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Research Article

Genotoxicity and Chromosomal Instability: A Comprehensive Review of Aberration Types, Mechanisms, and Applications

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ABSTRACT

Chromosomes experience structural or numerical alterations known as chromosomal aberrations when normal chromosomal integrity is compromised. These changes are brought on by damage to DNA, errors in replication, or defects in the mitotic spindle during cell division. While aneuploidy and polyploidy are instances of numerical aberrations, which involve differences in the number of chromosomes, structural aberrations include chromosomal splits, deletions, translocations, bridges, and stickiness. Since chromosomes store essential genetic information, any alteration in their number or structure may have an impact on cellular function and compromise genomic stability. Since chromosomal abnormalities immediately show harm to genetic material, they are commonly accepted as trustworthy indicators of genotoxicity. Environmental contaminants, pesticides, industrial chemicals, radiation, and medications can all cause chromosomal damage that manifests during mitosis. An elevated rate of aberrations indicates that a drug could interfere with chromosomal segregation or disrupt DNA integrity. Analysis of chromosome aberrations is an integral part of genetic toxicology and safety assessment. Chromosome aberration analysis is widely applied in environmental monitoring, cancer research, occupational health, regulatory toxicology and pharmaceutical development. They can be used in environmental studies to determine the genetic impacts of pollutants. They are utilized to predict genotoxicity potential of developing compounds before clinical exposure.

1. INTRODUCTION

Long DNA molecules that are tightly wound around histone proteins to form chromatin make

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up the highly dynamic nucleoprotein complexes known as chromosomes. Their arrangement guarantees accessibility for transcription, replication, and repair while enabling effective packing of genetic material. Chromosomes go through exact segregation during mitosis or meiosis and precise duplication in the S phase of the cell cycle. DNA repair pathways, spindle assembly checkpoints, cohesin complexes, and centrosome function all closely control this process[1]. Any interference with these regulatory systems leads to chromosomal abnormalities and jeopardizes genomic integrity.

Chromosome segments can be deleted, duplicated, inverted, or incorrectly reconnected when repair processes including homologous recombination (HR) or non-homologous end joining (NHEJ) function incorrectly. This results in ring chromosomes, dicentric chromosomes, inversions, translocations, deletions, and duplications. These structural changes can change the dosage of genes, activate oncogenes, or interfere with tumor suppressor genes [2].

The primary cause of numerical aberrations is nondisjunction events that occur during meiosis or mitosis. Numerous malignancies and developmental problems are characterized by aneuploidy. About 0.5–1% of live births in humans have chromosomal abnormalities [3]. Nevertheless, they are far more common in early embryonic loss, accounting for 50–60% of spontaneous abortions in the first trimester. About 1 in 700 babies are born with trisomy 21 (Down syndrome), which is linked to congenital cardiac abnormalities and intellectual disabilities [4]. While Klinefelter syndrome (47, XXY) affects around 1 in 600 men and is associated with infertility and hypogonadism, Turner syndrome (45, X) affects 1 in 2500 female births and causes ovarian failure and low stature [5].

The genesis of cancer is largely dependent on structural chromosomal rearrangements. Ninety to ninety-five percent of patients of chronic myeloid leukemia have the Philadelphia chromosome t(9; 22) (q34; q11), which causes the BCR-ABL fusion oncogene to develop [6]. The predictive usefulness of chromosomal abnormalities in peripheral blood cells as biomarkers is shown by epidemiological studies that show that people with these abnormalities have a two to three times higher chance of developing cancer [7].

Chromosome abnormalities in plants result in heritable mutations, decreased seed viability, pollen sterility, inhibited root elongation, and decreased mitotic activity. The Allium cepa test, a trustworthy biomarker of ecosystem genotoxic stress, may identify chromosomal damage caused by environmental contaminants such heavy metals, industrial effluents, and pesticides [8].

All things considered, chromosomal abnormalities are important markers of genomic instability that have significant effects on environmental health, carcinogenesis, developmental problems, and reproductive failure. Clinical genetics, toxicology, cancer, and regulatory risk assessment all still rely heavily on their research.

2. Historical Background of Chromosomal Aberration Studies

Walter Sutton and Theodor Boveri developed the chromosome theory of inheritance at the beginning of the 20th century, which laid the scientific groundwork for the study of chromosomal aberration. They separately postulated in 1902 and 1903 that chromosomes are the physical bearers of genetic information, and that Mendelian inheritance patterns may be explained by their activity during meiosis [9]. The conceptual foundation for associating genetic illnesses with chromosomal anomalies was supplied by this idea.

Table 1 represented studies conducted on chromosomes.

Table 1: Studies Condcted on Chromosomes.

Year	Scientist(s)	Discovery / Contribution	Key Findings	Significance in Chromosomal Aberration Studies	Reference No.
1902–1903	Walter Sutton & Theodor Boveri	Chromosome Theory of Inheritance	Proposed that chromosomes are physical carriers of genetic information and explain Mendelian inheritance through meiosis	Established the conceptual foundation linking chromosomal abnormalities with genetic diseases	[14]
1928	Hermann Muller	X-ray Induced Mutations in Drosophila melanogaster	Demonstrated that ionizing radiation causes heritable mutations; observed chromosomal breaks and rearrangements	Proved radiation as a clastogenic agent; connected environmental exposure to chromosomal damage	[15]
1938	Albert Levan	Effect of Colchicine on Mitosis	Identified C-mitosis due to spindle fiber inhibition; chromosomes fail to segregate properly	Demonstrated that chemicals can induce numerical aberrations (aneuploidy, polyploidy) without DNA breakage	[16]
1940s–1960s	Cytogenetic Researchers	Development of Plant Cytogenetic Models (Allium cepa, Vicia faba)	Enabled visualization of chromosomal bridges, laggards, micronuclei after exposure to mutagens	Provided simple, cost-effective systems for studying chromosomal damage	[17]
1960s onwards	Mammalian Cytogenetic Studies	Development of Mammalian Cell Culture Assays	Allowed direct assessment of chromosomal aberrations in human and animal cells	Laid the foundation for modern genotoxicity and regulatory safety testing	[18]

Hermann Muller's 1928 discovery that X-rays might cause mutations in Drosophila melanogaster was a significant breakthrough in the understanding that ionizing radiation can result in genetic damage that is heritable[10]. Radiation exposure causes chromosomal breakage, deletions, and translocations that are apparent during cell division, according to later cytological research. Radiation is a potent clastogenic agent, as evidenced by the frequent appearance of dicentric chromosomes and chromosomal fragments in irradiated cells.

Albert Levan made another significant discovery in 1938 when he showed how colchicine affected plant cell mitosis[11]. By interfering with microtubule polymerization, colchicine prevents the development of spindle fibers. Levan explained a disorder called C-mitosis, where chromosomes stay dispersed throughout the cell due to improper segregation. This finding was significant because it demonstrated that chemicals may create numerical chromosomal abnormalities (polyploidy and aneuploidy) without actually damaging DNA. For example, failing cytokinesis causes root tip cells treated with colchicine to frequently become polyploid.[12]

Because of their big chromosomes and high mitotic index, plant models like Allium cepa and Vicia faba were utilized extensively in cytogenetic study after these findings [13]. Following chemical or radiation exposure, these techniques made it possible to clearly see chromosomal bridges, laggards, and micronuclei. The discipline was further broadened by mammalian cell culture techniques, which made it possible to directly evaluate chromosomal damage in both human and animal cells.

These historical turning points collectively created the experimental and scientific basis for contemporary chromosomal aberration tests utilized in genetic toxicology and safety assessment.

3. Classification of Chromosomal Aberrations

CA are divided into numerical and structural kinds according to the type of chromosomal abnormality. Because it aids in determining the underlying mechanism of damage and whether the causative agent interferes with the mitotic spindle to disrupt chromosomal segregation (aneugenic activity) or directly damages DNA (clastogenic action), this categorization is essential in cytogenetics[19].

Physical alterations in chromosome architecture are known as structural chromosomal aberrations, and they are typically caused by DSB in DNA. Ionizing radiation, oxidative stress, alkylating agents, insecticides, and other genotoxic substances can all cause these fractures. Aberrant rejoining of chromosomal fragments can happen when DNA repair processes like HR or NHEJ operate incorrectly. The following are examples of structural abnormalities: dicentric chromosomes (chromosomes with two centromeres), ring chromosomes, deletions (loss of a chromosome segment), duplications (gain of a segment), inversions (reversal of a segment), and translocations (exchange of segments between non-homologous chromosomes)[20]. These changes may contribute to cancer and developmental abnormalities by activating oncogenes, disrupting gene expression, or deactivating tumor suppressor genes.

Contrarily, numerical chromosomal aberrations refer to variations in the number of chromosomes rather than their structure. The main cause of these anomalies is non disjunction during meiosis or mitosis brought on by deficiencies in the spindle machinery, aberrant centrosomes, or checkpoint failure. Aneuploidy, or the gain or loss of

individual chromosomes, and polyploidy, or the acquisition of whole sets of chromosomes, are examples of numerical aberrations [21]. Aneuploidy is frequently seen in genetic conditions like trisomy 21 and is a hallmark of several malignancies.

Therefore, a clear framework for comprehending genotoxicity mechanisms and evaluating genetic risk in clinical and toxicological investigations is provided by the categorization of chromosomal abnormalities into structural and numerical groups.

3.1 Structural Chromosomal Aberrations

Due to the simultaneous disruption of both strands of the DNA helix, double-strand breaks are regarded as one of the most serious types of DNA damage. Chromosome fragments may be destroyed, misjoined, or altered if these breaks are not appropriately repaired by processes such (HR) or (NHEJ), which might cause obvious structural abnormalities during metaphase analysis [22].

Depending on when the damage occurs during the cell cycle, structural aberrations are divided into two categories: chromatid-type and chromosome-type. Chromatid-type aberrations happen when just one sister chromatid is impacted by DNA damage that occurs after replication (during the S or G2 phase). On the other hand, chromosome-type aberrations develop when damage occurs during the G1 phase, before to DNA replication, and results in changes to both sister chromatids[23]. Because it sheds light on the stage of the cell cycle in which the harmful chemical acts, this difference is crucial in genotoxicity investigations.

Typical structural chromosomal abnormalities include ring chromosomes, dicentric chromosomes (two centromeres), acentric fragments (without a centromere), reciprocal translocations (exchange of segments between non-homologous chromosomes), deletions (loss of a chromosome segment), duplications (gain of a segment), and inversions (reversal of a segment within the chromosome)[24]. Major inducers of these structural alterations include ionizing radiation, heavy metals (such as lead and cadmium), alkylating chemicals, petroleum derivatives, pesticides, and some chemotherapeutic medications.

Because structural chromosomal abnormalities can result in gene loss, gene fusion, altered gene expression, chromosomal instability, and the activation of oncogenes or inactivation of tumor suppressor genes, they are of great biological significance. Chromosome translocations, for instance, are commonly seen in hematological malignancies, where they aid in the development of cancer[25]. Structural abnormalities are therefore important indicators of genotoxic exposure and carcinogenic risk.

3.1.1 Chromosome and Chromatid Breaks

The simplest and most fundamental types of structural chromosomal abnormalities are chromosome and chromatid breaks. During metaphase analysis, they manifest cytologically as discernible gaps or discontinuities in chromosomal structure. The main cause of these fractures is DNA (DSBs), which are not precisely repaired by cellular repair systems. DNA double-strand breaks are regarded as essential lesions in genomic stability because they directly jeopardize chromosomal integrity [26].

The breaking of both sister chromatids at the same location results in chromosome breakage. These usually occur when DNA damage is caused prior to DNA replication, during the G_1 phase of the cell cycle. The break is replicated as replication goes on, giving both sister chromatids the same lesions.

Chromatid breaks, on the other hand, often happen when DNA damage occurs during the S or G phase following replication and only impact one sister chromatid [27]. Important details on the timing of exposure to genotoxic substances may be gleaned from this distinction between chromosome-type and chromatid-type breaks.

Chromosome and chromatid breaks are known to be induced by clastogenic agents, which include ionizing radiation, alkylating drugs (like cyclophosphamide), heavy metals, petroleum derivatives, and environmental contaminants. For instance, alkylating chemicals frequently cause chromatid-type aberrations, whereas X-ray irradiation results in chromosome-type breaks and acentric fragments[28]. The translocation between chromosomes 9 and 22 in chronic myeloid leukemia, which results from DNA breakage and improper rejoining, is a well-known example of how chromosomal breakage can cause translocations in cancer cytogenetics [29].

Breaks in chromosomes and chromatids have important biological ramifications. They might lead to ring chromosomes, dicentric chromosomes, reciprocal translocations, deletions, and genetic material loss. Oncogenes, tumor suppressor genes, and chromosomal instability can all be caused by persistent or improperly repaired breaks. In order to stop genetically unstable cells from proliferating, severe DNA damage may cause apoptosis or checkpoint activation, which will stop the cell cycle [30]. As a result, chromosomal and chromatid breaks are important markers of genotoxic exposure and are essential for the development of genetic diseases and cancer.

3.1.2 Deletions

A deletion occurs when a section of a chromosome is permanently deleted due to DNA breaking and improper rejoining, resulting in a structural chromosomal abnormality. DS DNA breaks brought on by ionizing radiation, oxidative stress, replication mistakes, or exposure to clastogenic chemicals are often the source of deletions. Partial monosomy, in which one copy of a certain gene is absent from the genome, results when a fragmented chromosomal fragment lacks a centromere (acentric fragment), which prevents it from attaching to the spindle machinery during cell division and causes it to be lost [31].

There are two primary categories of deletions: interstitial and terminal deletions. Terminal deletions occur when a break happens near the end of a chromosome and the distal fragment is lost. Two breaks inside a single chromosome cause interstitial deletions, which result in the reconnecting of the surviving ends and the loss of an internal region [32]. Since bigger deletions eliminate several genes, the severity of the phenotypic effects depends on the extent of the deleted area.

Deletions frequently have major biological implications because they result in permanent gene loss. Cell cycle control, developmental signaling, and metabolic pathways can all be affected by the loss of vital genes. For instance, Cri-du-chat syndrome, which is characterized by intellectual impairment and developmental delay, is brought on by the deletion of chromosome 5's short arm (5p deletion)[33]. Similarly, by eliminating important regulatory controls on cell proliferation, the deletion of tumor suppressor genes like TP53 or RB1 aids in the development of cancer [34].

Developmental defects, congenital deformities, decreased cell viability, and an increased risk of cancer are among the aberrant outcomes of deletions. Large deletions are incompatible with life under extreme circumstances and can cause spontaneous abortion. Therefore, chromosomal

deletions are an important class of structural abnormalities that have significant effects on carcinogenesis and genetic illness.

3.1.3 Duplications

A structural chromosomal abnormality known as a duplication occurs when a chromosome section is repeated, giving rise to an extra copy of one or more genes. When the number of gene copies surpasses the typical diploid condition, this results in a gene dosage imbalance. Proper cellular function depends on tightly regulated gene expression; therefore, an increase in gene copy number can disturb regulatory balance and cellular homeostasis [35].

When homologous chromosomes misalign during recombination, one chromosome gains more genetic information while the other loses it. This phenomenon is known as unequal crossing over. Replication errors, particularly replication slippage, may also produce tandem duplications. In somatic cells, misrepair of chromosomal breaks through (NHEJ) can generate duplicated segments [36].

Duplications may be divided into two categories: interspersed duplications, in which the repeated segment is introduced somewhere else in the genome, and tandem duplications, in which the duplicated segment is situated next to the original section. The size of the duplicated area and the functional significance of the genes involved determine the phenotypic impact of duplication.

Gene overexpression is the main cause of the aberrant outcomes of duplications. Elevated gene dosage can change regulatory networks, interfere with developmental signals, and disturb metabolic processes. For instance, Charcot-Marie-Tooth disease type 1A, a peripheral neuropathy marked by muscular weakness and sensory loss, is brought on by a duplication of the PMP22 gene on chromosome 17 [37]. Segmental duplications are also commonly seen in cancer cells, when oncogene amplification leads to unchecked cell division [4].

In terms of biology, duplications can result in developmental abnormalities, metabolic imbalance, genetic instability, and heightened vulnerability to cancer. Duplications are important contributions to genetic diseases and carcinogenesis, although being typically less severe than deletions due to their long-term effects on gene regulation and chromosomal stability.

3.1.4 Inversions

When a chromosome section splits twice and the intervening portion is reinserted in the opposite (180°) orientation, it results in an inversion, a structural chromosomal anomaly. Inversions change the linear arrangement of genes inside the chromosome, but they often do not result in a net loss or gain of genetic material, in contrast to deletions or duplications. Usually, inversions result from aberrant recombination events during meiosis or from improper repair of DNA DSB [38].

Depending on whether the centromere is involved, inversions can be divided into two primary categories. When just one chromosomal arm is involved and the centromere is absent, this is known as a paracentric inversion. On the other hand, a PI spans both chromosomal arms and contains the centromere [39]. Because the two kinds have different meiotic implications, this differentiation is crucial.

Despite the fact that people with balanced inversions frequently have normal phenotypes, meiosis can cause issues. An inversion loop is created during pairing in order to correctly align homologous chromosomes. It is possible for

aberrant chromatids to form if crossing over takes place within this loop. Recombination can result in dicentric (two centromeres) and acentric (no centromere) chromosomes in paracentric inversions; these are often nonviable. Recombination can produce chromosomes with deletions and duplications in pericentric inversions, which can produce imbalanced gametes [40].

The biological repercussions of inversions include inhibition of recombination within the inverted area, creation of defective gametes, lower fertility, recurrent miscarriage, and higher risk of secondary chromosomal abnormalities in kids. For instance, while many carriers of pericentric inversion of chromosome 9 continue to be clinically normal, it has occasionally been linked to reproductive issues [41].

Therefore, inversions are important in reproductive genetics and cytogenetic analysis even if they do not directly change gene dosage because of their effects on meiotic recombination and chromosomal stability.

3.1.5 Translocations

The exchange or rearrangement of chromosome segments between non-homologous chromosomes is a characteristic of structural chromosomal abnormalities known as translocations. They are mostly caused by double-strand breaks in DNA that are not properly repaired by means of (NHEJ). Normal chromosomal architecture is altered when genetic material is changed due to the accidental joining of damaged chromosome ends from separate chromosomes [42].

Robertsonian and reciprocal translocations are the two main categories of translocations. Segments of two non-homologous chromosomes are swapped in RT, but no genetic material is lost or gained overall. Although they may have reproductive issues, people with balanced RT frequently have normal phenotypes. Atypical chromosomal pairing during meiosis can result in imbalanced gametes, raising the possibility of infertility, repeated miscarriages, or children with congenital defects [43].

In a Robertsonian translocation, two acrocentric chromosomes—typically chromosomes 13, 14, 15, 21, or 22—fuse at or close to their centromeres. Short arms, which typically carry repeating ribosomal RNA genes, are lost as a result of this fusion, which creates a single big chromosome. One well-known example is the Robertsonian translocation of chromosome 21, which, if inherited, can result in familial Down syndrome [44].

Translocations are very important in the biology of cancer. Oncogenes or fusion genes that promote malignant transformation are activated by certain chromosomal translocations. The translocation of chromosomes 9 and 22, which creates the Philadelphia chromosome and results in the BCR-ABL fusion gene in chronic myeloid leukemia, is a well-known example[45]. These rearrangements cause chromosomal instability in tumor cells, change the way genes are regulated, and encourage unchecked cell division.

Changes in gene expression, oncogene activation, infertility, repeated pregnancy loss, and genomic instability are among the aberrant outcomes of translocations. Translocations are therefore important in both cancer cytogenetics and clinical genetics.

3.1.6 Ring and Dicentric Chromosomes

The main cause of ring and dicentric chromosomes, which are intricate structural chromosomal abnormalities, is incorrect DNA

DSB repair. These anomalies, which are commonly seen after exposure to ionizing radiation and potent clastogenic chemicals, are thought to be signs of significant chromosomal damage [46].

When two chromosomal terminal ends split and then fuse together to form a circular shape, ring chromosomes are created. Genetic material is partially deleted as a result of the frequent loss of distal chromosomal segments devoid of centromeres throughout this process. Because ring chromosomes' circular form obstructs normal chromosomal alignment and separation, they may multiply and segregate improperly during mitosis. Ring chromosomes 14 and 20, for instance, have been linked to growth abnormalities, developmental delays, and epilepsy[47]. The quantity of genetic material lost during ring formation determines the clinical severity.

Dicentric chromosomes contain two centromeres and are typically formed when broken chromosome fragments from different chromosomes fuse abnormally. Spindle fibers cling to both centromeres during mitosis and draw them in opposing directions to the poles during anaphase. The mechanical stress caused by this opposing strain frequently leads to chromosomal breakage and the development of anaphase bridges [48]. As a result, dicentric chromosomes are extremely unstable and are thought to be indicative of chromosomal damage brought on by radiation.

Chromosome breaking during anaphase, mitotic arrest, apoptosis, and chronic genomic instability are among the aberrant outcomes of ring and dicentric chromosomes. Barbara McClintock was the first to define the recurring breakage–fusion–bridge cycle, which leads to cancer and progressive chromosomal rearrangements[49]. In biological dosimetry, dicentric chromosome tests are frequently employed to quantify radiation dosage in exposed people because of their significant correlation with radiation exposure [50].

All things considered, ring and dicentric chromosomes are serious structural anomalies that jeopardize chromosomal integrity and are crucial for the development of cancer, radiation biology, and genetic illness.

3.1.7 Anaphase Bridges

When chromosomes fail to segregate correctly during the anaphase stage of mitosis or meiosis, cytogenetic abnormalities known as anaphase bridges are seen during cell division. Sister chromatids often split apart and travel in opposing directions to the cell's poles. However, the chromatids stay physically attached when there are structural chromosomal defects, such as dicentric chromosomes, chromosome stickiness, or incorrectly repaired DNA DSB. The consequence is an anaphase bridge, which is a stretched strand of chromatin that is visible between the dividing cell's two poles [51].

The existence of dicentric chromosomes, which have two centromeres, is one of the most frequent sources of anaphase bridges. The chromosome is stretched during anaphase by the mechanical stress created by spindle fibers attaching to both centromeres and pulling them in opposing directions. Bridge formation can also result from chromosomal ends fusing together due to telomere dysfunction or malfunctioning DNA repair mechanisms [52]. This anomaly is known to be induced by ionizing radiation, chemical mutagens, and other clastogenic agents.

The breakage–fusion–bridge (BFB) cycle, which Barbara McClintock initially described, is a significant effect of anaphase bridges. Mechanical stress causes the stretched chromosome to break at the end of this cycle. Repeated rounds of breaking

and rearrangement may result from the broken ends fusing once more in later cell cycles [53]. New chromosomal rearrangements, gene amplifications, deletions, and general genomic instability are the outcomes of this process.

In cytogenetic tests, anaphase bridges are regarded as potent markers of clastogenic damage and are also linked to an elevated mutation rate. In order to evaluate the potential for chromosomal damage caused by chemicals and environmental contaminants, genotoxicity testing commonly uses their presence [54].

All things considered, anaphase bridges are a clear symptom of extreme chromosomal instability and are important for mutagenesis and carcinogenesis. Table 2 represented types of aberration.

Table 2: Types of Chromosomal Aberration

Type of Aberration	Definition / Mechanism	Cell Cycle Phase	Key Features	Major Biological Consequences	Example
Chromosome Breaks	Breakage of both sister chromatids at the same site due to DNA double-strand breaks (DSBs)	G_1 phase (before replication)	Visible discontinuity in both chromatids	Gene loss, translocations, dicentric formation, apoptosis	X-ray–induced chromosome breaks
Chromatid Breaks	Break affecting only one chromatid after DNA replication	S or G_2 phase	Single chromatid gap or break	Mutation, chromosomal instability	Alkylating agent–induced damage
Deletions	Loss of a chromosomal segment due to breakage and failure of rejoining	Any phase (commonly G_1)	Terminal or interstitial loss	Partial monosomy, developmental defects, cancer risk	Cri-du-chat syndrome
Duplications	Repetition of a chromosome segment due to unequal crossing over or replication errors	Meiosis / S phase	Tandem or interspersed repeats	Gene dosage imbalance, overexpression	Charcot-Marie-Tooth disease type 1A
Inversions	Chromosome segment reinserts in	Meiosis	Paracentric (no centromere) or Pericentric	Suppressed recombination,	Pericentric inversion of chromosome 9

	reverse orientation after two breaks		(includes centromere)	abnormal gametes, infertility	
Reciprocal Translocations	Exchange of segments between non-homologous chromosomes	Any phase (DSB misrepair)	Balanced or unbalanced rearrangement	Oncogene activation, infertility	Chronic myeloid leukemia (Philadelphia chromosome)
Robertsonian Translocations	Fusion of two acrocentric chromosomes at centromere	Meiosis	Single large chromosome formed	Familial Down syndrome, miscarriage	Down syndrome (familial type)
Ring Chromosomes	Terminal breaks followed by end-to-end fusion forming circular chromosome	Any phase	Loss of distal fragments	Developmental delay, epilepsy, instability	Ring chromosome 14
Dicentric Chromosomes	Chromosome with two centromeres due to abnormal fusion	Any phase	Pulled to opposite poles during mitosis	Anaphase bridges, breakage–fusion–bridge cycle	Radiation-induced dicentrics
Anaphase Bridges	Failure of chromatid separation during anaphase	M phase	Stretched chromatin between poles	New rearrangements, increased mutation rate	Observed in radiation exposure

3.2 Numerical Chromosomal Aberrations

Errors in chromosome segregation during mitosis or meiosis are the primary source of numerical chromosomal aberrations, which are variations in the number of chromosomes in a cell. In contrast to structural anomalies, they are caused by flaws in the spindle machinery, centromere function, or kinetochore–microtubule attachment rather than chromosomal breakage. The most frequent process is nondisjunction, which results in daughter cells with uneven amounts of chromosomes when sister chromatids or homologous chromosomes fail to separate correctly [55].

These anomalies fall into two categories: polyploidy (gain of whole sets of chromosomes) and aneuploidy (loss or gain of individual chromosomes). Down syndrome, which results from trisomy of chromosome 21 owing to meiotic nondisjunction, is a well-known example of aneuploidy [56]. Turner syndrome, which is caused by the loss of one X chromosome, is another example [57]. Additionally prevalent in cancer

cells, aneuploidy promotes chromosomal instability and tumor growth [58].

Neugenic drugs like vincristine and colchicine, which interfere with correct chromosomal segregation and impair spindle fiber development, are the primary cause of numerical aberrations [59]. These anomalies are important from a clinical and toxicological standpoint since they can result in cancer, infertility, developmental problems, and spontaneous abortion. Rather of direct DNA damage, numerical aberrations are used as indications of spindle toxicity in genotoxicity testing.\

3.2.1 Aneuploidy

The term "aneuploidy" describes a chromosome number that differs from the typical diploid set due to the acquisition or deletion of one or more distinct chromosomes. One of the most prevalent numerical chromosomal anomalies, it typically results from lagging chromosomes during anaphase, nondisjunction, or spindle failure[60]. Chromosomes do not segregate evenly when spindle fibers do not adhere correctly to the centromere (kinetochore), resulting in daughter cells that have excess or absent chromosomes.

Nondisjunction, which can happen during mitosis, meiosis I, or meiosis II, is the main mechanism. Cells with trisomy (2n+1) or monosomy (2n−1) result from this. Down syndrome is a well-known example, which is brought on by meiotic nondisjunction and results in an extra copy of chromosome 21 [61]. Turner syndrome, in which one X chromosome is missing, is another example [62]. Tumor cells are also commonly found to be aneuploid, which promotes chromosomal instability and the development of cancer [63].

Gene dosage imbalance occurs in aneuploid cells, which means that the aberrant chromosome count modifies the amounts of gene expression. Normal development, regulatory processes, and cellular metabolism are all disrupted by this imbalance [64]. Clinically, aneuploidy is linked to cancer, infertility, recurrent miscarriages, and birth defects.

The presence of lagging chromosomes, vagrant chromosomes, multipolar divisions, and micronuclei, which show aneugenic activity of the investigated substance, are indicators of aneuploidy in cytogenetic tests such the Allium cepa test[65]. Consequently, in the assessment of genotoxicity, aneuploidy is a significant indicator of spindle toxicity.

3.2.2 Polyploidy

When whole sets of chromosomes multiply, a cell is said to be polyploid if it has more than two complete chromosomal complements (e.g., 3n, 4n). It frequently happens as a result of endoreduplication, which is DNA replication without succeeding cell division, cytokinesis failure, or suppression of spindle formation [66]. The cell does not physically split as a result, but the number of chromosomes doubles.

Often, spindle poisons that disrupt microtubule assembly cause polyploidy. Colchicine is a well-known example; it binds to tubulin and inhibits the production of spindle fibers, resulting in chromosomal doubling without appropriate segregation [67]. Polyploidy in plants is frequently a healthy and normal process that promotes the growth of new species and increases size and vigor. Nonetheless, aberrant polyploidy in human cells is often associated with the development of illness and genetic instability [68].

Polyploid cells are commonly seen in tumors and may have a role in chromosomal instability and malignant transformation, according to cancer

biology [69]. Depending on the biological environment, persistent polyploidy may cause tumor growth, death, or cell cycle halt [70].

3.2.3 C-Mitosis

The distinctive numerical chromosomal abnormality known as C-mitosis (colchicine-mitosis) is brought on by total suppression of spindle fiber development, which results in metaphase arrest with chromosomes dispersed erratically throughout the cytoplasm. After administering colchicine to cells, Albert Levan was the first to report this phenomena [71]. It is regarded as a traditional sign of spindle poisoning action.

Spindle fibers pull sister chromatids to opposing poles after aligning chromosomes at the metaphase plate during normal mitosis. Because spindle formation is inhibited during C-mitosis, chromosomes are unable to move or align correctly. As a result, the cell is unable to finish its regular segregation. The cell may either re-enter interphase without cytokinesis or stay stopped in metaphase, resulting in cells with polyploidy, or duplicate sets of chromosomes [72].

Spindle-disrupting drugs such vincristine and colchicine, which prevent microtubule polymerization, frequently cause C-mitosis [73],[74].

Prolonged exposure can result in chronic polyploidy, chromosomal instability, and decreased cell viability, even though C-mitosis may be reversible if the chemical agent is eliminated early [75]. In genotoxicity investigations, it therefore functions as a significant indicator of spindle toxicity.

4. Mechanisms of Chromosomal Aberration Formation

Numerous interrelated molecular and cellular processes that jeopardize genome stability give rise to chromosomal abnormalities. DNA (DSBs), which are thought to be the most serious kind of DNA damage since both strands of the DNA helix break at the same time, are one of the main starting events. Ionizing radiation, UV exposure, chemical clastogens, environmental contaminants, and endogenous metabolic byproducts like reactive oxygen species can all cause DSBs [76].Structural chromosomal abnormalities such deletions, translocations, dicentric chromosomes, and ring chromosomes can result from improperly joining non-homologous pieces or from chromosome fragments remaining unrepaired if these breaks are not precisely healed. The Philadelphia chromosome, which is formed by the reciprocal translocation of chromosomes 9 and 22 in chronic myeloid leukemia, was initially identified by Janet Rowley [77] and is a typical example of DSB misrepair.

The effectiveness and precision of cellular DNA repair processes, especially (NHEJ) and (HR), are critical in determining the outcome of DSBs. Without the need for a homologous template, NHEJ ligates damaged DNA ends directly and is active throughout the cell cycle. Despite its speed, NHEJ is prone to errors and can result in translocations and intricate chromosomal rearrangements by causing tiny insertions, deletions, or misjoining of unrelated chromosome segments [78].

On the other hand, when a sister chromatid is available as a template, homologous recombination, a high-fidelity repair process, mostly functions during the S and G_2 stages. Although HR guarantees precise repair, genetic instability and cancer susceptibility are significantly increased by abnormalities in HR-related genes, such as BRCA1 and BRCA2 [79]. A

primary contributing factor to structural chromosomal abnormalities is an imbalance between these repair processes.

Replication stress is another important factor in the development of chromosomal abnormalities. DNA lesions, oncogene activation, nucleotide depletion, or interference with replication machinery can all cause replication stress, which is the slowing or stopping of DNA synthesis. Replication forks that have been stopped may collapse, forming additional DSBs that are challenging to properly repair [80].

Chromatid breakage, chromosomal fragmentation, and incomplete replication are caused by persistent replication stress and manifest as structural abnormalities during metaphase analysis. It is now known that chromosomal instability in many malignancies is primarily caused by replication stress [81].

Another important factor in chromosomal damage is oxidative stress. DNA bases can be damaged and single- and double-strand breaks can result from reactive oxygen species (ROS), which are produced both endogenously during mitochondrial respiration and exogenously by radiation, heavy metals, and xenobiotics. Chromosome deletions, breaks, and rearrangements are more likely when antioxidant defense systems are overloaded because oxidative lesions build up and obstruct DNA replication and repair [82].

Age, neurological diseases, and carcinogenesis are all closely linked to chronic oxidative stress.Apart from DNA-targeted processes, the spindle machinery that is in charge of precise chromosome segregation can also be disrupted, leading to chromosomal abnormalities. The spindle fibers that divide sister chromatids during anaphase and arrange chromosomes at the metaphase plate are made of microtubules. Spindle dysfunction is caused by substances called spindle poisons or aneugens, such as vincristine and colchicine, which obstruct microtubule polymerization or depolymerization [83].Aneuploidy, polyploidy, lagging chromosomes, and C-mitosis are examples of numerical chromosomal abnormalities that result from chromosomes failing to segregate evenly. For instance, in plant tests like the Allium cepa test, spindle inhibition brought on by colchicine results in distinctive C-mitotic patterns [84].In general, spindle malfunction and mistakes in chromosome segregation are the major causes of numerical chromosomal abnormalities, while DNA damage and flawed repair mechanisms are the main causes of structural chromosomal aberrations. The kind and degree of chromosomal abnormalities are ultimately determined by the interaction of DNA DSBs, compromised repair pathways, replication stress, oxidative imbalance, and spindle disruptions. Interpreting the results of genotoxicity tests and assessing the genetic hazards associated with industrial, pharmacological, and environmental agents need an understanding of these pathways.[85]

5. Endogenous and Exogenous Causes of Chromosomal Aberrations

When endogenous factors—which come from within the cell—combine with external factors—which come from exposure to the environment, the workplace, or a treatment—chromosomal abnormalities result. Both groups are essential for causing damage to DNA, upsetting chromosomal integrity, and preventing regular cell division. For instance, DNA cross-linking caused by the exogenous chemical agent Mitomycin C, an anticancer medication, prevents replication and causes chromosome breakage and structural abnormalities during mitosis[86]. Drug safety, environmental toxicity, and genetic risk

assessment all depend on an understanding of these causal variables (1,2).

5.1 Endogenous Factors

Numerous endogenous (internal) and exogenous (external) factors that harm DNA or obstruct chromosome segregation can result in chromosomal abnormalities. In the end, these variables cause structural or numerical chromosomal abnormalities by either directly causing DNA strand breaks or indirectly interfering with replication and repair processes[87].

Reactive oxygen species (ROS), which are produced during regular metabolism, are one of the most important endogenous factors. Oxygen undergoes partial reduction during mitochondrial oxidative phosphorylation, producing reactive compounds such hydrogen peroxide, superoxide anion, and hydroxyl radicals. These compounds are normally neutralized by antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase[88]. On the other hand, oxidative stress happens when ROS generation surpasses antioxidant capability. ROS may create single-strand breaks, alter DNA bases (for example, by forming 8-oxoguanine), and create double-strand breaks if lesions are found on opposing strands. Chromosome translocations, rings, dicentrics, and deletions occur when such damage is not repaired [89]. Excess ROS causes chromosomal instability in real-world biological contexts, such as aging and chronic inflammatory disorders.

Deamination and spontaneous base loss are significant endogenous sources. Because DNA is chemically fragile, it can undergo hydrolytic events such deamination, which turns cytosine into uracil, and depurination, which results in the loss of adenine or guanine. These procedures disrupt the DNA backbone by producing mismatched bases and abasic sites. Chromatid breakage and structural abnormalities may happen if replication continues before appropriate repair [90]. For instance, chromosomal damage and point mutations may arise if uracil residues created by cytosine deamination are not repaired.

During DNA synthesis, replication mistakes are also unavoidable, particularly in cells that divide quickly. Strand breakage and incomplete replication products can result from nucleotide misincorporation, replication fork stalling, or fork collapse. Replication stress, a characteristic of cancer cells, is increased by circumstances like nucleotide imbalance or oncogene activation. Chromosome fragmentation and chromatid-type abnormalities are often caused by improper resolution of stalled forks [91-92].

Chromosome aberrations are also greatly influenced by outside influences.Ionizing radiation, such as X-rays and gamma rays, damages DNA and chromosomal proteins by directly causing double-strand breaks in DNA and indirectly producing free radicals. It is frequently employed as a positive control in cytogenetic tests and causes distinctive abnormalities such translocations, dicentric chromosomes, ring chromosomes, and deletions [93].

Thymine dimers and other photoproducts are primarily created by ultraviolet (UV) light, which distorts the DNA helix and prevents replication. Double-strand breaks are not directly caused by UV, however replication mistakes and secondary chromosomal abnormalities can result from unrepaired photolesions. Skin malignancies are closely linked to long-term exposure [94].

Heavy metals and industrial chemicals including lead, mercury, cadmium, and chromium cause oxidative stress, block enzymes that repair DNA,

and disrupt the control of the cell cycle. Increased chromosomal abnormalities in exposed workers have been associated with occupational exposure [95].

Reactive metabolites produced by petroleum products and polycyclic aromatic hydrocarbons (PAHs) attach covalently to DNA to create DNA adducts and increase oxidative stress. Chromosome breakage and the risk of cancer have been linked to prolonged exposure [96].

Herbicides and pesticides are significant genotoxins in agriculture. While some damage spindle fibers to operate as aneugens, others act as clastogens, breaking chromosomes. Agricultural laborers exposed to these chemicals have greater frequency of chromosomal aberrations, according to cytogenetic research [97].

Some medications, such as spindle inhibitors like vincristine and anticancer medications like cyclophosphamide, purposefully damage DNA or interfere with mitosis to kill cancer cells, but they can also produce chromosomal abnormalities in healthy cells. Chromosome aberration testing is thus required for preclinical medication safety assessment [98].

Lastly, a number of synthetic colors and food additives have shown clastogenic potential in experimental systems when ingested in high doses, underscoring the necessity of ongoing toxicological monitoring [99].
In general, inherent DNA instability and metabolic byproducts are the main sources of endogenous processes, whereas exposure to environmental, occupational, nutritional, or medicinal variables is the source of exogenous factors [100]. Both types eventually lead to chromosomal abnormalities and jeopardize genome stability.

6. Detection and Assessment of Chromosomal Aberrations

The foundation of cytogenetic analysis and genetic toxicology is the identification and evaluation of chromosomal abnormalities. Numerous cytogenetic methods and bioassays have been created to detect chromosomal changes brought on by genotoxic substances, both structurally and numerically. These approaches, which vary from sophisticated molecular cytogenetic methods to traditional light-microscopy-based tests, each provide distinct benefits in terms of sensitivity, specificity, and mechanistic understanding[101]. When combined, they offer a thorough assessment of genotoxic risk in clinical, pharmacological, and environmental contexts.

6.1 Allium cepa Chromosomal Aberration Assay

One of the most used plant-based cytogenetic assays for assessing the genotoxic and cytotoxic effects of chemical and environmental contaminants is the Allium cepa chromosomal aberration assay. Since onion root meristem cells have a modest number of big chromosomes (2n = 16) and significant mitotic activity, chromosomal aberrations may be clearly seen under a light microscope, making them ideal for cytogenetic investigation. For instance, this test is frequently used by researchers to evaluate the genotoxicity of industrial effluent that is released into rivers. This assay's sensitivity and dependability for environmental monitoring are well established [102]. This technique involves letting onion bulbs sprout in distilled water before exposing them to varying amounts of a test material, such as pesticides, heavy metals, medications, or tainted water samples. Following exposure, root tips undergo hydrolysis, fixation, staining (such as acetocarmine), and microscopic inspection. The mitotic index (MI), which shows the proportion of

dividing cells, is one of the main endpoints assessed. Cytotoxicity is indicated by a decrease in MI. For instance, it has been demonstrated that exposure to water tainted with cadmium considerably lowers the mitotic index in onion root cells [103]. Chromosome stickiness, anaphase bridges, lagging and vagrant chromosomes, micronuclei production, C-metaphase, and multipolar divisions are among the many chromosomal abnormalities that the assay may identify[104].The Allium cepa test is widely used in environmental biomonitoring because of its ease of use, affordability, repeatability, and close applicability to mammalian genotoxicity systems. For instance, this technique has been used to assess agricultural runoff including pesticide residues in order to identify chromosomal abnormalities and increased micronucleus frequency in exposed root cells [105].

6.2 Mammalian Chromosomal Aberration Test

A common regulation cytogenetic test for identifying structural (clastogenic) and numerical (aneugenic) chromosomal aberrations in mammalian cells is the Mammalian Chromosomal Aberration Test. Because mammalian systems directly relate to risk assessment for human health, it is commonly employed in pharmaceutical, chemical, and environmental safety evaluations. International regulatory recommendations, such as those published by the International Council for Harmonization (ICH) and the Organization for Economic Co-operation and Development (OECD), propose the test [106].This experiment can be carried out in vitro using cultivated mammalian cell lines or in vivo, usually using rodent bone marrow cells (such those of mice or rats). Chinese hamster ovary (CHO) cells, V79 lung fibroblast cells, and human peripheral blood lymphocytes are examples of frequently utilized cell systems. For instance, CHO cells are favored due to their stable karyotype and high mitotic index, while human lymphocytes are commonly employed in pharmacological research due to their near resemblance to human genetic material [107].In order to mimic in vivo metabolism, cells are subjected to varying doses of the test drug both with and without metabolic activation (often a S9 liver fraction). A spindle inhibitor, such as colchicine or colcemid, is given after exposure to stop cells at metaphase, when the chromosomes are most visible and compacted. After that, the cells are extracted, preserved, stained (usually using Giemsa), and examined under a microscope to check for chromosomal abnormalities [108]. Chromosome splits, gaps, deletions, fragments, dicentric chromosomes, and translocations are among the structural abnormalities that the test can identify. Additionally, it detects numerical alterations like endoreduplication and polyploidy. For example, spindle poisons like vincristine cause polyploidy and aneuploidy (aneugenic effects), whereas alkylating drugs like cyclophosphamide cause chromosomal fractures and fragments (clastogenic effects) [109]. This assay is a necessary part of genotoxicity testing batteries that are necessary prior to medication approval since it may identify both clastogenic and aneugenic pathways. It is essential for determining possible mutagenic or carcinogenic risks and guaranteeing the genetic safety of industrial chemicals and medications [110].

6.3 Micronucleus Assay

A popular and extremely sensitive cytogenetic method for identifying chromosomal damage and genomic instability at the cellular level is the micronucleus test. In both experimental research and regulatory toxicology, it is regarded as one of the most trustworthy techniques for assessing genotoxicity [111]. Micronuclei are tiny, spherical, extranuclear entities that develop in the cytoplasm

of interphase cells, and the test detects their production.Acentric chromosomal fragments—chromosome portions without a centromere—or whole chromosomes that malfunction in their segregation during mitosis are the source of micronuclei. Such chromosomes or fragments produce distinct, smaller nuclei at telophase if they are not integrated into the major daughter nuclei. Therefore, structural or numerical chromosomal abnormalities are clearly indicated by the presence of micronuclei [112].The capacity of the micronucleus assay to identify both clastogenic (chromosome breakage) and aneugenic (chromosome loss or spindle apparatus failure) effects is one of its main benefits. Aneugens like spindle poisons disrupt chromosomal segregation, resulting in whole-chromosome micronuclei, whereas clotogens like ionizing radiation and alkylating chemicals create chromosome pieces that generate micronuclei [113].Numerous biological systems, such as bone marrow erythrocytes, peripheral blood lymphocytes, and cultured mammalian cells, can be used for the experiment. Pharmaceuticals and chemicals are often evaluated for regulatory safety using in vivo micronucleus testing in rodent bone marrow. In human biomonitoring investigations, the cytokinesis-block micronucleus (CBMN) test in peripheral blood lymphocytes is frequently employed [114].

Micronucleus frequency is widely used in radiation biology, occupational exposure assessment, environmental monitoring, and medication safety review due of its significant correlation with cancer risk and long-term genetic harm. It is a fundamental test in genetic toxicology because of its ease of use, affordability, and repeatability.

6.4 Sister Chromatid Exchange (SCE)

A cytogenetic event known as sister chromatid exchange (SCE) occurs when two sister chromatids of the same chromosome exchange DNA segments with one another during DNA replication. Exchanges between sister chromatids often do not modify the genetic sequence since they are genetically identical copies created during the S phase of the cell cycle. Nonetheless, a higher frequency of SCEs is a crucial sign of cellular DNA damage and repair activity [115].When a thymidine analog, such as bromodeoxyuridine (BrdU), is added to freshly produced DNA over the course of two cell cycles, SCEs are visible utilizing differential staining methods. Sister chromatids show alternating light and dark patterns after staining (usually using the fluorescence + Giemsa method), making crossing spots easy to see under a microscope [116].A higher frequency of SCE is indicative of increased replication stress, DNA damage, and faulty DNA repair processes, particularly homologous recombination repair. Despite not being structural chromosomal abnormalities like deletions or translocations, SCEs are a sign of replication fidelity issues and genomic instability. As a result, SCE analysis is regarded as a sensitive indicator of genotoxic exposure and is especially helpful in identifying mutagenic agents' subtle or low-dose effects [117].For instance, it has been demonstrated that people who work with benzene, a known genotoxic chemical used in the petrochemical sector, have noticeably higher SCE frequencies in their peripheral blood lymphocytes than people who are not exposed to it [118]. Similarly, recognized inducers of SCE production include ionizing radiation and chemotherapeutic drugs like mitomycin C.

The study of Bloom syndrome, a rare autosomal recessive condition marked by impaired DNA helicase activity, has also benefited from SCE analysis. SCE frequencies are significantly higher

in patients with Bloom syndrome, which is indicative of poor DNA repair and a high risk of cancer [119].

SCE analysis is therefore still a valuable research and biomonitoring technique for assessing the genotoxic potential of environmental, pharmacological, and medicinal agents as well as the effectiveness of DNA repair and replication fidelity.

6.5 Advanced Cytogenetic Techniques

Recent developments in molecular biology have produced sophisticated cytogenetic methods that enable high-resolution, accurate identification and characterization of chromosomal abnormalities. Modern methods may detect subtle, complex, and submicroscopic genetic mutations, significantly enhancing diagnostic and research applications compared to classical karyotyping, which only identifies big structural abnormalities [120].

Fluorescence in situ hybridization (FISH) is one of the most crucial methods. FISH detects translocations, deletions, duplications, and numerical anomalies by using fluorescently labeled DNA probes that hybridize to certain chromosomal regions. For instance, FISH is frequently used to identify the Philadelphia chromosome-formed BCR-ABL fusion gene in chronic myeloid leukemia, enabling precise diagnosis and therapy tracking [121].Comparative genomic hybridization (CGH), which allows for the identification of DNA copy number differences throughout the genome without the need of metaphase chromosomes, is another potent technique. To determine chromosomal gains and losses, CGH compares the DNA of the patient with that of a normal reference. For example, CGH is frequently used to detect chromosomal abnormalities in solid tumors and in cases of developmental delay that cannot be explained [122]. By giving each chromosome a distinct fluorescent hue, spectral karyotyping (SKY) makes it easier to identify intricate chromosomal rearrangements. When many translocations and marker chromosomes are prevalent, as in acute leukemias with complicated karyotypes, SKY is very helpful in cancer cytogenetics [123]. Furthermore, array-based cytogenomics, such as array CGH, combines cytogenetics with microarray technology to identify submicroscopic duplications and deletions with remarkable sensitivity. The identification of microdeletions in DiGeorge syndrome, which are not detectable by standard karyotyping, is a clinical example [124]. These cutting-edge cytogenetic methods have transformed chromosomal analysis and are extensively used in genetic counseling, prenatal screening, cancer detection, and toxicological investigations. They offer comprehensive understandings of genomic instability and disease causes.

7. Biological, Environmental, and Toxicological Significance

Since chromosomal abnormalities are a direct reflection of genomic instability, a basic mechanism behind many human disorders, they have enormous biological relevance [125]. Uncontrolled cell proliferation or programmed cell death can result from structural and numerical chromosomal changes that compromise gene integrity, change gene dosage, and interfere with regulatory mechanisms. Carcinogenesis is one of the most serious biological effects of chromosomal abnormalities. Certain chromosomal rearrangements that either inactivate tumor suppressor genes or activate oncogenes are characteristics of many malignancies. For instance, a reciprocal translocation between chromosomes 9 and 22 results in the Philadelphia chromosome seen in chronic myeloid leukemia,

which produces the BCR - ABL fusion gene that promotes the growth of malignant cells [126].Likewise, solid tumors are often linked to deletions in tumor suppressor genes like TP53. Chromosome abnormalities are trustworthy indicators for evaluating cancer risk and prognosis because persistent chromosomal instability raises mutation rates and encourages malignant transformation [127].

Developmental abnormalities and reproductive toxicity are very closely linked to chromosomal abnormalities [128]. Chromosome anomalies in germ cells can result in congenital deformities, frequent spontaneous abortions, or infertility. Aneuploidy and other numerical abnormalities are a major contributor to genetic diseases and embryonic lethality. For example, one of the most prevalent chromosomal causes of intellectual impairment is trisomy 21, which causes Down syndrome and is caused by an extra copy of chromosome 21 [129]. Offspring may inherit structural rearrangements, such as balanced translocations in parents, which raises the possibility of developmental defects and genetic disorders. Therefore, assessing the genetic safety of industrial chemicals and medicines requires cytogenetic surveillance of reproductive cells.

Chromosome abnormalities are sensitive markers of genetic harm caused by pollution in environmental toxicology [130]. In exposed species, environmental pollutants such pesticides, petroleum hydrocarbons, heavy metals (like lead and cadmium), and industrial effluents can cause spindle disruptions, micronuclei production, and chromosomal breakage. For instance, in plant bioassays like the Allium cepa test, it has been demonstrated that agricultural runoff containing pesticide residues increases chromosomal abnormalities and micronucleus frequency [131]. There have also been reports of increased chromosomal damage in people exposed to air pollution and benzene at work. These discoveries offer early warning indicators of environmental pollution as well as possible long-term ecological and public health hazards.

Chromosome aberration investigations are crucial from a toxicological and pharmacological standpoint to guarantee medication safety prior to human exposure [132]. To assess clastogenic and aneugenic potential, regulatory bodies like the Organization for Economic Co-operation and Development (OECD) mandate thorough genotoxicity testing of novel chemical entities. For instance, preclinical tests have shown that alkylating chemotherapeutic drugs, such as cyclophosphamide, have clastogenic action by causing chromosomal breakage [133]. When chromosomal damage is identified during preclinical testing, harmful substances can be removed or structurally altered, shielding patients from long-term negative consequences like heritable mutations or subsequent malignancies. Chromosome aberration analysis is therefore still a crucial part of environmental protection plans, regulatory toxicology, and public health decision-making.

8. Regulatory and Pharmaceutical Importance

When developing and approving novel medications, chromosomal aberration testing is crucial from a pharmaceutical and regulatory standpoint. To guarantee that novel chemical entities do not provide intolerable genetic hazards to people, international regulatory bodies need thorough genotoxicity evaluation [134]. Before a drug can move on to clinical trials or marketing authorization, agencies like the United States Food and Drug Administration (US-FDA), the World Health Organization (WHO), the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

(ICH), and the Organization for Economic Co-operation and Development (OECD) require genotoxicity testing batteries that include chromosomal aberration assays. Guidelines like OECD Test Guidelines for Genetic Toxicology and ICH S2(R1) specify these needs [135].Because they can result in gene mutations, carcinogenesis, or heritable genetic disorders, chromosomal abnormalities—whether structural (breaks, deletions, translocations) or numerical (aneuploidy, polyploidy)—are important markers of genomic instability [136]. For instance, a number of anticancer drugs, including cyclophosphamide, are recognized clastogens that cause chromosomal breakage in mammalian cells; these results are carefully analyzed to differentiate between long-term genetic danger and intended therapeutic cytotoxicity [137]. Pharmaceutical firms can terminate, reformulate, or structurally change dangerous substances prior to human exposure by identifying their genotoxic potential early in preclinical research.

Crucially, medication research does not always end when a chromosomal aberration test yields a positive result. Rather, it prompts further mechanistic research to ascertain whether the impact is threshold-dependent, subsequent to cytotoxicity, or direct DNA damage [138]. After that, a thorough risk-benefit analysis is carried out. Certain genotoxic risks may be tolerated for life-saving medications like chemotherapeutic medicines if the therapeutic benefits greatly exceed any possible long-term harms. All things considered, regulatory frameworks guarantee that medications that reach the market are both effective and genetically safe. Therefore, chromosomal aberration testing is essential for evaluating medication safety, adhering to regulations, and safeguarding the public's health from unforeseen genetic effects.

8. Future Perspectives

In order to improve the predicted accuracy of genotoxicity evaluation, the future of chromosomal aberration research depends on the integration of sophisticated molecular, omics, and computational technologies with traditional cytogenetics . For the identification of structural abnormalities including chromosomal breakage, deletions, translocations, and aneuploidy, traditional cytogenetic analysis—which is based on microscopic inspection of metaphase chromosomes—remains crucial. But when paired with molecular techniques like fluorescence in situ hybridization (FISH), scientists can see submicroscopic changes and pinpoint the exact location of chromosomal rearrangements. For instance, FISH is frequently used to detect HER2 gene amplification in breast cancer, allowing for focused treatment choices and demonstrating how chromosomal analysis is improved by molecular cytogenetics .

Cellular reactions to genotoxic substances may be understood at the systems level through the use of omics technologies, such as transcriptomics, proteomics, metabolomics, and genomics . As early indicators of genomic stress before overt chromosomal abnormalities manifest, transcriptome profiling can identify early activation of DNA repair genes, such as p53-regulated pathways, following exposure to ionizing radiation, rather than only identifying obvious chromosomal damage. Analyses of proteomics can also reveal changes in the expression of DNA repair enzymes after alkylating chemical treatment, providing mechanistic information about genotoxic reactions.

By utilizing quantitative structure–activity relationship (QSAR) models and artificial intelligence algorithms to estimate the potential for chromosomal damage based on chemical structure

and biological interaction data, advances in computational toxicology and in silico modeling further enhance predictive genotoxicity testing. Computational screening, for instance, has been used to estimate the genotoxic risk of new drug candidates before in vivo testing, which lowers the expense of animal usage and development.

In contrast to traditional two-dimensional cultures, emerging alternative models such as three-dimensional (3D) cell cultures, organoids, and genetically modified human cell lines have better physiological relevance. These days, thousands of chemicals may be quickly screened for chromosomal damage markers like micronucleus production using high-throughput screening technologies. Testing efficiency may be greatly increased by using automated high-content imaging equipment, which, for example, can measure micronuclei in cultured human cells after they have been exposed to environmental toxins.Synergy across cytogenetics, molecular biology, omics sciences, and computer modeling should make chromosomal aberration research more accurate, predictive, and mechanistically enlightening. These developments will improve environmental genotoxicity monitoring, speed up safer medication development, and fortify global regulatory decision-making procedures.

9. CONCLUSION

It is commonly acknowledged that chromosomal abnormalities, which show how chemical, physical, or biological agents affect the integrity of genetic material, are sensitive and trustworthy markers of genomic instability and genotoxic stress. Researchers may learn a great deal about the fundamental mechanisms of DNA damage, such as how certain substances or environmental exposures interfere with regular cellular functions, by closely examining these structural and numerical chromosomal alterations. This knowledge is essential for determining the possible hazards provided by medications, industrial chemicals, and environmental contaminants, as well as for comprehending the genesis of numerous illnesses, including cancer and congenital abnormalities.

Therefore, the assessment of chromosomal abnormalities serves as a link between basic research and real-world applications in toxicology, pharmacology, and environmental safety, directing regulatory policies as well as public health initiatives. The capacity of cytogenetic methods to identify minute genetic alterations and offer mechanistic insights will be greatly improved as they develop further—through developments in molecular cytogenetics, imaging technologies, and high-throughput approaches. Its continued importance in both research and applied science is highlighted by this continuous improvement, which guarantees that chromosomal aberration testing will continue to be a vital component in safeguarding human health, guaranteeing medication safety, and keeping an eye on environmental risks.

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