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ABSTRACT

Tale of the Tail: Clinical and Functional Properties of Novel VHL Mutation (S214L) Consistent with Type 2A Phenotype and Low Risk of Renal Cell Carcinoma

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This report describes the clinical and functional properties of a novel von Hippel Lindau variant (X214L) in families with a Type 2A phenotype. The same or similar VHL point mutations were identified in several Type 2A families. This stop codon mutation predicts the translation of a "runon" protein, extending the length of the normal VHL protein by 14 amino acids. We identified four families with pheochromocytoma-dominant VHL phenotypes who carry stop codon mutations. Although the elongated VHL protein length is the same, the amino acid encoded by the stop codon mutation is different in three of the four families, making shared family origin very unlikely. Western blot was conducted using VHL null renal clear carcinoma cell lines that expressed wild type or X214L mutant pVHL. The predicted 14 amino acid extended protein was stably expressed. The X214L mutant pVHL downregulated HIFá expression in a normal, canonical hydroxylationdependent, manner. Defective variant regulation of JunB protein expression was identified. Thus we concluded that the gene variant, X214L, appears to be a deleterious mutation associated with a Type 2A VHL phenotype. Jun B seems to be the targeted part of the VHL machinery that leads to tumor development in germline carriers of this variant. The variant's ability to regulate HIF, predicts for a low risk of clear cell renal carcinoma.