

High resolution array-CGH analysis apparently balanced translocations reveals complex chromosomal rearrangement and cryptic deletions associated with the phenotypes

Joaquim, T.M.¹; Grangeiro, C.H.P.¹; Genaro, F.G.O.¹;
Albuquerque, C.G.P.^{1,3}; Huber, J.³; Squire, J.A.^{1,2}; Martelli, L.R.^{1,3}

Abstract/Resumo

Apparently balanced chromosomal rearrangements (ABCR) are estimated to occur in one in 600 individuals and in only about 7% of cases the ABCR is associated with an abnormal phenotype. Several studies, including this one, have demonstrated that the phenotypic effects might be associated with genomic imbalances are not always close to the ABCR breakpoint regions. In this phenotype-genotype correlative study we used array-CGH (platform 2x400K – Agilent®) to investigate six patients who carried an ABCRs and who had clinical findings reported at the genetics clinic. The findings differed among the patients, ranging from intellectual disability, developmental milestones delay, speech delay, dysmorphisms and behavioral disorders. Array-CGH analyses suggested that the rearrangements were “truly balanced” in 5 patients. Cryptic imbalances were found in 2, one of these was detected near from the rearranged area and the other was classified as an incidental finding. In the first case, diagnosed as a *de novo* complex translocation t(2;10;12)(q33;q24;q24.3) aCGH detected a 238,447 Kb loss encompassing the *C10orf11* gene at 10q22.2, which is 20 Mb distant from the ABCR breakpoint region. A deletion at 2q33.1 (145,292kb loss) caused by a submicroscopic insertion from the 10q23 *PTEN* region was also detected. *PTEN* multicolor FISH confirmed this aberration. Previous studies of the *C10orf11* gene suggest that its haploinsufficiency could contribute to the cognitive defects and other dysmorphisms detected in our patient. The second ABCR was a t(3;15)(q29;q15) with no imbalance detected at the breakpoint regions. However an incidental 1.5 Mb deletion was seen at 2q24.2, that included the *PSMD14* and *TBR1* genes that have previously been linked to brain disorders and behavioral defects. According to the literature deletions at a considerable distance from breakpoints may be unrelated to the rearrangement, or they may reflect a more complex mechanism, that promotes both interchromosomal exchange and intrachromosomal deletion. This study provides additional evidence that ABCRs may be more complex at the genomic level, hiding cryptic rearrangements that could be associated with abnormal phenotypes.

Keyword/Palavras-chave: Chromosomal rearrangement; Apparently balanced translocation; array CGH; Genotype-Phenotype correlation

1 Department of Genetics - Ribeirão Preto Medical School, University of São Paulo, SP, Brazil, tatianamozer@usp.br.

2 Department of Pathology and Legal Medicine - Ribeirão Preto Medical School, University of São Paulo, SP, Brazil

3 Medical Genetics Division - Clinical Hospital of Ribeirão Preto, University of São Paulo, SP, Brazil.