Evaluation of a Rare PMS1 Germline Variant as a Putative Hereditary Breast Cancer Risk Allele

Xu, Kelly (School: South Burlington High School)

Currently, mutations in the BRCA1 and 2 genes are estimated to explain approximately 15 percent of hereditary breast cancer cases. However, studies have established that 50 percent of women with hereditary breast cancer lack known genetic alterations, highlighting an unmet need. A collaborative sequencing study generated a list of potential variants that may play a role in the disease. One of these variants occurred in the PMS1 gene, which encodes for a non-canonical member of the DNA mismatch repair machinery (MMR). Mutations resulting in MMR loss of function define the hereditary cancer predisposition syndrome known as Lynch Syndrome. Therefore, we reasoned a germline variant in PMS1 may act as a driver of hereditary breast cancer risk. Furthermore, the identified variant (c.605G>A) occurs in a predicted exonic splicing enhancer site in exon 6 and has been predicted to affect splicing of PMS1 mRNA. The purpose of this project was to test the hypothesis that splicing of PMS1 mRNA is disrupted when this variant is present. Using standard molecular biology techniques (PCR/RT-PCR and Sanger sequencing), analysis of genomic DNA and mRNA concluded that this variant does not alter splicing of PMS1 mRNA relative to the control. These results are significant, as it suggests that this variant is not deleterious, contradicting a prediction made in an earlier paper. In conclusion, it's demonstrated that a rare germline variant in the PMS1 gene (c.605G>A) does not alter splicing of PMS1 mRNA. However, whether this alteration impacts protein function remains to be addressed.