The Relationship between Renal Cell Carcinoma and Lynch Syndrome – More Investigation is Needed

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Background

Lynch syndrome is an inherited cancer predisposition syndrome with increased lifetime risks for colorectal cancer, uterine cancer, small bowel cancer, ovarian cancer, and transitional cell carcinoma of the renal pelvis, as well as other malignancies. Mutations in *MLH1, MSH2, MSH6, PMS2*, and *EPCAM* are known to cause Lynch syndrome. The risk to develop transitional cell carcinoma of the ureter and renal pelvis is thought to be 4-12%. We sought to determine whether other types of renal cell carcinoma are increased in Lynch syndrome.

Methods

Ambry Genetics created a multi gene test, RenalNext, to assess for alterations in 18 genes linked with hereditary renal cell carcinoma. This test included sequencing and deletion/duplication analysis of the following genes: *FH, FLCN, MET, MITF, MLH1, MSH2, MSH6, PMS2, PTEN, SDHA, SDHB, SDHC, SDHD, TP53, TSC1, TSC2, VHL* as well as duplication/deletion analysis of *EPCAM.* Patients were selected clinically by their provider based on personal and/or family history of renal cell carcinoma.

Results

201 RenalNext tests have been reported as of May 31, 2014. Eighteen (9.0%) were positive for a pathogenic mutation. Of the 18 mutations, three were identified in *PMS2* (14.3%) and one was identified in *MSH2*. Three of these met clinical criteria for Lynch syndrome testing and all had a personal diagnosis of renal cell carcinoma (3 clear cell carcinomas, one unspecified).

Forty samples (19.9%) had a VUS in one or more genes. VUSs were identified in 14 of the 18 genes on the panel, with 17 of 46 (37.0%) total VUSs being in a Lynch syndrome gene (1 in MSH2, 2 in *MLH1*, 3 in *MSH6* and 11 in *PMS2).* The VUS rate for *PMS2* was noted to be significantly higher in the RenalNext cohort compared to other multi-gene test cohorts at Ambry Genetics (5.5% compared to 2.1%) (p value =0.002).

Twenty four individuals tested had a personal or family history that met revised Bethesda Guidelines (11.9%). Of these, 14 tested negative (66.7%), four had VUSs is non Lynch syndrome genes (16.7%), one had a VUS in *MSH6* (4.2%), four tested positive (3 in *PMS2*, 1 in *FLCN*), and one had a likely pathogenic VUS in *MSH2* and a VUS in *FLCN* (20.8% positive overall).

Conclusions

Lynch syndrome mutations and VUSs were identified in more patients with non-transitional cell renal cell carcinoma than expected. Additionally, more individuals and families who underwent RenalNext testing met the Bethesda guidelines for Lynch syndrome screening than expected. It is unknown if the renal cell carcinomas present in this population are due to Lynch syndrome mutations or other genetic or environmental factors. More research is needed to address the possible association. Clinicians evaluating patients for a personal or family history of renal cancer should be alert for indicators of Lynch syndrome.

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