**Core F: Genetics Specific Aims:**

The goal of the Genetics Core of DIAN is to provide genetic information on a sample of cognitively normal and demented individuals from ADAD kindreds, who have been characterized using a uniform protocol that includes a clinical assessment, psychometric tests, neuroimaging, and biomarker measurement as part of a longitudinal study of autosomal dominant AD. It is anticipated that collection of these data will facilitate clinical and basic science investigations of the pathogenesis of AD. An inherent strength of this application is the use of standard and uniform protocols across all components of DIAN, reducing or eliminating the variability inherent in many multi-site studies. To achieve the goals of the Genetics Core five specific aims are proposed.

1. Receive participant nonfasted blood samples from Clinical Core co-ordinators at all sites, extract the DNA and bank the DNA sample. A parallel set of blood samples will be shipped by the coordinators to the NCRAD. NCRAD will then send an aliquot of the banked DNA to the Genetics Core.

2. Determine whether each participant carries a disease causing mutation or has normal gene sequence. Prior to participant recruitment the disease-causing mutation for the participant's family will have been established through a CLIA-approved laboratory. We will sequence the exon known to contain the disease-causing mutation for each family. If we observe the expected mutation no further sequencing will be performed. If the sequence is normal we will sequence all the remaining exons of the gene to confirm that the sequence is normal and that no sample swap has occurred.

3. Determine *APOE* genotype for each participant and generate a DNA fingerprint for each sample.

4. Perform quality control analysis on NCRAD and Genetics Core samples to confirm origin of the sample. For those samples with discrepancies, a third DNA sample will be examined by extracting DNA from the buffy coat received by the Biomarker Core at the time of lumbar puncture. When all discrepancies have been resolved data is entered into the Redcap database maintained by Core C. Work with all Cores to resolve apparent genotype/phenotype discrepancies after each data freeze.

5. Obtain additional genotype data on all mutation carriers enrolled in DIAN and perform exploratory analyses to test whether novel AD genes identified through GWAS and sequencing of late onset AD cases also influence variation in age at onset of changes in biomarker endophenotypes in FAD kindreds.

**Interactions with other Grant Components**

In her role as Associate Director of the Knight ADRC and DIAN, Dr. Goate has weekly leadership meetings with Drs. Morris, Holtzman, Bateman, Buckles, and Moulder (Principal Investigator, Associate Directors and Executive Directors, respectively of DIAN). At this meeting we discuss issues critical to the success of DIAN. Dr. Goate also serves on the Steering Committee and the Resource Allocation Review Committee (Core A). Core F interacts with the clinical coordinators at each DIAN site to generate and update the pedigree structure for each family and to obtain family mutation information and documentation. Core F and Clinical Core personnel meet monthly to discuss and approve potential families for discovery genetic testing and recruitment into DIAN. Core F interacts with Mr. Scot Fague of Core C to confirm entry of data into the RedCap database and to investigate apparent discrepancies between the genotype and phenotype data after each biannual data freeze. Distribution of mutation status to any investigator requires Dr. Goate's approval to provide maximum security for this most sensitive piece of data.