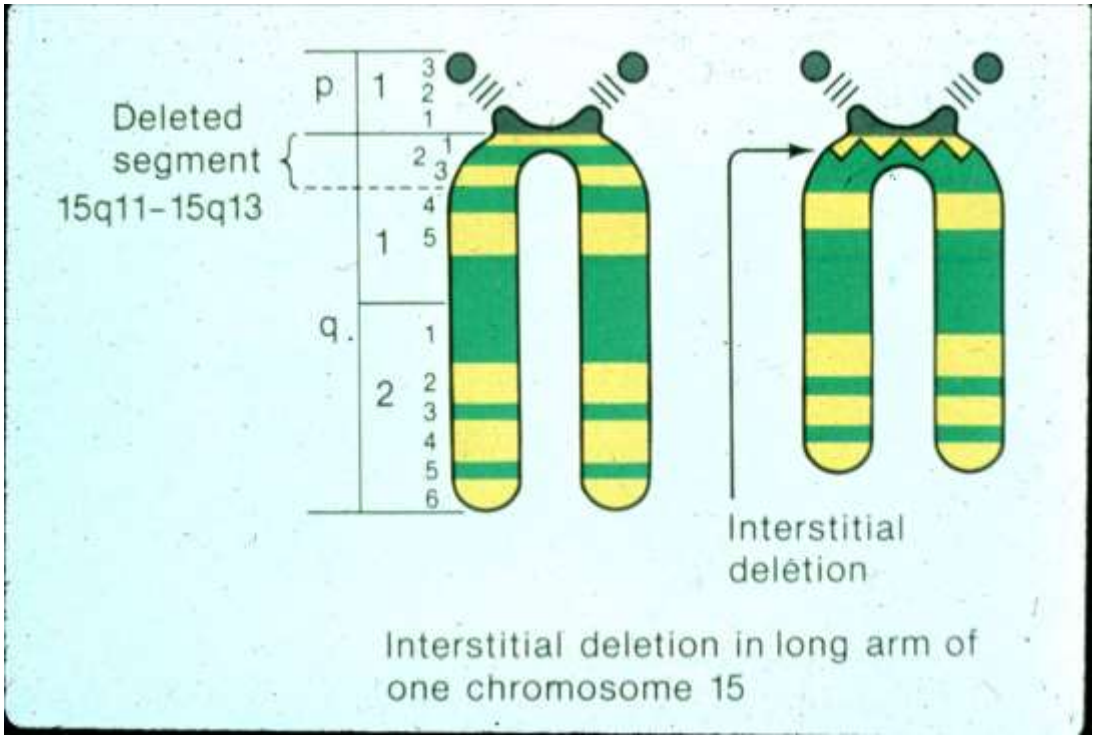
C.The imprint must be capable of affecting gene expression (i.e. turning genes on or off).
D.Imprinting is not a permanent alteration since it must be erased in the germ cell line of every individual so that new imprinting may be introduced.

Example of Imprinting in Humans

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

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.
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.

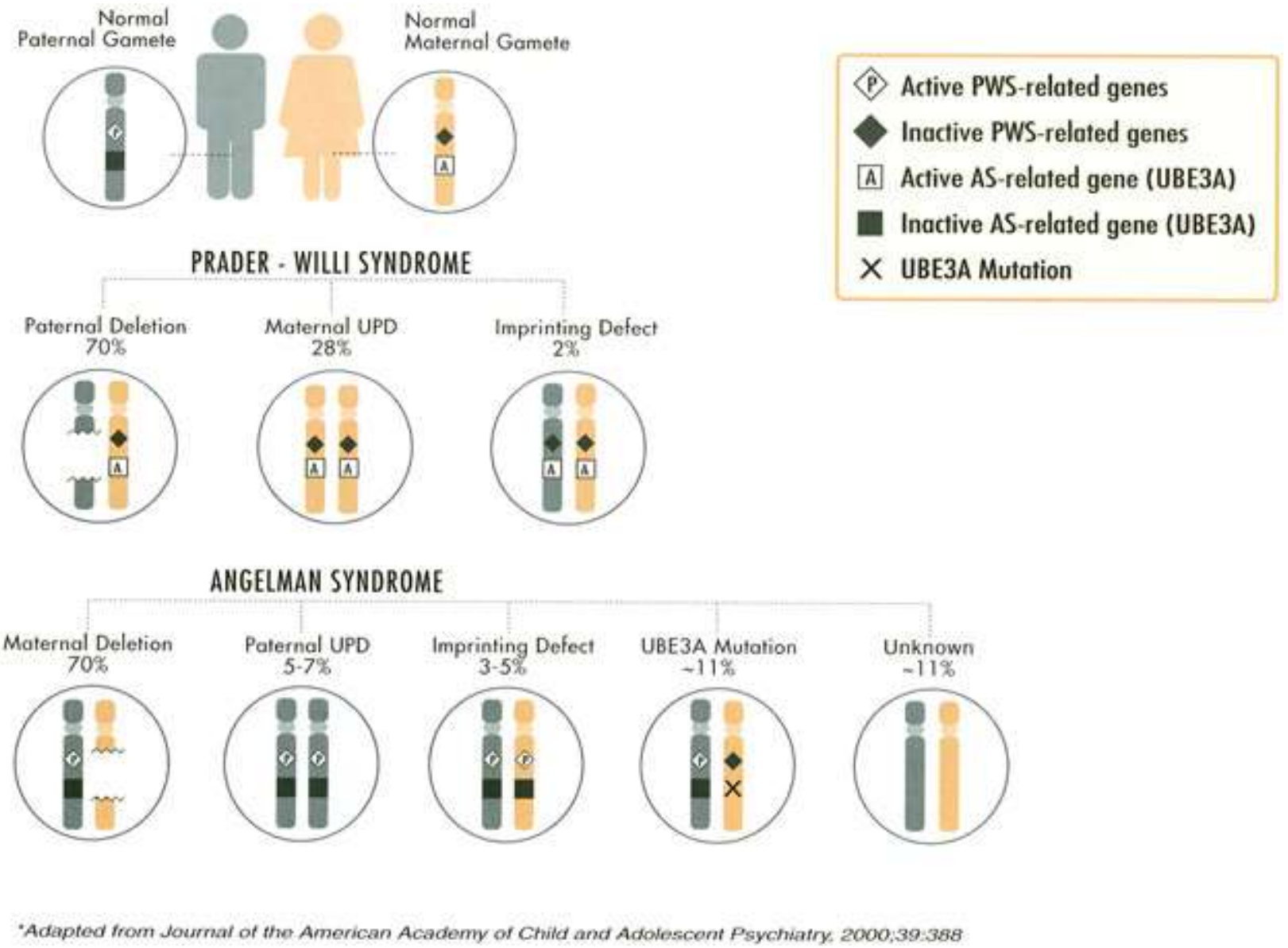
PWS & AS both involve chromo 15q11-13



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

- Some defects in mitochondrial genes prevent cells from making enough ATP and result in diseases that affect the muscular and nervous systems
  - For example, mitochondrial myopathy (**myopathy** is a muscular disease) and Leber's hereditary optic neuropathy (damage to nerves)