Racial/Ethnic Differences in Pediatric Brain Tumor Diagnoses in Patients with Neurofibromatosis Type 1

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Objective To evaluate evidence for differences in pediatric brain tumor diagnoses by race and ethnicity using a cross-sectional study design in individuals with neurofibromatosis type 1 (NF1).

Study design Subjects with NF1 were ascertained from the NF1 Patient Registry Initiative and through a clinical record database of patients at a large academic medical center. Logistic regression was employed to calculate ORs and 95% CIs to analyze differences in the odds of brain tumor diagnosis by race (White, Black, Asian, other/unknown) and ethnic (Hispanic vs non-Hispanic) groups.

Results Data from a total of 1546, 629, and 2038 individuals who were ascertained from the NF1 Patient Registry Initiative, clinical records, and pooled datasets were analyzed, respectively. After adjusting for birth year, we observed a significantly reduced odds of brain tumor diagnoses in individuals self-identified or clinically reported as Black (OR = 0.13, 95% CI 0.05-0.31), Asian (OR = 0.15, 95% CI 0.04-0.64), and other/unknown (OR = 0.61, 95% CI 0.41-0.93) race compared with those with reported as White race. There was no significant difference in the odds of pediatric brain tumor diagnosis by Hispanic ethnicity.

Conclusions Consistent with prior smaller studies, these data suggest that pediatric brain tumor diagnoses vary by race in individuals with NF1. Reasons underlying observed differences by race warrant further investigation. *(J Pediatr 2015;167:613-20).*

Neurofibromatosis type 1 (NF1) is an autosomal dominant medical condition. Although estimates vary, it was recently suggested that the birth incidence may be as high as 1 in 2000.[1] NF1 is associated with several clinical manifestations, including benign and malignant tumors,[2-7] cognitive delays, behavioral issues,[8-10] autism,[11,12] and cardiovascular disease and abnormalities.[13,14] Although the condition exhibits complete penetrance with all individuals showing some signs of the disease, the expression of the clinical signs and symptoms is highly variable between individuals, even in the same family.[15]

NF1 predisposes individuals to tumors that involve the central nervous system, including malignant and benign brain tumors. In this regard, individuals with NF1 are at high risk for the development of pediatric brain tumors, particularly gliomas that predominate in the optic pathway and brainstem, although other brain tumor types have been reported to occur in NF1.[16,17] Optic pathway gliomas (OPGs) that are detected in 15-20% of children can result in visual compromise or early onset puberty.[18] Because of their frequency, OPGs are included as one of the clinical diagnostic criteria for NF1.[19,20]

Defining the factors that modify pediatric brain tumor risk in patients with NF1 is critical for the development of risk prediction models and may inform our understanding of pediatric brain tumor etiology. However, risk factors for pediatric brain tumors in NF1 have not been clearly defined. Some studies have indicated that the greatest risk factor for development of OPGs, which have been most well studied, is patient age, with the vast majority of tumors arising within the first 6 years of life.[18] There is also suggestive evidence that the prevalence of OPG diagnoses differs by ancestral background with lower rates reported in individuals with African compared with those with European ancestries.[21-25]

Using data from the NF1 Patient Registry Initiative (NPRI) and medical chart review of a case series of individuals with NF1 ascertained through a large academic medical center, our objectives were to: (1) examine differences in the frequency of pediatric brain tumor diagnoses overall and for individuals identified with OPGs specifically by race and ethnicity in individuals with NF1 in a larger sample size than

CIDER	Clinical Investigation Data Exploration Repository
NF	Neurofibromatosis
NF1	Neurofibromatosis type 1
NPRI	NF1 Patient Registry Initiative
OPG	Optic pathway glioma

previously reported; and (2) conduct a literature review of past reported evidence of differences in pediatric brain tumor diagnoses in NF1 by race/ethnicity.

Methods

This study used a cross-sectional study design with both information on the exposure and the outcome collected at the same time. Participants from the NPRI (https://nf1registry.wustl.edu) were eligible if they had complete questionnaire data, enrolled in the NPRI between May 17, 2011 and December 30, 2014, and provided information about brain tumor diagnosis history. Registry methods have been previously reported in detail.[26-28] Briefly, adults and children with self- or parent/legal guardian-identified NF1 from anywhere in the world, respectively, are eligible to participate in the web-based registry. Following consent, individuals ≥18 years of age at registration or a parent/legal guardian of individuals <18 years of age provide contact information and complete the appropriate version, either adult or minor, of the 30- to 45-minute questionnaire. The questionnaires contain 11 sections that inquire about demographic, doctor information, clinical (including NF1 clinical signs), and psychosocial history. Participant electronic data and records are stored at Washington University in St. Louis behind a secure firewall. The Institutional Review Board at Washington University in St. Louis approved this study.

This study also included subjects ascertained from the Clinical Investigation Data Exploration Repository (CIDER), a comprehensive inpatient and outpatient research patient data warehouse created by the Washington University Center for Biomedical Informatics (http://cbmi.wustl.edu/?q=project/cider). Patients with NF1 documented in their medical records from July 1, 1997 to June 1, 2014 were eligible for the study. Select demographic information, including birth date, sex, and race/ethnicity, and clinical history information (including NF1 and brain tumor diagnoses), was abstracted from records for all subjects in the CIDER database with an NF1-related *International Classification of Diseases, Ninth Revision* code (237.70, or 237.71). NF1 diagnoses for patients identified using *International Classification of Diseases, Ninth Revision* codes were validated through review of their medical records for NF1 clinical signs as previously described.[29]

Link Plus (http://www.cdc.gov/cancer/npcr/tools/registryplus/lp.htm), a probabilistic record linkage program created by the Center for Disease Control and Prevention's Division of Cancer Prevention and Control, was used to identify individuals included in both the NPRI and CIDER datasets for the pooled analysis. Only unique individuals were included in the pooled dataset.

Race and ethnicity were measured slightly differently for NPRI and CIDER subjects, necessitating harmonization for these variables. For NPRI subjects, participants were asked to report their race through the question "What race do you consider [yourself/the participant] to be? (Select as many as apply)." Respondents could check a box for the following options: American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White, or they could check a box indicating that they did not wish to provide race information. For the purposes of this analysis, each participant's race was classified as White, Black, Asian, or other/unknown. The other/unknown category included race selections with very few subjects (American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander), multiple race categories, and those whose race was unknown (either because it was missing or the participant elected not to provide this information). For subjects identified through CIDER, race was reported in medical records as White, Black, Hispanic, Asian, unknown, or other. Race was classified into the same categories listed above for NPRI subjects. Individuals identified as Hispanic through medical records were coded as missing and excluded from the pooled and CIDER-specific analysis for race. For NPRI subjects, Hispanic ethnicity was captured through the question "Do you consider [yourself/the participant] to be Hispanic or Latino?" For medical records in which Hispanic ethnicity was clearly noted no additional details on race background were abstracted (ie, White, Black, Asian). The data were collapsed further into White and other race for some analyses when there were small numbers, with other including all race categories besides White.

Pediatric brain tumors were defined as those diagnosed in individuals <18 years of age. For NPRI subjects, brain tumor diagnoses were ascertained through the question "Has the participant [Have you] ever been diagnosed with a brain tumor?" The possible responses to this question were "Yes," "No," and "Don't Know." If the respondent selected "Yes," they were further prompted to specify the age at diagnosis with the following question "How old was the participant [were you] when the brain tumor was diagnosed?" Pediatric brain tumors diagnosed <18 years of age were defined based on responses to these 2 questions. The NPRI questionnaire did not inquire about specific brain tumor subtypes; however, we were able to ascertain this information for a subset of respondents from whom we confirmed brain tumor presence through medical records or through a write-in response on the NPRI questionnaire to a question that asked about other cancer/tumor diagnoses in the participant. Treatment for brain tumors was ascertained for those who responded yes to having been diagnosed with a brain tumor through a question that asked participants to check boxes if they received any of the following treatments for their brain tumor: a chemotherapy, radiation therapy, surgery, or "I don't know". For subjects ascertained from CIDER with NF1, medical records were reviewed and abstracted for clinically verified positive brain tumor history. A description of brain tumor type, initial diagnosis age recorded in the record, and any treatment (chemotherapy, radiation therapy, or surgery) were also abstracted.