KING SAUD UNIVERSITY
COLLEGE OF MEDICINE
FOUNDATION BLOCK

LECTURE 4
Atypical Patterns of Inheritance

HUMAN GENETICS 433

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

Color index:

Red → Important

Yellow → Noted

Green → Explanation

If you have any questions please contact us :
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Codominance

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

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

***In one gene there are " two alleles" in heterozygous state .**

***AB blood groups* are " codominant " because they don't have antibodies .**

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

Pseudodominant inheritance

Homozygous recessive (affected)

Heterozygous recessive (carrier)

	r	r
R	R r	R r
r	r r	r r

Pseudodominant

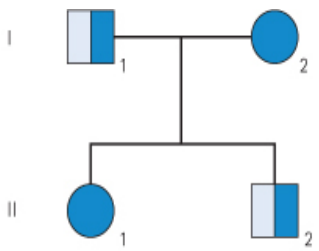
Homozygous recessive (normal)

Heterozygous dominant (affected)

	r	r
R	R r	R r
r	r r	r r

Dominant

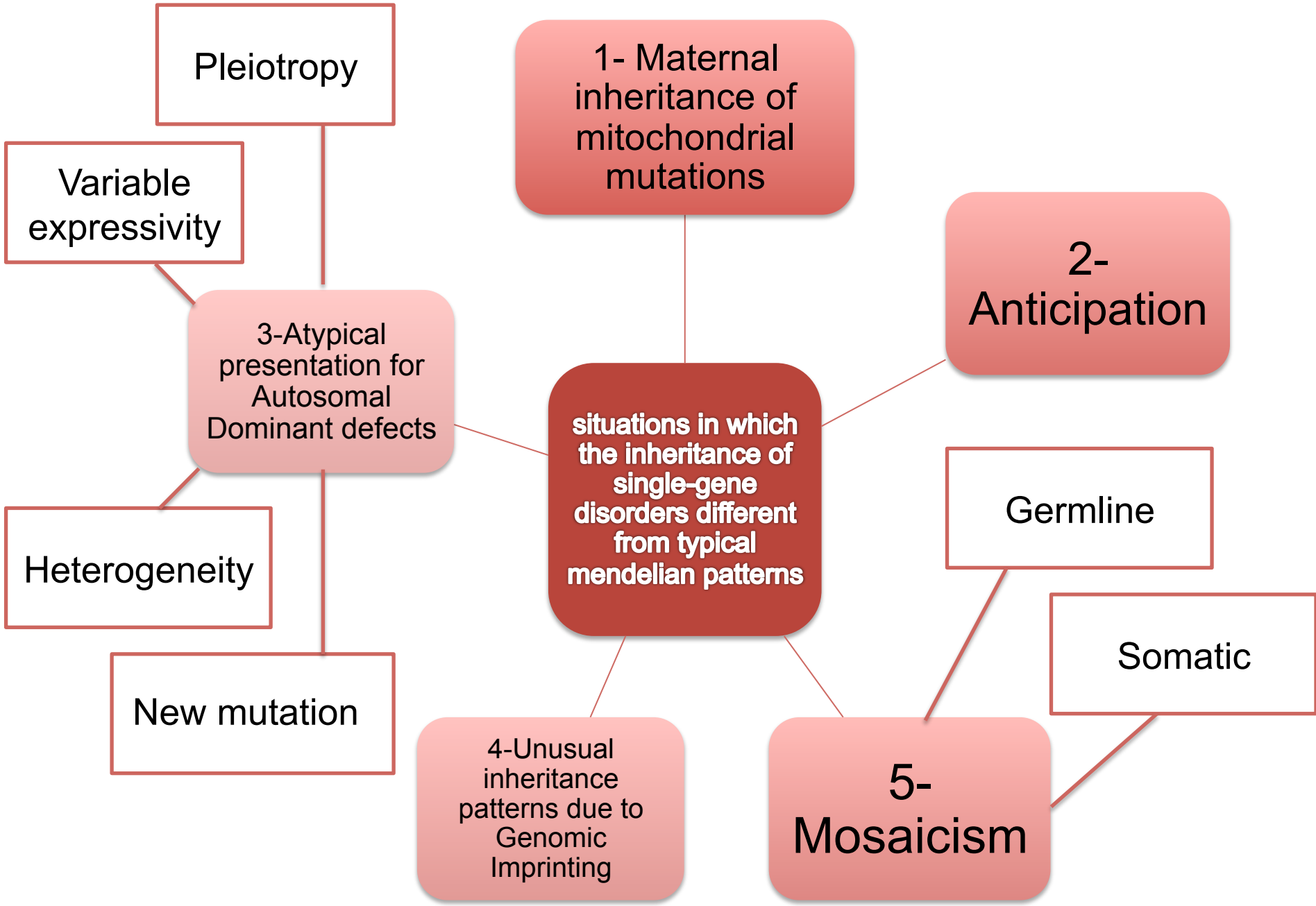
- **Same results (in one generation) leading to confusion in clinical settings as the clinician will perceive dominant features without knowing the underlying alleles carried by parents .**
- E.g. A woman homozygous for an autosomal recessive disorder whose husband is heterozygous for the same disorder. Their children have a 1 in 2 (50%) chance of being affected.



enny & Ellard: Emery's Elements of Medical Genetics 12E www

← Pedigree

pedigree method used to calculate or to see the possible generations .


Pleiotropy
Variable expressivity
3-Atypical presentation for Autosomal Dominant defects
Heterogeneity
New mutation
1- Maternal inheritance of mitochondrial mutations
situations in which the inheritance of single-gene disorders different from typical mendelian patterns
2- Anticipation
Germline
Somatic
5- Mosaicism
4-Unusual inheritance patterns due to Genomic Imprinting

1- MITOCHONDRIAL INHERITANCE

mtDNA(1) 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)

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) because during fertilization only the sperm genetic materials are transmitted while the mitochondria within cytoplasm from the mother

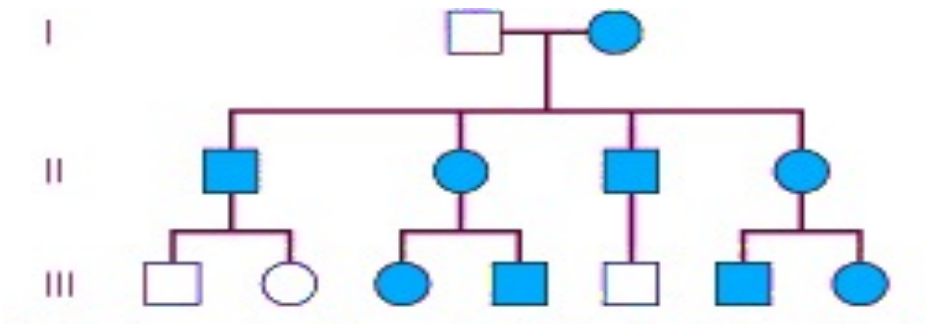
- The defective gene is present on the mitochondrial chromosomes.
- Effect generally energy metabolism
- Effect more those tissues which require constant supply of energy e.g ***muscles***

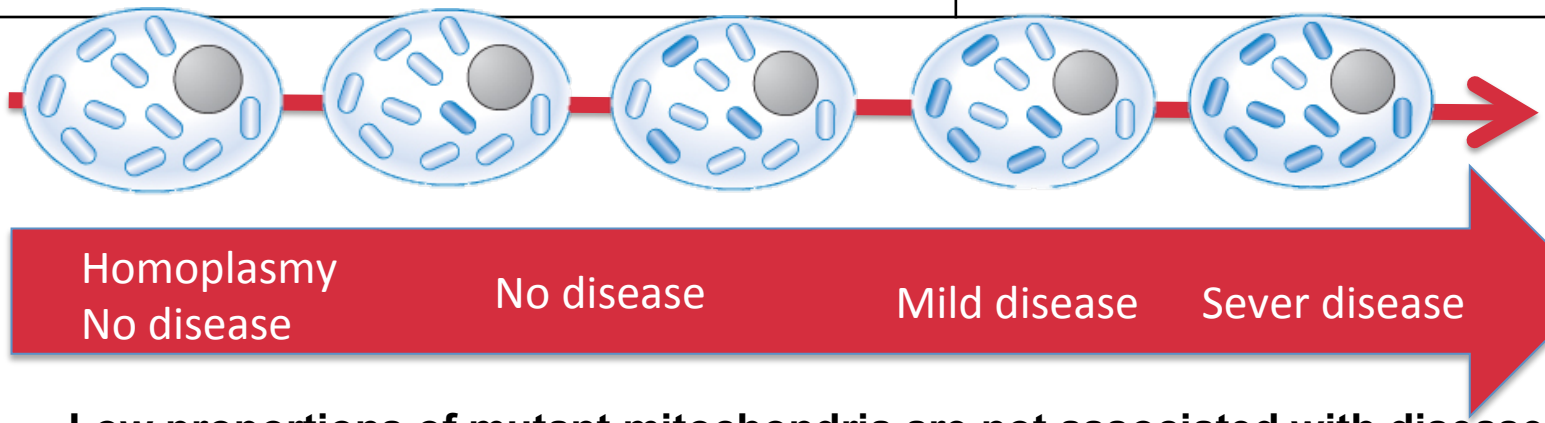
Affected mother transmits the disorder equally to all her children, but father does not

(1) mtDNA= Mitochondrial DNA

Homoplasmy vs. Heteroplasmy

Homoplasmy	Heteroplasmy
in most persons, the mtDNA from different mitochondria is identical.	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.



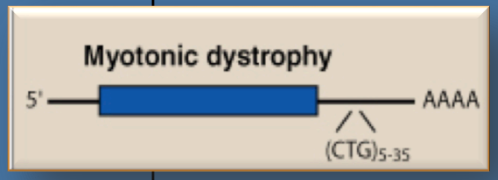


e.g. **Lebers hereditary optic neuropathy (LHON)**(1)

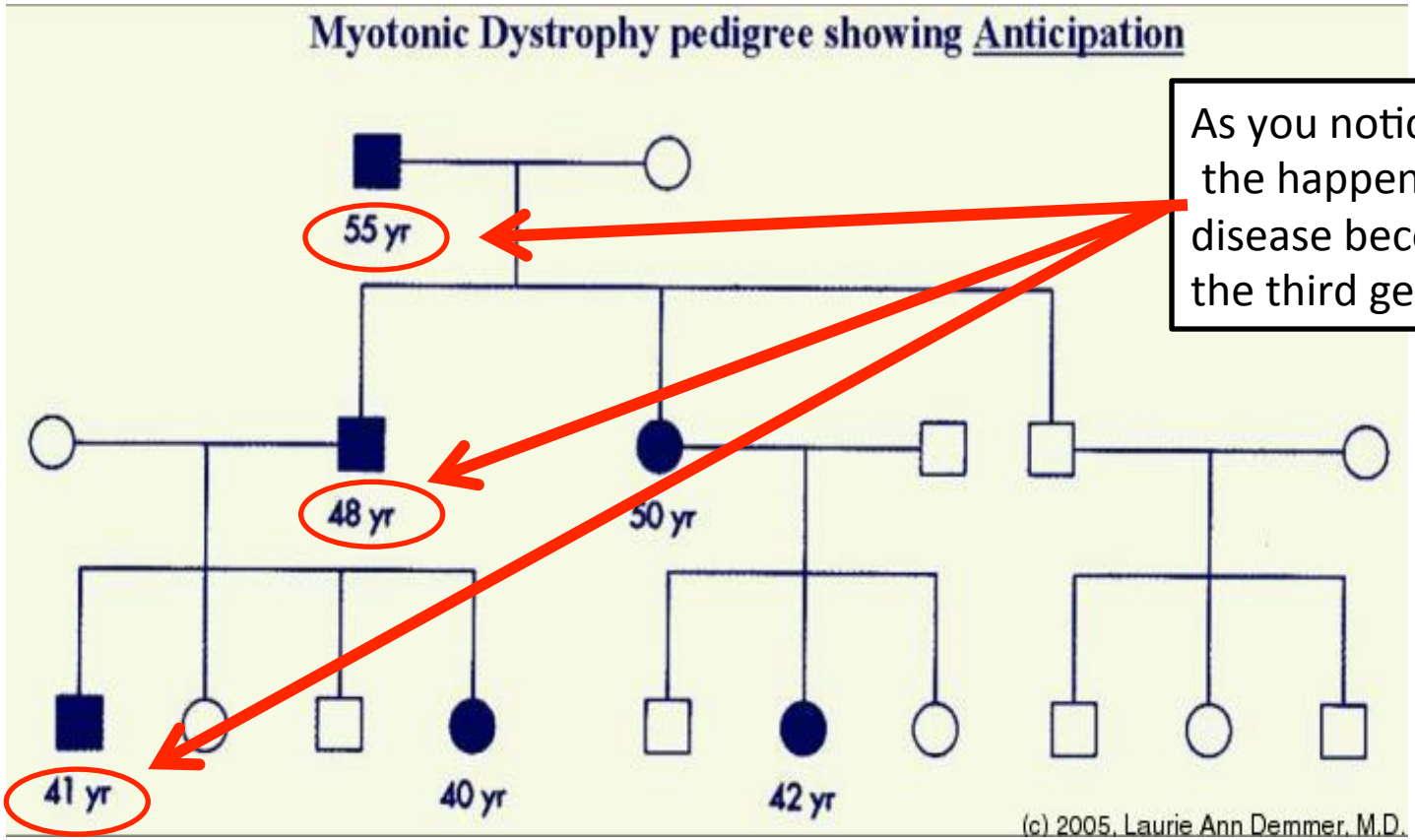
- **Low proportions of mutant mitochondria are not associated with disease**
- **As the proportion increases, the disease will be manifested**

(1) **Rapid Optic nerve death → blindness in young adult life**

Type of a typical inheritance of single-gene disorders	What happens	The reason	Others
ANTICIPATION * It means when the gene pass from generation to generation .	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 disease = Huntington disease. = Myotonic dystrophy.
Myotonic Dystrophy	Autosomal dominant disease	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.



As you notice here..
the happening of the disease become earlier in the third generation

Father is affected here & the mother is normal

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.**

1) 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:

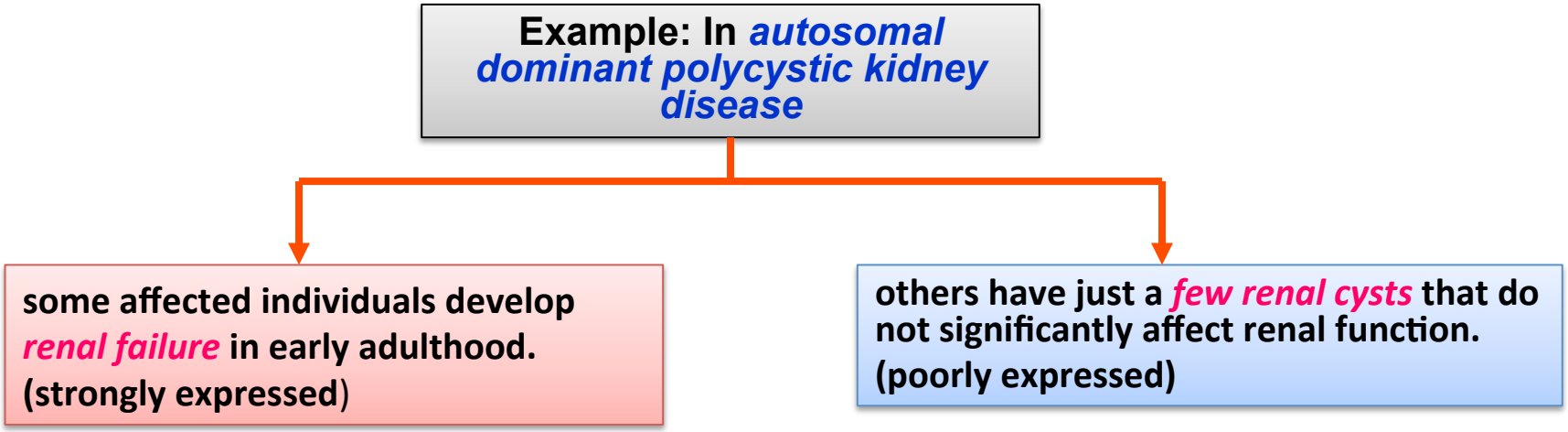
- **In tuberous sclerosis (a genetic disorder that causes non-malignant tumors to form in many different organs) affected individuals can present with either learning difficulties, epilepsy, a facial rash.**

- **PKU (a metabolic genetic disorder leading to malformation of the enzyme PHA) can cause mental retardation and reduced hair and skin pigmentation by any of a large number of mutations in a single gene.**

*** PKU disease : only affect the skin, caused by changes in genes.**

2) Variable expressivity

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



3) 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 (genes that counteract the effect of the mutation).**
  - **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 (example of a new mutation)

- **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**

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

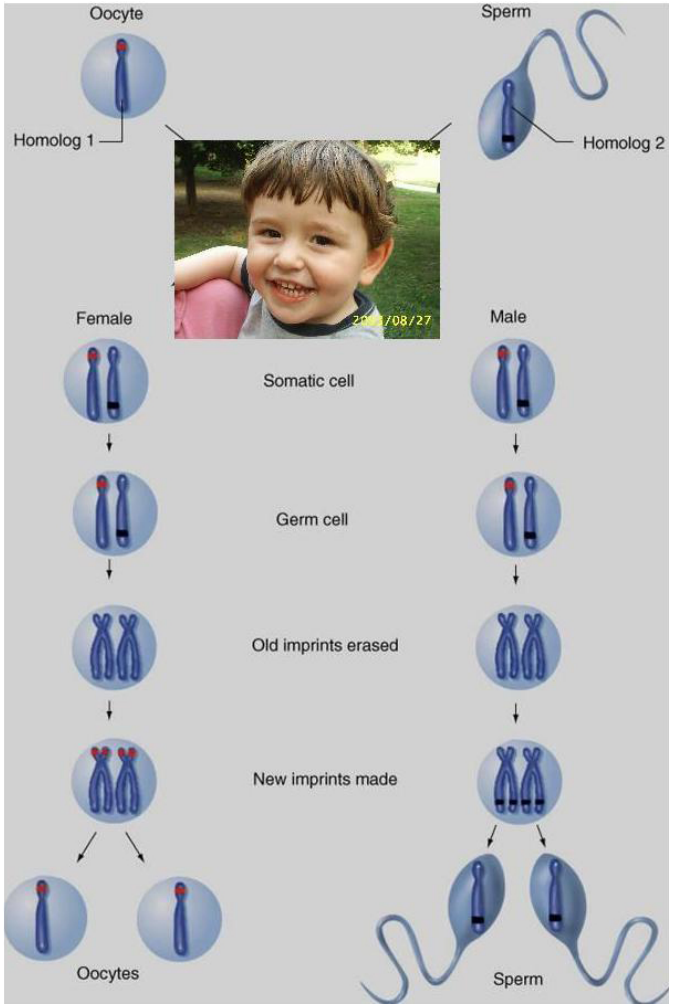
There are many diseases of ** polygenic disorders ** controlled by genes

Genomic Imprinting

- Certain chromosomes retain a memory or “imprint” of parental origin that influences whether genes are expressed or not during gametogenesis.
- Examples: Prader-Willi & Angelman syndromes, Silver-Russell syndrome

Prader-willi syndrome: deletion of (15q11-13) in paternally inherited chromosome 15.

Angelman syndrome: deletion of (15q11-13) in maternally inherited chromosome 15.



Atypical Patterns of Inheritance

Co-dominant Alleles
2 allelic traits expressed in the heterozygous state
E.g. Blood group AB

Pseudo-dominant
In autosomal recessivedisorder

Polygenic Disorders
Congenital : Cleft lip
Late-onset :Hypertension, Diabetes, Alzheimer

Single-GeneDisorders

Pleiotropy
Single gene gives rise to 2 or more unrelated affects.
-Tuberous Sclerosis: learning difficulties or facial rash or epilespy
-PKU: mental retardation and reduced hair or skin pigmentation.

Anticipation
***Recent generations have the disease earlier or with greater effect than in earlier generations**
***Reason: expansion of trinucleotide within or near a coding gene.**

Mitochondrial Mutations
*Mitochondria and its DNA is inherited from the mother.
*mtDNA contain 37 genes.
*Affects tissues that require energy e.g. Muscles.
*Homoplasmy means all mtDNA are identical.
*Heteroplasy means some are normal and some are defected.
e.g. LHON

VariableExpressivity
E.g. Autosomal Dominant Polycystic Kidney
***Some : develop reanal failure in early adulthood.**
***Others: have few renal cycts "not dangerous"**

E.g. Myotonic Dystrophy
***Autosomal dominant disease. On chromosome 19.**
***triplet repeat in '3 untranslated region of myotonic gene.**
***clinical signs : Myotonia, Cataracts, Testicular atrophy.**

New Mutations
Sudden unexpected appearance of a mutation that wasn't in the family history before.

ReducedPenetrance (Heterogeneity)
due to -modyfing effects of other genes.
-interaction of the gene with environmental factors.

Achondroplasia
Short-limb dwarfism.
Mutation in the FGFR3 gene on chromosome 4p16.3

MCQs

1)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

Answer: (d)

2)Myotonic dystrophy is an example of a disease showing:

A. Pseudodominant inheritance
B. Anticipation
C. Pleiotropy
D. New mutation

Answer: (b)

3)6 month-old infant presents severe mental retardation and hypopigmentation. In your investigations you find that there are high levels of serum phenylalanine.
What disease do you suspect?

A. PKU
B. Tuberous sclerosis
C. Silver-Russell syndrome
D. Prader-Willi syndrome

Answer: (a)

MCQs

4)Diabetes is considered as one of the:

A. Codominant traits
B. Pseudodominant inheritance
C. Polygenic disorders
D. Mitochondrial inheritance

Answer: (c)

5)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

Answer: (d)

6)On which of the following is the Angelman syndrome gene expressed?

A. Paternal chromosome
B. Maternal chromosome
C. Both a + b
D. None of the above

Answer: (b)

MCQs

7)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

Answer: (c)

Human Genetics Team

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