

The Laws of the Ring: Governing Mechanisms, Diagnostic Standards, and Therapeutic Potentials for Human Constitutional Ring Chromosomes

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Rec date: March 20, 2018; Acc date: March 30, 2018; Pub date: April 03, 2018

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Abstract

Human constitutional ring chromosomes are a rare type of chromosome structural abnormalities. The cytogenomic analysis of ring chromosome cases revealed different genomic imbalances and ring structures, variable levels of dynamic mosaicism, and selective karyotype evolution in different tissues. This cytogenomic heterogeneity is likely correlated with variable clinical manifestations of generalized features of 'ring chromosome syndrome', chromosome-specific and segmental aneuploidy related phenotypes, and risks of infertility and various types of cancers. Better understanding of the 'biologic law' governing ring chromosome formation and its mitotic segregation can contribute to the 'diagnostic law' guiding toward best practice in genetic analyses and the 'therapeutic law' for evidence-based treatment and management of ring chromosome disorders. Collaborative efforts are needed to study the biological processes involving ring chromosome formation, mitotic segregation and cell-autonomous correction, to develop cytogenomic diagnostic standards, and to generate registry of ring chromosome cases with defined genomic structures and dynamic mosaicism and detailed clinical manifestations. These efforts could provide more reliable karyotype-phenotype correlations for developing chromosome-specific guidelines and recommendations for genetic counseling and clinical treatment.

Keywords: Ring chromosome; Dynamic mosaicism; Breakage-fusion-bridge cycle; Variable clinical manifestations; Diagnostic standards; Chromosome therapy

Introduction

Human constitutional ring chromosomes are a rare type of chromosome structural abnormality with an estimated occurrence of 1 in 50,000 newborns; given an average global birth rate of 1.85% on a total population of 7.6 billion in 2017, it was estimated that there are about 2,800 newborns carrying a ring chromosome annually [1-3]. Recently, an online Human Ring Chromosome Registry was validated using reported ring chromosome cases in the Chinese population [3]. The major findings revealed from this case series were as follows. First, the relative frequencies for ring chromosome varied; the most frequently seen were ring chromosomes 13, X, 22, 15, 14, and 18 and the least seen were 16, 17 and 19. Second, genomic imbalances were detected in majority of cases analyzed by microarray or genomic sequencing. Third, variable clinical manifestations of developmental delay, dysmorphic facial features, intellectual disability, microcephaly, and hypotonia were noted in most autosomal ring chromosomes [3]. The application of various genomic technologies has further characterized the genomic structures and imbalances in the human ring chromosomes [4-7]. Cell-autonomous correction of ring chromosomes in human induced pluripotent stem cells (iPSC) has provided insight into potential chromosome therapy [8]. Better understanding of the 'biologic law' governing ring chromosome formation and its mitotic segregation can contribute to the 'diagnostic law' guiding toward best practice in technology-driven genetic analyses and the 'therapeutic law' for evidence-based treatment of ring chromosome disorders [9].

Literature Review

Governing mechanisms from ring formation to mitotic segregation

The study of chromosomal and genomic structures from cases with a ring chromosome proposed three mechanisms for the ring chromosome formation [1-3]. The first mechanism is the fusion of telomeric or sub-telomeric regions at distal short arm and long arm from the same chromosome which forms a so-called 'complete ring' chromosome without any loss and gain of genetic material [1]. The second mechanism is the fusion of either a double-strand break at one end and telomere at the other or double-strand breaks at both ends of a chromosome to form an 'incomplete ring' with loss of genetic material [1-6]. The third mechanism is through an inverted duplication deletion rearrangement to form complex ring, supernumerary ring, neocentromeric or acentric marker chromosome involving segmental deletion and duplication [2,7]. A study of 14 ring chromosome cases found that two cases had a complete ring and twelve cases were incomplete rings [1]. Of the 19 cases studied by chromosome and genomic analyses in the Chinese case series, one case had a complete ring and 18 cases were incomplete rings [3]. These observations suggested that approximately 10% of constitutional ring chromosomes were formed by a telomeric or subtelomeric fusion and 90% involved a fusion of one or two double-strand breaks. The inverted duplication deletion mechanism likely resulted in intra-/inter-chromosomal small supernumerary ring chromosome and acentric or neocentromeric marker chromosomes [2].

Cells with a ring chromosome formed by the initial break-fusion mechanisms could present a dynamic mosaicism by a breakage-fusion-

bridge cycle during mitosis [2,3]. A ring chromosome replicated in the S phase with none, one (or odd number), or two (or even number) sister chromatid exchanges will generate intact ring, dicentric ring, or interlocked rings, respectively. Through the mitosis, the dicentric or interlocked ring chromosomes require a breakage event and thus show lagging at anaphase and nondisjunction into telophase. A dicentric chromosome can persist through mitosis and cytokinesis by forming a long chromatin bridge coated with nuclear membrane between the two daughter cells; this bridge resolves into single stranded DNA by the cytoplasmic 3' repair exonuclease 1 (TREX1) and induces nuclear envelope rupture [10]. Mis-segregated dicentric or interlocked ring chromosomes are captured in a micronucleus and experience further break-fusion rearrangement to form ring chromosome variants or to lose the ring chromosome [2,3]. The initial ring chromosome and derived ring chromosome variants may experience cellular selection for a karyotypic evolution. For example, the break-fusion-bridge cycle induced chromothripsis and somatic rearrangement of chromosome 21 was noted in pediatric B-lineage acute lymphoblastic leukemia [11]. Furthermore, it was speculated that the formation of a ring could induce epigenetic changes by spreading of heterochromatinization and dysregulate the gene expression [12].

It was hypothesized that the initial break-fusion event for ring chromosome formation and the break-fusion-bridge cycle in mitotic segregation vary for different ring chromosomes, and thus present differences in ring chromosome instability. More studies on larger case series of ring chromosomes are needed to fully understand the underlying mechanisms involving the cell cycle arrest by anaphase lagging, cell death by resultant segmental or whole chromosome aneuploids, and the selection process for karyotypic evolution.

Diagnostic standards for defining ring chromosome structure and behavior

Cell-based karyotyping and fluorescence *in situ* hybridization (FISH) testing are routinely used to detect ring chromosomes and to define their dynamic mosaicism; DNA-based array comparative genomic hybridization (aCGH) and genomic sequencing have been introduced to characterize the genomic structure and imbalances in the ring chromosomes [3-7]. Current cytogenetic laboratory guidelines have a general principle for analyzing mosaic chromosomal findings but are not specific for analyzing ring chromosomes and measuring dynamic mosaicism. For all constitutional ring chromosomes, an integrated cell-based and DNA-based cytogenomic approach should be implemented to 1) differentiate complete ring chromosomes from incomplete or partial ones, 2) delineate genomic structure and imbalances in the ring chromosomes, and 3) define levels and nature of ring chromosome instability for dynamic mosaicism. There is an urgent need for consensus on defining levels of ring chromosome instability and their correlation with clinical findings. Outlines for diagnostic recommendations and guidelines for ring chromosomes have been proposed [3,5]. Further reviews and revisions by peer experts are needed to generate consensus and up-to-date standards toward best practice on diagnostic procedures and result interpretation.

Evidence-based clinical treatment and potential chromosome therapy

The term 'ring chromosome syndrome' was proposed by shared features of short stature and developmental delay in earlier observations from a collection of cases with a ring chromosome [13].

However, phenotypes ranging from relatively healthy to variable manifestations of developmental delay, dysmorphic facial features, intellectual disability, microcephaly and hypotonia were noted in autosomal ring chromosomes [3,14]. Syndromic or non-syndromic phenotypes from distal and interstitial deletions or duplication have been reported in ring chromosome cases [3-6]. Specific phenotypes like epilepsy correlating with ring chromosomes 14 and 20, Wilms tumor in a ring chromosome 11, an increased risk for retinoblastoma with a ring chromosome 13, infertility in patients with ring chromosomes X, Y, 21 and 22, and Turner syndrome in ring chromosome X were noted [3]. Clinical phenotypes from patients with a ring chromosome 21 were classified into three groups: 1) relatively normal phenotype with reproduction problems, 2) Down syndrome like phenotype due to the ring duplication, and 3) abnormal phenotypes from ring chromosome instability and segmental deletions and duplications [5]. All these findings indicated that the clinical heterogeneity of cases with a ring chromosome most likely correlates with the cytogenomic heterogeneity. The interpretation and prediction of clinical manifestations should be based on the characterized genomic structure, segmental imbalances, and dynamic mosaicism of a ring chromosome.

Discussion

Treatment of specific symptoms such as anticonvulsive therapy for epilepsy in ring chromosomes 14 and 21 and growth hormone supplement for ring chromosome 18 have been effective [3,15]. Recently, evidence-based guideline recommendations for clinical diagnosis and management of ring chromosome 14 syndrome have been proposed by an ad hoc task force [15]. The major symptoms in patients with a ring chromosome 14 include epilepsy, hypotonia, recurrent infections, vision and hearing complications, respiratory complications, and communication and language disorders. The recommendations outlined general management and specific treatments for each symptom. Advices for taking care of a child with this rare and complex syndrome were offered to parents. This chromosome-specific symptom-oriented disease management and treatment could be used as a model for other ring chromosomes.

Reprogramming human fibroblasts containing ring chromosomes 13 and 17 to iPSC found the correction of ring chromosome through a compensatory uniparental disomy (UPD) mechanism [8]. This cell-autonomous correction involved first the loss of ring chromosome and then the duplication of the homolog normal chromosome in five to ten cell culture passages; the correction ratio varied from different iPSC clones. A potential strategy for chromosome therapy to correct ring chromosome or other chromosome abnormalities was proposed [16]. Cells containing a ring chromosome could be reprogrammed in *in vitro* cell cultures to induce ring loss and trigger compensatory UPD, and the corrected cells could be used in cell therapy. However, there are technical limitations, procedure risk, and ethical considerations in this strategy. The cytogenetic results in ring chromosome cases did not observe *in vivo* cell-autonomous correction. Trisomy rescue, monosomy compensatory, and resultant UPD were known in the prenatal findings of fetoplacental discrepancy and confined placenta mosaicism. Cellular reprogramming to iPSC may be a necessary step to trigger compensatory UPD. Further study to understand the mechanisms of ring chromosome loss and compensatory UPD is needed for practical chromosome therapy.

Collaborative efforts for human ring chromosomes

Ring chromosome cases reported in the literature are less than 1% of its occurrence; the cytogenomic and clinical findings from this small portion of cases could be biased for more severe phenotypes and thus missed a large portion of mild and subclinical cases [3]. The development of this online Ring Chromosome Registry has provided an interactive platform to compile and curate cytogenomic and clinical findings for ring chromosome cases. For registering cases into this registry, a task force by clinical cytogeneticists and geneticists will be organized to develop diagnostic standards and registering criteria. Accumulation of more ring chromosome cases with defined genomic structures and dynamic mosaicism and detailed clinical manifestations will provide better karyotype-phenotype correlation for developing chromosome-specific guidelines and recommendations for genetic counseling and clinical treatment.

Conclusion

Furthermore, collaborative studies are needed for better understanding of the biologic, diagnostic and therapeutic laws for human constitutional ring chromosomes. The dynamic mosaicism of ring chromosome provides an *in vivo* system to monitor cellular function affected by ring chromosome variants or ring chromosome loss. The cell-autonomous correction of ring chromosomes in iPSC cells provides insight into a potential therapeutic approach. Joint efforts for in-depth research on the governing mechanisms, standardized diagnostic practice, and better treatment approach will benefit patients with a ring chromosome.

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