MEDICINE
KING SAUD UNIVERSITY

436 TEAM
HUMAN GENETICS

Human genetics:

Atypical Patterns of Inheritance

For revision only

- **Important**
- **Notes**

Objectives:

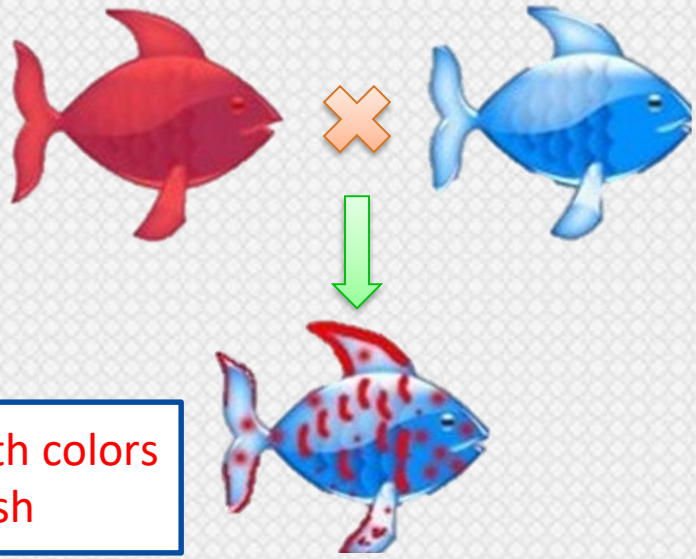
By the end of this lecture, students should be able to appreciate the possibility of atypical patterns of inheritance with special emphasis on:

1. Codominant traits
2. Pseudo-dominant 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: two allelic traits that are both expressed in the heterozygous state

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



* This picture shows codominance , you can notice both colors red and blue on the second generation of this fish

Possible genotypes, phenotypes & gametes formed from the four alleles: A1, A2, 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

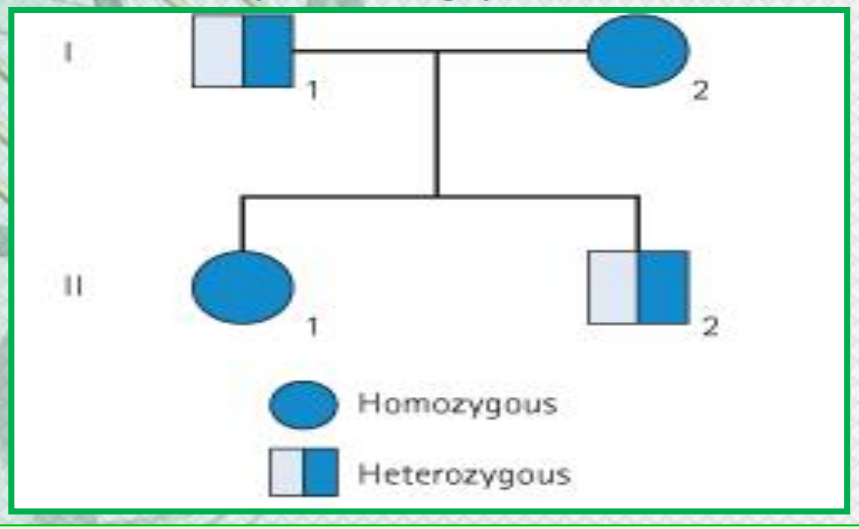
A & B are codominant

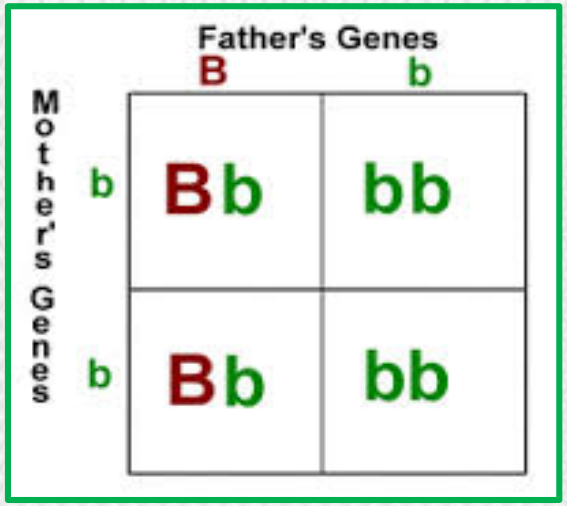
A is dominant

B is dominant

PSEUDODOMINANT INHERITANCE

Pseudodominance: appearance of a recessive phenotype in a heterozygote containing the recessive gene on one chromosome and a deletion or only part of the dominant gene on the corresponding part of the homologous chromosome





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)

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

1. Maternal inheritance of mitochondrial mutations
2. Anticipation
3. Atypical presentation for Autosomal Dominant defects
   - Pleotropy
   - Variable expressivity
   - Reduced penetrance
   - New mutation

Unusual inheritance patterns due to

1. Genomic Imprinting
2. Mosaicism
   - Somatic
   - Germline

Mitochondrial inheritance

Mitochondrial DNA (mtDNA)

Mitochondrial disorders (next slide)

* Each cell contains thousands of copies of mitochondrial DNA with more being found in cells having high energy requirement (e.g. brain & muscle).

*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)

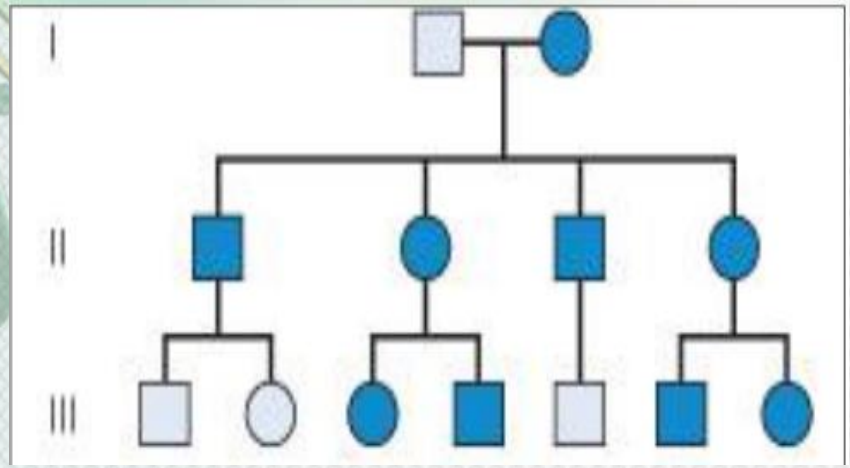
*Mitochondria (& their DNA) are inherited from the mother (through ova)

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 (LHON):

It is the rapid Optic nerve death, which leads to blindness in young adult life

Mitochondrial inheritance



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

*Note that there are no carriers in mitochondrial inheritance, either affected or not.

Homoplasmy vs. Heteroplasmy

Homoplasmy

in most persons, the mtDNA from different mitochondria is identical

Heteroplasmy

The presence of two population of mtDNA in a cell:

The normal mtDNA and the mutant mtDNA

The proportion of mutant mtDNA varies between cells & tissues

Leads to range of phenotypic severity in mitochondrial inheritance

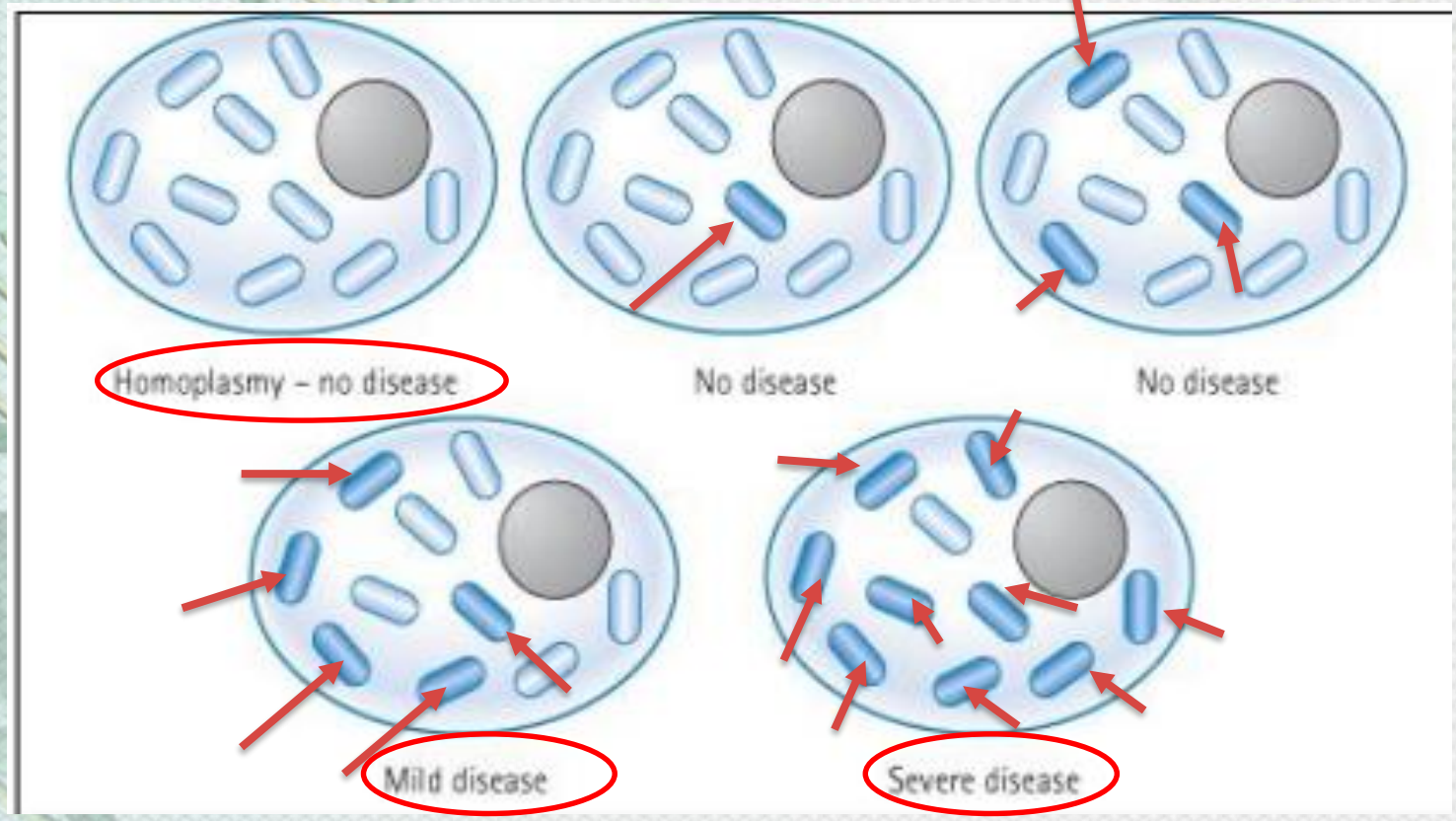
mtDNA is the (mitochondrial DNA), which is different than genomic DNA in the nucleus.

Low proportion of mutant mitochondria

Not associated with disease

Higher proportion of mutant mitochondria

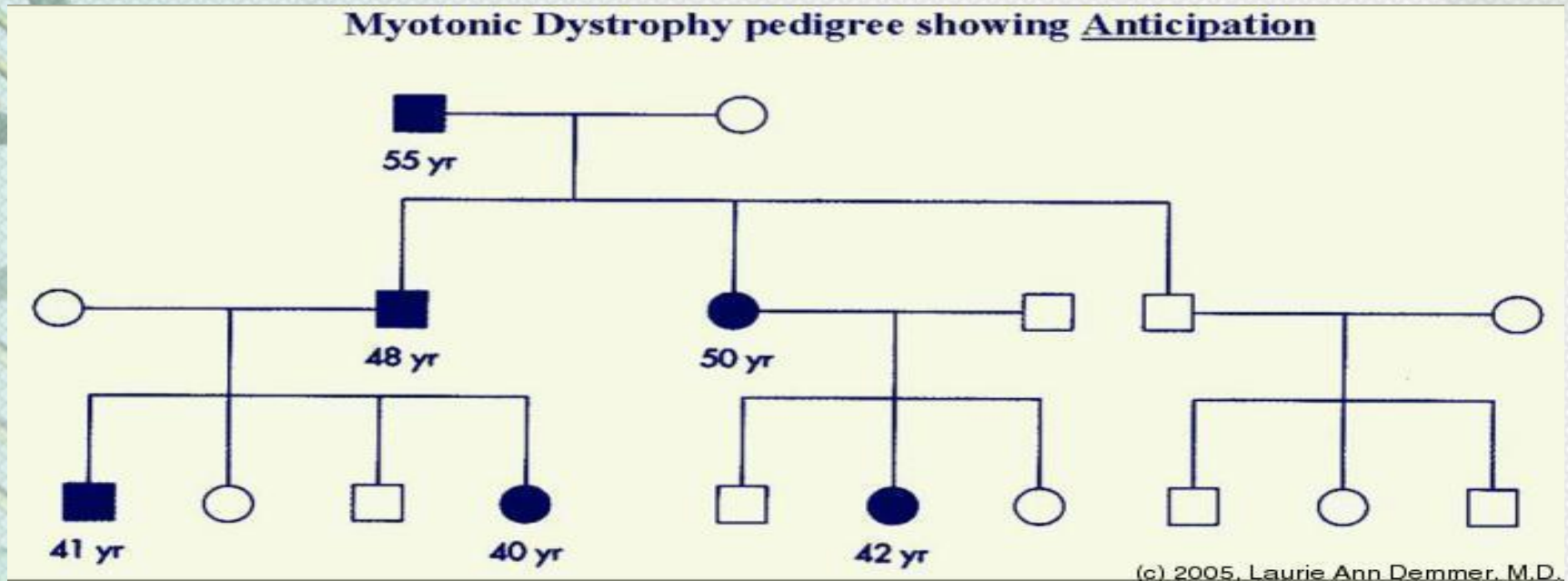
The severity of the disease


Homoplasmy – no disease
No disease
No disease
Mild disease
Severe disease

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

The affected gene is on chromosome 19

The mutation is triplet repeat (CTG) expansion in the 3' untranslated region of the myotonic dystrophy gene

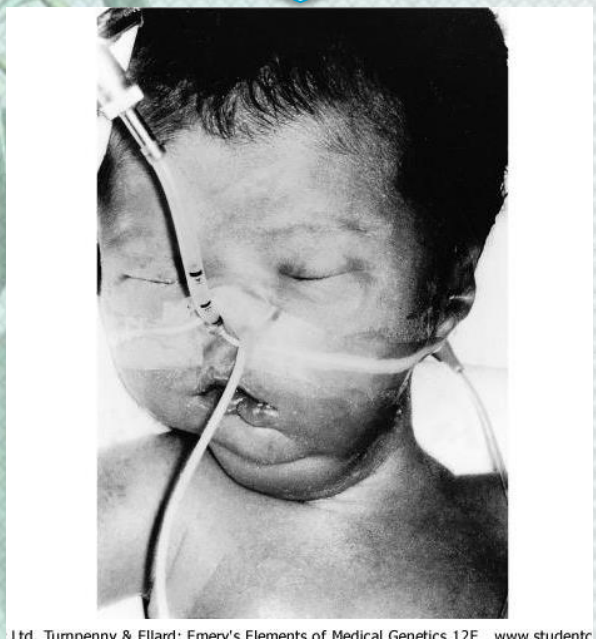
Relatively common

Myotonic dystrophy is a common multi-system disorder that affects the skeletal muscles .

Clinical manifestations:

– Myotonia (Muscular loss & weakness)
– Cataracts
– Testicular atrophy
– Heart disease: arrhythmia
– Dementia
– Baldness

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



Ltd, Turnpenny & Ellard: Emery's Elements of Medical Genetics 12E www.studentc

Atypical presentation for Autosomal Dominant defects

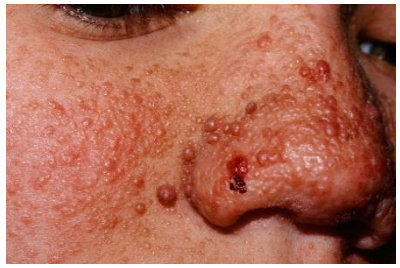
- It is common for autosomal dominant disorders to manifest in *different systems* of the body *in a variety of ways*.

- When providing *genetic counseling* to individuals at risk for autosomal dominant inherited disorders, there are <u>three atypical presentations</u> that need to be taken into account:

1- Pleiotropy:

<u>A single gene that may give rise to two or more apparently unrelated effects.</u>

Example: **Tuberous sclerosis** → when affected individuals can present **either**:
- learning difficulties
- epilepsy
- a facial rash
- **or,** all features



2- Reduced penetrance:

In some individuals heterozygous for gene mutations giving rise to certain autosomal dominant disorder

there may be no abnormal clinical features, representing so-called *reduced penetrance* or "skipping a generation"

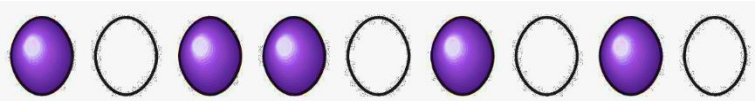
Reduced penetrance might be due to:

* Modifying effects of other genes
* Interaction of the gene with environmental factors

More Explanation (from 435 team) :

Penetrance refers to the proportion of people with a particular genetic change (such as a mutation in a specific gene) who exhibit signs and symptoms of a genetic disorder.

If some people with the mutation do not develop features of the disorder, the condition is said to have reduced (or incomplete) penetrance.



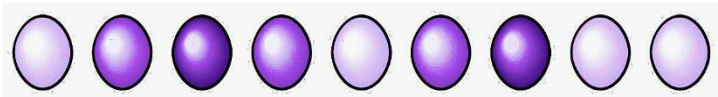
3- Variable expressivity:

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

Example: ***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



These two additional pictures are to clarify the difference between reduced penetrance and variable expressivity. Each oval shapes represents an individual. We can notice that in in "reduced penetration" not 100% showed abnormal clinical features. While in variable expressivity all individuals showed phenotype but not the same.

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 "***new mutation***"!!

eg. 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)…

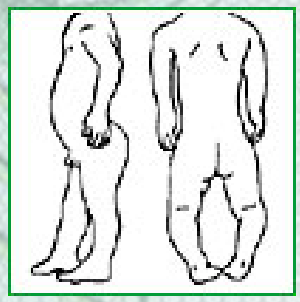
(continue next slide)

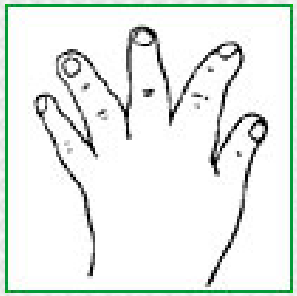
تابع

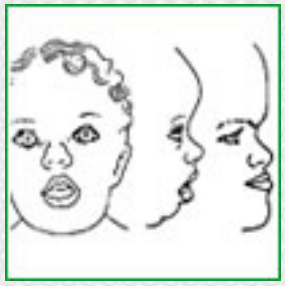
- The offspring of persons with achondroplasia had a 50% chance of having achondroplasia
- **What other possible explanations for the 'sudden' appearance of achondroplasia?**
  - non-penetrance: One of the parents might be heterozygous for the mutant allele but so mildly affected that it has not previously been detected
  - Variable expressivity

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

So, achondroplasia is caused mostly by a new mutation but could be caused from the three reasons above







Complex traits

-What is it?

A condition 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

-Examples:

1- Digenic inheritance where a disorder has been shown to be due to the additive effects of heterozygous mutations at two different gene loci.

تابع

Complex traits

2- 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 disprders

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

- **quantitative inheritance** is a model that can explain the pattern of inheritance for many relatively common conditions , including :

congenital malformations

such as : cleft lip and palate

late-onset condition

such as:

- Hypertension

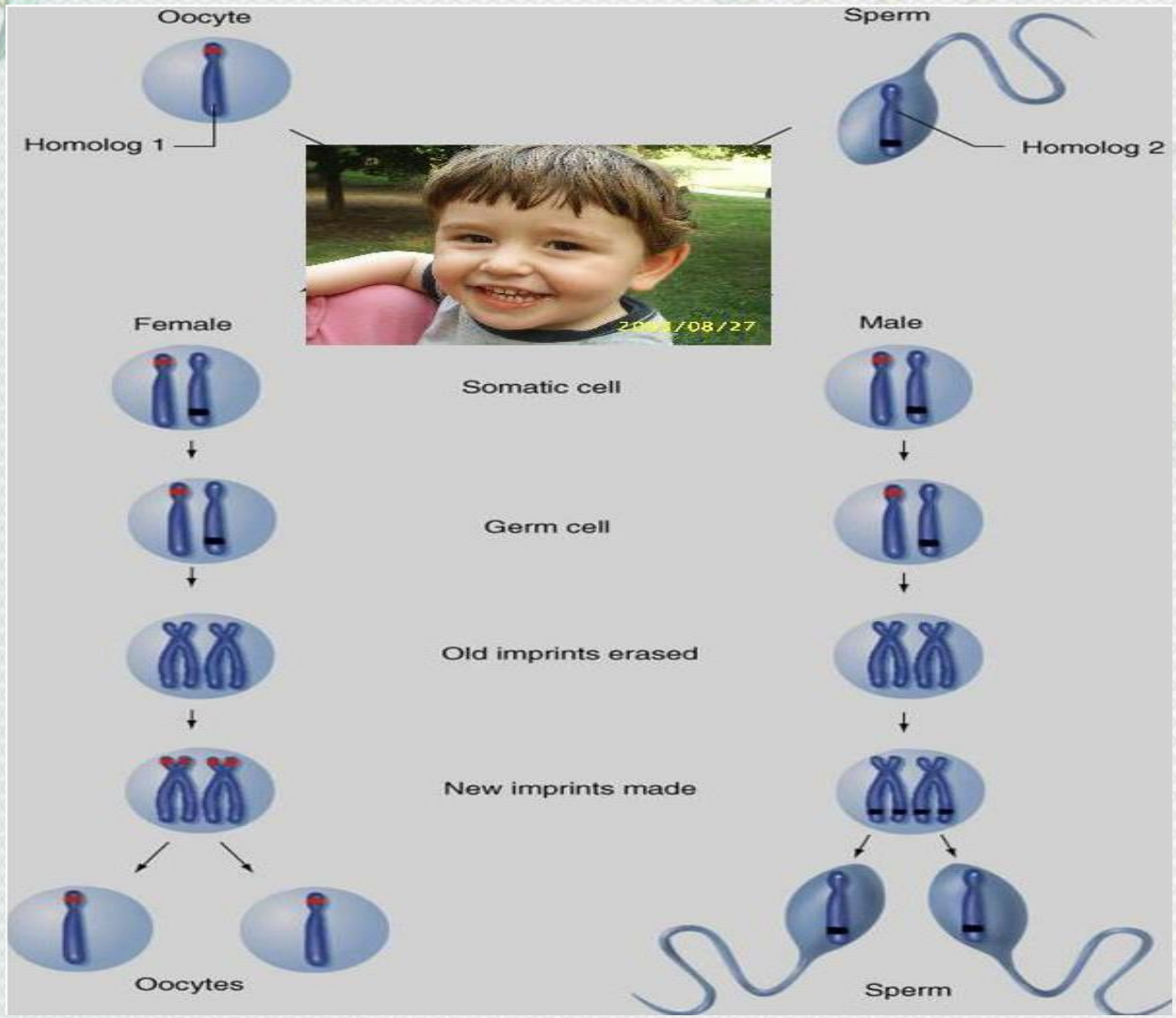
-Diabetes mellitus

-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 an example of non-mendelian inheritance

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



Quiz:

- **what is the phenotype for (A1B)**

1- A1B 2- A2B 3-A 4-B

- **The affected gene in Myotonic dystrophy is on chromosome**

1- 21 2- 19 3- 11 4- 9

- **The sudden unexpected appearance of a condition arising as a result of a mistake occurring in the transmission of a gene is called:**

1- Reduced penetrance 2- New mutation 3-Variable expressivity 4- Pleiotropy

- Another one!

https://www.onlineexambuilder.com/huaman-genetics-lecture-4/exam-43318

Thank You !

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