

# **HUMAN GENETICS**

## **Lecture Four**

### **ATYPICAL MODE OF INHERITANCE**

# Objectives:

*By the end of this lecture, students should understand 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

# Codominant traits

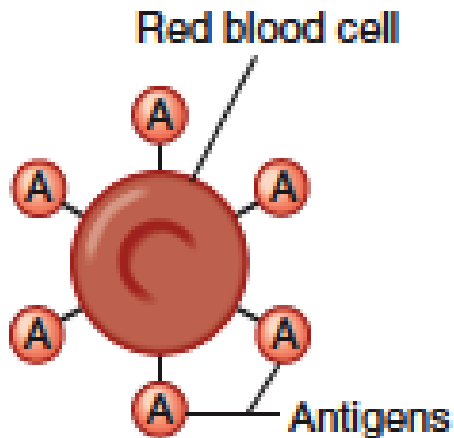
- This pattern occurs when the heterozygote expresses both alleles simultaneously without forming an intermediate phenotype.

*For example,*

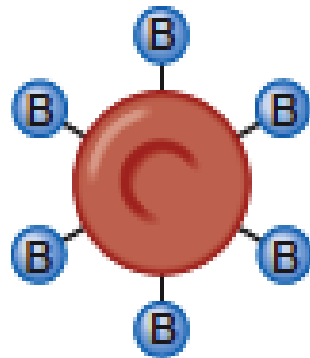
in blood typing, an individual carrying the A and B alleles has an AB blood type.

- most genes exist in multiple alleles

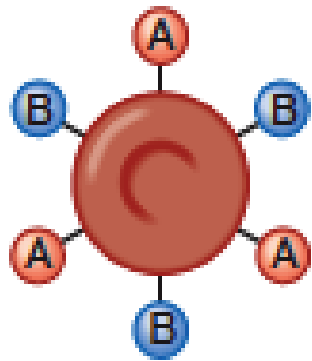
# CODOMINANCE INHERITANCE



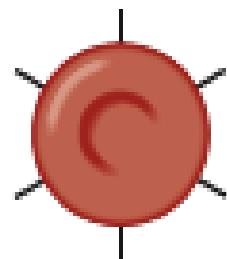
ABO blood type A  
( $I^A I^A$  or  $I^A i$ )



ABO type B  
( $I^B I^B$  or  $I^B i$ )



ABO type AB  
( $I^A I^B$ )



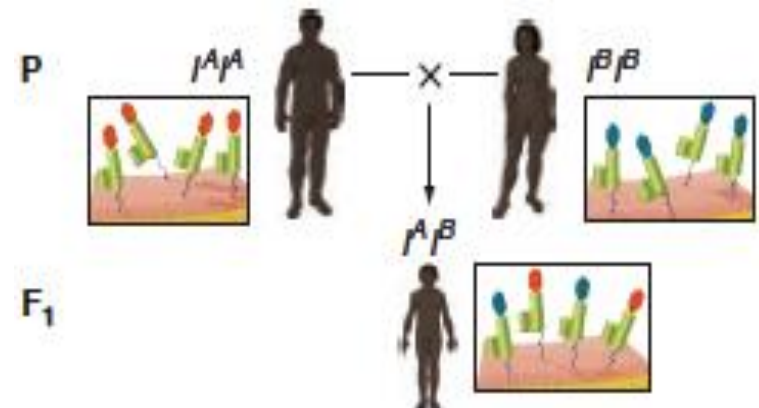
ABO type O  
( $ii$ )

	Type A $I^A$ $I^A$	
Type B $I^B$	$I^A I^B$ AB	$I^A I^B$ AB
	$I^A I^B$ AB	$I^A I^B$ AB

	Type A $I^A$ $i$	
Type B $I^B$	$I^A I^B$ AB	$I^B i$ B
	$I^A I^B$ AB	$I^B i$ B

	Type A $I^A$ $I^A$	
Type B $I^B$	$I^A I^B$ AB	$I^A I^B$ AB
	$I^A i$ A	$I^A i$ A

	Type A $I^A$ $i$	
Type B $I^B$	$I^A I^B$ AB	$I^B i$ B
	$I^A i$ A	$ii$ O



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

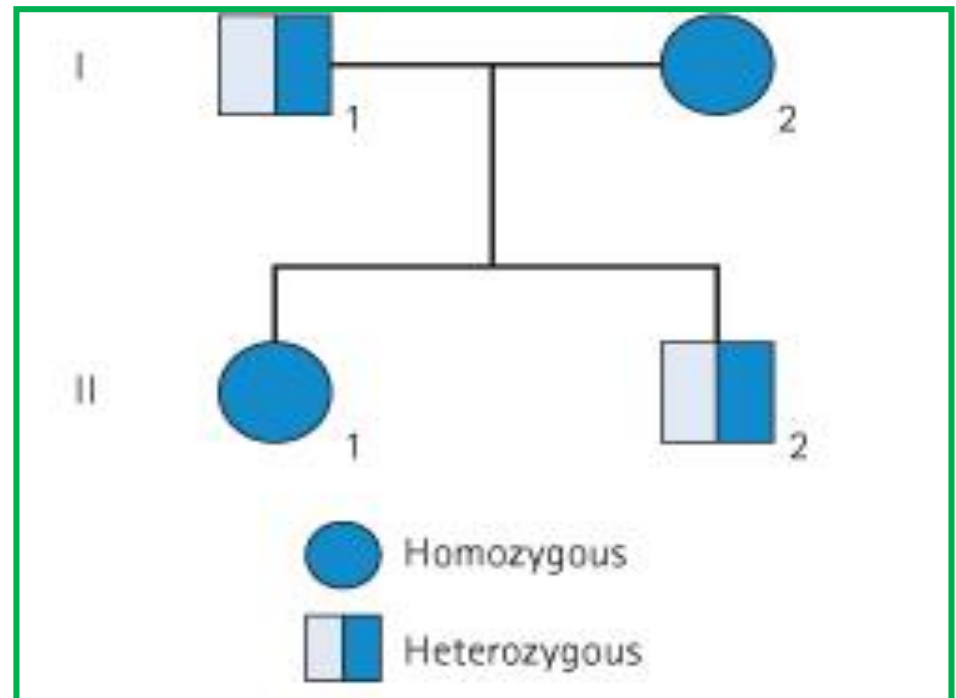
Genotype	Phenotype	Gamete
$A_1A_1$	$A_1$	$A_1$
$A_2A_2$	$A_2$	$A_2$
BB	B	B
OO	O	O
$A_1A_2$	$A_1$	$A_1$ or $A_2$
$A_1B$	$A_1B$	$A_1$ or B
$A_1O$	$A_1$	$A_1$ or O
$A_2B$	$A_2B$	$A_2$ or B
$A_2O$	$A_2$	$A_2$ or O
BO	B	B or O

# **PSEUDODOMINANT INHERITANCE**

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

# Pedigree: 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**



# **Atypical inheritance of single-gene disorders**

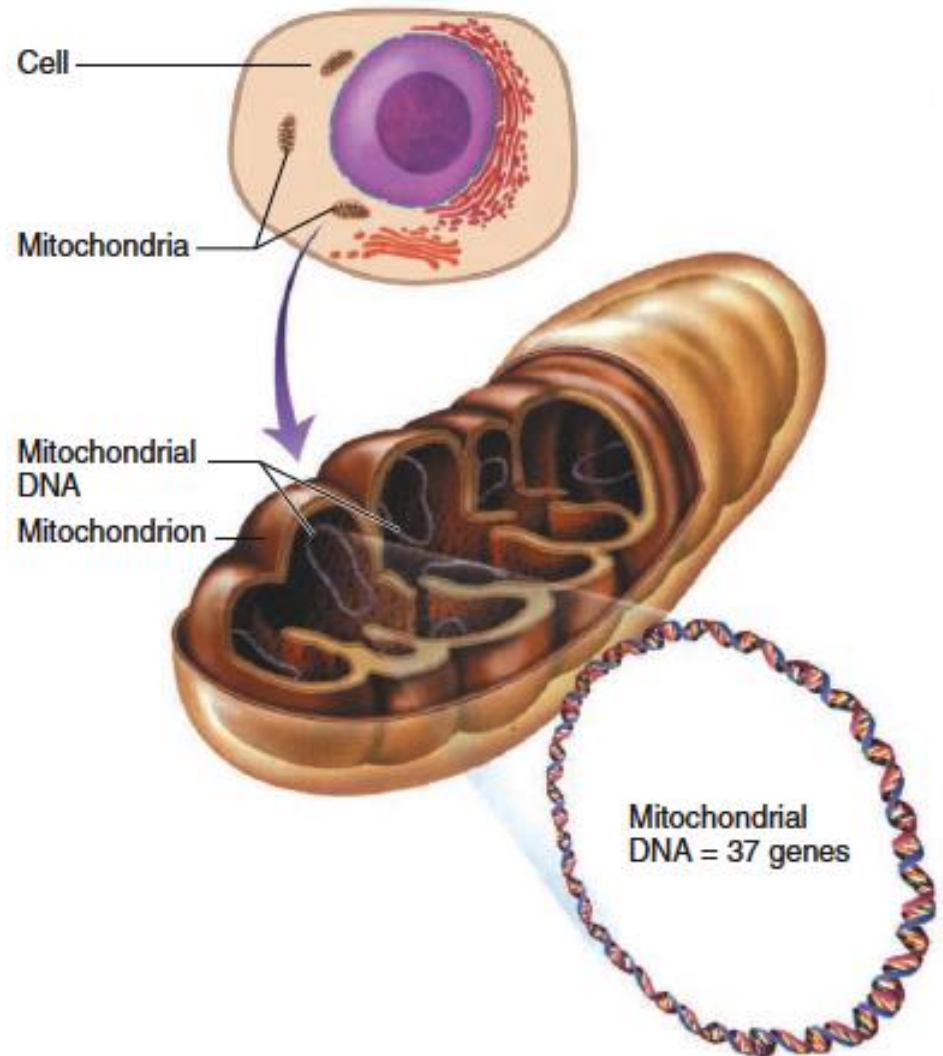
What are the situations in which the inheritance of single-gene disorders diverges from typical mendelian patterns?



- Maternal inheritance of mitochondrial mutations
- Anticipation
- Atypical presentation for Autosomal Dominant defects:
  - Pleiotropy
  - Variable expressivity
  - Reduced penetrance
  - New mutation
- Unusual inheritance patterns due to Genomic Imprinting
- Mosaicism:
  - Somatic mosaicism
  - Germline mosaicism

# MITOCHONDRIAL INHERITANCE

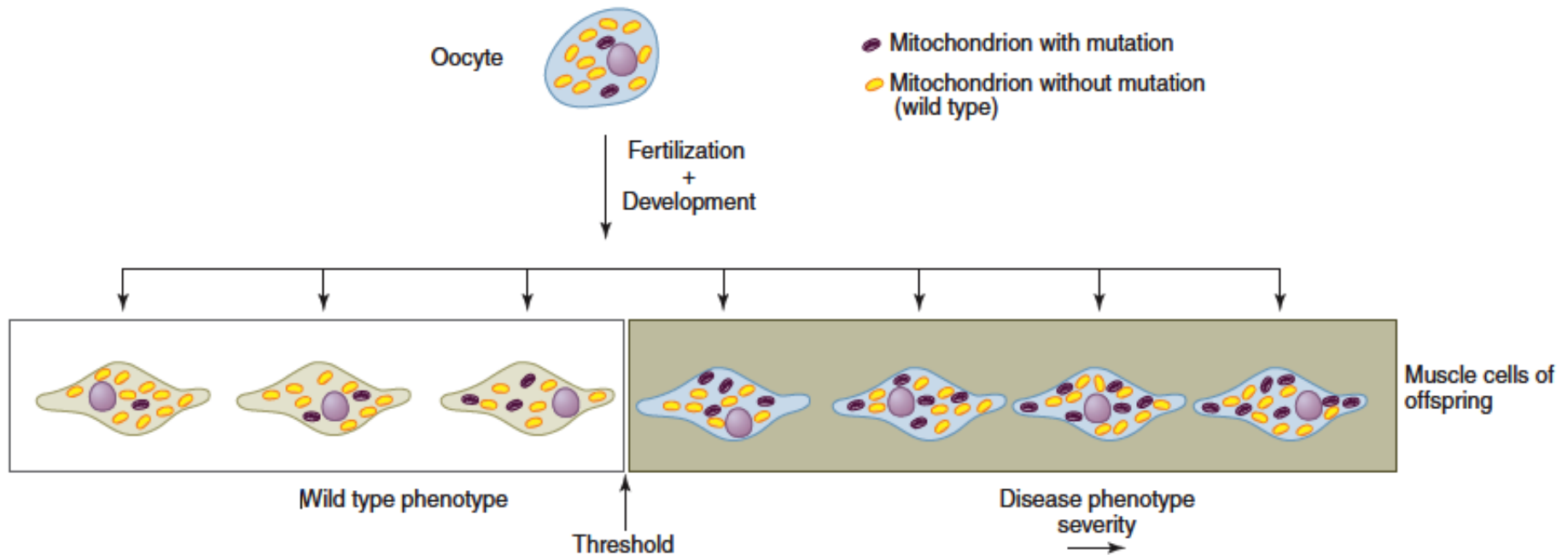
- Each cell contains thousands of copies of mitochondrial DNA with more being found in cells having high energy requirement (e.g. brain & muscle)
- Mitochondria (& their DNA) are **inherited from the mother** (through ova)
- mtDNA is a **small circular double-stranded** molecule containing **37 genes** (coding for rRNA, tRNA, and some of the proteins of the mitochondrial electron transport chain)



# Homoplasmy vs. Heteroplasmy

- **Homoplasmy** = normally the **mtDNA** from different mitochondria is almost **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 → a range of phenotypic severity in mitochondrial inheritance.

# Mitochondrial inheritance



- Mitochondria and their genes are passed only from the mother.
- Cells have many mitochondria. If an oocyte is heteroplasmic, differing numbers of copies of a mitochondrial mutation may be transmitted.
- The phenotype reflects the proportion of mitochondria bearing the mutation.

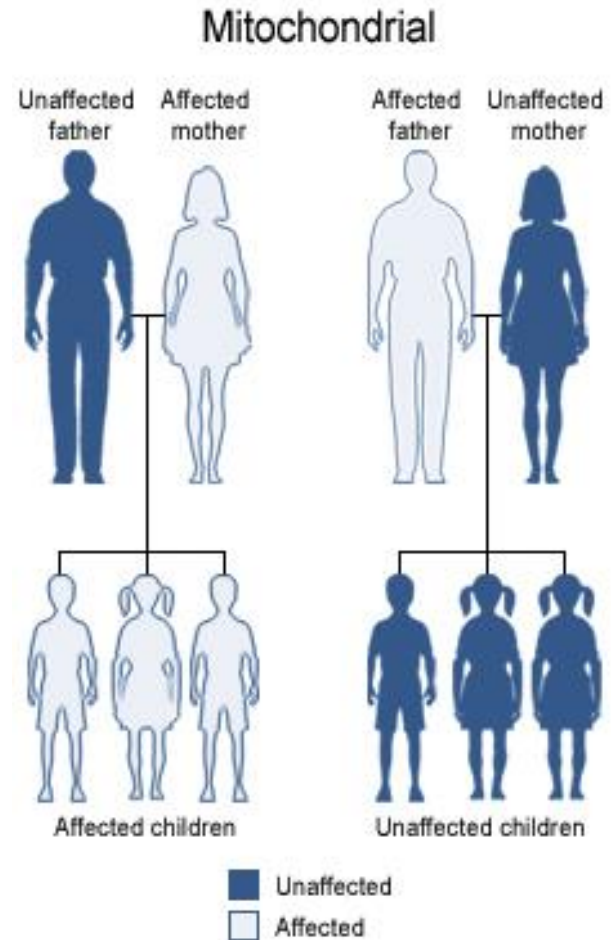
## - Typical Example of Mitochondrial Disorders

Leber hereditary optic neuropathy (LHON)

Rapid Optic nerve death → blindness in young adult life

# Mitochondrial inheritance

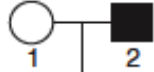

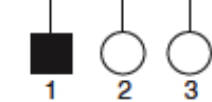
Males do not transmit the disease as the cytoplasm is inherited only from the mother since the mitochondria are present in the cytoplasm



# 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

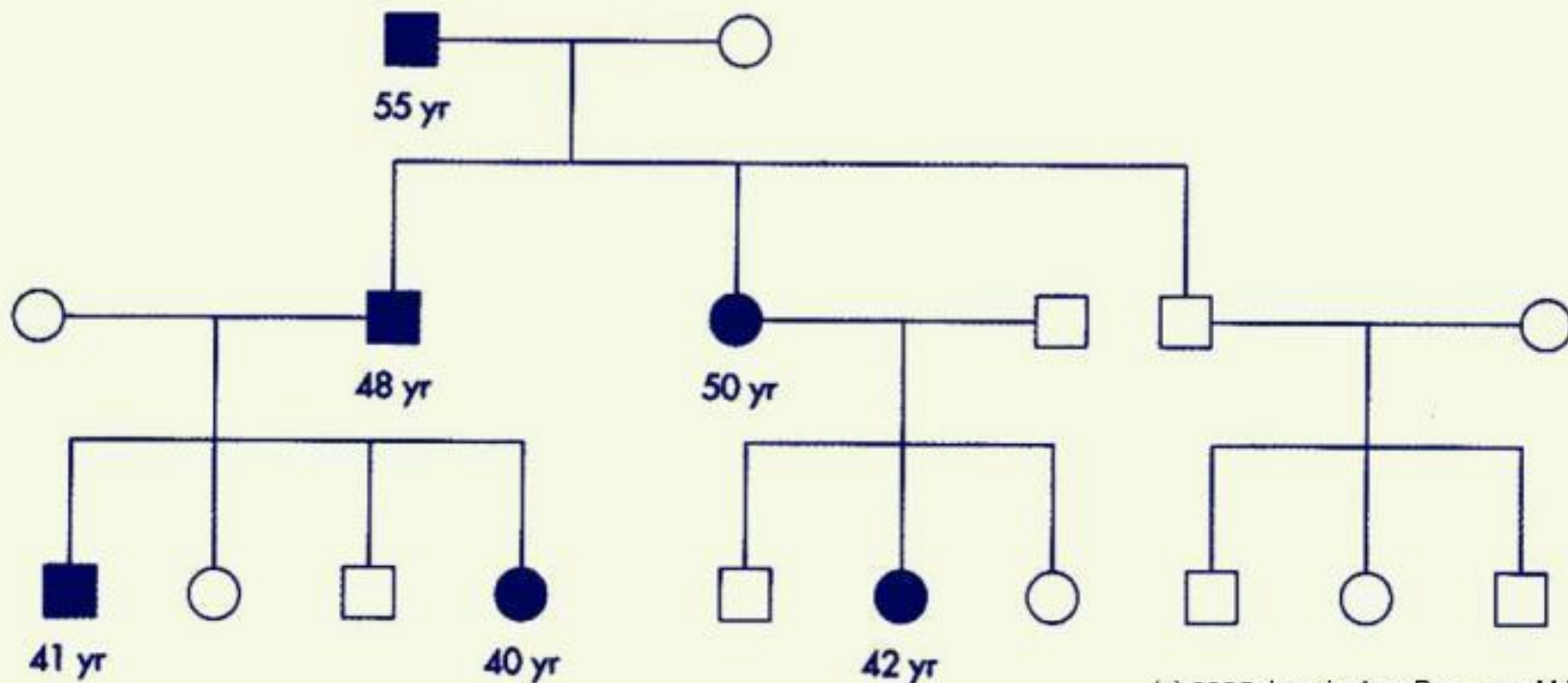
## Myotonic Dystrophy

Pedigree		Age of onset	Phenotype	Number of copies of GAC mRNA repeat
I		Older adulthood	Mild forearm weakness, cataracts	50–80
II		Mid-adulthood	Moderate limb weakness	80–700
III		Childhood	Severe muscle impairment, respiratory distress, early death	700+



# Pedigree analysis for Myotonic dystrophy

Myotonic Dystrophy pedigree showing Anticipation



(c) 2005, Laurie Ann Demmer, M.D.

# PLEIOTROPY

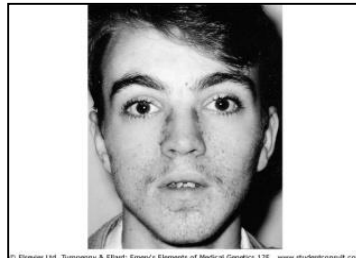
- A single-gene disorder with many symptoms, or a gene that controls several functions or has more than one effect, is termed *pleiotropic*.

- Causes autosomal dominant disorders

- Example:

**tuberous sclerosis**

affected individuals can present with either learning difficulties, Epilepsy, facial rashes , or all features





# 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

# 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**

# 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**

# 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:*** 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.

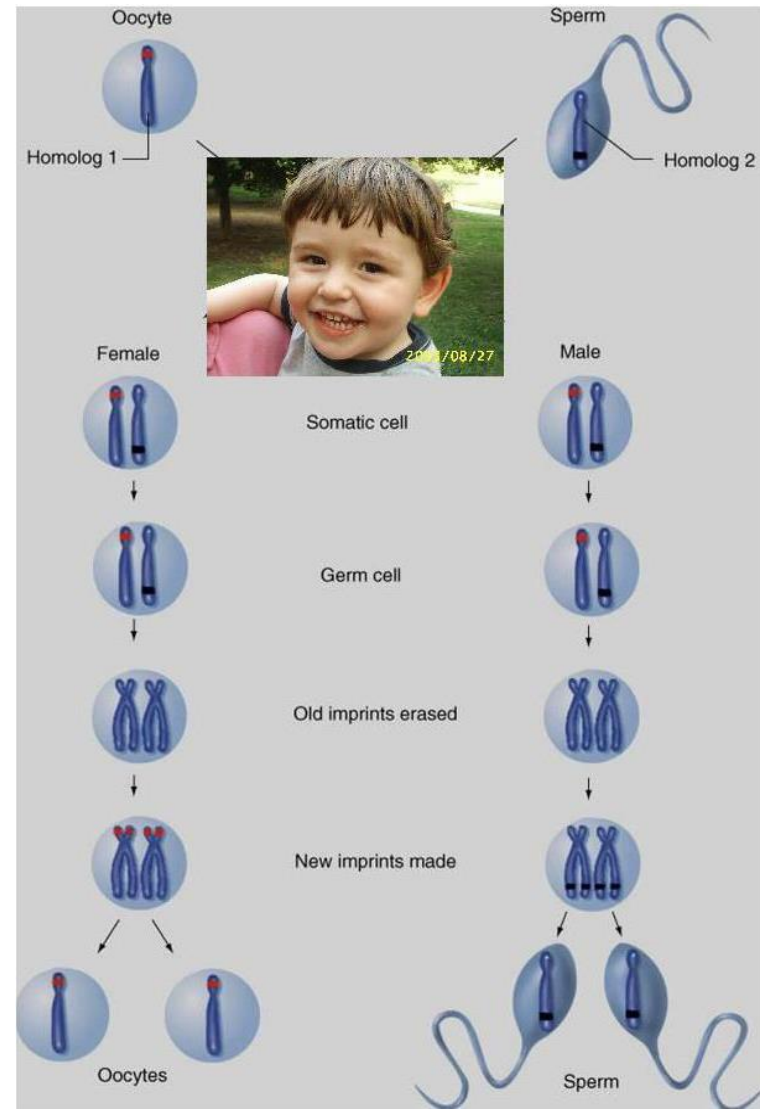
# MULTIFACTORIAL/POLYGENIC DISORDERS

- 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 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*

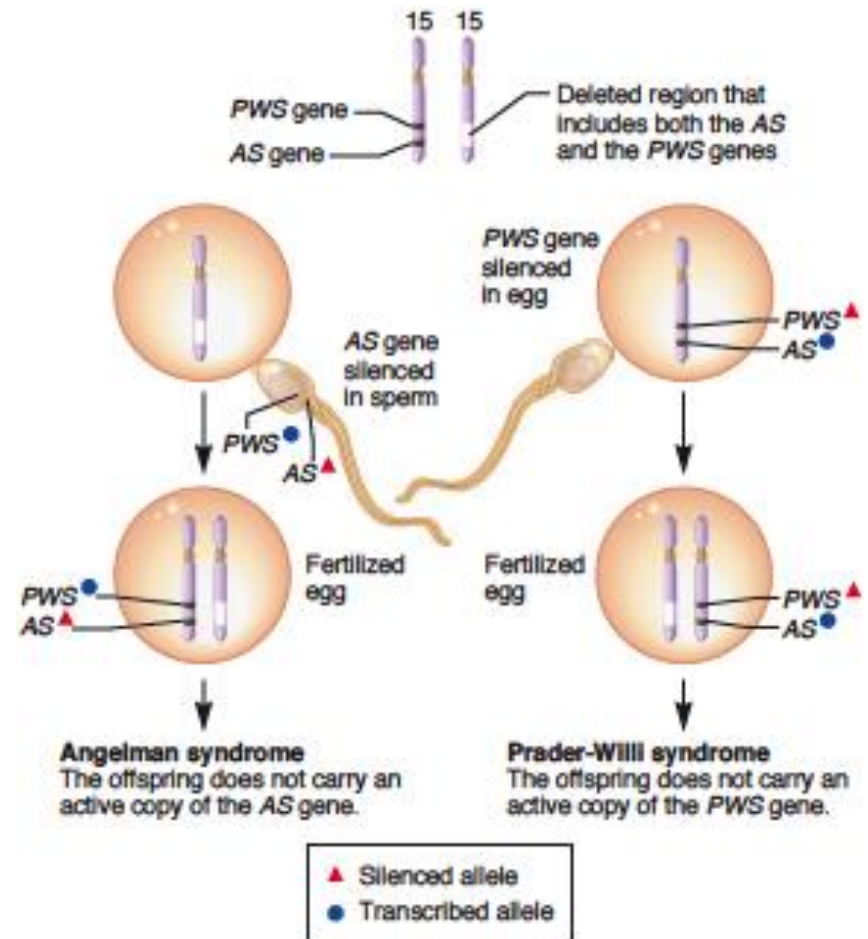
Certain chromosomes retain a memory or “imprint” of parental origin that influences whether genes are expressed or not during gametogenesis





# The role of imprinting in the development of Angelman and Prader-Willi syndromes

- A small region on chromosome 15 contains two different genes designated the AS gene and PWS gene in this figure.
- If a chromosome 15 deletion is inherited from the mother, Angelman syndrome occurs because the offspring does not inherit an active copy of the AS gene (left).
- Alternatively, the chromosome 15 deletion may be inherited from the father, leading to Prader-Willi syndrome. The phenotype of this syndrome occurs because the offspring does not inherit an active copy of the PWS gene (right).



# Take home Messages:

- 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.