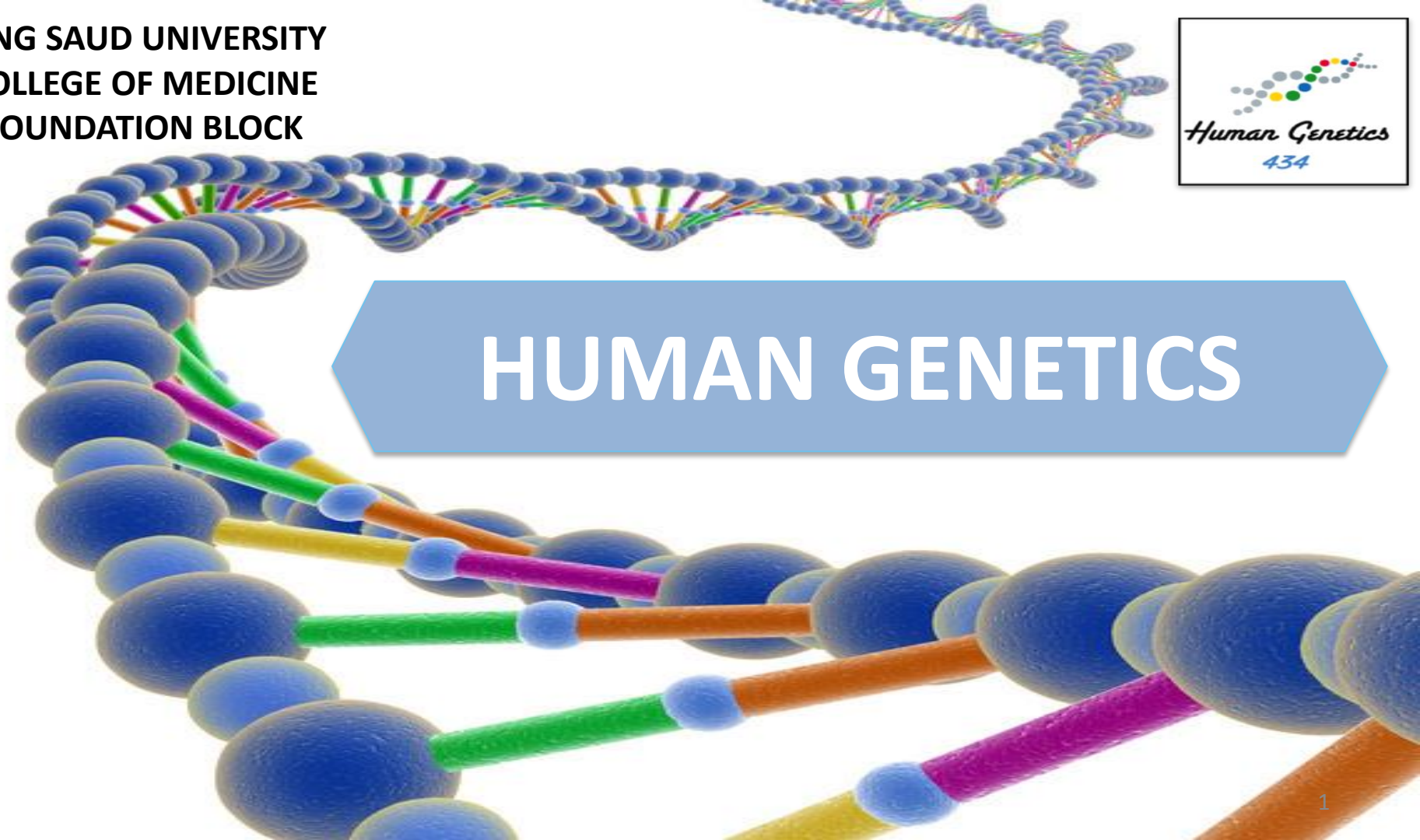
KING SAUD UNIVERSITY
COLLEGE OF MEDICINE
FOUNDATION BLOCK

Human Genetics
434



HUMAN GENETICS

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

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ATYPICAL PATTERNS OF INHERITANCE

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Inheritance of Codominant Alleles

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

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

If the alleles are **different,** the dominant allele usually will be **expressed**, while the effect of the other allele(the recessive), is **masked**. In **codominance**, however, neither allele is recessive and the phenotypes of both alleles are **expressed.**

Possible genotypes, phenotypes & gametes at the ABO locus

Genotype	Phenotype	Gamete
AA	A	A
BB	B	B
OO	O	O
AB	AB	A or B
AO	A	A or O
BO	B	B or O

Don't be confused here, the third column is for the possible genotypes of **gametes(zygote)**

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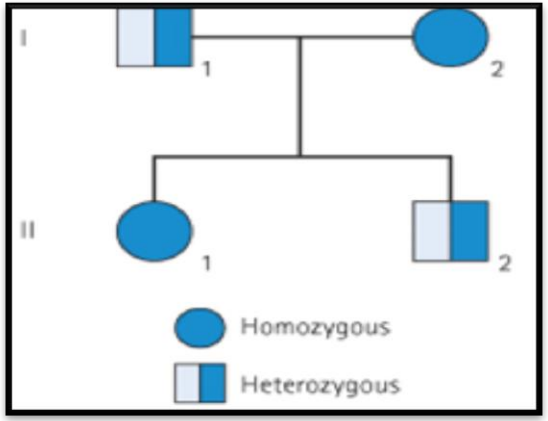
PSEUDODOMINANT INHERITANCE

- 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 (homozygous) i.e. pseudodominant

Pseudodominance is the situation in which the inheritance of an autosomal recessive trait **mimics an autosomal dominant pattern.**



Pedigree:
Pseudodominant inheritance

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Atypical inheritance of single-gene disorders

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

- ✧ Mitochondrial Inheritance
- ✧ Anticipation
- ✧ Atypical Presentation For Autosomal Dominant Defects
- ✧ Multifactorial/ Polygenic Disorders

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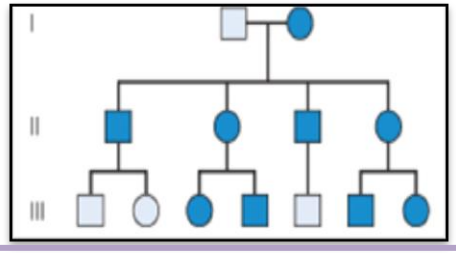
Mitochondrial Inheritance

Mitochondrial DNA (mtDNA)

- Mitochondria (& their DNA) are inherited from the **mother (through ova).**
- mtDNA is a small circular double-stranded molecule containing **37 genes .**



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

Mitochondrial Disorders

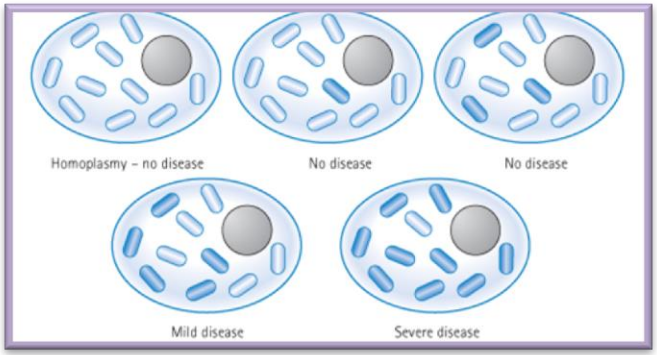
- The defective gene is present on the mitochondrial DNA.
- Show maternal inheritance:
  - Affected **mother** transmits the disorder **equally to all** her children
  - Affected **father does not** transmit the disease to his children.
- Example of **Mitochondrial Disorders**:
  - Lebers hereditary optic neuropathy (Rapid Optic nerve death → blindness in young adult life)

Mitochondrial Inheritance

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 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 i**ncreases**, the disease will be **manifested.**

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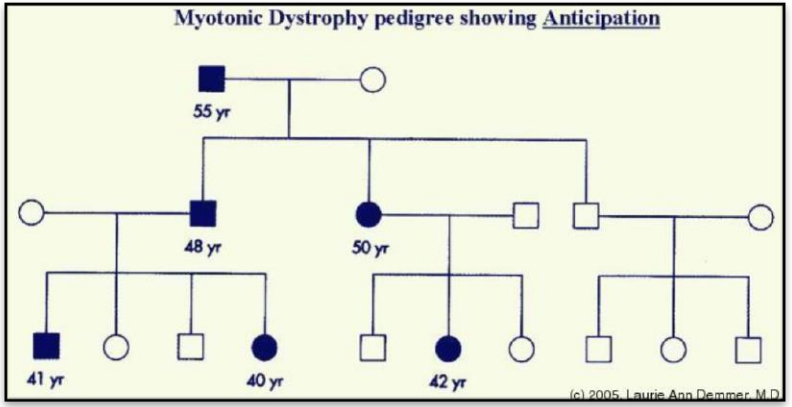
ANTICIPATION

- 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.

- Examples of diseases showing anticipation:
  Huntington disease
  Myotonic dystrophy

  - Autosomal dominant disease.

  - the expansion of trinucleotide repeat polymorphisms in the 3' on this gene in chromosome 19 is the reason of anticipation phenomena in myotonic dystrophy.



Pedigree:
Myotonic Dystrophy

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Atypical presentation for Autosomal Dominant defects

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.

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.

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**.

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 cyst**s that do not significantly affect renal function

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.**

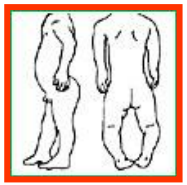
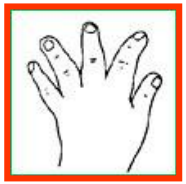
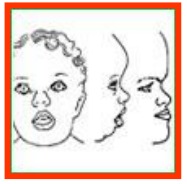
Achondroplasia

- 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.

- 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
  - Variable expressively
  - 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.
- **Digenic inheritance:** where a disorder has been shown to be due to the additive effects of **heterozygous mutations at two different gene loci .**
- Example: **retinitis pigmentosa**, (is caused by **double heterozygosity** for mutations in **two unlinked genes**)

Monogenic inheritance refers to genetic control of a phenotype or trait by a single gene. Less commonly, the interaction of only two genes is required for expression of a phenotype. a mechanism referred to as **digenic inheritance**

MULTIFACTORIAL/POLYGENIC DISORDERS

- Human characteristics could be determined by the interaction of **many genes**, each exerting a small additive effect(**quantitative inheritance).**
- Example:
  -congenital malformations such as **cleft lip and palate.**
  -late-onset conditions such as:
  Hypertension, Diabetes, Alzheimer
- The prevailing view is that **genes at several loci** interact to generate a **susceptibility** to the effects of **adverse environmental** trigger factors.(these environmental factor are only harmful if the person is susceptible to that disease)

Genomic Imprinting

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

(If the allele inherited from the father is imprinted, then only the allele from the mother is expressed. And vise versa)

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.

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