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Chapter

Background, Diagnosis, Types, Management/Prevention and Implications of Chromosomal Abnormalities

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Abstract

Chromosomal abnormalities are caused by both meiotic and mitotic errors, and can be found in both reproductive and somatic cells. Meiotic and mitotic errors, on the other hand, may result in the development of abnormal copies of chromosomes. Somatic cell chromosomal abnormalities cause mosaicism, which implies that certain cells are normal while others express the abnormality. Fascinating genetic chromosomal discoveries have given answers to mysteries in children suffering from premature growth/retardation, ambiguous genitalia, metabolic disorders, dysmorphic syndromes, primary amenorrhea, infertility, recurrent pregnancy loss, and cancers. Many factors influence the risk of chromosomal abnormalities, including advanced maternal age, environmental factors such as smoking, alcohol intake, and exposure to chemicals/radiation, and family history. It is an inevitable fact that majority of chromosomal abnormalities arise spontaneously and are not treatable. Much attention has not been devoted to the study of chromosomal abnormalities in order to better understand the pathogenesis and rising prevalence of various clinical conditions. This chapter will address the relationship of chromosomal abnormalities in various conditions with the goal of increasing awareness of causes and furthering diagnosis, management/treatment, counseling, and prevention options. Furthermore, preimplantation and prenatal testing can be planned from the laboratory bench to the clinical bedside using sophisticated molecular techniques.

Keywords: Chromosomal abnormalities, Counseling, management, Prenatal, Infertility

1. Introduction

Genetic material exists as a compact mass in relatively confined volume at cellular level as chromatin within the nucleus and the packaging of the chromatin is flexible and changes during the cell cycle. At the time of division, interphase chromatin becomes firmly packed, and individual chromosomes become visible as separate entities. A chromosome is a component for segregating genetic material during the cell division process. A structure known as a centromere is observed in the chromosome [1]. Kinetochore is a structure that connects the centromere to microtubules at the broader cellular level. A eukaryotic chromosome is made up of long linear

segments of DNA, as well as telomeres, which anchor the ends and are stretched by a specific mechanism that avoids the challenges of replicating the ends of linear DNA.

Chromatin has a scattered appearance, i.e. euchromatin, and includes the bulk of transcriptionally active genes. Some chromatin sections are densely packed, which is known as heterochromatin, and are normally inactive transcriptionally. The building blocks of chromatin are nucleosomes, which comprise 200 base pairs of DNAs arranged by an octamer in the basic proteins in a bead-like shape. Histones are protein components that form an inner core (**Figure 1**). The coiling of nucleosomes into a helical form present in interphase chromatin as well as mitotic chromosomes is the second level of organization [2]. Euchromatin is cyclically interchangeable with mitotic chromosomal packing, which is much more compact. Heterochromatin is equally dense in the packing of mitotic chromosomes. The chromatin mass includes up to double the protein content of DNA. Changes in chromatin structure are achieved through interaction with new proteins or through alterations to existing chromosomal proteins. Non-histone proteins include chromatin proteins other than histones that are transferable between tissues and species.

Each chromosome has a single long helix of DNA that is folded into a fiber and runs the length of the chromosome. Various chromosomes have different banding patterns; certain staining procedures allow chromosomes to look as a sequence of striations known as G bands. Bands typically have lower GC content than interbands, and genes are clustered in the GC rich region. Each chromosome's distinctive banded structure is caused by the folding of deoxy ribonucleoprotein fiber. The microtubules attached to the kinetochores forming in its central section's hold chromosome on the mitotic spindle. Centromeres contain heterochromatin, which is densely packed with satellite DNA sequences. A centromere is essential for segregation, and a single break produces one piece with the centromere and an acrocentric fragment. A telomere is crucial for chromosomal end stability. It is made up of simple repeats in which a C + A rich strand has the sequence C (A/T). The telomere is reproduced by a particular process, usually the complement of template RNA primers in the telomere, which generates a primer that is expanded by enzyme reverse transcriptase activity [3].

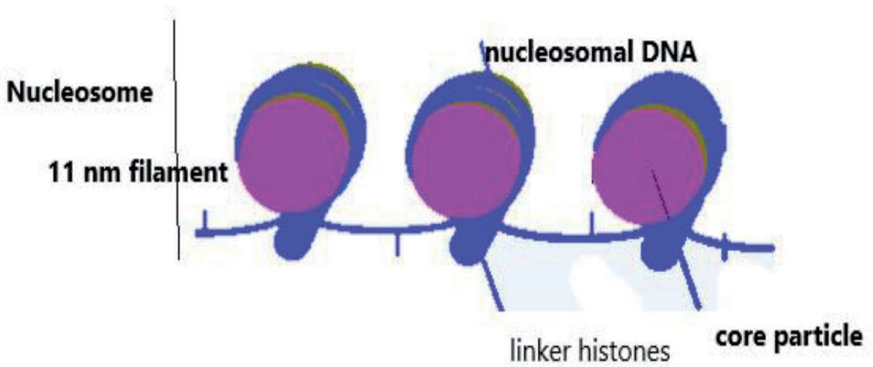

Figure 1.
Chromatin structure, nucleosome, and histone proteins are depicted in a cartoon.

1.1 Chromosome

Chromosomes are thread-like structures packed with histone proteins that contain the genetic material from which children inherit features from their parents. Deoxyribose nucleic acid (DNA) generates proteins that aid in human growth and development. Humans have 23 pairs of chromosomes, which are separated into autosomes (22 pairs) and allosomes (one pair as X and Y). Chromosomes divide to

generate gametes during meiotic division. Homologous chromosomes are a set of chromosomes (23 pairs = 46 chromosomes) inherited from the maternal side and the other from the paternal side [4].

1.2 Types of chromosomes

Each chromosome possesses a centromere, which is critical for chromosome placement and visible during metaphase. The centromere separates the chromosomes into two arms, the p arm (short arm) and the q arm (long arm). They are classified into four types based on the position of their centromeres: metacentric, submetacentric, acrocentric, and telocentric.

1.2.1 Metacentric chromosomes

Where the centromere is precisely situated at the center, dividing the chromosomes into two equal sections [chromosomes 1, 3, 16, 19, 20]. The two P and q arms are equally separated from the centromere and are referred to as m (**Figure 2**).

1.2.2 Sub metacentric chromosomes

Where the centromere is off-center on the chromosome [4, 5, 6, 7, 8, 9, 10, 11, 12, 17, 18, and X]. The shape of the sub metacentric chromosome is L, and it is labeled as sm. It contains unequal p and q arms (**Figure 2**).

1.2.3 Acrocentric chromosomes

Centromeres are generally found near the end of the chromosome, near the telomere [13, 14, 15, 21, 22, Y chromosome]. The p arm of the acrocentric chromosome contains nucleolar organizing regions that code for r RNA. Balanced and unbalanced translocations arise as a result of acrocentric chromosome centromeric region breakdown and fusion (**Figure 2**).

1.2.4 Telocentric chromosomes

The human genome contains no telomeric chromosomes. In mouse anaphase, telocentric chromosomes are generated predominantly. If only one arm is detected on the telocentric chromosome (**Figure 2**).

Non-disjunction of chromosomes occurs during meiotic and mitotic cell division (that is, inappropriate separation of sister chromatids during anaphase of meiosis I, II, and mitosis, resulting in an aberrant number of chromosomes, which leads to abnormalities). This nondisjunction is caused by inactive enzymes such as topoisomerase and helicase (binds sister chromatids in anaphase) [5].

Figure 2.
Representation of metacentric, sub metacentric, acrocentric and telocentric chromosomes.

2. Diagnosis

There are some conventional and commonly used methods or techniques for detecting chromosomal abnormalities. The following are the four most popular techniques:

1. Karyotyping

2. Fluorescent InSitu Hybridization (FISH)

3. Chromosomal microarray

4. Quantitative Fluorescent – Polymerase Chain Reaction (QF- PCR).

2.1 Karyotyping

Karyotyping is a laboratory procedure that is used to diagnose chromosomal abnormalities both numerical and structural as well as related disorders. Samples for karyotyping can be peripheral blood, cord blood, bone marrow, amniotic fluid, or tissues. Lymphocytes are cultured in a medium and metaphase is arrested by the addition of colchicine. Later, the cells are treated with a hypotonic solution and fixed (3:1 methanol: acetic acid) on a glass slide with Carnoy's fixative before staining the chromosomes with Giemsa.

There are numerous banding techniques available for chromosomal distinction and arrangement; the most commonly used banding technique is GTG- banding. Based on the size, position of the centromere, and banding patterns, heterochromatin regions are AT rich and are darkly stained, while euchromatin regions have light bands. Chromosomes are reported in accordance with the standard nomenclature scheme (ISCN-International System for Human Cytogenomic Nomenclature) 2020. The total number of autosomes is mentioned first, followed by commas (,) and sex chromosomes in the description of human karyotype. The + and – signs represents the gain and loss of chromosomes.

If chromosomes are structurally rearranged or aberrant, structural designations such as del, dup, inv., and so on are used, and the structurally altered chromosomal numbering is given in brackets. If the rearrangement occurs inside or between two chromosomes, it is separated by a semicolon (;), male patient with Down syndrome and inversion 9 is stated as 47, XY, +21,inv(9). If the karyotype comprises mosaicism, two distinct cell lines are designated: 47, XY,+21,inv(9)/46,XY. Microdeletions, duplications and insertions which are smaller than 5 Mb in size, cannot be detected by the method of karyotyping has its own limitations. It does not recognize both homozygosity and loss of heterozygosity [6]. Infertility, primary amenorrhea, developmental delay, mental impairment, Hematological cancers, Fragile X syndrome, and other frequent disorders that necessitate chromosomal analysis. Limitations of Karyotyping can be fulfilled by next advanced tests like FISH and Microarray.

2.2 FISH

Fluorescent insitu hybridization is a technique that uses fluorescence probes to localize a portion of DNA, which then attaches to a specific target region that can be observed using a fluorescent microscope.

There are three types of probes used in FISH diagnostics:

2.2.1 Locus specific probes

These probes locate a specific gene on a specific chromosome.

2.2.2 Whole chromosome probe

Where numerous smaller samples and various tints of fluorescent dyes, each probe binds to a specific segment of the chromosome, resulting in a chromosomal map. As a result, any abnormality, such as translocation, can be immediately noticed.

2.2.3 Centromeric repeat probes

The number of chromosomes was determined by a repeating binding sequence. It is widely used in prenatal diagnosis, minor chromosomal abnormalities, and malignancy differential diagnosis. The main advantage of FISH is that it minimizes the Turn Around Time (TAT), which is specific for recognizing minor chromosomal abnormalities, and it can also detect the proportion of mosaicism.

2.3 Chromosomal microarray

Chromosomal microarray is a cost-effective and high-resolution prenatal test, which is based on alterations in the genome, or copy number variations. It is capable of detecting the entire chromosome on a single microchip. It primarily looks for microdeletions, duplications, and aneuploidy. According to the International standard Cytogenomic array consortium, chromosomal microarray is a commonly utilized tool in prenatal diagnostics. It is one of the tools for detecting Cytogenomic imbalances that has been revolutionized in the present era of Cytogenomic. Identification of DNA copy number gains and losses aids in the diagnosis and treatment of a variety of hereditary disorders.

2.4 QF-PCR

Quantitative fluorescence-polymerase chain reaction (QF-PCR) is a prenatal diagnostic molecular technology used to detect chromosomal aneuploidies such as 13,18,21 and sex chromosomes. This is a rapid and more automated technique than FISH and Karyotyping since no fetal cells are cultured. DNA can be extracted from amniotic fluid, tissue, or chronic villus samples, and fluorescent primers are used for analysis. It is inexpensive, quick, Faster and only a small amount of the sample is required for diagnosis. It is more robust and requires less labor and time than other traditional procedures such as Karyotyping and FISH.

3. Chromosomal abnormalities

Chromosomal abnormalities are grossly divided into numerical abnormalities and structural abnormalities.

3.1 Numerical abnormalities

Numeric abnormalities caused by the loss or gain of one or more chromosomes, which can be aneuploidy or polyploidy.

3.1.1 Aneuploidies

The gain or loss of chromosome is also known as aneuploidy. When a single chromosome is removed from a pair of chromosomes called monosomy [7]. Trisomy or tetrasomy occurs when one or more chromosomes are gained. It can occur either in Autosomal or sex chromosomes. Down syndrome, Edward syndrome, and Patau's syndrome are autosomal aneuploidies, while Klinefelter syndrome, Jacob syndrome (XYY), and Turner syndrome are sex chromosomal Aneuploidies (**Figure 3**).

3.1.2 Polyploidy

It is a condition in which a normal diploid cell gains one or more sets of chromosomes. Polyploidy occurs as a result of chromosomal disjunction during mitosis and meiosis which are typically observed in plants and animals and are not seen in humans. These syndromes are associated with a variety of phenotypical problems such as developmental delay, recurrent miscarriages, infertility, congenital heart abnormalities, and so on. Triploidy is an uncommon disorder in which a complete haploid set of additional chromosomes is present, resulting in miscarriage or premature death. Tetraploidy is a condition where cell contains four sets of chromosomes which are infrequent and resulting in spontaneous abortions.

3.1.2.1 Autosome aneuploidies

The common autosomal aneuploidies are described below.

3.1.2.2 Down syndrome (DS)

DS is the most frequent chromosomal anomaly caused by the inheritance of an additional chromosome 21. Down syndrome manifests itself in a variety of ways, some of which are listed below.

1. Non-disjunction of chromosomes: This occurs during gamete development i.e., during meiosis the pair of chromosomes 21 in egg or sperm fails to separate (**Figure 4A**).

2. Chromosome 21 splits and attaches to another chromosome in a Robertsonian translocation (**Figure 4B**).

3. Mosaicism is a term used to describe the pattern of where few cells show normal chromosomes set while some cells show extra chromosome 21.

DS is a complex genetic disease that is compatible with human post-term survival, and it is the most common survivable autosomal aneuploidy. It is difficult since chromosome 21 has over 200 protein-coding genes that can have direct and indirect effects on homeostasis in cells, tissues, organs, and systems [8].

Clinical features: DS is characterized by a protruding tongue, peculiar fingerprints, pelvic dysplasia, low set ears, a short neck, chinkey eyes, a sandal gap, mental retardation, epicanthic skin folds, and congenital heart disease in more than half of patients. Down syndrome patients have a high copy number of genes on chromosome 21, which causes gene overexpression and phenotypic abnormalities. Prenatal diagnosis for Down syndrome: Ultrasound for nuchal translucency, Quad screen, Amniocentesis or CVS.

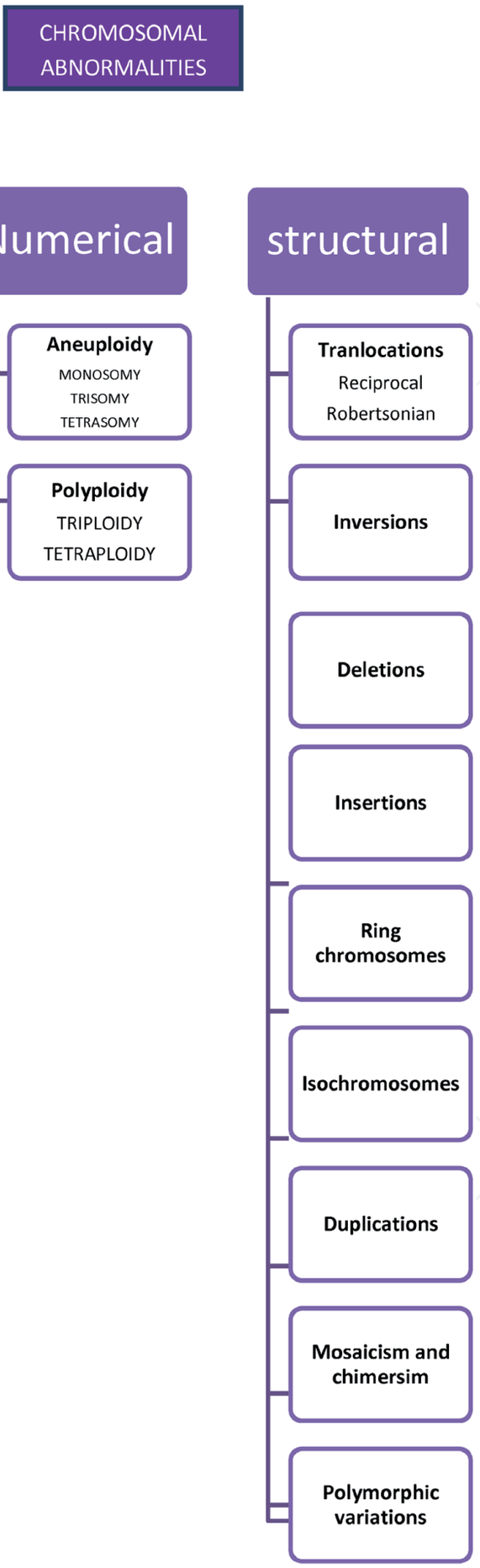

Figure 3.
Types of both numerical and structural abnormalities of chromosomes.

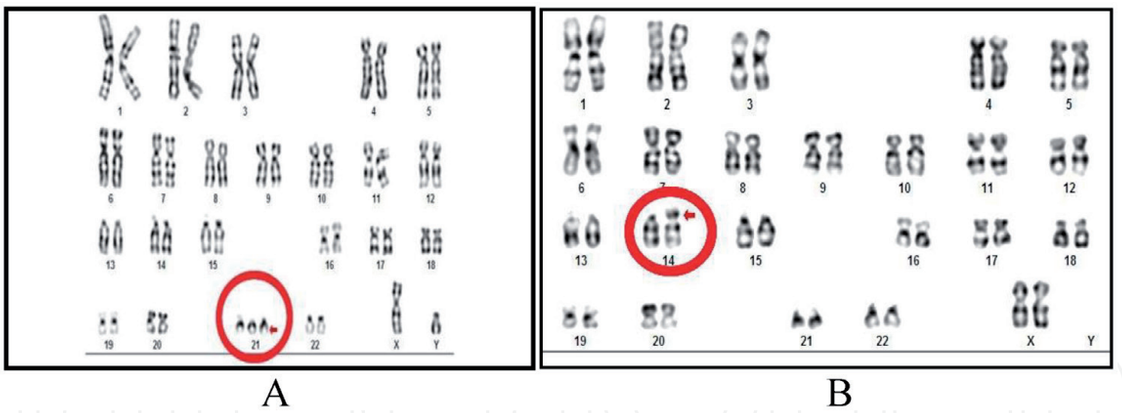

Figure 4.
Karyotype with 47, XY+21 indicating a free trisomy (A) and 46, XX rob t (14, 21); (q10;q10) indicating Robertsonian translocation.

Treatment/management: There is no specific cure for DS, however it can be managed through a comprehensive approach. Karyotyping is critical for establishing a diagnosis of DS and evaluating the syndrome's recurrence risk in following generations. To improve quality of life, DS should be addressed by a variety of specialists, including endocrinologists, cardiologists, audiologists, nutritionists, clinical geneticists/medical geneticists, and nutritionists [9]. DS patients need also get therapies such as occupational, speech, behavioral, and physical therapies in order to improve motor and communication abilities as well as manage or reduce behavioral difficulties, allowing them to live a normal social life.

3.1.2.3 Edward syndrome (ES)

Trisomy 18 is another term for ES (47, XY + 18 in males and 47XX + 18 in females), (**Figure 5**) named after the geneticist Edward who reported it, is caused by an extra copy of chromosome 18 caused by nondisjunction of meiotic gametes in sperm or egg. It mostly impacts fetal development and organogenesis.

Phenotypical characters: ES is characterized by microcephaly, cleft lip and palate, lung malformation, hypoplasia of skeletal muscles, growth retardation,

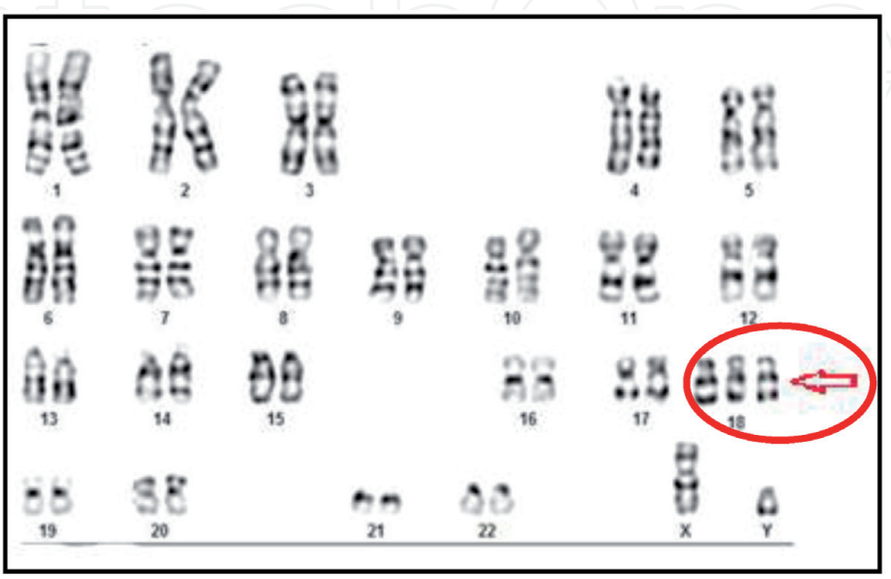

Figure 5.
Karyotype demonstrating trisomy 18 (47, XY, +18).

dysmorphic skull, cryptorchidism, neurodevelopmental delay, ventricular sept defects, low set ears, and other characteristics.

Treatment/management: There is no definitive treatment or management for children with trisomy 18, and there are ethical concerns because the condition has a high mortality rate. Because of its varying presentation, management focuses on correcting abnormalities and performing corrective operations as required.

3.1.2.4 Patau syndrome (PS)

PS, also known as trisomy 13 (47XY, +13 in males and 47XX,13 + in females) (**Figure 6**), is caused by an extra copy of chromosome 13 caused by nondisjunction and mosaicism. In comparison to other syndromes, the survival rate is lower.

Clinical features: Include cleft palate, polydactyly, and cranial deformities, as well as severe neurological abnormalities, ventricular septal defects, and seizures.

Treatment/management: Unfortunately, trisomy 13 has no known cure. It includes a variety of therapy and corrective operations based on the symptoms. Patients with cardiac defects may require cardiac surgery interventions, as well as other surgeries such as cleft lip repair, feeding tube placement, or corrective pediatrics or orthopedic surgeries, the use of hearing aids, specialized dietary feed, seizure prophylaxis, and urinary tract infection prevention antibodies.

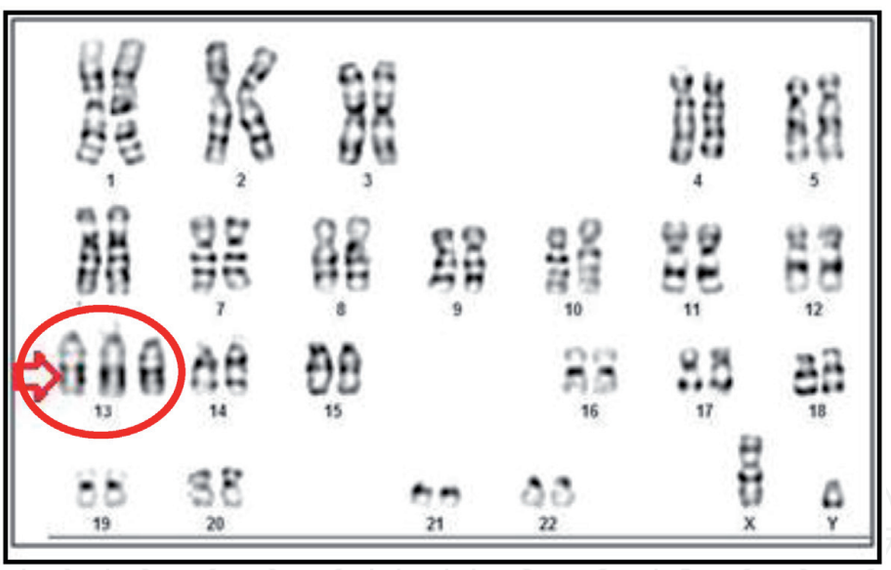

Figure 6.
Patau syndrome or trisomy 13 is indicated by the karyotype showing 47, XY, +13.

3.1.3. Allosome aneuploidies

3.1.3.1 Turners syndrome (TS)

TS is present in females and is caused by a total loss (45, X) (**Figure 7**) or partial loss of the X chromosome (deletion of the p arm 46, X, del (Xp), or isochromosome of the q arm), primarily due to a failure in the inheritance of the X chromosome from male paternal origin. Turner syndrome is frequently mosaic, with 45XO/46XX indicating the presence of two distinct cell lines.

Clinical features: Turner syndrome women have short stature, delayed puberty, a webbed neck, puffiness in the hands and feet, a congenital cardiac defect, and

Figure 7.
Karyotype 45, XO, indicating Turner syndrome.

infertility. Women with hypogonadotropic hypogonadism and undeveloped ovaries may benefit from hormone treatment, which may aid in the development of secondary sexual characteristics. Affected individuals are at a significant risk of developing autoimmune illnesses, type 2 diabetes, and renal abnormalities [10].

Treatment and management: TS is primarily treated or managed with hormonal therapy, such as injections of human growth hormone in the early stages of life to increase height. Hormone replacement therapy, such as estrogen, is used to faster the development of secondary sexual characteristics. Uterus transplantation is a recent advancement in treatment that is well-established in developed countries.

3.1.3.2 Klinefelter syndrome (KS)

KS is most common in men who have an additional X chromosome, resulting in a karyotype of 47, XXY (**Figure 8**). Incomplete meiotic division in gametes, such as egg or sperm, results in an extra copy of the X chromosome. There will be more than two copies of the X chromosome in some uncommon and severe situations, resulting in the karyotype 48XXXY, 49XXXXY. Another type of mosaic Klinefelter in which the intensity of symptoms may be reduced is mosaic Klinefelter.

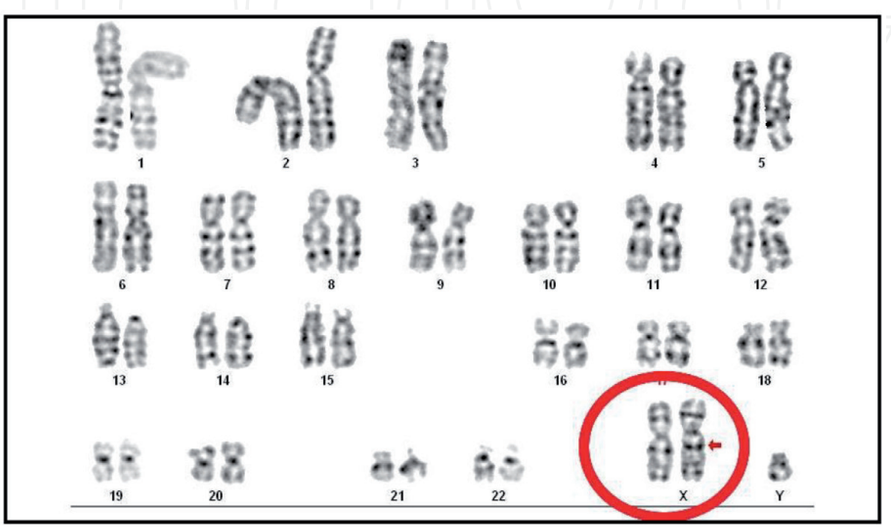

Figure 8.
Karyotype 47,XXY indicates Klinefelter syndrome.

Clinical features: Individuals with this syndrome may have delayed milde-stones, taller than average, have longer legs and shorter toes, have delayed or incomplete puberty, urogenital abnormalities, weak bones, gynecomastia (breast enlargement), hormonal imbalances, intellectual difficulty, and infertility.

Treatment/management: Hormone treatment in childhood may improve brain and neurological development. In cases of infertility, depending on the count and morphology of the sperm, assisted reproductive procedures such as Intra Cytoplasmic Sperm Injection (ICSI) may be a viable alternative [11].

3.1.3.3 Jacob syndrome (XYY) or XYY Syndrome

It is a unique sex chromosomal disorder in which people have an extra Y chro-mosome due to nondisjunction in meiotic II division and is only seen in males. This extra Y chromosome is the result of father's erroneous spermatogenesis. Jacob syndrome (XYY) [12] has the karyotype 47, XYY (**Figure 9**).

Clinical features: Tallness, muscle weakness, hypertonia, ADHD (Attention deficit hyperactivity disorder), altered testosterone, congenital cardiac problems, neurologi-cal abnormalities, and a curled pennis are all symptoms of this condition. This syn-drome is associated with a significant incidence of asthma and seizures, and symptoms vary from case to case. Individuals with this syndrome are more likely to be infertile.

Treatment/management: Jacob syndrome (XYY) is treated symptomatically and supportively. Speech therapy, occupational therapy, or school-based learning disability support may be effective. Individuals with this condition are usually quite amenable to early diagnosis and therapy. Other behavioral difficulties are addressed in accordance with their severity. Individuals with attention deficit and hyperactiv-ity disorder, as well as difficulty with social interactions and in certain severe cases they may face suicidal tendencies also.

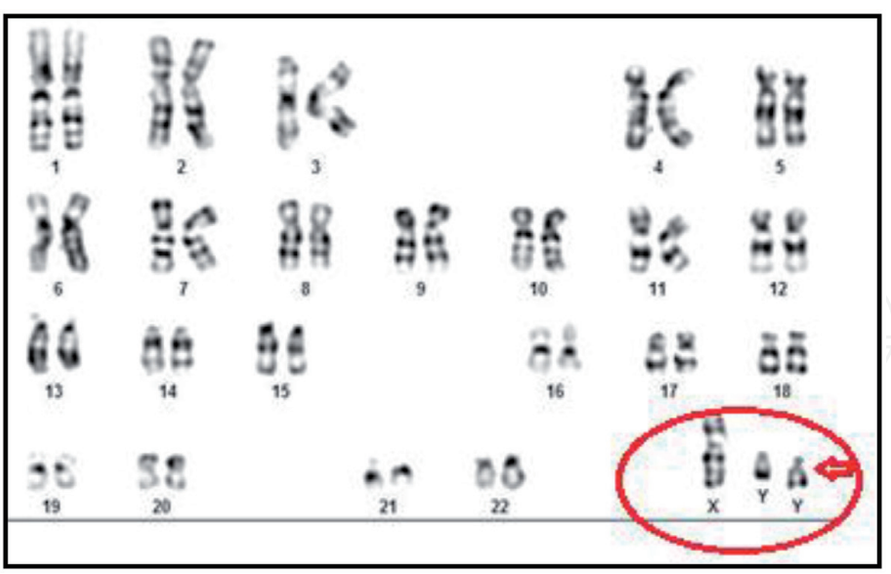

Figure 9.
Karyotype showing 47, XYY indicating Jacob Syndrome or XYY Syndrome.

3.2 Structural abnormalities

Structural abnormalities are caused by structural changes such as inappropriate joining or breaking of chromosomal segments and rearrangement of chromosomal segments, which results in incorrect lengths of the p and q arms of a chromosome. There is a chromosomal material exchange that modifies chromosome structure

with no loss of genetic material. Unbalanced rearrangement occurs when a portion of a chromosome is removed or lost. When compared to unbalanced chromosomal changes, balanced chromosomal changes are anticipated to have less of an impact because genetic information is retained. Infertility, spontaneous pregnancy loss, and hematological malignancies are all linked to structural defects. Translocations, inversions, deletions, insertions, ring chromosomes, isochromosomes, duplications, mosaicism, chimerism, and polymorphic variations are some of the major structural abnormalities (**Figure 3**).

3.2.1 Translocations

Translocations are defined as the rearrangement of chromosomes/segments between non-homologous chromosomes which have no genetic material loss or gain. These are divided into two types (**Table 1**):

1. Reciprocal translocation (Balanced).

2. Robertsonian translocation.

3.2.1.1 Reciprocal translocations

Where there is a translocation or exchange of parts from two separate chromosomes (**Figure 10**). Inheritance of translocation occurs when one parent has derived chromosomes and the other parent has a normal pair of chromosomes, resulting in three sorts of chromosomal passing possibilities:

- they can pass both normal chromosomes,
- one normal and another derivative,
- two derivative chromosomes.

S. no	Type of chromosomal abnormalities	Karyotypes
1.	Numerical abnormality -	
	Monosomy (Turner syndrome)	45,XO
	Trisomies- Edward syndrome	47,XX +18/47,XY +18
	Patau syndrome	47, XX+13/47, XY+21
	Down syndrome	47, XX+21/47, XY+21
2.	Sex chromosomes abnormalities – Klinefelter syndrome	47,XXY
	Jacob syndrome	47,XYY
3.	Structural abnormalities such as translocations-	46,XX,t(4;12)
	Reciprocal translocations	45,XY,t(14;21)
	Robertsonian translocations	46 XX,ins9
	Insertions	46,XX, (inv9) (p12 q13)
	Inversions	46, XY, dup7
	Duplications	46, XX, 4p-
	Deletions	45, XO/46,XX
	Mosaicism	46,XX, 9qh+/Yqh+
	Polymorphic variants	46,XX, r (21)
	Ring chromosomes	

Table 1.
The type of chromosomal abnormalities and the karyotype notation.

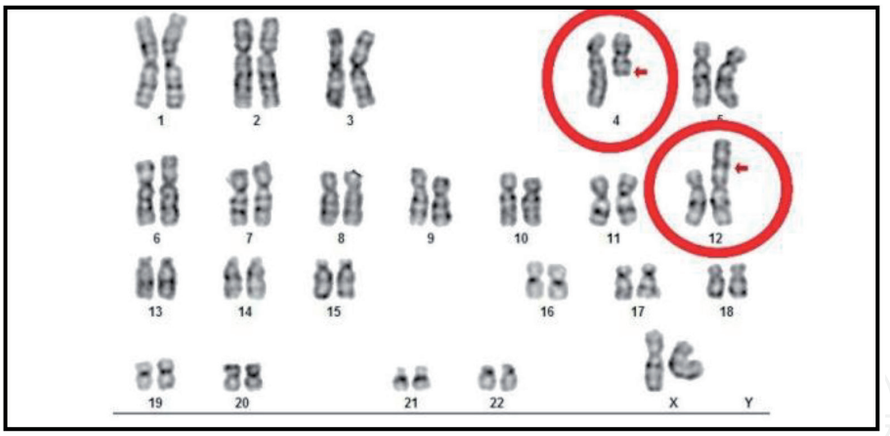

Figure 10.
Karyotype with 46,XX, t(4;12) demonstrating balanced reciprocal translocation among chromosomes 4 and 12.

The risk of translocation is proportional to the amount of chromosomal exchange, and it increases further when two defective chromosomes are received. De novo translocations are more perilous than inherited translocations. There may be multiple or triple reciprocal translocations at times [13].

3.2.1.2 Robertsonian translocation

This type of translocation occurs between (14, 15, 16, 21, 22) acrocentric chromosomes, in which one chromosome joins to another (D or G) (**Figure 11**). The fusion of two long arms of chromosomes 14 and 21 results in the translocated Downs syndrome phenotype. The presence of nucleolar organizing zones, satellite DNA (highly repetitive sequences), and r RNA sequences aids in the union of acrocentric centromeric regions, resulting in chromosome translocation. Parents with Robertsonian translocations have aberrant offspring due to incorrect meiotic division segregation. There is a greater likelihood that progeny will have abnormalities such as DS, PS, and so on. Carriers may exhibit a normal phenotype. Female carriers are more likely than male carriers to pass on the Down syndrome phenotype. Miscarriages, male infertility, and other complications result from Robertsonian translocation [14].

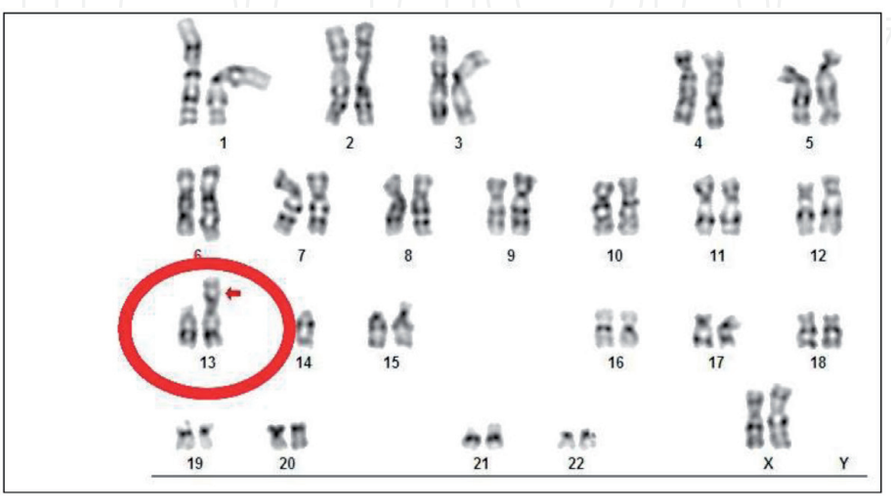

Figure 11.
A karyotype with 45, XX, rob t(13;14) indicating a Robertsonian translocation between 13 and 14 chromosomes.

3.2.2 Ring chromosomes

These are circular chromosomes, which result in the fusion of ends of a single chromosome due to a break in the terminal ends of both the p and q arms, resulting in some genetic material loss (**Figure 12**). Lilian Vaughan Morgan was the first to describe the ring chromosomes found in flies. The ring chromosome is denoted by the letter r and the chromosome number 46, XX, r(21) & 46, XY, r(1), etc., and it is a rare structural aberration [15]. Ring chromosome 14 and 20 syndrome is a common abnormality in epilepsy. The ring chromosome's phenotype is determined by the original deletion and instability caused by ring structure creation; there may be a loss or gain of certain secondary chromosome material, and carriers can be asymptomatic or cause major clinical symptoms. The majority of ring chromosome carriers are sterile. Cytogenetic studies such as karyotype and FISH demonstrate that ring chromosomes can be dicentric, interlocking, solitary, or multicentric. Because of the fragility of the ring structure during meiosis, inheritance is relatively uncommon in ring syndrome cases.

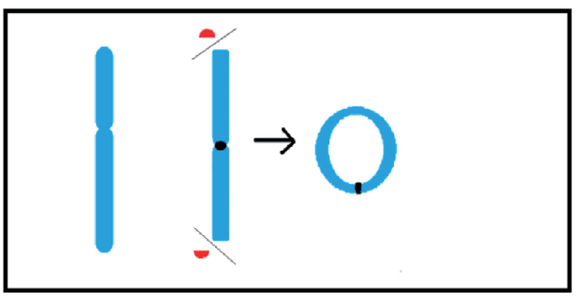

Figure 12.
Cartoon depicting the formation of a ring chromosome after breakage.

3.2.3 Inversions

Rearrangements of the same chromosome caused by reversal of gene order via breakage and reinsertion of fragment. Inversions are associated to reproductive difficulties such as recurrent pregnancy loss, infertility, position effect variation, and so on. Inversions can be classified as single inversion, complex inversion, homozygous inversion, or heterozygous inversion based on the segments and breaks. There are as follows (i) paracentric inversion and (ii) pericentric inversion.

3.2.3.1 Paracentric inversion

Inversions that occur within a single chromosome on a single arm without the participation of the centromere are classified as paracentric. During this process, chromosomes break and rearrange themselves by flipping 180 degrees. The effect of paracentric inversion is a loss of reproductive potential, and the chances of meiosis chromosome separation and alignment of non-inverted homologous chromosomes are reduced as a result of inversion, resulting in acentric or dicentric chromosomes, deletion of chromosomes, or sometimes balanced inversion in the case of even crossovers [16]. Because of the imbalanced chromosomal rearrangements, both men and women are at a significant risk of infertility (**Figure 13A**).

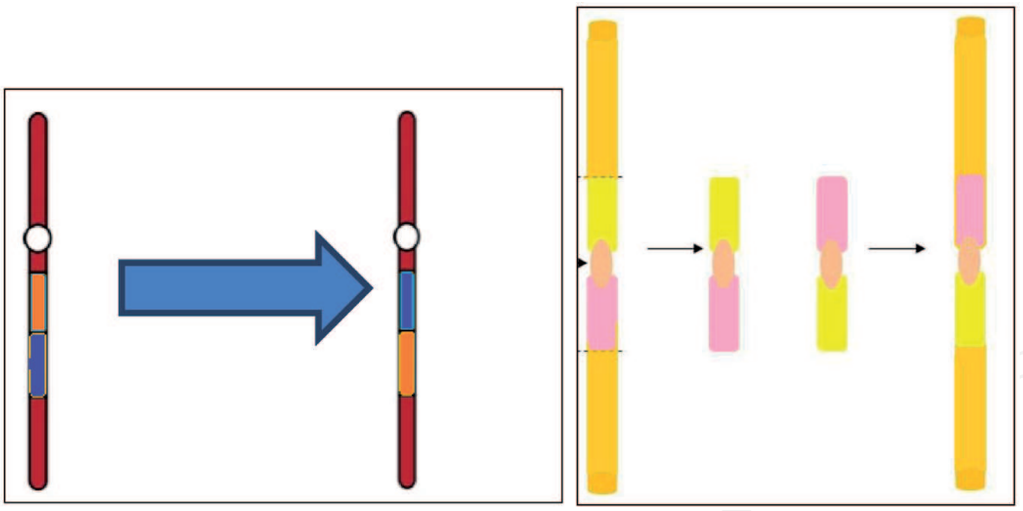

Figure 13.
Cartoon depicting paracentric inversion 13(A) and pericentric reverse 13(B).

3.2.3.2 Pericentric inversion

Inversion occurs when the centromere is involved, and there is a breakpoint on both arms and more frequently than paracentric inversion. Like paracentric inversion during meiosis chromatid separation, even crossings result in 50 percent balanced inversion and odd crossovers result in numerical abnormalities, which are aneuploidies caused by chromatid inversion, deletion, and duplication. One of the most prevalent examples of inversion is on chromosome 9, where the break point occurs between p arm p11 and long arm q 13. The female inversion 9 nomenclature is specified as 46,XX, (inv9) (p12 q13). Some of the most prevalent disorders associated with inversion 9 are Walker Warburg syndrome, newborn diabetes, and acute leukemia (**Figure 13B**).

3.2.4 Isochromosomes

Isochromosomes are defective chromosomes in which one chromosome has mirror images of a single chromosome arm, resulting in the loss of the other arm. Normal p and q arms will be present on the remaining homologous chromosome. Isochromes are created as a result of incorrect division, specifically U type strand division, which results in dicentric or bi centromeric chromosomes. Pallister-Killian syndrome, caused by isochromosome 12 p, and cat eye syndrome, produced by fusion of the short arm of chromosome 22 and on isochromosome 17q, are two syndromes related with isochromosomes [17].

3.2.5 Deletions

Deletions, which occur frequently spontaneously, result in the removal or fracture of a section from a chromosome, resulting in the loss of genetic material. One of the causes of deletion is exposure to radiations like as UV rays, X-rays, gamma rays, and so on. There are two categories of deletions; (1) *Interstitial deletion:* Deletion induced by two or more breaks in between the genes and (2) *Terminal deletion*: Deletion triggered by terminal ends (**Figure 14**). One typical example is cri du chat syndrome, which is caused by a deletion on the p 15.2 region of chromosome 5 [18]. Some deletions on chromosome 15 can be caused through inheritance from father and mother, such as Prader-Willi or Angelman syndrome (imprinting disorders).

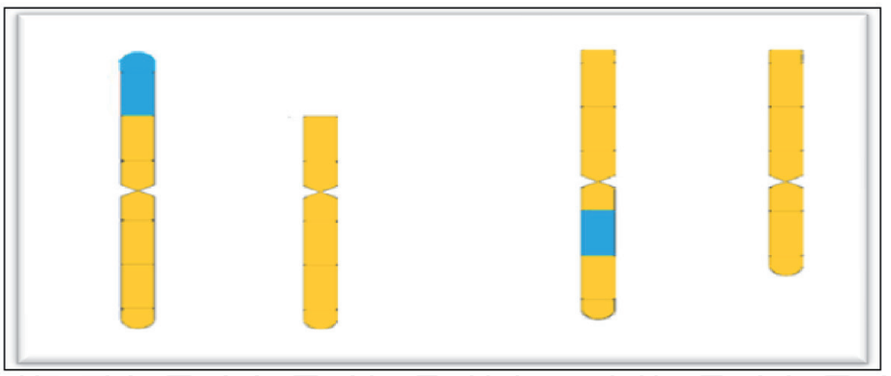

Figure 14.
Illustration of interstitial and terminal deletions on a chromosome.

3.2.6 Duplications

Duplication leads to the development of an extra copy of a chromosomal segment. Duplication does not pose a significant risk, but it does promote evolution. Some of the human genes produced by duplication through evolution are human globin genes; they arose from predecessors, some of which express in the embryonic stage and others in the adult stage [19]. Tandem duplication occurs when the duplicated gene is near to or contiguous to the original gene, whereas displaced duplication occurs when the duplicated region is far from the gene. *MECP2* duplication syndrome is a common occurrence in humans, particularly in men, and is caused by X chromosomal duplication. 7 q 11.23 duplication syndromes are another kind of duplication that causes numerous neurological phenotypic effects.

3.2.7 Polymorphic variants

Variants that occur in chromosomal heterochromatin regions. Variants in long arms are mainly found in the paracentric region of heterochromatin, and all acrocentric chromosomes have polymorphism. An increase or decrease in the lengths of chromosomes in the heterochromatin region can be represented by the symbols qh+, qh-., Polymorphic variations are a common anomaly reported in infertility and spontaneous miscarriages. They are regarded as normal because they have been identified in the general population. Yqh is the most prevalent polymorphic variation found in male infertility [20].

The most common polymorphic variants found in the long arm of chromosomes are 1qh+, 16qh+, 9qh+, and 1qh-, and short arm chromosome polymorphic variants are 14 ps+,15 ps+,13 ps+, and so on. These polymorphic variants can be identified using the silver NOR (Nucleolar Organizing Regions) banding technique (**Figure 15**).

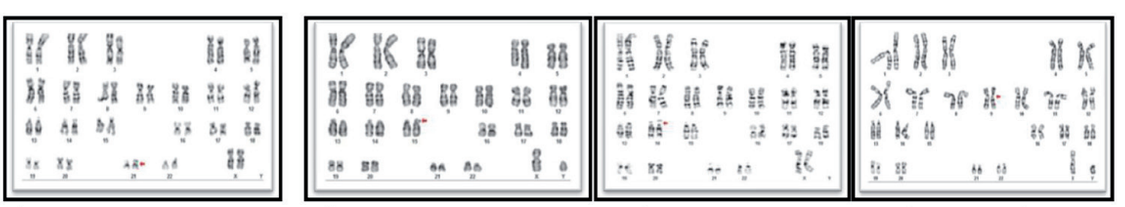

Figure 15.
Karyotype indicating 46,XX,21 ps+,46,XY,15 ps+,46,XX,14 ps+ and 46,XY,9qh+ polymorphic variants on chromosome 21,14,15 and 9. (A) 46 XX, 21 ps+, (B) 46 XY, 15 ps+, (C) 46,XX,14 ps+, (D)46,XY,9qh+.

3.2.8 Mosaicism

Mosaicism occurs during the developmental process. During zygote formation, distinct cell lineages emerge, resulting in diverse genotypes in different cells. Some cells have a normal set of chromosomes, while others have abnormal chromosomes. Mosaicism is classified into two categories based on cell origin: germ line mosaicism and somatic mosaicism. Germ line mosaicism develops in germ cells when the individual carrying the germ cells is not deformed but the children are. In somatic cells, where somatic mosaicism occurs. Confined mosaicism occurs in a variety of organs. Mosaicism can be inherited or occur sporadically [21]. Some patients with mosaic versions of Ret syndrome, Down syndrome, Klinefelter syndrome, and Cornelia de Lange syndrome have a lower risk than others.

3.2.9 Chimerism

Chimerism differs from mosaicism in that two distinct genotypes are produced as a result of the embryonic fusing of two zygotes. It can be a tetra gametic chimera in which identical or non-identical twins' fuse, resulting in male, female, or bisexual characteristics. For the first time, Taylor Muhl found chimersim. Another sort of chimersim is blood group chimersim, which occurs when a person has two separate blood cell types.

3.2.10 Insertions

Insertion occurs when a chromosomal fragment gets inserted into another chromosome or inside the same chromosome in a non-adjacent area (**Figure 16**). Insertions can cause a massive chromosomal rearrangement with numerous phenotypic effects. These repercussions are primarily determined by the size and location of the chromosome. There are two kinds of insertions: intrachromosomal insertions and interchromosomal insertions. Individuals who are carriers of intrachromosomal insertions are more likely to have a child with an aberrant or unbalanced karyotype.

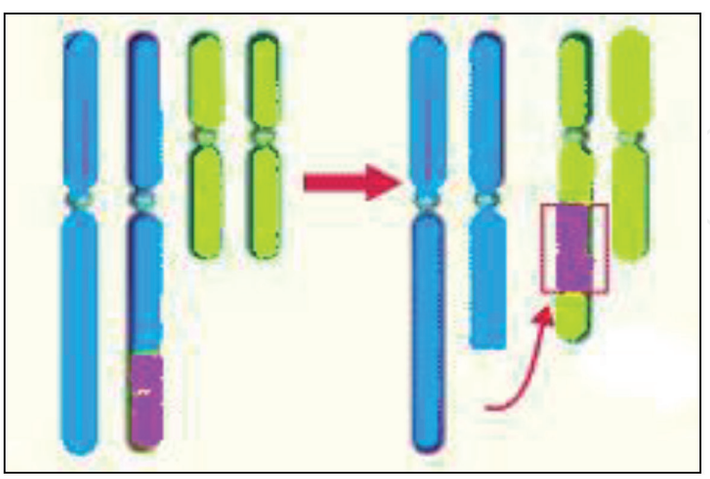

Figure 16.
Image representing insertion of chromosome segment.

3.3 Management and prevention

With the increasing incidence and prevalence of genetic conditions, it should be addressed and there is a need to focus and more attention towards the prevention

of genetic conditions to reduce the global burden with syndromes or birth defects. The government should take the initiative, for preventive strategies and measures adopted in tertiary care institutions or hospitals.

3.3.1 Prenatal screening

Prenatal screening programs have a significant impact on improved pregnancy outcomes. Between 11 and 13 weeks of gestation, NT scan should be performed, as well as other biochemical markers such as a double, triple, and quatriple marker at the proper gestational ages. An altered marker or scan, in the case of a substantial family history, such as a prior child diagnosed with a genetic condition, invasive prenatal testing is recommended either by chronic villus sampling (CVS) or amniocentesis.

Chronic villus sampling (CVS) is an invasive procedure performed on a growing placenta between 11 and 14 weeks of gestation. Under ultrasound guidance, a needle with a syringe is inserted transabdominally based on the position of the placenta, after which the tissue is removed and inspected. Based on the indication, the excised tissue was subjected to FISH and Karyotyping, Chromosomal microarray, or advanced molecular testing.

Amniocentesis is another invasive method performed by a professional radiologist between the gestational ages of 16 and 20 weeks after informed consent, in which a needle is introduced to aspirate amniotic fluid. Regardless of the prenatal diagnosis following CVS or amniocentesis, each individual has their own emotional, psychological, economical, and religious reasons for continuing the pregnancy or deciding for a medical termination in the event of abnormalities to decrease burden with the advent of genomics. Genetic testing for preimplantation embryos is being developed.

3.3.2 Pre-implantation genetic testing (PGT)

Is a genetic test that is conducted on embryos during IVF prior to implantation in the uterus. The term *PGT-A* involves the detection of Aneuploidies in all chromosomes whereas *PGT-SR* identifies structural rearrangements in all chromosomes such as translocations, inversions etc. *PGT-M* is for identification of a single gene condition with a known diagnosis in the family history. PGT is typically chosen for patients with advanced maternal age, recurrent pregnancy losses, and a strong family history of genetic disorders.

3.4 Implications of chromosomal abnormalities

Some common conditions, such as primary amenorrhea, infertility, recurrent pregnancy loss, syndromes such as Down, Edward, Patau, and hematological malignancies, are connected or associated with chromosomal abnormalities.

3.4.1 Primary amenorrhea

It is a condition in which females of reproductive age are unable to achieve menarche and lack certain secondary sexual characteristics. This is caused by monosomy X (45,XO) or isochromosome X or partial deletion on X chromosome, as well as other chromosomal abnormalities such as ring chromosome X. Following confirmation of diagnosis via karyotyping or FISH, appropriate care, such as hormonal therapy and subsequent ART (Assisted Reproductive Techniques) recommendations are elucidated.

3.4.2 Primary and secondary infertility

Primary infertility refers to the inability to conceive after two year of unprotected intercourse, whereas secondary infertility is inability to sustain to term pregnancy. These may be due to chromosomal abnormalities, hormone imbalances, anatomical inabilities, and other factors. One of the most common chromosomal abnormalities associated with infertility are Turner, Klinefelter, Swyer syndrome and translocations.

3.4.3 Recurrent pregnancy loss

The most common reason of recurrent pregnancy losses (RPL) is chromosomal abnormalities. Balanced translocations, inversions and polymorphic variants are commonly observed in RPL. Maternal age is one of the risk factors for recurrent pregnancy loss, which increases the incidence of trisomies.

3.4.4 Syndromes

Most of the common genetic syndromes are caused due to numerical and structural chromosomal abnormalities. DS is caused gain of chromosome 21, TS is due to monosomy X and Cri du chat is caused due to partial deletion on the chromosome 5 respectively. These syndromes are associated with clinical features like developmental delay, speech difficulties, hearing impairment, feeding difficulties, cardiac defects and intellectual disability.

3.4.5 Malignancies

Identification of chromosomal abnormalities is useful in the diagnosis, treatment, management, and prognosis of several hematological and solid malignancies. Specific chromosomal abnormalities can help in the differential diagnosis and therapy planning of various malignancies. Balanced translocations, inversions, partial deletions, trisomies, and other chromosomal abnormalities are common in hematological malignancies. Some of the translocations seen in acute myeloid leukemia are t (8:21) and t(9:22) in chronic myeloid leukemia, both of which result in the proliferation of numerous myeloid lineages. In the case of primary MDS, del 5q and del 7q, as well as translocations such as t(11:16) and t(3:21), have been often reported. Some structural rearrangements have a strong relationship with clinical and morphological characteristics.

4. Conclusion

Identification of Chromosomal abnormalities plays an immense role in the diagnosis, treatment/management, risk assessment, extended family screening and it also helps in taking appropriate informed decisions. Increasing awareness and implementation of certain genetic testing policies in the health care sector helps in prevention and control of genetic diseases.

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