Title:

Novel Susceptibility Variants in Adult and Pediatric Ependymoma

Authors:

Joshua D. Strauss[1-3], Priya B. Shetty[4,5], Spiridon Tsavachidis[4,5], Jinyoung Byun[4-6], Stephen C. Mack[7], Xiao Xiangjun[4-6], Terri S. Armstrong[8], Mark R. Gilbert[8] (on behalf of NCI-Connect), Lisa Mirabello[9], Smita Bhatia[10], Wendy M. Leisenring[11], Lindsay M. Morton[12], Gregory T. Armstrong[13], Jon Foss-Skiftesvik[14-16], Christian Munch Hagen[15], iPSYCH Consortium[17], Jonas Bybjerg-Grauholm[15], Manel Ghozal[18], Audrey Bonaventure[18], Jacqueline Clavel[18], Melissa L. Bondy[19] (on behalf of GICC), Christopher I. Amos[4-6], Michael E. Scheurer[1-5]

1. Center for Epidemiology and Population Health, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA
2. Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, Texas, USA
3. Texas Children's Cancer Center, Texas Children's Hospital, Houston, Texas, USA
4. Department of Medicine, Section of Epidemiology and Population Sciences, Baylor College of Medicine, Houston, Texas, USA
5. Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas, USA
6. Institute for Clinical and Translational Research, Baylor College of Medicine, Houston, Texas, USA
7. Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA
8. Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA
9. Clinical Genetics Branch, National Cancer Institute, Rockville, Maryland, USA
10. O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, Alabama, USA
11. Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
12. Radiation Epidemiology Branch, National Cancer Institute, Shady Grove, Maryland, USA
13. Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee, USA
14. Department of Neurosurgery, Rigshospitalet University Hospital, Copenhagen, Denmark
15. Danish Center for Neonatal Screening, Department of Congenital Diseases and Neonatal Genetics, Statens Serum Institut, Copenhagen, Denmark
16. Department of Pediatrics and Adolescent Medicine, Rigshospitalet University Hospital, Copenhagen
17. The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH)
18. French Institute of Health and Medical Research, University of Paris, Paris, France
19. Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, California, USA

Background:

Ependymoma is a malignancy of the neuroepithelium that encapsulates the spinal cord and ventricular system of the brain. Occurring in approximately two per million individuals annually, the rarity and poor outcomes of ependymoma result in a scarcity of targeted research and the need to expand our comprehension of disease etiology and genetic risk.

Materials and Methods:

Our study included 543 ependymoma patients and 5,934 disease-free controls that provided blood or saliva samples for analysis from nine cohorts. All cohorts were phased and imputed based on the 1000 Genomes Phase 3 reference panel using BEAGLE 5.4. Imputed cohorts were merged into three analytic groups and underwent quality control filtering. These groups consisted of pediatric subjects with whole genome sequencing (<18yrs old; 143 cases, 332 controls), pediatric subjects with genotyping (<18yrs old; 174 cases, 2340 controls), and adult subjects with genotyping (≥18yrs old; 226 cases, 3262 controls). Genome-wide association studies (GWAS) were conducted for each group, as well as a meta-analysis for the pediatric subjects and overall group using GMMAT. All models were adjusted for the first ten principal components to account for differences in ancestry between cases and controls.

Results:

Several overall and age-specific ependymoma risk loci were identified. Of note, significant pediatric variants were harbored on 1q34.2 (*CCDC30*), 7q21.3 (*DYNC1I1*), 11q13.4 (*SHANK2*), 12p13.2 (*PRR4*, *TAS2R14*), 12q23.1 (*LOC105369927*), 14q32.2 (Intergenic), 15q11.2 (Intergenic). The pediatric meta-analysis further identified 10q11.22 as an intergenic

locus. Adult ependymoma susceptibility variants were located on 1q34.2 (*CCDC30*), 4q35.2 (Intergenic), 7q31.31 (*LOC124901737*), 10p12.33 (*MRC1*), 11p15.4 (*TRIM66*), 15q11.1 (Intergenic), and 16q12.2 (*CES5A*). The overall meta-analysis identified several significant alterations to *CYFIP1* within the previously acknowledged 15q11.2 locus.

Conclusions:

This study represents the largest ependymoma-specific GWAS to date. We identified several novel loci and genes not previously reported specifically for ependymoma risk. Alterations to *CCDC30*, a member of the cancer-associated CCDC family, were ubiquitous throughout adult and pediatric ependymoma, potentially representing a strong global risk factor. The pediatric GWAS identified significant variants within *SHANK2*, *DYNC1I1*, and *TAS2R14*. *SHANK2* is involved in post-synaptic scaffolding and has previously been linked to psychiatric disorders, cognitive impairment, and several cancers, such as neuroblastoma. Interestingly, *DYNC1I1* has also been identified as a tumor suppressor in glioblastoma, a brain cancer more common among older adults compared to ependymoma. *TAS2R14* is a known tumor suppressor and notably regulates resveratrol transmission across the blood-cerebrospinal fluid barrier. The adult GWAS found significant variants within *MRC1* (also known as *CD206*) and *TRIM66*, both of which have been associated with glioma, as well as other cancers. Finally, significant alterations to *CYFIP1* were able to be detected from the overall meta-analysis. *CYFIP1* has commonly been connected to epithelial cancers, in addition to the gene's role in psychiatric disorders and cognitive impairment. In conclusion, the genetic risk of ependymoma appears to be influenced by multiple loci and genes previously associated with neurologic diseases. The age-

specific findings may permit further research into the etiological differentiation of ependymoma occurrence by age.