

# 21<sup>a</sup>

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## P50 | Cytogenetics & Genomics

### Nucleotide-level resolution of a complex chromosomal rearrangement associated with cognitive disabilities reveals chromothripsis

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Chromothripsis is an extreme form of complex chromosomal rearrangement (CCR), characterized by a localized shattering and random reassembly of genomic fragments. The aim of this study is the characterization at sequence-level resolution of a cytogenetically identified CCR 46,XY,t(7;14)(q21.13;q31),inv(15)(q21.2q26.1) associated with cognitive disabilities, and intrafamilial phenotype-genotype correlation analysis. Chromosomal alterations were mapped by large-insert whole genome sequencing (liWGS). Nucleotide-level resolution of breakpoints and intrafamilial segregation analysis were carried out by junction fragments amplification and Sanger sequencing, and high-resolution array analysis. The 7q21.13 breakpoint is localized 324 bp from the 3' end of CFAP69 transcript. Although in an intergenic region, the 14q31.1 breakpoint disrupts a lncRNA. Instead of the cytogenetically reported inv(15)(q21.2q26.1), liWGS analysis identified cryptic alterations resembling chromothripsis. It involves 9 breakpoints across 60 Mb, 7 of which within an 8 Mb region, disrupting PLCB2 (OMIM \*604114). Of the 8 resulting fragments, sized 4.5 kb to 52 Mb, 6 were reshuffled within this region, whereas a 489 kb fragment, encompassing C15orf53, was deleted, and a 645 kb fragment was inserted into 3p14.1, disrupting FRMD4B (OMIM \*617467). Additionally, both liWGS and array analysis identified a novel 5.3 Mb deletion on 3p12.1-3p12.3 encompassing the neuronal axon guidance receptor ROBO1 (OMIM \*602430), associated with dyslexia, and GBE1, causing the autosomal recessive glycogen storage disease (OMIM #232500). This deletion is unreported in the Database of Genomic Variants. A 3.1 Mb deletion affecting both genes has been reported with unknown pathogenicity in the DECIPHER database. Only the proband's son with reshuffled 15q14q21.1 region is phenotypically normal. Phenotype-genotype analysis of the remaining family members shows that they share overall similar cognitive disabilities independently from their genotypes. In conclusion, the proband's revised karyotype is 46,XY,t(7;14)(q21.13;q31.1),15q14q26.2cth, ins(3;15)(p14.1;q14),del(3)(p12.1p12.3). Despite the dramatic effect of chromothripsis on the genomic architecture at the 15q14q21.1 genomic region, comprising 6 dominant disease genes, it is most likely benign or subclinical. Presently, the major candidate genes for the cognitive disabilities are those affected by the 5.3 Mb deletion on 3p12.1-3p12.3.