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A de novo Complex Chromosome Rearrangement (CCR) involving chromosomes 5, 6 and 15

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Complex chromosomal rearrangements (CCRs) are structural abnormalities involving at least three breakpoints on two or more chromosomes with exchanges of chromosomal segments. The great majority of CCRs are combinations of translocations and are rare events, either familial or de novo. The number of breakpoints may vary from the simplest, with 3 breakpoints, to the most complex, with ≥ 8 breakpoints. The risk of abnormalities increases with the number of breaks.

According to the literature, about 70 % of CCRs are detected in phenotypically normal subjects, 20–25 % in patients with congenital abnormalities and/or mental retardation and 5–10 % in fetuses undergoing prenatal diagnosis. The majority of CCRs (70–75 %) are de novo; these are found in equal proportion between phenotypically normal (49 %) and abnormal subjects (51 %), due to submicroscopic imbalances or other genetic defects. These de novo CCRs appear to be preferentially of paternal origin.

The authors present the case of a 5-year-old boy with the clinical indication of developmental delay and a karyotype showing a complex apparently balanced translocation involving chromosomes 5, 6 and 15. High-resolution GTL banding, FISH and arrayCGH techniques were performed. Conventional and FISH analysis revealed the presence of 45 chromosomes, with only one free chromosome 15, and confirmed the complexity of the rearrangement demonstrating that the derivative of chromosome 6 is composed of 3 distinct segments derived from chromosomes 5, 6 and 15 with a deletion of the subtelomeric region of the short arm of chromosome 5. ArrayCGH technique detected a deletion of the segment 5p15.33–5p15.32, which includes the subtelomeric region, and another deletion in 15q11.2 that had not been observed by FISH.

The authors emphasize the importance of the combination of high-resolution GTL banding, FISH and arrayCGH studies in CCRs in order to clarify possible imbalances and thus allow better genetic counselling to patients and families.

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Application of aCGH for patients with clinical features of microdeletion 22q11.2 syndrome and negative result of the standard cytogenetic and FISH analyses

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Microdeletion 22q11.2 syndrome is one of the most frequent genomic disorders. The current state-of-art diagnostic procedure comprises karyotype and FISH testing with probes targeting the 22q11.2 locus. Due to its wide phenotypic spectrum, variable expression and highly diverse clinical features overlapping with other clinical entities, significant number of patients presenting clinical features of microdeletion 22q11.2 fail to reach diagnosis at standard cytogenetic testing. Here, we have performed further characterization of their genomic disorders using aCGH technique.

Twenty-six children fulfilling Tobias criteria but negative at standard cytogenetic evaluation of 22q11.2 were analyzed using whole-genome aCGH at 20 kb resolution (NimbleGen, Roche). The results were validated using specific qPCRs.

aCGH allowed for definite diagnosis in five (19 %) patients. A cryptic chromosomal unbalanced translocation involving the distal fragments of chromosomes 4p and 11q was detected in two siblings, one case had a well-known 1.9 Mb deletion at 1p36 and one patient had a novel pathogenic 2.7 Mb deletion at 6p25. In addition, five patients had interstitial duplications of average size 0.6 Mb, eventually classified as CNVs.

The results of our study shows that definite diagnosis using aCGH may be reached in a minor portion of the patients only, which undermines its clinical