Atypical mode of inheritance

HUMAN GENETICS

Red: important.
Pink: F-slides
Blue: M-slides
Green: doctor's Notes
Gray: extra

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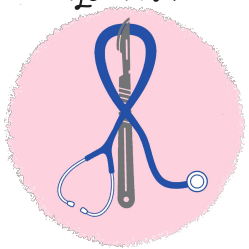


HUMAN GENETICS 441

MED441
KING SAUD UNIVERSITY

Objectives

01 Codominant traits &Pseudodominant inheritance

02 Heterogeneity & The mitochondrial inheritance

03 Anticipation &Pleiotropy

04 New mutation &Variable expressivity

05 Complex trait: multifactorial/polygenic

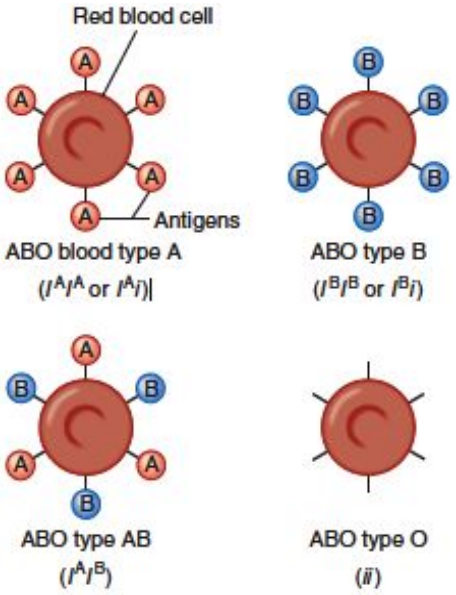
Codominant traits

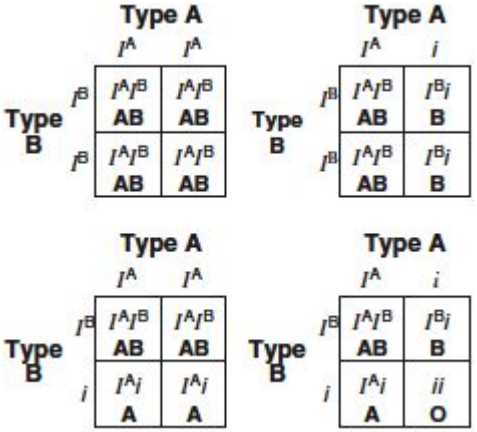
This pattern occurs when the **heterozygote** expresses both alleles simultaneously without forming an intermediate phenotype.

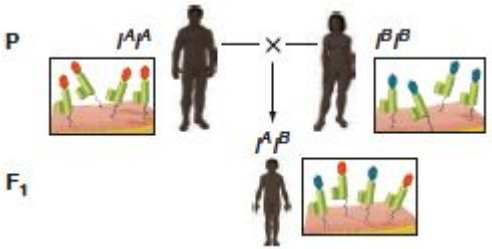
For example:

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

most genes exist in multiple alleles







PSEUDODOMINANT INHERITANCE

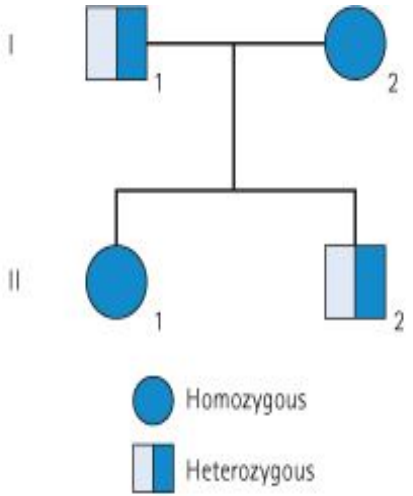
KEEP IN MIND

THIS SLIDE IS VERY IMPORTANT

A woman homozygous for an autosomal recessive

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

KEEP IN MIND

THIS SLIDE IS VERY IMPORTANT

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

Maternal mitochondrial mutations inheritance

Anticipation

Atypical autosomal dominant defects:

-Pleiotropy
-Variable expressivity
-Reduced penetrance
-New mutation

Unusual inheritance patterns due to genomic imprinting

Mosaicism:

-Somatic mosaicism
-Germline mosaicism

MITOCHONDRIAL INHERITANCE

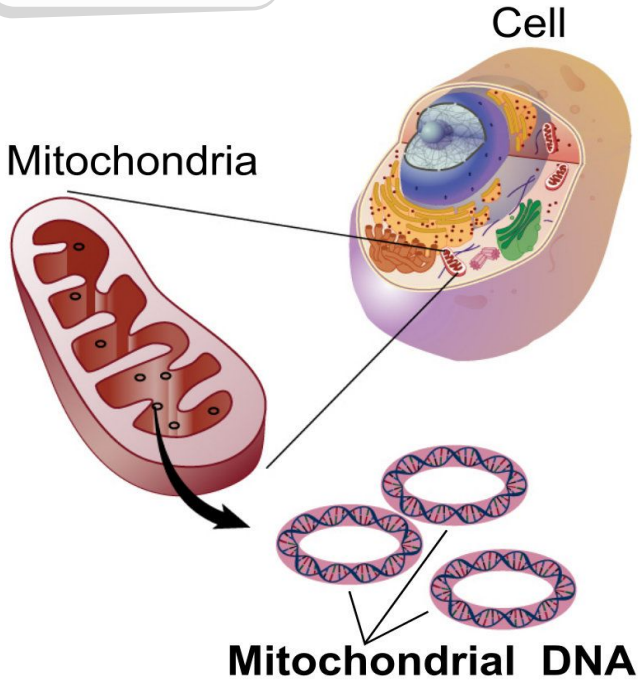
KEEP IN MIND

THIS SLIDE IS VERY IMPORTANT

Each cell contains many copies of mitochondrial DNA with more being found in high energy demanding cells (e.g brain & muscle).

Mitochondria & its DNA are inherited from the mother (cytoplasm; through ova).

mtDNA is small and circular containing 37 Genes (coding for rRNA, tRNA, and some of the proteins of the mitochondrial electron transport chain).



MITOCHONDRIAL INHERITANCE

- Mitochondria & their genes are passed from the mother.
- Cells have many mitochondria. If an oocyte is heteroplasmic, differing numbers of mitochondrial mutations may be transmitted.

KEEP IN MIND

THIS SLIDE IS VERY IMPORTANT

Leber Hereditary Optic Neuropathy (LHON).

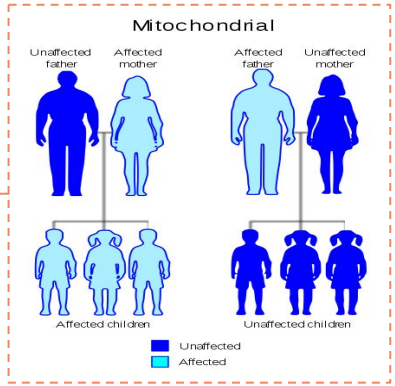
Example of an mitochondrial disorder:

Rapid optic nerve death Blindness in young adult life

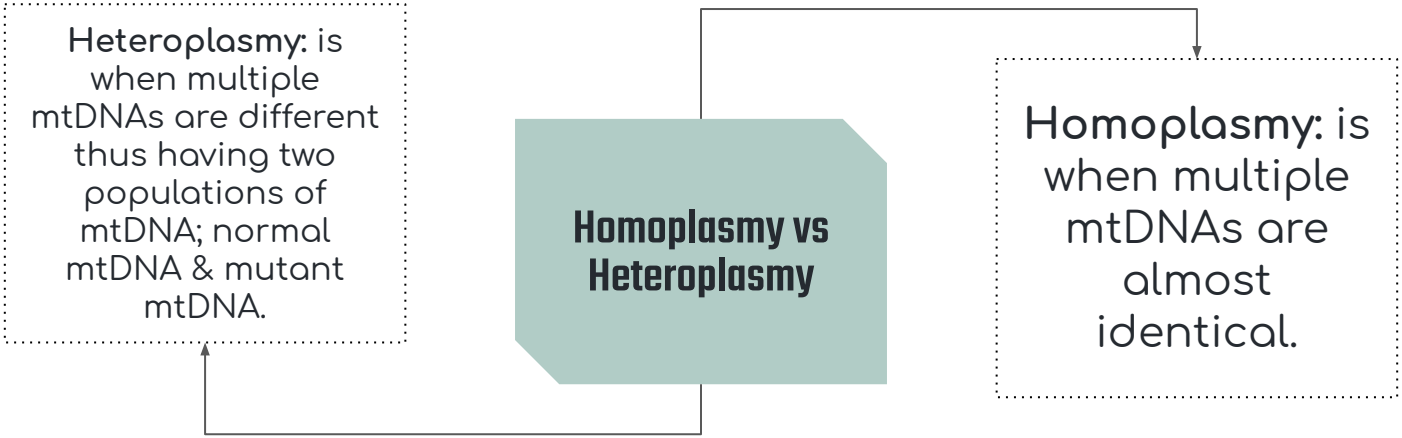
Thus males don't transmit the disease

Cytoplasm is inherited from the mother only

(since the mitochondria are present in the cytoplasm).



Homoplasmy vs Heteroplasmy



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

Anticipation

KEEP IN MIND

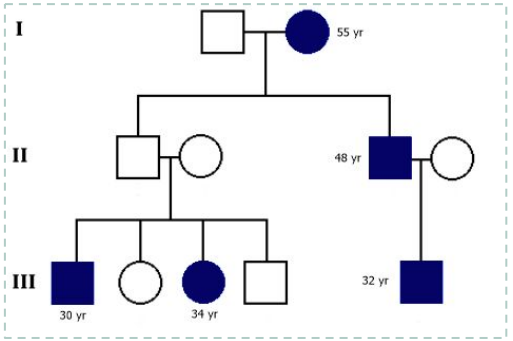
THIS SLIDE IS VERY IMPORTANT

- 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 anticipation diseases:

- Huntington disease
- Myotonic dystrophy

Myotonic dystrophy pedigree showing ANTICIPATION



PLEIOTROPY

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

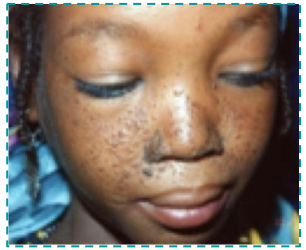
Pleiotropy

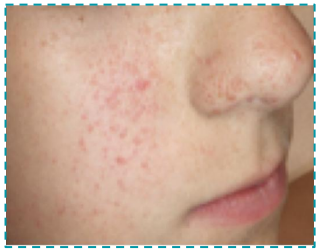
causes

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.
(the impact will be different from patient to patient)

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"

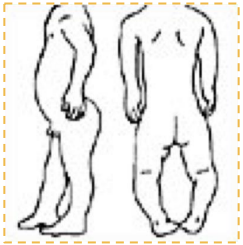
modifying effects of other genes	Reduced penetrance might be due to:	interaction of the gene with environmental factors

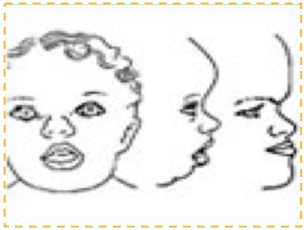
NEW MUTATIONS

- In autosomal dominant disorders an affected person will usually have an affected parent.
- 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:**
  1- Characteristic clinical and radiographic finding
  2- 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?

Variable expressivity

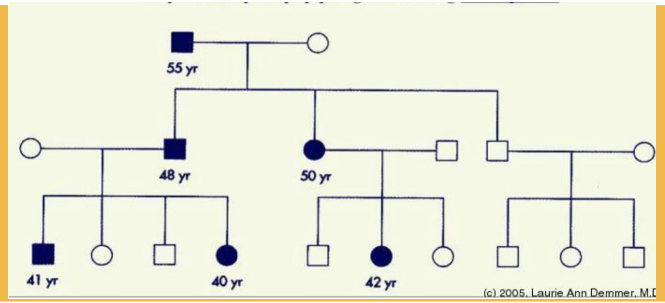
the family relationships not being as stated, e.g. non-paternity

non-penetrance: One of the parents might be heterozygous for the mutant allele but so mildly affected that it has not previously been detected

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: From where does the individual's get their mitochondrial DNA			
A.Father	B.Mother	C.Both	D.other ways
Q2:An example of codominant trait is blood type			
A.O-	B.AB+	C.O+	D.B+
Q3:The following pedigree shows: 			
A. Codominant trait	B. New mutations	C. anticipation	D. Pleiotropy

Answer Key: 1B - 2B - 3C

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Editing file

“Let’s go invent tomorrow rather than worrying about what happened yesterday.”

—Steve Jobs