

## Atypical Patterns of Inheritance

### Lecture Objectives

By the end of this lecture, students should be able to appreciate the possibility of atypical patterns of inheritance with special emphasis on:

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

## Inheritance of Codominant alleles

### Codominance

*Codominance*: two allelic traits that are both expressed in the heterozygous state.

Example: Blood group AB: the A and B blood groups are ***codominant***.

**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**

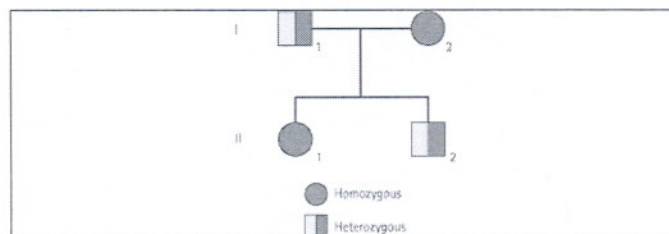
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OO	O	O
$A_1A_2$	$A_1$	$A_1$ or $A_2$
$A_1B$	$A_1B$	$A_1$ or B
$A_1O$	$A_1$	$A_1$ or O
$A_2B$	$A_2B$	$A_2$ or B
$A_2O$	$A_2$	$A_2$ or O
BO	B	B or O

**pseudodominant Inheritance**



## 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 i.e. homozygous ) i.e. pseudodominant

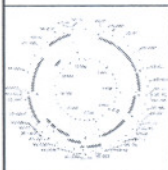
## Atypical inheritance of single-gene disorders

**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
    - Heterogeneity
    - New mutation
- Unusual inheritance patterns due to Genomic Imprinting
- Mosaicism:
  - Somatic mosaicism
  - Germline mosaicism

**MITOCHONDRIAL INHERITANCE**

## Mitochondrial DNA (mtDNA)



- 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)

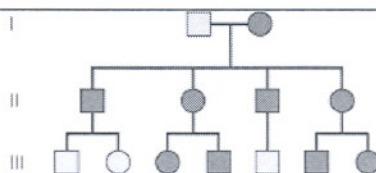
<http://ghr.nlm.nih.gov/chromosome=MT>

## Mitochondrial Disorders

- The defective gene is present on the mitochondrial chromosomes
- Effect generally energy metabolism
- Effect more those tissues which require constant supply of energy e.g ***muscles***
- Show maternal inheritance:
  - Affected mother transmits the disorder **equally to all** her children
  - Affected father **does not** transmit the disease to his children



## Mitochondrial Inheritance



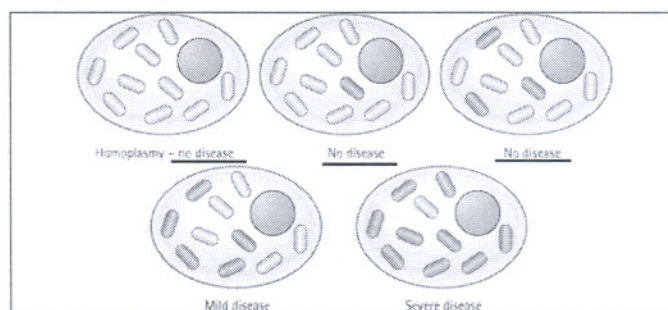
Males cannot transmit the disease as the cytoplasm is inherited only from the mother, and mitochondria are present in the cytoplasm.

## Homoplasmy vs. Heteroplasmy

- **Homoplasmy** = in most persons, the mtDNA from different mitochondria is 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.



The progressive effect of **Heteroplasmy** on the clinical severity of mitochondrial genetic disorders



**Low proportions of mutant mitochondria are not associated with disease**

**As the proportion increases, the disease will be manifested**

## Example of Mitochondrial Disorders

### Lebers hereditary optic neuropathy (LHON)

Rapid Optic nerve death → blindness in young adult life

<http://ghr.nlm.nih.gov/condition=leberhereditaryopticneuropathy>

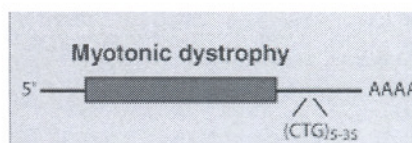
## ANTICIPATION

### Anticipation

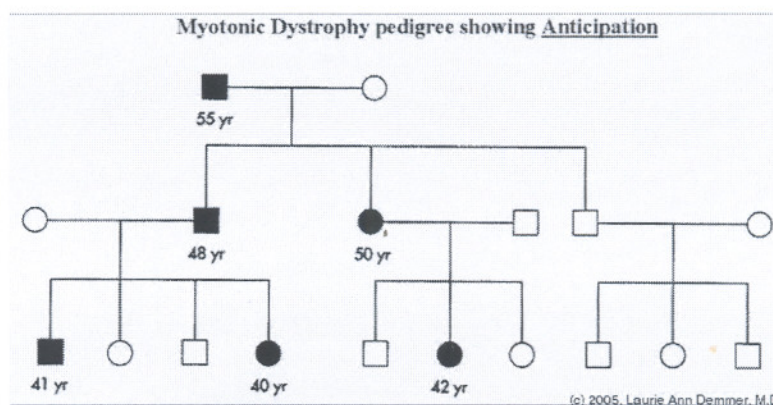
- A pattern of inheritance in which individuals in the most recent generations of a pedigree develop a disease **at an earlier age** or **with greater severity** than do those in earlier generation.
- The reason might be the gradual expansion of trinucleotide repeat polymorphisms within or near a coding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

## Myotonic Dystrophy

- Autosomal dominant disease
- Relatively common
- The affected gene is on chromosome 19
- The mutation is triplet repeat (CTG) expansion in the 3' untranslated region of the myotonic dystrophy gene
- Clinical manifestations:
  - Myotonia (Muscular loss & weakness)
  - Cataracts
  - Testicular atrophy
  - Heart disease: arrhythmia
  - Dementia
  - Baldness

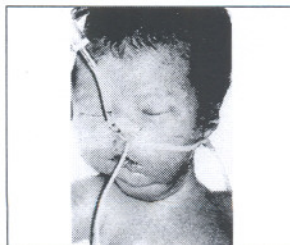


## Myotonic Dystrophy, CONTD.





## **Myotonic Dystrophy, CONTD.**



Newborn baby with severe hypotonia requiring ventilation as a result of having inherited myotonic dystrophy from his mother

**Atypical presentation for  
Autosomal Dominant defects**



*Pleiotropy, reduced penetrance and variable expressivity* of a mutant allele need to be taken into account when providing **genetic counseling** to individuals at risk for autosomal dominantly inherited disorders.

## Pleiotropy



It is common for autosomal dominant disorders to manifest in ***different systems*** of the body ***in a variety of ways***.

**Pleiotropy**:- a single gene that may give rise to two or more apparently unrelated effects.

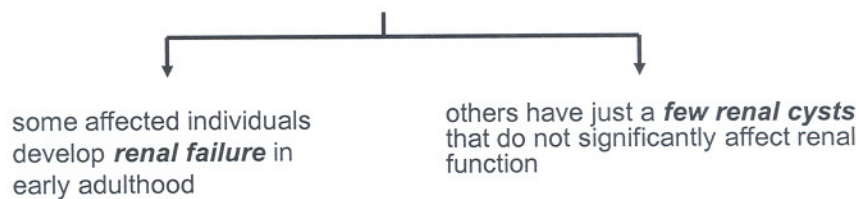
Example: In tuberous sclerosis: affected individuals can present with either

- learning difficulties,
- epilepsy,
- a facial rash,
- 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: In ***autosomal dominant polycystic kidney disease***:



## 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.



## 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.

## To summarize..

- 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.