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ABSTRACT

Evaluation of the Somatic Alterations of the VHL Gene in Renal Cell Carcinoma associated with von Hippel-Lindau Disease (VHL)

João Paulo Vidal, Ana Carolina, Ester Barreto, Fernanda Jehee, Sergio Romano, José Claudio Casali da Rocha

Centro de Estudos do Genoma Humano, Universidade de São Paulo; Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil

The clear cell renal carcinomas (ccRCC) are aggressive tumors, found sporadically or associated with hereditary syndromes. In VHL, 25% of patients will develop a ccRCC during their lifetime. Germline mutation in the VHL gene is now detected in virtually 100% of the VHL patients following stringent clinical criteria. In ccRCCs associated with VHL, a second mutational event occurs in somatic cells of tumors. The aim of this study was to evaluate the somatic mutational events involving the VHL gene of ccRCCs removed from eight VHL patients. In total, 30 ccRCCs and 8 paired normal renal tissues were included after pathology review. VHL gene methylation was addressed by MSPCR; Sanger sequencing of the VHL gene was used to detect point mutation, and we use MLPA to evaluate VHL locus deletions. In six patients, SNP Array 6.0 (Affymetrix) data of their tumors and normal kidneys were available, and CNV of 3p was assessed for further validation. Interestingly, germline point mutation could also be detected in the tumors, and sometimes helped to confirm LOH of the VHL locus. We could characterize new somatic alterations of the VHL gene in 25 of the 30 tumors studied, including one point mutation, and 23 large deletions of 3p-ter. VHL gene methylation was not detected in any of the tumors. High density SNP Array analysis showed to be a useful tool to evaluate cytogenetic alterations in ccRCC, with an advantage of defining accurately the extension of the loss of 3p-ter. In conclusion, a number of methods combined are necessary to accurately assess somatic alterations of the VHL gene in VHL RCC.