Abstract

Carriers of apparently balanced chromosomal aberrations (BCA) are usually phenotypically normal. However, it has been estimated that up to 27% of these BCA may be associated with an abnormal phenotype, most often caused by cryptic imbalances at the breakpoints, gene disruption by the breakpoint or via the position effect. In contrast to conventional karyotyping, molecular cytogenetic techniques enable more detailed BCA characterization and better correlation between genotype and phenotype of the patient.

The aim of this thesis was to evaluate the presence of copy number variants (CNVs) at breakpoints or elsewhere in the genome in patients with abnormal phenotype who carry *de novo* or inherited BCA.

54 BCA were investigated using array CGH (20 *de novo* cases, 27 inherited and 7 cases of unknown origin) including 32 reciprocal translocations, 6 robertsonian translocations, 12 inversions and 4 complex chromosomal rearrangements. If possible, the parents were also examined to ascertain the inheritance of the relevant CNVs. In order to specify microarray findings or exclude gene disruption, FISH was used in selected patients.

Among the patients included, in 31,5% (17/54) at least one (in 8 patients more than one) significant CNV was detected. Four cases carried cryptic imbalances only at the breakpoints, ten cases had only CNVs unrelated to the breakpoints, and in three individuals CNVs were detected both at breakpoints and elsewhere in the genome. In 17 patients 34 relevant CNVs were found; eight of them were pathogenic (23,5%), 5 likely pathogenic (14,5%), 16 of unknown significance (47%) and the remaining were likely benign or benign but localized at the breakpoints. In three cases the BCA showed a higher level of complexity, and probably originated from chromothripsis. The frequencies of imbalances detected in carriers of *de novo* and inherited BCA were similar, but there were differences in localization and clinical significance of the CNVs. Pathogenic breakpoint-associated imbalances were found exclusively in *de novo* cases. In five individuals with no CNVs causal monogenic mutation were identified, in most cases using sequencing.

Our results in accordance with previous studies show that a significant part of apparently BCA is in fact unbalanced, and that these rearrangements should be investigated using array CGH in carriers of both *de novo* and inherited BCA.

Key words: array CGH, copy number variant, apparently balanced chromosomal aberration, abnormal phenotype, *de novo* and familiar BCA