Validation of Rare Structural Variants in Portuguese Azoospermic Patients

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Abstract

Azoospermia affects approximately 15% of infertile males. Despite considerable research efforts in the last decades, in the majority of cases the cause remains unidentified. Chromosomal abnormalities and Yq microdeletions have been thoroughly studied, yet only account for 17% of azoospermic men. In fact, little is known about the contribution of the hemizygous X-linked and autosomal genes to male infertility. This study focuses on the validation of rare deletions encompassing candidate genes on the X chromosome and on the autosomes, previously identified by Affymetrix 6.0 SNP Array, in a cohort of 166 Portuguese individuals with severe spermatogenic impairment (non-obstructive azoospermia and severe oligozoospermia). As expected, the protein-coding genes *CXORF48*, and *MAGEA8*, as well as a miRNA (hsa-mir-4330) could not be amplified by PCR from the single X chromosome of the patients suspected of carrying deletions. These rearrangements will be further validated by aCGH (array Comparative Genomic Hybridization). Additionally, by MLPA analysis on 11p13 we confirmed a large deletion (~1Mb) spanning the *WT1* gene - a conserved transcription factor known to play a crucial role in gonadal differentiation. A retrospective clinical evaluation of this patient revealed partial gonadal dysgenesis, consistent with a causal role for the newly discovered deletion. These results reveal new candidate genes for a role in spermatogenic pathways and suggest that haploinsufficiency of proteins important for the development of the male reproductive system can lead to spermatogenic dysfunction.