What is the impact of ring chromosomes' mitotic instability on phenotypic severity? Insights from a Case Series and Systematic Review

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BACKGROUND

Human ring chromosomes (RCs) are rare rearrangements usually formed by terminal deletions followed by end-to-end fusion. Their instability during cell division leads to dynamic mosaicism, which is hypothesized to contribute to more severe phenotypes compared to patients with similar pure deletions. However, systematic phenotypic comparisons are still scarce in the literature.

OBJECTIVE

To investigate the contribution of mitotic instability of acrocentric ring chromosomes to the patient's phenotype.

METHODS

We analyzed three patients from our service with acrocentric ring chromosomes using G-banded karyotyping (200 metaphases) and chromosomal microarray (CytoScan™, Affymetrix). Clinical features were coded using the Human Phenotype Ontology (HPO). We then conducted a systematic review of the literature using predefined search terms in PubMed, Scopus, Embase, BVS, and Scielo to identify reported cases of acrocentric ring chromosomes or comparable pure deletions. Deletions were mapped to the GRCh37/hg19 assembly of the human genome, and patient comparability was assessed based on deletion size and gene content (OMIM and protein-coding genes). Phenotypic comparisons were performed based on major anomaly frequencies between patients with similar deletions

RESULTS

PATIENT 1 - 46,XX,r(14)(p11q32)[18]/45,XX,-14[2] - had a 6 Mb deletion at 14q32. Major anomalies included microcephaly, seizure, congenital heart disease, recurrent infections, and global developmental delay. Patients from the literature with similar pure 14q deletions presented with similar findings, except for seizures.

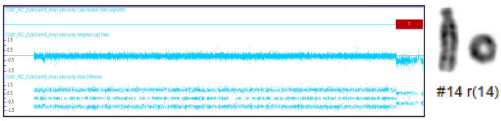

Figure 1. Karyotype and CMA results of Patient 1. Partial karyotype image of the ring chromosome 14 on the right and CMA plots showing the distal deletion identified in the long arm on the left.

PATIENT 2 - 46, XX, r(22)(p11q13)[20] - showed a 2.89 Mb deletion at 22q13 and presented with vestibular schwannoma, EEG abnormality, Parkinsonism, atypical behavior, global developmental delay, developmental regression, reduced eye contact, bronchiolitis, and mitral valve prolapse.

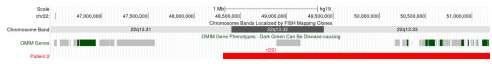

Figure 2. UCSC Genome Browser view showing a distal deletion on the long arm of chromosome 22 in Patient 2.

PATIENT 3 - 46,XX,r(22)(p11q13)[19]/45,XX,-22[1] - carried a 7.29 Mb deletion at 22q13 and showed multisystemic major anomalies, including bilateral hip dislocation, seizure, neonatal hypotonia, recurrent infections, congenital heart disease, and global developmental delay.

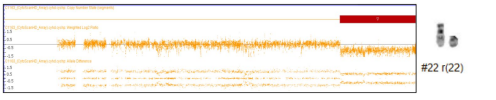

Figure 3. Karyotype and CMA results of Patient 3. Partial karyotype image of the ring chromosome 22 on the right and CMA plots showing the distal deletion identified in the long arm on the left.

Review of the literature revealed a total of 101 studies comprising 143 patients with acrocentric RC or pure distal deletions of acrocentric chromosomes. With our three cases, the final number consisted of 146 patients.

Phenotypic comparison between patients with RC and similar pure deletions revealed additional major anomalies in RC patients: refractory epilepsy in RC14 **(Figure 4)**, acute lymphoblastic leukemia, acute myeloid leukemia and thrombocytopenia in RC21 **(Figure 5)**, and schwannomas and meningiomas in RC22 **(Figure 6)**.

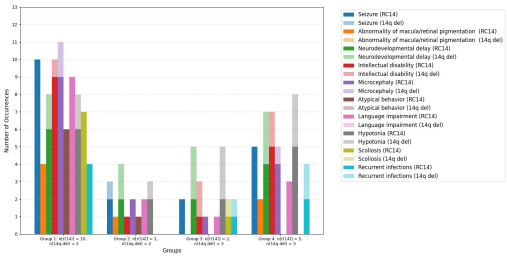

Figure 4. Bar chart showing the distribution of clinical features of RC14 and 14q Linear Deletions according to patient groups, defined based on the extent of deletions and the OMIM haploinsufficient genes encompassed by them. Seizure and abnormality of macula and abnormality of retinal pigmentation are exclusive to RC14

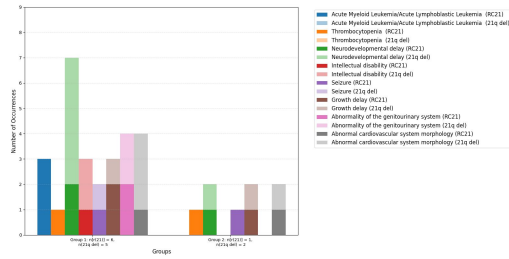

Figure 5. Bar chart showing the distribution of clinical features of RC21 and 21q Linear Deletions according to patient groups, defined based on the extent of deletions and the OMIM haploinsufficient genes encompassed by them. Acute myeloid leukemia, acute lymphoblastic leukemia and thrombocytopenia are exclusive to RC21.

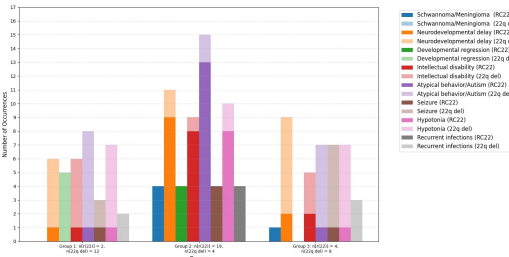

Figure 6. Bar chart showing the distribution of clinical features of RC22 and 22q Linear Deletions according to patient groups, defined based on the extent of deletions and the OMIM haploinsufficient genes encompassed by them. Schwannomas and meningiomas, tumor associated with Neurofibromatosis type 2, are exclusive to RC22 patients.

Ring loss or secondary rearrangements may underlie epilepsy in RC14 due to mosaic aneuploidy. RC21 carriers in this study, despite lacking *RUNX1* deletions, exhibited *RUNX1*-related hematological features, suggesting ring-specific mitotic instability as a driver of more severe phenotypes and predisposition to B-Acute Lymphoblastic Leukemia. In RC22, ring loss may act as a first hit for *NF2* inactivation, predisposing to neurofibromatosis type 2-related tumors.

CONCLUSION

Additional major anomalies were observed only in RC patients, supporting that patients with rings of chromosomes 14, 21 and 22 can present with a more severe phenotype, possibly due to the mitotic instability of the ring.

REFERENCES

ACKNOWLEDGEMENTS

Financial support: FAPESP (#2024/02492-2; #2022/16766-1)