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## DIAN Study and Sample Description

The Dominantly Inherited Alzheimer Network (DIAN; U01AG032438) studies the development of dominantly inherited AD in verified mutation carriers in comparison with their non-carrier siblings, who serve as a naturally occurring control group. All DIAN participants are assessed longitudinally with comprehensive and state-of-the-art clinical, cognitive, genetic, imaging, and biomarker protocols, and all data are collected in a standard and uniform manner for entry into a central repository. DIAN's specific aims are:

1. Establish an international, multicenter registry of individuals (mutation carriers and noncarriers; asymptomatic and symptomatic) who are biological adult children of a parent with a known causative mutation for AD in the *APP*, *PSEN1*, or *PSEN2* genes, in which the individuals are evaluated in a uniform manner at entry and longitudinally thereafter with standard instruments to include:
  - a. The clinical and cognitive batteries of the Uniform Data Set (UDS) and additional neuropsychological and personality measures
  - b. The Alzheimer's Disease Neuroimaging Initiative (ADNI) structural (magnetic resonance imaging, or MRI), functional (18Fluorodeoxyglucose positron emission tomography, or FDG PET), and amyloid imaging (Pittsburgh Compound-B, or PIB) PET protocols
  - c. In accordance with the ADNI protocols, collection of biological fluids (blood; CSF) for DNA analysis and assays of putative biomarkers of AD
  - d. Uniform histopathological examination of cerebral tissue in individuals who come to autopsy
2. In asymptomatic individuals, compare mutation carriers and noncarriers to determine the order in which changes in clinical, cognitive, neuroimaging, and biomarker indicators of AD occur prior to the occurrence of dementia.
3. In symptomatic individuals, compare their clinical and neuropathological phenotypes with autosomally dominant Alzheimer's disease (ADAD) those of late-onset "sporadic" AD (using the data sets established by ADNI and by NACC).
4. Maintain an integrated data base incorporating all information obtained from individuals in the registry to permit analyses within, between, and among the various data domains and also to disseminate the data to qualified investigators in a user-friendly manner.

DIAN is substantially supported by ADNI's imaging protocols and by the Alzheimer's Disease Cooperative Study (ADCS). This support notably strengthens DIAN's goal to obtain data in a standard and uniform manner by providing clinical and cognitive monitoring of all DIAN sites, providing uniform neuropathologic assessments of autopsied DIAN cases, and extending the standardized procedures to image and biomarker data collection and quality control through established ADNI protocols.

### Sample Characteristics (targeted):

- Up to 400 participants, age 18 and older
- Members of a family with a known pathogenic mutation for AD; must be a child of an affected parent, although the mutation may be identified in consanguineous relatives (currently in one of three genes: *APP*, *PSEN1*, *PSEN2*).
- 80% asymptomatic and 20% symptomatic
- 50% of the asymptomatic sample will be mutation carriers and 50% will be noncarriers (consistent with autosomal dominant inheritance)

- Age distribution such that 50% are within 3 years of parental age at onset (AAO) and 30% are 3 to 10 years before parental AAO

**Inclusion Criteria:**

- Written informed consent obtained from the participant and collateral source prior to any study-related procedures.
- Participant is aged  $\geq 18$  inclusive **and** the child of an affected individual (clinically or by testing) in a pedigree with a known mutation for autosomal dominant AD.
- Participant is cognitively normal or if demented does not require nursing home-level care.
- Participant has identified two persons (minimum of one) who are not his/her full-blooded siblings and who can serve as collateral sources for the study.
- Participant is fluent in English at the 6<sup>th</sup> grade level or above [Note: Although DIAN participants initially were limited to English speakers, translations of the DIAN protocols into other languages is under way.].

**Visit Frequency:**

The follow-up interval will be determined by the age of the individual in relation to the parent's AAO. The affected parent's AAO is used as the index for the frequency of assessments as follows in table below. The age of onset of the parent is defined as the age when the *first progressive change* in cognition or behavior was noted. The clinician determines the age of onset after careful discussion with a reliable collateral source, the participant and any other sources of information that are useful for determination (e.g. medical records, other family members).

Visit frequency based on participant age and parental age at onset (*takes precedent over AAO)	
Index: Parent's age at onset of dementia	In-person assessment interval
4 or more years younger	every 3 y
3 years younger to 3 years older	annual
4 or more years older	initial in-person visit and one additional in-person visit 3 years later.
*Cognitive decline at an in person visit	annual
*Cognitive decline suspected at remote follow-up	in-person visit

**Procedures:**

All participants are expected to complete:

- Clinical assessment
- Cognitive assessments
- Blood for genetic analysis
- MRI (3T)
- FDG PET
- Pittsburgh Compound B (PIB) PET
- Lumbar puncture for cerebrospinal fluid (CSF) and fasted blood
- Autopsy (possible)

Participation in all assessments is expected but not mandatory except for the clinical and cognitive batteries. The clinical assessment, MRI, PET PIB, FDG PET, psychometric testing, and CSF studies may be completed over a few days or in several visits spread over no more than 12 weeks. All participants are invited to provide autopsy permission in the event of death.

**Please see:**

- "Data and Tissue Available for Sharing" document for a detailed list of the measures/data/tissues that are available for sharing from DIAN
- "Data and Tissue Sharing, Notifications, Publications, and Authorship Policies" for DIAN policies and procedures for data sharing and publications.
- "DIAN Data Dictionary"