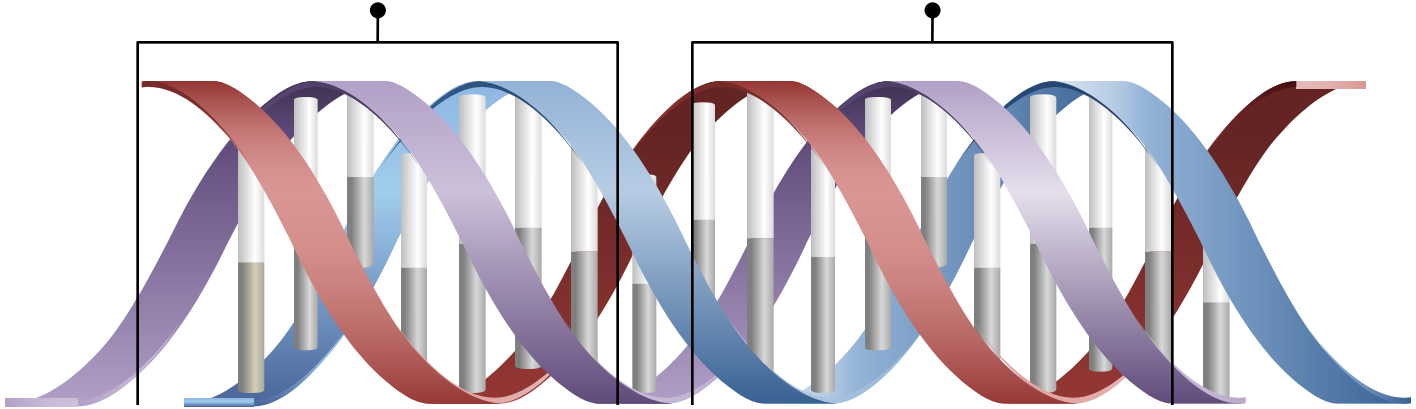
جامعة الملك سعود
King Saud University

Human Genetics 439

Lecture 4

ATYPICAL MODE OF INHERITANCE



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MED439

Objectives:

By the end of the lecture, the student should:

- Codominant traits
- Pseudodominant inheritance
- The mitochondrial inheritance
- Anticipation
- Pleiotropy
- Variable expressivity
- Heterogeneity
- New mutation
- Complex trait: multifactorial/Polygenic

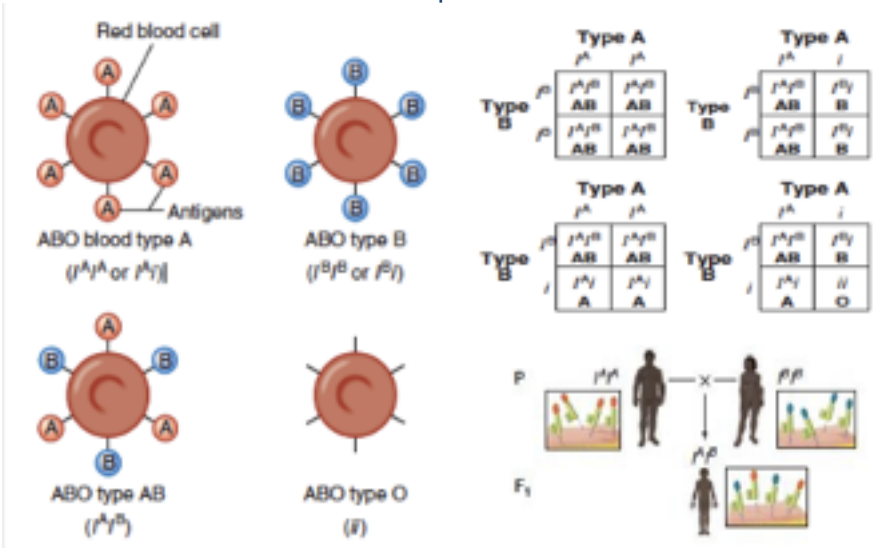
Codominant traits

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



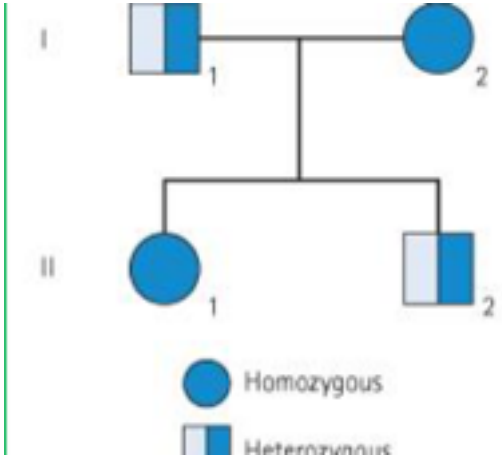
PSEUDODOMINANT INHERITANCE

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

•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?

Autosomal Dominant defects:

- Pleotropy
- Variable expressivity
- Reduced penetrance
- New mutation

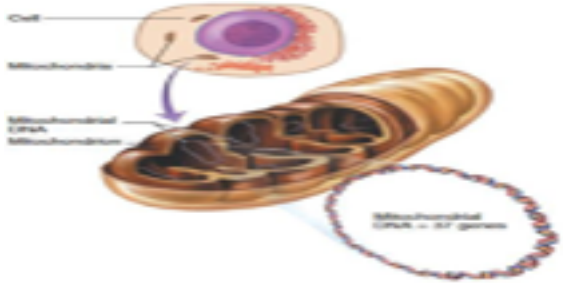
- Maternal inheritance of mitochondrial mutations
- Anticipation
- Atypical presentation for Autosomal Domain defects

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. (is having one generation (one genotype) in mitochondria).

Heteroplasmy: the presence of **two populations of mtDNA** in a cell; the normal mtDNA & the mutant mtDNA. (is having two generations (two genotypes) in mitochondria).

The proportion of mutant mtDNA varies between cells & tissues → a range of phenotypic severity in mitochondrial inheritance.

MITOCHONDRIAL INHERITANCE

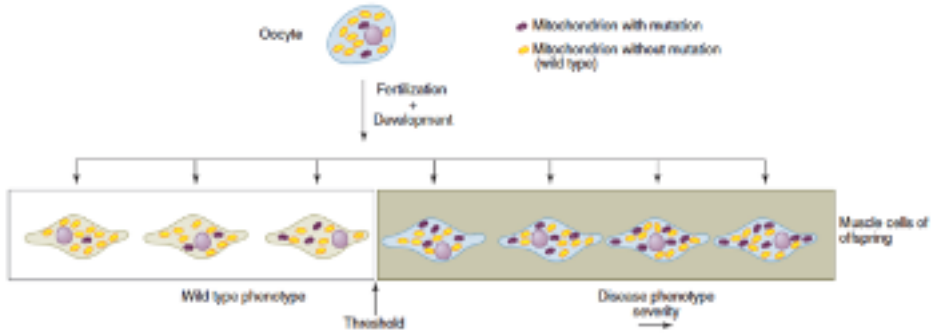
Mitochondria and their genes are passed only from the mother.

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:

- (LHON) Leber hereditary optic neuropathy
- Rapid Optic nerve death ↓ blindness in young adult life

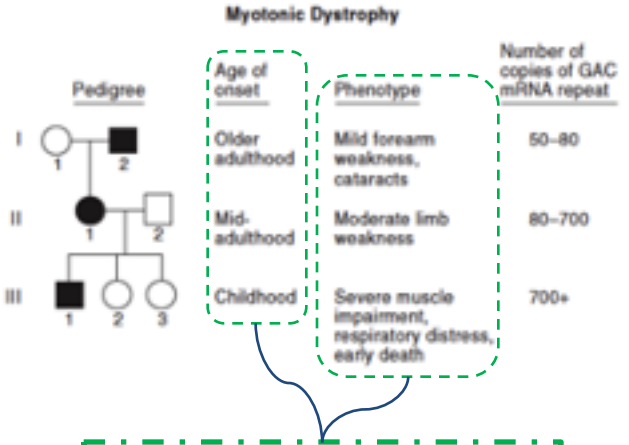


Males do not transmit the disease as the cytoplasm is inherited **only from the mother since the mitochondria are present in the cytoplasm.**

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.

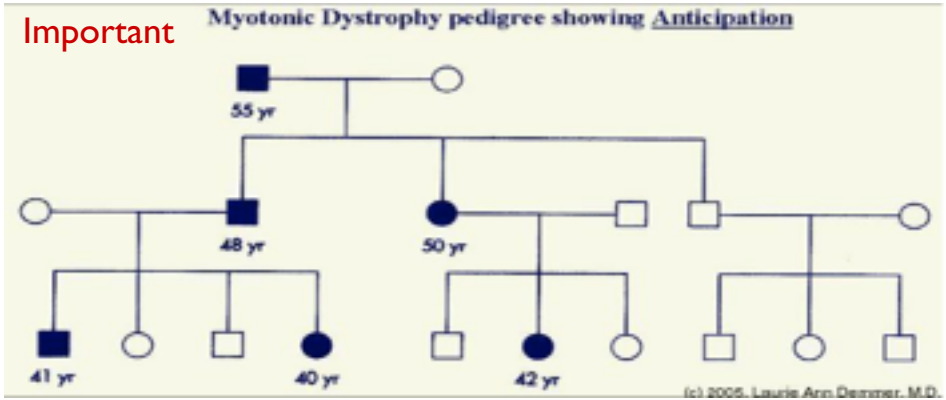
ANTICIPATION

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



Notice how the age of onset gets earlier and how the Severity (phenotype) increases with every generation

Important

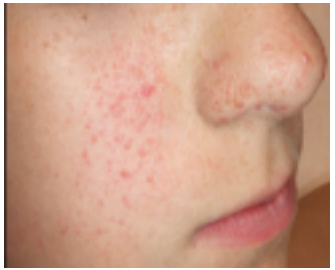


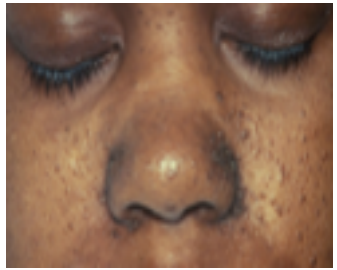
You can see how the age of onset decreases here with every generation

PLEIOTROPY

- -single-gene disorder with many symptoms, or a gene that controls several functions or has more than one effect, is *called* **pleiotropic.**(would impact multiple function)
- **Causes autosomal dominant disorders.**
- **Ex:(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.(the impact will be different from patient to patient)

Ex:

Autosomal dominant polycystic kidney disease

Some develop **renal failure** in early adulthood

Some devoleb **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 gene with environmental factors**

NEW MUTATIONS

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

Coffee reading

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.

MCQs

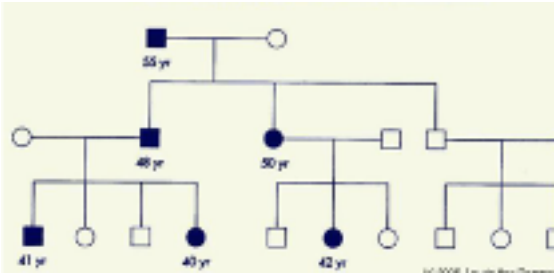
Q1: this pattern occurs when the heterozygote expresses both alleles simultaneously without forming an intermediate phenotype

A-Recessive trait	B-Codominant trait	C-both	D-other

:Q2: From where the individual gets his/her mitochondrial DNA

A- inherited from the father	B-inherited from the mother	C- both	D-other

:Q3: Myotonic dystrophy pedigree showing



A-Achondroplasia	B-NEW MUTATIONS	C-PLEIOTROPY	D-anticipation

MCQs answers

1) B
2) B
3) D

Boys team

- Nawaf Alghamdi
- Ahmed Alkhawashki
- Bassam Alasmari
- Rayan Alzahrani
- Khalid AlOsaimii
- Abdulrahman Alswat
- Abdulmalik Mokhtar
- Hadi AlHemsi
- Hesham Alsqabi
- Yazeed Alomar
- Mohammed Benhjji
- Badr Alshahrani
- Homoud Algadheb

Girls team

- Ghaida Alasiri
- Arwa Alqahtani
- Albandri Ahmad
- Aljohara Albnyan
- Aljohara alshathry
- Alanoud Alshahrani
- Raghad Alasiri
- Renad Alhomidi
- Sara Alharbi
- Taif Almutiri
- Abeer Awad
- Ghada Alabdi
- Noura Almassad
- Hind Almutywea

Team Leaders

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