Differential association of Lynch syndrome genes with colorectal and breast cancer

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Introduction

Lynch syndrome (LS) is an inherited condition that greatly increases the risk of multiple cancers, including colorectal, endometrial, and ovarian cancer. Pathogenic variants in *MSH2* and *MLH1* are identified in 70-90% of LS families whereas *MSH6* and *PMS2* are estimated to account for 10-30% and *EPCAM* for 1-3%[1]. The spectrum of cancer risks associated with variants in these genes has been reported to vary by gene, with *MLH1* and *MSH2* conferring a higher risk for colorectal and endometrial cancer and an earlier age of onset. Recent evidence has also suggested that some of these genes differentially increase breast cancer risk, although reports of this risk are conflicting[2–4].

To investigate the differential frequency of colorectal, breast, and ovarian cancer among LS genes, we analyzed 664 individuals who were referred for multi-gene panel testing for hereditary cancer risk. In contrast to some traditionally studied LS cohorts in which individuals were selected based on personal history of colorectal cancer, this cohort contains individuals with diverse clinical histories, including those with a personal history of breast cancer.

Methods

We analyzed a cohort of 664 individuals who received NGS panel testing for hereditary cancer risk from Color Genomics via a 19- or 30-gene panel and were identified to have a pathogenic or likely pathogenic (hereafter referred to as pathogenic) variant in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*. In *PMS2*, exons 12-15 were not analyzed. In *EPCAM*, only large deletions and duplications including the 3' end of the gene were analyzed. Variants were classified according to the American College of Medical Genetics and Genomics 2015 guidelines for sequence variant interpretation[5], and all variant classifications were signed out by a board certified medical geneticist or pathologist.

As only pathogenic variants in *EPCAM* that affected *MSH2* were analyzed, *EPCAM* variants were combined with *MSH2* for this analysis. Individuals with more than one pathogenic variant or a homozygous variant were excluded from the analysis. Familial relationships were not assessed. Personal history of cancer was based on information reported by the individual, and phenotype analysis was limited to individuals with sufficient information. Statistical analyses were performed using a Welch Two Sample t-test or X^2 test with Yates correction.

Results

Figure 1. Gene spectrum in cohort

In contrast to some previous LS cohorts, the majority of individuals in this cohort had a pathogenic variant in *PMS2* (29.5%) or *MSH6* (27.9%) rather than *MLH1* (17.2%) or *MSH2* (25.5%). Overall, the cohort consisted of 61.0% females and 39.0% males.

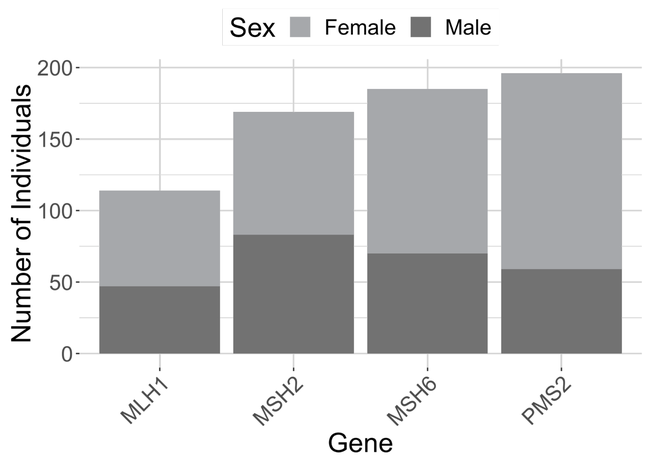


Figure 2. Age at testing by gene

The mean age of testing for those with a pathogenic variant in *MLH1* (44.8 years) was greater than *MSH6, MSH2,* and *PMS2* (48.5 years) (1-tailed t-test, p = 0.01).

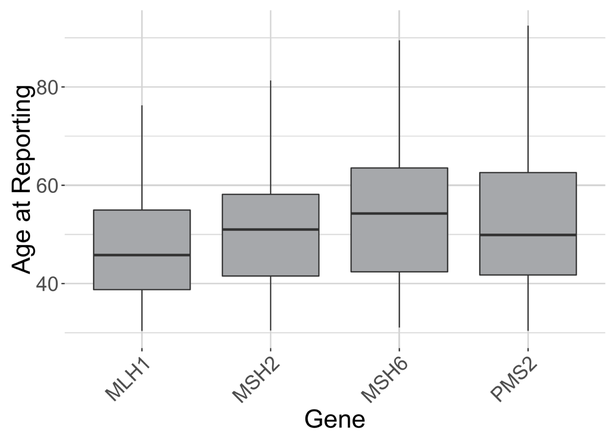


Figure 3. Ovarian cancer frequency by gene

Of the 307 females who reported ovarian cancer status, 10 reported a history of ovarian cancer. *MLH1* had a higher fraction of individuals with ovarian cancer (mean age of diagnosis 43.0 years), and no individuals with a pathogenic variant in *PMS2* reported ovarian cancer.

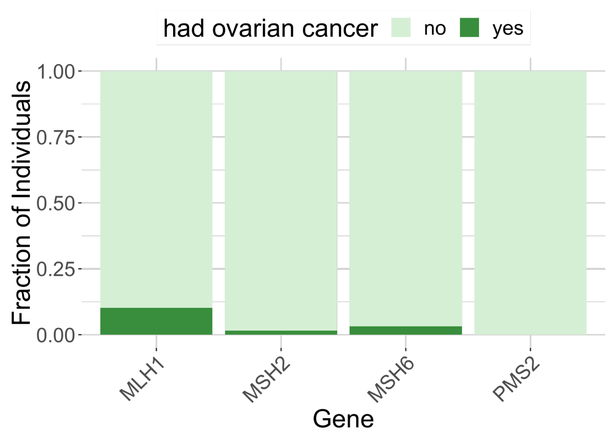


Figure 4. Colorectal cancer frequency by gene

Of the 509 individuals who reported colorectal cancer status, 73 reported a history of colorectal cancer. As expected, colorectal cancer was more associated with *MLH1* and *MSH2* than with *MSH6* and *PMS2* (X^2 test, $p < 0.01$).

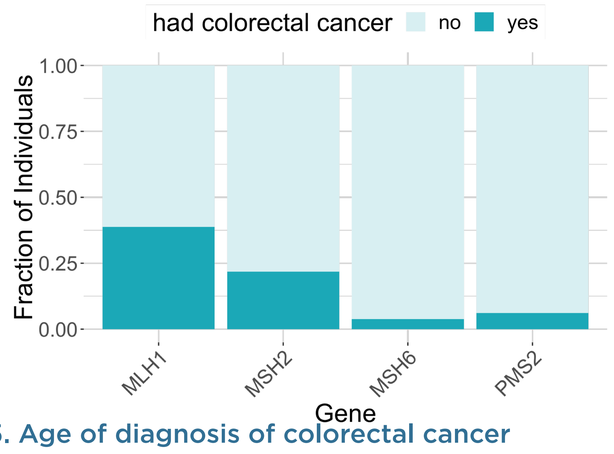


Figure 5. Age of diagnosis of colorectal cancer

Mean age of diagnosis of *MLH1* and *MSH2* combined (41.2 years) is less than *MSH6* and *PMS2* combined (48.9 years) (1-tailed t-test, p = 0.02).

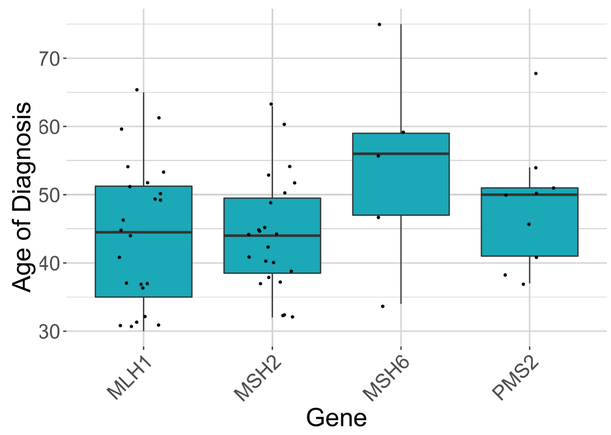


Figure 6. Breast cancer frequency by gene

Of the 310 females who reported breast cancer status, 37 reported a history of breast cancer. Breast cancer was reported less frequently with *MLH1* than the other 3 genes combined but was not significantly different (X^2 test, p = 0.26).

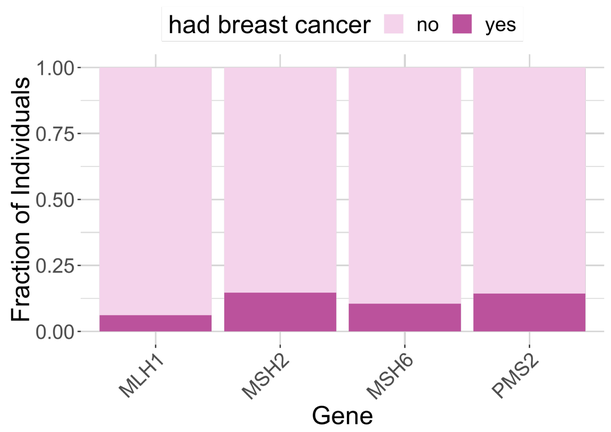
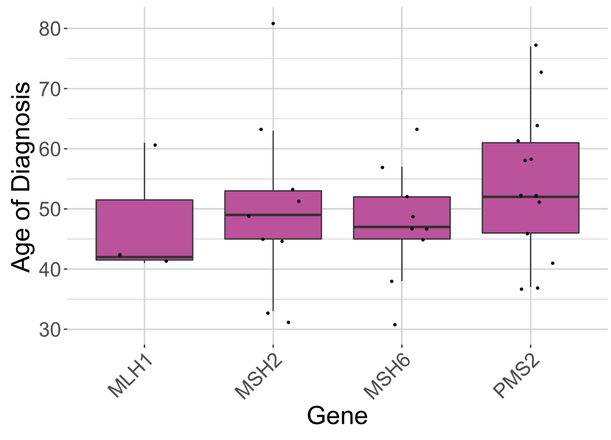


Figure 7. Age of diagnosis of breast cancer

Mean age of diagnosis of *MLH1* and *MSH2* combined (47.8 years) is not different from *MSH6* and *PMS2* combined (50.6 years) (2-tailed t-test, p = 0.57).



References

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2. Roberts, M. E. *et al. Genet. Med.* (2018).
3. Pande, M. *et al. Fam. Cancer* (2012).
4. Win, A. K. *et al. J. Clin. Oncol.* (2012).
5. Richards S, Aziz N, Bale S, *et al. Genet Med.* (2015)

Conclusions

- In line with previous reports[1], *MLH1* and *MSH2* were more strongly associated with colorectal cancer than *MSH6* and *PMS2* in this cohort.
- Breast cancer frequency did not vary by gene, in contrast to previous reports[2]. Similarly, the age of diagnosis of breast cancer for *MLH1* and *MSH2* did not differ from *MSH6* and *PMS2.*
- Further research on larger and more clinically diverse cohorts is warranted to better define the differential association of breast, ovarian, and other cancers among the Lynch syndrome associated genes.