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ABSTRACT

Somatic Alteration of the VHL Gene in Sporadic Renal Cell Carcinomas as a Potential Biomarker

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VHL alterations have been described in a high percentage of sporadic clear-cell renal-cell carcinomas (ccRCC). In most recent years, drugs targeting the pVHL/HIF pathway, such as sunitinib, sorafenib, temsirolimus and bevacizumab have proven beneficial for the treatment of ccRCC. We previously described that VHL mutation or promoter hypermethylation was associated with advanced tumor stage. As loss of the VHL function contributes to the pathogenesis of ccRCC, it is reasonable to speculate that VHL inactivation might be a prognostic or predictive factor and could be applied as a bio-marker in ccRCC. Since the publication of this data, there have been at least 11 other studies on alteration status of VHL, some of which support the prognosis hypothesis, some do not. This could be due to several reasons, such as different detection methods applied, the number of cases studied or the limited observation time. We have improved our detection rate of VHL alterations significantly by introducing the MLPA (Multiplex Ligation-dependent Probe Amplification) technique. Applying the now-a-day most comprehensive analysis techniques, including whole gene sequencing, MLPA, promoter methylation analysis and 3 p loss of heterozygosity studies, we extended out initial study by the number of cases studied and the observation time. As a single center study, we included 129 cases of RCC for a follow-up time of 12 to 17 years. Genotype-phenotype association and survival curves demonstrate the prognostic importance of VHL alteration for ccRCC. These findings will be discussed in the light of the results of recent studies.