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REVIEW ARTICLE

An Update on Chromothripsis: Biology, Mechanisms and Applications

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ABSTRACT

Chromosomal mis-segregation events in cancer are increasingly being recognized as driving factors behind the pathology. Despite the existence of several checkpoints in the cell to monitor and stop events leading to cancerous growth newer research data are discovering several forms of structural variations in wide range of cancers. Chromothripsis characterized by tens to hundreds of structural rearrangements resulting in intricate changes to one or a few chromosomes has become a remarkable and mysterious occurrence in biology. The resulting derivative chromosome is very different from its original structure, and it has been found to have a unique mutation signature in a number of malignancies. The present review aims to summarize the current knowledge in this area with sections dedicated to Genomic instability and chromothripsis, causes and consequences and Chromosome dynamics and chromothripsis. Last two sections are directed towards the spectrum of diseases affected by chromothripsis and the therapeutic approaches. The topic offers several useful insights into biology of genome stability and chromosomal dynamics. Detailed cell biology and live-cell study and omics research will help uncover the genotype-phenotype relationship and pave way for therapeutic interventions.

KEYWORDS

• Chromoplexy • Genomic instability • ecDNAd • DRR-DNA damage response

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INTRODUCTION

For the eukaryotic cells to proliferate healthily, precise chromosomal segregation and adaptability must be orchestrated during the cell division cycle. Both healthy and cancerous cells can experience chromosomal mis-segregation events despite the existence of cell cycle checkpoints (Bolhaqueiro *et al*., 2019). In cancer cells with unstable chromosomes, the ratio of chromosomal missegregation events may be 100 times (Maiato *et al*., 2023). The proper operation of the cell depends on the intricate system that is the genome, especially the karyotype. Since the early days of cytogenetic technology, complex chromosomal rearrangements (CCRs) have been a fascinating area of research. The phrase "complex chromosomal translocations" was first used to characterize situations in which two chromosomes swap portions more than once, producing many derived chromosomes (Dufton and Bouzayen 2021). In the realm of genetics, chromothripsis—named after the Greek word thripsis, which means "shattering"—has become a remarkable and mysterious occurrence (Pellestor *et al*., 2025) in biology. Tens to hundreds of structural rearrangements are quickly acquired during this process, resulting in intricate changes to one or a few chromosomes (Korbel and Campbell, 2013). The resulting derivative chromosome is very different from its original structure, and it has been found to have a unique mutation signature in a number of malignancies, especially those of the brain, blood, and bone. Numerical (monosomies, trisomies, tetrasomies, etc.), structural chromosomal changes, such as chromatid breaks, ring chromosomes, (Hosea, *et al*., 2024), balanced translocations, deletions, inversions (Li, *et al*., 2013), and non-condensed whole chromosomes, or chromosomes with impaired heterochromatin condensation, among others (Gridina and Fishman, 2022). Multiple chromosomal alterations in the genomes of cancer cells are the outcome of a sequential process where mutations build up over time.

Genomic instability and chromothripsis

Any catastrophic event that results in intricate chromosomal rearrangements is referred to as "chromoanagenesis." When numerous complex rearrangements take place at one or more chromosomal loci during a single catastrophic event, this is known as chromoanagenesis (Pellestor *et al*., 2022). A subset of chromoanagenesis is chromothripsis. Another process known as chromoanasynthesis has been discovered in addition to chromothripsis. A replication process disturbance, such as a sequential stop of replication forks or a breach of replication mechanisms mediated by microhomology, is the basis for chromoanasynthesis (Ngo *et al*., 2026). Lastly, chromoplexy is a different kind of chromosomal arrangement in which several chromosomes are translocated and frequently deleted at breakpoints in a chain-like process (Krupina *et al*., 2023).

The existence of gene copies (two or three copies) in addition to deletions and typically copied chromosomal areas is the primary distinction between chromoanasynthesis and chromothripsis. The number and distance between breakpoints, copy number states, and the arrangement and orientation of segments at joining points are some of the features that distinguish the three types (Poot, 2018). Chromothripsis is caused by different processes than other chromoanagenesis disorders. The phenotypic repercussions of the rearrangement, such as chromosome pulverization in micronuclei, reversible apoptosis, and dicentric chromosome splits into pieces, are largely determined by the genomic areas implicated (Koltsova *et al*., 2019). Numerous methods have been used to support an ongoing study examination into the mechanisms of chromothripsis. One such technique is the selective induction method for human Y chromosome mis-segregation (Ly *et al*., 2017). Telomere damage, ionizing radiation exposure, viral infections, and abnormal epigenetic regulation have all been suggested as possible triggers. In chromothripsis, the broken chromosome or chromosomes undergo random religation, producing many DNA segments and highly altered offshoot chromosomes (Rosswog *et al*., 2021). Numerous carcinogenic insults, such as tumor suppressor inactivation, oncogene amplification, and the creation of oncogenic gene fusions, might result from these chromothriptic rearrangements (Molenaar *et al*., 2012; Teles Alves *et al*., 2013). According to research, some chromosomes-17, 8, 12, 11, and 6-are more commonly implicated

in this phenomena. One example is the critical TP53 gene on chromosome 17p13.1, which controls apoptosis, DNA damage responses (DDRs), and cell cycle checkpoints (Cumbo *et al*., 2020). However, certain chromosomes seem to be more often affected by germline chromothripsis, with chromosome 5 being the most prevalent, followed by chromosomes 7, 3, and 9 (Nazaryan-Petersen and Tommerup, 2016). Micronuclei with bigger chromosomes and lower gene density are more likely to experience nuclear envelope rupture. Different methods of origin or selective pressures in various cellular environments may be indicated by the difference in chromosome participation between somatic and germline chromothripsis. This may be because chromothripsis can manifest in different cell types depending on their cycling state .Studies reported massive constitutional chromosomal rearrangements similar to those of chromothripsis in cancer in some patients with congenital developmental disorders (Nazaryan *et al*. 2014). In comparison with chromothripsis in cancer, these instances of apparent germline chromothripsis showed minimal DNA loss, presumably reflecting the selection against haploinsufficiency or complete loss of gene function due to monoallelic gene expression. Several research studies provide insights into the genomic basis for the difference observed the types of chromosomal rearrangements. One of the hallmark features of chromothripsis is interspersed loss and preservation of heterozygosity, which suggests a ''shatter-and-stitch'' process of one chromatid (Cai *et al*., 2014). This is in sharp contrast to chromoanasynthesis, which reflects extra synthesis of DNA segments (Ngo, *et al*., 2026). Although extra synthesis can lead to alternating DNA copy numbers, it does not necessarily result in LOH: LOH occurs by DNA deletion or gene conversion. Another difference between chromoanasynthesis and chromothripsis is that adjacent chromosomal ends in chromothripsis (especially in the germline) often result from one DNA DSB, whereas segmental breaks in chromoanasynthesis are separated by longer distances (0.01;1 Mb) and appear to result from template-switching events. replication-based DNA repair contributes to chromothripsis, as evidenced from examples of templated insertion sequences (Chiang *et al*. 2012). Chromoanasynthesis results in one aberrant chromosome with duplicated segments due to extra DNA synthesis; in contrast, chromothripsis generally gives rise to one or multiple derivative chromosomes with either massive DNA loss (in cancer) or no apparent DNA copy number alterations (in the germline). Distinction between chromothripsis and chromoanasynthesis is also evident in a more recent report of germline genomic rearrangements Kloosterman *et al*. (2012). Figures 1 and 2 illustrate chromosomal alterations.

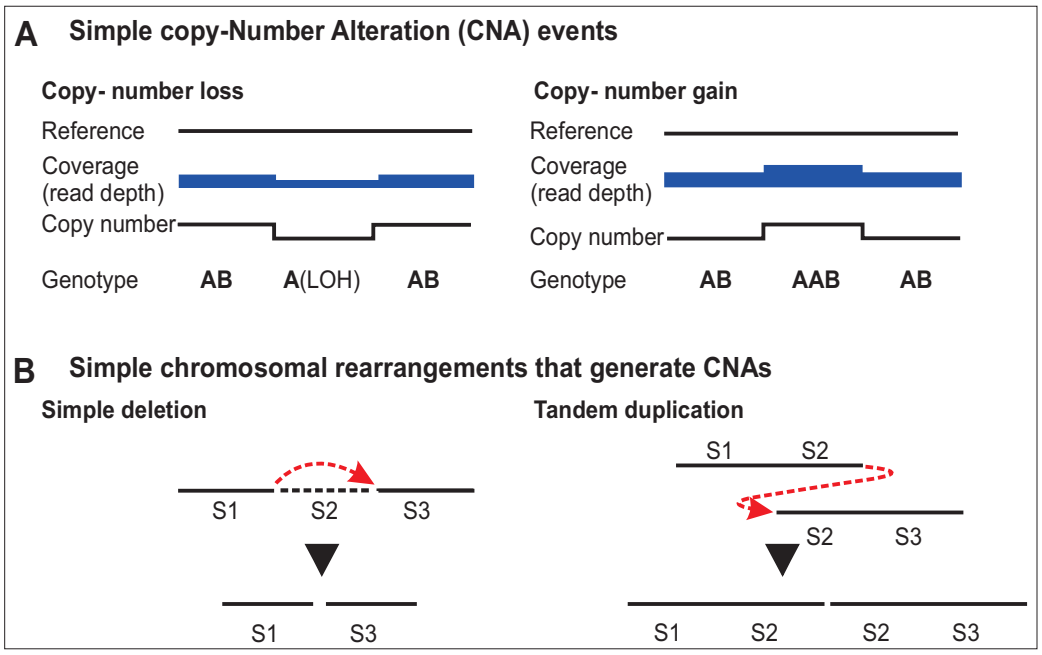


Figure 1: Characteristics of simple and complex chromosomal rearrangements A, B-Copy number losses or gains

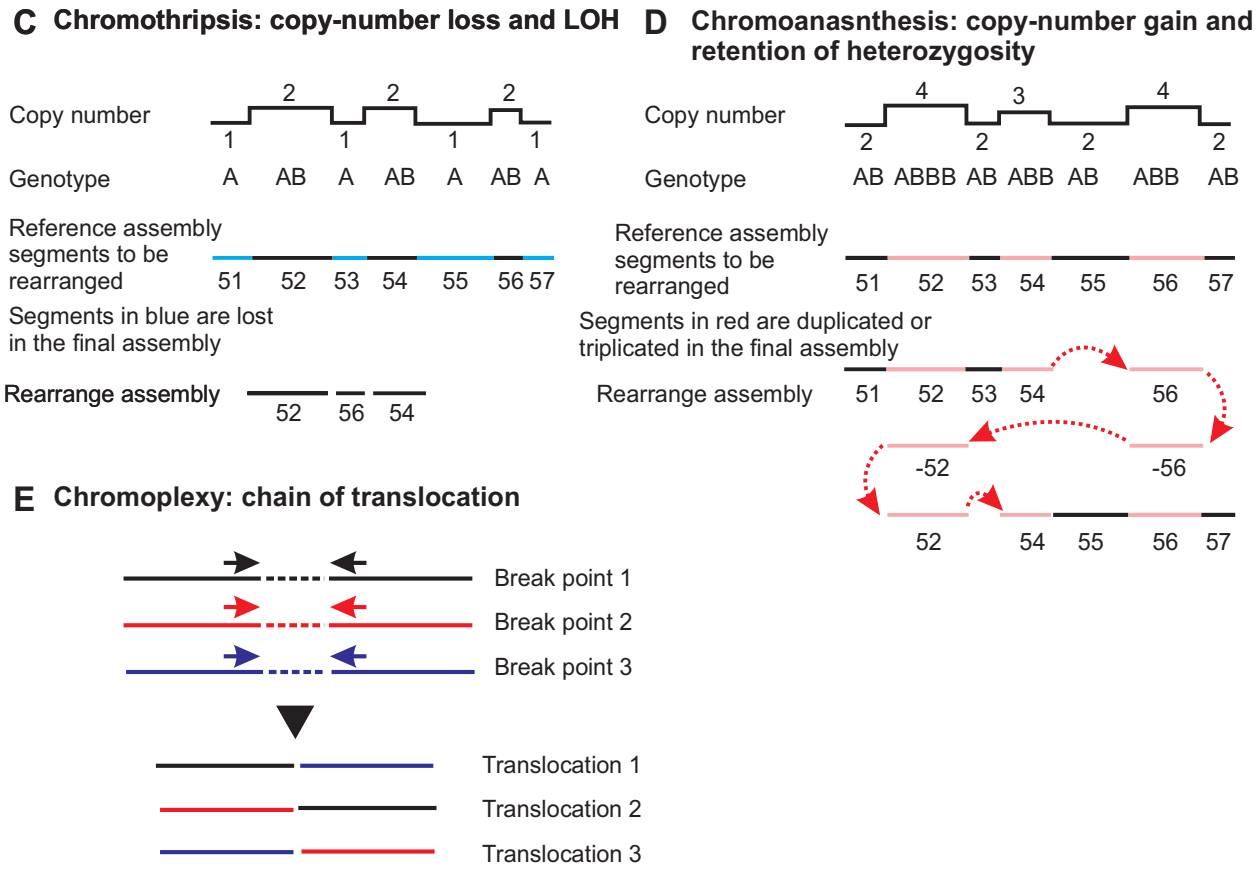


Figure 2: Characteristics of simple and complex chromosomal rearrangements; **C, D, E** - Chrothripsis: chromoanasynthesis: Chromoplexy

Causes and consequences

In order to maintain genome stability, cells are continually at danger of DNA damage from both internal and external sources (Cannan and Pederson, 2016). They quickly react to these threats using built-in mechanisms (Ciccia and Elledge, 2010). DNA damage repair (DDR) checkpoints that compel cell cycle arrest, aid in DNA repair, and start apoptosis are the result of this reaction (Petsalaki and Zachos, 2020). DDR checkpoints allow chromosomal segregation when injured cells begin mitosis, while being largely active during interphase (Sekelsky, 2017). The alternative end-joining repair protein DNA polymerase θ and sustained DNA damage signals are triggered by DNA breaks during mitosis (Clay *et al*., 2021). It's interesting to note that this coordinated signaling acts as a preventative mechanism, reducing the development of micronuclei, in addition to aiding in the segregation of damaged chromosomes. Double strand breaks (DSBs) are the most dangerous kind of DNA damage because they can result in chromosomal translocations or structural changes associated with carcinogenesis (Cannan and Pederson 2016). Micronuclei are created during mitosis when chromosomes with DSBs are improperly segregated (Clay *et al*., 2021). DSBs are major causes of genomic instability, requiring cells to use a variety of repair processes, such as microhomology-mediated end joining (MMEJ), non-homologous end joining (NHEJ), and HR (Groelly *et al*., 2023). However, amplifications, deletions of repetitive regions, and loss of heterozygosity may result from HR using the homologous chromosome rather than the sister chromatid.

The mechanisms by which genome instability causes chromothripsis include: a) NHEJ can cause point mutations and minor deletions by directly fusing DSB termini with few to no processing; b) MMEJ's reliance on short microhomology stretches for annealing and ligation makes it extremely error-prone, resulting in the emergence of small insertions/deletions (indels) or proximal amplifications (Audibert and Soutoglou, 2023); c) recent research indicates that chromothripsis may also cause disruptions within DNA

repair pathways (Ratnaparkhe *et al*., 2018). Research has indicated potential mechanistic connections between chromothrips and breakage-fusion-bridge (BFB) cycles (Mardin *et al*., 2015). Bridge extensions and cytoplasmic actomyosin contractility were found to be essential conditions for bridge rupture by Umbreit *et al*. (2020). BFB can also be triggered by telomere protection loss, which causes the DNA repair mechanism to identify unprotected chromosomal ends like DSBs. In G1, oncogene flanking region translocate, producing a dicentric chromosome (Lee, *et al*., 2023). These dicentric chromosomes can be concurrently drawn to opposing poles during anaphase, creating a bridge. Since the bridge's resolution results in chromosomes lacking telomeres, BFB may recur in subsequent cell divisions (Maciejowski and de Lange, 2017). The formation of micronuclei signifies the start of chromothripsis, a phenomenon brought on by a series of DNA damage events during a single-cell division (Zhang *et al*., 2015). Interestingly, a large amount of this damage happens during interphase when the micronuclei's nuclear membrane bursts, revealing contained chromosomes to the cytoplasm (Onoja *et al*., 2026). Complex rearrangement sequences or circularized ecDNA structures are created when the DNA repair machinery takes over and randomly reassembles the broken DNA segments (Zhang *et al*., 2026). Multiple rounds of chromothripsis and the integration of damaged DNA may be involved in the evolution of ecDNAs. Dicentric chromosomes are produced as a result of translocation. A chromosomal bridge is created as a result of the dicentric chromosome's subsequent replication and the segregation of dicentric sister chromosomes during mitosis. When this bridge breaks, the resultant pieces frequently circularize into ecDNAs (Jiang and Chan, 2024). Additionally, the cohabitation of several amplicons in the same specimen raises the possibility that ecDNAs go through multiple steps and eventually change into multifragment structures (Chen *et al*., 2023).

Chromosome dynamics and chromothripsis

Accurate chromosomal attachment to spindle microtubules, chromosome congression, anaphase segregation, and the construction of a spindle mid-zone upon mitotic exit are all necessary for error-free mitosis (Pleuger and Westermann 2026). This helps to generate the genomes of the two daughter cells by ensuring that identical sets of chromosomes are precisely segregated to each spindle pole. According to research from the Cancer Genome Atlas, chromosomal stability disruption during cell division causes gastric carcinogenesis (Cancer Genome Atlas Research Network, 2014). Indeed, chromosome missegregation, which frequently occurs in cancer cells, can result in structural and numerical chromosomal changes that increase phenotypic variety and provide a substrate for natural selection (Devillers *et al*., 2024). Chromosome segregation defects can lead to the development of aberrant structures such chromatin bridges or micronuclei, which are commonly seen in a variety of human neoplasms (Fenech, 2021). Chromosome mis-segregation during mitosis, in which individual chromosomes fail to correctly connect to the mitotic spindle, is a prominent cause of chromothripsis. This results in delayed segregation and subsequent integration into micronuclei (Mazzagatti *et al*., 2024). In the subsequent cell cycle, chromatin trapped in these bridges during mitotic mistakes may micronucleate, increasing the incidence of rearrangements and fragmentation events. Chromosome mis-segregation into micronuclei or chromatin bridges has been linked to defective centromere assembly in aberrant micronuclei, which contributes to the persistence of chromosomal abnormalities (Duan *et al*., 2026).

Every chromosome must have a single centromere in order to preserve genomic integrity. There are several ways that dicentric chromosomes, which have two active centromeres, can arise (Rothkamm and Lloyd 2014). This includes the fusion of sister chromatids or non-homologous chromosomes, which is frequently caused by telomere dysfunction and results in the ligation of broken sister chromatids after DNA replication or the exposing of chromosome ends (Liddiard *et al*., 2016; Warecki *et al*., 2023). Dicentric chromosomes are essential for the production of ecDNA. However, research into the precise mechanisms underpinning ecDNA production is still continuing (Shoshani *et al*., 2021). Pulverization may take place during mitosis, especially in spermatogonia, which

go through multiple mitotic divisions before entering meiotic prophase, according to spatial characterisation of chromothripsis rearrangements on particular chromosomal locations (Lin *et al*., 2023). However, chromothripsis may also happen during interphase when chromosomes are loosened throughout the nucleus, according to examples involving several chromosomes (Ly and Cleveland 2017). In order to ensure that crucial events are completed before cells move on to the next stage, cell cycle checkpoints are crucial feedback regulatory mechanisms that regulate the cell cycle development. Because of their reliance on checkpoints, cells can continue through the cell cycle even in the face of potentially dangerous mistakes that could eventually jeopardize cell viability or promote cell transformation.

In both mitosis and meiosis, chromosome segregation errors are prevented through the action of spindle assembly checkpoint (SAC), which actively monitors the attachment status of kinetochores to spindle microtubules (McAinsh and Kops, 2023). SAC is effective in preventing most chromosome attachment errors however it is not sensitive to sense the merotelic attachments, where a single kinetochore attaches to microtubules oriented to both spindle poles (Cimini, 2023). Thus, merotelic attachment can escape the SAC and error correction machinery. SAC exerts its regulatory control over the anaphase promoting complex/cyclosome functions via the formation of mitotic checkpoint complex (MCC) (Bodrug *et al*., 2021). The "wait anaphase" signal is molecularly embodied by this MCC-mediated inhibition of the anaphase promoting complex/cyclosome (APC/C), which includes a variety of mechanisms (Yatskevich, *et al*., 2021). Chromosome instability seen in cancer cells has been linked to SAC dysfunctions (Huang *et al*., 2019). According to Kouznetsova *et al*. (2019), these abnormal attachments may cause chromosomes to lag during anaphase or misalign during metaphase. Furthermore, during cytokinesis, mis-segregated chromosomes may sustain damage or become encased in micronuclei, which are spatially separated from the main nucleus during interphase (Devillers *et al*., 2024).Defects in the SAC machinery cause deadly imbalances in the genome, which negatively affect cellular fitness, impede cell proliferation, and even result in cancer. The SAC machinery is a strong system to protect genome integrity (McAinsh, *et al*., 2023). In cancer cells, chromosome mis-segregation can lead to structural and numerical changes that promote phenotypic variety and serve as a foundation for natural selection (Bakhoum and Cantley, 2018). Chromosome segregation abnormalities frequently appear as chromatin bridges or micronuclei, which are frequently seen in a variety of human neoplasms (Zych *et al*., 2024). These structures cause chromothripsis, in which a chromosome breaks into many acentric pieces (Zhang *et al*., 2015).

DNA topoisomerase 2-binding protein 1 (TOPBP1), an essential component for DNA replication and DDR, is drawn to DNA damage sites indicated by phosphorylated H2AX (γH2AX) when DNA DSBs are produced during mitosis. The mediator of DNA damage checkpoint protein 1 (MDC1) is necessary for this process (Pappas *et al*., 2023). When this recruitment is disrupted, as demonstrated by MDC1 depletion, DNA damage persists and the number of micronuclei harboring acentric chromatin fragments increases (Leimbacher *et al*., 2019). The identification of proteins that mediate the coalescence of broken chromosomes in mitotic cells was made possible by the subsequent study findings. Initially identified as an oncogenic inhibitor of the tumor suppressor protein phosphatase PP2A, cancerous inhibitor of PP2A (CIP2A) has several functions in chromothripsis, G2/M checkpoint, and DDR (Nagelli and Westermarck 2024; Yam *et al*., 2022). According to Laine *et al*. (2021), CIP2A is selectively necessary for the mitotic progression of DNA-damaged cells, but it is not necessary for normal mammary gland development or uninterrupted mitosis. They also described a direct connection between TOPBP1 and CIP2A. It's interesting to note that in mammary epithelial cells, CIP2A inhibition increased TOPBP1 and RAD51 recruitment to chromatin caused by DNA damage (Laine *et al*., 2021). During cell division, CIP2A and TOPBP1 physically repair damaged chromosomes (De Marco Zompit *et al*., 2022). According to recent research, the fragments created by chromosomal breaking during cell division are tethered by the CIP2A–TOPBP1 complex

(Lin *et al*., 2023). As previously documented, CIP2A–TOPBP1 exhibits two recruitment modalities to mitotic DNA damage: one mode reacts to chromosome breaks and depends on MDC1, while the other mode functions independently of MDC1 and is associated with poor DNA replication (Adam *et al*., 2021).

Chromothripsis, pathogenesis and associated disorders

Chromothripsis, also referred to as chromosomal shattering, is a mutational occurrence in which one or a few chromosomes experience significant fragmentation in a single catastrophic event, followed by the DNA fragments being reassembled in an error-prone manner (Philippos *et al*., 2025). Errors during mitosis, such as chromosome missegregation into micronuclei or the creation of chromatin bridges between daughter cells, often cause chromothripsis. Chromosomes are exposed to nucleases within these delicate structures, which causes fragmentation. According to recent studies, the enzyme N4BP2 is a crucial driver that enters micronuclei and causes DNA breaks, causing a wave of genomic rearrangements that hasten the development of tumors and their resistance to treatment. Highly rearranged chromosomes are created when DNA repair pathways re-ligate the broken DNA in a random order (Kumar *et al*., 2026).

Chromosome instability-induced genomic rearrangements play a significant role in a number of clinical syndromic disorders (Taylor *et al*., 2019) and cancer (Drews *et al*., 2022; Bakhoum *et al*., 2018). Multiple genomic abnormalities are acquired as a result of chromothripsis, also known as chromosomal shattering, an extreme form of chromosomal instability (Voronina 2020). Dozens to hundreds of double-stranded DNA (dsDNA) breaks that are concentrated on one or a few chromosomes, followed by error-prone reassembly of the resultant DNA fragments, are the hallmarks of this catastrophic event. Based on their clustering, orientation, and related copy-number variations, analyses of cancer genomes have shown unique patterns of structural variants caused by chromosome instability (Steele *et al*., 2022). Neuroblastoma sequencing reveals chromothripsis and neuritogenesis gene abnormalities. As a result, extensive fragment losses mixed with a significant number of altered fragments are observed. Chromothripsis, like other forms of chromosomal instability, is associated with aggressive malignancy and a bad prognosis, which emphasizes the need to comprehend how and why cells develop chromothripsis as well as any vulnerabilities that these cells may have (Molenaar, 2012). Table 1 is a summary of cancer phenotypes associated with chromothripsis

Table 1: List of cancer phenotypes associated with chromothripsis

Cancer type	Result	Reference
Basal-like breast cancers	-	
Colon adenocarcinomas	-	
Ovarian cancers	-	
Renal adenomas	-	Malhotra *et al*. 2013
Lung adenocarcinomas (2%)	+	
Lung squamous cell carcinomas, (15%)	+	
Glioblastomas (39%)	+	
Head and neck squamous carcinoma	+	Zack *et al*. 2013
Glioblastoma (16%)	+	
Colorectal cancer), and a variety of	+	Kloosterman *et al*. 2011b
Melanoma	+	Berger *et al*. 2012
Small-cell lung cancer	+	Iwakawa *et al*. 2013
Prostate cancer	+	Wu *et al*. 2012
Brain tumors	+	Molenaar *et al*. 201
Blood malignancies	+	MacKinnon and Campbell 2013

If chromosomal fragments are not reintegrated into the derivative chromothriptic chromosome, they may either be lost to the cell or self-ligate to form circular extrachromosomal DNA (ecDNA) structures. The simultaneous acquisition of many changes resulting from chromothripsis can drive cells a shortcut to cancerous states. It can also result in the activation of oncogenes and/or loss of tumor suppressor genes. With different numbers of breakpoints and copy-number oscillations, chromothriptic chromosomes can exhibit a variety of alteration types, usually between two or three states (canonical chromothripsis) or between numerous states (non-canonical chromothripsis) (Voronina, 2020).

Chromothripsis plays a causal role in cancer due to the simultaneous creation of many structural variants, which are genomic abnormalities that amplify, delete, or rearrange chromosome material (Li *et al*., 2020). These alterations can significantly alter a cell's phenotype by interfering with gene function, regulation, or dosage. According to recent pan-cancer research, chromothripsis is present in 30–50% of malignancies (Cortes-Ciriano *et al*., 2020). Crucially, as chromothripsis produces several cancer drivers, it is expected to play a causal role in the development of tumors in a significant portion of these cancers (Shoshani 2020;Bolkestein 2020). The overall prevalence of the different basic forms of chromothriptic patterns varies significantly between adult and pediatric malignancies. Sarcomas, the majority of carcinomas, high-grade gliomas, and melanomas have the highest prevalence of chromothripsis, while benign lesions and hematopoietic malignancies hardly ever exhibit chromothripsis. Interestingly, within a single tissue, the frequency of chromothripsis varies significantly among cell types (Cortes-Ciriano *et al*., 2020; Gröbner *et al*., 2018). For example, the incidence of chromothripsis varies greatly among brain tumors originating from different cell lineages, ranging from around 0% in pilocytic astrocytomas to almost 100% in certain subtypes of medulloblastoma (Waszak *et al*., 2018).

The percentage of chromothripsis in each affected chromosome and the number of chromosomes affected by chromothripsis vary greatly among tumor types (Bolkestein *et al*., 2020). Nearly 80% of breast tumors have several chromosomes with chromothripsis, with chromosomes 11 and 17 being the most frequently damaged, according to the study group. Chromosome 12 is most commonly impacted in liposarcoma (Voronina, 2020). Additionally, chromothripsis-affected chromosomal areas are enriched for cancer drivers unique to each type of tumor. Furthermore, in a number of tumor forms, chromothripsis is closely associated with p53 inactivation. This correlation is not uniform. Therefore, inhibition of checkpoint proteins other than p53 may accelerate chromothripsis or increase cell survival following chromothripsis. Crucially, other types of chromosomal instability, like genome doubling, are also linked to p53 inactivation. It is still unclear whether types of chromosomal instability are associated with chromothripsis and how much this relationship depends on p53 (Gröbner *et al*. 2018). Table-2 is a short list of genes implicated in Chromothripsis.

Table 2: Genes implicated in Chromothripsis

Gene	Reference
TP53	Rausch *et al*. 2012
CDKN2A	Zack *et al*. 2013
MYC	Stephens *et al*. 2011
TERT	Beroukhim *et al*. 2010
HMGA1 and HMGA2	Mehine *et al*. 2013
ALK	Rausch *et al*. 2012
MAFB	Rustad *et al*. 2020
FANCA	Fontana *et al*., 2018
RB1	Abaigar *et al*. 2016

Current therapeutic interventions

Therapeutic potential may arise from the distinct type of genomic instability found in chromothriptic tumors, which is associated with abnormalities in DNA damage and cell cycle checkpoints. In genetic mouse models and human tumors, such as melanomas, breast cancers, and Sonic hedgehog (SHH) medulloblastomas with a germline TP53 variant, chromothripsis has been strongly linked to defective homologous recombination repair (Ratnaparkhe *et al*., 2018; Simovic *et al*., 2021).

Although chromothripsis itself can inactivate DNA repair genes, pre-existing abnormalities in DNA repair can assist chromothripsis (for instance, in the case of germline mutations, the repair deficiency predates chromothripsis) (Cortes-Ciriano *et al*., 2020). When the alternative repair mechanisms necessary for cancer survival are therapeutically blocked, a defect in homologous recombination repair and other DNA repair pathways renders tumor cells susceptible to selective killing, a strategy known as synthetic lethality (Kaufman *et al*., 2015). The use of poly(ADP-ribose) polymerase (PARP) inhibitors to treat homologous recombination-deficient breast and ovarian malignancies, among other tumor types, is a well-known example of synthetic lethality (Kaufman *et al*., 2015). Particle irradiation combined with PARP inhibition prolongs survival and improves treatment efficacy in patient-derived xenografts of chromothriptic medulloblastoma. In mice with chromothriptic tumors, this combination of agents-which is already approved for the treatment of several cancers regardless of the presence of chromothripsis-was able to halt tumor growth and cause cancer cells to undergo apoptosis, demonstrating the potential usefulness of combining these two classes of inhibitors (Kats *et al*., 2023).

Another anticancer tactic that might be applied to chromothriptic tumors is the induction of mitotic catastrophe, albeit there isn't enough concrete proof of its suitability. A cell-intrinsic oncosuppressive mechanism known as "mitotic catastrophe" is triggered by the detection of mitotic failure and leads a faulty cell to either cell death or senescence (Siri *et al*., 2021). Mitotic catastrophe is an antiproliferative process that precedes and differs from apoptosis, necrosis, or senescence, but it is not a mechanism of cell death (McGee *et al*., 2015). Tumor growth is facilitated by the failure of mitotic catastrophe in cancer cells, which is brought on by mutations in cell cycle checkpoints or the absence of tumor suppressor genes. Nonetheless, certain characteristics of chromothriptic tumors, like elevated chromosomal instability and replication stress, may present weaknesses that could be exploited by inducing mitotic catastrophe. A mitotic catastrophe can be caused by a variety of stimuli and pharmacological agents, including as radiation and chemotherapy, which damage DNA, and medications like microtubule-targeted medicines that disrupt the mitotic machinery or obstruct proper chromosomal segregation. In this case, mitotic catastrophe induction aims to increase chromosomal instability and DNA damage to the point where cancer cells can no longer withstand the damage and die (Vitale *et al*., 2011).

By producing cytosolic DNA and activating the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) pathway, chromosomal instability can also initiate an immunological response against tumor cells (Chen *et al*., 2025; Beernaert *et al*., 2023). When viral and other microbial infections produce harmful dsDNA, this pathway normally triggers an innate immune response. Dinucleotide cyclic GMP-AMP (cGAMP), which is produced when cGAS binds to cytosolic dsDNA, binds to STING and initiates the subsequent synthesis of inflammatory cytokines and type I interferons (IFNs). Over the past few years, there has been a lot of research efforts over the source of the cytoplasmic dsDNA that triggers cGAS in anticancer immune responses. Numerous studies have demonstrated that micronuclei are a significant source of immunostimulatory dsDNA and that cGAS recruitment and activation can result from nuclear envelope rupture surrounding micronuclei (Harding *et al*., 2017). Nevertheless, conflicting findings from other research indicate that the observed build-up of cGAS in micronuclei does not result in the activation of the cGAS–STING pathway or the stimulation of downstream IFN signaling (Takaki *et al*., 2024; Sato *et al*., 2024). Researchers found that chromatin bridges, not micronuclei, play a key role in cGAS activation when they used a panel of antimitotic medications to cause mitotic mistakes. Another study has demonstrated that histone-bound DNA is present in micronuclei produced by DNA damage or mitotic mistakes, and it has demonstrated that these chromatin structures prevent cGAS activation.

However, several tumors suppress cGAS-STING signalling to avoid immune detection. Therefore, possibilities to target tumor cells may arise if this route is reactivated. Tumors with an innate capacity to trigger STING

signalling and subsequent IFN production may be selectively targeted by treatment with TREX1 inhibitors (Tani *et al*., 2024; Toufektchan, *et al*., 2024). These investigations have shown that by breaking down cytosolic DNA, the catalytic subunit of TREX1 reduces excessive activation of the cGAS–STING pathway in the micronuclei of cancer cells, protecting these tumors from immune surveillance. Consequently, TREX1 deletion or blockage decreased tumor development, extended longevity in animal cancer models, and enhanced tumor immune infiltration through higher activation of the cGAS–STING pathway (Lim *et al*., 2024; Jiang *et al*., 2020). Additionally, analysis of The Cancer Genome Atlas (TCGA) data revealed that TREX1 is extensively upregulated in cancer cells, potentially to prevent the accumulation of cytosolic DNA and the formation of micronuclei. This finding increases the likelihood that TREX1 inhibition could be employed as an anticancer strategy. STING agonists, some of which have already demonstrated promise in preclinical research (cyclic dinucleotides) and clinical trials (vadimezan), may also be used to increase activation of the cGAS–STING pathway in tumor cells (Ramanjulu *et al*., 2018). STING agonists may increase the effectiveness of cancer immunotherapies, such as immune checkpoint inhibitors, cancer vaccines, and chimeric antigen receptor (CAR) T cell treatment, according to a number of lines of evidence (Gao *et al*. 2022). Studies implicate promoting chromosomal instability in cancer cells using medications like paclitaxel or vincristine given in conjunction with tocilizumab may be a successful therapeutic approach to counteract both IL-6 signalling and cGAS–STING activation (Bakhoum *et al*., 2018).

ecDNAs may be therapeutically a7ddressed due to their growing involvement in promoting drug resistance and tumor heterogeneity. Oncogene amplification and reintegration into the genome, ecDNA creation and spatial organization into hubs, and other elements of ecDNA biology are pertinent to cancer (Chowdhry *et al*., 2023). For instance, the discovery that checkpoint kinase 1 (CHK1) is necessary for ecDNA-dependent cancer cells to survive led to the creation of BBI-335, a small-molecule inhibitor of CHK1, which is presently being studied as a treatment for a variety of ecDNA-containing cancers in a phase I clinical trial (NCT05827614) (Horak *et al*., 2021). Additional research on ecDNA-targeted strategies is the use of bromodomain and extraterminal (BET), hydroxyurea to restore medication sensitivity and PARP inhibitors to increase the frequency of ecDNA reintegration (Wu *et al*., 2022).

The production of fusion genes in cancer cells impacted by chromothripsis is another possibility that might be used for therapeutic advantage. Precision oncology may be able to take advantage of vulnerabilities created by fusion genes that provide druggable targets (like MET fusions). Fusion genes produced by early chromothripsis may be found in most tumor cells and represent targets unaffected by intratumoural heterogeneity because chromothriptic tumors usually undergo at least one clonal event (Voronina *et al*., 2020).

DISCUSSION

According to Zhang *et al*. (2024), the transformation of a normal cell into a cancerous cell is typically understood as the result of numerous independent genetic defects accumulating one after the other. These lesions and balanced structural rearrangements, such as hit cancer genes that disrupt tumor suppressors or activate proto-oncogenes, influence cells and cause their progeny to progressively amass the required "hallmarks of cancer," in addition to somatic point mutations (Hanahan 2022). An "explosive" method of rapid instability of the cellular genome was found in nature thanks to the discovery of chromothripsis. Chromothripsis is now well acknowledged as a common mutational condition. Although it is still unknown how frequently these kinds of events occur in cancer, numerous new research data indicate that they might be more frequent than first thought. Primary tumors (Cortés-Ciriano *et al*., 2020), liquid tumors (Chen 2024), and cancer cell lines (Voronina *et al*., 2020) can all develop chromothripsis. The notion that a portion of cancer genomes might not be connected to the slow evolution of the

genome has first generated a lot of preliminary discussion (Gerstung *et al*., 2020). To pinpoint the exact rearrangements that resulted from chromothripsis several criteria have recently been developed Viz., 1. Clustered DNA breaks are a characteristic of chromothripsis-affected cells' genomes. 2. Several DNA breaks that occur close to one another. 3. Large sections of DNA that are unaffected by rearrangements encircle the clustered regions. 4. A portion of the chromosomal fragments may be translocated due to chromothripsis. 5. One paternal copy (haplotype) of chromosomes is often affected by chromothripsis. 6. Chromosome fragments resulting from chromothripsis are mixed together in an random order. 6. The fragment is either preserved or deleted in the new chromosome following chromothripsis. These standards are susceptible to debate and are not all-inclusive; rather, they are meant to provide standards for the detection of chromothripsis. New concepts will probably surface as this field of study advances, necessitating a reassessment and modification of the chromothripsis traits. Chromothripsis has been described as complicated patterns of alternating variations in the number of gene copies (normal, increased, or with loss) along a chromosome or chromosomal region by the International System for Human Cytogenetic Nomenclature since 2013 (ISCN 2024). Not only is genome instability a defining feature of cancer, but it also facilitates development.

The transition from precancerous tissue to malignant tumors is accelerated by disruption of genome maintenance and increased rates of somatic mutations (e.g., due to disruption of DNA repair machinery or greater damage) (Rahal *et al*., 2024). An evolutionary perspective on chromothripsis provides a number of insights. According to Qin *et al*. (2026), the mature tumor is biased to retain genetic alterations that are advantageous to the growth of the tumor and to have lost harmful alterations. We might overlook intermediate stages in the creation of the rearranged chromosome whose signatures were lost during tumor evolution if we simply consider the selection endpoint (Alons and Dow 2021). There are reasons to believe that there would be benefits if the oncogenic alterations could be acquired all at once (at least from the perspective of the aspiring cancer cell), as research indicates that cancer can develop through progressive mutational accumulation (Shi, *et al*., 2026). One clear benefit is speed, as combinatorial acquisition of smaller-impact genetic alterations can quickly accumulate a substantial phenotypic effect (Zhang and Bozic, 2024). The fact that intermediate stages of tumor development may potentially be harmful is another possible benefit of all-at-once or "punctuated equilibrium" processes (Matthew *et al*., 2014).

Chromothripsis has now been identified in many cancer types and in some congenital diseases. The flurry of genome sequencing has also uncovered other classes of complex rearrangements (chromoanasynthesis and chromoplexy), which also appear to originate from single catastrophic events. These discoveries have expanded our view of the mechanisms by which genomes can evolve. However, few limitations are is necessary to overcome before these studies become a routine procedure in cancer screening. First the detection of the rearrangements poses technical constraints. Another technical challenge in solving the genomic Rubik's cube for the chromothriptic chromosome is the difficulty of interpreting paired-end sequences in the context of other overlapping rearrangements. Short-read alignment errors, tumor heterogeneity, aneuploidy, and the masking effect of other structural rearrangements placed on top of chromothripsis are additional complications. Hence, the frequency of chromothripsis may be underestimated as a result of all these technical aspects.

CONCLUSION

Chromothripsis represents a catastrophic genomic event characterized by extensive chromosomal rearrangements occurring in a single cellular crisis. Its underlying mechanisms involve complex DNA breakage and erroneous repair processes, often linked to micronuclei formation and replication stress. This phenomenon plays a significant role in cancer development, congenital disorders, and genomic instability. Advances in understanding chromothripsis have improved insights into tumour evolution and therapeutic resistance. Emerging applications include its

potential as a biomarker for diagnosis and prognosis. Continued research is essential to fully elucidate its biological impact and clinical utility.

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