

Loss of heterozygosity (LOH) Analysis in individuals with developmental delay/congenital anomalies previously investigated for 22q11.2 Deletion Syndrome

Sgardioli, I.C.; Molck, M.C.; Copelli, M.M.; Vieira, T.A.P.;
Gil-da-Silva-Lopes, V.L.

Abstract/Resumo

Loss of heterozygosity (LOH) also called absence of heterozygosity (AOH) or regions of homozygosity (ROH) can be detected by SNP-array analysis. It is observed in regions identical by descent or occurs because of errors in the mechanisms of recombination between homologous chromosomes, DNA replications or DNA repair. The 22q11.2 deletion syndrome (22q11.2DS) has a prevalence of 1/4000 live births and an extensive clinical variability. About 30% of individuals with 22q11.2DS clinical suspicion have been diagnosed with the typical 22q11.2 deletion and other genomic imbalances are often reported related to similar phenotypes. However, most of patients remain without an etiological diagnosis. Currently, there are few studies about LOH in individuals with developmental delay/congenital anomalies. The aim of this study is to describe the preliminary results of LOH analysis in individuals with clinical suspicion of 22q11.2DS. Inclusion criteria was individuals with clinical suspicion without the typical 22q11.2 deletions, previously tested by Fluorescent in situ Hybridization (FISH) or Multiplex Ligation Probe-dependent Amplification (MLPA). Exclusion criteria was parental consanguinity. A total of 124 individuals were investigated by chromosomal microarray analysis (CMA) using the CytoScan HD or 750K Array (Affymetrix®). Data were compared with a database composed by 114 control individuals from Brazilian general population. We considered only LOH biggest than 3Mb and not frequent (<1%) in control individuals. The presence of LOH was more often in the patients than in the control group (12,1% against 3,5%). In the patient group the LOH size were between 3,3Mb and 46,2Mb (average size 22,7Mb) and in the control group it was between 3,1Mb and 8,5Mb (average size 6,0Mb). It was observed only one large LOH for almost all patients, and for almost all the control group it was observed two small LOHs. Among patients with LOH, six also carried VOUS (variants of uncertain significance) and one had a pathogenic imbalance. Laboratorial confirmations and genotype-phenotype correlation are in progress. Our results clearly show a higher proportion and bigger size of LOHs in individuals with developmental delay/congenital anomalies and a possible applicability of LOH analysis as a diagnostic approach in individuals with the same characteristics of the present sample.

Support: Fapesp and CNPq

Keyword/Palavras-chave: Loss of heterozygosity (LOH); absence of heterozygosity (AOH); regions of homozygosity (ROH); chromosomal microarray analysis (CMA); 22q11.2 deletion syndrome (22q11.2DS)