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Racial/ethnic differences in pediatric brain tumor diagnoses in Patients with Neurofibromatosis Type 1

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Abstract

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 (NPRI) and through a clinical record database of patients at a large academic medical center. Logistic regression was employed to calculate odds ratios (ORs) and 95% confidence intervals (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 NPRI, 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.

Conclusion—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.

Keywords

optic gliomas; race; ethnicity; risk; brain tumors

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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 which predominate in the optic pathway and brainstem, although other brain tumor types have been reported to occur in NF1 (16, 17). Optic pathway gliomas are detected in 15–20% of children, among whom they 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 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 six 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 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 30–45 minute questionnaire. The questionnaires contain 11 sections that inquire about demographic, 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 7/1/1997 to 6/1/2014 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 (ICD-9) code (237.70, or 237.71). NF1 diagnoses for patients identified using ICD-9 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 data harmonization for these variables. For NPRI subjects, participants were asked to self-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 (i.e., 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 two 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 (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, surgery) were also abstracted.

Statistical analyses

All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.3 (SAS Institute, Cary, NC). Bivariate analyses were used to compare self- and medical record reported demographic and clinical characteristics by pediatric brain tumor group (questionnaire or medical record documentation of a history of pediatric brain tumor vs. no history of pediatric brain tumor). Specifically, differences in sex, race, ethnicity, birth year category, household education, residency, and having a treating NF medical specialist were compared between pediatric brain tumor groups. P-values were calculated using the chi-square test.

Multivariate logistic regression was employed to assess differences in the odds of a reported pediatric brain tumor diagnosis by race and ethnicity after adjusting for birth year. We ran models for the pooled data and data stratified by source where numbers were sufficient. We also ran subgroup analyses specific for OPGs for subjects among whom brain tumor subtype information was available. There were minor differences in reporting of pediatric brain tumor diagnoses between subjects contained in both the NPRI and CIDER datasets that could not be resolved. Specifically, 5 of 36 individuals who reported a pediatric brain tumor diagnosis on the NPRI questionnaire were not reported to have a brain tumor diagnosis in CIDER. Two out of 100 individuals who did not report a pediatric brain tumor diagnosis on the NPRI questionnaire had documentation of a brain tumor diagnosis in the CIDER dataset. There were also some discordant classifications for race (n=21) and ethnicity (n=5) between NPRI and CIDER datasets for subjects contained in both datasets. This was due to being classified as Unknown/Other for one data source where the other data source indicated White (n=18) or African American/Black (n=3) race. For ethnicity, 4 of 5 individuals were reported as "Hispanic" in the NPRI and "non-Hispanic" in CIDER. We conducted a sensitivity analysis to address discrepancies in reporting of brain tumor diagnoses and race/ethnicity between CIDER and the NPRI where the discrepancy could not be resolved. We ran two separate logistic regression models for the pooled data where the information on

brain tumors and race/ethnicity was captured from the CIDER dataset and the reverse where information on these variables was captured from the NPRI dataset for subjects included in both data sources.

All models were adjusted for birth year. All tests were two-sided with *p*-values <0.05 being considered statistically significant.

Literature Review

A thorough search of the literature for relevant papers and books was conducted to identify previous research reporting differences in the frequency of brain tumor diagnoses by race/ethnicity in individuals with NF1. Several academic databases, including Academic Search Premier, PubMed, and Google Scholar, as well as university library resources were used to find sources. Search terms for our study included: “NF1 pediatric brain tumor race,” “NF1 optic pathway glioma race,” “NF1 optic nerve tumor race,” “optic glioma race characteristics,” “NF1 and optic gliomas,” “demographics of optic gliomas,” “trends in optic gliomas.” and “relationship between NF1 and optic gliomas.” Only papers focusing on patients with NF1 that reported racial identities, brain tumor history, and age at diagnosis were included. Citation lists from articles obtained through database and library searches were then reviewed to find additional resources.

RESULTS

A total of 1546 NPRI participants and 629 CIDER patients were included who met the eligibility criteria. In the pooled dataset that comprised subjects identified through both NPRI and CIDER, there were a total of 2038 unique individuals, including 149 individuals from both data sources. In bivariate analyses, there were significant differences by sex (p=0.02), race (p<0.0001), and birth year category (p<0.0001) between pediatric brain tumor cases and non-cases with a higher percentage of pediatric brain tumor cases being male, White, and born after 2001 than non-cases. There was no significant difference in the frequency of pediatric brain tumor diagnoses by ethnicity in the pooled dataset (p=0.79). A similar pattern was observed in both data sources for race and birth year category, although modest differences were found between data sources for sex and ethnicity. For NPRI subjects, similar patterns were observed for pediatric brain tumor cases and non-cases for household education with percentages varying less than 5% at each educational level. Finally, slightly fewer pediatric brain tumor cases had a reported residence outside of the United States compared with non-cases among subjects ascertained from the NPRI and more pediatric brain tumor cases were reported to have an NF1 specialist (Table I).

Unadjusted estimates for the association between race/ethnicity and pediatric brain tumor s are reported in Table II (available at jpeds.com). In birth year adjusted models, Black (OR=0.13; 95% CI 0.05–0.31) vs. White race was significantly inversely associated with pediatric brain tumor diagnosis history. Similarly, those with reported Asian (OR=0.15; 95% CI 0.04–0.64) and Other/unknown (OR=0.61; 95% CI 0.41–0.93) race were less likely to have a pediatric brain tumor diagnosis history than those with reported White race. Hispanic vs. non-Hispanic ethnicity was not significantly associated with pediatric brain tumor history (OR=0.71; 95% CI 0.43–1.18). Patterns were similar for race (White vs. Other)

when the data were analyzed by source (NPRI vs. CIDER). For ethnicity, although the OR estimates were non-significant for both data sources, they were in opposite directions, but it is important to note that the CIDER estimate was based on very few subjects (Table III). Furthermore, models adjusted for birth year, sex, and data source were constructed, but did not yield any material differences with models adjusted solely on birth year. As such, to create a parsimonious model, sex and data source were dropped from the final model presented in Table III. To account for differential reporting of race/ethnicity and brain tumor diagnosis history between data sources, we conducted a sensitivity analysis in which data on these variables was obtained from NPRI instead of CIDER for subjects contained in both data sources. There were no material differences in the results (Table IV; available at jpeds.com).

For a subset of individuals for whom brain tumor subtype information was available (n=140 in the pooled dataset) through medical records or through participant/legal guardian reported other cancer type on the NPRI questionnaire, we examined the association between OPG diagnosis and race; results were similar to the main findings with ORs of 0.17 (95% CI 0.02–1.24), 0.22 (95% CI 0.08–0.60), and 0.56 (95% CI 0.31–1.01) for Asian, Black, and Unknown/Other vs. White race respectively. We also examined whether the same pattern by race was present for symptomatic OPGs vs. no brain tumor diagnosis. From the 140 subjects in the pooled dataset, 78, 61, and 1 individual had no evidence of treatment, reported treatment, and unknown treatment, respectively. Individuals with “Other” race were significantly less likely to have a report of a treated OPG vs. no OPG than those with White race (OR=0.32; 95% CI 0.14–0.71). There was no significant difference in the odds of having a treated OPG vs. an untreated OPG by race with an OR of 0.70 for “Other” compared with White race (95% CI=0.26–1.92) (data not shown).

DISCUSSION

The current study sought to examine racial and ethnic differences in the frequency of pediatric brain tumor diagnoses among patients with NF1 with a larger sample size than previously reported. The results of this large cross-sectional study suggest that individuals with African ancestry and possibly Asian ancestry are less likely to have a past pediatric brain tumor diagnosis compared with those of European ancestry. These results are consistent for both OPGs overall and treated OPGs.

A number of previous studies have examined the association between race and ethnicity and OPG diagnoses, the most frequent brain tumor type among patients with NF1. Although most previous studies did not have the main objective of determining racial/ethnic differences in the frequency of OPG diagnoses in individuals with NF1, many provided sufficient information to evaluate differences (21–25). Consistent with the present study, prior research suggests that individuals with European ancestry (reported as White or Caucasian) have a greater frequency of OPG diagnoses compared with those with African ancestry and possibly other backgrounds as summarized in Table V.

A higher frequency of pediatric brain tumor diagnoses in certain racial/ethnic groups could be explained by genetic, environmental, or social factors or a combination of these factors

that correlate with race/ethnicity. We are careful to note that race and ethnicity classifications are controversial and may serve only as markers of other factors correlated with the probability of being diagnosed with a brain tumor (30). It has previously been hypothesized that both genetic and environmental factors influence pediatric brain tumor risk; however, the specific factors involved remain poorly defined (31). With respect to the NF1 population, two small studies have reported data suggesting that the germline *NF1* gene mutation in individuals with OPGs tends to cluster toward the 5′ end of the *NF1* gene (32, 33). However, it seems likely that modifying genes also play an important role. A higher frequency of brain tumor diagnoses among individuals with NF1 with European versus African ancestry may be explained by differences in the frequency of risk alleles between different ancestral populations; empirical evidence supporting this hypothesis as an explanation for differences in cancer incidence by race classification has been shown for childhood leukemia (34, 35).

Social factors must also be considered as an explanation for differences in the prevalence of pediatric brain tumor diagnoses by race. Optic gliomas are often asymptomatic and may never come to the attention of a physician in the absence of a MRI scan or ophthalmology evaluation (23). Therefore, access to care and particularly an NF specialist could explain differences in the frequency of pediatric brain tumor diagnoses by race (36). Some evidence for this hypothesis was observed for NPRI subjects with ~37% of White subjects reporting an NF specialist vs. ~25% of Black subjects, which could indicate a lower MRI screening rate for optic gliomas in Blacks than Whites. However, among NPRI pediatric subjects without brain tumors identified in those who reported Black/African American race, the frequency of participants with Black race reporting NF specialists was slightly higher (38.9%) compared with participants reporting White race (34%) (data not shown). In addition, a similar excess of brain tumor diagnoses among White compared with Black subjects ascertained from a large University hospital with a NF specialty center argues against detection bias by race as a primary explanation for these results.

This study has both strengths and limitations. Strengths of this study include the largest sample size to date with data pooled from an international NF1 patient registry as well as a large medical center's clinical records database. Although it was not possible to validate NF1 diagnoses for all NPRI subjects, our previously published work supports the validity of participant-reported NF1 diagnoses (28). With respect to self-reported pediatric brain tumor diagnosis from the NPRI, some misclassification may be present. However, for a subset of respondents reporting pediatric brain tumor diagnoses (n=78), medical records were obtained. Of these, 88.5% had documented evidence consistent with a pediatric brain tumor diagnosis. In addition, a small number of subjects contained in both the NPRI and the CIDER database had discrepant information on brain tumor diagnoses. On review of these cases, it was noted that the majority of these discrepancies could likely be attributed to insufficient records. Despite these limitations, the consistency of findings between the current study using two different data sources as well as past results from smaller studies, make it reasonable to infer that differential pediatric brain tumor diagnoses by race are not the result of data collection or measurement errors.

In conclusion, the results of our study and literature review strongly suggest differences in the frequency of pediatric brain tumor diagnoses by race among patients with NF1, similar to population-based reports for sporadic pediatric brain tumors (37). However, the underlying mechanism for the observed difference in the prevalence of pediatric brain tumor diagnosis by race is currently unknown. We are careful not to make any steadfast claims that implicate biologic determinants of health such as genetics over social and environmental factors that influence health outcomes and their ascertainment. Further research is needed to determine the underlying reasons for differences in the frequency of pediatric brain tumor diagnoses by race. These data may help inform the underlying biology of brain tumor development as well as brain tumor risk prediction in children with NF1.

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Abbreviations

CIDER	Clinical Investigation Data Exploration Repository
CI	confidence interval
NF1	Neurofibromatosis Type 1
NPRI	NF1 Patient Registry Initiative
ND	not determined
OR	odds ratio
OPG	optic pathway glioma

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Table I

Characteristics of sample by data source and pediatric brain turmor status.

	Pooled (n=2038)[a]			NPRI (n=1546)[b]		CIDER (n=629)[c]	
Characteristic	**Total (n=2038) N (%)**	**PBT cases (n=297) N (%)**	**Non-cases (n=1741) N (%)**	**PBT cases (n=220) N (%)**	**Non-cases (n=1326) N (%)**	**PBT casesa (n=113) N (%)**	**Non-cases (n=516) N (%)**
Sex							
Male	822 (40.4)	138 (46.5)	684 (39.3)	97 (44.1)	485 (36.6)	56 (49.6)	241 (46.7)
Female	1215 (59.7)	159 (53.5)	1056 (60.7)	123 (55.9)	839 (63.4)	57 (50.4)	275 (53.3)
Race							
White	1532 (75.4)	256 (86.8)	1276 (73.5)	196 (89.1)	1030 (77.7)	95 (85.6)	327 (64.0)
Black	191 (9.4)	5 (1.7)	186 (10.7)	0 (0)	73 (5.5)	5 (4.5)	122 (23.9)
Asian	71 (3.5)	2 (0.7)	69 (4.0)	1 (0.5)	68 (5.1)	1(0.9)	4 (0.8)
Other/Unknown	237 (11.7)	32 (10.9)	205 (11.8)	23 (10.5)	155 (11.7)	10 (9.0)	58 (11.4)
Ethnicity							
Hispanic	143 (7.1)	20 (6.7)	123 (7.2)	20 (9.1)	121 (9.3)	2 (1.8)	5 (1.0)
Non-Hispanic	1871 (92.9)	277 (93.3)	1594 (92.8)	200 (90.9)	1181 (90.7)	111 (98.2)	511 (99.0)
Birth year category							
<1969	473 (23.3)	7 (2.4)	466 (26.9)	6 (2.7)	395 (30.0)	2 (1.8)	93 (18.0)
1969–1984	453 (22.3)	17 (5.7)	436 (25.2)	16 (7.3)	359 (27.3)	4 (3.5)	95 (18.4)
1985–2001	532 (26.2)	124 (41.8)	408 (23.4)	85 (38.6)	274 (20.8)	51 (45.1)	152 (29.5)
>2001	571 (28.1)	149 (50.2)	422 (24.4)	113 (51.4)	289 (21.9)	56 (49.6)	176 (34.1)
Education							
High school or less	ND	ND	ND	50 (22.8)	344 (26.0)	ND	ND
Some college	ND	ND	ND	51 (23.3)	276 (20.9)	ND	ND
Associate, occupational, or technical degree	ND	ND	ND	36 (16.4)	255 (19.3)	ND	ND
Bachelors or above	ND	ND	ND	82 (37.4)	447 (33.8)	ND	ND
Residency							
US	ND	ND	ND	175 (81.0)	1004 (77.1)	ND	ND
Non-US	ND	ND	ND	41 (19.0)	299 (22.9)	ND	ND

	Pooled (n=2038)[a]			NPRI (n=1546)[b]		CIDER (n=629)[c]	
Characteristic	**Total (n=2038) N (%)**	**PBT cases (n=297) N (%)**	**Non-cases (n=1741) N (%)**	**PBT cases (n=220) N (%)**	**Non-cases (n=1326) N (%)**	**PBT casesa (n=113) N (%)**	**Non-cases (n=516) N (%)**
Reported having an NF specialist							
Yes	ND	ND	ND	135 (61.4)	475 (35.8)	ND	ND
No	ND	ND	ND	85 (38.6)	851 (64.2)	ND	ND

ND=not determined

[a] Pooled missing data: sex=1, race=7 birth year category=9; ethnicity=24

[b] NPRI missing data: sex=2, birth year category=9; country=27; ethnicity=24; education=5

[c] CIDER missing data: race=7

Table 2

online. Unadjusted associations between race/ethnicity and pediatric brain tumor history in the pooled, NPRI, and CIDER datasets.

	Pooled (n=2038)			NPRI (n=1546)			CIDER (n=629)		
	Non-cases (N=1736) N (%)	PBT cases (N=295) N (%)	OR (95% CI)	Non-cases (N=1314) N (%)	PBT cases (N=219) N (%)	OR (95% CI)	Non-cases (N=516) N (%)	PBT cases (N=113) N (%)	OR (95% CI)
Race[a]									
White	1276 (73.5)	255 (86.8)	1.0 (ref.)	1030 (77.7)	196 (89.1)	ND	327 (64.0)	95 (85.6)	ND
Black	186 (10.7)	5 (1.7)	0.13 (0.06–0.33)	73 (5.5)	0 (0)	ND	122 (23.9)	5 (4.5)	ND
Asian	66 (4.0)	2 (0.7)	0.15 (0.04–0.59)	68 (5.1)	1 (0.5)	ND	4 (0.8)	1 (0.9)	ND
Other/Unknown	205 (11.8)	32 (10.9)	0.78 (0.52–1.16)	155 (11.7)	23 (10.5)	ND	58 (11.4)	10 (9.0)	ND
Race[b]									
White	1276 (73.5)	256 (86.8)	1.0 (ref.)	1030 (77.7)	196 (89.1)	1.0 (ref.)	327 (64.0)	95 (85.6)	1.0 (ref.)
Other	460 (26.5)	39 (13.2)	0.42 (0.30–0.60)	296 (22.3)	24 (10.9)	0.43 (0.27–0.66)	184 (36.0)	16 (14.4)	0.30 (0.17–0.52)
Ethnicity[c]									
Non-Hispanic	1594 (92.8)	123 (7.2)	1.0 (ref.)	1181 (90.7)	200 (90.9)	1.0 (ref.)	511 (99.0)	111 (98.2)	1.0 (ref.)
Hispanic	277 (93.3)	20 (6.7)	0.94 (0.57–1.53)	121 (9.3)	20 (9.1)	0.98 (0.59–1.60)	5 (1.0)	2 (1.8)	1.84 (0.35–9.61)

ND=Not determined

[a] 7 individuals were excluded who had missing data on one or more variables in the model in the pooled dataset

[b] 7, 0, and 7 individuals were excluded who had missing data on one or more variables were excluded from the pooled, NPRI, and CIDER models, respectively

[c] 24 individuals were excluded from the pooled and NPRI models who had missing data on one or more of the variables in the model

Table 3

Birth year adjusted associations between race/ethnicity and pediatric brain tumor history in the pooled, NPRI, and CIDER datasets.

	Pooled (n=2038)			NPRI (n=1546)			CIDER (n=629)		
	PBT cases (N=298) N (%)	**Non-cases (N=1740) N (%)**	**OR[a] (95% CI)**	**PBT cases (N=220) N (%)**	**Non-cases (N=1326) N (%)**	**OR[a] (95% CI)**	**PBT cases (N=113) N (%)**	**Non-cases (N=516) N (%)**	**OR[a] (95% CI)**
Race[b]									
White	256 (86.8)	1269 (73.7)	1.0 (ref.)	196 (89.0)	1023 (77.9)	ND	95 (85.6)	327 (64.0)	ND
Black	5 (1.7)	185 (10.7)	0.13 (0.05–0.31)	0 (0)	72 (5.5)	ND	5 (4.5)	122 (23.9)	ND
Asian	2 (0.7)	67 (3.9)	0.15 (0.04–0.64)	1 (0.5)	66 (5.0)	ND	1 (0.9)	4 (0.8)	ND
Other/Unknown	32 (10.9)	202 (11.7)	0.61 (0.41–0.93)	23 (10.5)	152 (11.6)	ND	10 (9.0)	58 (11.4)	ND
Race[b]									
White	256 (86.8)	1269 (73.7)	1.0 (ref.)	196 (89.1)	1023 (77.9)	1.0 (ref.)	95 (85.6)	327 (64.0)	1.0 (ref.)
Other	39 (13.2)	454 (26.4)	0.37 (0.26–0.53)	24 (10.9)	290 (22.1)	0.40 (0.25–0.63)	16 (14.4)	184 (36.0)	0.28 (0.16–0.50)
Ethnicity[d]									
Non-Hispanic	122 (7.2)	1584 (92.9)	1.0 (ref.)	200 (90.9)	1171 (90.7)	1.0 (ref.)	111 (98.2)	511 (99.0)	1.0 (ref.)
Hispanic	20 (6.7)	277 (93.3)	0.71 (0.43–1.18)	20 (9.1)	120 (9.3)	0.66 (0.39–1.12)	2 (1.8)	5 (1.0)	1.35 (0.25–7.18)

ND=Not determined

[a] Adjusted for birth year

[b] 20, 13 and 7 individuals were excluded who had missing data on one or more variables were excluded from the pooled, NPRI, and CIDER models, respectively

[c] 35 individuals were excluded from the pooled and NPRI models who had missing data on one or more of the variables in the model.

Table 4

online. Birth year adjusted associations between race/ethnicity and pediatric brain tumor history in the pooled dataset with CIDER data as the primary data source for participants contained in both data sources.

	Pooled (n=2026[a])		
	Non-cases (N=1727) N (%)	**PBT cases (N=299) N (%)**	**OR[b] (95% CI)**
Race[c]			
White	1270 (74.3)	261 (87.9)	1.0 (ref.)
Black	182 (10.6)	4 (1.4)	0.10 (0.04–0.28)
Asian	68 (4.0)	1 (0.3)	0.07 (0.01–0.54)
Other/Unknown	190 (11.1)	31 (10.4)	0.65 (0.43–0.98)
Race[c]			
White	1270 (74.3)	261 (87.9)	1.0 (ref.)
Other	440 (25.7)	36 (12.1)	0.36 (0.25–0.52)
Ethnicity[d]			
Non-Hispanic	1568 (92.7)	277 (92.6)	1.0 (ref.)
Hispanic	124 (7.3)	22 (7.4)	0.75 (0.46–1.23)

[a] Note: 12 individuals present who were present in both data sources that were included in the pooled dataset in table 3 were not included in this analysis due to incomplete NPRI data bringing the total from 2038 to 2026.

[b] Adjusted for birth year

[c] 19 individuals were excluded who had missing data on one or more variables

[d] 35 individuals were excluded who had missing data on one or more variables

Table V

Review of studies reporting optic pathway glioma diagnoses in children with NF1 by race.

Citation/Study Location	Study design	Study population	OPG identification method	Cases and non-cases overall and by race	Prevalence	Comment
Pletcher et al, 1995 (24), NF Center of New Jersey, Newark, NJ	Retrospective chart review	63 patients with NF1	Symptoms or MRI	5 OPG cases 58 non-cases Caucasian: 4 cases, 15 non-cases African American: 0 cases, 29 non-cases Hispanic: 1 case, 12 non-cases Asian: 0 cases, 2 non-cases	White: 4/19 (21%) African American: 0/29 (0%) Hispanic: 1/13 (7.7%) Asian=0/2 (0%)	African Americans with NF1 had a lower frequency of OPG diagnoses compared to Hispanic and Caucasian populations
Saal et al, 1995 (25) Cincinnati Children's Hospital Medical Center, Cincinnati, OH and Children's National Medical Center, Washington D.C.	Retrospective chart review	272 patients with NF1	MRI scan	52 OPG cases[a] 220 no-cases African American: 0 cases, 48 non-cases 52 Caucasian/Hispanic cases	Caucasian/ Hispanic: 52/224 (23%) African American: 0/48 (0%)	The total number of Caucasians and Hispanics was not reported and was derived by subtracting 48 from the 272 total patients with NF1
Kaste & Pivnick, 1998 (22), St. Jude's Research Hospital and LeBonheur Children's Medical Center, Memphis TN	Retrospective chart review	58 patients with NF1	Cranial MRI scans between 1984–1997	20 OPG cases 38 non-cases Caucasian/Hispanic: 18 cases, 22 non-cases African American: 2 cases, 16 non-cases	Caucasian/ Hispanic: 18/40 (45%) African American: 2/18 (11%)	Caucasian/ Hispanic: 18/40 (45%) African American: 2/18 (11%)
King et al, 2003 (23), St. Louis Children's Hospital and Children's Memorial Hospital in Chicago, IL	Retrospective chart review	90 children with NF1 and OPGs	Chart review indicating MRI detected OPG	90 OPG cases Non-cases not included Asymptomatic: 39 Symptomatic: 51 Caucasian: 74 cases African American: 9 cases Hispanic: 6 cases Other: 1 case	Not reported	Reported significantly more Caucasian than African American children with OPGs (p=0.024) at Children's Memorial Hospital where racial demographics were known.
Blazo et al, 2004 (21), NF and Genetics Clinics at Baylor College of Medicine, Texas Children's Hospital, Waco, TX	Retrospective chart review/survey	84 children with NF1	MRI scan or prior MRI scans	24 OPG cases[a] 60 non-cases Caucasian (non-Hispanic):17 cases, 29 non-cases Caucasian (Hispanic): 5 cases, 21 non-cases African-American: 2 cases, 9 non-cases Asian: 0 cases, 1 non-case	Caucasian (Non-Hispanic): 17/46 (36.9%) Caucasian (Hispanic): 5/26 (16.1%) African American: 2/11 (18%) Asian: 0/1 (0%)	

OPG=optic pathway glioma

[a]The authors originally noted tumor types as optic nerve gliomas (25) and optic pathway tumors (21); however, because these tumors are the same as optic pathway gliomas, we elected to use consistent terminology across studies.