Medical Genetics

LECTURE 4

Atypical Patterns of Inheritance

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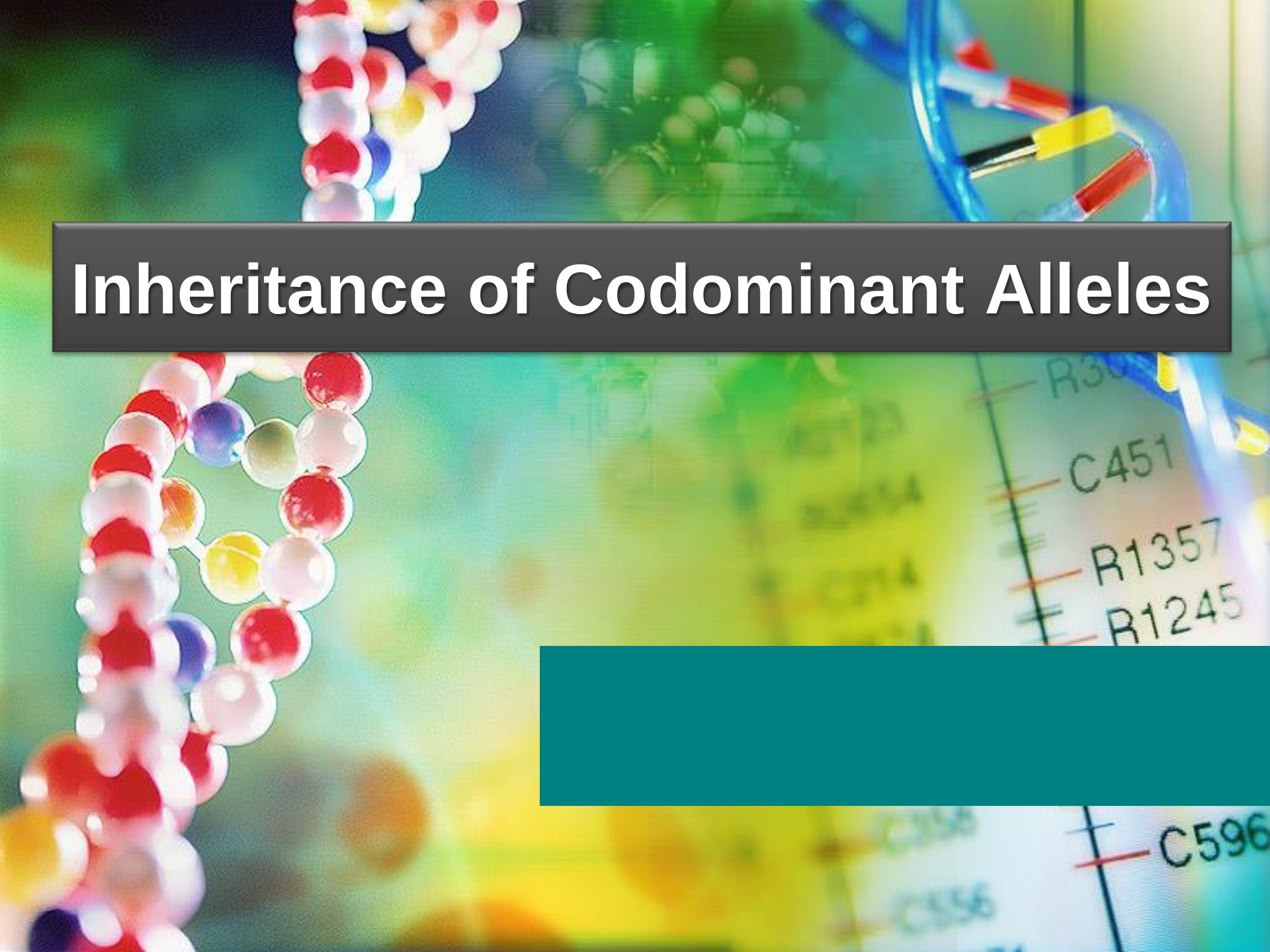
Lecture Objectives

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

1. **Codominant traits**
2. **Pseudodominant inheritance**
3. **The mitochondrial inheritance**
4. **Anticipation**
5. **Pleiotropy**
6. **Variable expressivity**
7. **Heterogeneity**
8. **New mutation**
9. **Complex trait: multifactorial/Polygenic**

Inheritance of Codominant Alleles



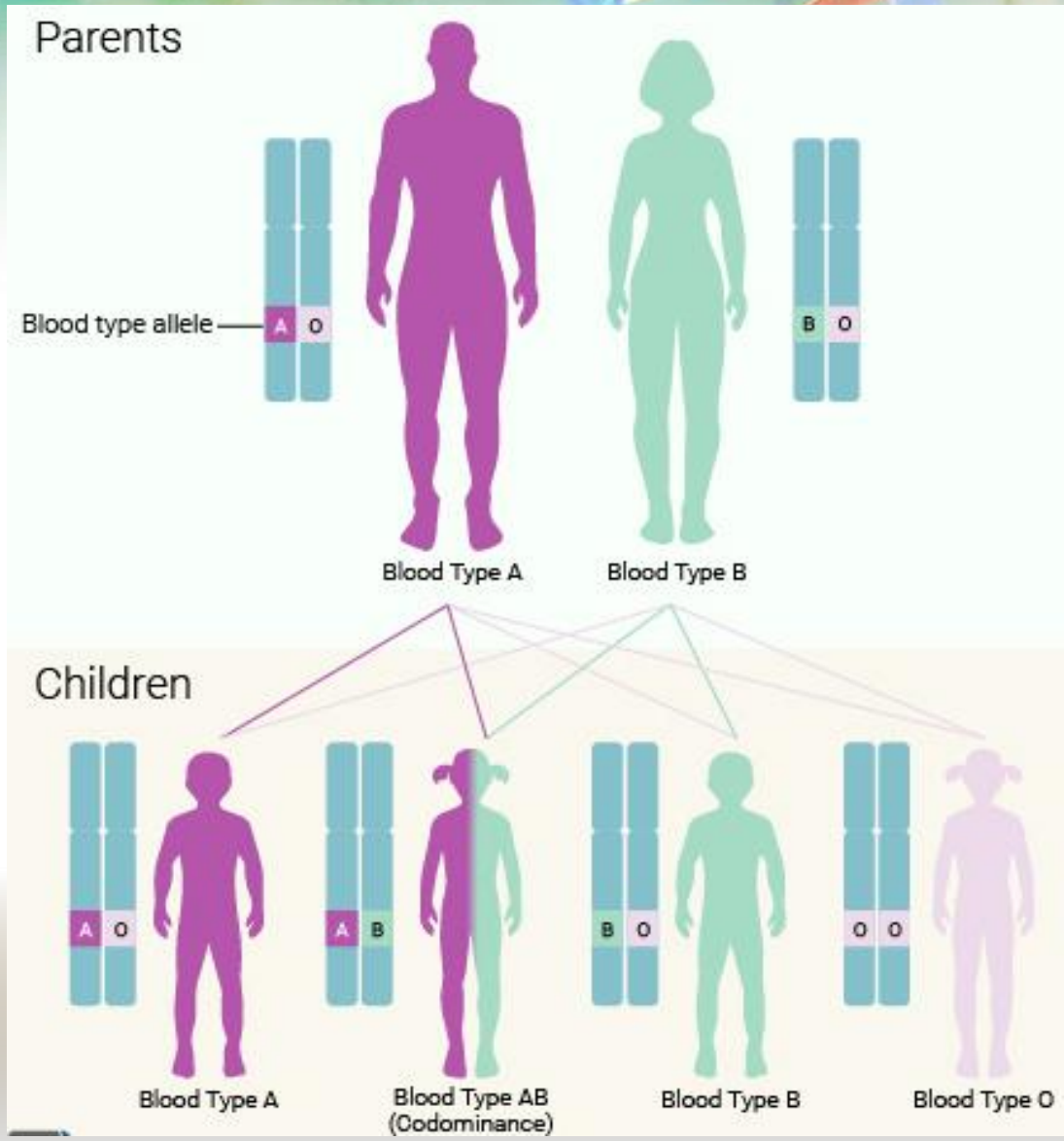
Codominance

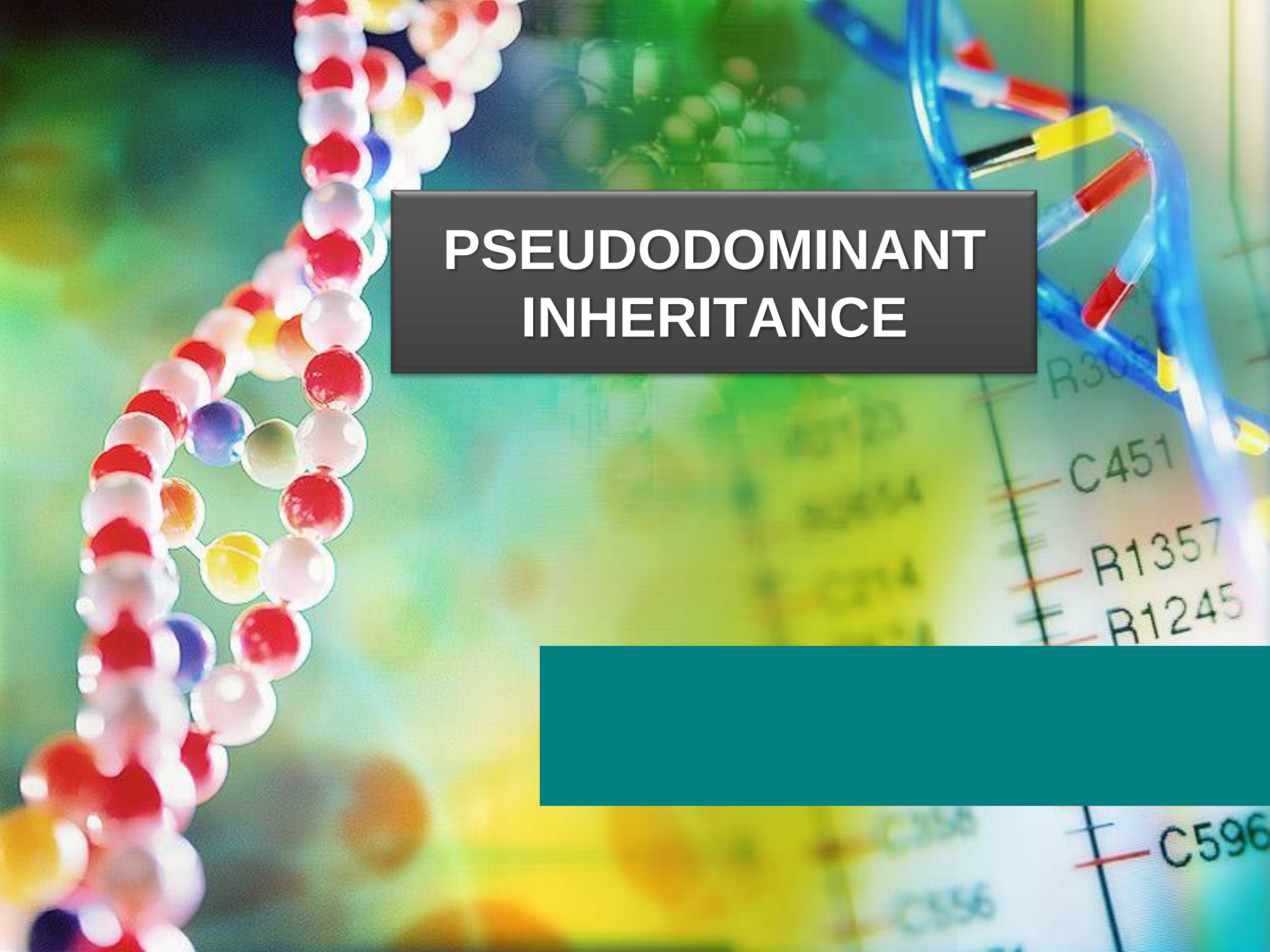
Codominance: two allelic traits that are both expressed in the heterozygous state.

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

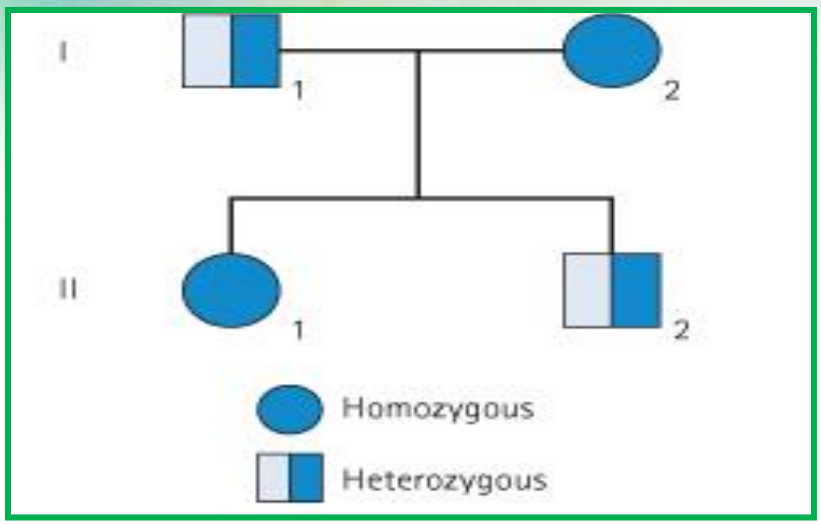
Possible genotypes, phenotypes & gametes formed from the four alleles: A_1, A_2, B, & O at the ABO locus

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

Pedigree: Pseudodominant inheritance

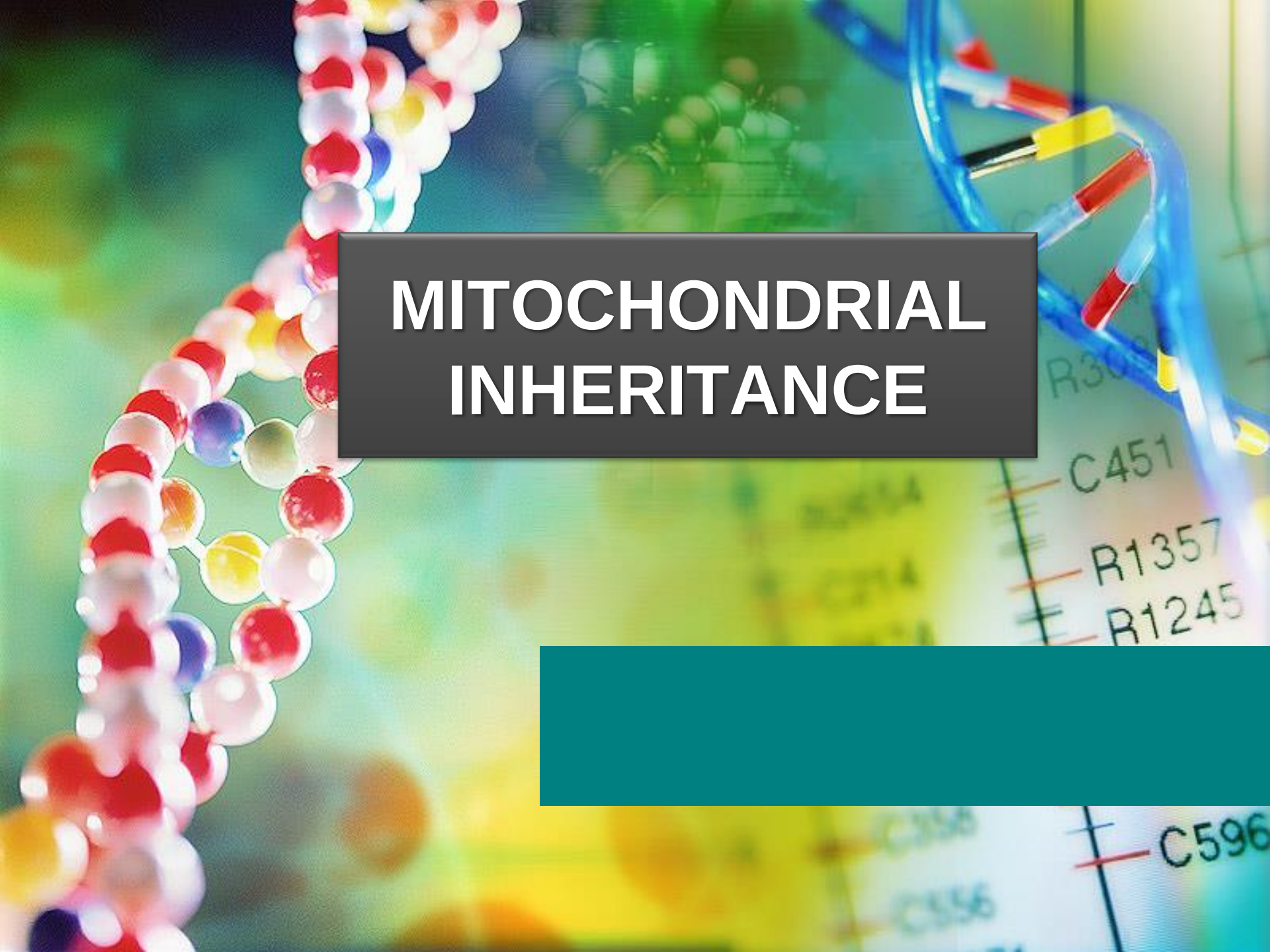


- A woman **homozygous for an autosomal recessive** disorder whose husband is **heterozygous** for the same disorder.
- Their children have a **1 in 2 (50%)** chance of being affected i.e. homozygous) i.e. **pseudodominant**

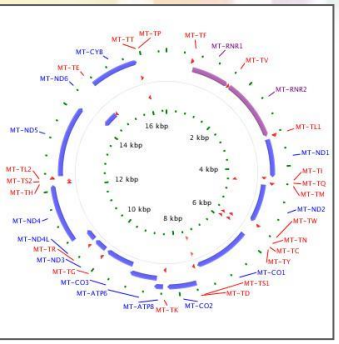
Atypical inheritance of single-gene disorders

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


MITOCHONDRIAL
INHERITANCE
C451
R1357
R1245
C596

Mitochondrial DNA (mtDNA)



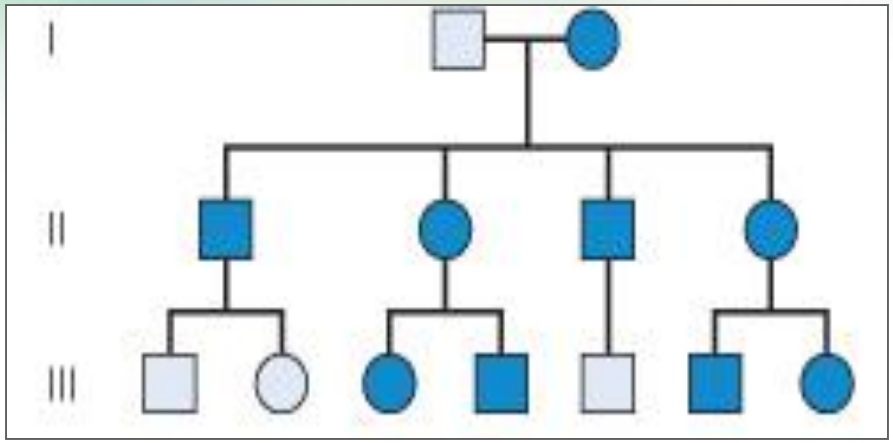
- Each cell contains thousands of copies of mitochondrial DNA with more being found in cells having high energy requirement (e.g. brain & muscle)
- Mitochondria (& their DNA) are **inherited from the mother** (through ova)
- mtDNA is a **small circular double-stranded** molecule containing **37 genes** (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

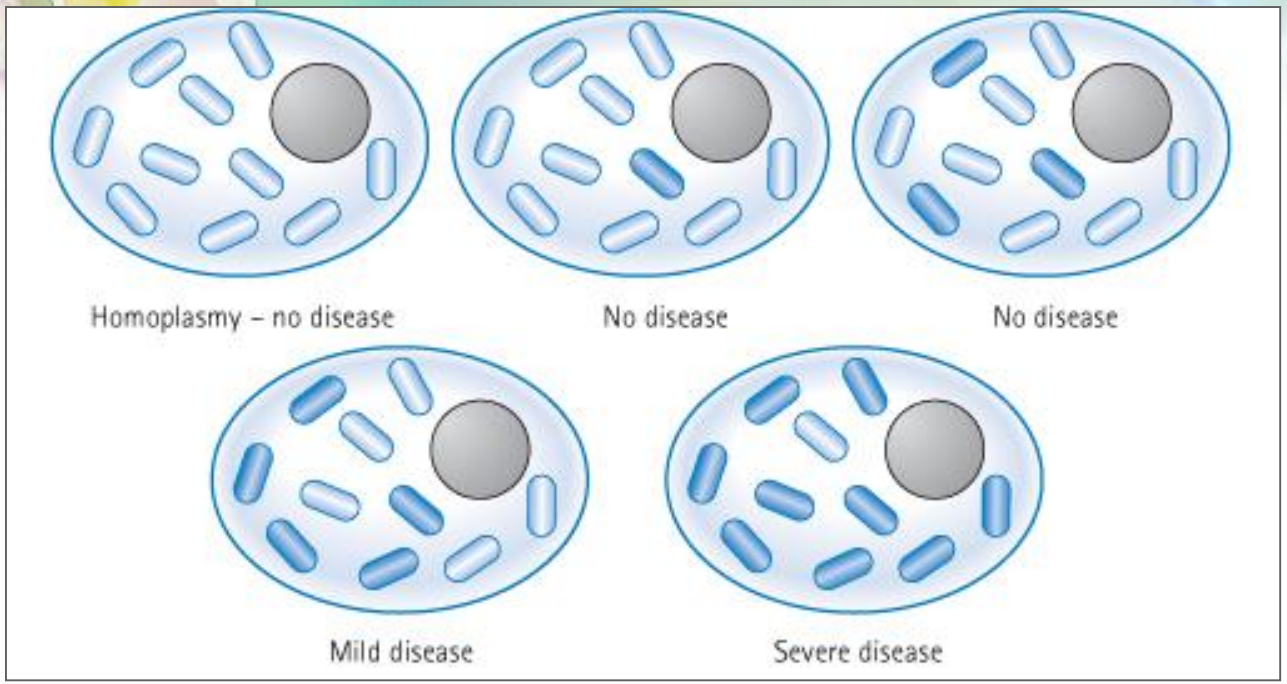


Males cannot transmit the disease as the cytoplasm is inherited only from the mother, and mitochondria are present in the cytoplasm.

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

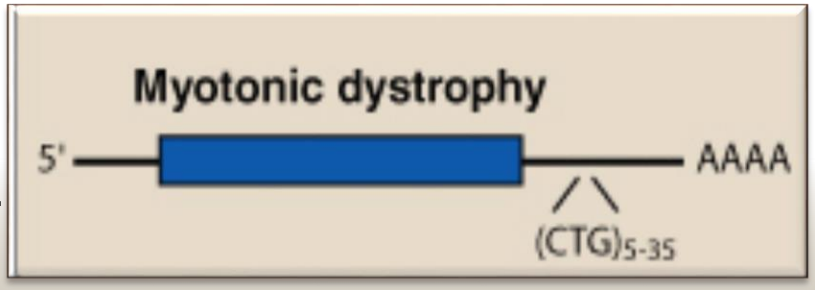
- A pattern of inheritance in which individuals in the most recent generations of a pedigree develop a disease **at an earlier age** or **with greater severity** than do those in earlier generation.
- The reason might be the gradual expansion of trinucleotide repeat polymorphisms within or near a coding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

  Huntington disease

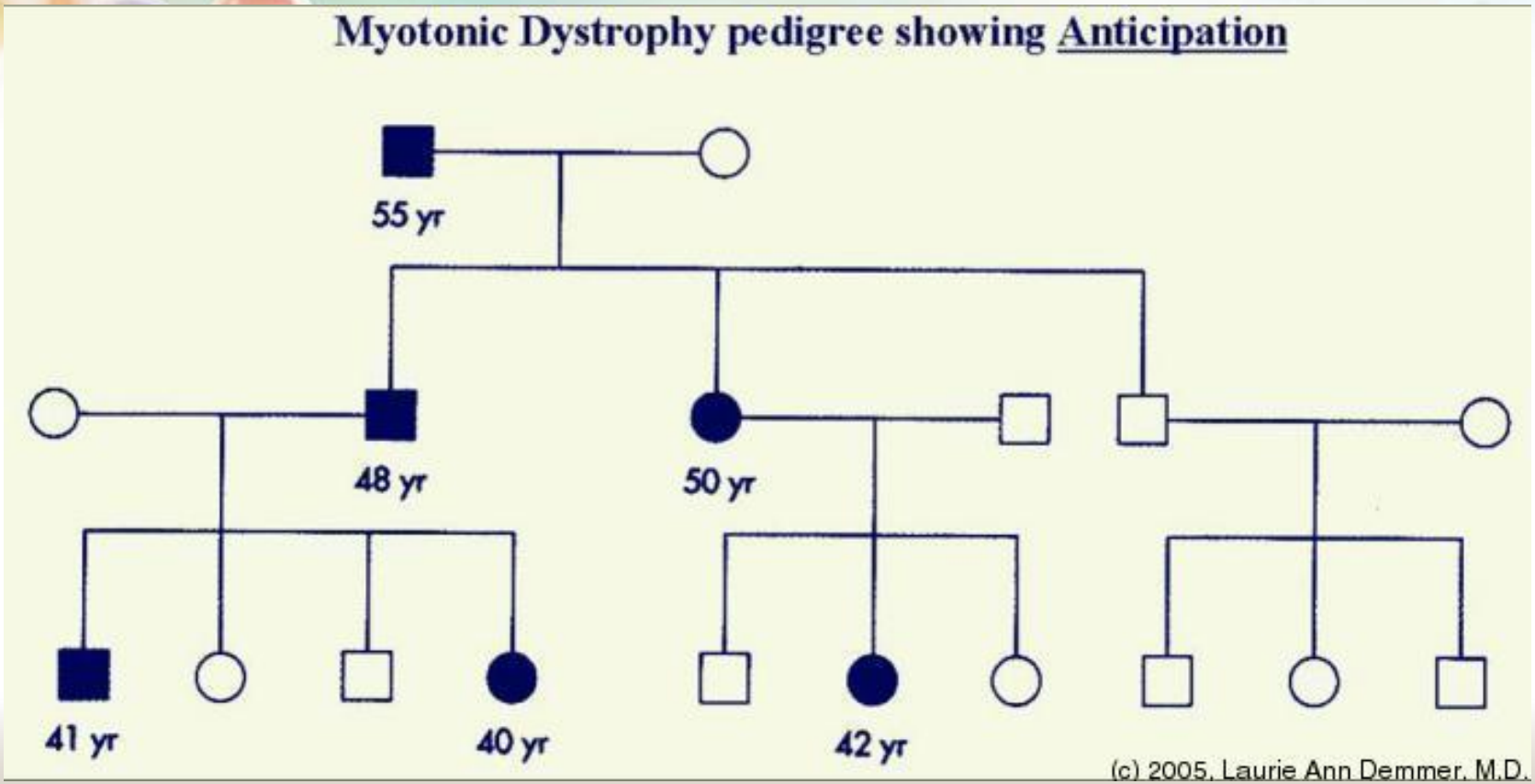
  Myotonic dystrophy

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.



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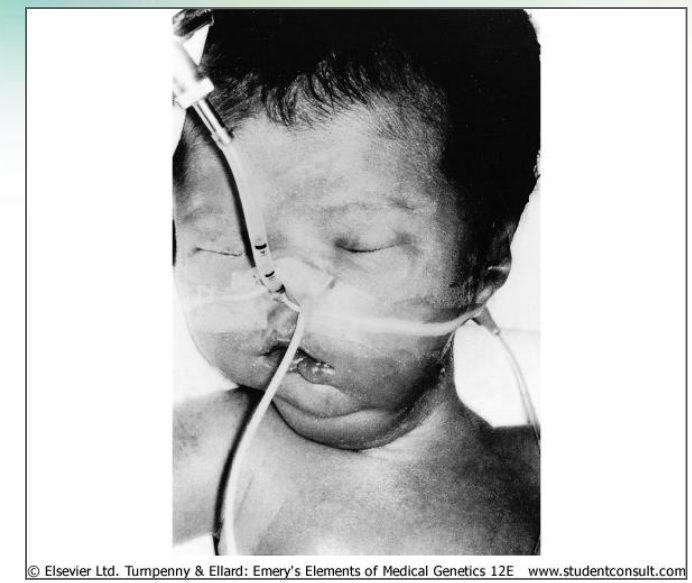
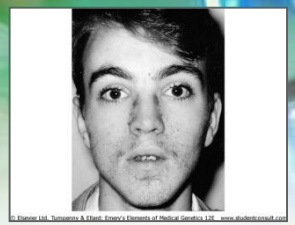


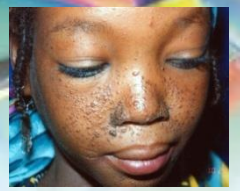
Newborn baby with severe hypotonia requiring ventilation as a result of having inherited myotonic dystrophy from his mother

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***:

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**

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*****.**

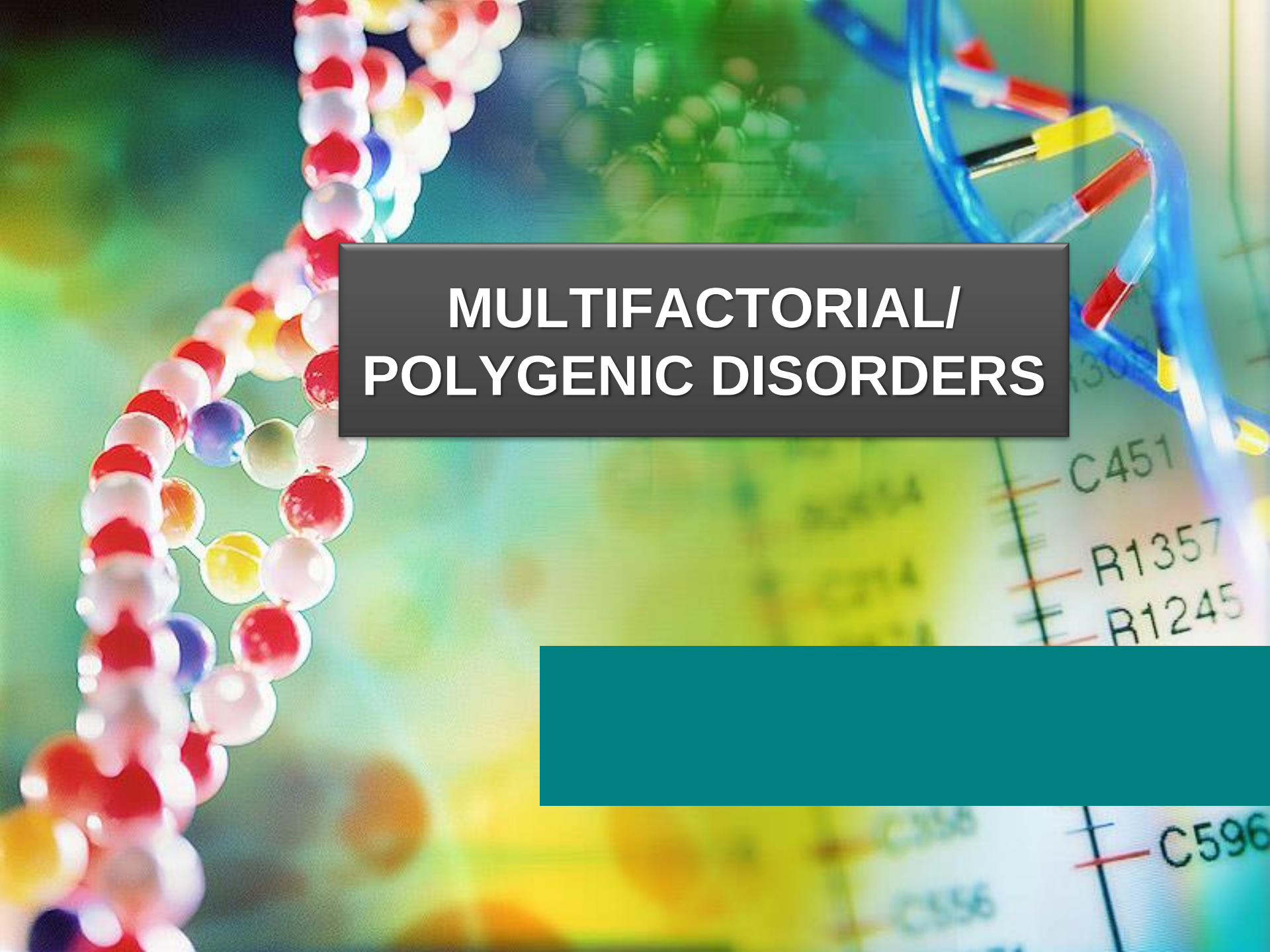
Achondroplasia

- 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

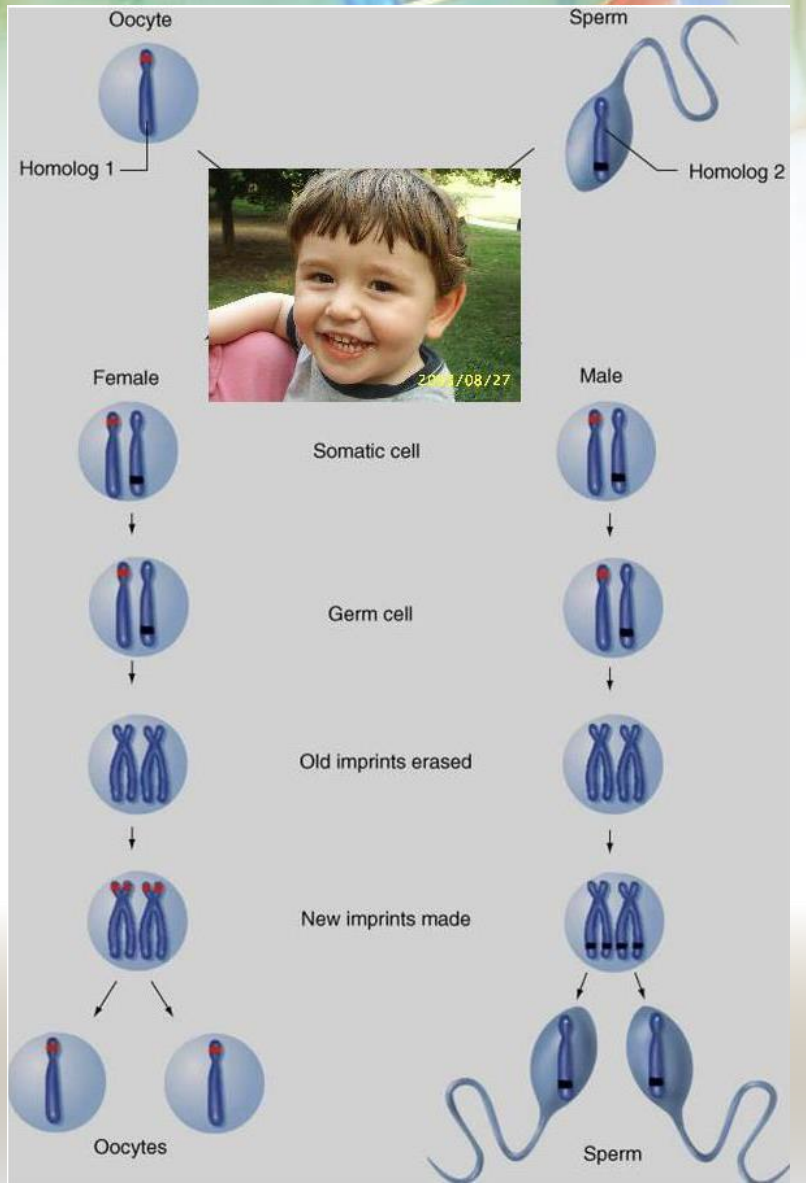
- Human characteristics such as height, skin color and intelligence could be determined by the interaction of **many genes**, each exerting a small additive effect.

- 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.

Genomic Imprinting

- Certain chromosomes retain a memory or “imprint” of parental origin that influences whether genes are expressed or not during gametogenesis



Take home Message:

- 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.


Thank you ☺