Melanoma Risk in POT1 Mutation Carriers from a MGPT Cohort

Kelly Fulk, Jeni Herrera-Mullar, Carrie Horton, Holly LaDuca

Background

POT1 (protection of telomeres 1), a gene which plays a critical role in telomere regulation, has recently been implicated in familial melanoma, glioma, and sarcoma. We aimed to determine the incidence of melanoma and other cancer types in individuals with *POT1* loss of function (LOF) alleles undergoing multigene panel testing (MGPT) for a variety of cancer indications.

Methods

We conducted a retrospective clinical data review of MGPT cases from January 2017 through December 2019 in which a *POT1* LOF variant (resulting in a premature stop codon or with deleterious splicing impact) was identified. Cases with a pathogenic/likely pathogenic variant in another gene were excluded. Tumor frequencies among *POT1* LOF carriers were compared with a subset of MGPT-negative probands tested during the same time frame using Fisher's exact test.

Results

Of the 115 *POT1* LOF carriers from our MGPT cohort, 75 (65%) were affected with cancer. Melanoma and sarcoma were among the five most common types of cancer in POT1 LOF carriers. Compared to individuals with negative MGPT results, *POT1* LOF carriers were 5.7-fold more likely to be diagnosed with melanoma (95% CI 3.2-10.3; p=<0.001) and 6.4-fold more likely to be diagnosed with sarcoma (95% CI 1.7-17.6; p=0.005). The mean age of melanoma diagnosis was 49 years, and 3/13 individuals had multiple melanoma diagnoses. The mean age of sarcoma diagnosis was 39 years. Breast, ovarian, and kidney cancers were also among the more common cancers observed in POT1 carriers; however, this likely reflects the ascertainment bias inherent in a cancer MGPT cohort, as there was no significant difference in the frequency of these cancers when compared to MGPT negatives. Family history review revealed 26 probands (22.6%) had at least one close relative with melanoma and six (5.2%) had at least one close relative with sarcoma. One proband (0.9%) had a personal diagnosis of astrocytoma at age 42 years, and 10 (8.7%) additional probands had at least one close relative with a glial cell tumor.

Discussion

This report represents the largest series of *POT1* LOF carriers to date. Results support an association between melanoma risk and *POT1* LOF variants, as well as possible enrichment of sarcoma. Furthermore, 10% of our cohort had personal or family history of glial cell tumors, which is consistent with previously published findings. Results from this retrospective MGPT cohort analysis validate the inclusion of *POT1* in MGPT, particularly when testing patients and families at high risk for melanoma and these other rare cancer subtypes.