Mendelian Inheritance

Single-gene mutations

- Autosomal genes (44 autosomes)
- X or Y (sex linked) (2 sex chromosomes)

Trait

- **Dominant**: expressed in the heterozygote
- **Recessive**: expressed in the homozygote
- **Co-dominant**: effects of both alleles expressed in the heterozygote

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Autosomal Dominant Inheritance

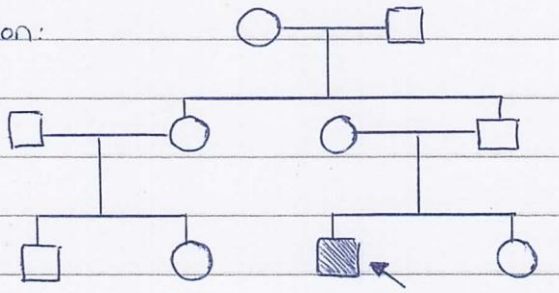
- General Char.
  - expressed in heterozygote.
  - Verticle transmission (found in each generation)
  - Males & females are affected.
  - Transmitted by individuals of both sexes.
- Pleiotropy: AD manifest in different systems.
- Variable expressivity: variation from person to person.
- Non-Penetrance: absence of phenotype despite presence of mutation?
  - modifying genes
  - environmental factors

* haploinsufficiency: phenotype between homozygotes of normal & mutant alleles

	B	b
b	Bb	bb
b	Bb	bb

50% affected

- New mutation:



* AD trait appears only in one individual in one generation.
* Other explanations: non-penetrance, variable expressivity, non-paternity
* Associated with increased paternal age (old males)

- Homozygosity for AD:
  - Earlier age of onset & more severe phenotype.
- Examples of AD diseases:

① Familial hypercholesterolemia (1:500):

- Defective LDL-receptor resulting in defective clearance
  - Xanthoma
  - Coronary artery disease

② Hypertrophic cardiomyopathy (1:500):

* Heart muscle enlargement → outflow obstruction → decrease in cardiac chamber size → reduced pumping of blood.

③ Familial adenomatous polyposis:

* Inherited colon cancer in which non-penetrance could occur resulting in skipped generation.

④ Huntington disease:

* Penetrance is age-dependent.

⑤ Achondroplasia:

* Full penetrance
* Gonadal mosaicism is common.

⑥ Myotonic dystrophy:

* Adult-onset of muscular dystrophy due to (trinucleotide repeat) mutation.

Autosomal Recessive Inheritance

- General Char.
  * Expressed in homozygote.
  * Heterozygotes are healthy (carriers)
  * Horizontal transmission (in sibship)
  * Males & females are affected.
  * Frequent with consanguinity (زواج الأقارب)
- Offspring of two heterozygotes:

25% → normal
50% → carrier
25% → affected

	A	a
A	AA	Aa
a	Aa	(aa)

- Pseudodominance: affected marries a carrier

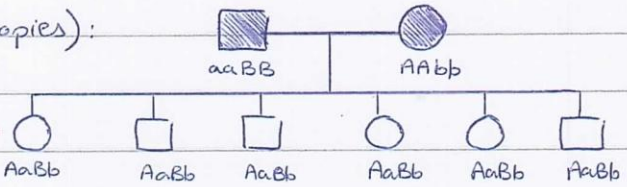
50% affected

	A	a
a	Aa	(aa)
a	Aa	(aa)

Autosomal Recessive Inheritance (cont...)

- Locus heterogenity (Genocopies):

Couples homozygous for mutant alleles at different loci could have all children healthy.

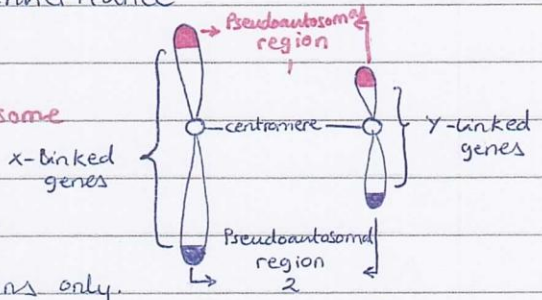


- Phenocopy:
  - Genetic phenotype being the result of environmental causes.
- Example of AR disease:
  - ① Sickle-cell disease:
    - Reduced survival time of RBCs → Chronic hemolytic anemia → repeated blood transfusions
    - HbA ($2\alpha, 2\beta$) —(mutation in the 6th amino acid: valine instead of glutamic acid)→ HbS
      (HbA: normal; HbS: abnormal)
- Degrees of relationship with proband:

Degree of relationship	Examples	proportion of genes in common
First	Parents to child, sibling to sibling	1/2 = 50%
Second	Uncles, aunts, nephews, nieces	1/4 = 25%
Third	First cousins, great-grandparents	1/8 = 12.5%

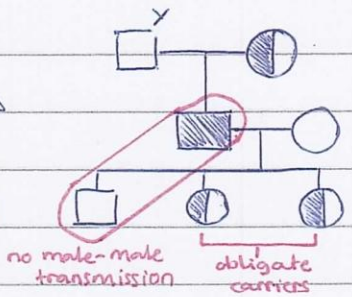
Sex-linked Inheritance

- Female: XX - Male: XY
  (hemizygous: only one X chromosome)
- No male-male transmission
- During male meiosis: crossing-over occurs in the pseudoautosomal regions only.



X-linked recessive

- Usually, only manifest in males.
- Transmitted by healthy heterozygous females
- All daughters of an affected male are obligate carriers, but non of the sons will be affected



- For carrier females:
  - Male pregnancy: 50% chance affected
  - Female pregnancy: 50% chance carrier

Sex-linked Inheritance (cont...)

X-linked recessive (cont...)

- Variable expression in a heterozygous female:
  - **X-inactivation:** 100 cell stage embryo → either Paternal or maternal X remains ON ← mitosis occurs ← a female is a mosaic of two different types of mitotic clones
- Females affected with x-linked recessive disorders:
  - Homozygosity.
  - Skewed X-inactivation
  - Turner syndrome (a female with only one X chromosome).

X-linked dominant

- Here, the heterozygous female will show the phenotype in addition to the affected male, but the severity will be less.
- Affected female:
  - Male pregnancy: 50% → affected
  - Female pregnancy: 50% → affected.

Y-linked inheritance

- Affected males only in the pedigree (male-male transmission).
- Example: the inheritance of the sex-determining region (SRY).

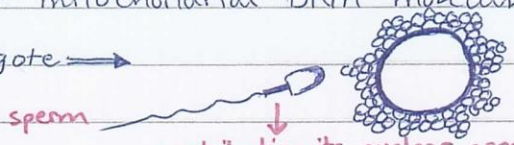
- Partial sex linkage: allowing male-male transmission to occur if the mutation is on the pseudoautosomal region of X chromosome. (where crossing-over happens between X & Y)
- Sex influence: some traits are more common in one sex than another (gout & baldness in males).

(4)

Non-Mendelian Inheritance

Mitochondrial Inheritance

- Human cells contain thousands of copies of the double-stranded circular mitochondrial DNA molecules.
- Formation of zygote →



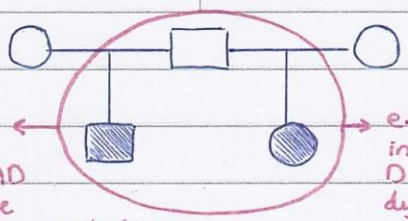
↓ contributing its nuclear genome not the mitochondrial genome

so, it is maternally inherited.

Mosaicism

- Occurrence of more than one cell line in the body caused by a mutation which arises early in development (post-fertilization)
- Resulting in some cells with the mutation & some without.
- Mosaicism can be

Germline	Somatic	Combination of both
✱ Person will not be affected. ✱ Mutation is passed to offspring. ✱ Commonly seen with AD & X-linked disorders ✱ Mutation will be present in all cells of the child developing from that germ cell.	✱ Somatic cells of the body are of more than one genotype → usually arising from a single fertilized egg cells ✱ Chimerism: genotypes arise from the fusion of more than one fertilized zygote.	



unaffected parent having more than one child with AD disorder → germline mosaicism not new mutation.

e.g. osteogenesis imperfecta & Duchenne muscular dystrophy

Uniparental Disomy

Uniparental Disomy

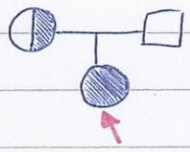
Isodisomy	Heterodisomy
two copies of the same homologue due to error in meiosis II	two different homologues from one parent, error in meiosis I

↓ Resulting in

↓ Trisomic rescue

↓ loss of a chromosome leading to the normal disomic state

Uniparental Disomy (cont) → Example →



A child with AR condition being born to a couple in which only one parent is a carrier

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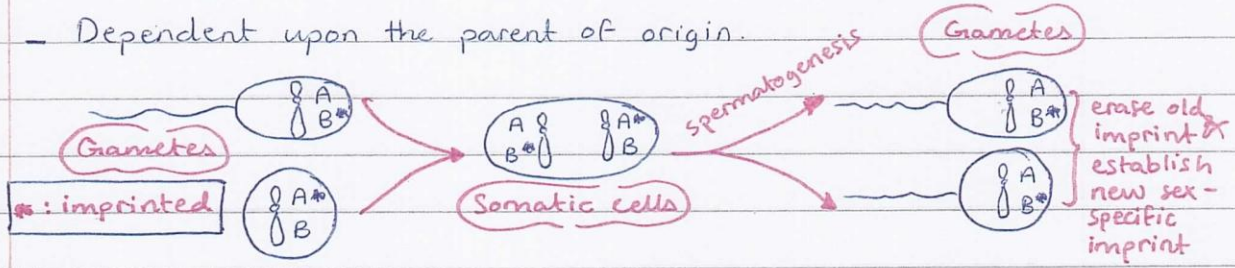
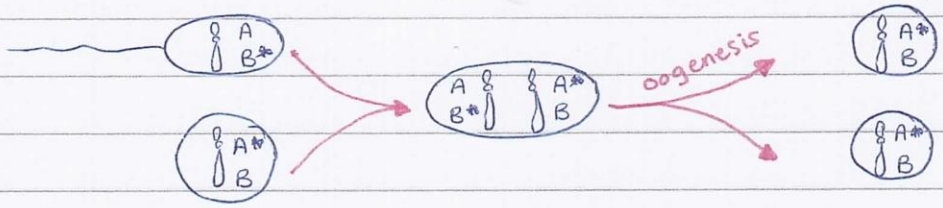
Genomic imprinting

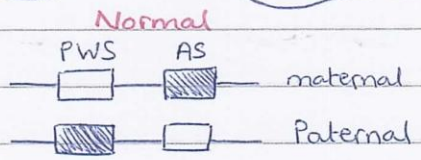
- Dependent upon the parent of origin.

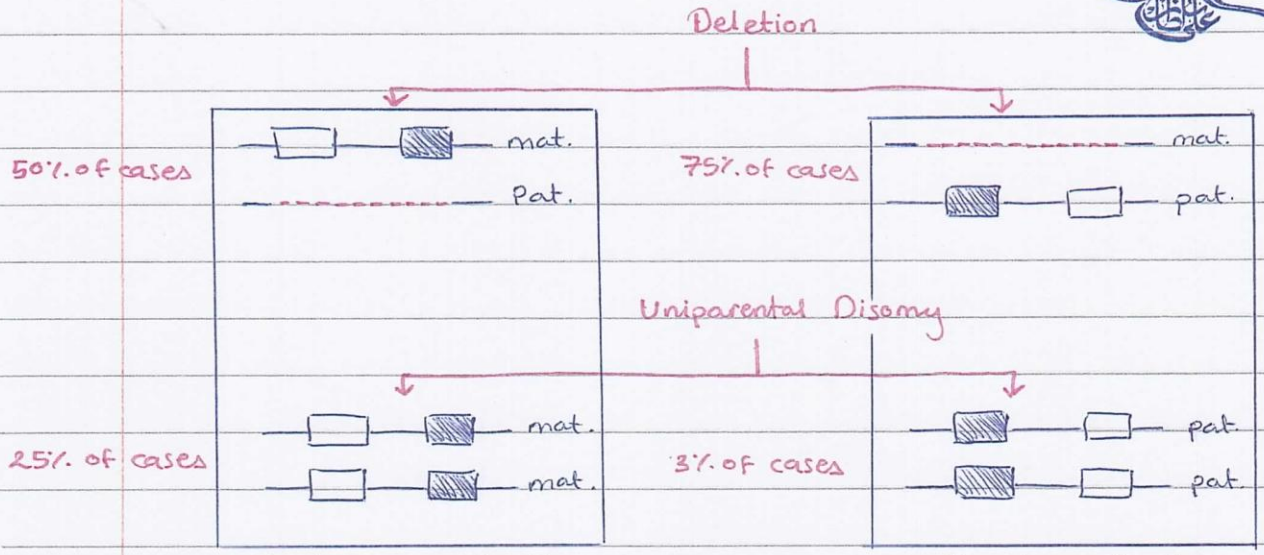




- Examples: Prader-Willi syndrome & Angelman syndrome

= active gene = inactive gene





Prader-Willi Syndrome (Chromosome 15)	Angelman Syndrome
- Short stature	- Happy affect
- Obesity	- Severe learning difficulties
- Learning difficulty	- Epilepsy

Genetic anticipation ⟹ in successive generations: * age of onset decreases
* Severity of phenotype increases.

caused by ↓

Trinucleotide repeat expansion

Lies within or adjacent to a disease associated gene. Pathogenic mutation occurs when trinucleotide repeat expands beyond the threshold size at meiosis

↳ mainly by: ① Unequal crossing-over between homologous chromosomes.
② Uequal sister chromatids exchange.

↓ leading to

Insertions & Deletions

- Examples:

① Huntington Disease:

* Caused by expansion of CAG repeat.
  - ↳ normally: 10-35 repeats.
  - ↳ When expanded: 36-120 repeats
    - ↳ resulting in: additional glutamine amino acid within the encoded protein.

② Fragile X syndrome (1:5000 males):

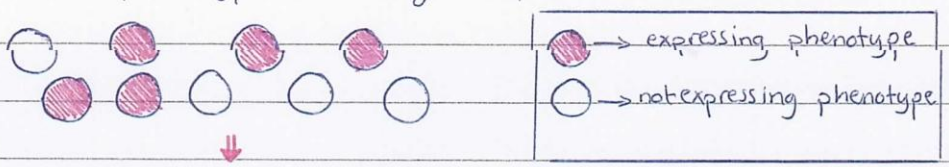
* Caused by expansion of CGG repeat.
  - ↳ normally: 6-54 repats.
  - ↳ When expanded:
    * pre-mutation: 55-200 repeats
    * full-mutation: >200 repeats

1- Expansion from pre to full occurs in carrier mothers during meiosis.

2- This mutation will lead to the loss of FMR protein production leading to significant learning disability in males.

Penetrance & Expressivity

- Penetrance: Sometimes, a person with the genetic mutation does not show the phenotype. 100% penetrance means that the phenotype is always expressed.



$$\text{Penetrance} = \frac{5}{9} = 55.6\%$$

- Expressivity: the variation of the expressed phenotype of a specific genotype.
- Age-related penetrance:
  - Some diseases, e.g. Hutington's disease or familial Alzheimer's disease, are diseases of late onset.