Lecture 2 **chromosomal abnormalities**

Objective

To understand changes in chromosomes number and structures and

the clinical syndromes associated with them

Chromosomal abnormalities

1- Changes in chromosomes number

A - increase in entire sets (polyploidy), lethal

B - increase or reduction in one chromosome (aneuploidy)

-Trisomy: having extra chromosome

-Monosomy: missing a single chromosome

2- Changes in chromosome structure

A – Translocation/ chromosomal breaks

B – Deletions

C – Fragile sites

The most common cause of aneuploidy is nondisjunction, the failure of chromosomes to disjoin normally during meiosis so the resulting gamete either lacks a chromosome or has 2 copies resulting in monosomic or trisomic zygote respectively.

Trisomy can be complete and present in all cells or it may be in mosaic

form.

Down syndrome

The only autosomal trisomy that allows survival until adulthood

Karyotype: 47,xx,+21 or 47,xy,+21 extra chromosome is maternal in origin in 97% of cases

Clinical findings:

Hypotonia, flat face, upward and slanted palpebral fissures and epicanthic folds, speckled irises(Brushfield spots),varying degrees of mental retardation and growth retardation, cardiac malformations, simian crease, short broad hands, hypoplasia of middle phalanx of 5^{th} finger, duodenal atresia, high arched palate.5% of patients with Down syndrome are the result of a translocation_ t(14q21q), t(15q21q), and t(13q21q) in which the phenotype is the same as trisomy 21 Down syndrome. Translocation 21;21 carriers have a 100% recurrence risk for a chromosomally abnormal child.

Trisomy 18, Edwards syndrome

Clinical findings:

Low birth weight, closed fists with index finger overlapping the 3rd digit

and the 5th digit overlapping the 4th, narrow hips with limited abduction, short sternum, rocker-bottom feet, microcephaly, prominent occiput, micrognathia, cardiac and renal malformations, mental retardation and lethal in 95% of cases in the 1st year.

Trisomy 13, Patau syndrome

Clinical findings: Cleft lip, flexed fingers with polydactyly, ocular

hypotelorism, low set malformed ears, small abnormal skull, cerebral

malformation, microphthalmia, cardiac malformations, scalp defects,

visceral anomalies.

Sex chromosomes aneuploidy

Klinefelter syndrome

80% have a male karyotype with 47,xxy

20% with 48,xxxy; 48,xxyy; 49,xxxxy or mosaicism 46,xy/47,xxy The greater the aneuploidy, the more sever the sexual and mental impairment. It is the most common cause of hypogonadism and infertility in males. Patients are phenotypically normal until puberty, puberty occurs at normal age but the testes remain small. Patients develop secondary sexual characteristics later, 50% develop gynecomastia, they usually do not have reduced intellect but may show deficits in language and executive functions.

Turner syndrome

Complete or partial absence of the 2nd sex chromosome(45, XO)

Common symptoms of Turner syndrome include:

- Short stature
- Lymphedema (swelling) of the hands and feet
- Broad chest (shield chest) and widely spaced nipples
- Low hairline
- Low-set ears
- Reproductive sterility4
- Rudimentary ovaries gonadal streak (underdeveloped gonadal structures that later become fibrosed)
- Amenorrhoea
- Increased weight, obesity
- Normal intelligence
- Increased carrying angle of elbow
- Webbed neck
- Bicuspid aortic valve

Noonan syndrome

AD disorder affects both sexes, similar to turner in their phenotype.

Structural abnormalities

Translocation

Transfer of material from chromosome to another.

Types :

1- Simple translocation, apiece of chromosome is separated from one chromosome and attached to another.

2- Reciprocal translocation, breaks in nonhomologous chromosomes and reciprocal exchange of the two broken segments.

3- Robertsonian translocation, involve two acrocentric chromosomes (13,14,15,21,22). Loss of short arm of 2 acrocentric chromosomes, then fusion of long arm of the 2 chromosomes.

Deletion

Cri-du-chat syndrome 5P : Due to deletion of short arm of chromosome 5

Clinical features:

LBW, poor growth, feeding problem, hyperactivity, aggression, unusual facial features.

Imprinting

Imprinting in human is noted by phenotypic differences seen in Prader –Willi and Angelman syndrome which are associated with deletion and uniparental disomy of the same region of chromosome 15. Lack of paternal segment of chromosome 15 result in Prader-Willi syndrome. Lack of maternal segment (same segment) of chromosome 15 result in Angelman syndrome.

Fragile sites

Fragile sites are regions of chromosomes that show tendency for separation, breakage or attenuation under particular growth conditions. They appear as a gap in the staining, significant site is the distal long arm of chromosome X and this result in Fragile X syndrome, accounts for 3% of male with mental retardation. Other features include: autistic behavior, characteristic facial features, long face, prominent jaw and mental retardation. Affected female also mentally retarded