CASE STUDY

CHARLES UNIVERSITY 2ND FACULTY OF MEDICINE AND UNIVERSITY HOSPITAL MOTOL

Empire Genomics Helps Show DNA Repair Machinery's Role During Germline Chromothriptic Chromosome Reassembly

Background

Complex chromosome rearrangements (CCRs) are structural variations (SVs) consisting of more than two chromosome breaks, resulting in exchanges of chromosomal segments. Balanced CCRs can exist and be transmitted without the accompaniment of a severe phenotype, but analyses at nucleotide resolution typically reveal higher complexity. Some CCRs exhibit germline chromothripsis, or multiple breakpoints and rearrangements within small regions. Germline chromothripsis can affect genes across a broad area, and is often associated with intellectual disability and developmental defects.

Objectives

In this study, several analyses were performed in order to identify and characterize the unexpected complex nature of a seemingly balanced de novo CCR in a young boy. Detailed analyses were used in an attempt to explain his symptoms, and to answer the question of whether or not the repair machinery may be responsible for handling small fragments from shattered chromosomes during germline chromothriptic chromosome reassembly.

Approach

The structure and mechanism of an apparently balanced de novo rearrangement of four chromosomes in a symptomatic boy were investigated. Microarray analysis was used to reveal two sizeable deletions, as confirmed by whole-genome mate-pair sequencing. Further complexity was revealed by Sanger sequencing. Multicolor fluorescent in situ hybridization and chromosome banding (mFISH, mBAND) were performed to better understand the CCR's complexity. Further FISH analyses were used to confirm the structural rearrangements, define the breakpoints, and verify the array findings, including the use of locus specific probes RP11-506O24 (1q23.3) and RP11-81H19 (1q24.3) manufactured by Empire Genomics.

Results

Results of extensive analyses, made possible in part by devices manufactured by Empire Genomics, reveal an unexpectedly complex, de novo CCR. The involvement of 11 segments from four participating chromosomes was confirmed, as was the presence of two deletions which could likely explain the patient's symptoms. Findings suggest that even tiny fragments from shattered chromosomes can be addressed by the repair machinery during germline chromothriptic chromosome reassembly.

Very short DNA segments can be detected and handled by the repair machinery during germline chromothriptic chromosome reassembly

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Lead Organization

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Diseases

- Complex chromosome rearrangements (CCRs)

Biomarkers Mentioned

- DNM3
- SUCO
- PAX9

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