# IDENTIFICATION OF COMMON GERMLINE VARIANTS ASSOCIATED WITH PEDIATRIC RHABDOMYOSARCOMA SURVIVAL: A REPORT FROM THE CHILDREN'S ONCOLOGY GROUP (COG)

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**Background:** Rhabdomyosarcoma (RMS) has one of the poorest survival rates among pediatric cancers, underscoring the need to identify factors which may be used to improve therapeutic options for these individuals.

**Materials/Methods:** We carried out a genome-wide association study of overall survival (OS) and event-free survival (EFS) in 920 RMS patients from COG protocols and randomly divided them into discovery (n=642) and replication (n=278) cohorts. Cases were genotyped on Illumina BeadChips and imputed using the Haplotype Reference Consortium. We used Cox regression to estimate a hazard ratio (HR) and P value for each common variant (minor allele frequency >5%) for OS and EFS while adjusting for age at diagnosis, tumor stage, subtype, and the top five principal components. We further conducted analyses by subtype: embryonal (ERMS, n=544) and alveolar (ARMS, n=268). Finally, we performed a meta-analysis of the results from the discovery and replication cohorts to generate a summary HR and P value for each single nucleotide polymorphism (SNP).

**Results:** We identified an intergenic SNP at chr8q21.13 that was associated with worse EFS across subtypes (HR=2.08, P=2.80x10-9) and had consistent effects across the discovery (HR=1.91, P=5.05x10-6) and replication (HR=2.62, P=7.16x10-5) cohorts. This SNP lies in a binding region for GATA2 and GATA3, transcription factors that contribute to cancer development. We also identified a significant association between a SNP at chr12q21.1 and worse EFS (HR=2.04, P=3.35x10-8) with consistent effects across the discovery and replication cohorts. Based on data from the Genotype-Tissue Expression project (GTEx), this SNP is associated with expression of SLCO1B1, a gene which encodes a liver anion transporter linked to RMS treatment-related toxicities. In subtype-specific analyses, we identified a SNP at chr17q21.32 that was significantly associated with worse ARMS OS (129 events; HR=3.18, P=3.12x10-8). In GTEx, this SNP is associated with expression and splicing of PITPNM3, KIAA0753, and MED31 across various tissues. No SNPs were significantly associated with ERMS OS or EFS.

**Conclusions:** In the first GWAS of RMS survival outcomes, we identified two SNPs that were significantly associated with worse EFS across RMS subtypes. Further, we identified a SNP that was associated with OS in ARMS patients, a subtype that is associated with worse outcomes. Additional investigation of the impact of these SNPs may further support their consideration for novel risk stratification protocols.

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