Genome-wide association study identifies new susceptibility regions associated with Ewing sarcoma risk

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Ewing sarcoma is an aggressive pediatric bone tumor predominantly observed in individuals of European ancestry. A defining characteristic of Ewing sarcoma is a fusion of a member of the ETS transcription factor family, usually the *FLI1* gene, with *EWSR1* resulting in an aberrant transcription factor which promotes cell transformation. A previous genome-wide association study identified candidate risk loci at 1p36.22, 10q21 and 15q15. A functional study of the 10q21 region has since localized the association signal to variation in a GGAA repeat motif that when bound by *EWSR1-FLI1* functions as an active regulatory element of *EGR2*. We performed an expanded genome-wide association study of 700 Ewing sarcoma cases and 1,400 ancestry matched controls. Our analysis strengthened previously published association signals at 1p36.22, 10q21 and 15q15 as well as identified two novel candidate loci: a locus on chromosome 6 and a locus on chromosome 20. The chromosome 6 locus is tagged by rs7742053 (OR=1.83, 95% CI=1.50-2.24, P-value=3.88×10^{-9}) while the chromosome 20 locus is tagged by rs12106193 (OR=1.98, 95% CI=1.65-2.37, P-value=1.33×10^{-13}). Notably, the estimated effect sizes of the associations are of greater magnitude than that observed in adult cancers. Extended haplotypes in these associated regions suggest a set of plausible candidate genes for future functional analyses. An additional promising Ewing sarcoma associated locus tagged by rs10627880 was identified on chromosome 3, but the locus achieved a significance shy of the genome-wide significance threshold (P-value=7.79×10^{-8}) and requires further replication and investigation. Collectively, our findings replicate prior Ewing sarcoma genetic associations and provide evidence for novel Ewing sarcoma susceptibility regions.