An update on *APC* p.I1307K Homozygosity: Observations from 74 Individuals from a Large Multigene Panel Testing Cohort

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300-word Limit

Background and Aim

APC c.3902T>A (I1307K) is a common pathogenic variant (PV) in the Ashkenazi Jewish (AJ) population with frequency nearing 4% (gnomAD V4.1.0). Unlike typical PVs in *APC*, it is associated with a small (1.7-fold) increased odds of colorectal cancer (CRC) in Ashkenazim. The cancer risk for homozygotes is unknown and published data is based on small samples. This work aims to quantitatively evaluate I1307K homozygotes' cancer risk.

Methods

We reviewed clinical/demographic data from a multigene panel (MGPT) tested cohort from May 2012-April 2024. This includes cohorts of comprehensive I1307K homozygotes (n=74), select I1307K heterozygotes (n=344), and MGPT-negative individuals (WT, n=19,810). Individuals with another PV were excluded. Comparisons were made using Fisher's exact test and Mann-Whitney U test.

Results

The age at testing and age at first cancer in the homozygotes was older relative to WT (61 vs. 52 years, p<.001 and 58.5 vs. 53 years, p=0.006). Although there was no difference between homozygote and WT groups for overall cancer or colon polyps, there was less overall cancer (OR=0.656, p<0.001) and a higher frequency of polyps (OR=1.74, p=0.019) in heterozygotes versus WT. There were no differences in CRC or multiple primary CRC frequencies in homozygotes or heterozygotes relative to WT.

Conclusions

Homozygotes did not have a higher odds of CRC versus WT, however, the expected observation that heterozygotes have increased odds of CRC was also not observed in this dataset. This could be due to the small effect size of the association in heterozygotes, bias in recruitment and phenotype reporting in this clinical cohort, the small number of cases available for this study, and/or other confounding factors including not accounting for ethnic genetic background. More sophisticated statistical models, including logistic regressions and power calculations, are planned and may further clarify the risk of CRC in these groups.

Characteristic	*APC* p.I1307K Homozygous				*APC* p.I1307K Heterozygous				Broad Panel Negative (WT)	
	Count	Percent	OR‡	p-value	Count	Percent	OR‡	p-value	Count	Percent
Total	85				524				19,810	
Excluded*	11				180				0	
Total Analyzed	**74**				**344**				19,810	
Sex										
Female	59	79.7%	0.761	0.343	273	79.4%	0.7440	**0.032**	16,600	83.8%
Male	15	20.3%			71	20.6%			3,210	16.2%
Ethnicity										
White	8	10.8%	0.110	**<0.001**	125	36.3%	0.519	**<0.001**	10,377	52.4%
African American	0	0.0%	N/A		10	2.9%	0.316	**<0.001**	1,715	8.7%
Hispanic	0	0.0%	N/A		5	1.5%	0.273	**<0.001**	1,016	5.1%
Asian	2	2.7%	0.771	1.000	3	0.9%	0.244	**0.004**	689	3.5%
Ashkenazi Jewish	56	75.7%	100.978	**<0.001**	143	41.6%	23.042	**<0.001**	593	3.0%
Middle Eastern	2	2.7%	7.308	**0.033**	7	2.0%	5.465	**<0.001**	75	0.4%
Mixed Ethnicity/Other/Unknown	6	8.1%	0.239	**<0.001**	51	14.8%	0.471	**<0.001**	5,345	27.0%
Age, median (IQR)										
Age at testing	61 (52.25-69)		N/A	**<0.001**	53.5 (42.75-64)		N/A	0.062	52 (42-62)	
Age at first cancer	58.5 (50.5-67.75)		N/A	**0.006**	54 (47-62)		N/A	0.638	53 (44-63)	
Age at first CRC†	55 (49-55)		N/A	0.447	55 (45-58)		N/A	0.662	50 (44-59)	
Overall cancer										
Yes	47	63.51%	1.494	0.103	149	43.3%	0.6560	**<0.001**	10,662	53.8%
No	27	36.49%			184	53.5%			8,582	43.3%
Not Provided	0	0.00%			11	3.2%			566	2.9%
Polyps										
Yes	15	20.27%	1.702	0.081	60	17.4%	1.4140	**0.019**	2,575	13.0%
No	12	16.22%			37	10.8%			1,662	8.4%
Not Provided	47	63.51%			247	71.8%			15,573	78.6%
CRC†										
Any number of CRC	5	6.76%	1.672	0.238	13	3.8%	0.9370	1.000	823	4.2%
>1 primary	1	1.35%	11.799	0.086	1	0.3%	2.5080	0.339	23	0.1%
No	69	93.24%			331	96.2%			18,987	95.8%

*Exclusion Criteria: Carries another LP/P Variant in any cancer gene AND/OR or (for *APC* only) had tumor characteristics consistent with Lynch (Microsatellite unstable and/or IHC-negative for MLH1, MSH2, MSH6, PMS2)

†Colorectal cancer excludes 'abdominal', 'duodenal', 'intestinal', 'bowel'

‡For Odds Ratio (OR): Fisher's exact test with WT as referent; For age at testing, age at first cancer and age at first CRC: Mann-Whitney U test.