Human Genetics Team

Human Genetics

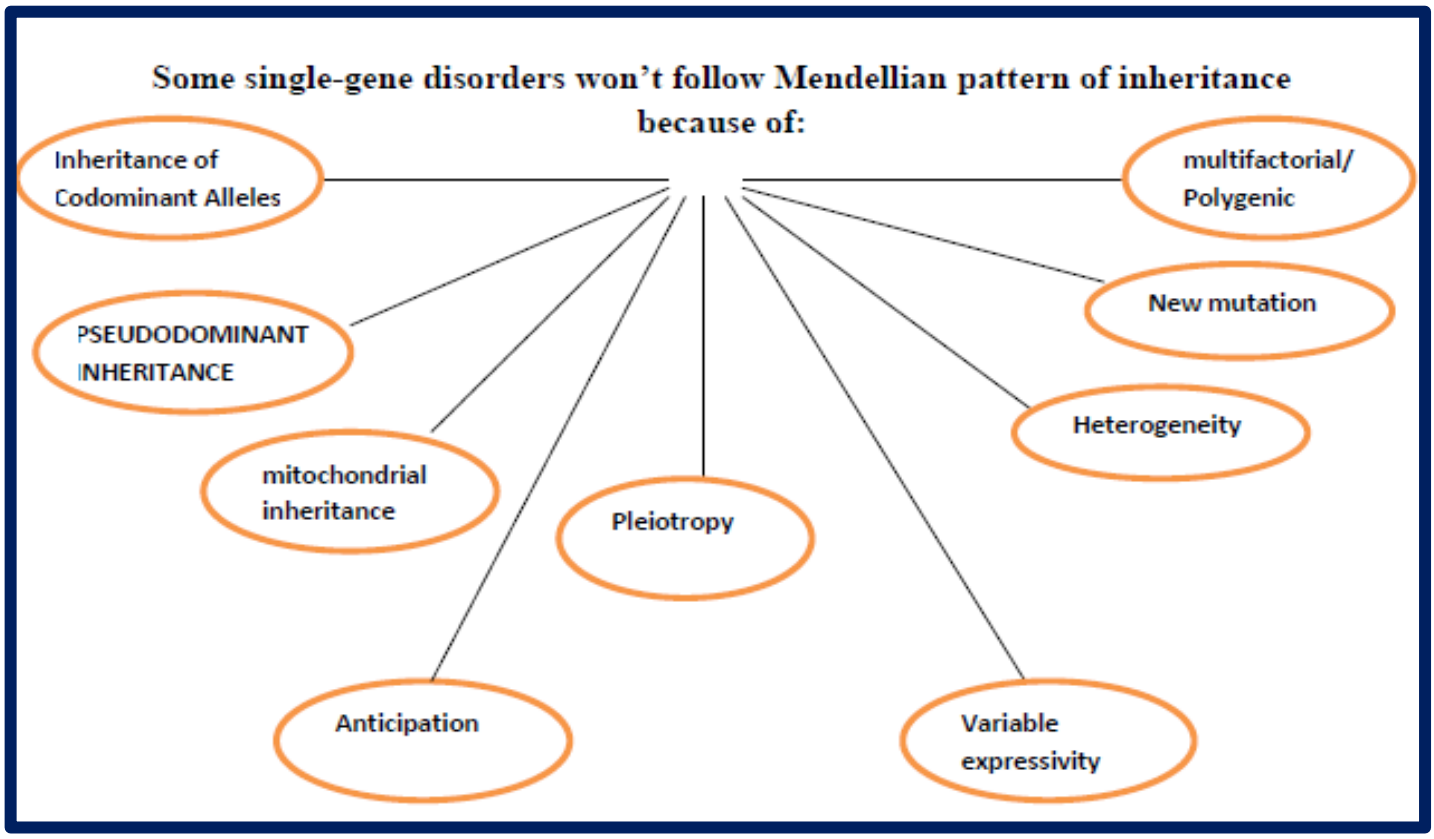
Lecture :4

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**



Codominance:

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

So basically it happens to dominant alleles

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:

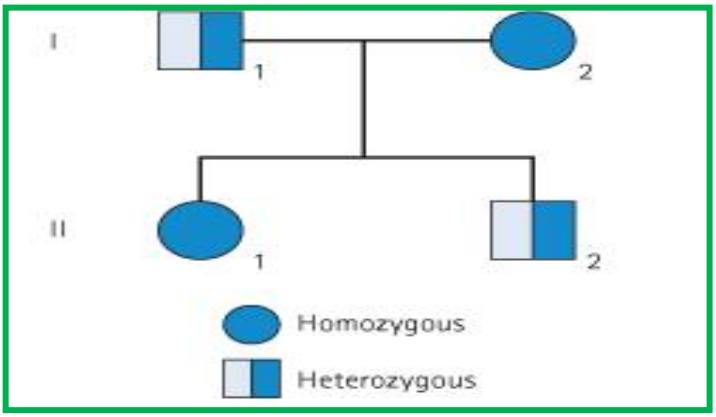
Genotype	Phenotype	Gamete
A_1A_1	A_1	A_1
A_2A_2	A_2	A_2
BB	B	B
OO	O	O
A_1A_2	A_1	A_1 or A_2
A_1B	A_1B	A_1 or B
A_1O	A_1	A_1 or O
A_2B	A_2B	A_2 or B
A_2O	A_2	A_2 or O
BO	B	B or O

عبارة عن اتحاد صفتين سائدتين في جين واحد مثل : فصيلة الدم AB

Pseudodominant inheritance Pedigree:

- **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



Pseudodominant: it is not dominant but it looks like dominant

It happens in recessive case only

Atypical inheritance of single-gene disorders

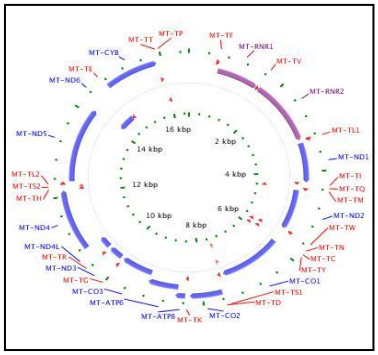
What are the situations in which the inheritance of **single-gene disorders** diverges from typical mandolin patterns?

- 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

Mitochondrial DNA (mtDNA)

Each Mitochondria has its own DNA which consist of 37 genes



- 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)

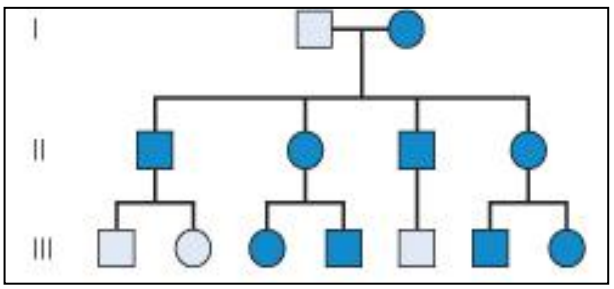
Mitochondrial Disorders:

- 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

هنا نلاحظ أن الأم المصابة نقلت المرض لكل أبنائها و بناتها ولكن الأبناء الذكور في الجيل الثاني لم ينقلوا المرض مع أنهم مصابين على عكس البنات

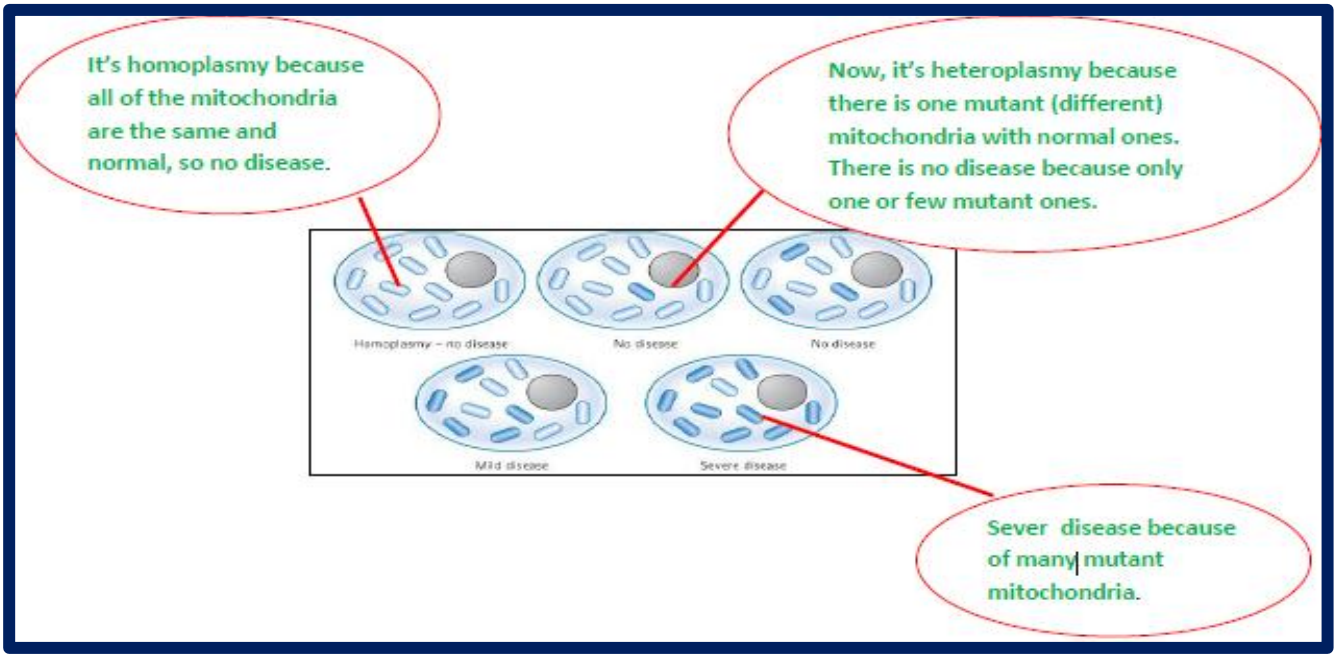


Homoplasmy vs. Heteroplasmy :

- **Homoplasmy** = in most persons, **the mtDNA** from different mitochondria is identical.**(normal)** **Same genotype of cell with normal alleles.**
- **Heteroplasmy** = the presence of two populations of mtDNA in a cell; **the normal mtDNA & the mutant mtDNA.(abnormal)** **Different genotype.**
- 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

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 cause is: the repetition of certain trinucleotide within or near the coding gene.

- 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

مثال للتوضيح:

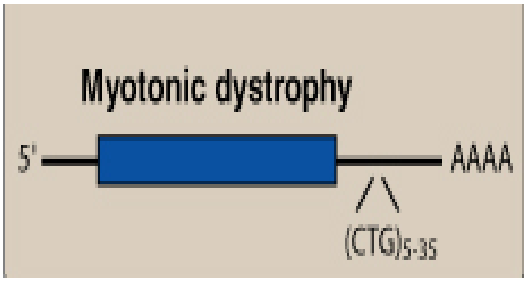
ظهر المرض في الجد في عمر السبعين

ظهر في الوالدين في عمر الخمسين

ظهر في الولد في عمر العشرين

وهو يحدث بسبب توسع حدث في الجين

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**

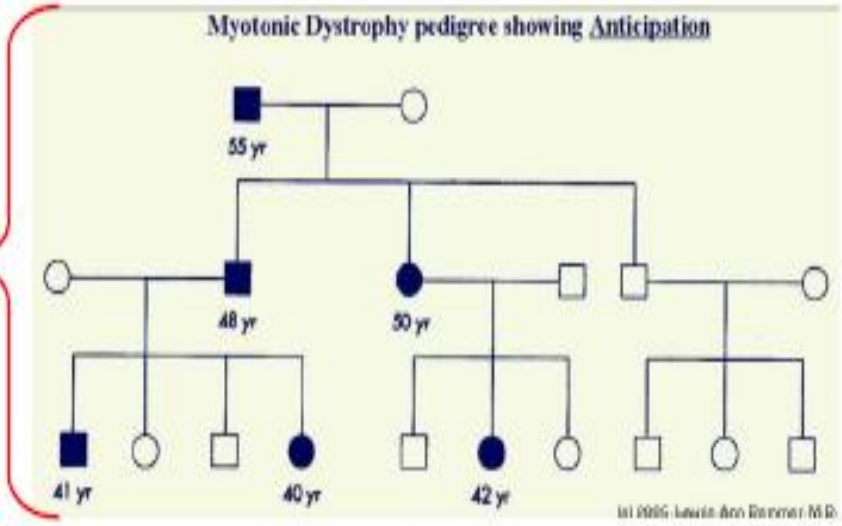
cataract: a clouding of the lens of the eye – إعتام عدسة العين

dementia: a state of serious emotional and mental deterioration.

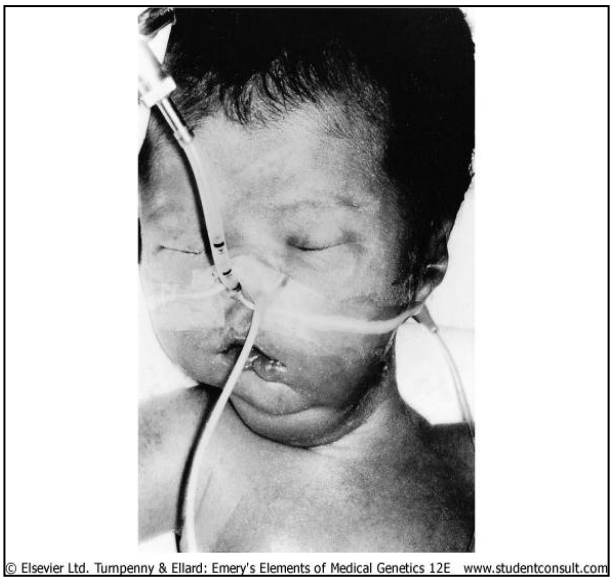
Baldness: صلع

Arrhythmia: an alteration in rhythm of the heartbeat either in time or force عدم انتظام ضربات القلب

في هذي الرسمة موضح ان الشخص المصاب بالمرض في الجيل الاول عمره 55 .. ولكن في الجيل الثاني يزداد انتشار المرض(شخصين) و في عمر اقل مثل ما هو موضح شخصين مصابين واعمارهم اصغر من اللي في الجيل الاول.. في الجيل الثالث ازداد انتشار المرض(3 اشخاص) لاشخاص اعمارهم اصغر من اللي في الجيل الثاني وهكذا ..



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



Atypical presentation for Autosomal Dominant defects :

i. ***Pleiotropy***

ii. ***Reduced penetrance***

iii. ***Variable expressivity***

All need to be taken into account when providing genetic counseling to individuals at risk for autosomal dominantly inherited disorders.

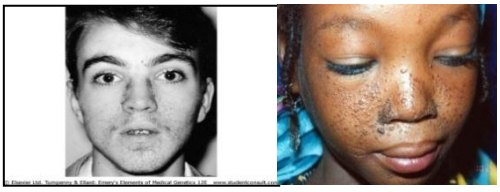
Pleiotropy

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**



One gene control more than on one phenotype

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

Variable expressivity : When the gene loss control the phenotype

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**

> **A person carry a disease but it's not necessary that this person will express (have) that disease because of reduced penetrance of this gene.**

- 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 :

1. 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: **(Two genes control a specific trait.)**

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.

2. 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*** **(Many genes control one trait)**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

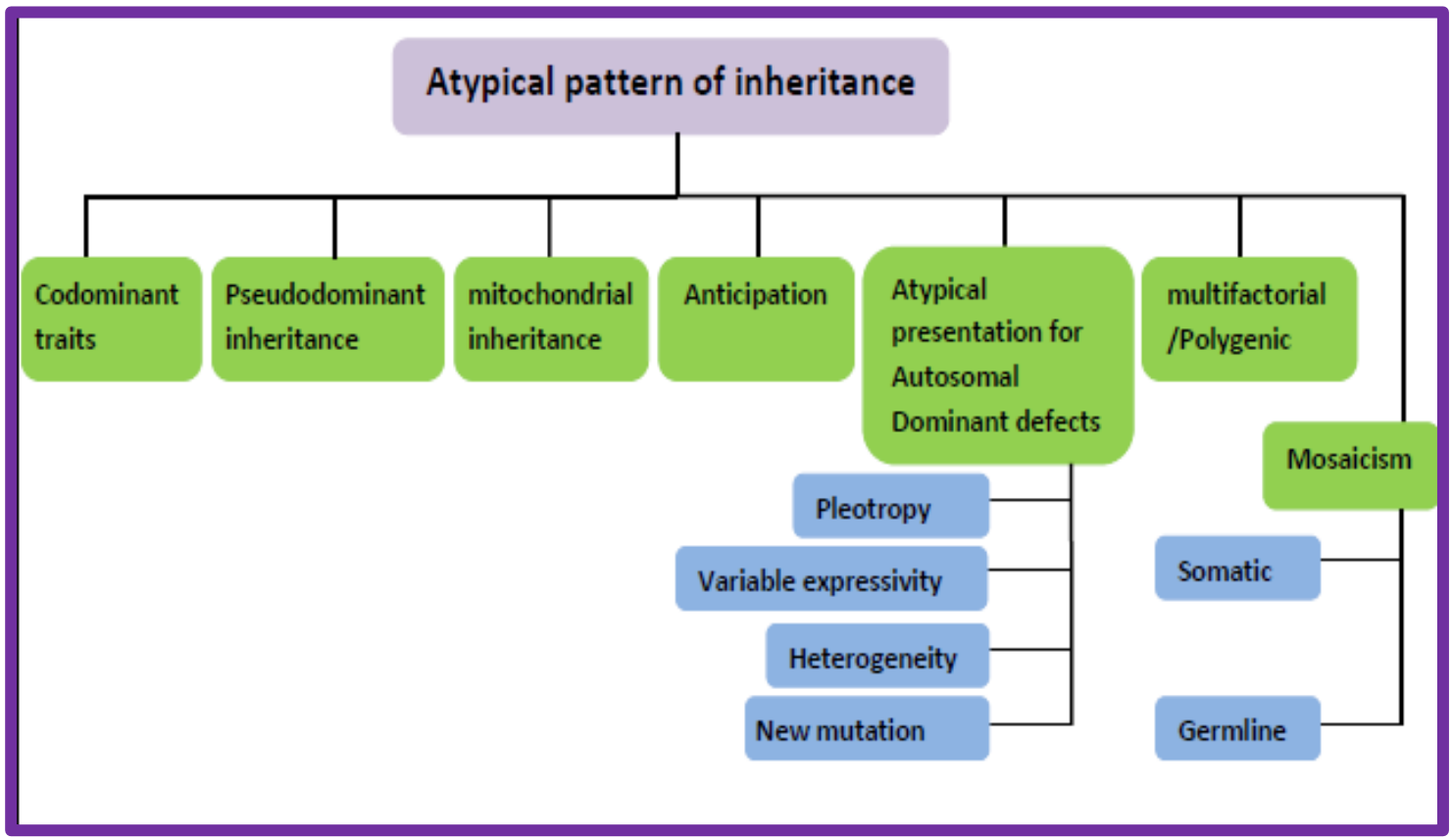
it depends on the"x" chromosome in the parents

- A chromosome which remembers the disease. The allele on that chromosome is normal (no mutation in the DNA).

- Imprinting is due to methylation and histone modifications in the chromosome.

Genomic Imprinting:

- Genomic imprinting is a genetic phenomenon by which certain genes are expressed in a **parent-of-origin**-specific manner.
- It is an inheritance process **independent** of the classical Mendelian inheritance.
- Imprinted alleles are **silenced** such that the genes are either expressed only from the non-imprinted allele inherited from the mother
- e.g. Beckwith–Wiedemann syndrome, Silver–Russell syndrome, *Angelman syndrome* and Prader–Willi syndrome



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.