APOEomic: Searching for APOE interacting risk factors using omics data

https://neurodegenerationresearch.eu/survey/apoeomic-searching-for-apoe-interacting-risk-factors-using-omics-data/

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Country

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Title of project or programme

APOEomic: Searching for APOE interacting risk factors using omics data

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NIH (NIA)

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01/07/2013

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4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Biotechnology... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Genetics... Human Genome... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION (provided by applicant): Recently, several genome-wide association studies (GWAS) have been published for late onset Alzheimer's disease (LOAD). Each GWAS that has been published to date has mapped the Apolipoprotein E (APOE) locus as the strongest LOAD risk signal within the human genome. This has led us and others to hypothesize that this large signal can 1. Overwhelm other smaller effects that are in epitasis with the APOE E4 locus and 2. Be de-convoluted into multiple risk loci mapping to the same area of the genome. The first hypothesis is plausible, considering that in our previous GWAS we mapped an effect that was only present in APOE E4 positive individuals. The second hypothesis is also valid in that this type of effect (i.e. multiple risk loci mapping to the same region of the genome) has been seen in other neurological diseases. For example, for Fronto-temporal Dementia Linked to Chromosome 17 (FTDP-17), mutations in both the microtubule associated protein Tau gene (MAPT) as well as Progranulin (PRGN) have been found. Both MAPT and PRGN map within the same linkage peak on chromosome 17. Thus, we propose to leverage our genome-wide and Next Generation Sequencing (NGS) genetic data, as well as transcriptome and proteome datasets to map novel risk loci for LOAD that are acting either in epistasis with or independently of the APOE E4 allele. We propose the following: To test our APOE E4 independent effects, we will perform additional NGS sequencing within the same region of chromosome 19 to capture additional effects (Aim 1a). We will also genotype the variants we found from our NGS in additional case control samples to determine whether they act independently of APOE E4 to increase risk for disease (Aim 1b). To follow our APOE E4 epistatic effects, SNPs which we found to act in conjunction with APOE E4 will be followed by examining an additional cohort (Aim 2a) as well as sequencing within the region to find additional variants (Aim 2b). Finally, we will map the downstream effects of any variants we map in Aims 1 or 2 by examining transcript expression and protein profiles (Aim 3), Our collaboration possesses the unique skills and datasets to perform this work. Drs. Huentelman and Myers have worked together for the greater part of their careers and have co-authored many publications using similar techniques as those proposed in this application. They have access to a unique cohort of ~ 1600 neuropathologically verified individuals, which will allow for both the analysis of risk variation as well as the downstream changes of those variants. They have recruited an additional cohort of ~ 18,000 clinically characterized samples from the University of Cardiff to replicate any effects. They also have access to both the computational power (48-core / 576GB memory computer and a separate 2,700-core cluster through Tgen and one of 5000 CPU at the University of Miami) as well as the expertise to execute the bioinformatics analysis involved in all Aims.

Lay Summary

PUBLIC HEALTH RELEVANCE: Our proposal seeks to understand whether there are additional risk genes and variants which act either independently or in synergy with the APOE E4 gene variant on chromosome 19. We will examine 1) Genome- wide association data, and 2) Novel DNA changes we have found through Next Generation and Sanger sequencing analysis looking at both risk for Alzheimer's disease as well as changes in gene and protein expression. We anticipate that several of these novel variants are involved in risk as well as changing the downstream function of their target genes.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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2016

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N/A

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N/A