HUMAN GENETICS

Lecture Four

ATYPICAL MODE OF INHERITANCE

Objectives:

By the end of this lecture, students should understand atypical patterns of inheritance with special emphasis on:

1. Codominant traits
2. Pseudodominant inheritance
3. The mitochondrial inheritance
4. Anticipation
5. Pleiotropy
6. Variable expressivity
7. Heterogeneity
8. New mutation
9. Complex trait: multifactorial/Polygenic

Codominant traits

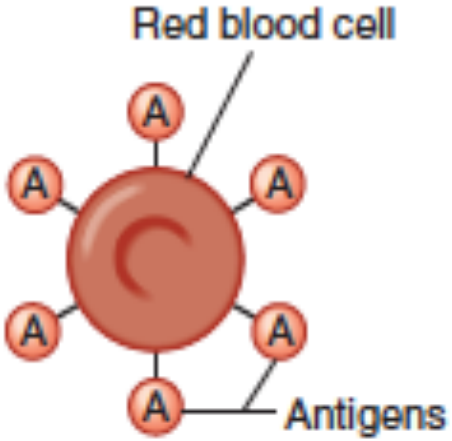
- This pattern occurs when the heterozygote expresses both alleles simultaneously without forming an intermediate phenotype.

For example,

in blood typing, an individual carrying the A and B alleles has an AB blood type.

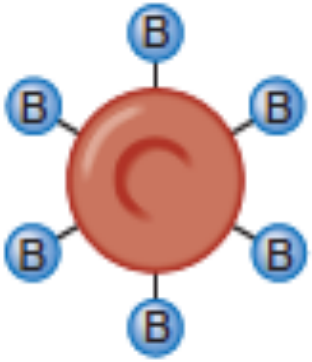
- most genes exist in multiple alleles

CODOMINANCE INHERITANCE



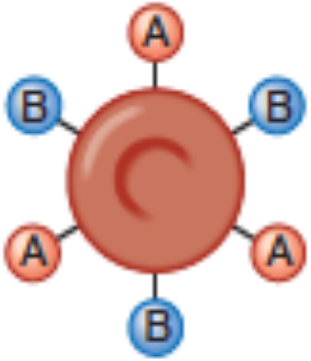
ABO blood type A

(I^AI^A or I^Ai)



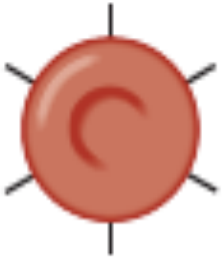
ABO type B

(I^BI^B or I^Bi)



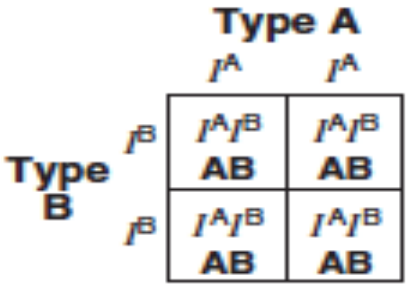
ABO type AB

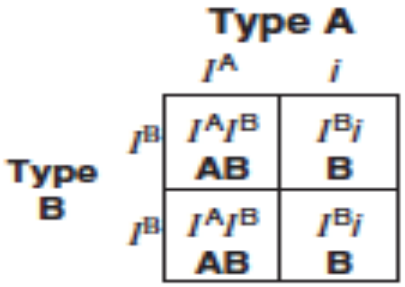
(I^AI^B)

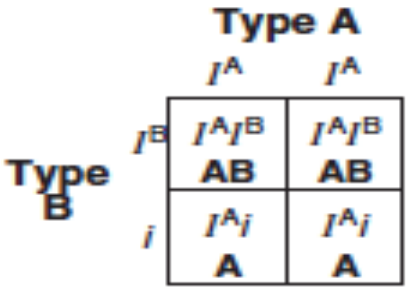


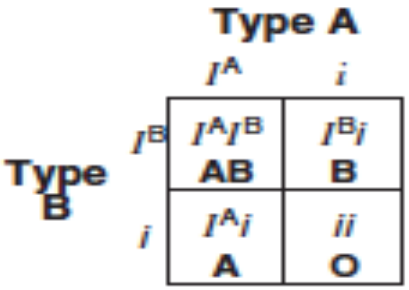
ABO type O

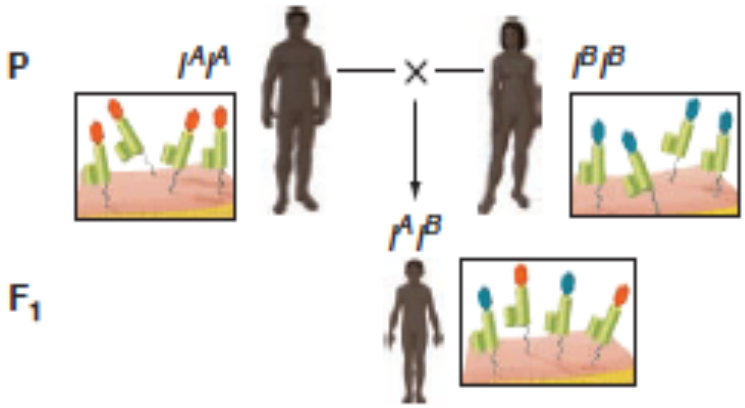
(ii)











Possible genotypes, phenotypes & gametes formed from the four alleles: A_1, A_2, B, & O at the ABO locus

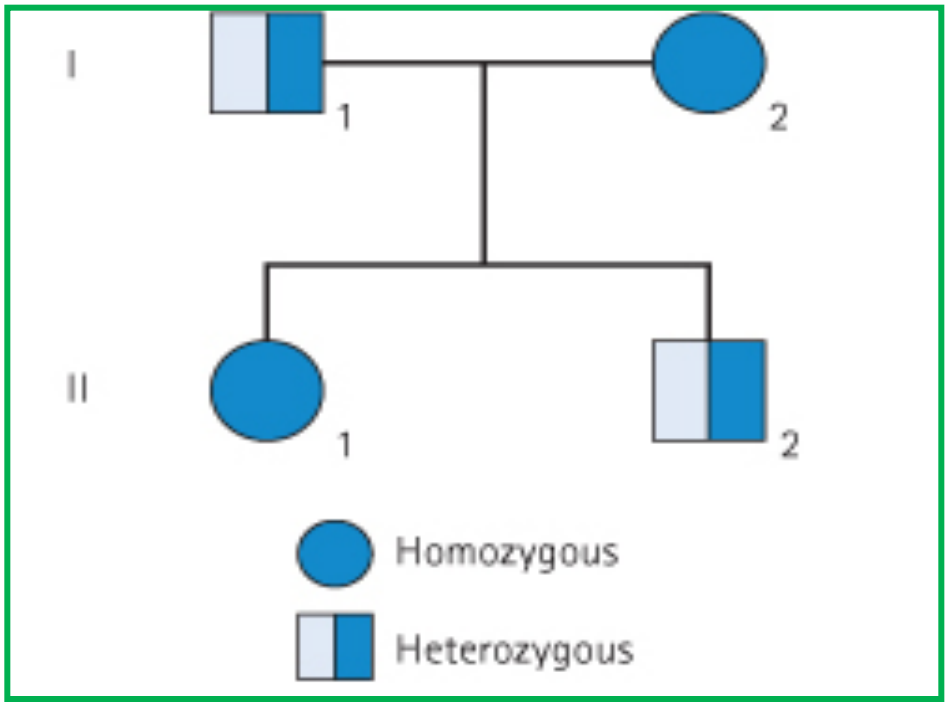
Genotype	Phenotype	Gamete
A_1A_1	A_1	A_1
A_2A_2	A_2	A_2
BB	B	B
OO	O	O
A_1A_2	A_1	A_1 or A_2
A_1B	A_1B	A_1 or B
A_1O	A_1	A_1 or O
A_2B	A_2B	A_2 or B
A_2O	A_2	A_2 or O
BO	B	B or O

PSEUDODOMINANT INHERITANCE

is the situation in which the inheritance of a recessive trait mimics a dominant pattern.

Pedigree: Pseudodominant inheritance

- A woman homozygous for an autosomal recessive disorder whose husband is heterozygous for the same disorder.
- Their children have a 1 in 2 (50%) chance of being affected (homozygous) i.e. pseudodominant



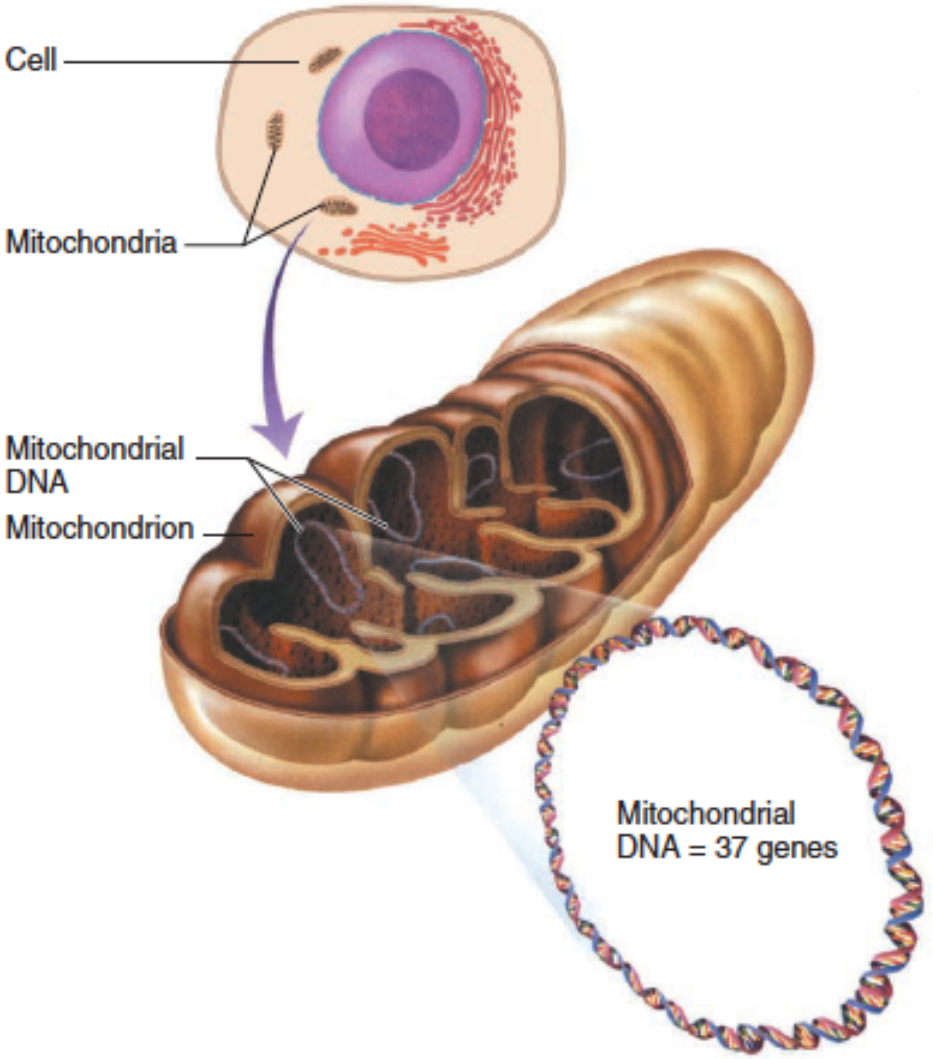
Atypical inheritance of single-gene disorders

What are the situations in which the inheritance of single-gene disorders diverges from typical mendelian patterns?

- Maternal inheritance of mitochondrial mutations
- Anticipation
- Atypical presentation for Autosomal Dominant defects:
  - Pleotropy
  - Variable expressivity
  - Reduced penetrance
  - New mutation
- Unusual inheritance patterns due to Genomic Imprinting
- Mosaicism:
  - Somatic mosaicism
  - Germline mosaicism

MITOCHONDRIAL INHERITANCE

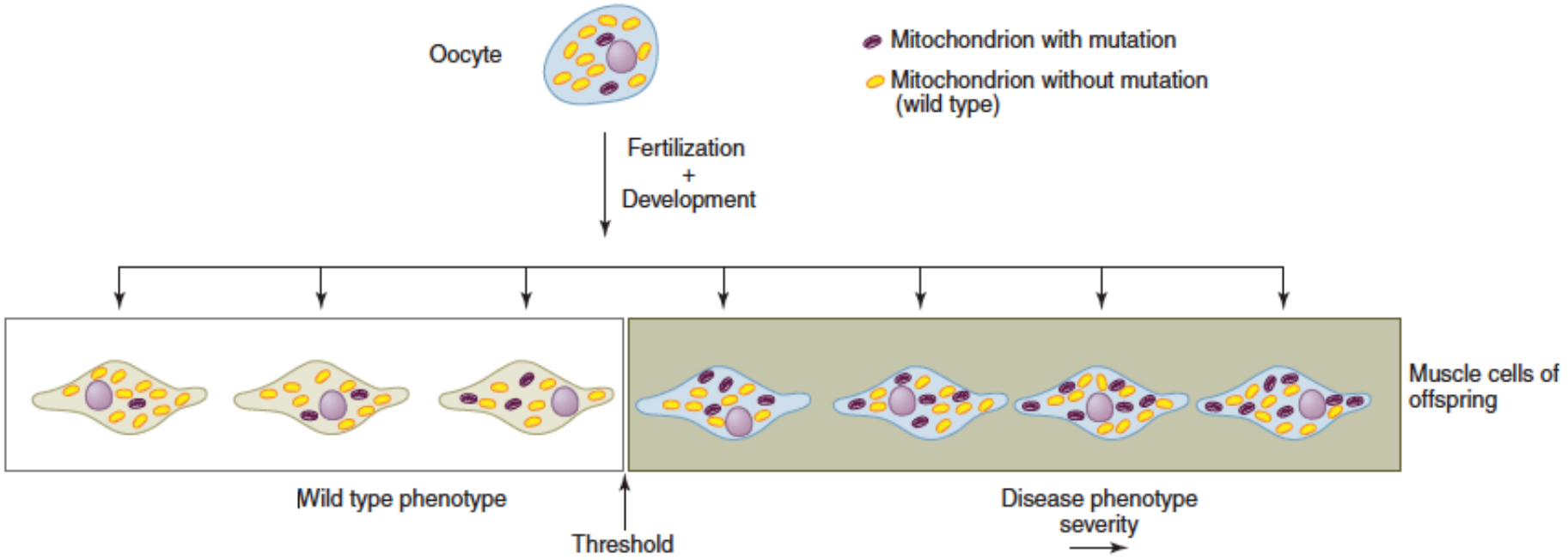
- Each cell contains thousands of copies of mitochondrial DNA with more being found in cells having high energy requirement (e.g. brain & muscle)
- Mitochondria (& their DNA) are **inherited from the mother** (through ova)
- mtDNA is a **small circular double-stranded** molecule containing **37 genes** (coding for rRNA, tRNA, and some of the proteins of the mitochondrial electron transport chain)



Homoplasmy vs. Heteroplasmy

- **Homoplasmy** = normally the mtDNA from different mitochondria is almost identical.
- **Heteroplasmy** = the presence of two populations of mtDNA in a cell; the normal mtDNA & the mutant mtDNA.
- The proportion of mutant mtDNA varies between cells & tissues → a range of phenotypic severity in mitochondrial inheritance.

Mitochondrial inheritance



- Mitochondria and their genes are passed only from the mother.
- Cells have many mitochondria. If an oocyte is heteroplasmic, differing numbers of copies of a mitochondrial mutation may be transmitted.
- The phenotype reflects the proportion of mitochondria bearing the mutation.

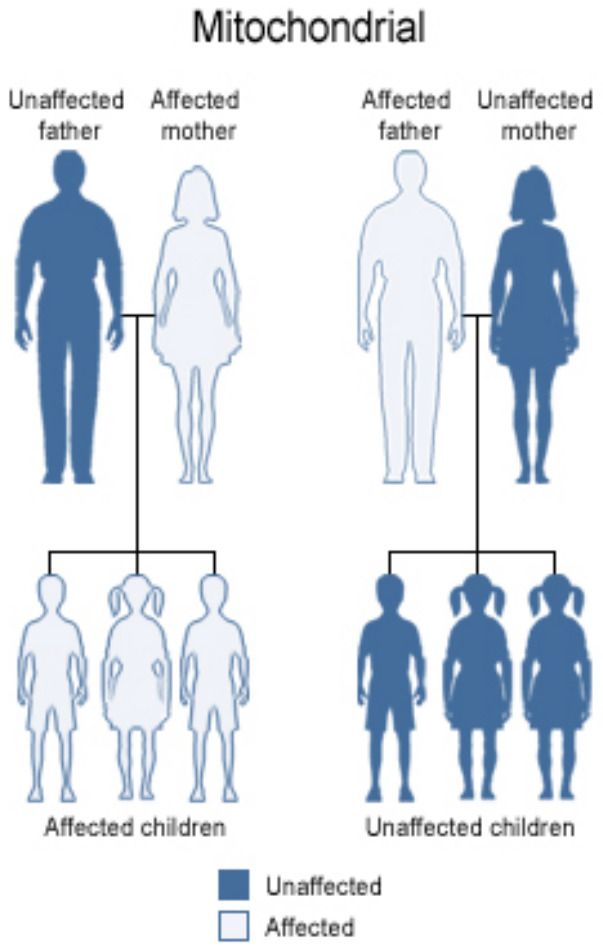
- Typical Example of Mitochondrial Disorders

Leber hereditary optic neuropathy (LHON)

Rapid Optic nerve death → blindness in young adult life

Mitochondrial inheritance

Males do not transmit the disease as the cytoplasm is inherited only from the mother since the mitochondria are present in the cytoplasm



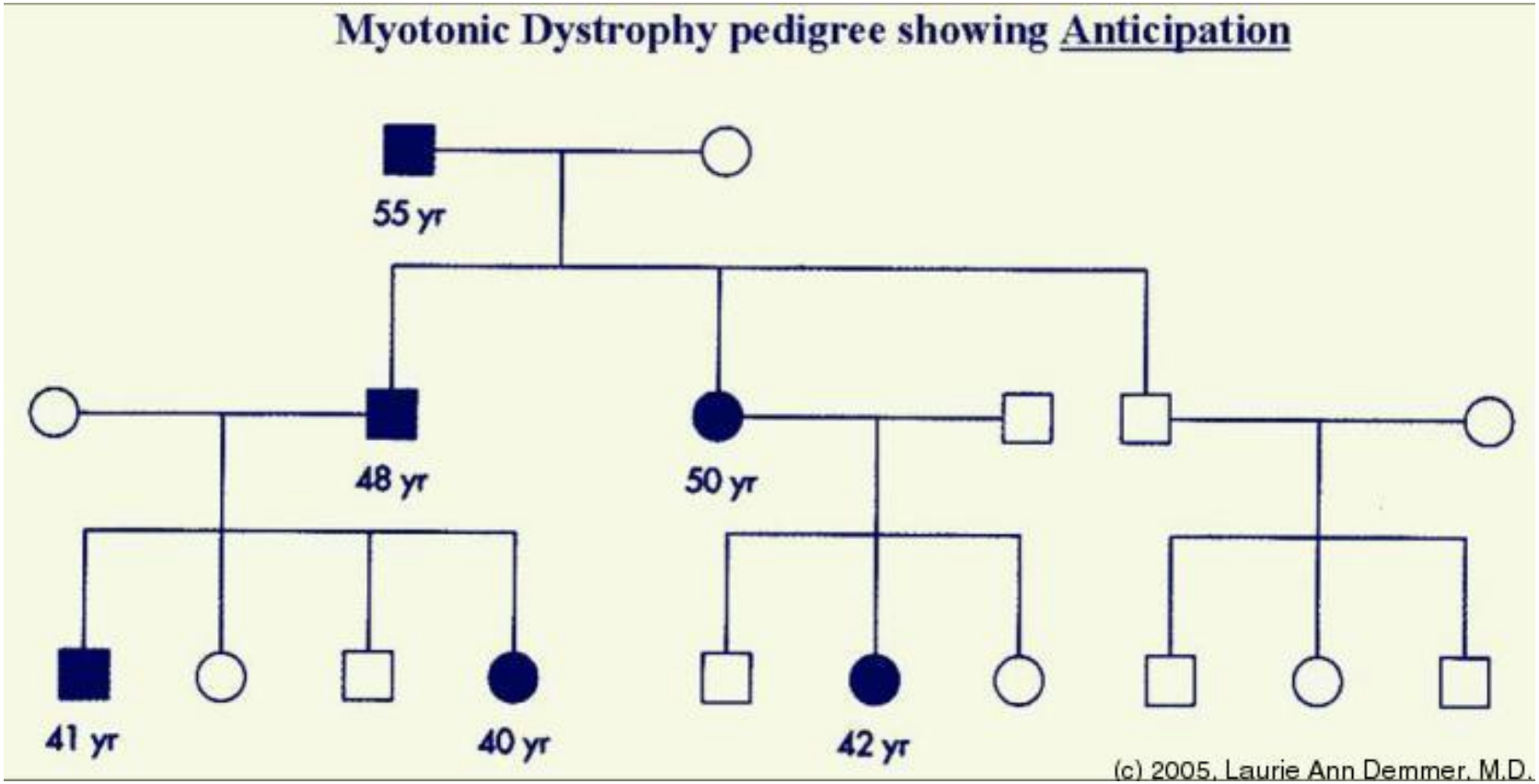
ANTICIPATION

- A pattern of inheritance in which individuals in the most recent generations of a pedigree develop a disease **at an earlier age** or **with greater severity** than do those in earlier generation.
- The reason might be the gradual expansion of trinucleotide repeat polymorphisms within or near a coding gene
- Examples of diseases showing anticipation:
  - Huntington disease
  - Myotonic dystrophy

Myotonic Dystrophy

Pedigree	Age of onset	Phenotype	Number of copies of GAC mRNA repeat
I (1, 2)	Older adulthood	Mild forearm weakness, cataracts	50–80
II (1, 2)	Mid-adulthood	Moderate limb weakness	80–700
III (1, 2, 3)	Childhood	Severe muscle impairment, respiratory distress, early death	700+

Pedigree analysis for Myotonic dystrophy



PLEIOTROPY

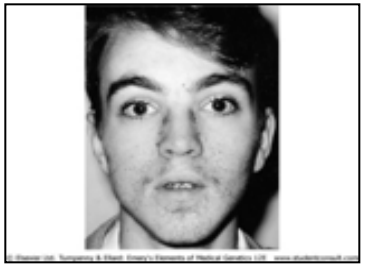
- A single-gene disorder with many symptoms, or a gene that controls several functions or has more than one effect, is termed ***pleiotropic*.**

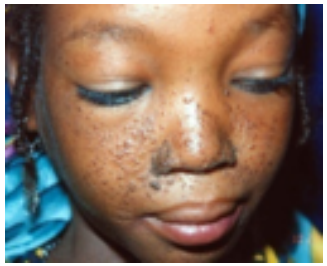
- Causes autosomal dominant disorders

- *Example:*

tuberous sclerosis

affected individuals can present with either learning difficulties, Epilepsy, facial rashes , or all features





VARIABLE EXPRESSIVITY

The clinical features in autosomal dominant disorders can show striking variation from person to person, even in the same family.

Example:

Autosomal dominant polycystic kidney disease

some affected individuals develop ***renal failure*** in early adulthood

others have just a ***few renal cysts*** that do not significantly affect renal function

REDUCED PENETRANCE

- In some individuals heterozygous for gene mutations giving rise to certain autosomal dominant disorders there may be no abnormal clinical features, representing so-called *reduced penetrance* or 'skipping a generation‘

- Reduced penetrance might be due to:
  - **modifying effects of other genes**
  - **interaction of the gene with environmental factors**

NEW MUTATIONS

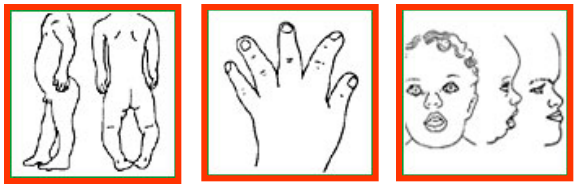
- In autosomal dominant disorders an affected person will **usually** have an affected parent.

- However, this is **not always** the case and it is **not unusual** for a trait to appear in an individual when there is no family history of the disorder.

- The sudden unexpected appearance of a condition arising as a result of a mistake occurring in the transmission of a gene is called a ***new mutation***.

Achondroplasia

- A form of short-limbed dwarfism, in which the parents **usually** have normal stature



- **Diagnosis/testing:**
  - Characteristic clinical and radiographic finding
  - Molecular genetic tests: mutation in the *FGFR3* gene on chromosome 4p16.3 (coding for fibroblast growth factor receptor 3)

- The offspring of persons with achondroplasia had a 50% chance of having achondroplasia

- What other possible explanations for the 'sudden' appearance of this disorder?

– non-penetrance: One of the parents might be heterozygous for the mutant allele but so mildly affected that it has not previously been detected
– Variable expressivity
– the family relationships not being as stated, e.g. *non-paternity*

MULTIFACTORIAL/ POLYGENIC DISORDERS

COMPLEX TRAITS

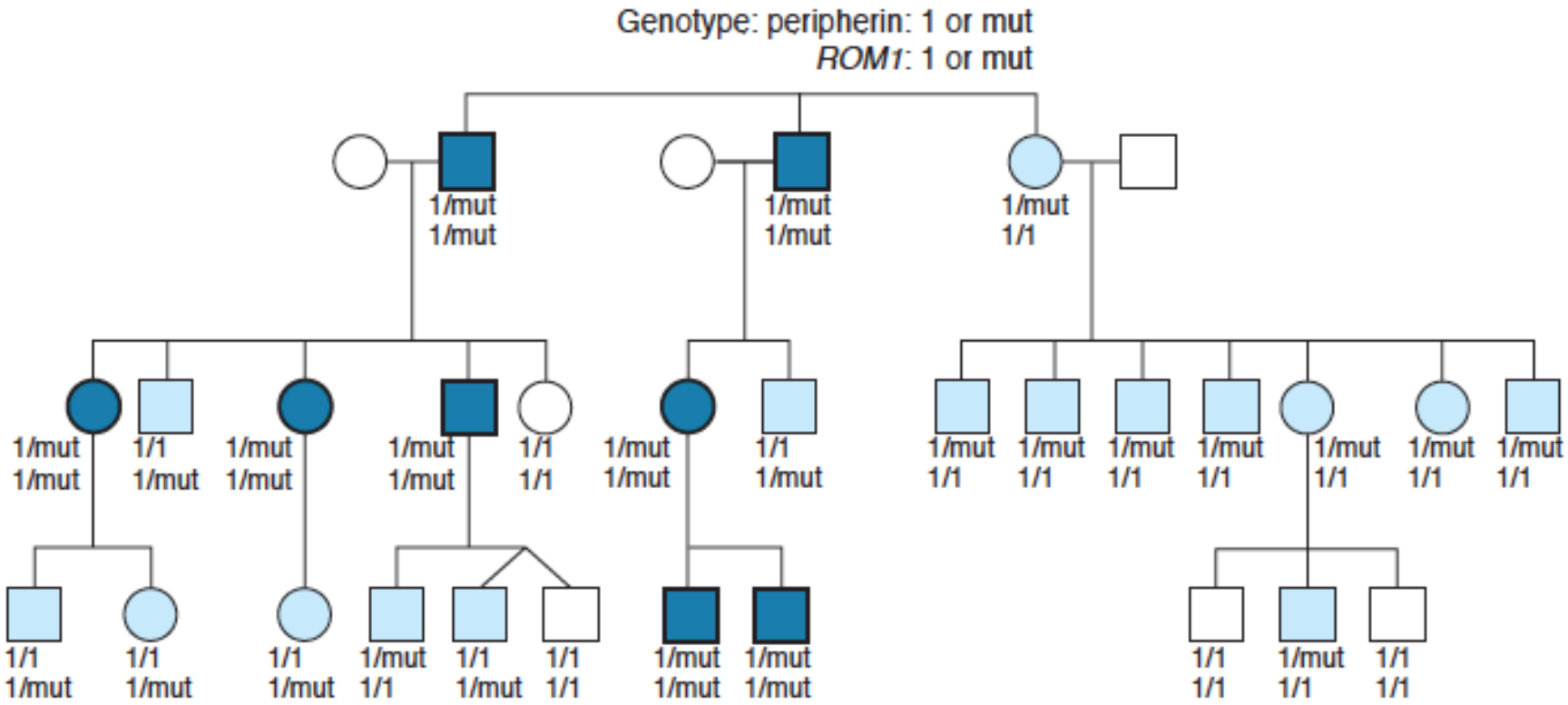
- Complex traits are conditions which are likely to be due to the interaction of more than one gene.

- The effects may be additive, one may be rate-limiting over the action of another, or one may enhance or multiply the effect of another.

- ***e.g.*** ***Digenic inheritance:*** where a disorder has been shown to be due to the additive effects of **heterozygous mutations at two different gene loci**

- In man one form of **retinitis pigmentosa**, a disorder of progressive visual impairment, is caused by **double heterozygosity** for mutations in **two unlinked genes**, which both encode proteins present in photoreceptors. Individuals with only one of these mutations are not affected.

PEDIGREE OF A FAMILY WITH RETINITIS PIGMENTOSA DUE TO DIGENIC INHERITANCE



MULTIFACTORIAL/POLYGENIC DISORDERS

- Human characteristics such as height, skin color and intelligence could be determined by the interaction of **many genes**, each exerting a small additive effect.

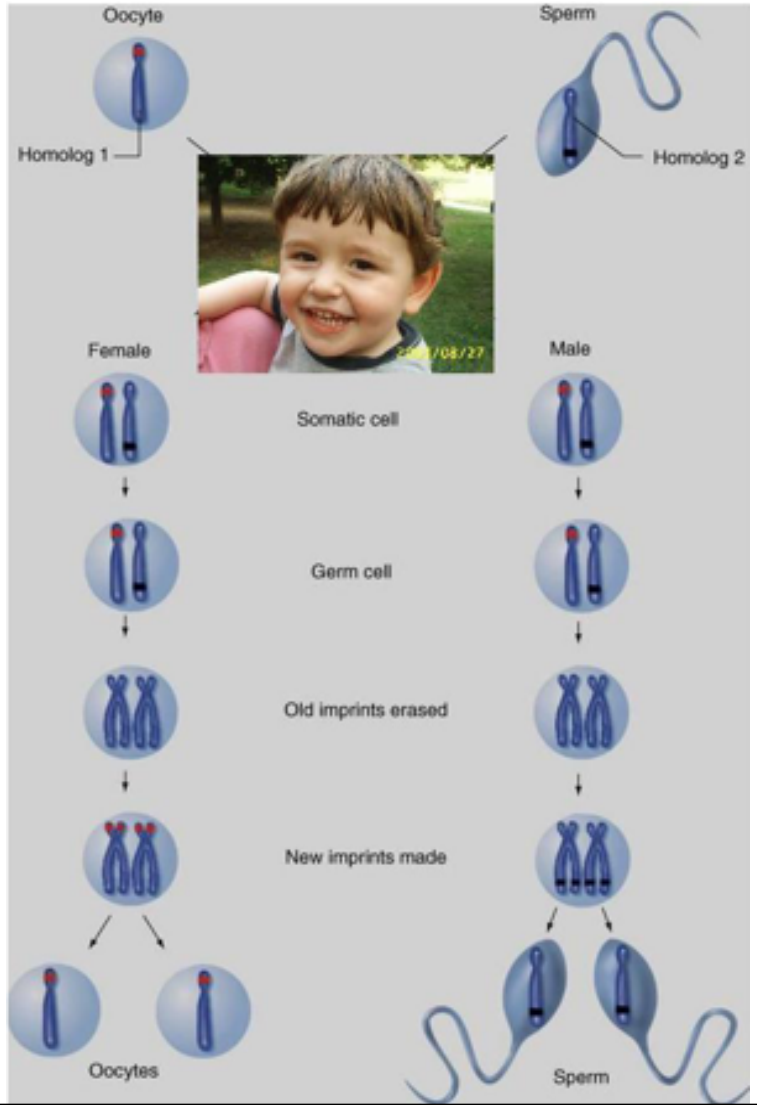
- This model of ***quantitative inheritance*** can explain the pattern of inheritance for many relatively common conditions including
  - congenital malformations such as cleft lip and palate
  - late-onset conditions such as
    - Hypertension
    - Diabetes mellitus
    - Alzheimer disease

- The prevailing view is that **genes at several loci** interact to generate a **susceptibility** to the effects of **adverse environmental** trigger factors.

GENOMIC IMPRINTING

An example of Non-Mendelian Inheritance

Certain chromosomes retain a memory or "imprint" of parental origin that influences whether genes are expressed or not during gametogenesis

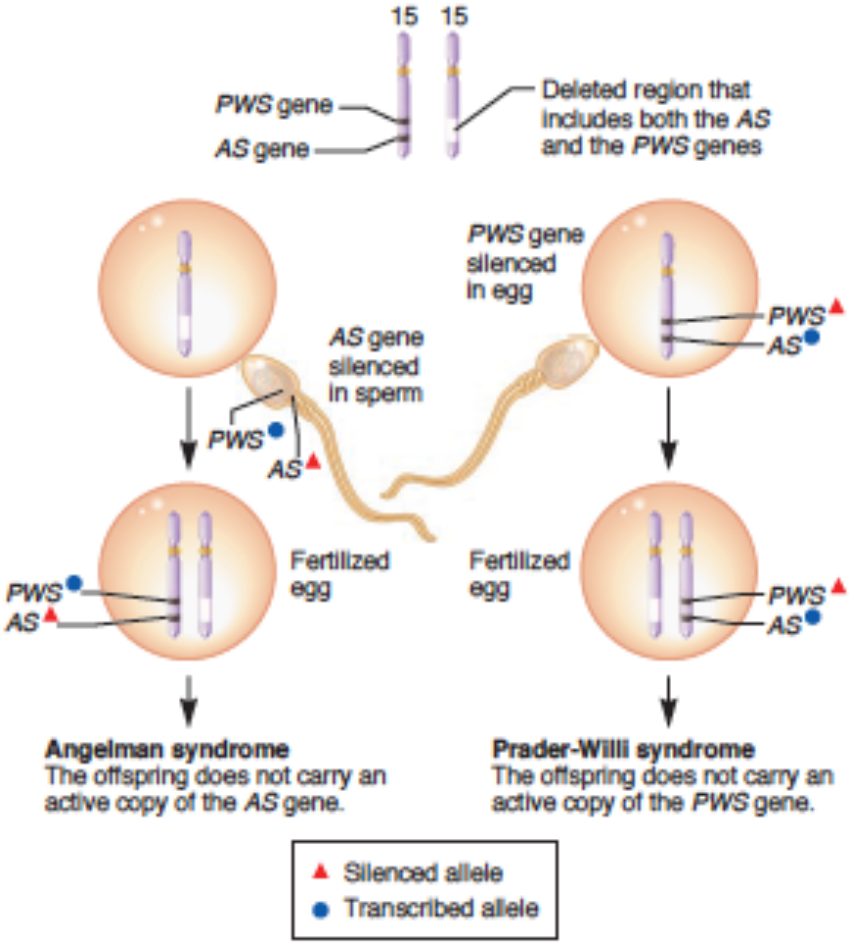


The role of imprinting in the development of Angelman and Prader-Willi syndromes

- A small region on chromosome 15 contains two different genes designated the AS gene and PWS gene in this figure.

- If a chromosome 15 deletion is inherited from the mother, Angelman syndrome occurs because the offspring does not inherit an active copy of the AS gene (left).

- Alternatively, the chromosome 15 deletion may be inherited from the father, leading to Prader-Willi syndrome. The phenotype of this syndrome occurs because the offspring does not inherit an active copy of the PWS gene (right).



Take home Messages:

- An accurate determination of the family pedigree is an important part of the workup of every patient
- Exceptions to Mendelian inheritance do occur in single-gene disorders.
- The inheritance pattern of an individual pedigree may be obscured by a number of other factors that may make the mode of inheritance difficult to interpret
- Some characteristics and many common familial disorders, do not usually follow a simple pattern of Mendelian inheritance.