## A016 Hundreds Of Common Germline Variants Predict Cancer Progression In Thirty-Three Different Cancer Types And Will Be Useful For Precision Oncology

Anindya Dutta, Ajay Chatrath, and Aakrosh Ratan
*University of Virginia, Charlottesville, VA*

**Introduction:** Precision oncology is focused on individualizing cancer treatment based on individual-specific genetic changes in cancers. Although germline mutations are known to increase an individual's risk of tumor formation, no previous study has reported Genome wide association studies (GWAS) for germline variants predictive of survival in cancer patients. **Methods:** Using Cox regression analysis we identify hundreds of prognostic germline variants from the pool of over four million variants present in The Cancer Genome Atlas whole exome sequencing and RNA sequencing datasets of thirty-three different cancer types. For each cancer type we control for known clinical and pathological co-variates that are currently used to predict outcome. **Results:** We identify hundreds of common germline variants with a Minor allele frequency >5% that predict bad or good prognosis in thirty-three different cancer types. For example, a variant in the GRB2 oncogene predicts poor outcome in gliomas (HR=20.4, $p<10^{-10}$) and is associated with activated RAS signaling and somatic mutations that further increase RAS activity. Another variant in the ANKDD1A gene changes an evolutionary conserved lysine to glutamic acid and predicts poor outcome (HR=1.73, $p<0.002$) in gliomas in the American patients collected by TCGA and in an independent collection of Asian patients in CGGA. Many of the prognostic germline variants significantly affect outcome in the same direction in different cancer types, suggesting common mechanisms of action. Adding the status of a predictive germline variant to the currently used clinical and pathological variates improves the specificity and sensitivity of prognosis in 17 different cancer types. The prognostically significant germline variants are often at or near genes known to impact pathways important for cancers, including known oncogenic and tumor-suppressive pathways, and several of them are eQTLs that affect the expression of genes that can be tied to oncogenesis or response to therapy. **Conclusions:** While somatic mutations in tumors are increasingly being used for personalized therapy of cancers, our results suggest that germline variants should also be considered in personalizing the prognosis and managing the therapy of cancers. In addition, significant fundamental research is necessary to determine how these germline variants affect the progression of a cancer.