Inherited Predisposition to Renal Cell Carcinoma (RCC)

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Approximately 3% of cases of RCC are recognised as having a genetic basis and a variety of syndromic and non-syndromic forms of RCC have been delineated. The identification of the molecular basis of inherited RCC, as exemplified by von Hippel-Lindau disease, has been fundamental to understanding the molecular mechanisms of sporadic of RCC and to the development of treatments for metastatic RCC. In addition, the identification of a pathogenic variant in a RCC predisposition gene (RCG) enables genetic testing of at risk relatives and surveillance for early RCC reducing morbidity and mortality. In our clinical practice individuals with features of inherited RCC (familial RCC and/or multiple RCC and/or early age at onset and/or syndromic features) are routinely tested for mutations in a five gene panel (*VHL, FH, FLCN, MET, SDHB*) and constitutional translocations with *FLCN* and *SDHB* mutations being the most common findings individuals without syndromic features. However, the overall diagnostic yield of testing is low and variants of uncertain significance (VUS) can pose difficulties. We have investigated the basis of the "missing RCC heritability" by undertaking panel, exome and genome sequencing in cohorts of individuals with features of inherited RCC to identify additional genetic causes for syndromic and non-syndromic cases. Our investigations have identified rare pathogenic variants in genes outside of those that are tested routinely (e.g. *CHEK2, MAX, TMEM127, TP53*) and additional potential candidate genes (e.g. *BRIP1*) that require point validation. Whilst expanding genetic testing for inherited RCC to a wider gene set would increase diagnostic yield the clinical utility of such an approach needs to be confirmed. A drawback to wider genetic testing is increased detection of VUS and we have sought to develop tools to aid variant interpretation for *FH* and *SDHx* genes using in vitro and in vivo metabolomics.