NACC Project #2002-04  
Genetics of AD with Psychosis

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Collaborating centers  
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Project description  
Recent genome scans in large cohorts of Late Onset Alzheimer Disease (LOAD) families have successfully identified several chromosomal regions with significant or suggestive linkage. While substantial progress is being made, the identification of novel linkages will probably require the identification and examination of restricted phenotypes.

This study is focused on the genetic architecture of AD with concomitant psychosis (LOAD+Psychosis, LOAD+P). LOAD+P occurs in approximately 50% of LOAD subjects, and is associated with more rapid cognitive and functional deterioration. We have proposed that LOAD+P represents a distinct phenotype suitable for genetic analysis. LOAD+P demonstrates familial aggregation and has been associated with candidate gene polymorphisms.

We recently analyzed publicly available genome scan data from the NIMH AD Genetics Initiative for linkage with LOAD+P. To evaluate the results of the linkage analysis, we first performed extensive simulations, which yielded critical values for genome-wide significant and suggestive linkage of 3.18 and 1.70, respectively. We identified one significant and two suggestive linkages, in APOE4 carriers: MLS = 3.52 on chr 2p; MLS = 2.01 on chr 6q; and MLS = 1.94 on chr 21q.

This study combines ADCs and investigators with expertise in the behavioral characterization of AD subjects, psychosis genetics, ascertainment and characterization of AD sibships, and AD genetics. Psychotic symptoms are thoroughly characterized in existing cohorts of affected sib pairs at the collaborating ADCs, and new affected sib pairs will be recruited and similarly characterized for psychosis.

The specific aims of this study are to: 1) Establish a collaborative network for the recruitment, behavioral characterization, and genetic analysis of affected sib-pairs with LOAD+P; 2) Confirm evidence for linkage to chromosomes 2p and 6q using LOAD+P phenotype to partition the population; and 3) Conduct preliminary examination of novel genetic models of LOAD+P, including use of psychosis severity as a covariate in linkage analysis of LOAD, and examination of relevant sub-phenotypes. It is anticipated that this study will provide the basis for a future collaborative R01 to examine the genetic determinants of LOAD+P.

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