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Alzheimer's disease genetics, a multiplex model

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Abstract

Statement of the Problem: As an aging population alzheimer's disease (AD) is a growing world-wide public health concern, with 13.9 million people expected to be living with dementia by 2060. Familial forms of AD follow a Mendelian inheritance, with heritability estimates (58-79%) showing a strong genetic component to sporadic AD. Multiplex Model: Over 40 genetic loci are associated with AD, and with polygenic risk profiling we are now able to correctly predict disease status around 80% of the time. Our analyses identify six biological pathways (immunity, endocytosis, cholesterol transport, ubiquitination, amyloid-β and tau processing) as pivotal in disease development. Epidemiological research also highlights a significant vascular component to AD development. The multiplex model assumes that changes to some, or all, of these model components act together to trigger a disease cascade, which ultimately results in the cell/synaptic loss observed in AD. AD could be triggered by a number of different patterns of deficits that may differ between tissues and over the course of disease development. Multi-omics approaches (Figure 1) allowed the identification of a gene-network enriched for both common and rare variants in AD. Conclusion & Significance: Genetic and environmental studies have changed our perception of AD, highlighting its multifactorial complexity. Application of genetic data to future research may include selection/enrichment for clinical trials and precision medicine, understanding of early disease development through risk related epidemiology, selective biomarkers and induced pluripotent stem cell models for single cell, multi-tissue/organoid and whole system chimeric analyses.

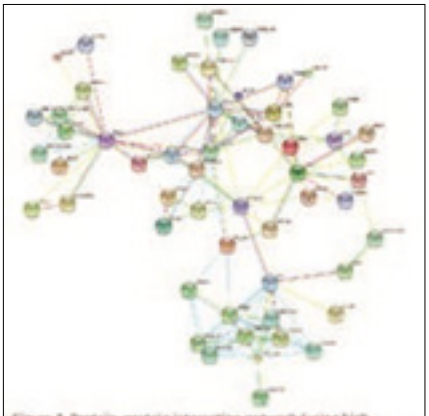

Figure 1. Protein-protein interaction network [using high-confidence human interactions from the STRING database] of 56 genes enriched for both common and rare variants associated with Alzheimer's disease risk. Colors of edges refer to the type of evidence linking the corresponding proteins: red, gene fusion; dark blue, co-occurrence; black, coexpression; magenta, experiments; cyan, databases; light green, text mining; mauve, homology. TREM2, PLCG2, and ABI3 are highlighted by red circles, SYK, CSF1R, and TYROBP are highlighted by blue circles, and INPP5D, SPI1, and CD33 identified as common variant risk loci are highlighted by black circles.

Biography

Dr Rebecaa Sims, is a Research Fellow at Cardiff University in Division of Psychological Medicine and Clinical Neurosciences. She is a neurogeneticist with over ten years experience in neurodegeneration research. She has a particular interest in the generation of large-scale powerful datasets and data analysis. She has a significant experience of International collaboration, maintaining networks and producing high quality publications. Her recent work has included leading genome-wide association projects, such as exome chip array studies. Her current work focuses on the translation of genetic findings to disease relevant induced pluripotent cell models, and utilizes Next Generation Sequencing (NGS) technology to identify novel risk loci for early-onset Alzheimer's disease..

Biography

1. Genetic risk of dementia modifies obesity effects on white matter myelin in cognitively healthy adults.
2. The multiplex model of the genetics of Alzheimer's disease
3. Genetic risk of dementia modifies the impact of obesity on limbic white matter and spatial navigation behavior in cognitively healthy adults

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