

Identification of *APC* I1307K Among a Cohort of Patients Undergoing a Pan-Cancer Gene Panel: Analysis of Ancestry-Based Cancer History

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Disclosures

- Paid speaker for Myriad Genetics

Background

- *APC* I1307K is a polymorphism present in approximately 10% of individuals of Ashkenazi Jewish (AJ) ancestry which has been associated with a moderately increased risk for colon cancer.
- With the inclusion of *APC* on many colorectal and pan-cancer gene panels, I1307K has been reported as an incidental finding.
- Data are lacking about the frequency and risks associated with *APC* I1307K among individuals of non-AJ backgrounds.

Methods: Genetic Testing

- We evaluated individuals who underwent testing with a 25 gene pan-cancer panel that included *APC*.
- The majority of individuals tested were ascertained for suspicion of hereditary cancer risk.
- Pathogenic variants (PVs) were defined as mutations classified as deleterious or suspected deleterious.
- All clinical data was obtained by health care provider report on the test request forms.

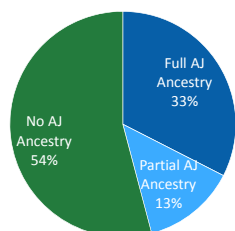
Methods: Cohort

- Individuals who underwent testing for the *BRCA1* and *BRCA2* common AJ founder mutations with reflex to the gene panel were excluded.
- The proportion of *APC* I1307K carriers was evaluated for tested individuals whose healthcare provider reported:
 - Full AJ ancestry (n=3,015)
 - Partial AJ ancestry (n=2,054)
 - No AJ ancestry (n=171,414)

Methods: Analysis

- Personal history of polyps and cancer and history of colorectal cancer among first- and second-degree relatives was assessed.
- Descriptive statistics and Fisher's exact test were utilized to compare those with *APC* I1307K to those with a negative panel test result.

Ancestry of I1307K Carriers



	N Tested	I1307K Carriers	Positive Rate
Full AJ Ancestry	3,015	191	6.3%
Partial AJ Ancestry	2,054	69	3.4%
No AJ Ancestry	171,414	321	0.2%

- APC* I1307K was identified in 581 tested individuals.
- The positive rate among individuals who indicated full AJ ancestry was higher than that observed for individuals of partial AJ or no AJ ancestry.

Ancestry of I1307K Carriers

Ancestry	N	% of Non-AJ I1307K Carriers
Western/Northern European	148	46.1%
Central/Eastern Europe	59	18.4%
Latin American	41	12.8%
Near/Middle Eastern	26	8.1%
Native American	1	0.3%
African	4	1.2%
Asian	0	0%
Other	2	0.6%
Multiple	40	12.5%

- The majority (64.5%) of I1307K carriers who indicated no AJ ancestry were of European ancestry.

Personal Cancer History

Cancer Type	I1307K Carriers			Mutation Negative		
	Full AJ Ancestry (n = 191)	Partial AJ Ancestry (n = 69)	No AJ Ancestry (n = 321)	Full AJ Ancestry (n = 2,824)	Partial AJ Ancestry (n = 1,985)	No AJ Ancestry (n = 171,093)
Breast	39 (20.4%)	12 (17.4%)	75 (23.4%)	516 (18.3%)	433 (21.8%)	49,053 (28.7%)
Colorectal	8 (4.2%)	4 (5.8%)	18 (5.6%)	74 (2.6%)	60 (3.0%)	5,229 (3.1%)
1-5 polyps	9 (4.7%)	1 (1.4%)	7 (2.2%)	64 (2.3%)	56 (2.8%)	2,744 (1.6%)
>5 polyps	5 (2.6%)	6 (8.7%)	6 (1.9%)	40 (1.4%)	25 (1.3%)	1,794 (1.0%)

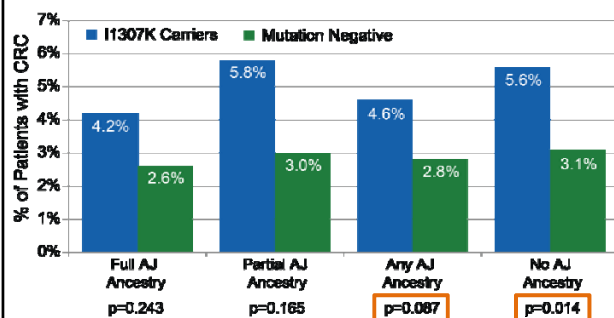
- There was a similar incidence of breast cancer among APC I1307K carriers relative to non-carriers of the same ancestry.

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- There was a higher incidence of colorectal cancer among APC I1307K carriers for all ancestries.

Personal History of Colorectal Cancer



Family History of Colorectal Cancer

	I1307K Carriers			Mutation Negative		
	Full AJ Ancestry (n = 191)	Partial AJ Ancestry (n = 69)	No AJ Ancestry (n = 321)	Full AJ Ancestry (n = 2,824)	Partial AJ Ancestry (n = 1,985)	No AJ Ancestry (n = 171,093)
1 st Degree Relative	39 (20.4%)	14 (20.3%)	44 (13.7%)	405 (14.3%)	226 (11.4%)	19,315 (11.3%)
2 nd Degree Relative	47 (24.6%)	24 (34.8%)	65 (20.2%)	603 (21.4%)	383 (19.3%)	30,048 (17.6%)

- There is a higher incidence of CRC in a first degree relative among APC I1307K carriers relative to non-carriers of the same ancestry.
 - Full AJ Ancestry: p = 0.022
 - Partial AJ Ancestry: p = 0.024
 - Overall: p < 0.001

Conclusions

- Our findings support previous studies showing an increased personal and family history of colorectal cancer among *APC* I1307K carriers of AJ ancestry compared to non-carriers.
- These data also show that there may be an increased risk of colorectal cancer among *APC* I1307K carriers of non-AJ ancestry.
- The increased incidence of colorectal cancer among individuals of AJ ancestry may not have reached statistical significance due to the exclusion of individuals who underwent founder mutation testing.

Conclusions

- This potential colon cancer risk warrants further investigation and may influence medical management decisions for *APC* I1307K carriers regardless of ancestry.