Genetic and Functional Analysis of Nested AD Risk Genes CTNNA3 and LRRTM3

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Research Abstract

? DESCRIPTION (provided by applicant): Genome-wide association studies (GWAS) in late-onset Alzheimer’s disease (LOAD) identified candidate genetic loci, however cannot unequivocally uncover the disease gene or variants. Further, GWAS variants do not explain the

full disease heritability. An important factor underlying this “”missing heritability”” may be rare functional disease variants of larger effect size that are missed by GWAS. Indeed, the recent identification of rare and strong AD risk variants in TREM2 via sequencing supports this hypothesis. Consequently, there are efforts for next-generation sequencing (NGS) in LOAD, however NGS comes with its own set of challenges. First, the large number of variants identified from NGS will require prioritization for downstream replication and functional studies. Second, appropriate assays are needed to test the functional consequences of these variants. Finally, NGS of large number of samples are still cost-prohibitive, precluding rapid functional assessment of variants. In this exploratory R21, we propose a cost-effective, novel alternative approach and plan to apply it to two intriguing nested candidate AD genes: CTNNA3 and LRRTM3. We will take advantage of existing and publicly available whole exome and genome sequence (WES, WGS) data to identify variants to test in our case-control cohort of ~11,000 subjects (Aim 1) and to assess the most promising, prioritized variants by in-vitro functional assays (Aim 2). Our preliminary data on the AD GWAS gene ABCA7, generated by this novel paradigm, as well as TREM2 findings, provide strong support for the feasibility of our approach. CTNNA3 and LRRTM3 reside in a linkage region of AD risk and amyloid ß levels identified independently by others and the co-PIs. They have opposite transcriptional orientation and strongly correlated gene expression levels in our published data, suggesting functional interactions. Both genes are implicated in synaptogenesis. We identified intronic variants in CTNNA3 that account for our Aß linkage signal. LRRTM3 influences APP processing. We showed protein interactions between LRRTM3, APP and BACE1 and herein demonstrate a role in long term potentiation. In summary, the nested CTNNA3/LRRTM3 are excellent candidate AD genes with potential roles in APP processing and/or synaptic physiology. We and others reported association of variants in both genes with AD risk, but replication has been inconsistent, which may in part be due to the lack of an assessment of rare variants. Our aims are: 1) To test rare variants in CTNNA3/LRRTM3 identified from 3 NIH funded NGS data, EVS (WES 4300 Caucasians, 2203 African-Americans), ADNI (WGS 246 Controls, 359 mild cognitive impairment, 184 AD), ADSP (584 subjects from 111 AD families), for AD risk association in our 11,000 subjects. 2) To test putative functional variants in CTNNA3/LRRTM3 in APP processing, cell toxicity and synaptic integrity. This exploratory R21 will enable a thorough and hypothesis-based study of two intriguing candidate AD genes and will also establish our cost-effective approach as a paradigm-shifting alternative to assess the deluge of genes being nominated in AD and other complex diseases.

Further information available at:

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