WGS of 9 patients allowed a better understanding of complex chromosomal rearrangements.

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Résumé

Constitutional Chromosomal Rearrangements (CCRs) are known to be responsible for 25% of intellectual disabilities. CCRs are used to be considered as complex when involving at least 3 breakpoints on two different chromosomes. Cytogenetic microarrays and whole genome sequencing (WGS) revealed rare much more complex situations with numerous breakpoints on a single chromosome overshooting the first definition. Henceforth grouped under the *chromoanagenesis* term mechanisms generating such rearrangements remain misunderstood and their definition elusive especially since such constitutional complex chromosome rearrangement (CCR) are rare.
We performed WGS for 9 probable constitutional chromoanagenesis: 4 cases with a minimum of 4 Copy Number Variations on a single chromosome and 5 cases with at least 10 chromosome breakpoints identified in patients with balanced chromosomal rearrangements characterized with WGS (ANI project). We analyzed paired-end WGS data using BreakDancer and ERDS respectively for breakpoint and CNV calling. Our Svagga pipeline was used for filtering and annotation.

All rearrangements appeared to be more complex than initially thought with a total of 232 breakpoints and a maximum of 74 breakpoints clustered in 4 hotspots for a single patient. No statistical significant imbalance was observed compared to random distribution regarding TAD disruption or purine/pyrimidine nucleotide at breakpoint. A statistical depletion of gene-disrupting breakpoints was observed compared to theoretical distribution (p=0,0016). Nucleotide resolution showed the combination of several repairing mechanisms within a rearrangement adding complexity to complexity.

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Gathering several exceptional observations we help to delineate the chromoanagenesis phenomenon. Breakpoint distribution compared to simpler rearrangements will help understand its origins and provide new insights in cytogenomics. The French Genomic Medicine Initiative 2025 will pave the way for whole genome sequencing and shall increase the diagnostic yield for rare diseases.

Mots-Clés: Intellectual disability / Cytogenetics / Chromothripsis