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Review Article

Chromothripsis: A Catastrophic Driver of Genomic Instability

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Abstract

The classical model of genomic instability portrays cancer evolution as a gradual, stepwise accumulation of mutations over decades. Chromothripsis, first described in 2011, challenged this paradigm by demonstrating that tens to hundreds of clustered chromosomal rearrangements can arise within a single catastrophic event, effectively compressing prolonged evolutionary change into one cell cycle. This review synthesizes current understanding of chromothripsis as a major driver of genomic catastrophe. We describe its defining genomic hallmarks and the mechanisms proposed to initiate chromothripsis, with particular emphasis on the micronucleus pathway, alongside alternative mechanisms involving breakage–fusion–bridge cycles and replication stress. Across these pathways, extensive chromosome fragmentation followed by error-prone repair can generate highly rearranged derivative chromosomes, including neochromosomes. The biological consequences are dichotomous: although most affected cells succumb to cell death, rare survivors can acquire multiple oncogenic alterations simultaneously, including oncogene amplification, tumor suppressor loss, and neomorphic gene fusions, thereby accelerating malignant transformation and therapeutic resistance. We survey chromothripsis across a broad spectrum of malignancies and congenital disorders. The review critically evaluates the prognostic significance of chromothripsis and emerging therapeutic implications, including potential vulnerabilities to PARP and ATR inhibition, and immune checkpoint blockade. Finally, we highlight unresolved questions and priorities for future research. Collectively, chromothripsis compels a fundamental reappraisal of genomic instability: rather than being exclusively a gradual process, it can occur as a sudden genomic catastrophe that reshapes the genome in a single event, with profound implications for biomarker discovery, cancer evolution, and precision oncology.

Keywords: Catastrophic evolution; Chromothripsis; Genomic instability; Micronucleus.

تفتت الكروموسومات: محرك كارثي لعدم الاستقرار الجينومي

الخلاصة

يُصوّر النموذج الكلاسيكي لعدم استقرار الجينوم تطور السرطان على انه تراكم تدريجي للطفرات على مدى عقود. وقد تحدث ظاهرة تفتت الكروموسومات، التي وصفت لأول مرة عام ٢٠١١، هذا النموذج، مُثبتةً امكانية حدوث عشرات إلى مئات من عمليات اعادة ترتيب الكروموسومات المتجمعة ضمن حدث كارثي واحد، مما يُكثّف فعلياً التغير التطوري المطول في دورة خلوية واحدة. تُقدّم هذه المراجعة توليفًا للفهم الحالي لظاهرة تفتت الكروموسومات باعتبارها محركاً رئيسياً للكارثة الجينومية. نصف هنا سماتها الجينومية المميزة والآليات المقترحة لبدء هذه الظاهرة، مع التركيز بشكل خاص على مسار النواة الصغيرة، إلى جانب آليات بديلة تشمل دورات الكسر والاندماج والجسور، وإجهاد التضاعف. عبر هذه المسارات، يُمكن ان يؤدي التفتت الواسع للكروموسومات، متبوعاً بإصلاح الخطأ، إلى توليد كروموسومات مشتقة مُعاد ترتيبها بشكل كبير، بما في ذلك الكروموسومات الجديدة. تتسم العواقب البايولوجية بطابعين متناقضين: فمع ان معظم الخلايا المتضررة تموت، إلا ان الخلايا النادرة التي تنجو قد تكتسب طفرات جينية سرطانية متعددة في آن واحد، بما في ذلك تضخيم الجينات السرطانية، وفقدان الجينات الكابتة للأورام، واندماج الجينات الجديدة، مما يُسرع التحول السرطاني الخبيث ومقاومة العلاج. نستعرض في هذه الدراسة ظاهرة تفتت الكروموسومات عبر طيف واسع من الأورام الخبيثة والاضطرابات الخلقية، كما تُقيّم هذه المراجعة الأهمية التنبؤية لتفتت الكروموسومات والآثار العلاجية الناشئة، بما في ذلك نقاط الضعف المحتملة لتثبيط PARP و ATR، وحجب نقاط التفتيش المناعية. وأخيرًا، تُسلط الضوء على الاسئلة التي لم تُحسم بعد وأولويات البحث المستقبلي. وبشكل عام، يُحتّم تفتت الكروموسومات اعادة تقييم جوهرية لعدم استقرار الجينوم: فبدلًا من ان يكون عملية تدريجية حصرياً، يمكن ان يحدث ككارثة جينومية مفاجئة تُعيد تشكيل الجينوم في حدث واحد، مع اثار عميقة على اكتشاف المؤشرات الحيوية، وتطور السرطان، وعلم الأورام الدقيق.

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INTRODUCTION

For decades, the prevailing model of cancer evolution was one of gradualism: a slow, stepwise accumulation of genetic alterations over years or decades, with successive mutations conferring selective advantages on emerging tumor cell populations [1-3]. This framework conceptualized tumorigenesis as a sequence of genetic events involving oncogene activation, tumor suppressor loss, and progressive chromosomal instability. Within this model, genomic instability was viewed primarily as a cumulative process, with repeated cycles of DNA damage and imperfect repair gradually reshaping the cancer genome. The emergence of high-resolution whole-genome sequencing, however, revealed that cancer genomes can also undergo profound structural change through highly punctuated events. In 2011, Stephens and colleagues identified a striking pattern of clustered chromosomal rearrangements in the genome of a patient with chronic lymphocytic leukemia [4]. Tens to hundreds of rearrangements, together with oscillating copy-number states and clustered breakpoints, were concentrated within a limited chromosomal region, suggesting that they had arisen during a single catastrophic episode rather than through successive rounds of mutation. The phenomenon was termed "chromothripsis," from the Greek *"chroma"* (color)

and *"thripsis"* (shattering), reflecting the extensive fragmentation and subsequent reassembly of one or a small number of chromosomes. Rather than representing a gradual accumulation of structural variants, chromothripsis can generate extensive genomic complexity within a single episode of catastrophic DNA damage [5-7]. This discovery fundamentally expanded the concept of genomic instability in cancer. A single catastrophic event can simultaneously generate multiple biologically consequential alterations, including oncogene amplification, tumor suppressor loss, complex rearrangements, and oncogenic fusion genes. In some cases, these changes may be incorporated into derivative or circular chromosomes and subsequently propagated through tumor cell divisions [8,9]. Chromothripsis therefore provides a striking example of how cancer evolution can proceed through abrupt genomic restructuring rather than exclusively through the gradual accumulation of mutations [10,11]. Figure 1 and Table 1 compare the gradual versus catastrophic evolution of genomes. Despite considerable progress, important questions remain regarding the origins and consequences of chromothripsis. What cellular processes initiate such extensive yet spatially restricted chromosome damage? Why are some chromosomes preferentially affected, while much of the genome remains relatively intact? And does chromothripsis confer distinctive biological, prognostic, or therapeutic properties compared with other forms of genomic instability? This narrative review examines chromothripsis as a major mechanism of catastrophic genomic instability. We first discuss its defining genomic features and detection approaches before examining the proposed mechanisms, including micronuclear rupture, telomere dysfunction, replication-associated damage, and aberrant DNA repair. We then consider its cellular and evolutionary consequences, its prevalence across human malignancies and developmental disorders, and its emerging clinical implications. Finally, we assess whether chromothripsis represents not only a mechanism of genomic catastrophe but also a potential source of clinically actionable vulnerabilities.

METHODS

A literature search was conducted using PubMed, Google Scholar, and ResearchGate. PubMed served as the primary database, while Google Scholar and ResearchGate were used as supplementary sources to identify additional relevant publications and grey literature. Identical search terms, as described above, were applied consistently across all three platforms. Studies were eligible for inclusion if they were peer-reviewed articles or preprints published in English between July 2001 and July 2026 and addressed chromothripsis, its underlying mechanisms, genomic consequences, biological significance, or therapeutic implications in cancer. Studies investigating the molecular and cellular mechanisms of chromothripsis, including chromosome mis-segregation, micronuclei, chromatin bridges, DNA damage and repair, replication stress, telomere crisis, and checkpoint dysfunction, were considered relevant.

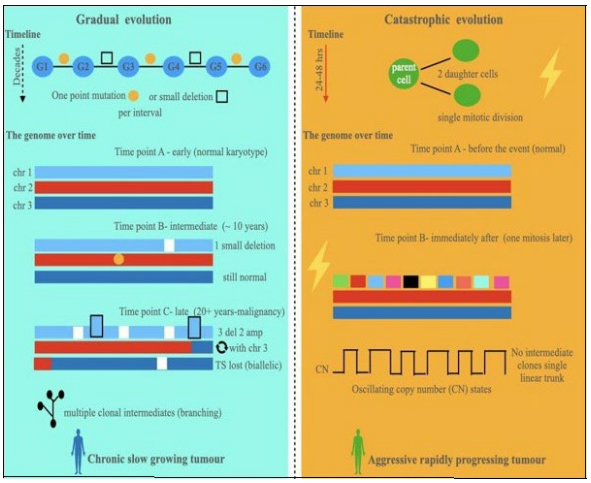


Figure 1: Parallel Comparison of Gradual and Catastrophic Genomic Evolution**. The left panel** illustrates the classical model of gradual tumor evolution, in which point mutations, small indels, and chromosomal translocations accumulate sequentially over decades. Multiple branching subclones arise, each acquiring incremental fitness advantages, ultimately leading to a heterogeneous tumor with moderate structural complexity. **The right panel** depicts chromothripsis as a catastrophic single-event model. Within a single cell cycle, one chromosome (chromosome 1) undergoes tens to hundreds of simultaneous double-stranded breaks, followed by error-prone reassembly. The resulting neochromosome exhibits oscillating copy-number states, focal oncogene amplifications, and homozygous tumor suppressor deletions—all acquired in one abrupt genomic hit. Importantly, the other chromosomes (2 and 3) remain structurally intact, highlighting the localized nature of the event. G: generation; del: deletion; amp: amplification; TS: tumor suppressor; CN: copy number; ; translocation, ;chromothriptic event.

Table 1: Key features of gradual evolution *vs*. catastrophic evolution (chromothripsis) of genomes

Feature	Gradual evolution	Catastrophic evolution
Time frame	Decades	One cycle 24-48 hrs
Number of events	Sequential (1-5 per decade)	Hundreds simultaneously
Chromosomal scope	Diffuse, multiple chromosomes	Localized (1-2 chromosomes)
Clonal architecture	Branched, heterogenous sub clones	Single dominant clone (truncal)
Copy number changes	Linear, incremental	Oscillating, abrupt jumps
Oncogene activation	Gradual amplification	High-level focal amplification, one step
Tumour suppressor loss	Sequential mono-/biallelic loss	Simultaneous biallelic deletion
Therapeutic response	Moderate, stepwise resistance	Often intrinsic resistance or rapid relapse
Prognosis	Variable, often indolent	Frequently poor (aggressive disease)

Studies characterizing the genomic features and detection of chromothripsis, as well as its effects on tumor evolution, oncogene activation, tumor suppressor loss, genomic instability, clinical outcomes, and therapeutic response, were also included. Studies involving human tumor specimens, cancer cell lines, animal models, organoids, or other appropriate experimental systems were considered where they

provided mechanistic or translational insight. Reviews were included for contextual and conceptual purposes and to identify additional relevant primary studies. Pre-2001 publications were only considered if they provided foundational evidence for concepts directly relevant to chromothripsis, such as chromosome instability, DNA repair, breakage–fusion–bridge cycles, micronuclei, and chromosome segregation. Studies were excluded if they were unrelated to chromothripsis or cancer, addressed chromosomal instability without substantive relevance to chromothripsis, mentioned chromothripsis only incidentally, or lacked sufficient information to address the objectives of the review. Studies focused exclusively on non-malignant conditions were excluded unless they provided important mechanistic or historical insights relevant to cancer. Duplicate publications and non-peer-reviewed materials other than eligible preprints or selected grey literature were excluded. Study screening and selection were conducted by the primary author using predefined inclusion and exclusion criteria. Potentially relevant studies were assessed by title and abstract, followed by full-text evaluation of eligible articles. Any uncertainties regarding eligibility were resolved through further assessment of the pre-specified criteria.

Defining the Catastrophic Event: Criteria and Detection

Although the term "chromothripsis" evokes genomic shattering, its identification relies on a constellation of genomic features rather than a single diagnostic hallmark [8,12-16]. The seminal description by Stephens and colleagues established several characteristics that remain central to its recognition: highly clustered structural rearrangements, usually involving one or a few chromosomes or chromosomal regions; numerous closely spaced breakpoints; and oscillation between two or more copy-number states. These patterns are consistent with extensive chromosome fragmentation followed by reassembly, during which some fragments are retained, others lost, and others reinserted in altered orientations [17-19]. The presence of rearrangements within the same tumor clone further supports their origin from a punctuated catastrophic event rather than prolonged stepwise accumulation. Chromothriptic regions may also contain complex breakpoint architectures, including inversions, deletions, translocations, and localized amplifications [20]. Breakpoint junctions can show short stretches of microhomology, consistent with repair through non-homologous end joining or alternative end-joining mechanisms. In some tumors, chromothripsis simultaneously generates oncogene amplification and tumor suppressor loss within the same rearranged region, illustrating how a single genomic catastrophe can produce multiple functionally important alterations [8,21]. Chromothripsis must also be distinguished from related forms of chromoanagenesis, an umbrella term denoting chromosome rebirth. Chromoanogenesis—a specific type of chromoanagenesis—is generally associated with replication-based mechanisms involving template switching and copy-number gains, whereas chromoplexy, a form of complex genetic realignment, involves chains of interdependent rearrangements, often affecting multiple chromosomes [22,23]. Although these processes can produce similarly complex cancer genomes, their characteristic genomic architectures and proposed mechanisms differ. The detection of chromothripsis has been transformed by whole-genome sequencing (WGS), which enables simultaneous assessment of structural variants, breakpoint clustering, and copy-number architecture at high resolution [24]. Long-read sequencing technologies, including PacBio and Oxford Nanopore platforms, can further resolve complex rearrangements and facilitate reconstruction of chromothriptic chromosomes that may be difficult to assemble from short-read data [25]. Computational approaches such as ShatterSeek have also enabled systematic identification of chromothripsis-like patterns across large sequencing datasets [8,26]. Nevertheless, detection remains challenging. Tumor purity, ploidy, subclonal heterogeneity, and overlapping forms of genomic instability can obscure canonical chromothriptic signatures [27]. Consequently, robust interpretation often requires integration of structural-variant, copy-number, allelic, and, where appropriate, transcriptomic data rather than reliance on any single genomic feature or computational classifier.

The Mechanistic Origins: How Does One Event Cause Such Chaos?

The conceptual transition from recognizing chromothripsis in sequencing data to understanding its biological origins has been a major focus of cancer genomics. How can extensive chromosomal rearrangement arise within a single episode while remaining largely confined to one chromosome or chromosomal region? Increasing experimental evidence points to the convergence of three interconnected processes: aberrant sequestration of chromosomal material into micronuclei, catastrophic disruption of these structures, and error-prone repair of the resulting DNA fragments [9,28-31]. Although this model is now strongly supported, chromothripsis appears to arise through multiple mechanisms rather than a single universal pathway [32].

The micronucleus pathway: A central model

The best-characterized mechanism involves micronuclei, small extranuclear structures that arise when whole chromosomes or acentric chromosome fragments fail to incorporate into the main daughter nuclei following mitosis [18,33-35]. Figure 2 depicts the five phases of the micronuclear pathway. Chromosomal mis-segregation can result from errors in kinetochore–microtubule attachment, centromere dysfunction, or telomere attrition and subsequent chromosome fusion. Once isolated from the primary nucleus, the micronucleus provides a spatially

restricted environment in which chromosome integrity can be progressively compromised. Micronuclear envelopes differ structurally and functionally from the primary nuclear envelope and can be deficient in nuclear pore complexes and lamina components such as lamin B [36]. These abnormalities can impair DNA replication and nuclear envelop integrity, ultimately promoting micronuclear rupture during interphase. Once the envelope ruptures, the exposed chromosomal DNA becomes vulnerable to degradation and extensive damage. Cytoplasmic nucleases, including TREX1, can degrade exposed DNA, while cytosolic DNA sensing through cGAS–STING can activate innate immune signalling [37]. At the same time, defective or asynchronous DNA replication within the micronucleus can generate replication-associated lesions and chromosome fragmentation. The resulting collection of DNA fragments provides the substrate for subsequent aberrant reassembly.

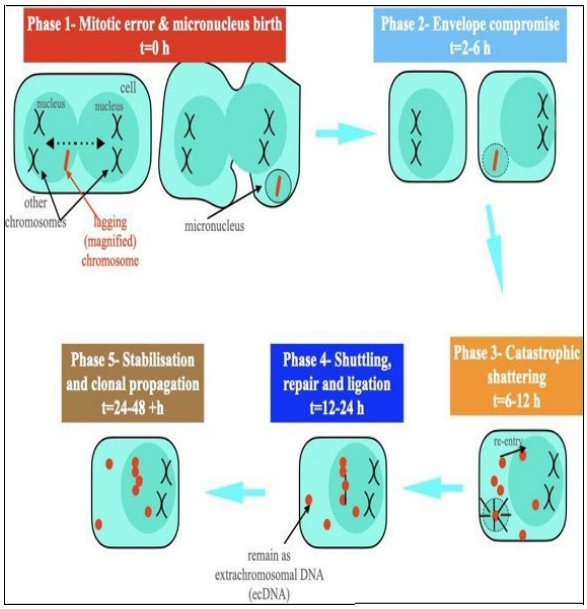


Figure 2: The five phases of Chromothriptic Catastrophe via the Micronuclear Pathway. This timeline illustrates the sequential events leading from a single mitotic error to a stably propagated neochromosome. **Phase 1**: A lagging chromosome (red) fails to segregate during anaphase and is excluded from the primary nuclei, forming a micronucleus. **Phase 2**: During interphase, the micronuclear envelope ruptures, exposing chromosomal DNA to the cytoplasmic milieu. **Phase 3**: A single catastrophic shattering event fragments the chromosome into dozens of double-stranded breaks within hours, generating a cloud of acentric pieces. **Phase 4**: Repair machinery (predominantly NHEJ and alt-EJ) shuttles fragments back into the primary nucleus and ligates them in a scrambled, non-contiguous order, often using microhomology. **Phase 5**: The reassembled neochromosome is transmitted to daughter cells, exhibiting oscillating copy-number states, focal oncogene amplifications, and tumor suppressor deletions. Time is indicated from the initial mitotic error to the first post-repair mitosis.

Alternative routes to chromosomal shattering

Although micronuclear rupture represents a leading model, other mechanisms may produce chromothriptic patterns. The breakage–fusion–bridge (BFB) cycle, for example, can arise following telomere dysfunction and chromosome end-to-end fusion [38,39]. When a dicentric chromosome is pulled towards opposite spindle poles during anaphase, the resulting chromatin bridge can rupture, generating structurally abnormal fragments. Repeated cycles of fusion and breakage can progressively amplify and rearrange chromosomal regions, and a particularly severe bridge rupture may generate a complex rearrangement pattern resembling chromothripsis [6,40]. Replication stress may provide an additional source of susceptibility. Oncogene activation, including aberrant MYC or RAS signaling, can increase replication demand, causing stalled forks, DNA lesions, and replication-associated chromosome breaks [41,42]. When such damage coincides with chromosome missegregation or micronuclear formation, the resulting combination of replication stress and mechanical chromosome disruption may substantially increase the likelihood of catastrophic rearrangement [43,44]. These mechanisms are therefore not necessarily mutually exclusive; chromothripsis may reflect the convergence of pre-existing replication or telomere-associated damage with a subsequent mitotic catastrophe.

The "Mis-Rejoining" phase: Reconstructing a broken genome

Following chromosome fragmentation, cell survival depends on the reassembly of at least some of the resulting DNA fragments. Under these circumstances, high-fidelity repair pathways may be insufficient to restore the original chromosome architecture, particularly when fragments are spatially dispersed or present in large numbers. Instead, repair can involve non-homologous end joining (NHEJ) and alternative end-joining pathways, including microhomology-mediated repair [45]. These mechanisms can join DNA fragments with limited sequence homology, allowing non-adjacent fragments to become connected and generating deletions, inversions, translocations, and other complex rearrangements [46,47]. Such error-prone rejoining helps explain the characteristic genomic architecture of chromothripsis, including clustered breakpoints, oscillating copy-number states, and retention of some fragments alongside extensive loss of others. Importantly, reassembly is unlikely to be entirely random. Cells that have these configurations are more likely to survive and grow, so fragments that contain important genes or genomic elements needed for replication and chromosome maintenance may be kept more often [48]. The resulting rearranged chromosome can subsequently be propagated through cell division and, in some cases, acquire substantial oncogenic potential through simultaneous tumor suppressor loss, oncogene amplification, or formation of fusion genes. However, chromothripsis is not inherently advantageous to the cell. Extensive chromosome damage can trigger apoptosis, senescence, or loss of proliferative capacity. Thus, the biological impact of chromothripsis depends not only on the extent of genomic damage but also on how the resulting fragments are repaired and which genomic configurations survive subsequent cellular selection [9,49].

Consequences of a Single Catastrophic Event: From Cell Death to Oncogenesis

The cellular consequences of chromothripsis span two extremes: extensive genomic damage can result in cell death, yet in a minority of cells, survival can produce a profoundly remodeled genome with substantial oncogenic potential [21]. This apparent paradox is central to understanding how a catastrophic event that is usually deleterious can nevertheless contribute to tumor evolution. The outcome depends on the extent of genomic damage, the integrity of cellular checkpoints, the efficiency and fidelity of DNA repair, and the selective advantages conferred by the resulting genomic configuration.

The immediate fate: A cellular bottleneck

Chromosome shattering generates extensive DNA damage that would normally activate a robust DNA damage response. Double-strand breaks are sensed through pathways involving ATM and ATR, leading to checkpoint activation, cell cycle arrest, and recruitment of DNA repair machinery [50-53]. When damage is irreparable or excessive, cells may undergo apoptosis, senescence, or permanent loss of proliferative capacity. Experimental models of micronucleus-associated chromothripsis have demonstrated substantial cellular attrition following chromosome fragmentation, highlighting the inherent lethality of this process [7,54]. Consequently, the chromothriptic cells detected in established tumors are likely to represent a selected population capable of tolerating or circumventing this damage. Defects in tumor suppressor and checkpoint pathways, particularly those involving TP53, can facilitate survival by weakening cell cycle arrest and apoptotic responses [55]. However, checkpoint disruption is not sufficient to ensure survival; the configuration of the reassembled genome and the extent to which essential genomic material is preserved also determine whether a damaged cell can proliferate [56]. Chromothripsis therefore creates a powerful evolutionary bottleneck in which extensive genomic damage is followed by stringent selection for viable cellular configurations.

The survivor's reward: Structural remodeling and oncogenic gains

For the minority of cells that survive, chromothripsis can generate multiple functionally important genomic alterations within a single evolutionary episode. Fragmentation and reassembly may produce focal oncogene amplification, tumor suppressor deletion, and complex structural rearrangements [11,57]. In some settings, rearranged DNA can contribute to the formation or amplification of extrachromosomal DNA (ecDNA), providing an additional mechanism through which oncogenic copy number can increase rapidly [58,59]. Oncogenes such as *MYC*, *EGFR*, *CDK4*, and *MDM2* may therefore become amplified as part of complex genomic rearrangements, although the specific consequences vary substantially between tumor types. Conversely, extensive fragment loss can result in deletion of tumor suppressor loci, including TP53, RB1, PTEN, and CDKN2A. The simultaneous occurrence of oncogene amplification and tumor suppressor loss illustrates how a single catastrophic event can generate several cooperating cancer-promoting alterations without requiring their sequential acquisition over multiple evolutionary stages. Chromothripsis can also generate complex gene fusions. Rejoining of non-adjacent DNA fragments may juxtapose previously unrelated genomic regions, producing in-frame fusion genes or other regulatory rearrangements with oncogenic consequences. These events can involve multiple genomic partners and may generate structurally complex rearrangements that differ from the simpler balanced translocations classically associated with recurrent fusion oncogenes [8,21,60].

Evolutionary advantages and clonal expansion

The critical consequence of chromothripsis is therefore not simply genomic damage but the possibility that a surviving cell emerges with a substantially altered fitness landscape. By simultaneously generating multiple driver alterations, chromothripsis can accelerate tumor evolution and bypass some of the sequential constraints imposed by gradual mutation accumulation [11,61,62]. The resulting clone may expand rapidly if the newly acquired genomic configuration promotes proliferation, survival, invasion, or resistance to therapy. Chromothripsis has consequently been associated with aggressive tumor phenotypes across several malignancies, including glioblastoma, sarcomas, and advanced prostate cancer [16,63-66]. However, its biological impact is context-dependent, and chromothripsis does not invariably confer an adverse outcome. In many cells, catastrophic genome damage remains lethal; in others, it may generate neutral or even disadvantageous rearrangements. Its oncogenic significance therefore lies in the rare but consequential intersection between catastrophic genome restructuring and subsequent clonal selection, through which a single episode of genomic instability can substantially redirect tumor evolution.

Chromothripsis in Human Disease: A Panoramic View

Once regarded as a rare genomic curiosity, chromothripsis is now recognized across a broad spectrum of human diseases. The increasing use of whole-genome sequencing has revealed its presence in diverse pathological contexts, ranging from aggressive malignancies to congenital developmental disorders [8,35,67,68]. These distinct settings are critical to understanding how catastrophic chromosome rearrangement can produce markedly different biological outcomes depending on cellular context, genomic configuration, and subsequent selection.

Cancer: The primary arena

Most studies of chromothripsis have focused on cancer, where its prevalence varies substantially between tumor types. Particularly high frequencies have been reported in several sarcomas, including osteosarcoma, as well as in glioblastoma and advanced prostate cancer [8,16,66]. Chromothripsis has also been identified across a wide range of other solid and hematological malignancies, although reported frequencies differ according to tumor type, disease stage, sequencing platform, and the criteria used for detection [69,70]. These observations suggest that chromothripsis is not restricted to a specific lineage but may provide a selective advantage in tumors capable of tolerating extensive genomic disruption. In several malignancies, chromothripsis has been associated with aggressive disease characteristics, genomic complexity, and poorer clinical outcomes, although these associations are not universal and may depend on tumor type and the specific genomic alterations generated [57]. Pan-cancer analyses have further demonstrated that chromothripsis genomes frequently coexist with other forms of genomic instability and alterations in DNA damage-response and cell-cycle pathways, consistent with the possibility that impaired checkpoint control facilitates survival following catastrophic genome damage [21,57,71].

Congenital disorders and developmental syndromes

Beyond cancer, chromothripsis has been identified in patients with congenital abnormalities, intellectual disability, and developmental delay [72,73]. Constitutional chromothriptic rearrangements may involve one or several chromosomes and can arise de novo during gametogenesis or early embryonic development. Their phenotypic consequences depend largely on the genomic regions affected and the balance between retained, deleted, and rearranged sequences, ranging from relatively mild developmental abnormalities to severe multisystem disorders. Several congenital syndromes have been associated with complex chromosomal rearrangements displaying chromothriptic features, including abnormalities affecting chromosomes 4, 7, 8, 11, and 18 [60,74,75]. In this setting, chromothripsis illustrates an important distinction from cancer: the same fundamental process of chromosome fragmentation and reassembly can produce developmental phenotypes rather than malignant transformation. Viability depends on whether essential genes and regulatory elements are preserved and whether the resulting rearrangement remains sufficiently compatible with normal development. Thus, cellular context and subsequent selection are critical determinants of the consequences of chromothripsis.

Chromothripsis in normal cells: A physiological process?

An emerging and more controversial area concerns reports of chromothripsis-like rearrangements in apparently normal cells, including cultured lymphocytes, pluripotent stem cells, and developing neural cells [63,76,77]. In the nervous system, catastrophic genomic rearrangement has been proposed as a potential source of somatic genomic diversity during neurodevelopment [78,79]. However, the extent to which such events represent genuine physiological chromothripsis remains uncertain. Experimental artifacts, culture-associated genomic instability, and differences in the criteria used to define chromothripsis may account for some observations. Current evidence therefore does not support a simple distinction between "physiological" and "pathological" chromothripsis [60,80]. Rather, these findings raise the possibility that catastrophic genome rearrangement can occur outside malignancy, while emphasizing that its biological consequences depend heavily on when and where the event occurs. Determining whether rare chromothoracic events contribute meaningfully to normal tissue biology or instead predominantly represent deleterious genomic accidents remains an important question for future research.

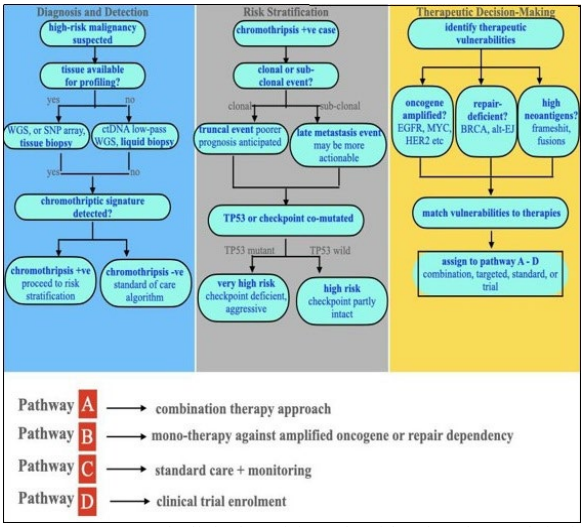


Figure 3: Proposed Clinical Decision Algorithm for Chromothripsis-Positive Malignancies. This flowchart integrates current genomic evidence into a practical framework for oncologists managing patients with aggressive or therapy-refractory tumors. The algorithm is divided into three phases: (1) Detection—emphasizing the role of whole-genome sequencing or liquid biopsy-based fragmentomics to identify chromothriptic signatures; (2) Risk Stratification—distinguishing clonal from subclonal events and assessing co-mutation status (particularly TP53) to refine prognosis; and (3) Therapeutic Decision-Making—matching identified structural vulnerabilities (oncogene amplifications, DNA repair dependencies, and neoantigen burden) to available or investigational therapies. The algorithm acknowledges that many recommendations remain experimental and advocate for clinical trial enrolment whenever feasible. This framework is intended to stimulate discussion and hypothesis generation rather than serve as a rigid protocol, reflecting the rapidly evolving nature of chromothripsis research. Abbreviation: WGS: whole genome sequencing; SNP: single nucleotide polymorphism; ctDNA: circulating tumor DNA; alt-EJ: alternative end joining.

Clinical and Therapeutic Implications

Recognition of chromothripsis as a distinct form of genomic catastrophe has important implications for

clinical oncology, extending beyond its biological significance to opportunities for improved prognosis, therapeutic targeting, and diagnostic refinement [27,75]. However, translating these insights into routine practice remains challenging. Figure 3 depicts an outline of a clinical decision algorithm for chromothripsis-positive cancer cases.

Chromothripsis as a prognostic biomarker

Across multiple tumor types, chromothripsis is associated with adverse clinical outcomes, including shorter progression-free and overall survival, increased metastatic potential, and resistance to conventional chemotherapy and radiotherapy [81,82]. This aggressive phenotype reflects the simultaneous oncogene amplification, tumor suppressor loss, and extensive structural rearrangement generated by chromothripsis. Importantly, clonality appears to influence its prognostic significance: clonal chromothripsis, affecting a large proportion of tumor cells, is generally associated with poorer outcomes than subclonal events [83]. Incorporating chromothripsis status into established risk-stratification models could therefore improve prognostic assessment and identify patients requiring intensified surveillance or early therapeutic intervention.

Therapeutic vulnerabilities: Exploiting the catastrophe

Although chromothripsis promotes tumour aggressiveness, the genomic instability it generates may also create therapeutic vulnerabilities [66,84]. Chromothriptic cells can become dependent on DNA damage-response and repair pathways, including alternative end joining (alt-EJ) and non-homologous end joining (NHEJ), potentially sensitizing them to DNA repair inhibitors [85]. PARP inhibitors may be particularly relevant in tumors harboring homologous recombination deficiencies, while ATR and CHK1 inhibitors represent promising strategies for exploiting replication stress [86,87]. In addition, chromothripsis-associated focal amplifications may generate actionable targets, including EGFR in glioblastoma, MDM2 in sarcomas, and HER2 in breast cancer. The increased mutational burden and potential neoantigen generation associated with chromothripsis may also enhance tumor immunogenicity, providing a rationale for immune checkpoint blockade [88,89].

Diagnostic hurdles and the path forward

Clinical implementation is currently limited by diagnostic challenges. Conventional cytogenetics and FISH lack sufficient resolution, while targeted sequencing panels may miss the complex copy-number oscillations and structural rearrangements characteristic of chromothripsis. Whole-genome sequencing is still the most complete method, but it is expensive and requires a lot of computing power. Emerging strategies, including circulating tumor DNA fragmentomics and low-pass whole-genome sequencing, may offer scalable non-invasive alternatives [9,24,90]. Nevertheless, their clinical sensitivity and specificity require prospective validation. Until robust, accessible detection strategies are established, chromothripsis will remain primarily a research biomarker rather than a routine component of clinical decision-making. Unanswered questions, future directions, and concluding perspectives are essential for better comprehending chromothripsis. As chromothripsis has evolved from a striking genomic observation into a well-established phenomenon, the field is approaching an important transition from description to mechanistic and translational understanding [35, 91]. Although considerable progress has clarified its molecular basis and clinical associations, fundamental questions remain regarding how catastrophic events are initiated, how shattered chromosomes are reassembled, and how chromothriptic clones subsequently evolve. Addressing these questions will determine whether insights into chromothripsis can be translated into clinically actionable strategies [92].

The trigger: What determines chromosomal vulnerability?

A central unresolved question is why specific chromosomes undergo catastrophic fragmentation while others remain unaffected. The micronucleus pathway provides a plausible mechanism for chromosome isolation and subsequent DNA damage but does not fully explain why particular chromosomes are preferentially targeted. Replication stress, fragile genomic regions, chromatin organization, and three-dimensional nuclear architecture may collectively influence susceptibility [93-95]. Defining these determinants could reveal biomarkers of chromothripsis risk and identify mechanisms that determine whether damaged cells undergo apoptosis or survive and propagate catastrophic rearrangements.

Chromosomal reassembly: Stochastic or regulated?

The mechanisms governing the reassembly of shattered DNA also remain incompletely understood. Although fragment ligation is often considered largely stochastic, emerging evidence suggests that genomic features such as replication origins, transcriptionally active regions, and essential genes may influence fragment retention and ordering [96-99]. Integrating single-cell sequencing, long-read sequencing, and live-cell imaging of DNA repair could clarify the spatial and temporal dynamics of reconstruction and establish general principles applicable to other forms of complex structural variation.

Evolutionary dynamics and therapeutic opportunities

Chromothripsis can generate substantial fitness advantages by simultaneously altering multiple oncogenic and tumor-suppressive pathways. However,

the resulting genomic instability may also impose a fitness cost, potentially creating transient vulnerabilities during early clonal expansion. This raises the possibility of therapeutic windows in which dependence on DNA damage-response pathways is greatest [100,101]. Longitudinal liquid biopsy approaches, including analysis of circulating tumor DNA and fragmentomic signatures, may ultimately enable real-time detection of chromothriptic clones and facilitate treatment during such vulnerable states. Prospective studies will be essential to determine whether these concepts can be translated into clinical benefit.

Beyond Cancer

The contribution of chromothripsis to non-malignant disease remains poorly defined. Its potential involvement in aging, neurodevelopment, neurodegeneration, and chronic inflammation warrants further investigation. Micronuclear DNA can activate the cGAS–STING pathway, raising the possibility that recurrent or low-level chromosomal catastrophe could contribute to inflammatory phenotypes associated with aging [102,103]. Reports of chromothriptic signatures in neurons further suggest that this phenomenon may have broader biological relevance than previously recognized [104].

Conclusion

Chromothripsis has fundamentally expanded the classical view of genome instability, demonstrating that cancer evolution can proceed through abrupt, catastrophic genomic change rather than solely through gradual accumulation of alterations. A single event can simultaneously generate oncogene amplification, tumor suppressor loss, and complex structural rearrangements, profoundly reshaping tumor evolution. These features also create potential diagnostic, prognostic, and therapeutic opportunities, including exploitation of DNA repair dependencies and chromothripsis-associated genomic alterations. Realizing this potential will require deeper mechanistic insight, improved detection technologies, and prospective clinical validation. Ultimately, chromothripsis represents not merely a form of genomic catastrophe but a powerful lens through which to understand the remarkable plasticity, resilience, and vulnerability of the human genome.

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Data sharing statement

The data that supports the findings of this study are available from the corresponding author upon a reasonable request.

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