Germline *MET* pathogenic variants in papillary renal cell carcinomas type I: specific phenotype in French population and novel germline pathogenic variant *MET* c.3389T>C, p.(Leu1130Ser)

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Abstract

Hereditary papillary renal cell carcinoma (HPRCC) is a rare inherited renal cancer syndrome characterized by bilateral and multifocal papillary type 1 renal tumors (PRCC1). Activating germline pathogenic variants of *MET* gene were identified in HPRCC families. We reviewed the medical and molecular records of a large French series of 158 patients screened for *MET* oncogenic variants (153 index-cases and five relatives). *MET* pathogenic variant rate was 10.4% (16/153) with 37.5% among patients with familial PRCC1 and 3.3% among patients with sporadic PRCC1 presentation. The phenotype in *MET* mutated cases was characteristic as PRCC1 tumors were mainly bilateral (82.3%) and multifocal (85.8%). Histologically, six out of seven patients with *MET* germline pathogenic variant harboured biphasic squamoid alveolar PRCC. Genetic screening identified in four index-cases a novel missense pathogenic variant within the tyrosine kinase domain: *MET* c.3389T>C, p.(Leu1130Ser). Functional assay confirmed its oncogenic effect with a constitutive phosphorylation of ERK protein and an abnormal focus formation induced. The genotype-phenotype correlation between *MET* pathogenic variants and PRCC1 presentation should encourage to widen the screening, especially toward non-familial PRCC1. This precise phenotype also constitutes a strong argument for the classification of novel missense variants within the tyrosine kinase domain when functional assays aren't accessible.

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