HEREDITY-GENES & DISEASE

The nucleus is the genetic factory; it contains a **diploid** number of chromosomes (46) i.e. 22 pairs of autosomes + 1 pair of sex chromosomes.

Chromosomes are important in:
1-Cell division
2-Carry hereditary traits on genes
3-Have genes responsible for protein synthesis (structural proteins, hormones, receptor proteins, intracellular messengers and enzymes)
NB: Somatic cells are **diploid**
Germ cells (ovum/sperm) are **haploid** (half the number of chromosomes)

- A chromosome is 1 molecule of DNA (as a double helix). This may carry up to 50,000 genes & its basic structure is the nucleotide (base pair+ribose+phosphate)[1]
- Gene is the unit of the chromosome responsible for synthesis of 1 specific protein which may be composed of 1-20,000 nucleotides(base pairs)

GENETIC DISORDERS

- **Congenital disorders**: disorders due to events occurring just before birth which are not necessarily inherited e.g. exposure to teratogens [2](radiation-viruses-drugs) or spontaneous mutation during pregnancy
- **Genetic disorders**: diseases due to gene abnormality (structural or functional) & may or may not be inherited e.g. Hemophilia

N.B. A genetic defect in somatic cells is non transmittable whilst in germ cells (ovum /sperm) it is Inherited

- **Inherited disorders**: are gene defects transmitted from generation to generation

[1]NB: chromosomes can't be seen in light microscopy except in some phases of cell cycle: metaphase-mitosis. Resting cells have a dark nucleus- Active cells getting ready for protein synthesis or mitosis have a paler larger granular appearing nucleus

[2] Teratogens are substances which cause genetic mutation in a developing embryo

TYPES OF ERRORS

SOMATIC

Errors in the tissue stem cell population may occur due to spontaneous mutation or an external teratogen(virus-irradiation-drugs). Such mutations may be responsible for:

a- reversible growths i.e. hyperplasia-hypertrophy-congenital abnormality etc.…

b- tumor cells(irreversible)

GERM cells (ovum /sperm): errors in germ cells result in genetic or hereditary disease.

These manifest as:

1. Chromosomal abnormality
2. Single gene abnormality
3. Metabolic disorders(ERRORS OF METABOLISM)
4. Multifactorial

1-CHROMOSOMAL ABNORMALITY

A) Abnormalities in **number** of chromosomes

1-Polypoid:Increased number of chromosomes by an exact multiple of diploid e.g.: **tetraploid** /octaploid (4/8 sets of chromosomes i.e. extra diploid sets)

a- if it occurs in somatic cells, it produces **hypertrophy**

b- if it occurs in germ cells, it is **incompatible with life.**

2-Aneuploid Increased or decreased number of chromosomes, but not by a multiple of the haploid e.g. **triploid** (3 whole sets of chromosomes i.e. an extra haploid set

a- if it occurs in somatic cells, it leads to **neoplasia**.

b- if it occurs in germ cells as monosmy (less by 1 chromosome) or **trisomy** (more by 1 chromosome, trisomy21) e.g. **Down's syndrome**

3-Heteroploid: any chromosome number other than normal diploid

4-Mosaicism: Presence of more than one population of cells with normal chromosome number and the other with extra or missing chromosomes

B) Abnormalities in **structure** of chromosomes

-Accidental breaks with bad repair & abnormal fusion as in spontaneous mutations or exposure to teratogens(irradiation-viruses-drugs)

-Deletion:missing a part of chromosome

-Duplication:extra

-Translocation = reciprocal exchange of chromosome segments (segments exchange places on 2 chromosomes)

-Dysjunction with random fusion=breaking usually at centromere but with abnormal random fusion

c) Abnormalities in **sex** chromosomes : **Turners** syndrome XXX & **Kleinefelters** syndrome XYY

2-SINGLE GENE DISEASE

Genes on chromosomes **affect function** i.e. the distribution pattern of genes is important for they act either by **enhancing** or **suppressing** neighboring genes

Inherited single gene disorders
1) Autosomal dominant: The mutated gene is dominant to its allele[3] . All offspring are affected (homozygous & heterozygous) e.g. familial hypercholesterolemia, adult polycstic kidney,multiple exostosis and polyposis coli
2) Autosomal recessive: The mutated gene is recessive to its allele some offspring are affected (only homozygous) e.g.Thalassemia & mental retardation
3) Sex linked on chromosome X, usually recessive (carrier), appearing in males with the female acting as a carrier for the abnormal gene e.g. hemophilia& Duchenne muscular dystrophy. Rarely if the abnormal gene is dominant, it will appear in both sexes

Syndromes Associated with Sex Chromosome Abnormalities

(1) *Klinefelter's syndrome:* Male with karyotype (47, xxy). The syndrome is characterized by eunuchoid built, infertility, atrophic testis and gynecomastia.
(2) *Turner's syndrome:* Female with karyotype (45, x). The syndrome is characterized by atrophic ovaries, infantile external genitalia, lack of secondary sex characteristics, amenorrhea and congenital heart disease specially aortic coarctation.
(3) *47, xxx syndrome:* Female showing normal physical and reproductive development. However there may be difficulty in auditory perception and receptive and expressive language skills.
(4) *47, xyy syndrome:* Tall male with no apparent abnormality in physical and reproductive development. There may be a risk of criminal behaviour.

3-METABOLIC DISORDERS (Errors of metabolism)

These are inherited disorders of single genes **which code** for **enzymes.**
Mechanism is like single gene abnormality but the result is defective **enzyme** synthesis
Carbohydrates: glycogen storage disease
Lipids & amino acids:lysosomal storage disease
Membrane transport enzymes:cystic fibrosis

[3] alleles are DNA sequences that code for a gene, but sometimes the term is used to refer to a non-gene sequence.

4-MULTIFACTORIAL

Multifactorial disorders require the interaction of environmental and genetic factors as diabetes mellitus and hypertension.

GENETIC CANCER SYNDROMES

- Neurofibromatosis type 1 (von Recklinghausen disease)
- Multiple endocrine neoplasms (MEN)
- Familial breast cancer
- Familial adenomatous polyposis coli