VAN DER WOUDE SYNDROME/POPLITEAL PTERIGIUM SYNDROME: CLINICAL AND GENETIC VARIABILITY IN BRAZILIAN PATIENTS WITH IRF6 GENE MUTATIONS

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Van der Woude syndrome (VWS) is mainly characterized by pits of the lower lip and orofacial cleft, caused by different mutations in the IRF6 gene. Besides this classical clinical picture, a more severe phenotype associated with popliteal pterygium, syndactyly, pyramidal skinfold of halluces, and genital hypoplasia has been reported, resulting in the so-called popliteal pterygium syndrome (PPS). Both these syndromes display a high degree of inter - and intrafamilial phenotypic variation confirming the broad spectrum of IRF6 mutations involving the VWS/PPS. In this report we performed mutational analysis of the IRF6 gene in six Brazilian patients with VWS/PPS phenotype. Five of them had a pathogenic mutation while one had only a SNP in splice site of exon 4 (c.175-5C>G). In four cases, the pathogenic mutation involved the argenine 84 residue, being Arg84Cys in three patients with typical VWS, and Arg84His in one patient with full PPS phenotype. The patient with full PPS phenotype also had the SNP c.175-5C>G. The other pathogenic mutation, the Ala61Asp, was observed in one patient with a mild PPS phenotype and in his mother who had a typical VWS. Our data showed that the mutation in the amino acid 84, highly correlated with the PPS phenotype, could also lead to typical VWS phenotype. In addition, both phenotypes can segregate within the same family indicating that they may represent a continuous spectrum of the same condition. Other modifier genes or stochastic agents could lead to clinical variability.

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