Largest GWAS of osteosarcoma prioritizes *BRAP* as a candidate susceptibility gene

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Abstract Body: 2,499/2,500 characters (including spaces)

Osteosarcoma (OS) is the most common primary bone tumor in children and adolescents, and metastatic disease remains largely incurable. There are few known predisposing factors for sporadic OS. Large genome-wide association studies (GWAS) to identify common genetic susceptibility loci have been limited due to the rarity of OS. Here, we conducted the largest multi-institutional GWAS to date including 2,530 OS cases and 62,650 controls across multiple ancestries.

In a meta-analysis across three European ancestry sets (1,794 total cases and 59,540 controls), we identified two loci associated with OS at genome-wide significance. The top SNP was located at 12q24.13 (rs741334, $P=4.0x10^{-9}$, odds ratio [OR]=1.3, 95% confidence interval [CI]=1.2–1.4) and was also significant in a combined meta-analysis across all ancestries ($P=8.5x10^{-9}$). A second signal at 14p21.3 was significant only in the European ancestry sets ($P=3.4x10^{-8}$, OR=1.9, 95%CI=1.5–2.3). We also identified suggestive ancestry-specific susceptibility loci in the African ancestry case-control set (240 cases and 2,627 controls; 1q41: $P=1.65x10^{-7}$, OR=2.3, 95%CI=1.7–3.1) and in one Latin American set (206 cases and 190 controls; 10q21.1: $P=9.96x10^{-8}$, OR=3.1, 95%CI=2.0–4.6). Interestingly, the 1q41 SNP was intronic in *ESRRG*, a gene involved in osteoblast differentiation and bone formation.

The top signal at 12q24.13 localized to a gene-dense region with high linkage disequilibrium and evidence for pleiotropy. We conducted several *in silico* analyses to characterize this locus and provide insights into potential functional mechanisms. Fine-mapping with epigenetic data from OS cell lines identified 14 causal SNPs. Among these SNPs, ENCODE enhancer-gene interaction models for OS cell lines and primary osteoblasts identified significant regulatory interactions for rs601663, which localized to the first intron of BRCA1-associated protein (*BRAP*). This SNP was predicted to alter the binding of multiple transcription factors including ZIM3. Separately, we identified *BRAP* as the top gene associated with OS in a transcriptome-wide association study (TWAS) meta-analysis across 48 GTEx tissues. BRAP directly binds and regulates BRCA1, which is part of the homologous recombination (HR) repair pathway; importantly, a large fraction of OS tumors have been reported to harbor an HR deficient mutational landscape.

In the largest GWAS of OS, we identified new genetic susceptibility loci and prioritized *BRAP* as an OS candidate gene.

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