15 Years of Longitudinal Genetic, Clinical, Cognitive, Imaging, and Biochemical Measures in DIAN

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Abstract

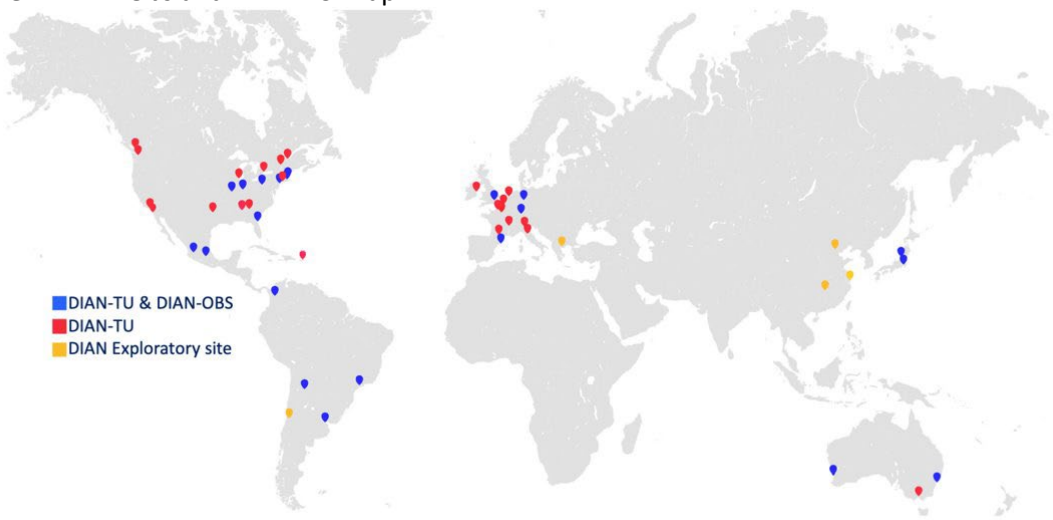
This manuscript describes and summarizes the Dominantly Inherited Alzheimer Network Observational Study (DIAN Obs), highlighting the wealth of longitudinal data, samples, and results from this human cohort study of brain aging and a rare monogenic form of Alzheimer's disease (AD). DIAN Obs is an international collaborative longitudinal study initiated in 2008 with support from the National Institute on Aging (NIA), designed to obtain comprehensive and uniform data on brain biology and function in individuals at risk for autosomal dominant AD (ADAD). ADAD gene mutations in the amyloid protein precursor (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) genes are deterministic causes of ADAD, with virtually full penetrance, and a predictable age at symptomatic onset. Data and specimens collected are derived from full clinical assessments, including neurologic and physical examinations, extensive cognitive batteries, structural and functional neuro-imaging, amyloid and tau pathological measures using positron emission tomography (PET), flurordeoxyglucose (FDG) PET, cerebrospinal fluid and blood collection (plasma, serum, and whole blood), extensive genetic and multi-omic analyses, and brain donation upon death. This comprehensive evaluation of the human nervous system is performed longitudinally in both mutation carriers and family non-carriers, providing one of the deepest and broadest evaluations of the human brain across decades and through AD progression. These extensive data sets and samples are available for researchers to address scientific questions on the human brain, aging, and AD.

Background and Summary

The vast majority of AD dementia is sporadic and generally occurs in older ages, but a small proportion (less than 1%) of AD dementia is caused by mutations in the Aβ precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) genes with almost 100% penetrance, generally at predictable younger ages. This form of AD is known as autosomal dominant AD (ADAD). ADAD is thought to have an underlying pathogenic process similar to that of the more common sporadic AD and thus may hold the key to understanding the pathogenesis of AD and identification of effective treatments for both ADAD and sporadic AD. To leverage this population's potential for AD research, the DIAN Obs was established in 2008. It aims to track individuals from families with known ADAD mutations, employing a wide array of cognitive assessments and biomarker tests. Since inception time, the DIAN Obs has amassed a substantial repository of clinical and biomarker data and samples, facilitating a deeper understanding of ADAD's natural history.

The DIAN Obs cohort has been longitudinally followed for over 15 years and is amongst the most deeply phenotyped cohorts of brain aging, function, and AD measures in predominantly 18 to 55-year-old people. The inaugural year of DIAN Obs included ten performance sites in three countries (US, UK, and Australia) with English as the language for all initial sites. The continued success of DIAN Obs has since grown to twenty-three performance sites in eleven countries and supporting seven languages: English, Spanish, German, Japanese, Korean, French, and Portuguese (Figure 1 and Supplement Table 1). A total of 664 participants have enrolled in DIAN Obs; currently the study has 314 currently active participants.

Figure 1: DIAN Obs and DIAN-TU Map

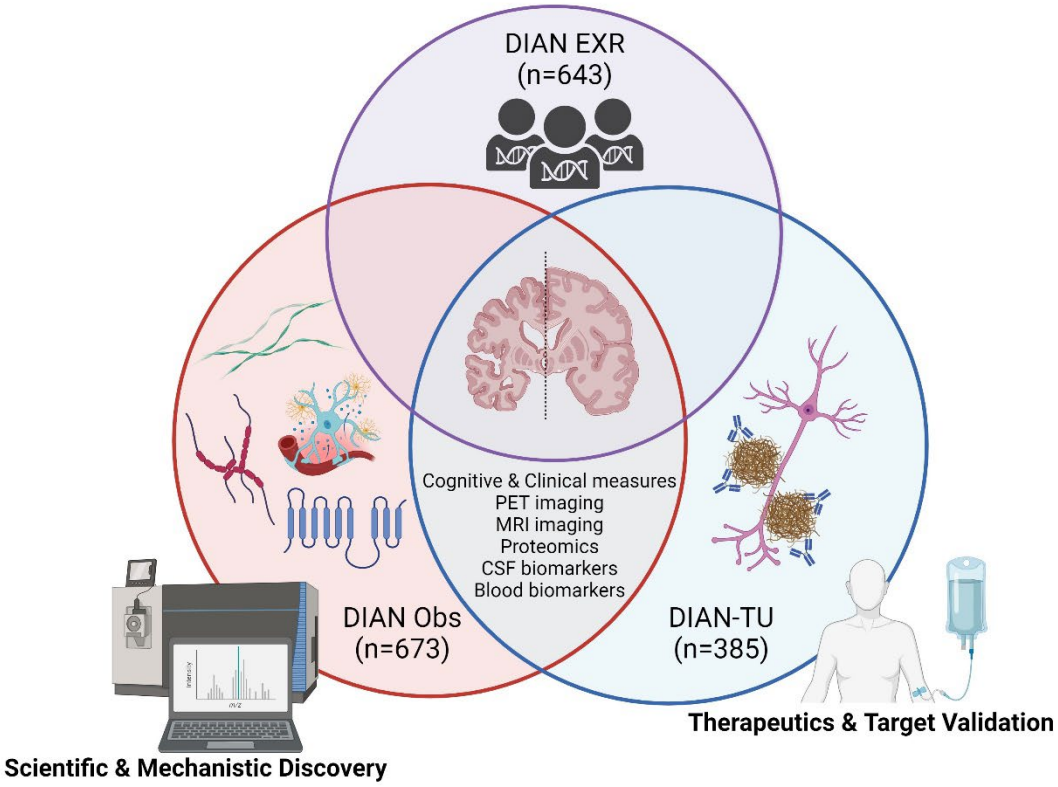


DIAN Obs is the key scientific and discovery study for ADAD and also provides natural history information for the DIAN-Trials Unit (DIAN-TU), which is the therapeutic and target validation platform for treatment and prevention trials. The DIAN-TU [dian.wustl.edu/our-research/clinical-trial/][6-7] is a global research effort established in 2012 to design and conduct clinical trials for the prevention or treatment of ADAD. Data from DIAN Obs and DIAN-TU studies were designed to be conducted together, with nearly identical protocols, including cognitive and clinical assessments, biomarker measures, and quality control.

Participant outreach, recruitment, and retention for both DIAN Obs and DIAN-TU are facilitated via the international DIAN Expanded Registry (DIAN EXR) [dian.wustl.edu/our-research/registry], established in 2012 for individuals who are or may be affected by ADAD. DIAN EXR serves as a collaborative research effort not only to facilitate study referral to DIAN Obs and DIAN-TU, but also to support educational and outreach activities with ADAD family members.

DIAN Obs and DIAN-TU have distinct purposes with differing eligibility requirements and site locations allowing the DIAN EXR to act as a central mechanism for navigation and referral of interested registrants to potential research opportunities (Figure 2).

Figure 2: Coordination of DIAN Obs, DIAN-TU, and DIAN EXR

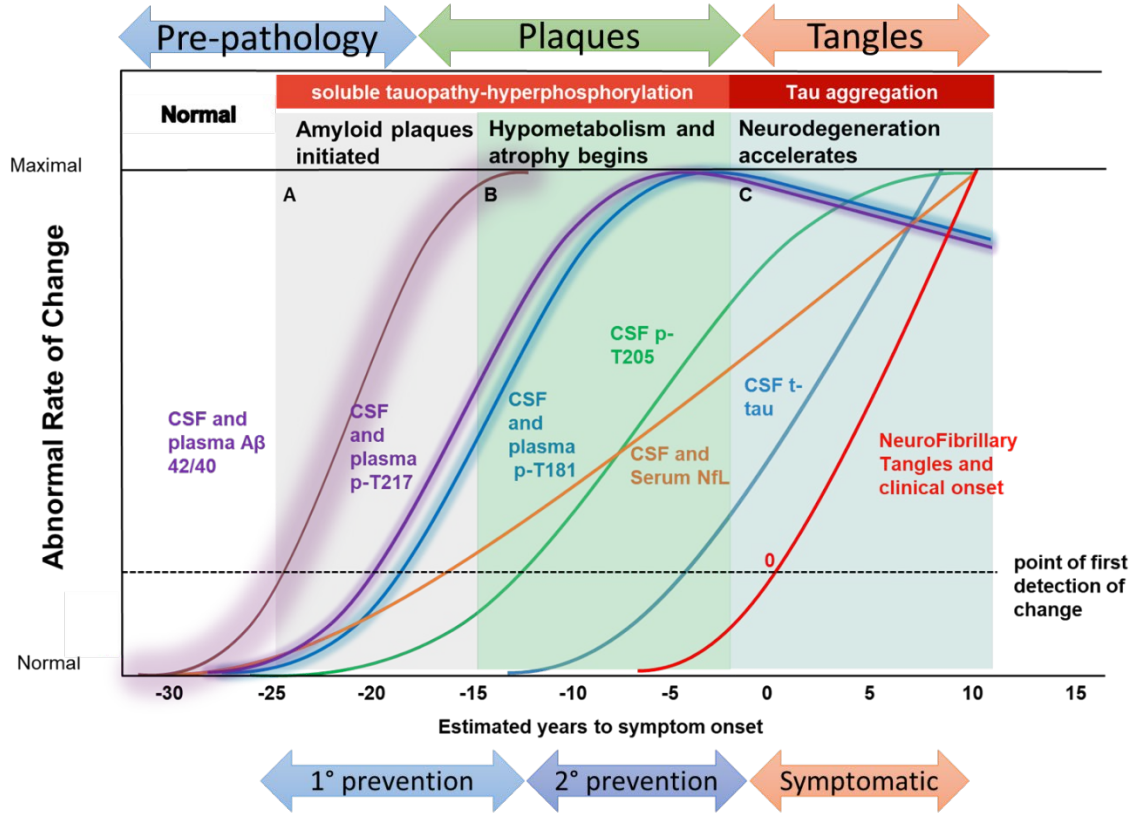


The main scientific hypotheses of DIAN Obs aim to address fundamental questions regarding the pathophysiology of AD. First, AD biomarker changes identify mutation carriers (MCs) many years before symptomatic AD develops, thus supporting the concept of preclinical AD. Second, the initial biomarker changes in the preclinical stage of ADAD involve Aβ42, followed by changes related to neurodegeneration, followed by cognitive decline. Third, the clinical and neuropathological phenotypes of ADAD will reflect those of "sporadic" late onset AD (LOAD). DIAN Obs emphasizes longitudinal data as it provides more accurate and precise information on the magnitude and rate of change for biofluid and imaging biomarkers throughout the preclinical stage of ADAD.

DIAN Obs has provided seminal advances in the understanding of brain health, the onset and progression of ADAD, and how this compares to the more common sporadic AD (Figure 3). In 2012, DIAN Obs described a comprehensive order of clinical, cognitive, imaging, and biomarker changes that occur across time span two decades before and a decade after symptom onset. Amyloid plaques continuously accumulate for 15-20 years before symptom onset, defining an amyloid growth phase,[1–4] while tau tangles appear and accumulate in the transition to and during the symptomatic phase.[5] A series of biochemical changes in CSF and blood begin with amyloid-beta 42/40 decreasing, followed closely by p-tau217/181/231 associated with amyloid plaques, then p-tau205, neurofilament light chain

(NfL), and total tau increasing before the appearance of tangles. Cortical hypometabolism begins five to ten years before symptom onset, and cortical atrophy five years before symptom onset. Finally, changes in cognitive performance are detected several years before onset.

Figure 3: ADAD Onset & Progression compares to Sporadic AD



*Adapted from Barthelemy et al, Nat Med 2020.

DIAN-TU implements therapeutic trials in a trial platform with the goal to slow, delay, or prevent dementia in the ADAD population.[6,7] DIAN Obs and DIAN-TU implement harmonization efforts to ensure the combination and comparability of DIAN-TU and DIAN Obs protocols including International Council for Harmonisation Good Clinical Practice (ICH GCP) guideline compliance. These harmonization efforts increase longitudinal data and sample resources that can be combined across DIAN Obs and DIAN-TU. The Biostatistics Core enables the ability to link coded participant data across the DIAN Obs and DIAN-TU, enabling combining and comparing across the studies. Key measures harmonized include electronic capture of clinical and cognitive assessments, sample collection protocols, and imaging (MRI and PET).

Methods

A. Overview

Washington University in St. Louis is the recipient of a U19 grant from the NIA and serves as the DIAN Obs Coordinating Center which oversees both scientific and administrative center and as a performance site. The DIAN Obs Coordinating Center consists of eight Cores: Administration, Clinical, Genetics, Cognition, Imaging, Biomarker, Neuropathology, and Biostatistics and three scientific Projects: Amyloid-β, Tau, and Novel Mechanisms. All performance sites have access to adequate numbers of potential

DIAN Obs participants and the resources and capabilities to conduct all elements of the DIAN Obs protocol.

B. Institutional Review Board & Consenting Statement

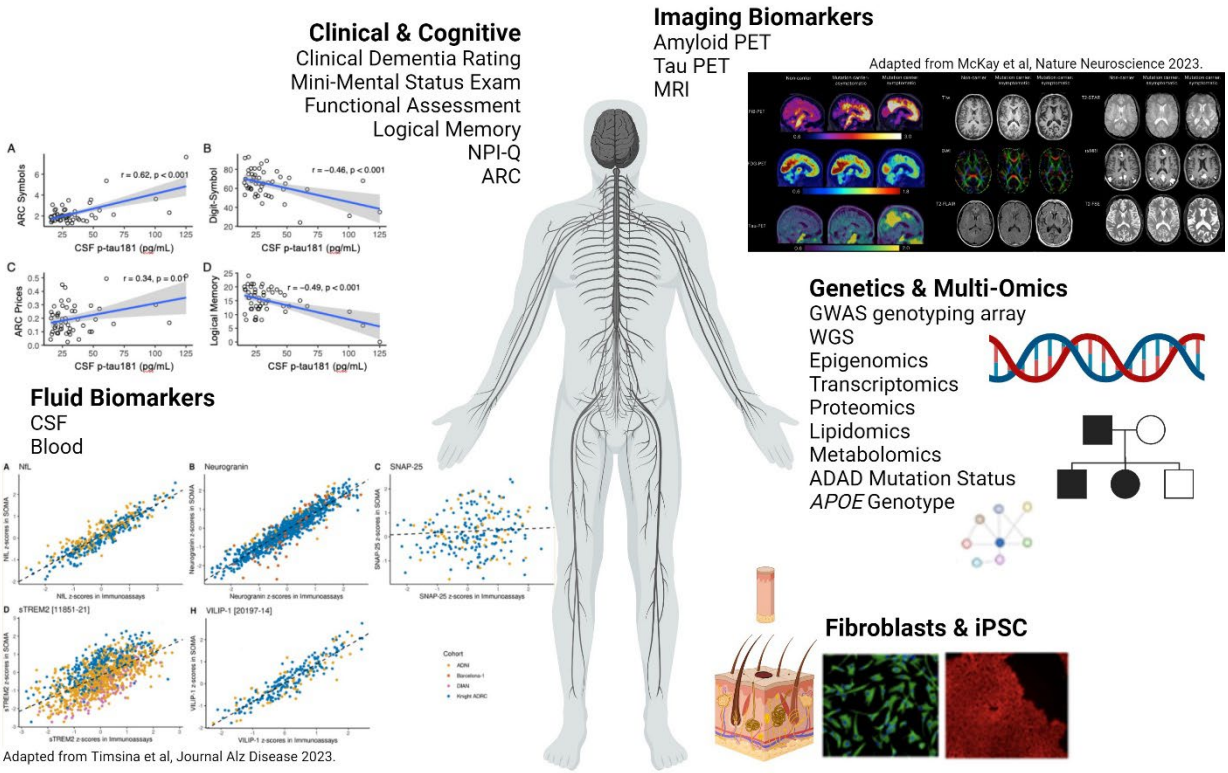
The Institutional Review Board (IRB) of Washington University School of Medicine in St. Louis approved the study with the IRB ID# 201106339, and research was performed in accordance with the approved protocols. Participants review and discuss the consent form with performance site study team prior to being asked to sign the informed consent for study participation. A copy of the consent is provided to participants and the original is maintained in the participant's research record.

C. Administration Core

The DIAN Obs Administration Core provides oversight and management of the DIAN Obs project including: coordinating activities of the other Cores, scientific research Projects, and subcontractors; managing and supporting the DIAN Obs Steering Committee; seeking and facilitating feedback from the External Advisory Committee; interacting with the NIA liaisons; and managing activation, maintenance, and data collection of all performance sites.

The Administration Core has established a web-based system to support data and tissue resource dissemination to investigators. The DIAN Obs data and biospecimen application form is available on the DIAN website (dian.wustl.edu). All requests are reviewed by relevant Core Leaders, the Study Director, and DIAN Obs Steering Committee. Upon receiving request approval, with appropriate institutional review board (IRB)/institutional ethics committee (IEC) approvals and data and tissue sharing agreements, data and/or biospecimens are shared with support from the related Cores and Biostatistics Core. The DIAN Obs Data and Tissue Sharing, Notifications, Publications, and Authorship Policies [DIAN Publication Policy] govern the sharing of DIAN Obs resources and guidelines for publications. As of December 2022, DIAN Obs has received 288 data requests and 114 tissue requests, with 231 and 85 requests fulfilled respectively. An overview of resources that may be requested is provided in Figure 4.

Figure 4: Overview of DIAN Obs Resource Requests

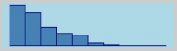
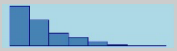
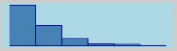


D. Clinical Core

The Clinical Core oversees clinical protocol execution and associated activities, encompassing participant recruitment, retention, clinical evaluations, CSF and blood sample acquisition, safety protocols, and quality control initiatives. Enrollment eligibility criteria include being 18 years of age or older and having a known pathogenic ADAD mutation in the family with a risk of inheriting the mutation. All DIAN Obs participants have access to genetic counseling and testing.

Upon participant consent, a visit anniversary date is established, initiating the DIAN Obs visit schedule with a frequency of one to three years. In-person site visits commence with the initial assessment and subsequently alternate with remote assessments for asymptomatic participants. Symptomatic participants undergo annual in-person evaluations under the current protocol. Table 1 details clinical and cognitive data collection procedures and data availability. A comprehensive list of current and former DIAN Obs performance sites is included as a Supplement.

Table 1: Clinical Core Available Resources & Data

Data:	Number of participants	Total assessment count	Number of participants with only 1 assessment	Number of participants with >1 assessment	Mean assessments among participants with >1 assessment	Distribution of assessment count[b]
Estimated Parental Age at Onset	671	1653	227	444	3.21	
Demographics	673	1431	288	385	2.97	
Health history	673	1659	229	444	3.22	
Family history	673	673	673	NA	NA	NA
Medications	605	NA	NA	NA	NA	NA
Physical & Neurologic exam findings	673	1647	231	442	3.20	
Clinician Judgment of Symptoms	673	1659	229	444	3.22	
Clinician Diagnosis, including Cognitive Status & Dementia	673	1659	229	444	3.22	
Informant Demographics	673	1432	287	386	2.97	
Exercise Questionnaire	673	1659	229	444	3.22	
Hollingshead Index of Social Position	673	1145	376	297	2.59	
Clinical Dementia Rating (CDR)	673	1659	229	444	3.22	
Geriatric Depression Scale (GDS)	672	1653	230	442	3.22	
Functional Assessment Questionnaire (FAQ)	670	1648	230	440	3.22	
Mini-mental Status Exam (MMSE)	671	1621	239	432	3.20	
Digit Span	673	1658	230	443	3.22	

Data:	Number of participants	Total assessment count	Number of participants with only 1 assessment	Number of participants with >1 assessment	Mean assessments among participants with >1 assessment	Distribution of assessment count[b]
Category fluency for animals & vegetable	673	1658	230	443	3.22	
Neuropsychiatric Inventory-Q (NPI-Q)	672	1652	231	441	3.22	
United Parkinson's Disease Rating Scale (UPDRS)-Motor	673	1640	233	440	3.20	
Hachinski Ischemic Score & Cerebrovascular Risk Factors	673	1639	234	439	3.20	

Abbreviations: NA, Not Applicable

[a] DIAN Obs Data Freeze 17 (DF17) was used to compute these numbers. There are 673 participants in DF17. The cutoff for DF17 was 6/30/2023.

[b] The leftmost bar represents participants with exactly 1 assessment, 2nd leftmost bar represents participants with exactly 2 assessments, etc.

E. Genetics Core

The goals of the Genetics Core are to obtain and bank tissue for genetic and multi-omic studies, as well as to generate, process, and/or harmonize genetic and multi-omic data. At each DIAN Obs in-person initial visit, whole blood is collected and used for ADAD mutation status, *APOE* genotype, genome-wide association study (GWAS) genotyping array, and whole genome sequencing (WGS). At each DIAN Obs in-person initial and follow up visit, buffy coat blood and PAXgene blood tubes are collected for longitudinal assessment of DNA methylomics and RNA transcriptomics, respectively. Additionally, the Core obtains and banks dermal fibroblasts then generates induced pluripotent stem cells (iPSCs) (Table 3). These resources support DIAN Obs Projects and are available to the research community with an approved data and/or tissue request.

The Genetics Core provides central determination and confirmation of gene sequence, whether normal or disease-causing mutation carrier, and *APOE* genotype on each of the 673 total study participants derived from 251 families. Table 2 presents the distribution of genetic variants and carrier status, categorized by gene. The Core, in coordination with the Clinical Core and DIAN EXR, maintains and curates a list of pathogenic mutations as well as confirms that new DIAN families carry an ADAD mutation.

The Genetics Core generates GWAS genotyping array, WGS, and *APOE* genotype data for all individuals. This data has been leveraged to generate polygenic risk scores (PRSs) for LOAD risk, onset, and progression, as well as Parkinson's disease risk. Recent studies indicate that in DIAN Obs ADAD, LOAD

risk PRS is not significantly associated with mutations status, but is associated with levels of CSF Aβ, total-tau, and p-tau, suggesting that known AD risk variants may modify age at onset (AAO) in the ADAD population Polygenic risk score of sporadic late-onset Alzheimer's disease reveals a shared architecture with the familial and early-onset forms - PubMed (nih.gov).

Table 2: Genetics Core Available Resources & Data

Data:
ADAD Mutation Status
APOE Genotype
Genome-wide association Study (GWAS) genotyping array
Whole Genome Sequencing (WGS)
Polygenic Risk Scores for:
○ AD (risk, onset, progression),
○ Parkinson's disease (risk)
○ Frontotemporal dementia (risk)
Multi-omics:
○ DNA methylomics: brain & blood
○ RNA transcriptomics: brain & blood
○ Proteomics: brain, CSF, & plasma
○ Metabolomics & lipidomics: brain, CSF, & plasma
Tissue & Cell Lines:
DNA/Cell lines
Dermal Fibroblasts
Induced Pluripotent Stem Cells (iPSCs)

Finally, the Genetics Core serves as a central repository for increasingly rich multi-omic data.[9,10] Currently, this catalog includes: DNA methylomics (Illumina MethylationEPIC 850k array) for brain (44 participants) and buffy coat blood (790 longitudinal samples from 266 participants); RNA-seq for brain (44 participants) and blood (575 longitudinal samples from 319 participants); and proteomics (SomaLogic 7k) and metabolomics/lipidomics (Metabolon HD4) for brain (44 participants), CSF (495 participants), and plasma (495 participants). These data have been used to identify circular RNAs in brain associated with AD and AD pathology[41, 86], as well as to identify proteins associated with carrying an ADAD mutation and change between 20 to -30 years before the onset, some of them even before some of the validated biomarkers.

Table 3: DIAN Obs Mutation Status Distribution

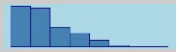
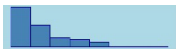
***PSEN1* (N = 436, 89 unique variants)**	
mutation	272
no mutation	164
***PSEN2* (N = 50, 8 unique variants)**	
mutation	28
no mutation	22
***APP* (N = 120, 14 unique variants)**	
mutation	68
no mutation	52

F. Cognition Core

A primary goal of the Core is to maintain the cognitive assessment battery to align with scientific aims and to incorporate novel measures and novel assessment methodologies that are more sensitive to early cognitive changes in ADAD. The Cognition Core serves the overall grant by overseeing rater training and maintaining rigorous quality control (QC) and documentation standards that ensure the fidelity of longitudinal cognitive assessments. In addition, the Cognition Core plays a pivotal role in maintaining the

consistency of cognitive assessments across various languages, ensuring culturally relevant translations and adaptations across different sites and countries. These methodologies will improve reliability in measurement of the key features of ADAD. The assessment of cognition is central for achieving the scientific aims of all DIAN Obs Projects and Cores. The Cognition Core works with the Project and Core leaders to ensure that fully validated cognitive data is available for DIAN Obs data freezes and provide guidance on appropriate cognitive measures and data analyses to support Project and Core aims. Refer to Table 4 for Core data availability. Novel methods implemented in the Cognition Core include the use of remote cognitive testing via Ambulatory Research in Cognition (ARC), and the development of novel remote cognitive tasks including tests of long-term forgetting and statistical learning paradigms.

Table 4: Cognition Core Available Resources & Data

Data:	Number of participants	Total assessment count	Number of participants with only 1 assessment	Number of participants with >1 assessment	Mean assessments among participants with >1 assessment	Distribution of assessment count[b]
Trailmaking A & B	673	1648	232	441	3.21	
Wechsler Adult Intelligence Scale-Revised (Logical Memory)	673	1655	232	441	3.22	
Word list recall (immediate & delayed) designed specifically for DIAN	572	1275	198	374	2.88	
Letter Fluency for F-A-S	572	1275	198	374	2.88	
Boston Naming test[c]	587	1365	196	391	2.99	
International Personality Item Pool (IPIP)[d]	393	820	185	208	3.05	

Abbreviations: NA, Not Applicable

[a] DIAN Obs Data Freeze 17 (DF17) was used to compute these numbers. There are 673 participants in DF17. The cutoff for DF17 was 6/30/2023.

[b] The leftmost bar represents participants with exactly 1 assessment, 2nd leftmost bar represents participants with exactly 2 assessments, etc.

[c] The last Boston Naming test was collected on 10/6/2020.

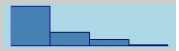
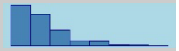
[d] The last IPIP was collected on 10/25/2021.

G. Imaging Core

The Imaging Core is responsible for the acquisition, QC, processing, and analysis of the MRI and PET neuroimaging data for DIAN Obs. The imaging data set collected in DIAN Obs participants to date represents a highly valuable resource for AD research. It has supported cross sectional analysis of PET and MRI data to develop a timeline for imaging biomarkers in ADAD. Carriers of AD-causing mutations and their non-carrier (NC) siblings are enrolled and followed in the Clinical Core through the

international DIAN Obs performance sites. Participants undergo structural and functional MRI, amyloid PET, tau PET, and metabolic PET imaging in conjunction with their clinical visits. The Core obtains and analyzes longitudinal imaging data that is fully integrated with clinical, psychometric, and CSF biomarkers, and allow for mutation-specific genotype-phenotype analysis. MRI data are processed using the Freesurfer Imaging suite to derive regions of interest. These regions are then used to process the PET data. Imaging Core data formats available are outlined in Table 5. A neuroimaging specific resource paper detailing in-depth imaging protocols has recently been published.[5,11]

Table 5: Imaging Core Available Resources & Data

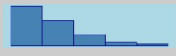
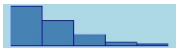
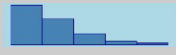
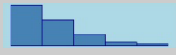
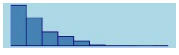
Data:	Number of participants	Total assessment count	Number of participants with only 1 assessment	Number of participants with >1 assessment	Mean assessments among participants with >1 assessment	Distribution of assessment count[b]
MRI scans	643	1541	226	417	3.15	
MRI quantitative measurements[c]	593	1409	201	392	3.08	
AV-1451 Tau PET scans and quantitative measurements[d]	67	99	44	23	2.39	
MK-6240 Tau PET scans and quantitative measurements	31	37	26	5	2.20	
PiB PET scans	600	1318	234	366	2.96	
PiB PET quantitative measurements	549	1169	220	329	2.88	
FDG PET scans	577	1221	233	344	2.87	
FDG PET quantitative measurements	540	1117	223	317	2.82	

[a] DIAN Obs Data Freeze 17 (DF17) was used to compute these numbers. There are 673 participants in DF17. The cutoff for DF17 was 6/30/2023.
[b] The leftmost bar represents participants with exactly 1 assessment, 2nd leftmost bar represents participants with exactly 2 assessments, etc.
[c] Quantitative measurements from MRI scans include the volume and thickness of various brain regions.
[d] Quantitative measurements from PET scans include the concentration of amyloid-beta plaques measured by PiB PET scans, tau tangles measured by Tau PET scans, and metabolic activity assessed by FDG PET scans within various brain regions.

H. Biomarker Core

The DIAN Obs Biomarker Core is a high-capacity biorepository enabling high-throughput processing while maintaining high-quality, gold-standard biomarker measurements of cerebrospinal fluid (CSF) and plasma samples available to investigators upon completion and approval through the DIAN tissue request process. The Biomarker Core obtains measures of the following biomarker analytes using the Lumipulse automated assay platform: CSF (Aβ1-40, Aβ1-42, total tau [t-tau], p-tau 181). Data and sample availability is outlined in Tables 6 and 7. Core samples may be leveraged in a longitudinal manner, in conjunction with extensive clinical and biological data, to study both traditional and exploratory biomarkers. With the main priority of the Biomarker Core to evaluate fluid biomarker profiles in ADAD participants comparing MCs to NC, DIAN Obs, along with others, have helped give insight to expected biomarker trajectories given the availability of expected AAO in MC individuals.[1,12] The Biomarker Core has demonstrated that fluid biomarkers changes begin during the preclinical period (20-30 years before expected symptom onset). However, collection and analysis of additional longitudinal samples are required to define the patterns of change of known and novel fluid biomarkers that happen right when an individual progresses from asymptomatic (or preclinical) to symptomatic. Given the minimally invasive nature of phlebotomy, the field is invested in the identification of plasma biomarkers. In response to the needs in the field, DIAN Obs' scientific Projects will measure and analyze established markers of amyloid (Aβ and %p-tau217 ratio) and tau (MTBR243) deposition, inflammation (GFAP, sTREM2), and neurodegeneration (NfL) in CSF and plasma.

Table 6: Biomarker Core Available Resources & Data

Data:	Number of participants	Total assessment count	Number of participants with only 1 assessment	Number of participants with >1 assessment	Mean assessments among participants with >1 assessment	Distribution of assessment count[b]
CSF	596	1260	249	347	2.91	
Plasma	665	1620	231	434	3.20	
INNOTEST CSF Aβ40	462	843	224	238	2.60	
INNOTEST CSF Aβ42	462	844	223	239	2.60	
INNO-BIA AlzBio3 CSF Aβ42	461	839	222	239	2.58	
INNO-BIA AlzBio3 CSF t-Tau	460	832	229	231	2.61	
INNO-BIA AlzBio3 CSF p-Tau181	460	840	222	238	2.60	
LUMIPULSE CSF Aβ40 & Aβ42	577	1231	239	338	2.93	
LUMIPULSE CSF t-Tau	550	1128	246	304	2.90	
LUMIPULSE CSF p-Tau181	570	1209	240	330	2.94	

INNO-BIA Plasma Aβ40 & Aβ42	547	1199	191	356	2.83	

[a] DIAN Obs Data Freeze 17 (DF17) was used to compute these numbers. There are 673 participants in DF17. The cutoff for DF17 was 6/30/2023.
[b] The leftmost bar represents participants with exactly 1 assessment, 2nd leftmost bar represents participants with exactly 2 assessments, etc.

I. Neuropathology Core

The Neuropathology Core houses the network's post-mortem tissue. DIAN sites are supported in providing intact fixed hemi-brain specimens for uniform neuropathologic examination. Neuropathology Core efforts includes maintaining unfixed frozen and formalin-fixed tissue; a resource supporting DIAN's Projects and available to the research community with an approved tissue request.

Fixed hemibrains are prepared in standard fashion (hemispheres coronally; cerebelli parasagittally; brainstems axially), digitally photographed, and sampled for histology, generating a set of 17 formalin-fixed, paraffin-embedded (FFPE) tissue blocks, representing the following areas: Middle frontal gyrus; anterior cingulate gyrus at the level of the genu of the corpus callosum; precentral gyrus; superior and middle temporal gyri; inferior parietal lobe (angular gyrus); occipital lobe (including the calcarine sulcus and peristriate cortex); posterior cingulate gyrus and precuneus at the level of the splenium; amygdala and entorhinal cortex; hippocampus and parahippocampal gyrus at the level of the lateral geniculate nucleus; striatum (caudate nucleus and putamen with nucleus accumbens) and olfactory cortex; lentiform nuclei (globus pallidus and putamen) at the level of the anterior commissure with the nucleus basalis of Meynert; thalamus with subthalamic nucleus; midbrain; pons; medulla oblongata; cerebellum with dentate nucleus; and cervical spinal cord. Remaining wet formalin-fixed tissue is kept in formalin in perpetuity as a research resource.

The Core prepares histology slides from a uniform set of seventeen FFPE blocks from each case. These are stained with hematoxylin and eosin for histomorphologic assessment, and with immunohistochemistry (IHC) for the more common neurodegenerative lesions, using antibodies for Aβ (10D5, Eli Lilly), phosphorylated tau (PHF1, Feinstein Institute for Medical Research, Manhasset, NY), α-synuclein (LB509,MilliporeSigma), and phosphorylated TAR DNA-binding protein of 43 kDa (pTDP-43, Cosmo Bio USA). This protocol enables the Neuropathology Core to identify and rigorously stage the pathological underpinnings of the major classes of neurodegenerative diseases. Histological slides are then reviewed and scored, using published semi-quantitative scoring criteria for histopathological lesions. These data inform formulation of diagnoses for each case (using consensus staging and neuropathological criteria for AD [Khachaturian, CERAD, NIA-Reagan Institute, and NIA-AA][13-19] and for non-AD disorders[20-28]). To date a total of 41 DIAN participant specimens have been secured. Core data and sample availability is outlined in Table 8.

Table 7: Neuropathology Core Available Resources & Data

Data	Value	Frequency (Percentage)
A Score (Thal phase)	5	33 (100)

B Score (Braak)	6	32 (97)
B Score (Braak)	5	1 (3)
C Score (CERAD)	3	33 (100)
Sex	Male	17 (52)
Race	White	28 (85)
Race	Other	4 (12)
Race	Asian	1 (3)
Hispanic	Yes	4 (12)

[a] DIAN Obs Data Freeze 17 (DF17) was used to compute these numbers. There are 673 participants and data from 33 brain autopsies in DF17. The cutoff for DF17 was 6/30/2023.

J. Biostatistics Core

The activities of the Biostatistics Core enhance the research objectives of DIAN by imparting a smooth transition from the database to statistical analyses, providing appropriate statistical analysis resources to all Cores and Projects, and developing longitudinal statistical models to test the preclinical hypotheses of DIAN on all major biomarkers of AD. The Core provides application of methodological significance as it is a necessity of state-of-the-art longitudinal statistical models to adequately estimate and compare the longitudinal rates of change on multi-modal biomarkers during the preclinical and symptomatic stages, and to assess their predictive power to cognitive decline.

The high dimensional data from Imaging Core from many modalities (MRI, PiB PET, Tau PET over a large number of brain regions) and the omics data from the Genetics and Multi-Omics Core present another unique analytic challenge to DIAN Obs. The Biostats Core seeks biologically meaningful dimension reduction, and conduct analyses to combine imaging markers and omics markers into composites for the test of critical hypotheses. Principal component analyses and partial least square analyses[29-30] will be implemented, as well as methodologies developed by the Core[31-32]. We will also analyze longitudinal rates of change for these biomarkers jointly through general linear mixed models and correlate the rates of changes across modalities.

The Biostatistics Core have recently published multiple novel statistical methods driven by DIAN Obs database: analysis of biomarkers subject to detection limits[33], correlations with family-clustered design[34], diagnostic accuracy with ROC surface[35], detection of unknown changepoints (in age) from multiple longitudinal biomarkers[36], and a novel Bayesian ADAD progression model[37]. The Core continues to expand these models, and tackle other emerging analytic challenges from DIAN Obs: measurement errors in the EYO, small sample inferences on MCs who 'escaped' from their expected AAO, and high dimensional longitudinal data from imaging and omics. To control the false discovery rate (FDR), the Benjamini and Hochberg procedure is utilized[38].

K. Scientific Projects

In 2019, DIAN Obs added three scientific Projects to the study: Project 1: Amyloid-beta, Project 2: Tau, and Project 3: Novel Mechanisms. The goal of these scientific projects are to uniquely address central scientific questions which require significant DIAN Obs Core involvement.

Project 1 aimed to define the impact of ADAD mutations and amyloidosis on amyloid β proteoforms in CSF and plasma. This was accomplished using an IP-mass spectrometry approach to capture major Aβ proteoforms in plasma, CSF, and brain. Specifically we monitored Aβ37, 38, 39, 40, 42, and 43 in CSF, plasma, and brain homogenates and observed that Aβ isoform patterns of change differ. Additionally, Project 1 aimed to describe the impact of ADAD mutations in human iPSC-derived neurons and the relationship of brain proteoforms with histologic amyloid structure.

The next phase of this project will combine cell-based characterizations of individual ADAD variants with mass-spectrometry, IHC, and ELISA based measures of Aβ burden in brain parenchyma, cerebrovasculature, CSF, and blood from ADAD pathogenic variant carriers participating in DIAN Obs and DIAN-TU. This will provide a path toward the understanding of molecular composition and variant-level diversity of deposited and soluble Aβ species and compare these to the biochemical properties of each variant. These studies will offer a unique bench-to-bedside investigation of which types of Aβ are likely to be pathogenic, which are likely to deposit in brain and vessel walls, and how anti-amyloid therapies alter the balance of soluble Aβ species in the CNS and peripheral circulation.

The goal of Project 2 is to quantify the amount and regional distribution of tau pathology utilizing PET to illustrate differences between mutation carriers and non-carriers, investigate connections between tau pathology and other biomarkers as well as cognitive decline. The Project also aimed to validate the specificity and sensitivity of tau PET tracers (MK6240, AV1451, & PI2620) in postmortem tissue. Project 2 works to measure using mass spectrometry tau proteoforms in CSF, brain tissue, and iPSC-derived neurons, relating them to mutation status, EYO, AD biomarkers, and cognitive measures.

Initial work done within the Project used samples collected through 2017. During the study's current grant cycle, analyses have expanded to CSF on samples collect since 2017. This expanded analysis included 411 total samples which captured 67 individuals with longitudinal visits. From these samples, the Project derived measures of p-tau phosphorylated at different sites. Also these sample were used to generate MTBR-tau243 data.

Project 3 aims to map molecular interactions providing greater explanation on how ADAD mutations, inflammation, synaptic function, and associated therapeutic targets may influence one another. The molecular profiling is completed by transcriptomics and mass spectrometry-based proteomics. Project 3 also explores defining profiles of targeted and novel fluid markers of neuroinflammation and injury to evaluate biomarker levels pre-clinically to progression to predict cognitive decline. Targeted inflammation markers in CSF include YKL-40, sTREM2, and progranulin (via immunoassay), and neuronal injury markers include CSF VILIP-1, neurogranin, SNAP-25, and NfL and plasma NfL.

L. Future Initiatives

DIAN Obs has led major scientific advances in the understanding of AD stages, CSF and plasma biomarkers, mechanistic links to therapeutic targets, and enabled ground-breaking prevention and

interventional trials. DIAN Obs has helped define the sequence, timing, and magnitude of longitudinal AD biomarker changes decades before symptoms begin. This work directly led to the development and implementation of primary and secondary prevention trials for ADAD and the validation of the amyloid-tau-neurodegeneration (ATN) criteria. DIAN Obs intends to build on these advances to further understand major contributors to disease progression, resilience, and heterogeneity, and target validation for future therapeutics.

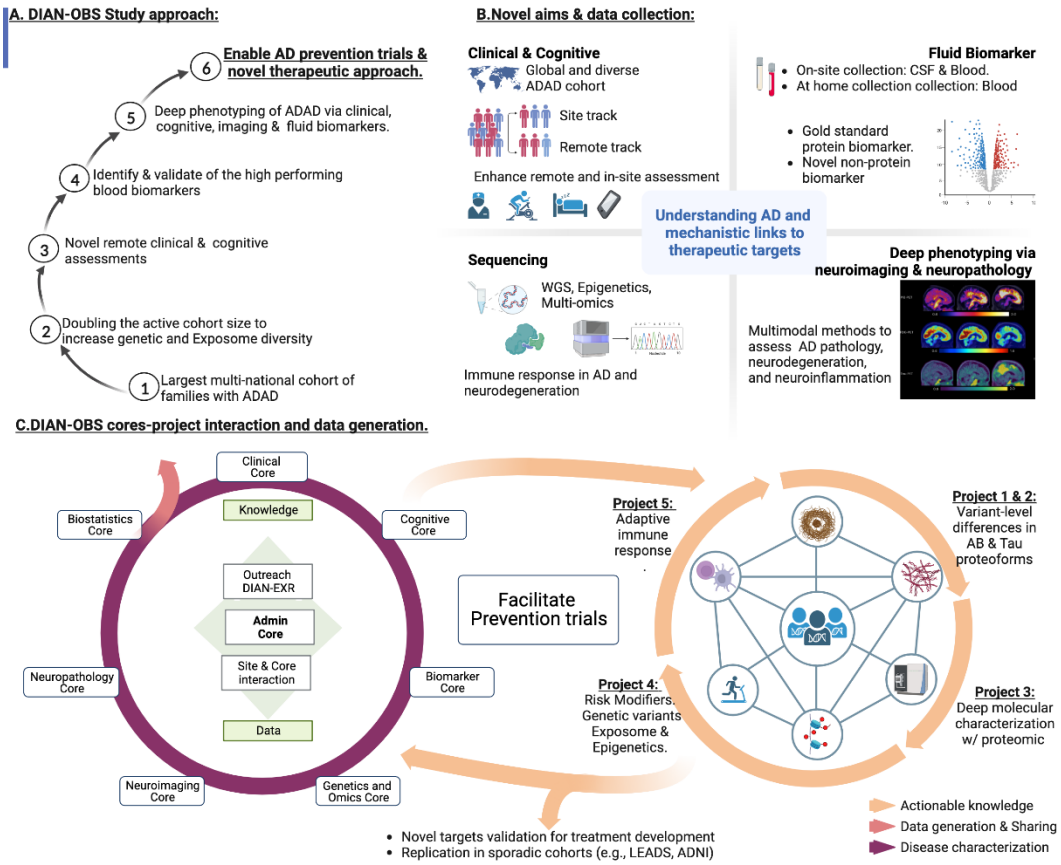
As DIAN prepares for its next phase, study hypotheses will expand and move to be supported by home based remote assessments, smartphone-based applications, and wearable technologies. Home health nurses visits are being incorporated into the DIAN protocol allowing for clinical and cognitive assessments and biospecimen samples to be collected at visits occurring in years between a participant's in-person visit. Additionally, the Cognition Core will extend the use the ARC smartphone application to include novel measures of long-term forgetting rates, which has been shown to be highly sensitive in preclinical ADAD. Another novel task is a measure of statistical learning that assesses evaluates learning rates over several consecutive days. Pilot data show that this is extremely sensitive to AD biomarkers in a sporadic AD population and is well tolerated by participants. Finally, DIAN will increase the generation and leverage of omic technologies to not only answer the main questions of the study but also generate new hypotheses and discover new biomarkers.

DIAN will continue its outreach to new families and regions of the world. The success demonstrated with DIAN's South American performance sites has laid the groundwork to explore additional sites in Chile and Puerto Rico. There is a need to expand diversity in populations minimally represented in the DIAN cohort, with discussions initiated with potential collaborators in South Africa, Morocco, and Nigeria. There is also interest in re-establishing performance sites in the Western United States serving families previously identified in the region by former DIAN sites.

DIAN will maintain its lead role in defining the profiles of targeted and novel fluid markers of neuroinflammation and neuronal and synaptic injury over the course of the disease and evaluate the ability of biomarker levels at baseline, and longitudinal change over time, to predict cognitive decline. The landscape of biomarkers is expected to change rapidly due to amyloid removal treatments approaches. During the next years, DIAN plans to explore different omic layers to better characterize ADAD, but also to identify novel biomarkers.

Two new scientific projects are being planned to examine modifiers of risk (Project 4) and immune contributors (Project 5). The aims of Project 4 include defining the clinical and molecular profile of ADAD family members at the extremes of risk and protection, and evaluating the impact of genetic, non-genetic, and epigenetic factors on AAO and progression in ADAD families. Project 5 will examine T cells in relation to increased areas of tauopathy and neurodegeneration as well as changes in T cell populations, including Aβ- and Tau-specific T populations detection in the peripheral blood.

Figure 5: DIAN Obs Comprehensive Study Approach



Technical Validation

The undertaking of the longitudinal follow-ups on DIAN Obs participants over a wide spectrum of biomarkers requires working with diverse research teams and at the same time attaining a common goal by following a unified protocol and methodology. This demands additional effort on the statistical data QC. The Biostatistics Core implements cross-Cores and Projects data QC before formal statistical analyses are conducted. These QC procedures are in addition to the standard Core- and Project-specific QC, and crucial for safeguarding the validity of statistical inferences.

The Clinical and Cognition Cores have transitioned to electronic Clinical Outcome Assessments (eCOA) using a single vendor to: minimize burden on sites, follow 21 C.F.R. § 11 (Part 11) compliance more easily, and better harmonize the collection, storage and QC assessments of DIAN Obs. Contracted Clinical Research Associates (Monitors) perform site monitoring for compliance of the DIAN Obs protocol and accurate entry of data into the electronic data capture (EDC) system. The monitors track query resolution, enrollment, and help the Clinical Core track completion rates.

The collection, processing and storage of repository samples under Good Clinical Practices (GCP) using Part 11 compliant systems ensures the high quality of samples from which biomarker measurements will be available to approved investigators, we are enabling the scientific community to nominate and validate biomarkers in a highly phenotyped and homogeneous cohort.

Sites upload data to the DIAN Central Archive (DCA) managed by Flywheel. Scans undergo an initial automated QC of the DICOM for protocol deviations and PHI, then quarantined until cleared by PET

University of Michigan) and MRI (Mayo Clinic) subcontractors. The University of Michigan reviews each PET for adherence to the specified tracer acquisition protocol including acquisition parameters, reconstruction method and parameters, smoothing kernel, application of image corrections (normalization, attenuation, scatter, randoms), pixel size and slice thickness, and upper and lower energy thresholds. For MRI, Mayo specialists review each session for protocol compliance and for image quality including intensity inhomogeneity and non-linearity issues.

Genetics Core QC procedures begin with receipt of samples when sample data is entered into the DIAN Obs database. Extracted DNA tubes are barcoded, and all subsequent DNA sample handling is tracked using barcoded tubes that are connected to the sample ID number. To avoid screening DNA samples for the wrong mutation, each site writes the familial mutation on the sample tube and on the family history form, as well as provides the Genetics Core with documentation from the physician or clinical laboratory that originally identified the mutation. If this information is missing or inconsistent, Genetics Core personnel contact the site coordinator to verify mutation information for the family. In addition to barcoded scanning and tracking we collect multiple samples from the same individual. Four tubes of whole blood are drawn at the participant initial visit, with two sent to the Genetics Core and two sent to National Centralized Repository for Alzheimer's Disease (NCRAD at Indiana University School of Medicine). Whole blood and buffy coat blood samples received at the Genetics Core are derived from independent blood draws. ADAD mutation and *APOE* genotype are verified by comparing results across whole blood WGS and buffy coat blood whole exome sequencing (WES). Sample identity is verified by PLINK or KING genetic relatedness fingerprinting analysis of GWAS genotyping array, WGS, and WES. If fingerprinting data from these samples are concordant no further analyses are performed. If they are discordant we will DNA fingerprint the sample from NCRAD. Since NCRAD whole blood samples are drawn at the same time as the Genetics Core whole blood samples, they should be concordant unless a swap/mislabeling has occurred after blood draw. All the results from these QC procedures are recorded in the DIAN Obs database.

Data Availability

Precautions to ensure confidentiality are taken by DIAN and recipients of DIAN Obs data. The final dataset is stripped of DIAN Obs identifiers and re-coded with dummy IDs prior to release and transferred only with encryption and password protection by the Biostatistics Core. For all analyses, data is provided in a blinded way with the outcome variables and then unblinded after the results of the analysis are returned to the DIAN Biostats Core. This ensures blinding, avoids bias and multiple comparisons (p-hacking).

Conclusions

The DIAN has provided seminal discoveries in AD pathophysiology and helped define the current understanding of the sequence of events that begin two decades before the first symptom onset, and progress through a decade of dementia. These advances are made on one of the world's largest deeply phenotyped cohorts of both normal brain aging and AD progression. The data and sample sets are available to address questions and hypotheses on human brain function, aging, and AD, and with further utilization, promises to have even larger impacts.

Acknowledgements

Data collection and sharing for this project was supported by The Dominantly Inherited Alzheimer Network (DIAN, U19AG032438) funded by the National Institute on Aging (NIA), the Alzheimer's Association (SG-20-690363-DIAN), the German Center for Neurodegenerative Diseases (DZNE), Raul Carrea Institute for Neurological Research (FLENI), Partial support by the Research and Development Grants for Dementia from Japan Agency for Medical Research and Development (AMED) (JP23dk0207066), the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), Korea Dementia Research Center (KDRC), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (HI21C0066), and Spanish Institute of Health Carlos III (ISCIII). This manuscript has been reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. We acknowledge the altruism of the participants and their families and contributions of the DIAN research and support staff at each of the participating sites for their contributions to this study.

A full list of DIAN members appears in the Author Contributions.

Competing Interest

RJB, Professor of Neurology at Washington University's School of Medicine (WUSM) receives lab research funding from the National Institutes of Health, Alzheimer's Association, BrightFocus Foundation, Rainwater Foundation, Association for Frontotemporal Degeneration FTD Biomarkers Initiative, Tau Consortium, Novartis, Centene Corporation, Association for Frontotemporal Degeneration, the Cure Alzheimer's Fund, Coins for Alzheimer's Research Trust Fund, The Foundation for Barnes-Jewish Hospital, Good Ventures Foundation, DIAN-TU Pharma Consortium, Centene Corporation, Tau SILK Consortium (AbbVie, Biogen, Eli Lilly and Company and an anonymous organization), the NfL Consortium (AbbVie, Biogen, Bristol Meyers Squibb, Hoffman La Roche, and an anonymous organization).
RJB has received honoraria as a speaker/consultant/advisory board member from Eisai, F. Hoffman-LaRoche, Janssen, Biogen; and reimbursement of travel expenses from Korean Dementia Association, American Neurological Association, Fondazione Prada, Weill Cornell Medical College, Harvard University, CTAD, FBRI, Beeson Foundation, Adler, Alzheimer's Association Roundtable, Duke Margolis Roundtable, Bright Focus Foundation, Tau Consortium Investigator's, NAPA Advisory Council on Alzheimer's Research. RJB serves as principal investigator of the DIAN-TU, which is supported by the Alzheimer's Association, GHR Foundation, an anonymous organization and the DIAN-TU Pharma Consortium (Active: Biogen, Eisai, Eli Lilly and Company/Avid Radiopharmaceuticals, F. Hoffman-La Roche/Genentech, and Janssen. Previous: Abbvie, Amgen, AstraZeneca, Forum, Mithridion, Novartis, Pfizer, Sanofi, and United Neuroscience). The DIAN-TU-001 Clinical Trial is supported by Pharmaceutical Partners Eli Lilly and Company, F. Hoffman-La Roche and Janssen, the Alzheimer's Association, NIH U01AG042791, NIH U01AG42791-S1 (FNIH and Accelerating Medicines Partnership), NIH R01AG046179, NIH R56AG053267, NIH R01AG053267, NIH U01AG059798, NIH R01AG068319, Avid Radiopharmaceuticals, GHR Foundation, and an anonymous organization. In-kind support has been received from CogState, Cerveau, Signant Health and Eisai Corporation. RJB is a co-founder of C2N Diagnostics and receives income from C2N Diagnostics for serving on the scientific advisory board. Washington University (WU) has equity ownership interest in C2N Diagnostics. C2N Diagnostics will be analyzing samples from the Knight Family DIAN-TU-001 trial of E2814 for primary, secondary, and exploratory endpoints. Should the DIAN-TU trials impact the value of C2N Diagnostics, WU and RJB could directly benefit. TLSB has received funding from the National Institutes of Health and Siemens; has a licensing agreement from Sora Neuroscience but receives no financial compensation; has received honoraria for lectures, presentations, speakers bureaus, or educational events from Biogen and Eisai

Genetech; has served on a scientific advisory board for Biogen; holds a leadership role in other board, society, committee, or advocacy groups for the American Society for Neuroradiology (unpaid) and Quantitative Imaging Biomarkers Alliance (unpaid); and has participated in radiopharmaceuticals and technology transfers with Avid Radiopharmaceuticals, Cerveau, and LMI. JPC serves as the chair of the American Neurological Association Dementia and Aging Special Interest Group and is on the medical advisory board of Humana Healthcare. CC receives research support from: Biogen, EISAI, Alector and Parabon. The funders of the study had no role in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. Dr. Cruchaga is a member of the advisory board of Vivid genetics, Halia Therapeutics Adx Healthcare and ADMit. JH is a paid consultant for F. Hoffmann-La Roche, Ltd., Takeda, and Lundbeck, and is on the Data Safety and Monitoring Board for Eisai. JJLG is supported by NIH-NIA (K01AG073526), the Alzheimer's Association (AARFD-21-851415, SG-20-690363), the Michael J. Fox Foundation (MJFF-020770), the Foundation for Barnes-Jewish Hospital and the McDonnell Academy. EMD received support from the National Institute on Aging, an anonymous organization, the GHR Foundation, the DIAN-TU Pharma Consortium, Eli Lilly, and F Hoffmann La-Roche; has received speaking fees from Eisai and Eli Lilly; and is on the data safety and monitoring board and advisory boards of Eli Lilly, Alector, and Alzamend. JCM is the Friedman Distinguished Professor of Neurology, Director, Knight ADRC; Associate Director of DIAN and Founding Principal Investigator of DIAN. He is funded by NIH grants # P30 AG066444; P01AG003991; P01AG026276; U19 AG032438; and U19 AG024904. RJP receives research funding from the National Institutes of Health and the National Institute on Aging. AER has received funding from National Institute on Aging, National Institute of Neurological Disorders and Stroke, Alzheimer's Association, JPB Foundation, and Donors Cure. AG serves on the scientific review board for Genentech and the scientific advisory board Muna Therapeutics. PRS receives funding from the National Health and Medical Research Council (Australia) grants 1176716 and 2022057 and the Medical Research Future Fund (Australia) grants 1200428 and 1200428. He is a director (unpaid) of the Australian Dementia Network Ltd. NCF reports consulting fees from Biogen, Eisai, Ionis, Lilly, Roche/Genentech, and Siemens – paid to UCL; he has served on a Data Safety Monitoring Board for Biogen; he acknowledges grant support from the Alzheimer's Society, Alzheimer's Research UK, Rosetrees Trust, the Sigrid Rausing Trust, the UK Dementia Research Institute and the UK NIHR UCLH Biomedical Research Centre. All other authors have no competing interests to disclose.

Supplement

Supplementary Table 1 – DIAN Obs Clinical Sites (current & former)

Site	Location	Site Leader	Activation Year	Status	# of Enrolled Participants
Washington University[i]	St. Louis, MO USA	Randall Bateman	2008	Current	124
University of California Los Angeles	Los Angeles, CA USA	John Ringman	2008	Former	52
University of Munich	Munich, Germany	Johannes Levin	2013	Current	51
University of Tubingen	Tubingen, Germany	Mathias Jucker	2012	Current	45
University College London	London, UK	Nicolas Fox	2008	Current	41
University of Pittsburgh	Pittsburgh, PA, USA	Sarah Berman	2012	Current	40
Indiana University	Indianapolis, IN USA	Martin Farlow	2008	Current	39
Edith Cowan University	Perth, Australia	Ralph Martins	2008	Current	38
Brigham & Women's Hospital	Boston, MA USA	Jasmeer Chhatwal	2008	Current	35
University of New South Wales	Sydney, Australia	Peter Schofield	2008	Current	31
Columbia University	New York, NY USA	James Noble	2008	Current	30
Butler Hospital	Providence, RI USA	John Huey	2008	Current	28
Grupo Neurociencias de Antioquia	Medellin, Colombia	Francisco Lopera	2021	Current	27
University of Melbourne	Melbourne, Australia	Colin Masters	2008	Former	24
FLENI[ii]	Buenos Aires, Argentina	Ricardo Allegri	2015	Current	20
	Salta, Argentina	Patricio Chrem	2021	Current	11
Mayo Clinic	Jacksonville, FL USA	Gregory Day	2013	Current	9
Asan University[iii]	Seoul, South Korea	Jae-Hong Lee	2015	Current	8
University of Osaka	Osaka, Japan	Hiroshi Mori	2017	Former	7
Hirosaki City University	Hirosaki, Japan	Mikio Shoji	2017	Former	5
University of Tokyo	Tokyo, Japan	Yoshiki Niimi	2017	Current	5
University of Southern California	Los Angeles, CA USA	John Ringman	2016	Former	4
Niigata University	Niigata, Japan	Takeshi Ikeuchi	2017	Current	4
Hospital Clinic i Provincial	Barcelona, Spain	Raquel Sanchez-Valle	2019	Current	2
Institute Nacional de Neuro	Mexico City, Mexico	Ana Luisa Sosa	2023	Current	0
University of Guadalajara	Guadalajara, Mexico	Victor Sanchez	2023	Pending	0
University de Sao Paulo	Sao Paulo, Brazil	Leonel Takada	2023	Pending	0
McGill University	Montreal, Canada	Pedro Neto-Rosa	2023	Current	0
				Total Enrolled:	**673**

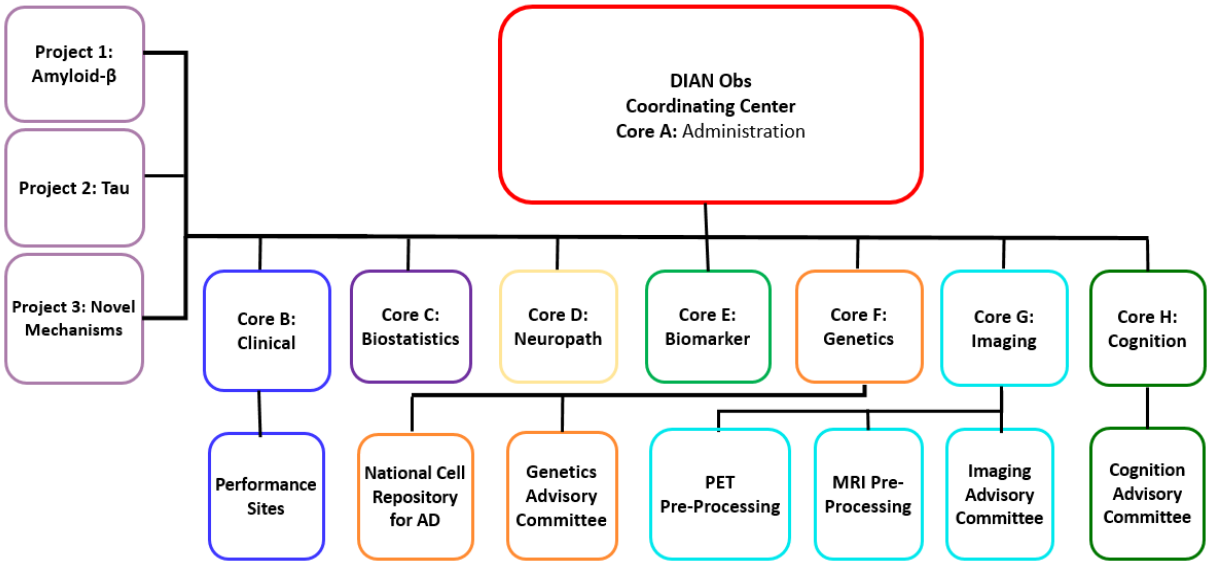
i. Washington University in St. Louis is also the DIAN Coordinating Center.
ii. FLENI Salta satellite site
iii. Asan University reactivated in 2022.

Supplementary Table 2 – DIAN Obs Participant Entry Characteristics at Enrollment

N = 673* *(Target 80% Asymptomatic, 20% Symptomatic) (*Table based on 657 participants. 16 Mutations in Process)*	**Asymptomatic** *510 (75.78%)* *457 with confirmed mutation status*		**Symptomatic** *163(24.22%)* *144 with confirmed mutation status*	
	243 (NC) (48.80%)	255 **(MC)** (51.20%)	17 (NC) (10.69%)	142 **(MC)** (89.31%)
Age, Mean (SD)	36.51 (10.95)	33.39 (9.17)	39.59 (12.56)	45.96 (9.78)
Gender (% Female)	142 (58.44%)	146 (57.25%)	9 (52.94%)	77 (54.23%)
Parental Age of Onset, Mean (SD)	47.56 (6.46)	48.20 (7.21)	46.00 (6.26)	45.47 (8.72)
Education, Mean (SD)	14.89 (2.82)	14.75 (2.85)	11.88 (3.69)	13.60(3.40)
MMSE, Mean (SD)	29.05 (1.31)	29.08 (1.21)	27.88 (1.50)	22.08 (6.99)
ApoE4+ ***1 E4***	69 (28.40%)	71 (27.84%)	4 (23.53%)	35 (24.65%)
2 E4	3 (1.23%)	2 (0.78%)	0 (0.0%)	7 (4.93%)

MC = Mutation Carrier; NC = Non-carrier
*Table statistics based on 657 participants with confirmed mutation data available as of 06/30/2023(inclusive). Of them 397 (60.43%) are mutation carriers, 260 (39.57%) are mutation non-carriers.

Supplementary Figure 1: DIAN Obs Organizational Structure



Supplementary Note 1 – Author Contributions: DIAN Consortium List

Please see 'DIAN Consortium Author List 2023.xlsx' document.

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