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

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BACKGROUND

- *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[1].
- Management guidelines exist for *MSH6*, a moderate penetrance Lynch Syndrome gene.
- The cancer risk for homozygotes is unknown and published data is based on small samples[2].
- **AIM: This work aims to quantitatively evaluate I1307K homozygotes' CRC risk among individuals from a clinical diagnostic setting.**

METHODS

- All individuals homozygous for I1307K were curated.
- Select individuals who 1) were heterozygous for *APC* I1307K; or 2) were heterozygous for *MSH6* (likely) pathogenic variants; or 3) had no actionable variants on a 90-gene comprehensive cancer panel (wildtype, WT) were fully curated.
- Individuals with other (likely) pathogenic variants in any gene were excluded.
- Statistical analyses utilized testing of bivariate association using Fisher's exact or two-sample t-test and multivariate logistic regression model adjusting for ethnicity, sex, age. Statistical models used WT and *MSH6*-positives as control cohorts.

RESULTS

Table 1. Patient Clinical History and Demographics

	Homozygous (N=74)	Heterozygous (N=340)	*MSH6* (N=372)	WT (N=19,809)
Sex				
F	59 (79.9)	270 (79.4)	277 (74.5)	16,599 (83.8)
M	15 (20.3)	70 (20.6)	95 (25.5)	3,209 (16.2)
Ethnicity				
White	8 (10.8)	123 (36.2)	199 (53.5)	10,376 (52.4)
African American/Black	0	10 (2.9)	79 (21.2)	1,715 (8.7)
Hispanic	0	5 (1.5)	8 (2.2)	1,016 (5.1)
Ashkenazi Jewish	56 (75.7)	141 (41.5)	10 (2.7)	593 (3.0)
Asian	2 (2.7)	3 (0.9)	12 (3.2)	689 (3.5)
Mixed Ethnicity	2 (2.7)	2 (0.6)	4 (1.1)	251 (1.3)
Middle Eastern	2 (2.7)	7 (2.1)	1 (0.3)	75 (0.4)
Other	0	3 (0.9)	3 (0.8)	189 (1.0)
Unknown	4 (5.4)	46 (13.5)	56 (15.1)	4,905 (24.8)
Current Age				
Mean (SD)	60.4 (13.2)	53.6 (14.7)	52.9 (13.3)	51.9 (13.7)
Range (min, max)	34, 92	18, 92	17, 87	6, 95
Age at First CRC diagnosis (Figure 2)				
N	5	13	60	863
Mean (SD)	52.5 (5.7)	52.1 (13.0)	51.2 (11.7)	52.5 (12.5)
Range (min, max)	45, 59	26, 72	17, 81	12, 95
Polyps				
Yes	15 (20.3)	60 (17.6)	63 (16.9)	2,575 (13.0)
No	12 (16.2)	36 (10.6)	42 (11.3)	1,662 (8.4)
Not Provided	47 (63.5)	244 (71.8)	267 (71.8)	15,572 (78.6)
CRC Incidence				
Any number of CRC	5 (6.8)	13 (3.8)	76 (20.4)	885 (4.5)
>1 primary	1 (1.4)	1 (0.3)	7 (1.9)	23 (0.1)
No	69 (93.2)	327 (96.2)	296 (79.6)	18,924 (95.5)

Figure 1. Odds Ratios for CRC

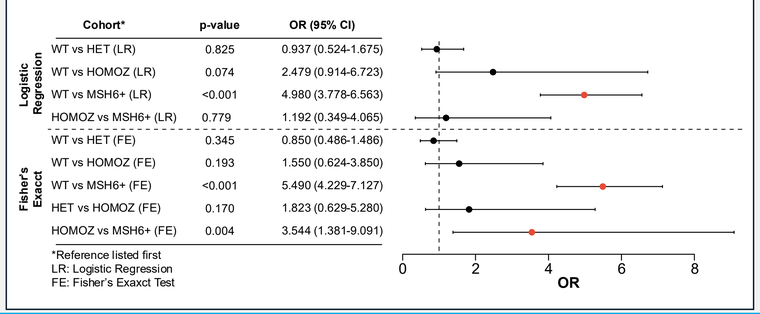

Figure 2. Age at first CRC diagnosis (all ethnicities)

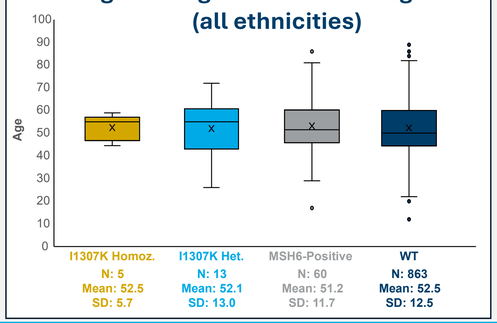

Table 2. Power calculations projecting the required minimum sample size.

Detectable OR->	OR 2	OR 2.2	OR 2.4	OR 2.6	OR 2.8	OR 3.0	OR 3.2	OR 3.4	OR 3.6	OR 3.8	OR 4.0
Homozygote	369	271	210	169	140	119	103	90	80	72	65
Heterozygote	1,715	1,260	976	786	651	553	479	418	372	335	302
Homozygote	246	179	137	110	90	76	65	57	50	45	40
Wildtype	65,852	47,916	36673	29,446	24,092	20,344	17,400	15,258	13,384	12,046	10,708

* Power 80%, alpha 0.05: the ratios between cohort sample sizes is assumed to be consistent for the calculation of required sample sizes

Figure 1: OR and 95% CI for CRC incidence in individuals with different genotypes. Above dashed line: Logistic Regressions accounting for ethnicity, sex, and age; Below dashed line Fisher's Exact Test. Red is p<.05.

Figure 2: Box and whisker plot depicting the age at first colorectal cancer diagnosis among individuals of all self-reported ethnic backgrounds. Mean and interquartile ranges are shown with outliers depicted as dots. The number of individuals, mean and standard deviation are provided above each box. No statistical differences.

Table 2: Power calculations for the sample size needed to detect an OR of variable size comparing Homozygotes to Heterozygotes or Wildtype. With the current homozygous sample size (N=74), there is approximately 80% power to detect an OR of 3.0 when compared to WT (in blue) and an approximate OR of 3.8 when compared to Heterozygotes (in yellow).

CONCLUSIONS

- **We failed to detect a significantly different odds for CRC in I1307K Het. vs WT (Figure 1).**
- **APC I1307K homozygotes trend towards increased odds of CRC compared to WT (OR=2.479 [0.914-6.723], p 0.074-Figure 1).**
- **The age at first CRC diagnosis is not statistically different among any cohorts (Figure 2)**
- **Small effect sizes continue to limit the ability to detect significantly distinct odds of CRC between APC I1307K heterozygotes and homozygotes, necessitating as many as 567 homozygotes to detect an odds of CRC of 1.78 (similar to literature heterozygotes[1] [Table 2]).**
- **In this cohort, *MSH6*-positives have a statistically significant odds of CRC compared to WT (OR 4.98, p<.001). Power calculations support ability to detect an OR of 4 given current homozygous sample sizes. Therefore, APC I1307K homozygotes have statistically lower odds of CRC than *MSH6*-related Lynch Syndrome (Figure 1, Table 2).**

REFERENCES

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