HUMAN GENETICS

Lecture Three: Atypical Mode of Inheritance

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Objectives:

- By the end of this lecture, students should understand atypical patterns of inheritance with special emphasis on:
- Codominant traits
- Pseudodominant inheritance
- The mitochondrial inheritance
- Anticipation
- Pleiotropy
- Variable expressivity
- Heterogeneity
- New mutation

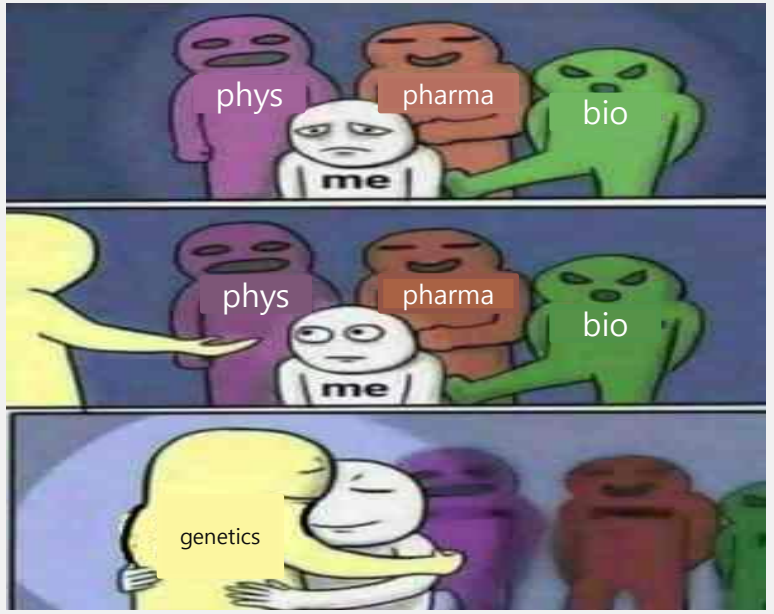
Codominant traits

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

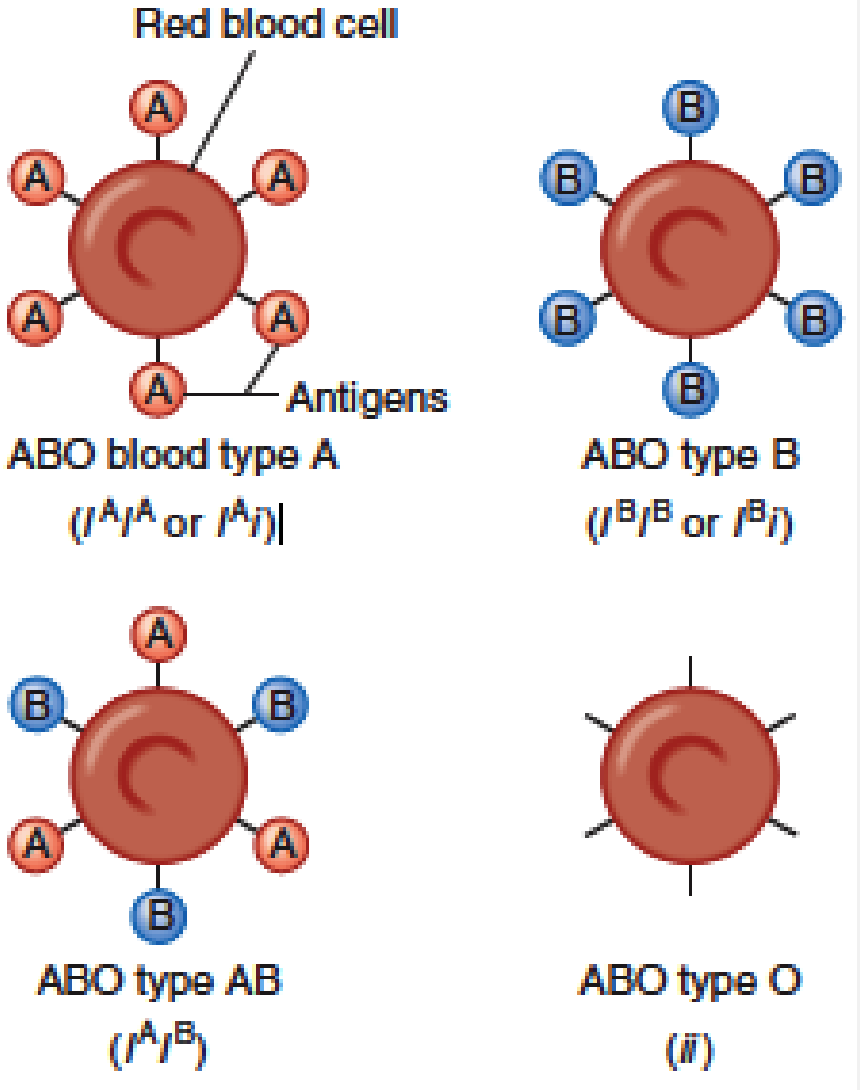
For example:

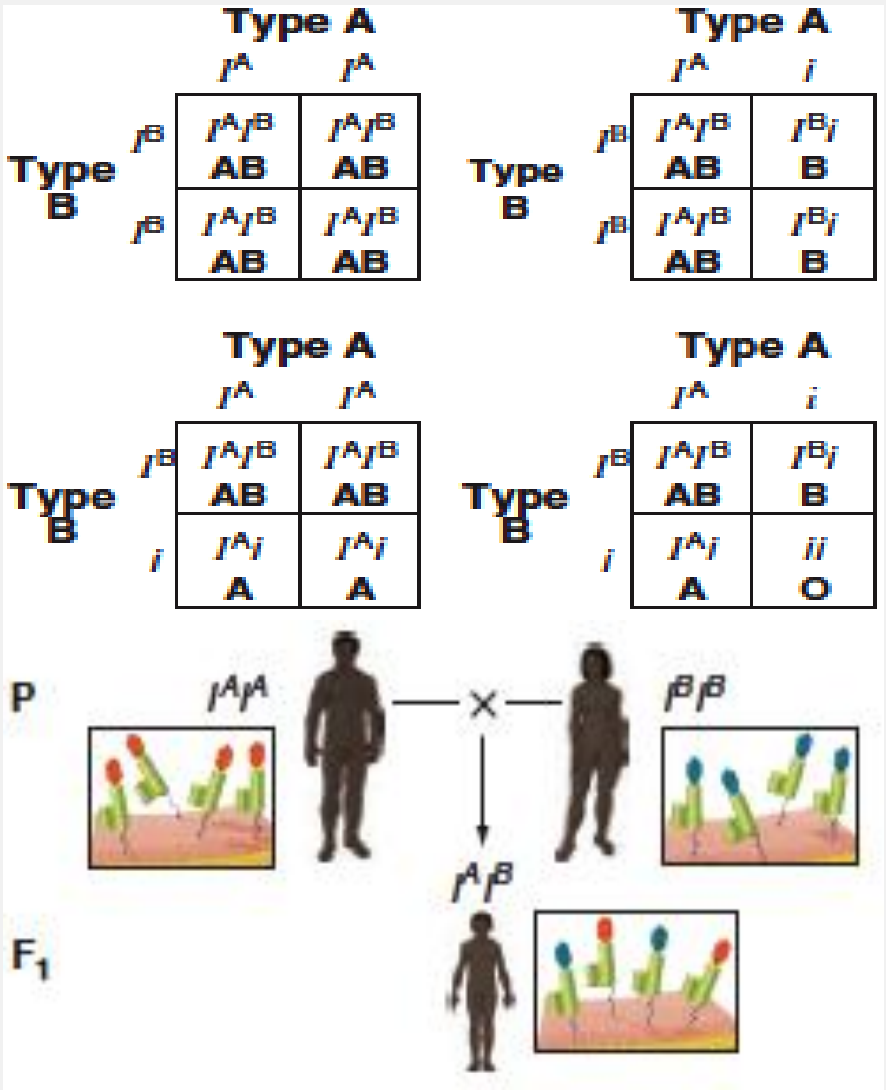
in blood typing, an individual carrying the A and B alleles has an AB blood type.

- most genes exist in multiple alleles



Codominance inheritance





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

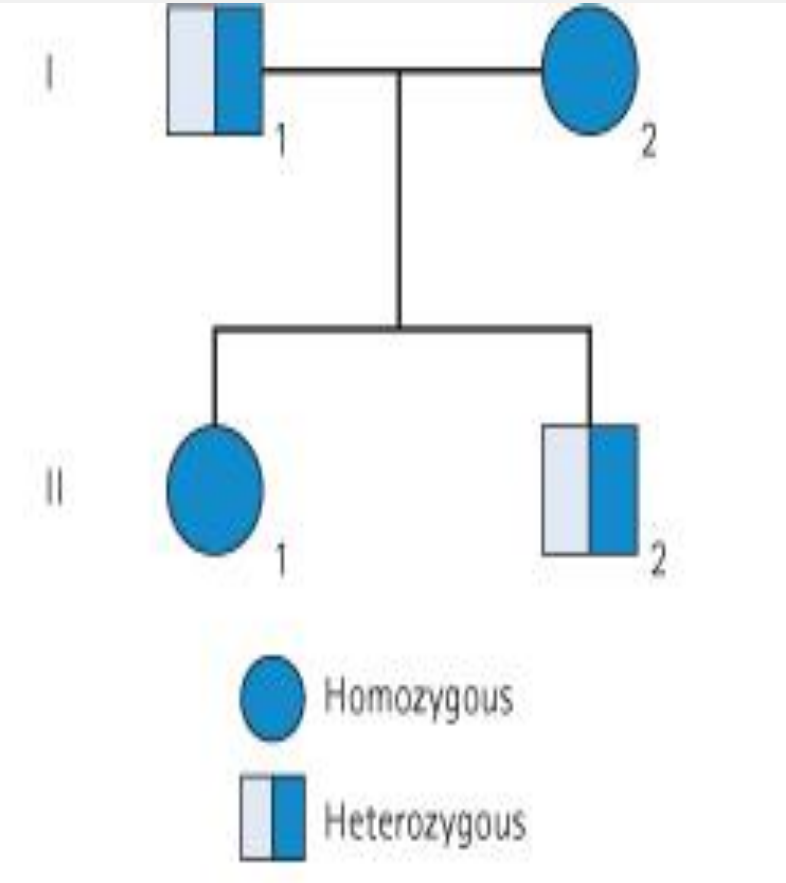
Gamete	Phenotype	Genotype
A1	A1	A1A1
A2	A2	A2A2
B	B	BB
O	O	OO
A1 or A2	A1	A1A2
A1 or B	A1B	A1B
A1 or O	A1	A1O
A2 or B	A2B	A2B
A2 or O	A2	A2O
B or O	B	BO

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 :

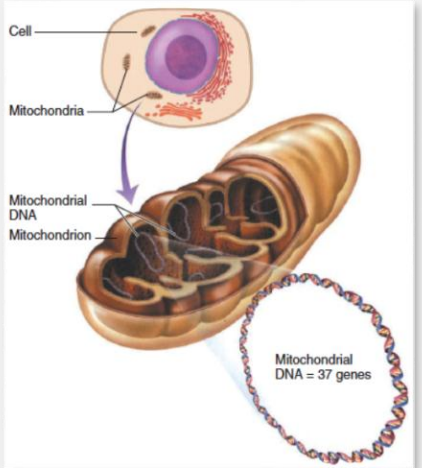
What are the situations in which the inheritance of single-gene disorders diverges from typical mendelian patterns ?

- Maternal inheritance of mitochondrial mutations.
- Anticipation.
- Atypical presentation for Autosomal Dominant defects: 1-Pleiotropy, 2-Variable expressivity, 3-Reduced penetrance, 4-New mutation.

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)

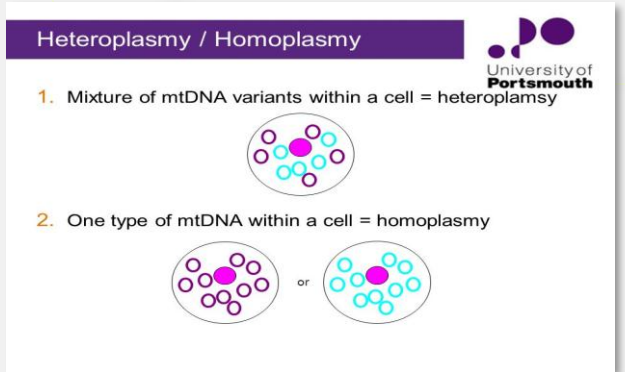
Mothers pass it to their children (male and female)



Important information:
All doughters and sons all affected if the mother affected
>>it's only inherited from the mother

HOMOPLASMY VS. HETEROPLASMY

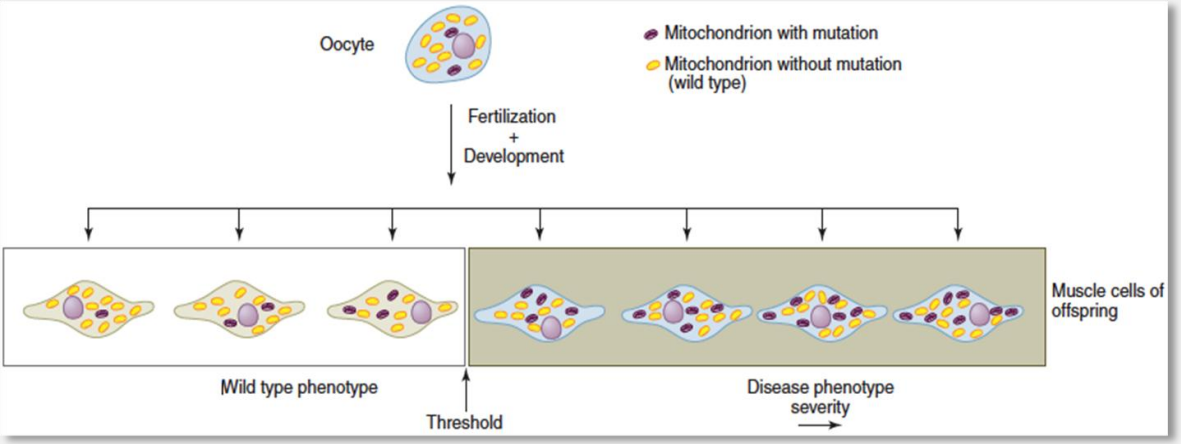
- Homoplasmy = normally the mtDNA from different mitochondria is almost identical.
- Heteroplasmy = the presence of two populations of mtDNA in a cell; the normal mtDNA & the mutant mtDNA.
- The proportion of mutant mtDNA varies between cells & tissues
  a range of phenotypic severity in mitochondrial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



Important information:
Homoplasmy: is having one generation (one genotype) in metochondria

Hetroplasmy: is having two generations (two genotypes) in metochondria

Mitochondrial inheritance :

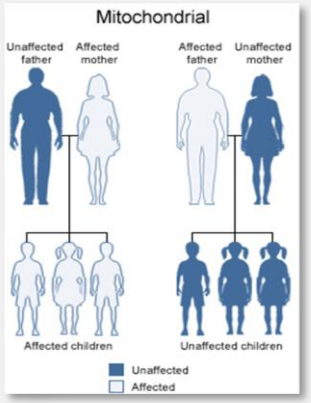


Mitochondrial Inheritance

Mitochondrial Disease

- 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

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



NOTE:

- The presence of 3 or less mutations in the mitochondria will not cause abnormality.
- The presence of more than 3 mutations in the mitochondria will cause abnormality, And the more mutations the more severe is the abnormality

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 onset of the disease differ from generation to another

The reason might be the gradual expansion of trinucleotide repeat polymorphisms within or near a coding gene

Examples of diseases showing anticipation:

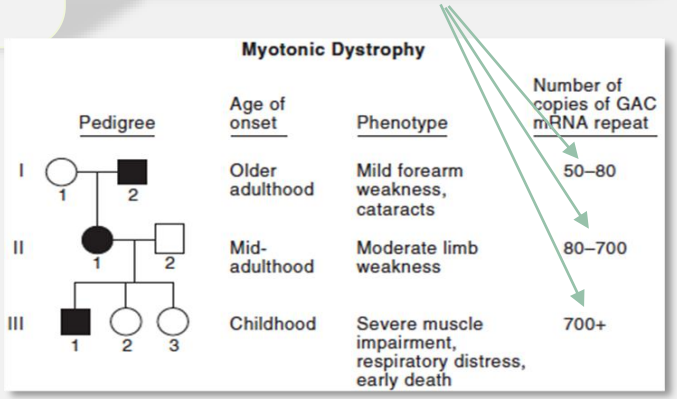
- Huntington disease
- Myotonic dystrophy

Huntington Disease

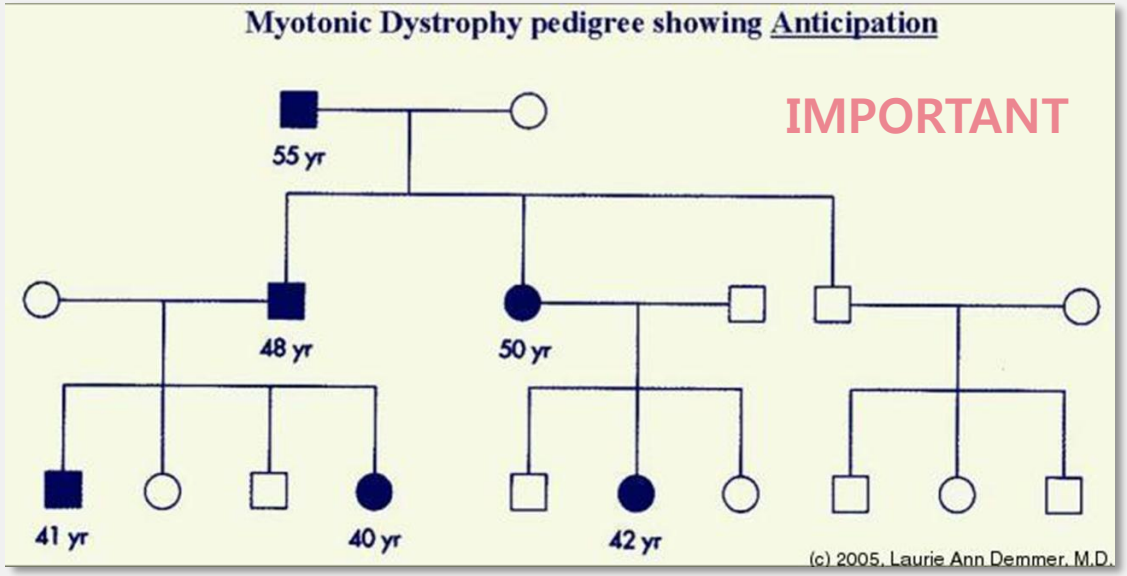
Myotonic dystrophy

*e.g. the grandmother had hypothyroidism at 60
The mother had the disease at 40
She get the disease at 30
So, in each generation the disease starts at earlier age

Severity increases as the number of GAC mRNA repeat increase



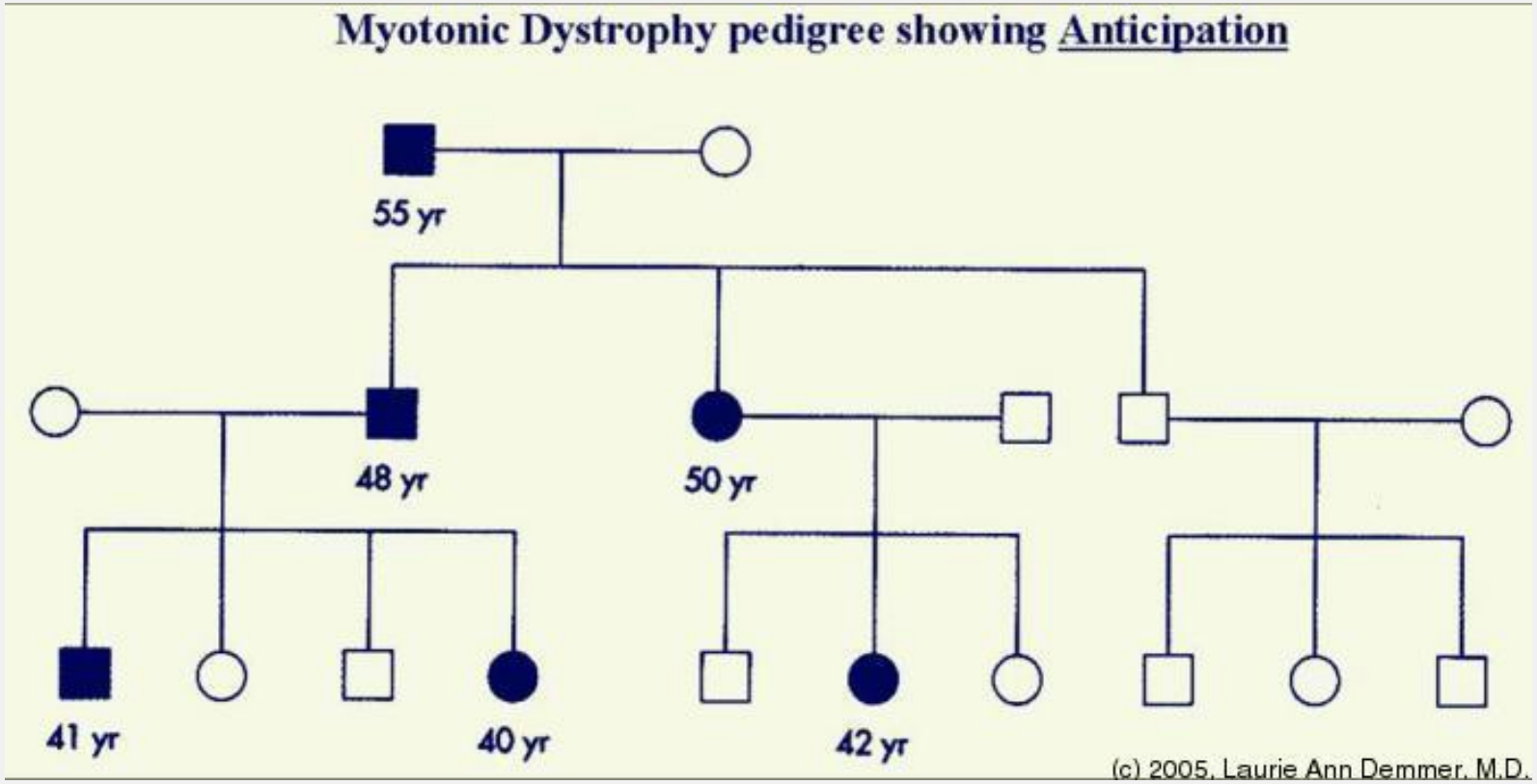
PEDIGREE ANALYSIS FOR MYOTONIC DYSTROPHY



*المرض يظهر في كل الأجيال لكن في كل جيل وقت ظهور المرض يكون أبكر.

Important information:
if this pedigree is without age, it will be "Autosomal dominant"
If it is with age Then it will be "Autosomal dominant with anticipation"

Pedigree Analysis for Myotonic Dystrophy



If this pedigree is without age, it will be "Autosomal dominant"
If it is with age Then it will be "Autosomal dominant with anticipation"
- 437 Note

Pleiotropy

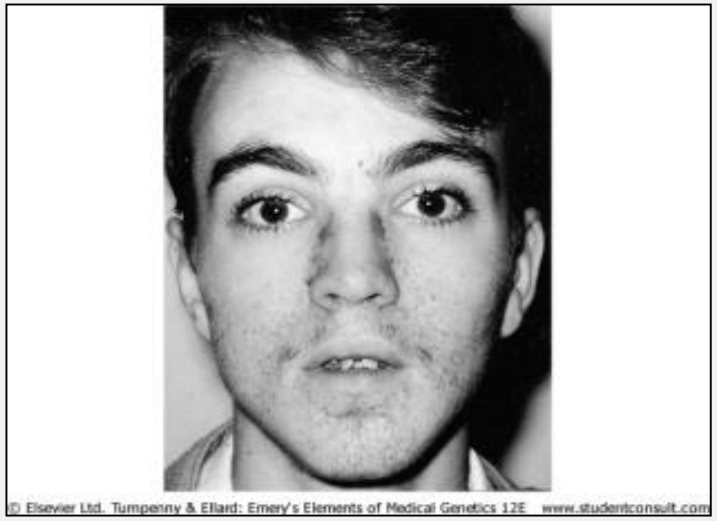
A single-gene disorder with many symptoms, or a gene that controls several functions or has more than one effect, is termed ***pleiotropic.***

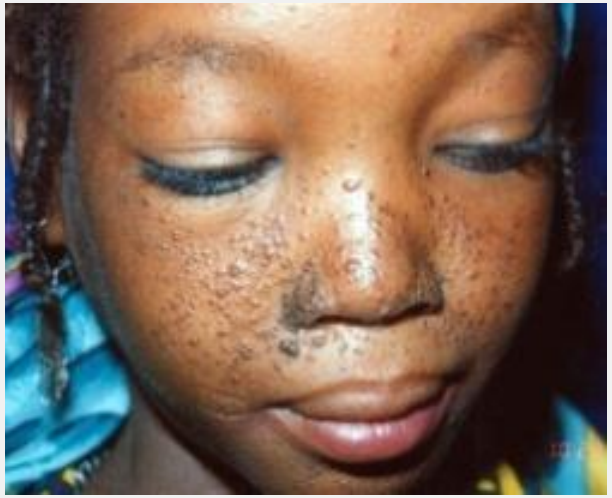
- Causes autosomal dominant disorders

- *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

* كل الأشخاص اللي يحملون الصفه -dominan- راح تظهر الصفه عندهم لكن تختلف الشدة

Important information:
The expression is different from patient to patient

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**

Important information:
Reduced penetance is: Skipping a generation

*مرض عائلي يغيب في جيل معين ثم يرجع يظهر مره ثانيه

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 a ppear 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*.**

Important information:
New mutation: The oncet of a disease and then it will become a dominant genotype (once it's there you will see it in the next generations)

Thank You

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شكر خاص لـ وليد المستشار

Special thanks to Team 437

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