جامعة الملك سعود
King Saud University

HUMAN GENETICS

Color index:
- Important
- Slides
- Drs' notes
- Extra information

LECTURE 4

Atypical Mode of Inheritance

EDITION FILE

OBJECTIVES

By the end of this lecture, the students should be 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. New mutation
8. Complex trait: multifactorial/Polygenic

Non-Mendelian Genetics

we suggest you to watch this. It'd be helpful

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

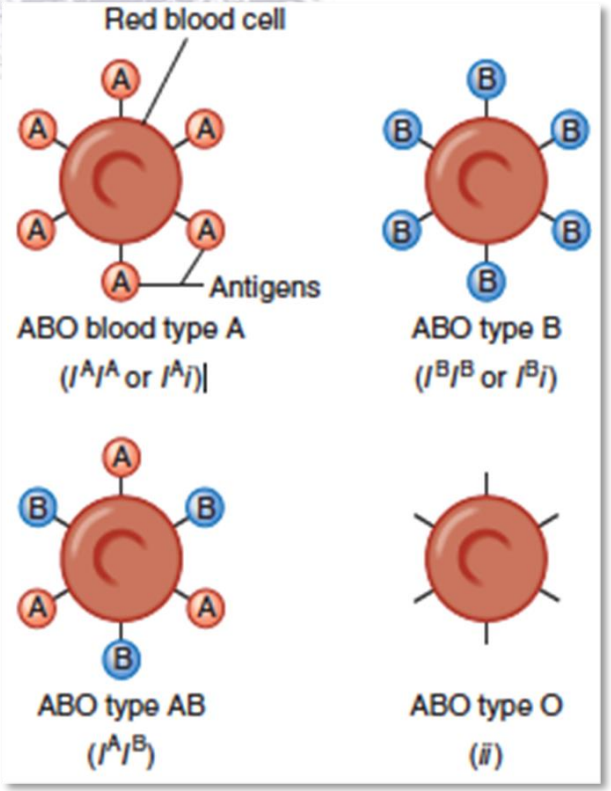
*Both are dominant → Both will occur.
e.g. Mother with blue eyes + Father with green eyes (both are dominant)
The child will have 1 green eye and 1 blue eye

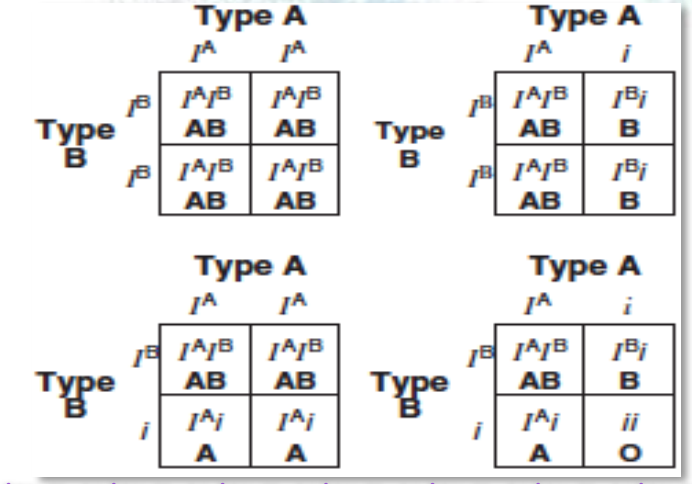
Co-dominance Inheritance

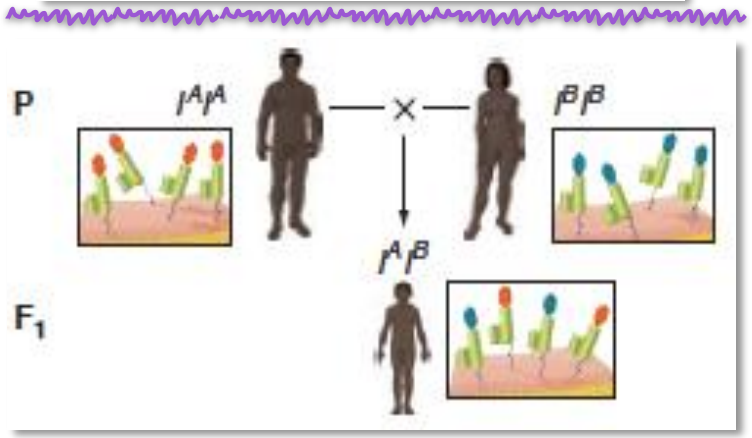
Inheritance of Blood type

CODOMINANCE INHERITANCE

Alleles of the ABO Blood Group Can Be Dominant, Recessive, or Codominant







POSSIBLE GENOTYPES, PHENOTYPES & GAMETES FORMED FROM THE FOUR ALLELES: A1, A2, B, & O AT THE ABO LOCUS

Read

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

PSEUDODOMINANCE INHERITANCE

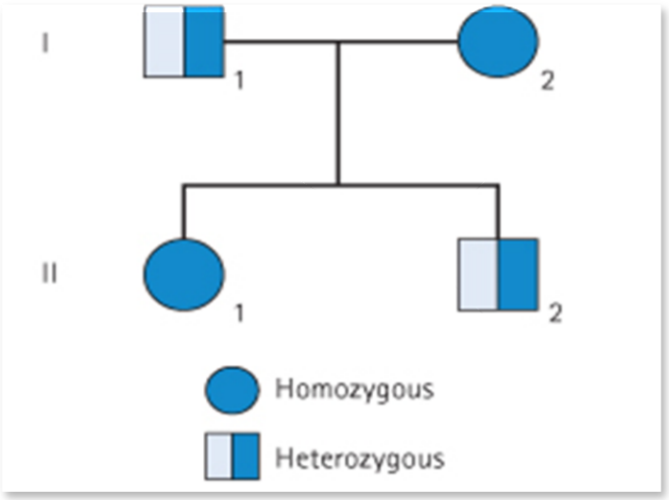
is the situation in which the inheritance of a recessive* trait mimics"يقلّد" a dominant pattern.

It's not dominant but it acts as it is.

*One copy of the gene but this copy is enough to show affected person

A PEDIGREE OF PSEUDODOMINANCE 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 ?

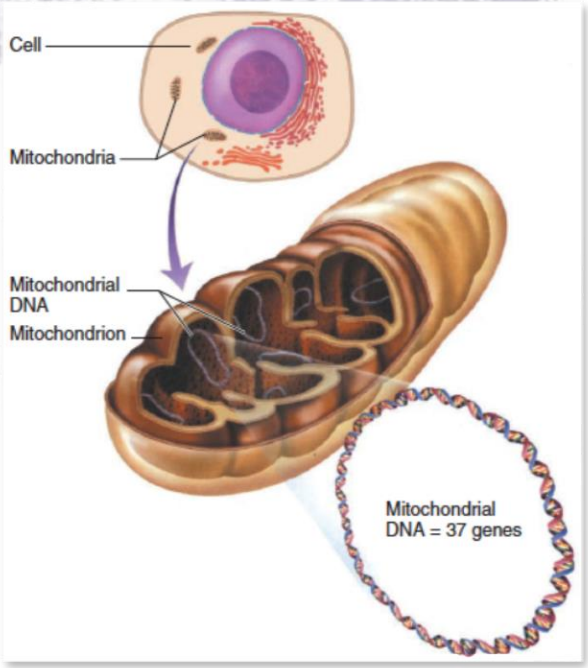
- Maternal inheritance of mitochondrial mutations
- Anticipation
- Atypical presentation for Autosomal Dominant defects:
  - Pleiotropy
  - Variable expressivity
  - Reduced penetrance
  - New mutation
- Unusual inheritance patterns due to Genomic Imprinting
- Mosaicism:
  - Somatic mosaicism
  - Germline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

The doctor has removed this one

MITOCHONDRIAL INHERITANCE

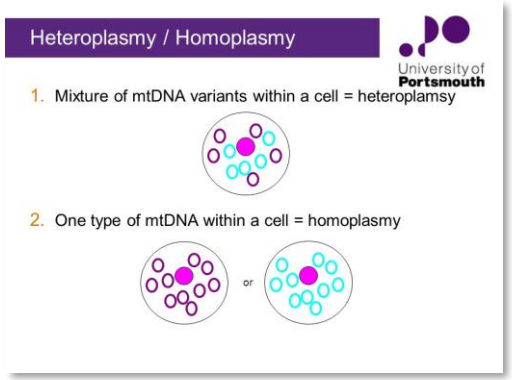
- Each cell contains thousands of copies of mitochondrial DNA with more being found in cells having high energy requirement (e.g. brain & muscle)
- Mitochondria (& their DNA) are inherited from the mother (through ova)
- mtDNA is a small circular double-stranded molecule containing 37 genes (coding for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

Mitochondria contains genetic material, and it is circular DNA or chromosome



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

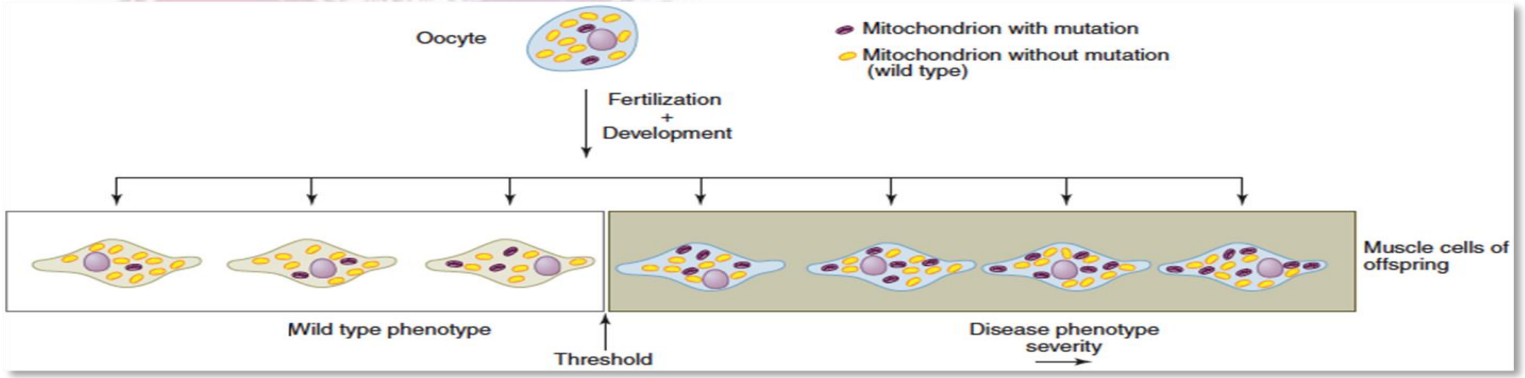
Mitochondria and their genes are passed only from the mother.

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:

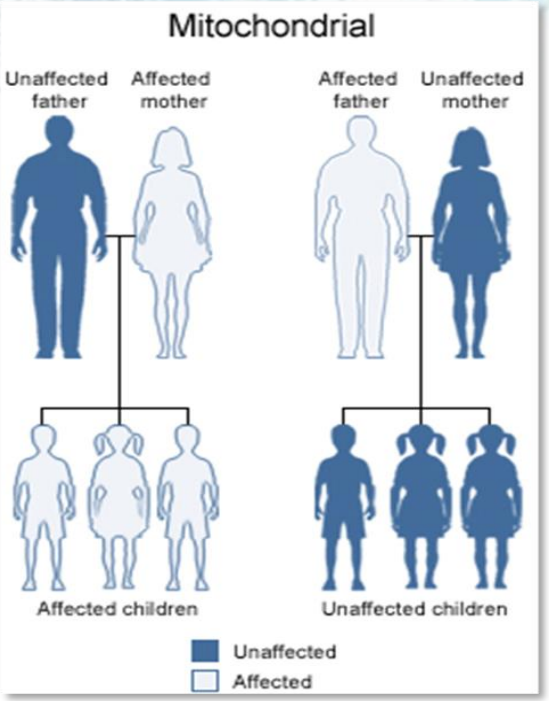
- Leber hereditary optic neuropathy (LHON):
  - Rapid Optic nerve death → blindness in young adult life



Mitochondrial Inheritance

Mitochondrial Disease

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 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:

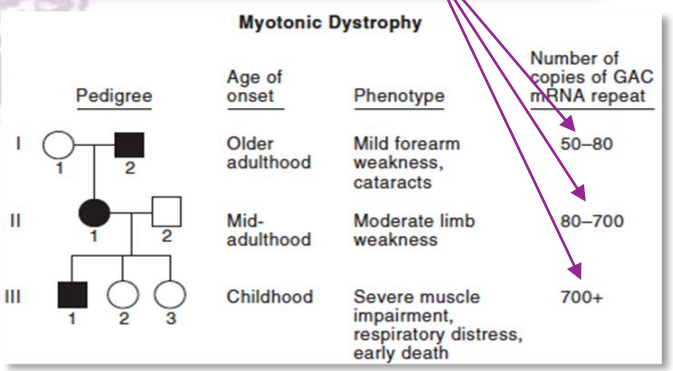
- Huntington disease
- Myotonic dystrophy

Myotonic dystrophy

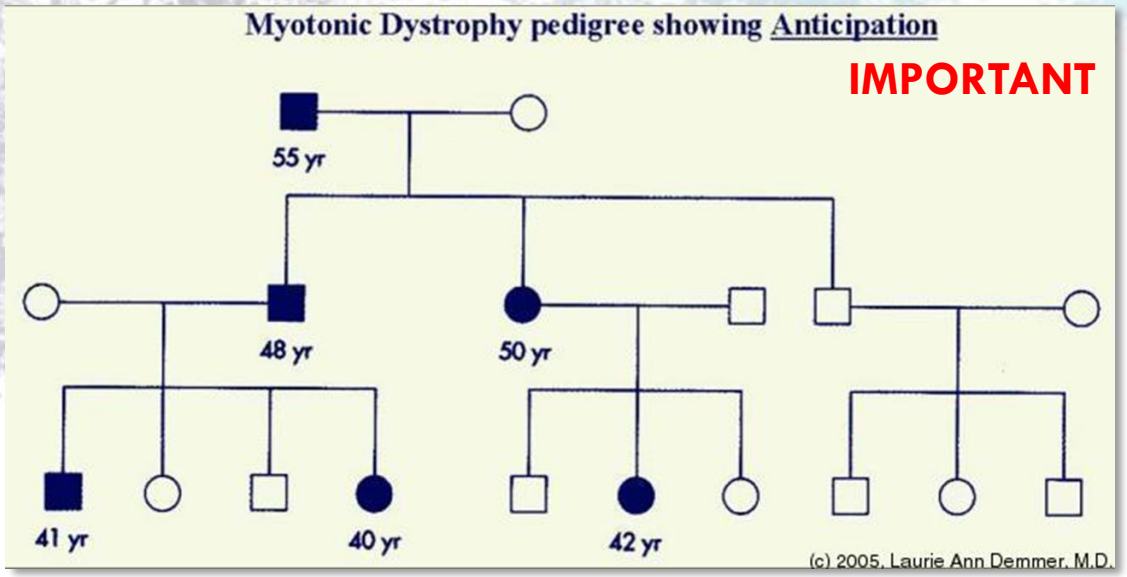
Huntington Disease

*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



if this pedigree is without age, it will be "Autosomal dominant"

If it is with age
Then it will be "Autosomal dominant with anticipation"

PLEIOTROPY

One gene will cause multiple abnormalities

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

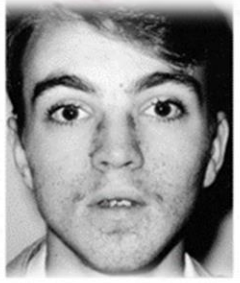
Causes autosomal dominant disorders

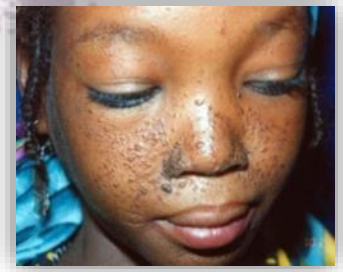
Example:

Tuberous sclerosis

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

Pleiotropy





Appears suddenly

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.

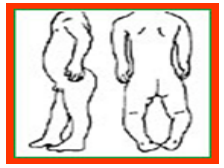
Important

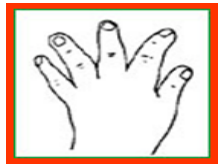
An example of New Mutations

ACHONDROPLASIA

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

Penetrance & Expressivity

Variable Expressivity & Incomplete Penetrance

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

COMPLEX TRAITS

Complex Vs Mendelian traits

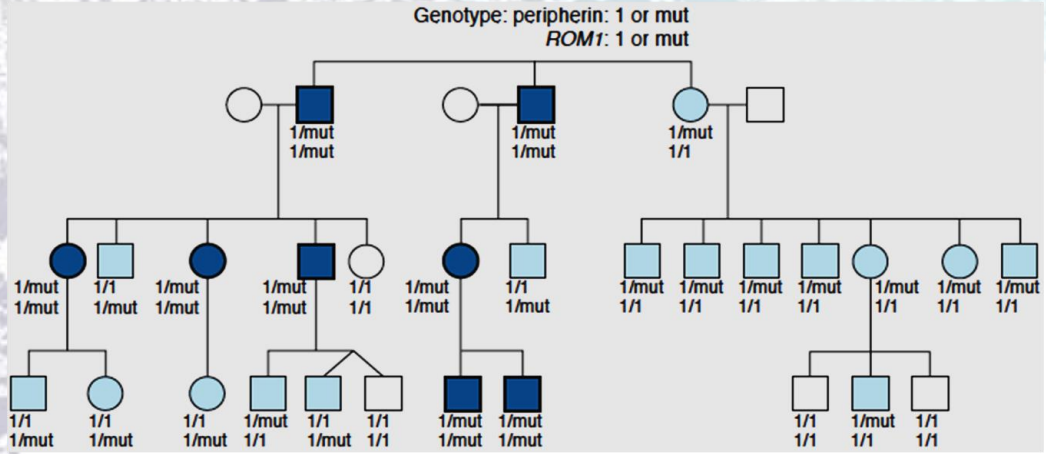
Complex traits are conditions which are likely to be due to the interaction of more than one gene.

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



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

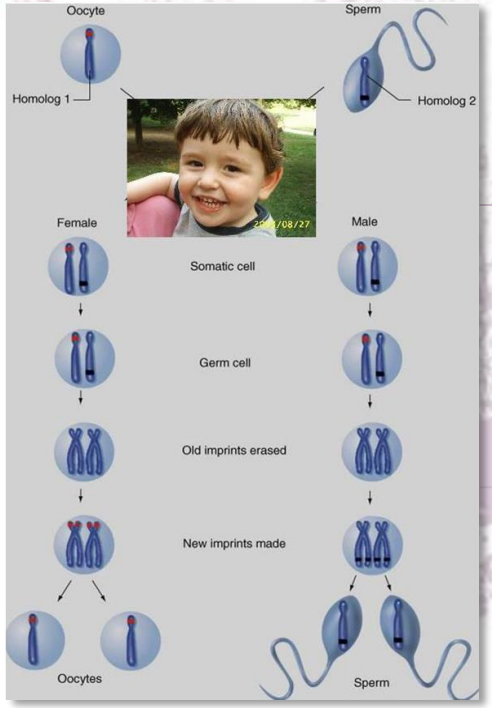
- congenital malformations such as:
  - cleft lip and palate
- late-onset conditions such as:
  - Hypertension, Diabetes mellitus, Alzheimer disease.

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

GENOMIC IMPRINTING

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

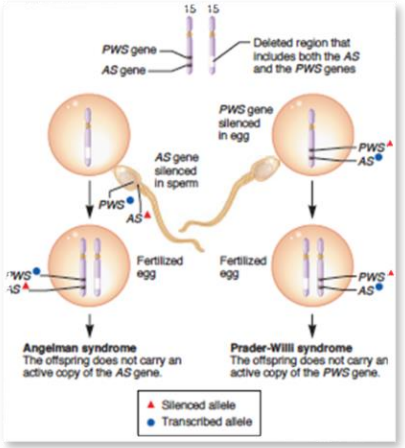
THE ROLE OF IMPRINTING IN THE DEVELOPMENT OF ANGELMAN AND PRADER-WILLI SYNDROMES

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).

Imprinting & Prader-Willi Vs. Angelman syndromes



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

1-If the genotype is AO what is the phenotype?
A. Blood group AB
B.Blood group B
C.Blood group O
D.Blood group A

2-**what is the phenotype for (A1B)?**
A. A1B
B. A2B
C. A
D. B

3-**Pseudodominant inheritance happens when there are:**
A. A heterozygous woman for an autosomal recessive disorder and a heterozygous man for the same disorder
B. A homozygous woman for an autosomal dominant disorder and a heterozygous man for the same disorder
C. A homozygous woman for an autosomal recessive disorder and a heterozygous man for the same disorder
D. A heterozygous woman for an autosomal dominant disorder and a heterozygous man for the same disorder

4-**Mitochondrial disorders are Transmitted from:**
A. Father to sons only
B. Father to all children
C. Mother to daughters only
D. Mother to all children

5-**A parent had Huntington disease at the age of 55 years old, her son and daughter developed the disease at an earlier age (almost 40 yr) with greater severity, this pattern of inheritance is:**
A. Anticipation
B. Mitochondrial inheritance
C. Pseudodominant inheritance
D. Reduced penetrance

6-**Myotonic dystrophy is an example of a disease showing:**
A. Pseudodominant inheritance
B. Anticipation
C. Pleiotropy
D. New mutation

- **9-When an individual has a gene mutation which normally gives rise to autosomal dominant disorder.**
But in this particular individual, there are no abnormal clinical features.
This condition is called:

A. Pleiotropy
B. Variable expressivity
C. Codominance
D. Reduced penetrance

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

A. Reduced penetrance
B. New mutation
C. Variable expressivity
D. Pleiotropy

- **11-The offspring of persons with achondroplasia has a ……. chance of having achondroplasia.**

A. 100%
B. 25%
C. 50%
D. 75%

- **12-This pattern occurs when the heterozygote expresses both allele simultaneously without forming an intermediate phenotype:**

A. Codominant traits
B. Achondroplasia
C. COMPLEX TRAITS
D. POLYGENIC DISORDERS

- **13-Achondroplasia considered as:**

A. Codominant traits
B. Anticipation
C. New mutation
D. Variable expressivity

- **7- The clinical features in autosomal dominant disorders can show striking variation from person to person, even in the same family:**

A. New mutations
B. Variable expressivity
C. Pleiotropy
D. Reduced penetrance

- **8-interaction of the gene with environmental factors can be the reason for:**

A. Reduced penetrance
B. New mutations
C. Pleiotropy
D. Variable expressivity

13-C
12-A
11-C
10-B
9-D
8-A
7-B
6-B
5- A
4- D
3- C
2- A
1- D

تمّ بحمدِ الله

نسعدُ باستقبالِ اقتراحاتكم و ملاحظاتكم على البريد الإلكتروني:
GeneticsTeam437@gmail.com

TEAM LEADERS:

Abdulmajeed Alwardi

Haifa Alessa

GIRLS TEAM:

Ghaida Alsanad

Munira Alhadlg

Batoul Alruhaimi

Dimah Alaraifi

Arjuwana Alaqeel

BOYS TEAM:

Abdullah Alzahrani

Abdulaziz Aljohani

Adel Alzahrani

Hamdan Aldossri

Khaled Aldosari