Novel specific susceptibility loci identified for pediatric and adult ependymoma in first histology-specific genome-wide association study

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Despite extensive research, a small proportion of the variants contributing to the genetic architecture of brain tumors have been reported. The published GWAS have been largely performed on pooled histological subtypes of glioma and most of these studies have been conducted primarily for adult tumors. Therefore, we aimed to perform the first GWAS specifically for ependymoma to identify the genetic variants associated with the risk of these tumors and to investigate the similarities/differences between the genetic architectures of adult and pediatric ependymomas.

Germline SNP-array data of ependymoma cases were obtained from nine studies or biobanks across the United States and Europe. Controls were randomly selected with the ratio of 10:1 from three of those studies and a separate publicly available database. Additionally, germline whole genome sequencing data on cases and controls from St Jude Cloud were utilized. In total, 483 pediatric cases and 265 adult cases and 5592 controls were included. The same quality control procedures were applied to all studies. Data were imputed based on the Haplotype Reference Consortium using EAGLE. Meta-analyses were performed based on GMMAT and logistic regression. The results were adjusted for sex, ancestry and PCs. PAINTOR was used to identify the plausible causal variants, and eQTL and gene enrichment analyses were performed.

We identified 16 independent significant SNPs which were specifically associated with pediatric ependymoma risk, of which 10 SNPs were plausible causal. The significant variants were located on 1q32.2 (*KCNH1*), 2p14 (*MEIS1-AS3*), 4p15.32 (*LDB2*), 6p21.32 (*HLA-DQA*), 6p21.33 (*BX927178/CR759828*), 7p21.3 (*UMAD1*), 11p12 (*LRRC4C*), 11q24.2 (*KRT18P59*), 14q24.3 (*SPTLC2*), and 21q11.2 (*LOC112268283/FEM1AP1*). The 18 identified independent significant SNPs associated with risk of adult ependymoma were located on 4p16.1 (*SORCS2*), 6p11.2, 6p21.31(*KCTD20*), 6p21.32 (*HLA-DQA1*), 7q31.32, 8p23.1 (*LOC157273*), 8q24.3 (*PLEC*), 10p13 (*PTER*), 11q23.3 (*GRIK4*), 19q13.11 (*CEP89*), and 22q11.1 (*XKR3*), of which 8 variants were plausible causal. One intronic variant associated with susceptibility of both pediatric and adult ependymomas was detected; rs68160486 (*CCDC85A* 2p16.1 $P_{\text{Pediatric}}=3.41\text{x}10^{-8}$, $P_{\text{Adult}}=2.12\text{x}10^{-8}$).

The genetic architectures of adult and pediatric ependymomas appear to largely differ from one another. We identified novel variants for these tumors that have not been previously reported for

GWAS of combined glioma subtypes. This analysis highlights the need to conduct additional GWAS of more refined glioma subtypes, perhaps even utilizing newer data on molecularly defined subtypes that are emerging in updated pathological classification schemes.