Identification of common germline variants associated with pediatric rhabdomyosarcoma survival: A report from the Children's Oncology Group (COG)

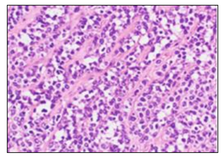
Bailey A. Martin-Giacalone[1], Michael E. Scheurer[1], Javed Khan[2], Stephen J. Chanock[2], Shengchao Alfred Li[3], Meredith Yeager[3], Deborah A. Marquez-Do[1], Donald A. Barkauskas[4], David Hall[5], Matthew T. McEvoy[1], Melissa A. Richard[1], Pagna Sok[1], Austin L. Brown[1], Aniko Sabo[1], Stephen X. Skapek[7], Douglas S. Hawkins[9], Rajkumar Venkatramani[1], Lisa Mirabello[2], Philip J. Lupo[1]

[1] Baylor College of Medicine, [2] National Cancer Institute, [3] Frederick National Laboratory for Cancer Research, [4] University of Southern California, [5] Children's Oncology Group, [7] University of Texas Southwestern Medical Center, [8] Seattle Children's Hospital

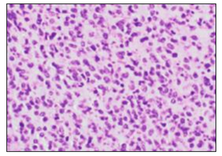
BACKGROUND

- Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma of childhood.
- RMS is classified into two major histological subtypes:

Alveolar RMS (ARMS)



Embryonal RMS (ERMS)



Skapek et al., 2019 Nat. Rev. Dis. Primers

- Survival is approximately 65% for children with intermediate-risk RMS[1]. Five-year survival significantly differs between the major histological subtypes:

RMS subtype	5-year survival[2]
All subtypes	61.8%
Embryonal RMS	73.4%
Alveolar RMS	47.8%

OBJECTIVES

Significance: There has been no genome-wide association study (GWAS) of RMS. This study will aid in determining whether germline variants may play a role in survival outcomes among children with RMS.

Purpose: Evaluate the association of common germline variants with 1) event-free survival (EFS) and 2) overall survival (OS) in an unselected cohort of children with RMS.

RESULTS

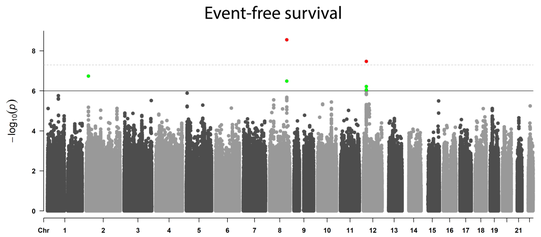


Fig. 1. GWAS of event-free survival across all RMS subtypes. Genome-wide associations were identified for chr8q21.13 and chr12q21.1

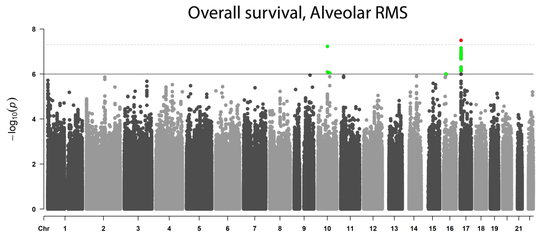


Fig. 2. GWAS of overall survival in ARMS cases. A genome-wide association was identified for chr17q21.32.

Table 1. *P*-value, hazard ratio (HR), and 95% confidence interval (CI) for the association of EFS with the top SNP at chr8q21.13 in each analytic group

8:123323659:C:T	P value	HR (95% CI)
Discovery	5.05e-06	1.91 (1.45, 2.52)
Replication	7.16e-05	2.62 (1.63, 4.20)
Meta-analysis	**2.80e-09**	**2.08 (1.64, 2.63)**

Table 2. *P*-value, HR, and 95% CI for the association of EFS with the top SNP at chr12q21.1 in each analytic group

12:21397321:A:G	P value	HR (95% CI)
Discovery	6.20e-07	2.16 (1.59, 2.92)
Replication	1.37e-02	1.79 (1.13, 2.85)
Meta-analysis	**3.35e-08**	**2.04 (1.58, 2.63)**

Table 3. *P*-value, HR, and 95% CI for the association of OS with the top SNP at chr17q21.32 in each analytic group

17:6480983:C:G	P value	HR (95% CI)
Discovery	6.23e-04	3.19 (1.93, 5.27)
Replication	1.43e-03	3.16 (1.56, 6.41)
Meta-analysis	**3.21e-08**	**3.18 (2.11, 4.79)**

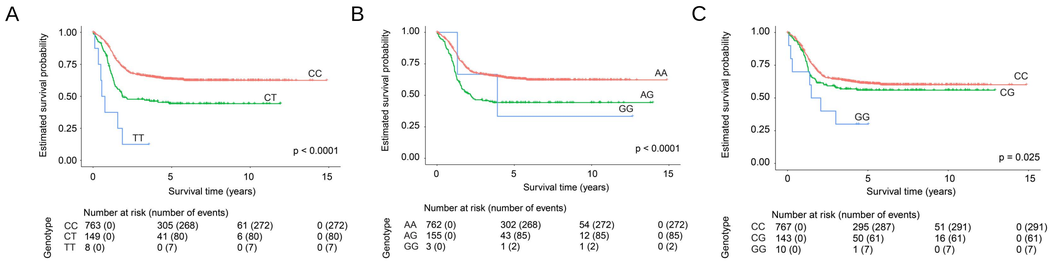
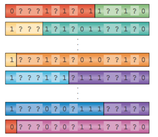


Fig. 3. Event-free survival of individuals by genotype of the top SNP at (A) chr8q21.13 and (B) chr12q21.1. (C) Overall survival of individuals with ARMS by genotype of the top SNP at chr17q21.32.

METHODS

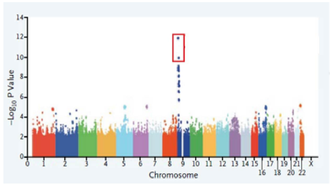
SNP-array
920 RMS cases from COG

Genotype calling
Quality control



Imputation
Haplotype Reference Consortium

GWAS
Cox hazards regression



Adjusted models:
- Age at diagnosis
- Histology
- Tumor stage
- Top 5 principal components

Manolio et al. 2010 *New Eng J Med*
Tam et al. 2019 *Nat Rev Genet*

CONCLUSIONS

- We identified two risk loci that are associated with event-free survival across all RMS subtypes, and we discovered a risk locus that is associated with overall survival in children with ARMS.
- Future investigation include functional annotation of these variants.
- Our work serves to provide knowledge for validation studies.

REFERENCES

1. Hawkins, D. S., Chi, Y. Y., Anderson, J. R., Tian, J., Arndt, C. A., Bomgaars, L., ... & Meyer, W. H. (2018). Addition of vincristine and irinotecan to vincristine, dactinomycin, and cyclophosphamide does not improve outcome for intermediate-risk rhabdomyosarcoma: a report from the Children's Oncology Group. *Journal of Clinical Oncology*, *36*(27), 2770.
2. Ognjanovic, S., Linabery, A. M., Charbonneau, B., & Ross, J. A. (2009). Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *115*(18), 4218-4226.