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Papillary renal cell carcinoma, glioma and colon polyps in a patient with novel *POT1* variant

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Background: *POT1* tumor predisposition (*POT1*-TPD) is a rare autosomal dominant cancer susceptibility syndrome with fewer than 100 families reported in the literature. It is caused by heterozygous pathogenic variants in the *POT1* (protector of telomeres 1) gene. Core cancers associated with *POT1*-TPD include cutaneous melanoma, chronic lymphocytic leukemia (CLL), glioma and cardiac angiosarcoma. Limited evidence suggests that other associated cancers may include colorectal, thyroid and breast angiosarcomas. Less than 100 families have been identified with POT1-TPD to date.
POT1 is part of the telomere shelterin complex which facilitates telomere protection and access. The majority of variants identified in this gene are classified as of uncertain significance due to insufficient data based on ACMG classification criteria.
Case presentation: We present a 56 year old woman with history of chronic left back pain. CT imaging showed a heterogeneously enhancing left renal mass concerning for malignancy. The patient underwent a radical nephrectomy and was diagnosed with papillary renal cell carcinoma (RCC), type 2. She reported a strong, but limited family history of cancer including a brother with lymphoma, mother and maternal aunt with melanoma, father who developed lung cancer and had history of smoking and multiple maternal and paternal relatives with cancer diagnoses of unknown primary. A multi-gene cancer panel revealed a heterozygous likely pathogenic variant in *POT1* (NM_015450.3(POT1):c.125-2A>G). She had a recent colonoscopy which was significant for 8 colon polyps (6 hyperplastic, 2 tubular adenomas) and underwent polypectomy. Follow up brain MRI was ordered based on *POT1*-associated cancer risks. This revealed a left orbitofrontal lesion with findings suggestive of primary glial neoplasm. The patient underwent craniotomy and was diagnosed with a grade 2 glioma with future plans to treat with radiation therapy and systemic chemotherapy. Due to the *POT1*-TDP-related cancer, family history of related cancer, and likely pathogenic variant, the patient was diagnosed with *POT1*-TDP.
The patient has past medical history of headache and obesity. She has a 15 year history of tobacco use with smoking a half pack of cigarettes per day which was discontinued 10 years prior to her presenting for medical attention. She reports moderate alcohol consumption with 4 to 5 drinks per week.
Conclusion: This is to our knowledge, the first reported case of papillary RCC in a person with *POT1*-TPD. *POT1*-TPD has a clear association with cutaneous melanoma, glioma and angiosarcoma. There are patients described with family history of renal cancer; however, those family members did not have genetic testing so it is unknown if they have the *POT1* familial variant. Interestingly, *POT1* is functionally expressed in human embryonic kidney, making it plausible that it increases risk for kidney cancer. While the patient has some risk factors for RCC, we cannot exclude the possibility that the RCC is associated with her diagnosis of *POT1*-TDP. Due to the rarity of *POT1*-TPD it is unclear if additional cancers outside of the core-described cancers are associated with this gene. Further studies are needed to define the *POT1*-TPD tumor spectrum and risks.
The *POT1* c.125-2A>G variant has not been reported in the literature and is not present in population databases. It is classified by the performing laboratory as likely pathogenic. This variant affects an acceptor splice site in intron 6 of the *POT1* gene and is predicted to result in aberrant RNA splicing. Description of this variant in a patient with a core cancer diagnosis (and with family history of core cancer diagnoses) supports the classification as likely pathogenic and may assist in the interpretation of future sequencing results.

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ePO47

Germline cancer predisposition variants in a cohort of early-onset Merkel cell carcinoma patients

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Introduction: Merkel cell carcinoma (MCC) is a rare and highly aggressive skin cancer that is associated with advanced age and immunosuppression. Most patients diagnosed with MCC are older than 70 years of age, with incidence below age 50 being rare. To date, no cases of familial MCC have been reported. To identify possible predisposition alleles in a cohort of 37 early-onset MCC patients, ages 18-49 (median age = 45 years, females = 17, males =27), we performed genome sequencing and subsequent clinical-grade analysis. We report findings from this cohort and discuss the benefits of genome sequencing in detecting germline variants in known cancer predisposition and DNA repair genes.
Methods: We performed genome sequencing on peripheral blood DNA from patients diagnosed with MCC prior to age 50. Analysis was carried out using the custom-enhanced analysis tool, SEQR, developed for the NIAID Centralized Sequencing Program. First-tier analysis focused on rare pathogenic and likely pathogenic variants in known cancer predisposition genes. Additionally, we identified rare variants of unknown clinical significance in the same group of genes.
Results: Our analysis identified variants in known cancer predisposition genes in 16/37 (43%) early-onset MCC patients across 14 autosomal genes. Notably, 5/37 (14%) of these patients were heterozygous for previously well-described pathogenic variants in cancer predisposition genes (*ATM* = 2, *BRCA1* = 2, and *BRCA2*). Furthermore, 4/37 (11%) patients had likely pathogenic variants in other known cancer predisposition genes (*FANCA*, *RAD54L*, *SMARCAD1*, and *TP53*). Additionally, 8/37 (22%) patients had very rare (minor allele frequency ≤ 3.5E-05) variants of uncertain clinical significance in cancer predisposition genes (*APC*, *ATM*, *ERCC4*, *FANCA*, *FGFR3*, *PTCH1*, *TSC1*, *WT1*). Genome-based copy number variant (CNV) analysis did not detect any underlying CNVs in *BRCA1* and *BRCA2*.
Conclusion: Our study demonstrates the clinical value of genomic workup in early-onset MCC patients and suggests that heritable cancer predisposition variants can increase the risk for MCC. As 6 (16%) patients carried variants strongly associated with familial cancer syndromes (*ATM*, *BRCA1*, *BRCA2*, and *TP53*), including inherited risk for breast and other malignancies, the genomic sequencing resulted in a high frequency of personal and familial benefit. Genetic counseling and cascade testing are indicated for patients and their families to ascertain the familial risk for inherited cancer predisposition. Further investigation