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Germline genetic variants in cancers of the bladder, renal pelvis, ureter, or urethra.

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Background: Studies cite that 10-24% of patients (pts) with urothelial carcinoma (UC) have a pathogenic germline mutation (mut), but few have looked at their association with clinical outcomes. We aimed to identify the frequency of germline pathogenic variants and variants of unknown significance (VUS) in all stages of UC, and hypothesized that they would be associated with cancer-related outcomes. **Methods:** We performed a retrospective review at our institution of all pts with a diagnosis of bladder, renal pelvis, ureter, or urethral cancer who underwent germline genetic testing from 2018 to 2024. **Results:** Sixty-four pts were included. The median number of genes tested was 77 (range 5-91) with 87.5% completing a panel of ≥67 genes. Of the 64 pts, 7 (11%) had a pathogenic germline mut, 18 (28%) had a VUS without a pathogenic mut, and 39 (61%) had no germline mut. Pathogenic muts were found in *EPCAM*, *MAX*, *MSH2*, *MSH6*, *MUTYH*, *PMS2*, and *POT1*. Among the 7 pts with a pathogenic mut, 5 (71%) had Lynch syndrome and 1 (14%) had a non-Lynch DNA Damage Repair gene mut in *POT1*. Sixty-two pts had urothelial histology, 1 pt had with rhabdomyosarcoma with a VUS in *RET*, and 1 pt had adenocarcinoma with a VUS in *POLD1*. Comparing pts with pathogenic muts (n=7) to those with no mut (n=39), we found no significant difference in median age at diagnosis (62 [range 46-76] vs 57 [range 20-86]), age at diagnosis ≥ 60 (4 [57%] vs 17 [44%]), sex (4 [57%] vs 13 [33%] female), race, ethnicity, smoking history (3 [43%] vs 15 [38%] never smoked), median number of 1st degree family members with a diagnosis of cancer (2 [range 1-6] vs 2 [0-4]), or clinical stage at diagnosis. However, there were significantly more pts with upper tract tumors in the group with a pathogenic mut compared to the group with no mut (6 [86%] vs 11 [28%], p=0.0072). Comparing the group with a VUS (n=18) to the group with no mut (n=39), there were no significant differences in demographic variables. However, variants among Blacks or African Americans are more likely to be classified as VUS (3/4 [75%] vs 14/59 [24%], p=0.02013). VUSes were also significantly overrepresented in pts with metastatic disease (9 [50%] vs 7 [18%], p=0.0242). Adjusting for clinical stage, pts with muscle-invasive UC and a pathogenic variant had significantly shorter overall survival (OS) compared to pts with no mut (log rank p= 0.034, median OS 43.2 months vs not reached). There was no significant difference in OS for non-muscle invasive or metastatic disease. **Conclusions:** Pathogenic germline variants were detected in 11% of pts with UC, were more common in upper tract disease, and were associated with shorter OS for muscle-invasive UC. VUS were found in rare histologic variants, which warrants further investigation, and were more common in metastatic disease and non-White pts, underscoring the need for studies in populations of diverse race and ethnicity. Our findings support genetic testing in all pts with UC. Validation in a larger cohort is ongoing. Research Sponsor: None.