Mutational and Functional Analysis of Genes Identified by GWAS Studies of Alzheimer’s Disease

https://www.neurodegenerationresearch.eu/survey/mutational-and-functional-analysis-of-genes-identified-by-gwas-studies-of-alzheimers-disease/

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Country

Canada

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Mutational and Functional Analysis of Genes Identified by GWAS Studies of Alzheimer's Disease

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CIHR

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The project/programme is most relevant to:

Neurodegenerative disease in general

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Research Abstract

Lay Summary

Alzheimer disease (AD) is an incurable neurodegenerative disorder which, as the 4th leading cause of death in adults, is a growing unmet medical need worldwide. Epidemiological studies have identified age and family history as principal risk factors, with genetic factors contributing ~40% of this risk. Half of the genetic risk is attributable to variants in APP, PS1, PS2 or APOE. We have shown that mutations in these genes cause AD by inducing accumulation of Abeta – a neurotoxic aggregation-prone proteolytic fragment of APP. Although the accumulation of Abeta is a widely accepted pathophysiological hallmark of AD, it does not explain several other features of AD (e.g. changes in lipid metabolism, defective autophagy, and progressive spreading of pathology across the brain). To identify other genes potentially involved in these unexplained aspects of AD, we have used a hypothesis-free GWAS approach. This has revealed that AD is associated with SNPs in 9 loci. The current program will focus on 4 of these loci because analysis of their genomic architecture reveals that: i) they each contain only a single gene (making them TRACTABLE GENETIC TARGETS); and ii) these genes had NOT PREVIOUSLY BEEN PREDICTED to play a causal role in AD. Significantly, we have also shown that these genes do not affect Abeta production (indicating that they constitute PROMISING LEADS INTO NOVEL ASPECTS OF AD BIOLOGY). We will identify: a) the disease-causing variants; b) the molecular effects of these variants; and c) the pathways within which these genes work to cause AD. This experiment is TRACTABLE BECAUSE WE HAVE ASSEMBLED NOVEL, CUTTING-EDGE biophysical, molecular, cellular and animal model tools. We will use these tools to assess the impact of these genes on currently unexplained features of AD. The discovery of AD-causing variants and understanding their role in AD will have MAJOR TRANSLATIONAL IMPACT by providing the previously unavailable basis for novel diagnostics and treatments.

Further information available at:

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