Defining Genetic Polygenic and Environmental Risk for Alzheimer’s disease using multiple powerful cohorts,focussed Epigenetics and Stem cell metabolomics

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Principal Investigators

Prof. Dr. J. van Swieten/ van der Flier

Institution

VU medisch centrum

Contact information of lead PI
Country

Netherlands

Title of project or programme

Defining Genetic Polygenic and Environmental Risk for Alzheimer's disease using multiple powerful cohorts,focussed Epigenetics and Stem cell metabolomics

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ZonMw

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01/12/2014

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3.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Through the pooling of our existing resources and novel analytical biostatistical/informatics methods, we will identify several new susceptibility genes for Alzheimer's disease (AD), produce the most comprehensive estimates of AD genetic risk available worldwide, test for G x E relationships in the largest sample of epidemiological cohorts collaborating to date and undertake focussed studies taking genetics and environmental findings into novel areas of research, using metabolomics, epigenetics and reprogrammed induced pluripotent stem cells (iPSC). We will pool our (i) SNP GWAS and replication data on a sample of 29,880 cases and 62,064 controls ; (ii) exome chip GWAS on a sample of 18,051 cases and 53,130 controls iii) whole exome sequencing on a sample of 4757 cases and 3800 controls with sample matching to control for population stratification, iv) re-imputation and analyses of all GWAS based on best estimates of genetic architecture and complex statistical analyses including: gene-wide, interaction and pathway approaches, (v) targeted resequencing and replication genotyping in a sample of up to 14,271 cases and 17,696 controls. We anticipate the identification of at least 10 new loci associated with AD. We will use these powerful resources to construct novel polygenic scores to define levels of AD risk both overall and within functional pathways implicated. We will take these polygenic score analyses and identify those at greatest and least risk of AD (overall and in pathways). We will study the interplay between genetic and environmental risk factors in our collection of epidemiological cohorts (i.e. the Rotterdam study, the 3C study, FHS, AGES, CHS, Cache County, CFAS, CC75C, UK BIOBANK, ALSPAC, Lothian, MAS, OATS & SCS), to assess relationships between genetic risk and environmental factors, exploiting a powerful cohort sample comprising 588,088 individuals from 14 cohorts, with the majority of the participants aged over 65. We will use biomarker data and characterise these individuals to understand triggers leading to AD. Finally, we will undertake focussed studies of iPSC metabolomics as a function of high and low genetic risk and epigenetics on higly selected brain regions with a uniform cell type, testing methylation changes on AD risk loci in those at high and low AD genetic risk to improve our understanding of the factors that trigger AD.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
Netherlands

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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N/A

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