

A genome-wide scan identifies a new locus associated with pediatric rhabdomyosarcoma

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Characters: 2,520 (2,520 maximum)

Background: Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and has one of the poorest survival rates among all pediatric cancers. The two major histologic subtypes of RMS are embryonal (eRMS) and alveolar (aRMS), which display differences in terms of age-incidence patterns and somatic mutations. Approximately 10% of RMS cases are associated with germline mutations in known cancer predisposition genes (e.g., *TP53*, *NF1*), but very little is known about the genetic susceptibility to the ~90% of RMS cases that are sporadic. We conducted the first multi-institutional genome-wide association study (GWAS) of RMS in 727 cases and 3,384 controls.

Methods: Phase 1 of the GWAS included 421 RMS cases from Children's Oncology Group clinical trials, Texas Children's Hospital, and the Universidad de Navarra. Controls (n=2,763) were cancer-free individuals included in previous studies at the National Cancer Institute (NCI). Phase 2 included 306 cases from the Childhood Cancer Survivor Study and 621 independent controls from NCI. Genotypes were generated using the Illumina OmniExpress or the HumanOmni5Exome array and imputed based on the 1000 Genomes Project. Analyses were restricted to those of European (EUR) ancestry, and controls were matched to the cases based on principal components and genotype platform. Assuming an additive genetic model in SNPTTEST, we used multivariable logistic regression models to estimate the odds ratio (OR), 95% confidence interval (CI), and *P* value for each variant on RMS overall and by two RMS subtypes: eRMS and aRMS.

Results: After quality control filtering and assessment of population substructure, there were 555 combined EUR RMS cases and 1,561 controls, which included: 1) 278 cases and 1,112 controls in phase 1; and 2) 277 cases and 449 controls in phase 2. In the combined set, we identified a new locus at chromosome 11p15.2 that was strongly associated with an increased risk of aRMS and significant at the genome-wide level (OR=2.3, $P=2.2 \times 10^{-8}$). Results were consistent across studies: phase 1 OR=2.3, 95% CI 1.7-3.2; and phase 2 OR=2.3, 95% CI 1.2-4.5. The top variant, rs12785926, mapped to an intron in the *PSMA1* (proteasome subunit alpha 1) gene. Based on data from GTEx, rs12785926 is significantly associated with *RRAS2* expression across multiple tissues. *RRAS2* is involved in cell proliferation and is somatically mutated in several tumors. When evaluating eRMS and RMS overall in the combined set, there were no variants significant at the genome-wide level.

Conclusion: In the first GWAS of pediatric RMS, we identified a susceptibility locus associated with the more aggressive aRMS subtype that has a poorer prognosis. Additional replication analyses are underway using DNA obtained from archived newborn blood spots linked to population-based cancer registries, as well as other institutional cohorts. Further investigation will advance understanding of RMS etiology and biology.