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

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***.

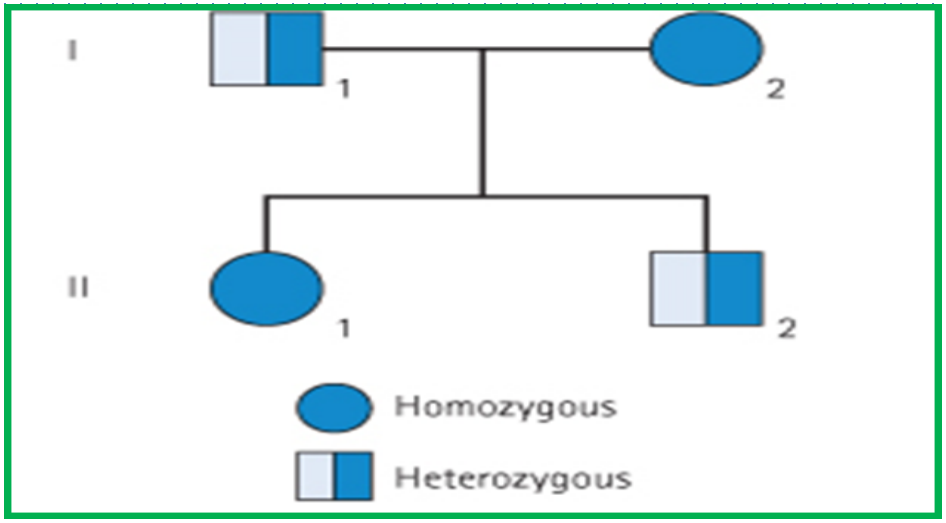
Possible genotypes, phenotypes & gametes formed from the four alleles: A_1, A_2, B, & O at the ABO locus

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

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.

Pseudodominant inheritance

Pseudodominant: is the situation in which the inheritance of a recessive trait mimics a dominant pattern

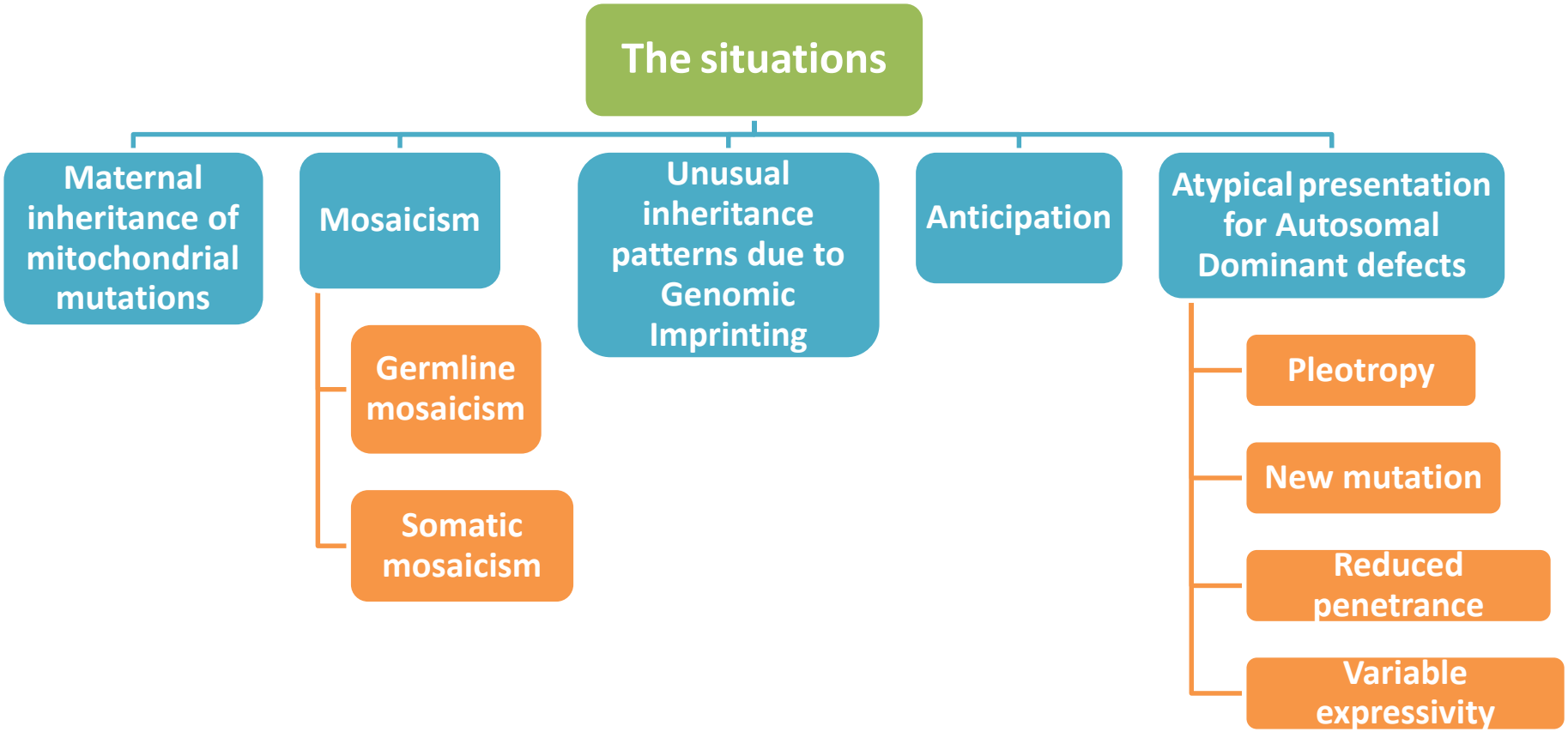


A woman homozygous for an autosomal recessive disorder whose husband is heterozygous for the same disorder.

Their children have a 1 in 2 (50%) chance of being affected (homozygous) i.e. pseudodominant

Atypical inheritance of single-gene disorders

The situations in which the inheritance of single-gene disorders diverges from typical mendelian patterns.



MITOCHONDRIAL INHERITANCE

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

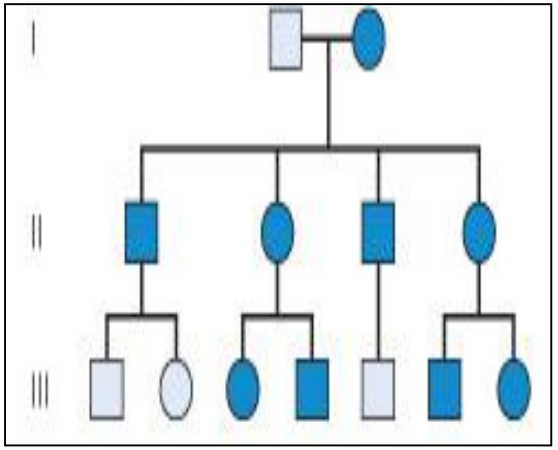
mtDNA is a small circular double-stranded molecule containing 37 genes (coding for rRNA, tRNA, and some of the proteins of the mitochondrial electron transport chain)

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

Mitochondrial Disorders

1. The defective gene is present on the mitochondrial DNA
2. Generally affects energy metabolism
3. Affect more those tissues which require constant supply of energy e.g *muscles*
4. 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

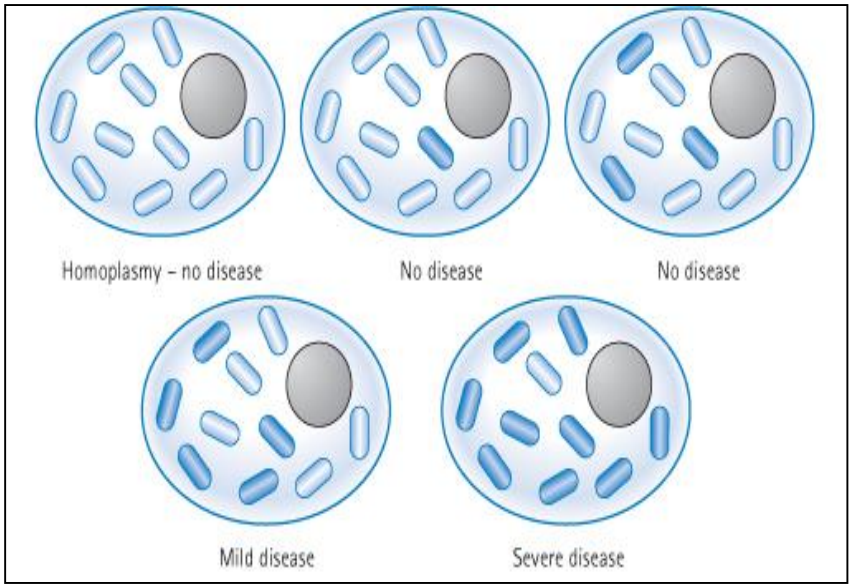
Note that there are no carriers in mitochondrial inheritance, either affected or not.

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

Leads to a range of phenotypic severity in mitochondrial inheritance

Low proportions of mutant mitochondria

not associated with disease

higher proportion of mutant mitochondria

the severity of the disease.

Example of Mitochondrial Disorders:

Leber hereditary optic neuropathy (LHON):

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

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

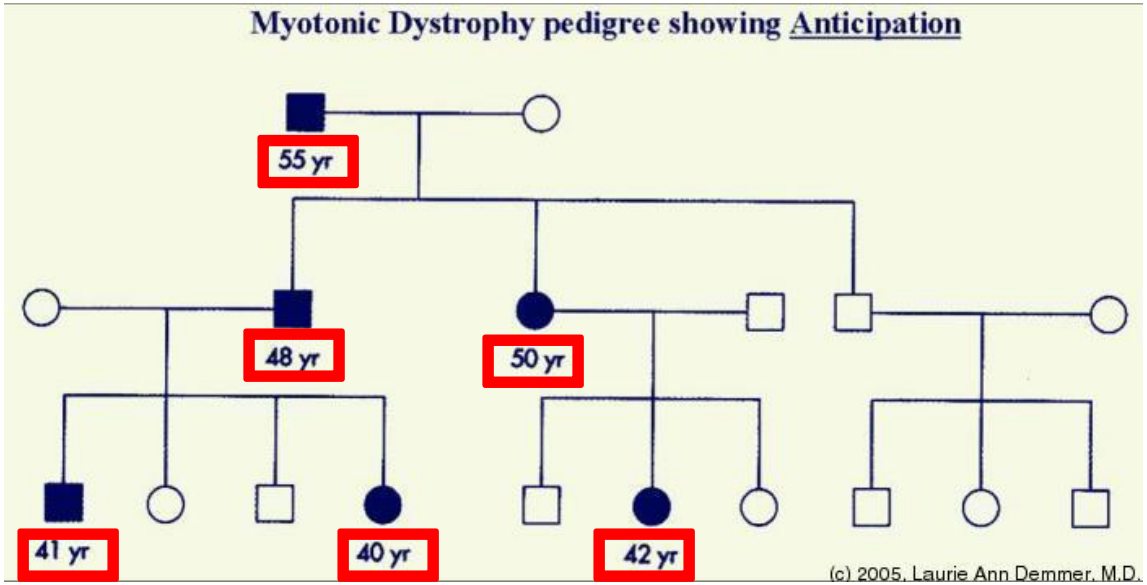
Anticipation

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.

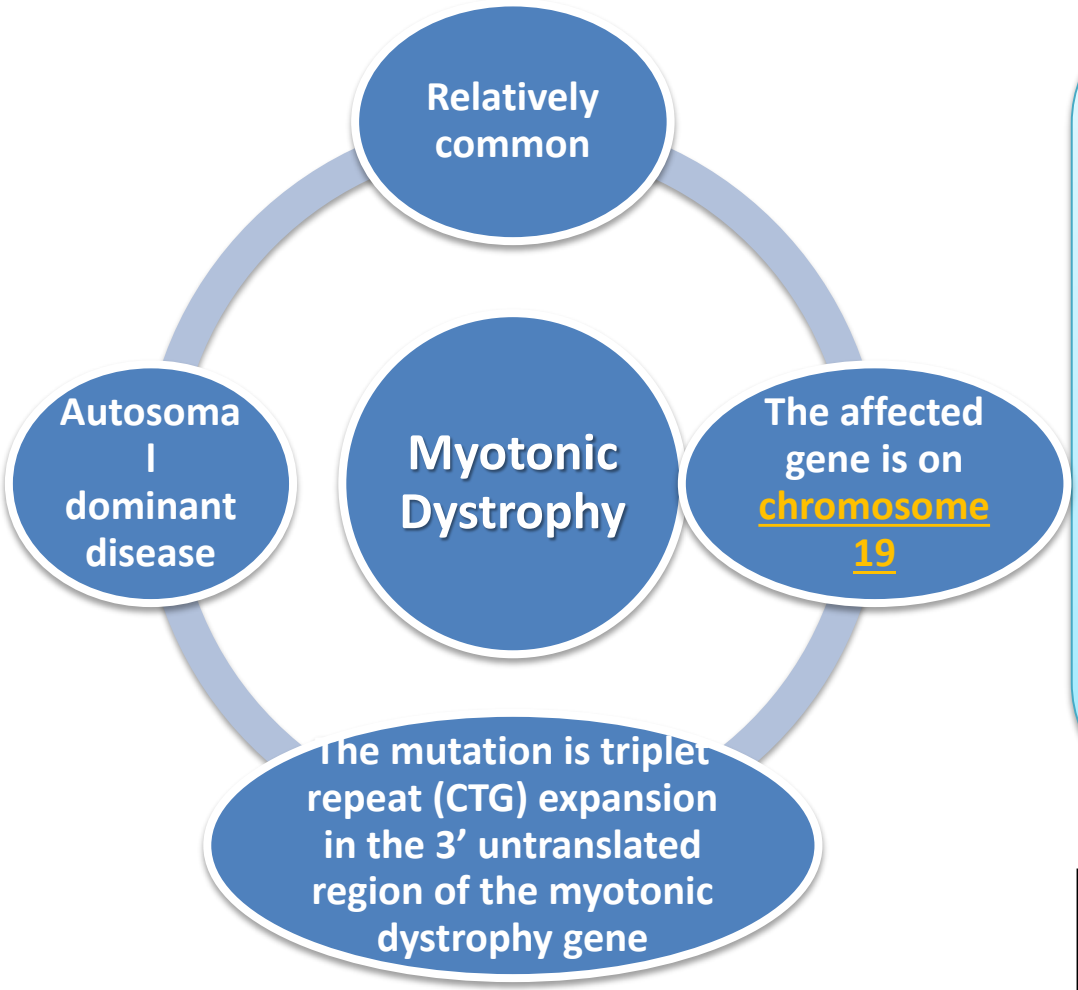
The reason might be the gradual expansion of trinucleotide repeat polymorphisms within or near a coding gene.
For instance, CDA CDA CDA CDA AUG……. …

Examples of diseases showing anticipation:

Huntington disease, hyperthyroidism and Myotonic dystrophy

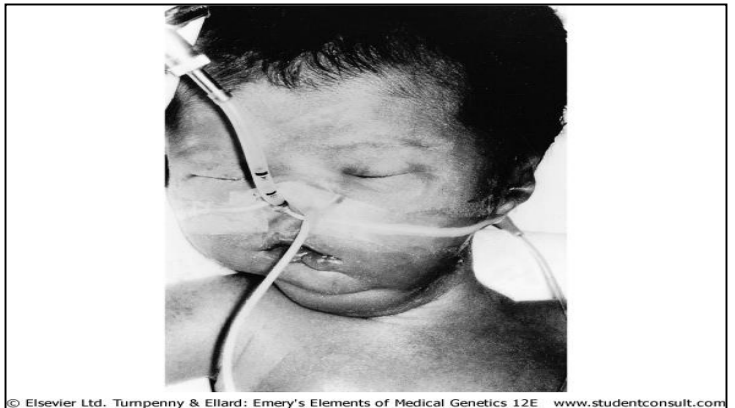


Myotonic Dystrophy



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

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



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

Atypical presentation for Autosomal Dominant defects: -

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

Pleiotropy:-

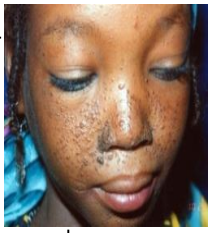
-What is it? a single gene that may give rise to two or more apparently unrelated effects

- Example:

tuberous sclerosis →

affected individuals can present with either:

-learning difficulties.
-epilepsy.
-a facial rash.
or, all features!



Reduced penetrance 'skipping a generation'

In some individuals heterozygous for gene mutations giving rise to certain autosomal dominant disorders there may be no abnormal clinical features representing

- Reduced penetrance might be due to:

1)modifying effects of other genes
2) interaction of the gene with environmental factors

More Explanation :

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.

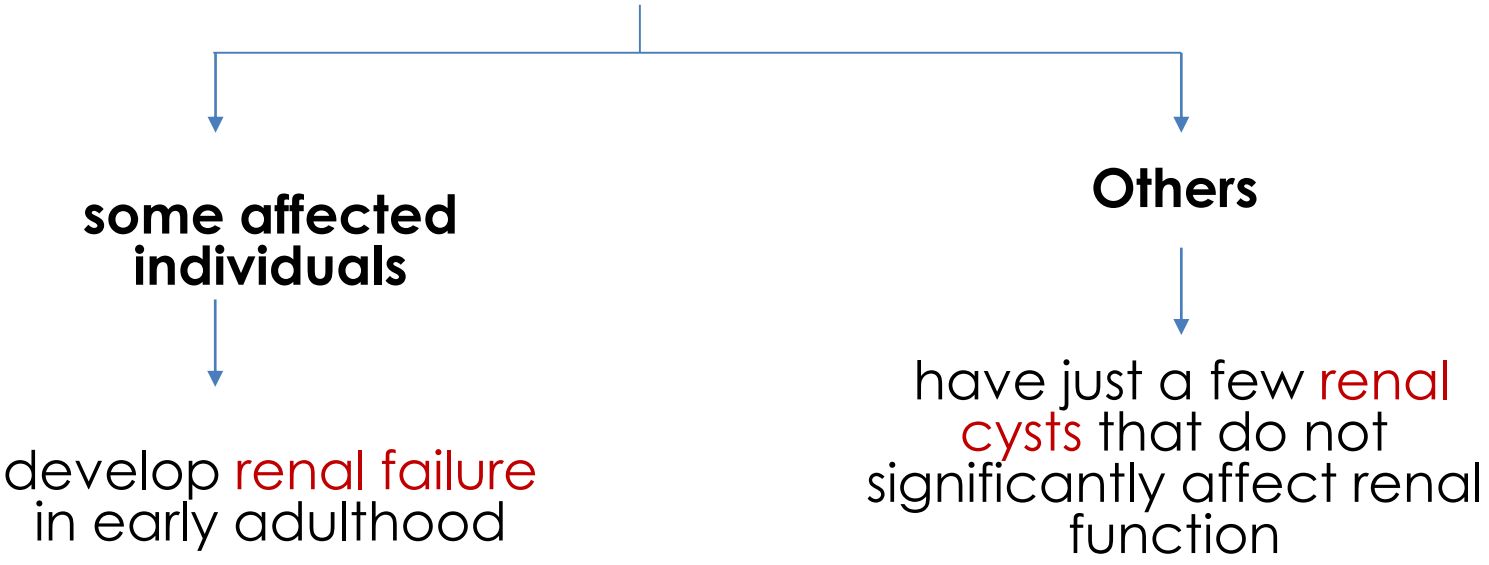
If some people with the mutation do not develop features of the disorder, the condition is said to have reduced (or incomplete) penetrance.

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



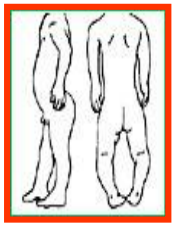
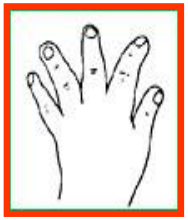
New mutations

-What is it? The sudden unexpected appearance of a condition arising as a result of a mistake occurring in the transmission of a gene

-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


- Example: *Achondroplasia*

What is it ? 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)

- What other possible explanations for the 'sudden' appearance of this disorder?

1)non-penetrance: One of the parents might be heterozygous for the mutant allele but so mildly affected that it has not previously been detected

2) Variable expressivity

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

- The offspring of persons with achondroplasia had a 50% chance of having achondroplasia

Complex Traits

-What is it? A condition which are likely to be due to the interaction of more than one gene.

-its effects:

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

-Example:

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

-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.
- **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

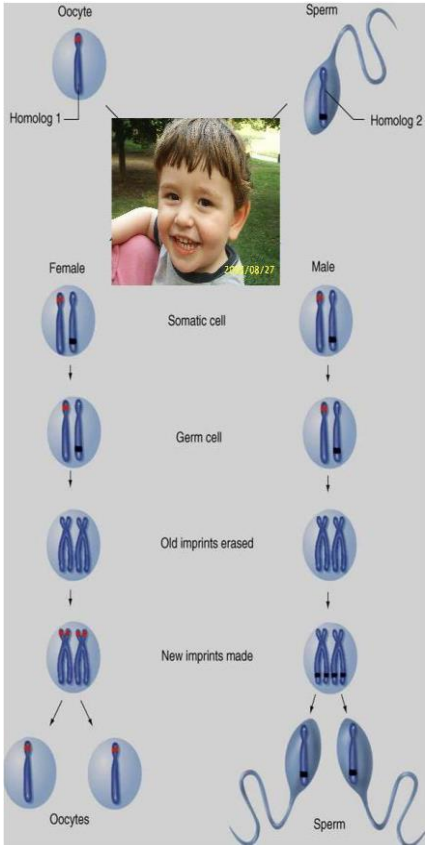
such as –

- 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



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.

Quiz Yourself :

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