Germline genetic variants in cancers of the urothelial tract and association with outcomes.

Kent Kamau, Lindsey Byrne, Debasish Sundi, Akshay Sood, Shang-Jui Wang, Yuanquan Yang, Lingbin Meng, Peng Wang, Danielle Elise Zimmerman, Elshad Hasanov, Fuat Bicer Bicer, Timothy D. Gauntner, Edmund Folefac, Paul Monk III, Steven K. Clinton, Amir Mortazavi, Katharine A. Collier; The Ohio State University Comprehensive Cancer Center, Columbus, OH; Division of Human Genetics, Department of Internal Medicine, The Ohio State University, Columbus, OH; Department of Urology, College of Medicine, The Ohio State University, Columbus, OH; Department of Radiation Oncology, College of Medicine, The Ohio State University, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, College of Medicine, The Ohio State University, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Division of Medical Oncology, Department of Internal Medicine, College of Medicine, The Ohio State University, Columbus, OH

Background: Studies cite that 10-24% of patients (pts) with urothelial carcinoma (UC) have a pathogenic germline variant (var), but few have looked at association with outcomes. We aimed to identify the frequency of germline pathogenic vars (PV) in UC and hypothesized they would be associated with cancer-related outcomes. Here we present germline results from the largest reported, fully clinically annotated cohort of pts with UC. **Methods:** We performed a single center retrospective review of all pts with a diagnosis (dx) of bladder, renal pelvis, ureter, or urethra cancer who underwent clinical germline targeted panel genetic testing from 2018 to 2024. We also included all pts with the same dx enrolled on an institutional protocol that performed germline whole exome sequencing (WES) for research. We analyzed the 77 genes from WES most frequently included in the targeted panels. We classified all vars as pathogenic, variant of unknown significance (VUS), or benign. **Results:** We included 267 pts. Median number of genes tested was 77 (range 1-93) with 83.9% of pts completing a panel of ≥77 genes. Of 267 pts, 48 (18%) had a PV, 138 (52%) had a VUS without a PV, and 81 (30%) had no germline var. The most common PVs were in *CHEK2 (n = 5/48 [11%])*, *ATM (9%)*, *MUTYH (9%)*, *MSH2 (9%)*, *TP53 (7%)* and *MLH1 (7%)*. Among the 48 pts with a PV, 12 (25%) had Lynch syndrome and 25 (52%) had a non-Lynch DNA Damage Repair gene var. Of 256 pts with urothelial histology, 47 (18%) had a PV. Of 7 pts with pure squamous histology, 1 (14%) had a PV in *ATM*, 4 (57%) had a VUS. Three pts with rare histologies of small cell, rhabdomyosarcoma, and adenocarcinoma had a VUS in *ATM, RET, or POLD1*, respectively. Of 48 pts with a PV, only 12 (25%) ever developed metastatic disease. Comparing pts with PVs (n=48) to not (n=219), we found no significant difference in median age at dx, age at dx ≥ 60, sex, race, ethnicity, smoking history, median number of 1st degree family members with a dx of cancer, or clinical stage at dx. Pts with a PV had no significant difference in primary tumor location, however pts with Lynch syndrome were more likely to have an upper tract tumor (p = 0.002). Adjusting for clinical stage, there was no significant difference in overall survival between pts with a PV compared to without. Three of 12 pts with Lynch received an immune checkpoint inhibitor (ICI) for non-muscle invasive, muscle invasive, or metastatic disease, respectively, and all had prolonged responses without recurrence at 44, 12, and 70 months of follow-up. **Conclusions:** Germline PVs were detected in 18% of pts with UC. We confirmed the association of Lynch syndrome with upper tract disease and favorable response to ICI. Germline genetics of rare histologic variants warrants further investigation. Our findings support genetic testing in all pts with UC, including early-stage disease. Further study of ICIs for early-stage UC in Lynch syndrome is needed. Analysis of a larger cohort and response to specific treatments is ongoing. Research Sponsor: None.