Dementia is more prevalent in Blacks than in Whites, likely due to a combination of environmental and biological factors. Paradoxically, clinical studies suggest an attenuation of APOE e4 risk of dementia in African ancestry (AFR), but a dearth of neuropathological data preclude the interpretation of the biological factors underlying these findings, including the association between APOE e4 risk and Alzheimer's disease (AD) pathology, the most frequent cause of dementia. We investigated the interaction between African ancestry, AD-related neuropathology, APOE genotype, and functional cognition in a postmortem sample of 400 individuals with a range of AD pathology severity and lack of comorbid neuropathology from a cohort of community-dwelling, admixed Brazilians. Increasing proportions of African ancestry (AFR) correlated with a lower burden of neuritic plaques (NP). However, for individuals with a severe burden of NP and neurofibrillary tangles (NFT), AFR proportion was associated with worse Clinical Dementia Rating sum of boxes (CDR-SOB). Among APOE e4 carriers, the association between AFR proportion and CDR-SOB disappeared. APOE local ancestry inference
of a subset of 309 individuals revealed that, in APOE e4 noncarriers, non-European APOE background correlated with lower NP burden and, also, worse cognitive outcomes than European APOE when adjusting by NP burden. Finally, APOE ε4 was associated with worse AD neuropathological burden only in a European APOE background. APOE genotype and its association with AD neuropathology and clinical pattern are highly influenced by ancestry, with AFR associated with lower NP burden and attenuated APOE ε4 risk compared to European ancestry.

Start date: 01-01-2019

End date: 01-01-2024

Last modified: 07-20-2022

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Global and local ancestry modulate APOE association with Alzheimer's neuropathology and cognitive outcomes in an admixed sample

Data type: human genomic data and non-human genomic data

The GDS Policy applies to all NIH-funded research that generates large-scale human or non-human genomic data as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, metagenomic, epigenomic, and gene expression data, irrespective of funding level and funding mechanisms (e.g. grant, contract, cooperative agreement, or intramural support). NIH Institute or Centers (IC) may expect submission of data from smaller scale research projects based on the state of the science, the programmatic priorities of the IC funding the research, and the utility of the data for the research community.

Part of the genomic data (genotyping with microarray) was generated with funds from NIH R01AG17917. The subset of data used in the current project and corresponding publications is being shared in anonymized, de-identified formats. To recover the linkage between this dataset and the original NIH R01AG17917 full dataset or other phenotypic data produced by USP on these individuals, a request must be submitted and approval will be registered in a Data Access Agreement.

Genomic research advances our understanding of factors that influence health and disease, and sharing genomic data provides opportunities to accelerate that research through the power of combining large and information-rich datasets. https://osp.od.nih.gov/scientific-sharing/policies/

Datasets can be directly accessed by researchers and institutions. Individual level phenotypic data with corresponding sample identifiers can be requested to corresponding researchers, approved and data will be shared after Data Access Agreement is signed by both parties.

Data repositories

Identify the data repositories to which the data will be submitted, and for human data, whether the data will be available through unrestricted or controlled-access.

Investigators should register all studies with human genomic data that fall within the scope of the GDS Policy in dbGaP by the time that data cleaning and quality control measures begin. After registration in dbGaP, investigators should submit the data to the relevant NIH-designated data repository (e.g., dbGaP, GEO, SRA, the Cancer Genomics Hub).
NIH-designated data repositories need not be the exclusive source for facilitating the sharing of genomic data, that is, investigators may also elect to submit data to a non-NIH-designated data repository in addition to an NIH-designated data repository. However, investigators should ensure that appropriate data security measures are in place, and that confidentiality, privacy, and data use measures are consistent with the GDS Policy.

Non-human data may be made available through any widely used data repository, whether NIH-funded or not, such as GEO, SRA, Trace Archive, Array Express, Mouse Genome Informatics, WormBase, the Zebrafish Model Organism Database, GenBank, European Nucleotide Archive, or DNA Data Bank of Japan.

Dataset of genomic data associated with this project is being submitted to the University of São Paulo Data Repository (https://metabuscador.uspdigital.usp.br/)

**Data submission expectations and timeline**

Investigators should submit large-scale genomic data as well as relevant associated data (e.g. phenotype and exposure data) to an NIH-designated data repository in a timely manner. Investigators should also submit any information necessary to interpret the submitted genomic data, such as study protocols, data instruments and survey tools. Genomic data undergo different levels of data processing, which provides the basis for NIH's expectations for data submission and timelines for the release of the data for access by investigators. These expectations and timelines are provided in the Supplemental Information. In general, NIH will release data submitted to NIH-designated data repositories no later than six months after the initial data submissions begins, or at the time of acceptance of the first publication, whichever occurs first, without restrictions on publication or other dissemination.

Dataset is expected to be deposited before August 2022 and available for download after publishing article (expectation August 2022).

**Informed consent and institutional certification**

Respect for, and protection of the interests of, research participants are fundamental to NIH's stewardship of human genomic data. The informed consent under which the data or samples were collected is the basis for the submitting institution to determine the appropriateness of data submission to NIH-designated data repositories, and whether the data should be available through unrestricted or controlled access.
For research that falls within the scope of the GDS Policy, submitting institutions, through their Institutional Review Boards (IRB's), privacy boards, or equivalent bodies, are to review the informed consent materials to determine whether it is appropriate for data to be shared for secondary research use. Specific considerations may vary with the type of study and whether the data are obtained through prospective or retrospective data collections. NIH provides additional information on issues related to the respect for research participant interests its "Points to Consider for IRB"s and Institutions in their Review of Data Submission Plans for Institutional Certifications" (updated in 2016 to "Points to Consider for Institutions and Institutional Review Boards in Submission and Secondary Use of Human Genomic Data under the National Institutes of Health Genomic Data Sharing Policy").

Data from all subjects is anonymized and de-identified as requirements of Brazilian local and national ethical committees (CEP/CONEP). This project was approved by the FMUSP IRB under code 22262613.0.0000.0065 upon written consent of the knowledgeable informants.

Exceptions to data submission expectations

In cases where data submission to an NIH-designated data repository is not appropriate, that is, the Institutional Certification criteria cannot be met, investigators should provide a justification for any data submission exceptions requested in the funding application or proposal. The funding IC may grant an exception to submitting relevant data to NIH, and the investigator would be expected to develop an alternate plan to share data through other mechanisms.

Part of the genomic data (genotyping with microarray) was generated with funds from NIH R01AG17917. The subset of data used in the current project and corresponding publications is being shared in anonymized, de-identified formats. To recover the linkage between this dataset and the original NIH R01AG17917 full dataset or other phenotypic data produced by USP on these individuals, a request must be submitted and approval will be registered in a Data Access Agreement.

Intellectual Property

NIH encourages patenting of technology suitable for subsequent private investment that may lead to the development of products that address public needs without impeding research. However, it is important to note that naturally occurring DNA sequences are not patentable in the U.S. Therefore, basic sequence data and certain related information (e.g.
genotypes, haplotypes, p-values, allele frequencies) are pre-competitive. Such data made available through NIH-designated data repositories, and all conclusions derived directly from them, should remain freely available, without any licensing requirements.

NIH encourages broad use of NIH-funded genomic data that is consistent with a responsible approach to management of intellectual property derived from downstream discoveries, as outlined in the NIH *Best Practices for the Licensing of Genomic Inventions* and Section 8.2.3. Sharing Research Resources, of the NIH Grants Policy Statement. NIH discourages the use of patents to prevent the use of or to block access to genomic or genotype-phenotype data developed with NIH support.

The dataset is approved for research purposes only. Phenotypic data access is subject of approval under reasonable request.