Underlying germline genetic architecture of pediatric sarcomas: evaluating the role of common and rare variants in 4,160 patients

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Some evidence suggests that pediatric sarcomas have both shared and distinct genetic profiles; however, large-scale efforts to characterize germline genetic susceptibility across these malignancies are limited by their rarity. We evaluated the role of common and rare variants in the genetic etiology of the more frequent pediatric sarcomas: osteosarcoma (OS); Ewing sarcoma (ES); and rhabdomyosarcoma (RMS), subcategorized into embryonal (ERMS) and alveolar (ARMS).

METHODS: We evaluated 4,161 European-ancestry cases with genotype data (1,843 OS, 733 ES, 1,585 RMS, and ~61,000 cancer-free adult controls) and 2,474 cases with exome or genome sequencing (1,002 OS, 579 ES, 893 RMS, and 1,057 controls; jointly called with the same QC). Analyses included: 1) estimating disease heritability for both common SNPs (MAF>3%; genome-wide) and rare loss-of-function (LOF) variants (MAF<1%; exome-wide); and 2) determining the frequency of rare predicted pathogenic (P) or likely pathogenic (LP; ACMG-AMP) variants in cancer susceptibility genes (CSG).

RESULTS: For OS, we conducted a new GWAS and determined that common variants explained 2.7% (SE 1.1%) of disease heritability, while rare LOF variants explained 12.7% (SE 1.5%; compared to 0.4% for synonymous variants). A similar pattern was observed for ERMS, where rare LOF variants explained a greater proportion of disease heritability (RMS 8.6%, SE 1.2%; ERMS 12.6%, SE 1.7%; ARMS n/a due to small sample size) compared to common variants from our new GWAS (0.9%, SE 1.6%). Conversely, common variants explained a greater proportion of ES heritability (5.4%, SE 0.5%) and of ARMS heritability (15.5%, SE 6.4%). For 113 established CSGs, and for the 60 moderate-to-high penetrant autosomal dominant (AD) genes, OS and ERMS had significantly (P_{exact}<0.01) more rare P/LP variants overall compared to controls; whereas ARMS and ES had significantly fewer P/LP variants than ERMS and OS, similar to the controls. We confirmed previously reported AD genes, and identified new genes, with an enrichment of P/LP variants in ERMS and OS compared to controls. For both ARMS and ES, the only AD gene significantly enriched for P/LP variants was *CHEK2*. For all cases, patients with a P/LP variant were significantly younger and had significantly more poor outcomes (ie, metastasis, stage 4 disease, and/or death) than those without. For 49 autosomal recessive CSGs, P/LP carrier frequencies were similar among all sarcomas (8-11%), and several specific genes had similar P/LP variant enrichment across sarcomas, and for ES and ARMS only, compared to controls.

CONCLUSION: In the largest set of pediatric sarcoma cases assembled to date, genetic susceptibility was largely driven by rare P/LP AD gene variants in tumor types not characterized by canonical somatic fusions (OS and ERMS). In contrast, fusion-driven tumor types (ES and ARMS) were driven more by common variants.