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ORIGINAL ARTICLE

African ancestry protects against Alzheimer's disease-related neuropathology

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Previous studies in dementia epidemiology have reported higher Alzheimer's disease rates in African-Americans when compared with White Americans. To determine whether genetically determined African ancestry is associated with neuropathological changes commonly associated with dementia, we analyzed a population-based brain bank in the highly admixed city of São Paulo, Brazil. African ancestry was estimated through the use of previously described ancestry-informative markers. Risk of presence of neuritic plaques, neurofibrillary tangles, small vessel disease, brain infarcts and Lewy bodies in subjects with significant African ancestry versus those without was determined. Results were adjusted for multiple environmental risk factors, demographic variables and apolipoprotein E genotype. African ancestry was inversely correlated with neuritic plaques ($P = 0.03$). Subjects with significant African ancestry ($n = 112$, 55.4%) showed lower prevalence of neuritic plaques in the univariate analysis (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.55–0.95, $P = 0.01$) and when adjusted for age, sex, APOE genotype and environmental risk factors (OR 0.43, 95% CI 0.21–0.89, $P = 0.02$). There were no significant differences for the presence of other neuropathological alterations. We show for the first time, using genetically determined ancestry, that African ancestry may be highly protective of Alzheimer's disease neuropathology, functioning through either genetic variants or unknown environmental factors. Epidemiological studies correlating African-American race/ethnicity with increased Alzheimer's disease rates should not be interpreted as surrogates of genetic ancestry or considered to represent African-derived populations from the developing nations such as Brazil.
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Introduction

Self-declared race and skin color are often used as surrogates for genetic ancestry, despite being poor biological classifiers, especially in countries with admixed populations where significant overlaps between groups exist.[1] Furthermore, racial categorization is modifiable by environmental factors such as sunlight exposure, socioeconomic level, physical appearance and cultural aspects.[2–4] The marked epidemiological differences in health status between racial groups in countries such as Brazil and the United States are likely a combination of genetic and environmental factors, particularly socioeconomic levels.[5,6]

Dementia is a complex phenotype caused by frequently overlapping neuropathological processes such as neuritic plaques and neurofibrillary tangles (Alzheimer's disease), small vessel disease and/or brain infarcts (vascular dementia) and synuclein deposits (Lewy body disease and Parkinson's disease), as well as other rarer alterations.[7] The clinical diagnosis of dementia is further influenced by the educational level, language and cultural

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aspects. Several studies have shown that African Americans are more frequently diagnosed with dementia (in general) and Alzheimer's disease than Caucasians.[8–12] These differences may be caused by genetic variants or the environment.[13–16] Few studies have focused on neuropathological post-mortem diagnosis and none on ancestry-informative marker (AIM) determined genetic ancestry.[17–19]

The quantitative assessment of ancestry using AIMs has been previously demonstrated to be useful in breast cancer epidemiology and lung-function prediction.[20,21] The population of Brazil is highly admixed, with major historic contributions from European immigrants, African slaves and native Amerindians.[22–24] The genetic structure of the population of Brazil is approximately 80% European, 15% African and 5% Amerindian, with significant variation between regions.[25,26]

Materials and methods

Study population

Brain samples from the Brazilian Aging Brain Study Group of the University of São Paulo Medical School, collected from 2004–2009, were studied.[27] Exclusion criteria included age at death of less than 50 years, causes of death or tissue condition that impeded neuropathological analysis, informants without knowledge of the functional status of subjects (minimum 1 visit/week) and violent/criminal deaths. Tissue donations were obtained in the municipal São Paulo Autopsy Service, in Brazil. The population base includes all inhabitants of the city of São Paulo, ~11 million people (5.6% of the population of Brazil), and study samples do not significantly deviate from census data for age, sex, race, years of schooling or socioeconomic levels[28] (data not shown). All tissue donations were made by next-of-kin after providing informed consent, and the study was approved by the institutional review boards of all participating institutions. Knowledgeable informants were interviewed by nurses trained specifically for the questionnaires, including cognitive evaluation (Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and Clinical Dementia Rating (CDR)) and demographics.[29,30]

Neuropathological assessment

All neuropathological diagnoses were carried out by two trained specialists (LTG and MPA). Brains were inspected macroscopically, and lesions of Alzheimer's disease (neuritic plaques and neurofibrillary tangles), Lewy bodies and small vessel disease (microinfarcts, lacunes and small vessel disease) were scored according to the accepted criteria.[31–33] Immunohistochemistry was done with antibodies against β-amyloid (4G8, 1/5000, Signet Laboratories, Dedhan, MA, USA), phospho-tau (PHF-1, 1/1000, gift from Peter Davies, New York City, NY, USA) and α-synuclein (EQV-1, 1/10 000, gift from Kenji Ueda, Tokyo, Japan). If TDP-43pathy was suspected, immunostaining for TDP-43 (1/500, ProteinTech Group, Chicago, IL, USA) was performed. All sections were submitted to antigenic retrieval. The reactions were detected using the Vectastain Elite ABC Kit method (Vector Laboratories, Burlingame, CA, USA). Neuritic plaques were classified as absent, mild, moderate or frequent. Neurofibrillary tangles were classified according to the Braak score of 0–VI (ref. 32).

Ancestry estimation and genotyping

Samples were genotyped for 90 single-nucleotide polymorphisms previously described from an AIM panel reported to efficiently separate Western European, African, Amerindian and East Asian populations.[34] The AIMs were genotyped using Sequenom MassArray from the Genotyping Facility of the Broad Institute of MIT and Harvard. Samples with more than 90% call rate were included in the analysis. Single-nucleotide polymorphisms with >5% no-call rate were excluded from the analysis. APOE genotype (single-nucleotide polymorphisms rs429358 and rs7412) was determined by RealTime PCR, in duplicates, as previously described.[35]

We estimated ancestry by modeling four ancestral populations ($k=4$) with admixture in Structure version 2.3.3 (100 000 burn-ins, 200 000 iterations, LOCPRIOR = 0), alongside samples from the Human Genome Diversity Panel and the HapMap (Phase I) project, both publicly available.[36–38]

Statistical analysis

Neuropathological variables (neuritic plaques, small vessel disease, infarcts, Lewy bodies) were dichotomized between presence and absence, and neurofibrillary tangles were divided between Braak score 0–III and IV–VI. Ancestry was analyzed as a quantitative variable and also dichotomized at 'significant' African ancestry (>2%) to separate the two major ancestry groups present—those with European-only ancestry from admixed individuals (mainly European and African). This cutoff was defined based on the level of African ancestry present in 90% of Caucasian samples from the Human Genome Diversity and HapMap Projects. Subjects of Asian origin ($n=6$) were excluded from analysis. No subjects were identified as Amerindian by next-of-kin.

Kruskal–Wallis test was used in the initial analysis and confirmed using Spearman's rank correlation (two-sided). Logistic regression was used to model the effect of African ancestry on the presence of neuropathology. Each pathology was considered a separate outcome. Analysis was carried out with adjustment for age at death, sex, years of schooling, socioeconomic level, APOE genotype and family reported cardiovascular risk factors (hypertension, diabetes, hypercholesterolemia, heart failure, arrhythmia, smoking, alcohol consumption and sedentary lifestyle). A subgroup analysis using ancestry restricted to self-declared whites (75% of the samples) was also done (Supplementary Figure 2). Significant findings were considered when $P<0.05$.

Results

Ancestry and race

The study consisted of 202 brain samples with complete genotyping, neuropathology and close relatives' interviews. There were 112 individuals (55.4%) with significant African ancestry (Table 1, Supplementary Figure 2). Non-white race and genetically determined African ancestry were highly correlated ($P<0.01$). Some self-declared whites were over 70% African, while a few non-whites had more than 99% European ancestry (Figure 1). Table 1 shows demographic characteristics for subjects with significant (>2%) African ancestry and those without. African ancestry was associated with lower educational ($P<0.05$) and socioeconomic levels ($P<0.01$). There were no differences in cognitive status between groups, as measured by IQCODE or CDR scale.

Ancestry and neuropathology

African ancestry was inversely correlated with neuritic plaques ($P=0.03$, two-sided Spearman's correlation), but not with other neuropathological changes ($P>0.20$ for neurofibrilary tangles, infarcts, small vessel disease and Lewy bodies). The odds ratio (OR) of each neuropathological change for African versus non-African ancestry is shown in Figure 2 and Table 2. The same analysis was done in self-declared Whites (75% of the sample), with similar results (Supplementary Figure 2).

The prevalence of Alzheimer's disease neuritic plaques was significantly lower in subjects with African ancestry (0.72, 95% confidence interval (CI) 0.55–0.95, $P=0.01$) (Figure 2). African ancestry also correlated with less pathology in the subgroup analysis restricted to self-declared whites (0.63, 95% CI 0.42–0.95, $P=0.02$) (Supplementary Figure 1). The prevalence of Alzheimer's related neurofibrilary tangles was higher in subjects with African compared with non-African ancestry, but this was not statistically significant. The prevalence of small vessel disease, brain infarcts and Lewy bodies was higher in subjects with African compared with non-African ancestry, but none were statistically significant. Self-declared race showed no statistically significant differences for any of the neuropathological end points (Supplementary Figure 1).

Adjustment for possible confounding factors did not alter the findings (Figure 3). Neuritic plaques were less prevalent in subjects with African ancestry when adjusted for age and sex (OR 0.47, 95% CI 0.25–0.89, $P=0.02$), when adjusting for age, sex and APOE4 status (OR 0.35, 95% CI 0.17–0.70, $P<0.01$), and when adjusting for all factors including socioeconomic level, educational level and cardiovascular risk factors (OR 0.43, 95% CI 0.21–0.89, $P=0.02$; Table 3, Figure 3).

Discussion

The Brazilian population is highly admixed, with >90% of its ancestry derived from African slaves and European immigrants, which makes it ideal for ancestry-related studies. Moreover, Brazilian law

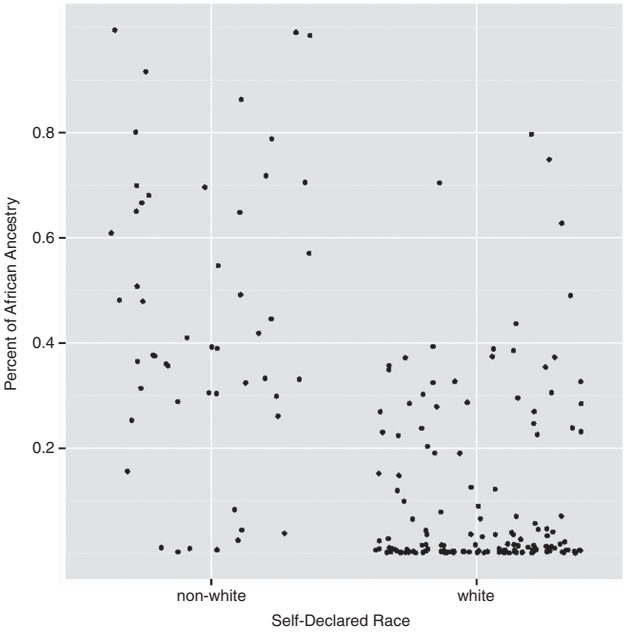

Figure 1 Individual African ancestry estimates according to self-declared race in Brazil.

Table 1 Study characteristics

	African ancestry	*Non-African ancestry*	P-*value*
Number	112	90	
Age at death (mean ± s.d.)	74.5 ± 11.9	76.9 ± 11.4	0.18
Gender (% female)	57.3%	60.0%	0.68
Socioeconomic level (mean ABIPEME score ± s.d.)	15.5 ± 9.4	20.3 ± 9.0	<0.001
Educational status (mean years of schooling ± s.d.)	3.7 ± 3.7	4.8 ± 3.8	0.03
Race (% self-declared White)	58.0%	95.5%	<0.001
Cognitive status (% CDR = 0)	67.2%	66.2%	0.85
Cognitive status (mean IQCODE ± s.d.)	3.44 ± 0.72	3.40 ± 0.68	0.81
APOE4 status (% positive)	26.8%	20.0%	0.26

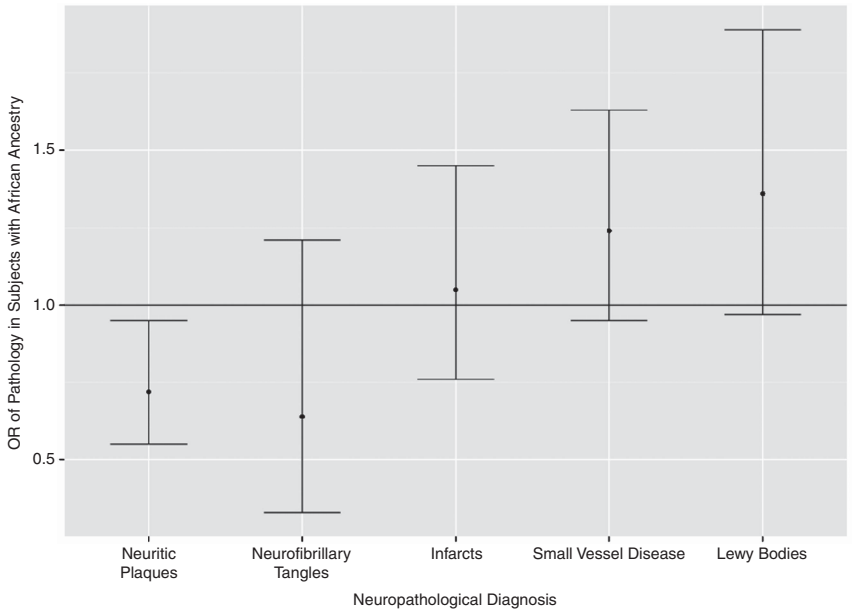

Figure 2 Odds ratio of neuropathological alterations.

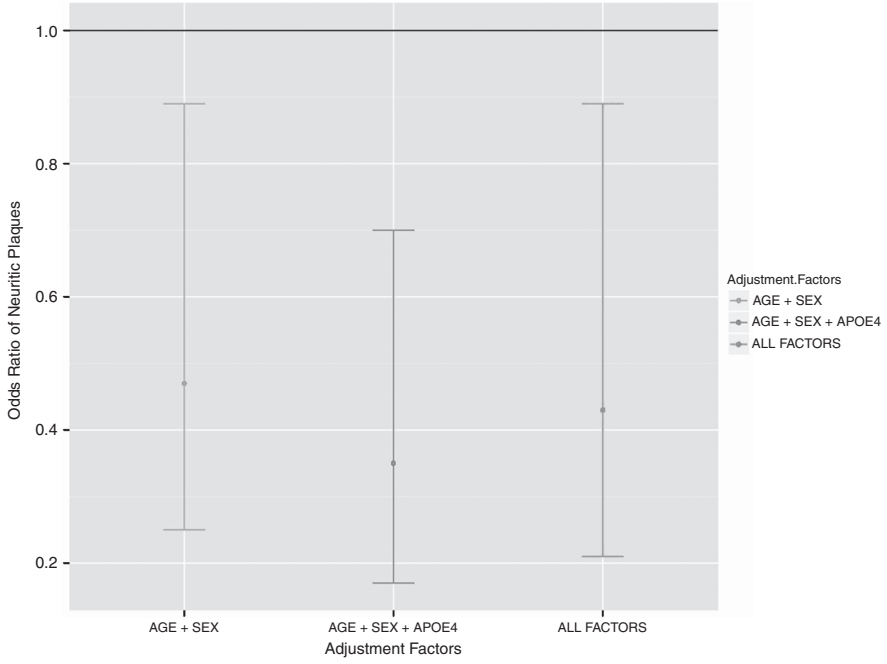

Figure 3 Odds ratio of presence of neuritic plaques, comparing African with non-African ancestry, adjusted for age and sex; age, sex and APOE4 status; and all factors.

mandates that autopsies be performed in all persons without a death certificate, which provides a large recruitment base for populational studies in neuropathology, without bias toward demented persons. The University of São Paulo alone performs more than 14 000 autopsies per year, encompassing the full range of demographic variation of the city. The centering of all samples in a single institution also greatly reduced inter-rater variation in both interviews and pathology.

Contrary to previous studies, our results show that African ancestry is highly protective of Alzheimer's disease neuropathology (neuritic plaques), with an adjusted OR of 0.43. This suggests that unknown genetic variants or environmental factors associated with African ancestry reduce the accumulation of

Table 2 Odds ratio (OR) of pathology, African versus non-African

	OR	*Lower*	*Upper*	P-*value*
Neuritic plaques	0.72	0.55	0.95	0.01
Neurofibrillary tangles	0.64	0.33	1.21	0.16
Arteriolosclerosis	1.24	0.95	1.63	0.18
Infarcts	1.05	0.76	1.45	0.78
Lewy bodies	1.36	0.97	1.89	0.14

Table 3 Odds ratio (OR) of subjects with African ancestry after adjustment for major factors

	Neuritic plaques			
	OR	*Lower*	*Upper*	P-*value*
Adjusted for age + sex	0.47	0.25	0.89	0.02
Adjusted for age + sex + APOE4	0.35	0.17	0.70	0.003
Adjusted for Age + sex + APOE4 + socioeconomic, education levels and cardiovascular risk factors	0.43	0.21	0.89	0.02

β-amyloid or increase its clearance. The results are robust and are not altered when studying only those who self-defined themselves as whites, when adjusting for APOE4 status only or when adjusting for age and sex only.

Previous studies with the United States population reported a significantly higher prevalence of dementia in African Americans when compared with Caucasians.[8–12] These differences could be due to cultural differences in the performance on cognitive screening tests, such as the Mini Mental Status Examination, genetic differences between races, environmental differences or likely a combination of factors.[13–16] In a study comparing dementia in Nigerians and African Americans, the former had significantly lower disease rates. Our data suggest that these results might be explained not only by environmental differences, but also by the European admixture present in African Americans.[39] Further studies are needed to confirm this.

Cardiovascular disease risk and stroke also vary between races, but statistical significance often disappears when adjustments for socioeconomic levels are applied.[14,40,41] Lower educational and socioeconomic levels in those with higher African ancestry may create important differences in disease susceptibility, which is independent of genetics, but confounds the analysis.

To our knowledge, few studies have compared autopsy-diagnosed cases in different races and none used AIMs.[17–19] The growing clinical use of AIMs was recently shown by Kumar *et al*[21] as a tool for improved lung-function prediction in African Americans, although this should only be considered an intermediary step toward the use of specific disease-related variants in personalized medicine.[42,43] Furthermore, dementia is a complex clinical phenotype that may be caused by widely diverse pathologies, and post-mortem diagnosis remains the gold-standard. The specific neuropathology of Alzheimer's disease, Lewy body dementia and vascular dementia may have different underlying biological and genetic causes, and should therefore be studied separately.

A few notes of caution regarding this study should be pointed out. First, although we adjusted for multiple environmental and social factors as well as APOE genotype, other untested environmental factors may be confounding our ancestry results. Second, African populations are highly variable (more so than Europeans), and therefore we cannot state from our data that this effect is applicable to all African populations.[13] It is unknown if there are population subgroups within Africa with different risk profiles for neuropathological alterations. Actually, our results reinforce the need for more Alzheimer's disease studies in the developing world, for trends identified in the United States may not be universal. Third, we have adjusted our analysis using known cardiovascular risk factors, to focus on unknown genetic factors, but many authors have suggested that ethnic/racial differences in dementia prevalence may in fact be derived from differences in these factors (for example, hypertension, diabetes). A future expansion of this data set is required to answer these questions with confidence, especially regarding vascular dementia.

In conclusion, our study shows, for the first time, that Alzheimer's neuropathological findings depend on the ancestral genetic background. It clearly demonstrates that the presence of neuritic plaques are reduced in persons with African ancestry in a population-based sample, independently of known confounding factors. This should serve as a basis for future genetic studies of Alzheimer's disease, as well as alert against overinterpreting epidemiological studies using race and clinically diagnosed dementia.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)