GENETICS

Sheet no. 8

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Ring Chromosomes (r)

In-ring chromosome we have cut in the p arm, after cutting it will rotate to form the donut-like structure.

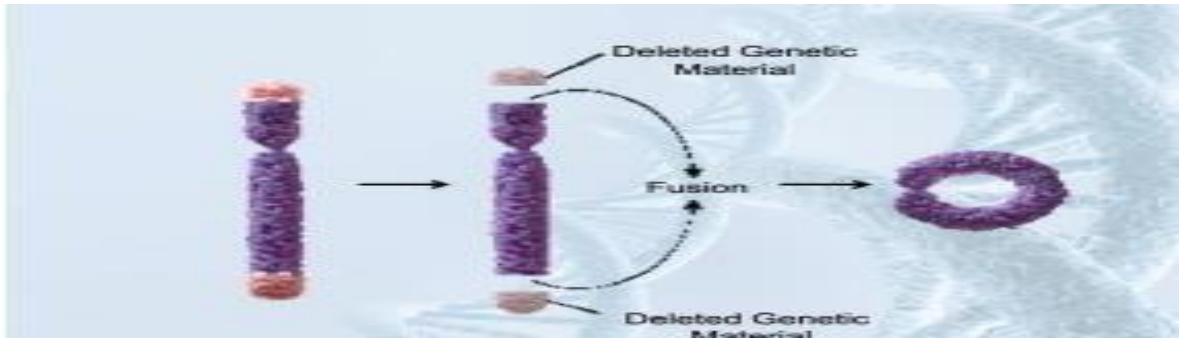
• Ring chromosomes, or rings, are donut-shaped structures that may involve one or more chromosomes

• Autosomal ring chromosomes are rare and usually arise de novo.(not caused by parents) happen by itself

• Rings have been reported for all chromosome pairs, although those involving chromosomes 13 and 18 are among the most common.

• Rings are traditionally thought to form as a result of breakage in both arms of a chromosome, with subsequent fusion of the ends and loss of the distal segments.

Ring chromosomes are often lost, resulting in a monosomy, example: loss of a ring X chromosome would produce Turner syndrome (45,X) , The karyotype of a female with a ring X chromosome is 46,X,r(X).



Insertions (ins)

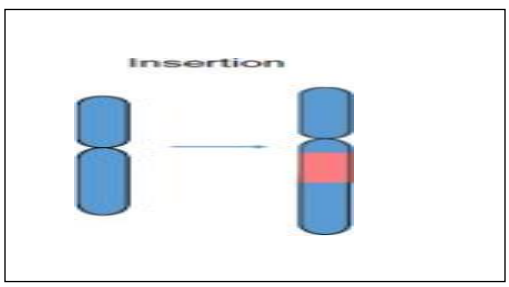
In general it is uncommon in human.

• As the name implies, an insertion involves the movement of a segment of intrachromosomal material from one chromosomal location into another.

• The recipient can be another chromosome or a different part of the chromosome of origin.

• The orientation of the inserted segment may be direct, retained in its original orientation, or inverted.

• Eg. 46,XX,ins(2)(p13q21q31)



Mosaicism

chromosome abnormalities can be classified into two types

• Constitutional abnormality: presents in all nucleated cells of the body

• Somatic (or acquired): presents in only certain cells or tissues of a person, who is therefore a genetic mosaic

It could occur in somatic and germ cells.

It could occur in Dawn syndrome.

Mosaicism : describe a situation in which different cells in the same individual have different numbers or arrangements of chromosomes

• It is called "mosaicism" because the cells of the body are similar to the tiles of a mosaic.

• A mosaic individual is made of 2 or more cells populations coming from one zygote .

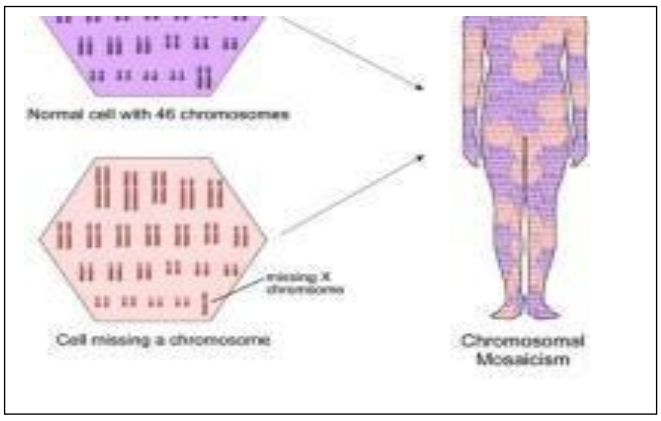
• Is denoted by a slash between the various clones observed, e.g. 46,XY / 47,XY,21+) .

• Usually due to a mitotic non-disjunction .

• Can affect any type of cells, including :

• * Somatic cells . it presents in patient without transporting.

• * Germ cells. It transports from parents.



Mosaicism vs chimerism

• Mosaicism: the presence of at least two genetically distinct, but related cell lines (clones) arising in the same individual

• e.g. Turner syndrome: 45, X [15] /46, XX [5] (the 5 represents to the number of healthy,15 is the number of affected cells)

• e.g. CML: 46,XX,t(9;22)(q34;q11.2)[9]/46,XX[11]

• Mosaicism can be found in 1% of Down Syndrome patients

• **Chimerism**: the presence of at least two genetically distinct cell lines that are derived from different conceptions

• e.g. tissue/organ transplants

• e.g. Bone marrow transplant patient: 46,XX[3]//46,XY[17]

Clinical presentation may be similar, variable, milder, or normal; may see skin pigmentation anomalies; may be identified by a recurrent cytogenetic abnormality in the children of parents who have normal karyotypes (i.e. gonadal mosaicism)

Mosaic loss of chromosome Y in blood cells increases morbidity and mortality in old age.

• Mosaic Klinefelter syndrome (46, XY/47, XXY) causes the small size of testes and reduced production of testosterone by the gonads.

• Frequency of low-level and high-level mosaicism has a role in sporadic retinoblastoma severity and the onset of the retinoblastoma.

Conventional Karyotype

Deletions, duplications, or rearrangements must be large enough (approximately >5 Mb) to be visualized under the microscope to be detected by conventional karyotype

ALL chromosomes and sex chromosome constitution

• Total number of chromosomes (aneuploidy)

• Size and structure of each chromosome

– Detects large chromosomal imbalances (e.g. subchromosomal deletion)

– Detects balanced translocations: where there is no loss of the total amount of genetic material

– Detects unbalanced translocations: where there is a change in the total amount of genetic material

• Small changes will not be detected.

Chromosomal Microarray (CMA)

• Chromosomal Microarray (CMA) is a microchip-based testing platform that allows automated analysis of many pieces of DNA at once

• ALL chromosomes and sex chromosome constitution

– CMA chips use probes that hybridize with specific chromosomal regions to detect copy number variations (CNVs)

• There are two types of Chromosomal microarray:

– Comparative Genomic Hybridization array (aCGH)

– Single Nucleotide Polymorphism (SNP) Array

• They are the first-tier test* for individuals with:

– Developmental disabilities

– Autism spectrum disorders

– Multiple congenital anomalies

– Mental retardation

– Prenatal: Microarray is useful when you have a fetus with: » 1 or more congenital abnormalities detected on ultrasound » Nuchal Translucency greater than 3.5mm

• aCGH and SNP arrays are used to detect copy number gains and losses.

Microarray CGH

• Array CGH is a significant advance in technology that allows the detection of chromosome imbalances that are too small to be detected by looking down the microscope

• It is faster and has a better resolution than available molecular cytogenetic tools.

• Array-CGH is the equivalent of conducting thousands of FISH experiments at once, and it provides better quantification of copy number

Cytogenetic microarray testing does detect:

- Micro-duplications or micro-deletions of chromosomal segments are minuscule to see under a microscope, but they contain various multiple genes.
- Abnormalities in a chromosome number (Down, trisomy, monosomy, etc.).
- Major unbalanced rearrangements of chromosome structure
- Mosaicism

Cytogenetic microarray testing does not detect:

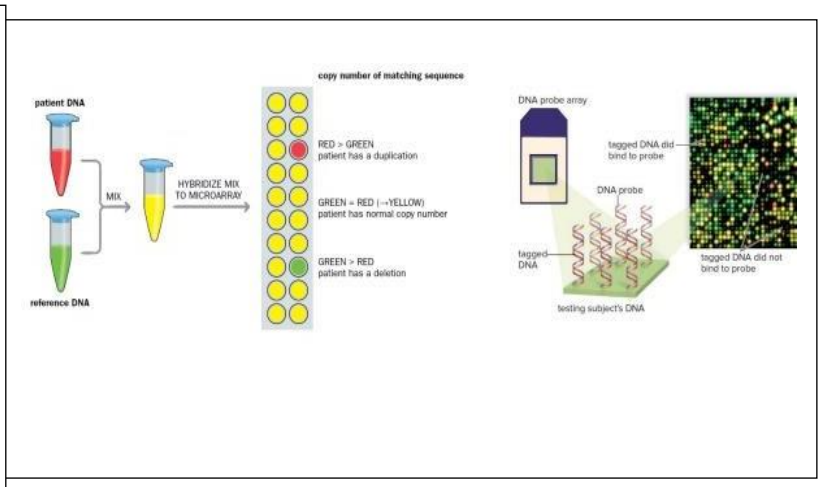
- Point mutations: Micro changes in the sequence of single genes
- Tiny deletions or duplications of DNA segments.
- Balanced chromosomal rearrangements, also known as balanced translocations and inversions.
- Low level mosaicism: Most cytogenetic microarray testing cannot detect mosaicism below 20-25%.

- Genomic DNA from the patients is labeled with one fluorescent dye, while a control sample is labeled with a different dye, and these samples are then co-hybridized to an array containing genomic DNA targets. - Chromosomal imbalance across the genome can be quantified and positionally defined by analyzing the ratio of fluorescence of the two dyes with the aid of computer software - The first-generation array had a coverage of about 1 MB. This resolution has been recently increased to cover the genome at a density of 10-100 kb

The green color means the patient has a deletion

Yellow color means the patient is normal

The red color means the patient has duplicated gene



In slip array there is no mixing in color like what happens in microarray

Single Nucleotide Polymorphism-Based Microarrays (SNP-array)

• In contrast to aCGH, SNP-based arrays do not directly compare a patient and a control specimen.

• SNP arrays compare the dosage of the patient at any given locus to a database of control individuals. As with aCGH, gains and losses of the genome are readily detectable using this method

• SNP arrays have the added advantage of being able to detect DNA base alterations, or genotyping, for any given SNP.

Phenotype depends on the genes that are deleted.

Microdeletions and microduplications Syndromes:

• Many dysmorphic syndromes are associated with small deletions that lead to genetic imbalance.

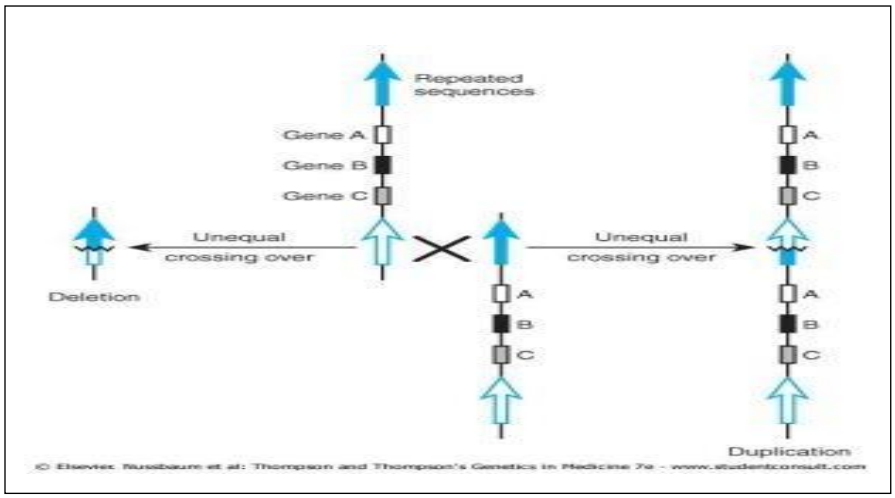
• These deletions produce clinically recognizable syndromes.

• Can be detected by high-resolution banding, FISH, a-CGH

• The term contiguous gene syndrome has been applied to many of them. i.e., haploinsufficiency for multiple contiguous genes within the deleted region

• For other disorders, the phenotype is apparently due to deletion of a single gene, despite the association of a chr. deletion with the condition

Model of rearrangements underlying genomic disorders. Unequal crossing over between misaligned sister chromatids or homologous chromosomes containing highly homologous copies of a long-repeated DNA sequence can lead to deletion or duplication products, which differ in the number of copies of the sequence. The copy number of any gene or genes (such as A, B, and C) that lie between the copies of the repeat will change as a result of these genome rearrangements.



Symptoms aren't needed in all following syndromes (1-4).

1)DiGeorge Syndrome Velocardiofacial Syndrome

Disease characteristics: Velocardiofacial Syndrome (VCFS) 3-megabase (Mb)deletion

• Congenital heart disease (74%)

• Palatal abnormalities (69%)

• Characteristic facial features

• Learning difficulties (70 - 90%)

• Many affected individuals can reproduce Diagnosis: 22q11 submicroscopic deletion

2)Duplication 22q11.2:

The problems range from isolated mild ID to multiple abnormalities with nonspecific dysmorphic features:

• Congenital heart disease

• Cleft palate

• Hearing loss

Postnatal growth deficiency

• Intellectual disability

• Delayed speech and language skills

• Behavioral issues

• Distinctive facial features.

Duplication 22q11.2

3)Cat Eye Syndrome (Schmid-Fraccaro Syndrome) Inverted Duplication22q11.2:

• Typical eye appearance

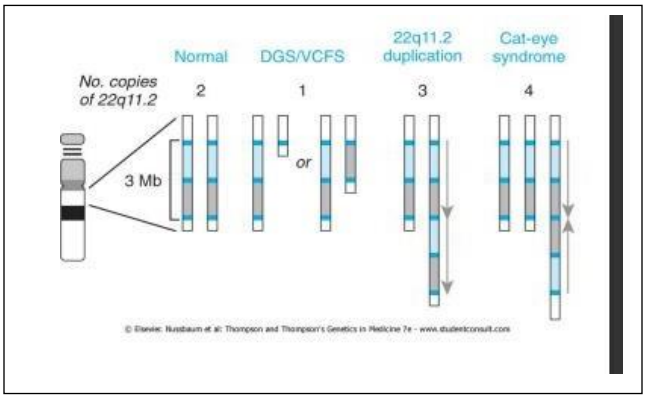
• Congenital heart disease (occasional)

• Intellectual disability

• Developmental delays

• Distinctive facial features

• Abnormalities in various organ systems.



4)Wolf-Hirschhorn Syndrome (- 4p)

✓ Partial monosomy of the short arm of chromosome 4

✓ 9 putative genes identified in this region


✓ Critical region at 4p16.3 – 165 kb segment

✓ Clinical features:

• Distinctive "greek helmet" facies

• Cardiac defects in 50%

• Mental retardation, Microcephaly

• Most are stillborn or die in infancy

• Frequent seizures

• 85-90% de novo deletions

• abnormal facies. Cardiac, renal, and genital abnormalities.

de novo deletion (WHSC1, WHSC2)------ 87% WHSC1=Wolf-Hirschhorn syndrome candidate 1 Translocation of 4p------- 13%

wide-spaced eyes and repaired cleft lip

REARRANGEMENT				
Disorder	Location	Type	Size (kb)	Repeat Length (kb)
Smith-Magenis syndrome	17p11.2	Deletion	4000	175-250
dup(17)(p11.2p11.2)		Duplication		
Charcot-Marie-Tooth (*CMT1A*)/HNLPP	17p12	Duplication	1400	24
		Deletion		
Williams syndrome	7q11.23	Deletion	1600	300-400
Neurofibromatosis	17q11.2	Deletion	1400	85
Sotos syndrome	5q35	Deletion	2000	400
Azoospermia (AZFc)	Yq11.2	Deletion	3500	230

V2