Title: Phenotype and Colorectal Cancer Risk in *APC* I1307K Homozygotes

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Background*: APC* p.I1307K is an Ashkenazi Jewish (AJ) founder mutation and confers a moderate increased risk of colorectal cancer (CRC). However, CRC risk in p.I1307K homozygotes has not been described and phenotypic data are limited.

Methods: *APC* p.I1307K homozygotes, without additional mutations, were identified through clinical testing at Ambry Genetics between 10/1/2012 through 03/01/2017. Personal history, with a focus on FAP-associated features, was collected from requisition forms, clinical records, and direct communication with clinicians, when available. The frequency of heterozygous and homozygous p.I1307K mutations found on multi-gene panel testing (MGPT) was compared in AJ individuals with CRC to those without. Statistical comparisons were made using Fisher's exact test.

Results: Of fourteen p.I1307K homozygotes found (Table 1), four (29.6%) had a history of CRC while 10 (71.4%) had no reported history of polyps. Eleven (78.6%) of the homozygous were found incidentally through MGPT. There was a trend towards an increased CRC risk in homozygotes compared to mutation negatives (n=3187) (OR 6.5 p=0.06 95% CI [0.6, 45.2] and compared to heterozygotes (n=232) (OR 4.5 p=0.1 95% CI [0.4, 33.3]), although these associations did not reach significance.

Conclusions: Similar to heterozygotes, *APC* p.I1307K homozygotes appear to have an increased risk for CRC. Homozygotes do not appear to be at increased risk for FAP-associated features, although one case had a desmoid tumor. This is the largest cohort of homozygotes reported thus far. Additional studies may help delineate if CRC risk is higher in homozygotes compared to the modest risk seen in heterozygotes.