Abstract.

Colorectal cancer (CRC) is the third most deadly cancer in the world. While Genome-wide Association Studies (GWAS) have been instrumental in identifying common pathogenic variants that increase risk for colorectal cancer and Polygenic Risk Scores (PRS) have been used to quantify a patient's risk for developing cancer, it has not yet investigated how PRS should be viewed in cases where patients deemed lower-risk develop cancer. The focus of this work was to identify the relative prevalence of pathogenic rare variants in CRC predisposition, which are currently excluded from conventional GWAS and PRS, among quartiles of PRS. I analyzed the PRS of 563, in conjunction with whole exome data for colorectal cancer patients from The Cancer Genome Atlas (TCGA), controlled for relevant epidemiological risk factors, and performed a multivariable logistic regression analysis to determine if pathogenic rare variants in CRC predisposing genes are statistically linked with patients whose PRS are in the lowest quartile. Results showed patients in the lowest quartile of PRS had the greatest effect size in predicting the presence of pathogenic rare variants within the cohort, although the results are not conclusive. Understanding why PRS models fail in the prediction of CRC will pave the way to identify actionable, high-risk variants for cancer predisposition that can influence screening strategies for patients and their families.