Received: 11 April 2024 | Revised: 24 July 2024 | Accepted: 26 July 2024

DOI: 10.1002/dad2.70000

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Disentangling the genetic underpinnings of neuropsychiatric symptoms in Alzheimer's disease in the Alzheimer's Disease Sequencing Project: Study design and methodology

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Funding information
NIH, Grant/Award Numbers: P30AG066462, U01AG079850, R01AG064614, U19AG074865, R01AG072547, U24AG056270, R01AG062268, R01MH120794

Abstract

INTRODUCTION: Neuropsychiatric symptoms (NPS) are highly prevalent in Alzheimer's disease (AD). There are no effective treatments targeting these symptoms.

METHODS: To facilitate identification of causative mechanistic pathways, we initiated an effort (NIH: U01AG079850) to collate, harmonize, and analyze all available NPS data (≈ 100,000 samples) of diverse ancestries with whole-genome sequencing data from the Alzheimer's Disease Sequencing Project (ADSP).

RESULTS: This study will generate a genomic resource for Alzheimer's disease with both harmonized whole-genome sequencing and NPS phenotype data that will be publicly available through NIAGADS. Primary analyses will (1) identify novel genetic risk factors associated with NPS in AD, (2) characterize the shared genetic architecture of NPS in AD and primary psychiatric disorders, and (3) assess the role of ancestry effects in the etiology of NPS in AD.

DISCUSSION: Expansion of the ADSP to harmonize and refine NPS phenotypes coupled with the proposed core analyses will lay the foundation to disentangle the molecular mechanisms underlying these detrimental symptoms in AD in diverse populations.

KEYWORDS
Alzheimer's disease, Alzheimer's Disease Sequencing Project, genetics, neuropsychiatric symptoms

Highlights

- Neuropsychiatric symptoms (NPS) are highly prevalent in Alzheimer's disease (AD).
- There are no effective treatments targeting NPS in AD.
- The current effort aims to collate, harmonize, and analyze all NPS data from the Alzheimer's Disease Sequencing Project.
- Core analyses will identify underlying genetic factors and mechanistic pathways.
- The harmonized genomic and phenotypic data from this initiative will be available through National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site.

1 | BACKGROUND

Alzheimer's disease (AD) is the sixth leading cause of death, and currently affects > 6 million people, in the United States.[1] AD is a progressive neurodegenerative disorder for which available therapeutics only minimally impact disease severity and progression.[2] Neuropsychiatric symptoms (NPS; e.g., aggression, psychosis, anxiety, apathy, depression, eating changes, agitation, sleep disturbances, repetitive behaviors) occur in 85% of AD patients,[3,4] and are associated with accelerated decline, out-of-home placement, increased costs, and greatly increased suffering of patients and families.[5–10] NPS can be a prodrome of AD[11] and related neurodegenerative disorders[12] and thus could be used in clinical settings to detect early cases of these disorders to target for treatment. In line with this notion, NPS have predicted mild cognitive impairment better than hippocampal atrophy in some studies.[13]

Despite their high prevalence and detrimental impact on quality of life of patients and caregivers, there remains a significant lack of treatments targeting these symptoms. Current pharmacological interventions for NPS have not fundamentally changed since their development 50 years ago, are often inefficacious, and can have serious adverse effects (e.g., risk of death associated with antipsychotic use).[14] Pharmacological treatments for NPS in AD have generally been borrowed from their indications for psychiatric illness, despite the evidence that the etiology, presentation, course, and treatment responsiveness of NPS in AD and primary psychiatric disorders are dissimilar. For example, psychosis in AD is much more likely to present with simple delusions related to memory symptoms than the complex delusional systems and auditory hallucinations characteristic of schizophrenia and has very different genetic associations than in schizophrenia.[15] Apathy is a common NPS in AD and does not respond to most pharmacological treatments used for primary depression.[16] While the previous scientific literature on the topic has demonstrated mixed results, recent evidence supports the efficacy of stimulants for the treatment of apathy in AD.[17] Atypical antipsychotic medications have the best evidence for the treatment of psychosis and agitation in AD, albeit with small effect sizes and association with increased mortality,[18] for which these treatments have a black-box US Food and Drug Administration warning. Improved pharmacological treatments for NPS in AD are urgently needed.

A better understanding of the etiologic mechanisms underlying NPS in AD is critical to develop improved treatments based on novel targets and strategies. Identification of disease-associated genetic variants can directly point to the underlying mechanistic pathways and pharmacological targets. However, genetic studies of NPS are limited. Previous efforts have mostly focused on common variants (via genome-wide association studies) and have had small sample sizes, limiting statistical power (especially for rarer variants and smaller effect sizes). Additionally, NPS phenotyping has been limited in these studies, with most either limited to psychosis only, or aggregate positive or negative for any NPS, an approach which likely overlooks important aspects of a complex clinical phenotype.[19–30] In addition, the degree of cognitive impairment can affect the presentation of NPS, especially for psychosis and aggression.[17–28] There is early evidence of differences in the prevalence and presentation of NPS in different racial and ethnic groups,[31–34] but these studies have been limited by relatively low numbers of participants.

To facilitate identification of genetic loci and mechanistic pathways underlying NPS in AD, we have initiated an effort (U01AG079850) to collate and harmonize all available NPS data in the Alzheimer's

Disease Sequencing Project (ADSP; adsp.niagads.org) and its follow-up study (Alzheimer's Disease Sequencing Project–Follow Up Study; ADSP-FUS),[35] and analyze these data to identify genetic loci and mechanistic pathways associated with NPS in AD. The ADSP is the leading national effort on AD genomics and to date includes > 70 cohorts (≈ 100,000 samples) of diverse ancestries with whole-genome sequencing (WGS) data (although many of these are healthy control participants). The ADSP-Phenotype Harmonization Consortium (ADSP-PHC; U24AG074855) collates and harmonizes cognitive, brain imaging, longitudinal clinical data, neuropathological data, cardiovascular risk data, and AD biomarkers. Expansion of the ADSP to NPS phenotypes will create the largest and most diverse genomics and phenotype AD-NPS dataset to date, allowing the examination of a wide range of critical hypotheses to disentangle the molecular mechanisms underlying these detrimental symptoms in AD. We expect that the collection and harmonization of NPS for these genetic data will allow researchers to sufficiently power investigations to examine racial and ethnic differences in genetic loci and mechanistic pathways underlying NPS in AD.

RESEARCH IN CONTEXT

1. **Systematic Review**: Relevant literature and related efforts were screened by reviewing PubMed, National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site, and the Database of Genotypes and Phenotypes for efforts exploring neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD).
2. **Interpretation**: NPS including aggression, psychosis, anxiety, apathy, and depression are highly prevalent in AD. NPS are associated with accelerated decline and decreased quality of life, and there are no effective pharmaceutical interventions targeting these symptoms. The current effort will collate, harmonize, and analyze all available NPS data from the Alzheimer's Disease Sequencing Project (ADSP) across ancestries.
3. **Future Directions**: Collation and harmonization of NPS phenotype data across ADSP cohorts will facilitate identification of genetic loci and mechanistic pathways associated with NPS in AD and examination of critical hypotheses and will inform the development of treatments for AD-associated NPS.

2 | METHODS

2.1 | Description of ADSP and ADSP-FUS

The ADSP was established in 2012 as one of the National Alzheimer's Project Act milestones for the genetics of AD and AD-related dementias (ADRD). It's overarching goals are to: (1) identify new genes involved in AD/ADRD; (2) identify gene alleles contributing to increased risk for, or protection against, the disease; (3) provide insight as to why individuals with known risk factor genes escape from developing AD/ADRD; (4) identify potential avenues for therapeutic approaches and prevention of the disease; and (5) fully reveal the genetic architecture of AD/ADRD in multiple race and ethnicity categories. All contributing samples were selected from well-characterized, diverse study cohorts of individuals both with and without an AD diagnosis as well as with and without known risk-factor genes. A subset of the cohorts has brain autopsy information. Details about the samples are available at the National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS; adsp.niagads.org) and the ADSP-PHC (https://www.vmacdata.org/adsp-phc). The ADSP generated three sets of genome sequence data for these samples as part of the Discovery Phase: (1) WGS from multiplex families, (2) whole-exome sequencing (WES) for AD cases and controls, and (3) WES of an enriched sample set comprising AD cases from multiply affected families and controls. To further assess the genomes in multiply affected families, an additional set of samples was sequenced with funding provided by the National Human Genome Research Institute as part of the Discovery Extension Phase. Samples for this portion of the study were drawn from the same families as in the Discovery Phase; in addition, a small number of Black families were included. The overarching goal of the subsequently established ADSP-FUS is to expand the ADSP to the richest possible ethnic diversity, to (1) enable identification of both shared and novel genetic risk factors for AD between populations, (2) move the field closer to enabling prediction of who will develop AD, (3) fully characterize AD subtypes by studying endophenotypes in diverse populations, (4) better understand the differences in the genetic underpinnings of AD pathogenesis among diverse populations, and (5) identify specific therapeutic targets based upon diverse populations. As such, existing AD cohorts were prioritized for the inclusion of rich ethnic diversity, autopsy-confirmed diagnoses, and the availability of longitudinal data. The ADSP-FUS parent program covers funds for the acquisition, archiving, sequencing, quality control, genome-wide genotyping, and data sharing of these samples. Harmonization of cognitive, AD biomarker, neuropathology, and brain imaging data is performed by the ADSP-PHC. As of March 2024, the ADSP/ADSP-FUS includes > 35,000 non-Hispanic White, 18,000 African ancestry, 9000 Asian, and 34,000 Hispanic samples, with additional samples per cohort and new datasets continuously being added.

2.2 | Integration with ADSP-PHC

The present effort will continuously harmonize the NPS data on all previously collected and newly added ADSP genetic samples that have this type of NPS data, capitalizing on the existing ADSP-PHC infrastructure including data use agreements to acquire NPS data and deliver harmonized phenotypes to NIAGADS for distribution to the research community. Figure 1 shows the integration of this project within the ADSP and ADSP-PHC; Figure 2 shows the various types of harmonized data that will be available on all samples. In brief, the ADSP-PHC

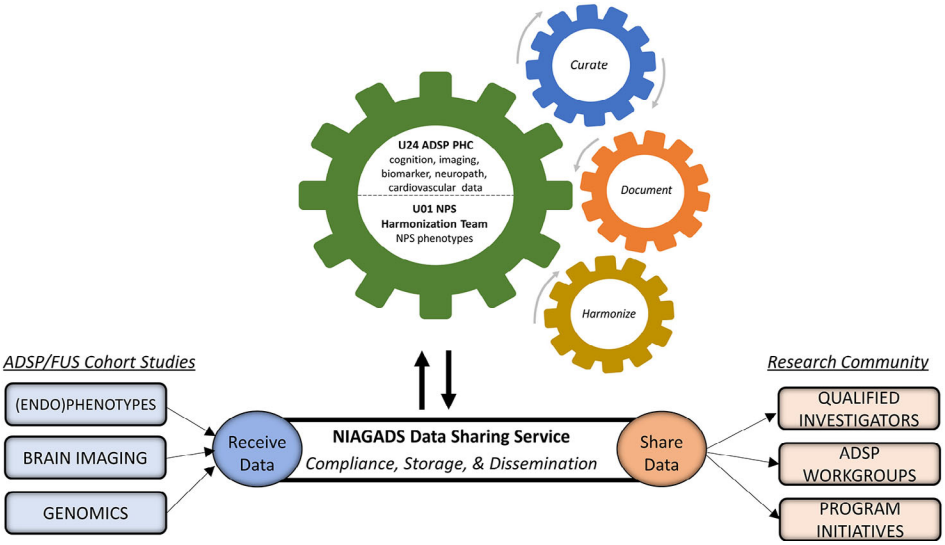

FIGURE 1 Integration of the present effort with the ADSP/ADSP-FUS and the ADSP-PHC. The current effort will capitalize on existing ADSP-PHC infrastructure including data use agreements to acquire NPS data and deliver harmonized phenotypes to NIAGADS for distribution to the research community. Additional (endo)phenotypes collated and harmonized by the ADSP-PHC include cognitive, brain imaging, biomarker, neuropathology, and cardiovascular data. ADSP, Alzheimer's Disease Sequencing Project; ADSP-FUS, Alzheimer's Disease Sequencing Project Follow Up Study; ADSP-PHC, Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium; NIAGADS, National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site; NPS, neuropsychiatric symptoms

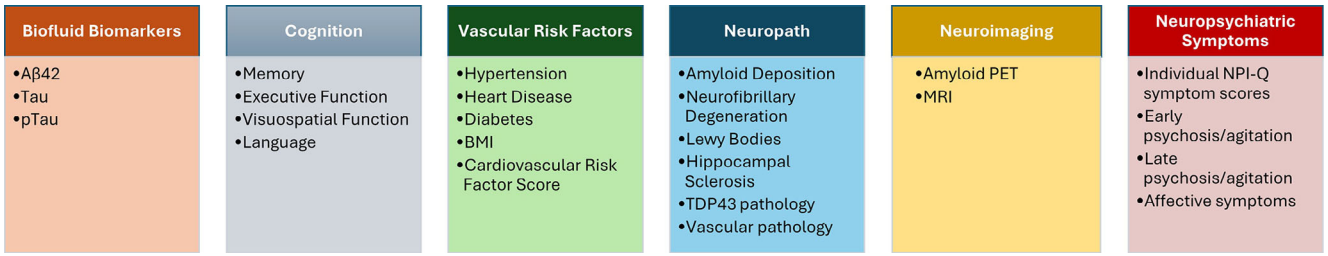

FIGURE 2 Types of data harmonized by the ADSP/ADSP-PHC in addition to neuropsychiatric variables harmonized through the current effort. Aβ, amyloid beta; ADSP, Alzheimer's Disease Sequencing Project; ADSP-PHC, Alzheimer's Disease Sequencing Project Phenotype Harmonization Consortium; BMI, body mass index; MRI, magnetic resonance imaging; NPI-Q, Neuropsychiatric Inventory Questionnaire; PET, positron emission tomography; pTau, phosphorylated tau; TDP43, TAR DNA-binding protein 43

curates, harmonizes, and deposits cognitive, neuropathological, brain imaging, and biofluid biomarker endophenotype data from ADSP cohort studies. These activities are coordinated with the established infrastructure of the Alzheimer's Disease Centers, the storage and dissemination infrastructure of NIAGADS, and the Image and Data Archive run by the Laboratory of Neuro Imaging (LONI) at the University of Southern California Mark and Mary Stevens Neuroimaging and Informatics Institute. Data flow from the National Alzheimer's Coordinating Center and the cohort studies into NIAGADS are accessed by the ADSP-PHC, are curated and harmonized, and are then redeposited into NIAGADS for sharing with ADSP workgroups, programs, and qualified investigators. Imaging data are coordinated on the back end through a collaborative agreement setup between LONI and NIAGADS. Embedded in this existing infrastructure, the present project will acquire NPS phenotypes and relevant meta-data from all cohorts, harmonize and refine them, and redeposit them into NIAGADS for sharing with the larger scientific community. Primary core analyses will (1) identify novel genetic risk factors associated with NPS in AD, (2) characterize the shared genetic architecture of NPS in AD and primary psychiatric disorders, and (3) assess the role of ancestry effects in the etiology of NPS in AD (see below).

2.3 | Harmonization and refinement of NPS phenotypes

Capitalizing on existing ADSP-PHC infrastructure, we will compile, harmonize, and generate phenotypes and sub-phenotypes relevant to NPS and make these available to the scientific community. All datasets will be harmonized using NPS data, history of psychiatric disorders prior to onset of AD (when this information is available), and history of medications used to treat NPS. Most studies used the Neuropsychi-

atric Inventory Questionnaire (NPI-Q),[36,37] a global measure of NPS completed by an informant. Many of the studies also collected the Geriatric Depression Scale[38] or the Center for Epidemiologic Studies Depression Scale,[39] both self-completed measures of depressive symptoms. Affected individuals are required to have AD and will be excluded if they have a diagnosis of a non-AD neurodegenerative disorder. Additional relevant data are being harmonized by other ADSP infrastructure (phenotype data through the ADSP-PHC, genomic data through the Genome Center for Alzheimer's Disease); these data include AD diagnosis, cognitive measures, demographics, disease stage (as operationalized by the Clinical Dementia Rating [CDR] Dementia Staging Instrument), age at onset of memory symptoms, medications, sex, race/ethnicity, and genomic data. All incoming data will be checked for quality, integrity, and consistency. We will also review the NPS data for details of administration of the measure, missingness, any inconsistencies in reporting, and the reliability of NPS reporting and measurement across different groups, languages, and cultures. We will also assess the impact of sex and ethnicity on the harmonized NPS phenotype across studies. To harmonize NPS data we will develop a common coding scheme in R to match variables and value formats from the different studies and also to calculate the refined phenotypes described below. We will develop R scripts to detect outliers and anomalous NPS data that will be reviewed by the investigators. All R scripts will be documented regarding development and purpose and will be made available to qualified investigators for review and use. We will compare summary statistics/distributions across studies and sites; outlier studies indicate potential coding errors or data collection bias and will be examined in depth. If necessary, we will create derived variables to harmonize variables with vastly different coding schemes or missing data. These NPS data will be coordinated with ADSP-PHC efforts to harmonize and provide magnetic resonance imaging; positron emission tomography; and neuropathological, biomarker, and cognitive data, increasing the scientific utility of the NPS data.

Most previous and current genetic studies of NPS in AD phenotypically classify participants as positive or negative either for any NPS or for a single NPS. This approach may be overly reductive and could overlook important aspects of a complex clinical phenotype. NPS often change over the course of the illness and can even improve as the illness progresses. For example, patients with AD will often have depression in early, but not late, stages of the illness.[40] AD patients frequently have multiple NPS and these different NPS are often highly co-linear. For example, depressed mood, anxiety, and irritability usually co-occur in AD, as do psychosis and agitation.[40] Examining a single NPS in isolation does not account for this significant co-linearity. Psychiatric disorders pre-existing AD are common, with ≈ 25% of individuals meeting criteria for a psychiatric disorder at some point in their lives,[41] further complicating the phenotyping of NPS in AD. To address these issues, analyses performed in this project will account for the stage of illness, pre-existing psychiatric illness, and treatment of NPS. In addition, we will calculate NPS symptom clusters based on recent findings. A cluster of psychotic symptoms (delusions and hallucinations) and agitation early in the course of AD defines a distinct phenotype of AD patients with important implications for disease course, morbidity, and mortality.[42] AD patients with early development of psychosis and agitation have a higher mortality, elevated caregiver burden, an earlier transition to out-of-home placement, and greater development of extrapyramidal symptoms, compared to AD patients who develop psychosis and agitation late in the course of the illness or who do not develop psychosis or agitation.[42] In addition, a cluster of "affective symptoms" including depression, anxiety, and irritability tends to appear early in the course of AD.[40,43] These symptoms are co-linear, especially in early AD, and have demonstrated specific genetic associations.[44] See the Methods section for calculation of these refined phenotypes, which will be made available to investigators. These calculated phenotypes will be examined by the phenotyping team to ensure that they are capturing the phenotypes described in the literature. If not, the calculated phenotypes will be modified to better match the published phenotypes and the rationale for the modification will be documented and made available. The calculated phenotypes will be compared to the raw data in genetic analyses and may show stronger or different genetic associations than the raw NPS data.

We will define, calculate, and provide all 12 individual symptom scores on the NPI-Q and the following three symptom clusters: early psychosis/agitation (EPA), late psychosis/agitation (LPA), and affective symptoms. EPA is defined as the presence (i.e., a non-zero score) of any of the delusion, hallucination, or agitation symptoms on the NPI-Q at a CDR of 0.5 or 1. Absence of EPA requires a score of zero on all these NPI-Q items for all CDR 0.5 or 1 visits. LPA is defined as the presence of any of the delusion, hallucination, or agitation symptoms on the NPI-Q at a CDR of ≥ 2. An absence of LPA requires a score of zero on all these NPI-Q items for all CDR ≥ 2 visits. Participants with the presence of delusion, hallucination, or agitation symptoms on the NPI-Q at CDR 0.5 or 1 and at a higher CDR (i.e., meeting criteria for both EPA and LPA) will be classified as EPA. For participants without psychosis to be classified as negative for both EPA and LPA (−PA), they will have to have scores of zero on the NPI-Q delusion, hallucination, or agitation symptoms at all visits and either a last observed Mini-Mental State Examination score ≤ 20 or a CDR ≥ 1. This is to avoid misclassification of participants as −PA who will later develop these symptoms. We will also define +PA as participants who meet criteria for EPA or LPA. The presence of the "affective symptom" (+AS) phenotype at a visit will be defined as the presence (i.e., a non-zero score) of any of the depression, anxiety, or irritability symptoms on the NPI-Q at any visit. The absence of affective symptoms will require the absence of the depression, anxiety, or irritability symptoms on the NPI-Q at all visits.

3 | RESULTS

3.1 | Dissemination of harmonized data

Like other ADSP-FUS data, the harmonized NPS data will be made available to the research community through NIAGADS (https://www.niagads.org/). Each data release will include information on data freezes, data provenance, specifics of variable coding/changes, and data dictionaries.

3.2 | Planned core analyses

We will use the resulting harmonized neuropsychiatric data for three immediate main core analyses: (1) to identify novel genetic risk factors associated with NPS in AD, (2) characterize the shared genetic architecture of NPS in AD and primary psychiatric disorders (e.g., depression, bipolar disorder, schizophrenia, anxiety disorders, obsessive compulsive disorder), and (3) assess the role of ancestry effects in the etiology of NPS in AD.

We will identify novel genetic variants and genes associated with risk of specific NPS in AD from WGS data using association, linkage, and segregation approaches within and across populations, incorporating important confounding variables such as social determinants of health as available. Polygenic and genetic risk scores will be used to characterize genome-wide risk across ancestries. Pathway analyses (informed by in silico functional annotation) will be used to assess the role of specific pathways and mechanisms. To characterize the shared genetic architecture of NPS in AD and primary psychiatric disorders we will estimate the heritability and genetic correlations across NPS in AD, and with individual primary psychiatric disorders to assess the genetic landscape of these phenotypes. Sets of traits showing genetic correlations will be assessed using multi-trait analyses to identify novel shared genetic factors. The role of specific variants identified in these analyses will be further validated by a variety of downstream analyses including colocalization, Mendelian randomization, and other approaches to assess confounding and causality and to identify treatment targets. A critical question about AD genetic risk that directly impacts the development of effective tools for genetic screening and treatment is whether variants and genes identified in one population have similar effects in both sexes and across populations. To assess the role of sex, all analyses will be repeated separately for each sex if sample sizes are sufficient. To assess the role of ancestry effects in the etiology of NPS in AD, we will identify genomic regions of differential risk for NPS across ancestries by performing admixture mapping in the Black and Hispanic cohorts and will assess the impact of local ancestry effects on NPS risk by inferring ancestry local to specific chromosomal segments and modeling risk using ancestry-aware frameworks. Finally, given that psychiatric symptoms are common in other neurodegenerative disorders (frontotemporal dementia, dementia with Lewy bodies, etc.), one hypothesis is that NPS may be impacted by comorbid, non-AD pathologies such as Lewy bodies, hippocampal sclerosis, TAR DNA-binding protein 43 proteinopathy, and so on. As such, we will evaluate NPS and NPS-associated genetic factors in the context of neuropathological data, when available.

4 | DISCUSSION

The described effort will expand the racially and ethnically diverse datasets of the ADSP-FUS and related efforts to include harmonized NPS data and will use these data to identify and describe genetic determinants, pathways, and polygenic effects underlying specific NPS in AD, and identify potential treatment targets. Additionally, we will explore the shared genetic architecture of NPS, primary psychiatric disorders, and dementia, and will comprehensively assess the role of ancestry in NPS genetic risk. While this effort requires collation of primary NPS data as well as all relevant meta-data from > 70 cohorts, we can capitalize on the extensive existing infrastructure by the ADSP, ADSP-PHC, and NIAGADS to collate and distribute data.

In addition to providing critical information on the molecular etiology of NPS in AD and observed disparities, this proposed collection, harmonization, and integration of NPS data across the full multi-ancestry set of ADSP-FUS cohorts will provide a critical complement to the ADSP-FUS at large, allowing for future analyses of a wide range of additional important hypotheses.

ACKNOWLEDGMENTS

This study was supported by NIH grants: P30AG066462 (CR), U01AG079850 (CR, GWB, EDH, MC, RS), R01AG064614 (CR, GWB), U19AG074865 (CR, MC), R01AG072547 (CR, GWB), U24AG056270 (CR, GWB), R01AG062268 (EDH), R01MH120794 (EDH).

CONFLICT OF INTEREST STATEMENT

There are no competing interests to report. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent.

DEI STATEMENT

This study was approved by all appropriate university institutional review boards and was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki and its later amendments. This study also addresses the topic of diversity, equity, and inclusion by including individuals of underrepresented populations, who are vastly underrepresented in AD research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Ray NR, Kumar A, Zaman A, et al. Disentangling the genetic underpinnings of neuropsychiatric symptoms in Alzheimer's disease in the Alzheimer's Disease Sequencing Project: Study design and methodology. *Alzheimer's Dement*. 2024;16:e70000. https://doi.org/10.1002/dad2.70000