Melanoma Risk in *POT1* Mutation Carriers From a Multigene Panel Testing Cohort

Kelly Fulk,[1] Jennifer Herrera-Mullar,[1] Carrie Horton,[1] Holly LaDuca[1]

[1]Ambry Genetics, Aliso Viejo, CA, 92656

BACKGROUND

- *POT1* (protection of telomeres 1) plays a critical role in the shelterin complex and telomere regulation.
- *POT1* has recently been implicated in familial melanoma, glioma, and sarcoma.
- The purpose of this study was 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 broad variety of cancer indications.

METHODS

- 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.
- Excluded cases with a pathogenic/likely pathogenic variant in another gene.
- Compared tumor frequencies among *POT1* LOF carriers with MGPT-negative probands tested during a subset of the same time frame using Fisher's exact test.

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Table 1. Demographics

	MGPT-negative (n=12344)		*POT1* LOF (n=119)	
	n	%	n	%
Ethnicity				
African American	836	6.7	6	5
Asian	466	3.7	3	2.5
Ashkenazi Jewish	701	5.7	9	7.5
Caucasian	7548	61.1	81	68
Hispanic	761	6.2	3	2.5
Other	614	5.0	7	4.2
Unknown	1010	8.2	0	0
Gender				
Female	11370	92.1	102	86
Male	974	8.0	17	14
Cancer History				
Personal hx of cancer	8394	68.0	41	35.3
No personal hx of cancer	3703	30.0	75	64.6

Table 2. Cancer Types Among *POT1* LOF Carriers

Cancer Type	n (%)	Mean Age of Onset (Range)
Breast	38 (33.0%) †	58 (37-78)
Melanoma	13 (11.3%)‡	39 (20-71)
Ovarian	7 (6.1%) †	59 (33-81)
Kidney	5 (4.3%) †	51 (30-83)
Sarcoma	4 (3.5%)	39 (5-70)

† Likely reflects 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.
‡ 3/13 had multiple melanoma diagnoses

Figure 2. Melanoma and Sarcoma Comparison

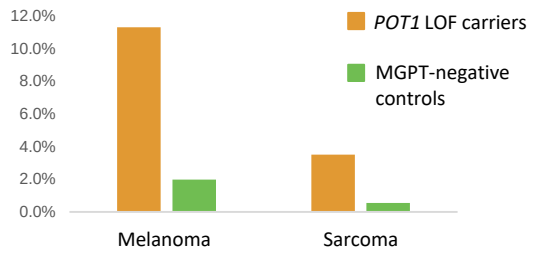
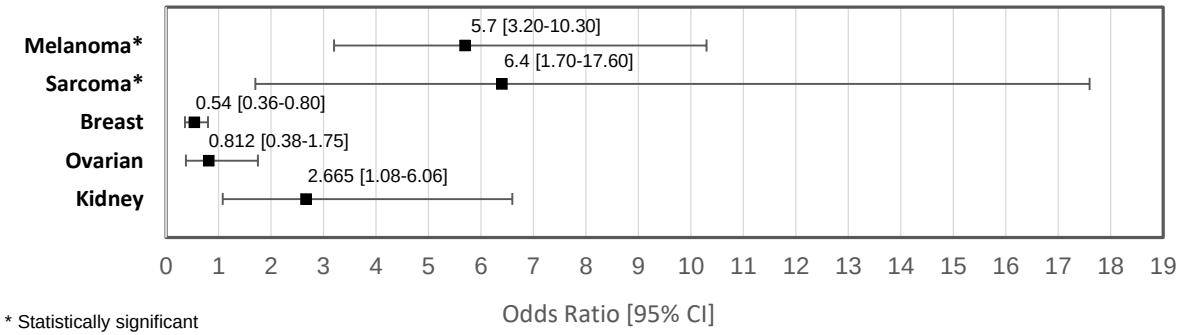


Figure 3. Odds Ratios Among *POT1* LOF Carriers Compared to MGPT-negative



* Statistically significant

ADDITIONAL RESULTS

- 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.

TAKE-HOME POINTS

- 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.
- 10% of our cohort had personal or family history of glial cell tumors, which is consistent with previously published findings.
- Results validate the inclusion of *POT1* in MGPT, particularly when testing patients and families at high risk for melanoma and these other rare cancer subtypes.

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