Investigation of the 22q11.2 candidate region in patients with midline facial defects with hypertelorism

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Abstract. Midline facial defects with hypertelorism (MFDH) are mainly characterized by ocular hypertelorism and bifid nose. They are often associated with structural and functional anomalies of the central nervous system similar to those found in 22q11.2 deletion syndromes. In addition, there are some isolated reports of MFDH and 22q11.2 deletion. These findings suggest that MFDH may be part of the spectrum of 22q11.2 deletion syndromes. To test this hypothesis, 10 individuals with MFDH were analyzed by fluorescent in situ hybridization (FISH), but no 22q11.2 deletion was detected. In view of this result, the TBX1 gene located within the 22q11.2 candidate region was screened. A new sequence variant (1132GA) was identified in one patient. This variant was not found in 110 control individuals genotyped. Considering the rarity of this condition and results of this study, the involvement of the 22q11.2 chromosomal region in the pathogenesis of MFDH could not be excluded.

Keywords: 22q11.2 deletion, frontonasal dysplasia, hypertelorism, midline, TBX1.
FISH was performed on cultured lymphocytes, with the use of a probe for the 22q11.2 region, the HIRA/TUPLE1 gene locus (Vysis®). It was not detected deletion in any patient.

Mutation screening of TBX1 gene by direct sequencing detected several synonymous single nucleotide polymorphisms (SNPs), already reported in the NCBI database. A previously described (Gong et al. 2001; Rauch et al. 2004) and synonymous alteration 297GA was found in patient 5. The most interesting finding was a new sequence variant detected in patient 8. This patient was heterozygous for the nucleotide alteration 1132G → A. This unreported transversion was observed in codon 378 and converted a glycine residue into a serine residue (G378S) in a conserved portion of the TBX1 protein. Results of in silico algorithms were concordant about the tolerance effect of G378S variation at the protein level. However, this type of investigation is not conclusive and only experimental studies could elucidate the real effect of this alteration in TBX1 protein function. It is also noteworthy that this sequence variant was not found in a group of 110 control individuals genotyped. Parental samples are not available, so we could not recognize if the change is de novo.

Considering the detected 1132G → A sequence variant, even though the cohort of patients analyzed was relevant, the involvement of the 22q11.2 chromosomal region in the pathogenesis of MDFH could not be excluded. As the clinical heterogeneity of MDFH, other genes expressed during craniofacial development could also play a role in the phenotype of this group of patients. Since the array technique simultaneously analyzes thousands of regions on the genome to detect copy number variations, it could be applied in future etiological studies of MFDH.

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