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Racial and ethnic differences in epilepsy classification among probands in the Epilepsy Phenome/Genome Project (EPGP)

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Summary Little is known about the ethnic and racial differences in the prevalence of generalized and focal epilepsy among patients with non-acquired epilepsies. In this study, we examined epilepsy classification and race/ethnicity in 813 probands from sibling or parent—child pairs with epilepsy enrolled in the Epilepsy Genome/Phenome Project (EPGP). Subjects were classified as generalized epilepsy (GE), non-acquired focal epilepsy (NAFE), mixed epilepsy syndrome (both generalized and focal), and unclassifiable, based on consensus review of semiology and available clinical, electrophysiology, and neuroimaging data. In this cohort, 628 (77.2%) subjects identified exclusively as Caucasian/white and 65 (8.0%) subjects reported African ancestry, including subjects of mixed-race. Of the Caucasian/white subjects, 357 (56.8%) had GE, 207 (33.0%) had NAFE, 32 (5.1%) had a mixed syndrome, and 32 (5.1%) were unclassifiable. Among subjects of African ancestry, 28 (43.1%) had GE, 27 (41.5%) had NAFE, 2 (3.1%) had a mixed syndrome, and 8 (12.3%) were unclassifiable. There was a higher proportion of subjects with GE compared to other syndromes among Caucasians/whites compared to subjects with African ancestry (OR 1.74, 95% CI: 1.04—2.92, two-tailed Fisher's exact test, $p = 0.036$). There was no difference in the rate of GE among subjects reporting Hispanic ethnicity (7.6% of total) when adjusted for race (Caucasian/white vs non-Caucasian/white; OR 0.65, 95% CI: 0.40—1.06, $p > 0.05$). The proportion of participants with unclassifiable epilepsy was significantly greater in those of African-American descent. In a group of patients with epilepsy of unknown etiology and an affected first degree relative, GE is more common among Caucasian/white subjects

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than among those with African ancestry. These findings suggest there may be geographical differences in the distribution of epilepsy susceptibility genes and an effect of genetic background on epilepsy phenotype. However, the results should be interpreted with caution because of the low numbers of African-Americans in this cohort and more limited diagnostic data available for epilepsy classification in these subjects compared to Caucasians/whites.

Introduction

Little is known about the distribution of epilepsy susceptibility genes and epilepsy syndromes among racial and ethnic groups. The photo-paroxysmal response (PPR), an electroencephalographic finding associated with idiopathic generalized epilepsy (GE), is more common among people of European ancestry than among those of African ancestry (Adamolekun et al., 1998; de Graaf et al., 1995) suggesting there may be variability in the prevalence of epilepsy syndromes among people of different ancestries. We examined the relationship between self-reported race and ethnicity and epilepsy type in a large cohort of individuals with epilepsy of unknown cause. Based on the distribution of the PPR, we hypothesized that GEs would be less common in subjects of African ancestry than Caucasians/whites.

Methods

Subjects

We examined epilepsy classification and race/ethnicity in 813 probands from sibling or parent—child pairs with epilepsy enrolled in the Epilepsy Phenome/Genome Project (EPGP), a multi-center, collaborative effort to collect detailed phenotypic and genetic data on a 3750 patients with epilepsy (Nesbitt et al., 2013; The EPGP Collaborative, 2013). Subjects were enrolled at 27 sites, all but four (Argentina, Australia, Canada and New Zealand) of which were in the United States. Subjects were eligible for the study if they were between ages 4 weeks and 60 years old, had no identifiable acquired cause of epilepsy, and had a living first degree relative with epilepsy. Another arm of EPGP also enrolled subjects with infantile spasms, Lennox—Gastaut syndrome, periventricular heterotopias and polymicrogyria but these subjects were not included in this analysis.

Data collection and phenotypic review

Phenotypic information was obtained through in-person or telephone semi-structured interviews and review of medical records as previously described (Nesbitt et al., 2013; Winawer et al., 2013). Relevant EEG, MRI and medical records were centrally reviewed by Electrophysiology and Imaging Cores. Subjects were assigned International League Against Epilepsy (ILAE) syndrome classification by the site investigator with review of a subset by the EPGP data review core. Subjects were also classified in broad categories as GE, non-acquired focal epilepsy (NAFE), mixed epilepsy syndrome (both NAFE and GE), and unclassifiable based on consensus review of available data. Race (Caucasian/white, African-American/black, Asian, Native-American/Alaska Native, Native Hawaiian/Other Pacific Islander, more than one race, other, and unknown) and ethnicity (Hispanic and non-Hispanic) was based on patient self report. In addition, we examined reported frequency of generalized tonic clonic seizures (GTCS) categorized in response ranges of 0, 1, 2—3, >3 to <20, >20 to 100, >100 and unknown.

Statistical analysis

Fisher's exact tests and chi-square tests were used to assess differences in the distribution of epilepsy classification and seizure frequency among groups.

Each site's institutional review board approved the study and each participant provided written consent.

Results

The distribution of ILAE epilepsy syndromes among the 813 probands is shown in Table 1. Because the low frequency of many specific syndromes among the probands precluded analysis of racial and ethnic differences within them, further analysis was restricted to the broad classification categories of GE, NAFE, mixed syndrome and unknown. The racial and ethnic categories of the subjects along with their epilepsy syndrome classification are shown in Table 2. Of the 813 probands, 628 (77.2%) identified exclusively as Caucasian/white and 37 (4.6%) as African-American/black. Of the 112 (13.8%) of subjects who identified as being of more than one racial background, 28 reported African-American/Black among their ancestries. Therefore, a total of 65 (8.0%) subjects reported African ancestry in this cohort. Of the Caucasian/white subjects, 357 (56.8%) had GE, 207 (33.0%) had NAFE, 32 (5.1%) had a mixed syndrome, and 32 (5.1%) were unclassifiable. Of the 65 subjects with African ancestry, 28 (43.1%) had GE, 27 (41.5%) had NAFE, 2 (3.1%) had a mixed syndrome, and 8 (12.3%) were unclassifiable (Fig. 1). The proportion of subjects with GE compared to other syndromes was significantly higher among those who self-reported Caucasian/white vs. African ancestry (OR 1.74, 95% CI: 1.04—2.92, two-tailed Fisher's exact test, $p = 0.036$).

Seventy-nine subjects (9.7% of total) identified themselves as having Hispanic/Latino ethnicity, which was recorded separately from race in the demographic forms. Among these subjects, 35 (44.3%) had GE, 28 (35.4%) had NAFE, 5 (6.3%) had a mixed syndrome, and 11 (13.9%) were unclassifiable. Of the non-Hispanics, 416 (56.7%) had GE, 244 (33.2%) had NAFE, 32 (4.4%) had a mixed syndrome, and 42 (5.7%) were unclassifiable. Generalized epilepsy was less common in subjects who self-identified as Hispanic (OR 0.61, 95% CI: 0.38—0.97, two-tailed Fisher's exact test, $p = 0.042$). However, when adjusted for race (white vs non-white), the

Table 1 Distribution of ILAE syndromes among probands.

ILAE syndrome classification	*N* (% of total probands)	
Focal epilepsy syndromes		
Localization related epilepsies NOS	15	(1.8)
Idiopathic localization-related epilepsies NOS	48	(5.9)
Benign childhood epilepsy with CT spikes (BECTS)	18	(2.2)
Childhood epilepsy with occipital paroxysms	1	(0.1)
Cryptogenic localization-related epilepsies	97	(11.9)
Temporal lobe NOS	49	(6.0)
Amygdalo-hippocampal	4	(0.5)
Lateral temporal	4	(0.5)
Parietal lobe	3	(0.4)
Occipital lobe	8	(1.0)
Frontal Lobe	10	(1.2)
Symptomatic localization-related epilepsies	4	(0.5)
Temporal lobe	7	(0.9)
Amygdalo-hippocampal	7	(0.9)
Lateral temporal	1	(0.1)
Frontal lobe	2	(0.2)
Generalized epilepsy syndromes		
Generalized epilepsies NOS	5	(0.6)
Idiopathic generalized epilepsies (IGE) NOS	151	(18.6)
Benign myoclonic epilepsy in infancy	2	(0.2)
Childhood absence epilepsy (CAE; onset at age $\leq$8)	128	(15.7)
CAE/JAE indistinguishable (onset age 9—11)	30	(3.7)
Juvenile absence epilepsy (JAE, onset age $\geq$12)	14	(1.7)
Juvenile myoclonic epilepsy (JME, onset age $\geq$10)	72	(8.9)
Epilepsy with GTCS on awakening	1	(0.1)
Epilepsies with seizures with specific modes of activation	5	(0.6)
Other generalized epilepsies not defined above	19	(2.3)
Late-onset IGE, NOS	3	(0.4)
CAE/JME indistinguishable	2	(0.2)
JAE/JME indistinguishable	6	(0.7)
Generalized cryptogenic or symptomatic epilepsies NOS	3	(0.4)
Epilepsy with myoclonic-astatic seizures	10	(1.2)
Epilepsy with myoclonic absences	3	(0.4)
Other cryptogenic or symptomatic epilepsy	1	(0.1)
Symptomatic generalized epilepsies NOS	1	(0.1)
Other symptomatic gen. epilepsies not defined above	1	(0.1)
Mixed focal and generalized epilepsy syndromes		
Epilepsies undetermined as to focal or generalized NOS	25	(3.1)
With both generalized and focal features NOS	38	(4.7)
Unknown		
Other undetermined epilepsies not defined above	3	(0.4)
Without unequivocal generalized or focal features	7	(0.9)
Isolated seizures or status epilepticus	1	(0.1)
Don't know	4	(0.5)

ILAE, International League Against Epilepsy; *N*, number; NOS, not otherwise specified; CT, centrotemporal.

rate of GE in Hispanic subjects was not significantly different from non-Hispanics (OR 0.65, 95% CI: 0.40—1.06, $p > 0.05$).

It is possible that that racial disparities to access to specialty care may preclude all but the most difficult to treat non-white patients from receiving care at comprehensive epilepsy centers. Some common GE syndromes, such as juvenile myoclonic epilepsy, are typically treatment-sensitive (Mohanraj and Brodie, 2007). It is possible that more Caucasian/white than non-white individuals with well-controlled epilepsy, which may include a higher proportion of GE, attend the epilepsy centers that were the primary source of EPGP participants. Therefore, we examined epilepsy severity by comparing subjects with a lifetime frequency of 3 or fewer GTCS to subjects with more frequent GTCS. The proportion of participants with $\leq$3 lifetime GTCs was lower among Caucasians/whites (54.2% [339/625]) than

Table 2 Epilepsy classification by self-reported race.

Epilepsy classification					
Race	GE	NAFE	NAFE & GE	Unclassifiable	Total for race
Caucasian/white	357 (56.8%)	207 (33.0%)	32 (5.1%)	32 (5.1%)	628 (77.2%)
African American/black	16 (43.2%)	16 (43.2%)	1 (2.7%)	4 (10.8%)	37 (4.6%)
African American/black ± other race	28 (43.1%)	27 (41.5%)	2 (3.1%)	8 (12.3%)	65 (8.0%)
Asian	7 (77.8%)	2 (22.2%)	0	0	9 (1.1%)
American Indian/Alaska Native	0	1 (50.0%)	0	1 (50.0%)	2 (0.2%)
More than one race (all)	56 (50.0%)	42 (37.5%)	4 (3.6%)	10 (8.9%)	112 (13.8%)
Other	7 (63.6%)	1 (9.1%)	0	3 (27.3%)	11 (1.3%)
Unknown	8 (53.3%)	4 (26.7%)	0	3 (20.0%)	15 (1.4%)
Total for classification	451 (55.5%)	272 (33.5%)	37 (4.6%)	53 (6.5%)	813

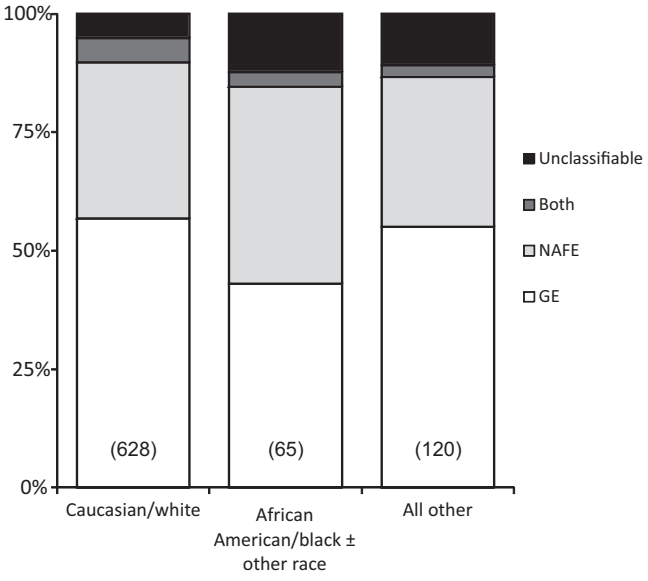

Figure 1 Plot demonstrating proportion of probands with each epilepsy classification for subjects who identified as exclusively White/Caucasian, subject who identified as Black/African-American exclusively or as one of their races, and all other groups. A lower proportion of idiopathic generalized epilepsy were seen among subjects with African ancestry. Among the same group, there were higher rates of unclassifiable epilepsies compared to other races. Number of subjects within each group are shown in parentheses.

among participants with African ancestry (61.5% [40/65]), ($p = 0.26$), suggesting epilepsy severity was not likely to be a confounder.

Another possible confounding factor is the higher number of unclassified cases among probands with African ancestry (12.1%) compared to Caucasians/whites (5.1%, OR 2.60, 95% CI: 1.08—5.78, $p = 0.034$). Racial and socioeconomic differences in access to care result in differences in the utilization of advanced diagnostic tests such as video-EEG monitoring or high-resolution MRI (Begley et al., 2009). These tests may improve diagnostic accuracy in patients with epilepsy. We reviewed the reasons that central reviewers cited for their inability to classify probands in Caucasians/whites (32 subjects) and those with African ancestry (8 subjects). In 1 Caucasian/white subject (3.1%) and 1 subject with African ancestry (12.5%), seizures occurred exclusively from sleep and an accurate semiology could not be determined. No diagnostic EEG was available for 10 Caucasian/white subjects (32.1%) and 5 subjects with African ancestry (62.5%). Four Caucasian/white subjects (12.5%) had inadequate history. There was conflicting data that could not be reconciled for 15 Caucasian/white subjects (46.9%) and 3 subjects with African ancestry (37.5%).

Discussion

In this cohort of patients, enriched for genetic contributions to their epilepsy by virtue of having a family history of first-degree relatives with non-acquired epilepsy, GE was more common in whites than in those with self-reported African ancestry, suggesting there may be racial differences in the prevalence of epilepsy syndromes. These results should be interpreted with caution due to the low number of subjects with African ancestry in this cohort and the higher proportion of unclassified epilepsy among these subjects compared to white subjects.

The proportion of subjects with African ancestry among the EPGP probands is lower than the proportion of African-Americans (12.9%, including individuals reported mixed race) reported in the 2010 U.S. Census (US Census Bureau, 2010). While this cohort included individuals recruited at sites outside the US who were predominantly Caucasian (85%), they accounted for only 4.6% of the total participants and even with their exclusion, there remains an under-representation of African-American individuals and an overrepresentation of Caucasian/white individuals compared to the general population. This increases the risk our findings are due to chance alone. The reasons for lower numbers of African-Americans than expected are not well understood, and probably included reduced access to tertiary epilepsy care (Begley et al., 2009), lower rates of participation in research (Shavers et al., 2002), in addition to possible racial differences in genetic epilepsy prevalence. The low proportion of subjects of African ancestry in the sample may serve as a potential threat to the generalizability of these findings. In addition, while we found GTC frequency was similar between groups, we did not examine whether rates of less severe but potentially disabling

seizures (e.g. CPS) were higher in African-American/black subjects compared to white subjects. If African-Americans with more disabling epilepsy are more likely receive subspecialty care that those with non-disabling seizures, there may be selection bias for NAFE, which is typically less treatment responsive than GE (Mohanraj and Brodie, 2006), among African-Americans in this cohort.

In addition, more subjects with African ancestry than whites fell into the unclassifiable epilepsy category, which typically occurred when there was insufficient certainty from available records and subject interview to determine epilepsy phenotype. The reasons for this are not clear but may include differences in access to diagnostic testing such as prolonged EEG monitoring which may be necessary for diagnostic certainty. Difficulty with classification due to insufficient EEG data may preferentially occur in subjects with GE. For instance, in subjects with GE with only GTCS, a confident syndrome classification can only be made if generalized spike-wave discharges are observed during EEG recording. Longer or more frequent EEG recording may be necessary to make the diagnosis in subjects with rare discharges. In addition, in some subjects with GE and rare interictal discharges, a brief routine EEG may only capture ''fragments'' of interictal discharges which can appear focal in one study and generalized in the next, leading to conflicting data (Pillai and Sperling, 2006). Both insufficient EEG data and conflicting data were frequent reasons why probands were unclassified, which occurred less often in whites. It is possible that if many of the unclassified subjects of African ancestry had GE, rates of GE in this group would approach those of whites.

Despite the potential confounders and acknowledged limitations of the study, these preliminary findings support the idea that the genetic variants influencing generalized epilepsy phenotypes including seizure types and EEG features may be less common among people of African origin, consistent with earlier reports of lower rates of PPR in this group (Adamolekun et al., 1998; de Graaf et al., 1995). If this possible explanation for our findings is true, we would expect that the rate of GE would be even lower in a sample of sub-Saharan Africans, since ~22% of genes in African Americans are derived from European ancestry (Zakharia et al., 2009). Further population-based studies are needed to understand the effect of genetic background and geographic origin on epilepsy phenotype.

Disclosures

Dr. Friedman receives salary support from The Epilepsy Study Consortium, a non-profit organization dedicated to improving the lives of epilepsy patients, and devotes 15% of his time to work done for the Consortium. The Consortium receives payments from a large number of pharmaceutical companies for consulting activities. All payments are made to The Consortium and not to Dr. Friedman directly. Several companies also support the Consortium's biennial Antiepileptic Drug Trials Symposium. Since there a so many companies contributing, the amount from each company toward Dr. Friedman's salary is minimal and is reviewed annually by NYU's conflict of interest committee. Ms. Falstrom has nothing to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2013.09.007.

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