# Functional Validation of the CD2AP Susceptibility Network in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/functional-validation-of-the-cd2ap-susceptibility-network-in-alzheimers-disease/

**Principal Investigators**

SHULMAN, JOSHUA M.

**Institution**

BAYLOR COLLEGE OF MEDICINE

**Contact information of lead PI**
**Country**

USA

**Title of project or programme**

Functional Validation of the CD2AP Susceptibility Network in Alzheimers Disease

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

€ 2,314,971.56

**Start date of award**

01/05/2016

**Total duration of award in years**

1

**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)... Brain Disorders... Dementia... Genetics... Human Genome... Neurodegenerative... Neurosciences

**Research Abstract**

? DESCRIPTION (provided by applicant): Genome-wide association studies (GWAS) have recently identified variants at 22 genomic loci associated with Alzheimer's disease (AD) susceptibility. Similar to other common, complex genetic disorders, AD is characterized by substantial locus heterogeneity and polygenic susceptibility. The critical next steps include understanding gene mechanisms and elucidating the genetic interactions that define functional pathways mediating AD risk. We have developed a successful cross-species validation strategy that links emerging susceptibility candidates to functional dissection of genes and pathways in the fruit fly, Drosophila melanogaster. Our studies to date of candidate genes from AD GWAS implicate a susceptibility network comprised of CD2AP and related mediators of cell adhesion, including CASS4, FERMT2, and PTK2B, and endocytosis, including PICALM, BIN1, AP-2?, and RIN3. The encoded proteins recapitulate a putative interaction network, supporting their coordinate function in nervous system health and disease. In preliminary studies, we further show that CD2AP, similar to other network candidates, localizes to the synapse, associates with synaptic vesicle proteins, and loss-of-function both impairs synaptic plasticity and enhances the neurotoxicity of Tau, which forms neurofibrillary tangle pathology characteristic of AD. The overall goal of this proposal is to extend our understanding of the genes and functional interactions that define the CD2AP susceptibility network and its contribution to AD pathogenesis. We hypothesize that dysfunction within the CD2AP regulatory pathway attenuates synaptic efficacy, and leads to enhanced vulnerability to Tau- induced neuronal injury in AD. We will first (AIM 1) exploit the rapid and powerful genetics available in flies for systematic functional dissection of conserved genes implicated in the CD2AP susceptibility network including epistatic mapping of pathway interactions. Next (AIM 2), we will employ mouse models to further elucidate the role of CD2AP at mammalian synapses and in Tau-mediated neurodegeneration. Lastly (AIM 3), for translation of our findings, the animal model studies will be coupled with analyses in human cohorts, examining regulatory changes in transcripts and proteins in relation to age-related synaptic loss, AD neuropathologic burden, and resulting cognitive impairment. IMPACT: By integrating emerging human genomic data with functional investigation in flies, mice and human brains, we will elucidate the CD2AP susceptibility network and define its role in synaptic health, Tau pathology, and AD risk, delivering a rich portfolio of preclinical data to support new therapeutic targets.

**Lay Summary**

PUBLIC HEALTH RELEVANCE: Alzheimer's disease is a devastating and incurable neurodegenerative disorder projected to affect 13 million individuals in the US by 2050. Integrating recent advances in human genetics with innovative model organism studies, we will elucidate novel mechanistic pathways responsible for Alzheimer's disease risk. An improved functional understanding of Alzheimer's disease genetic risk factors holds enormous potential for therapeutic breakthroughs.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Alzheimer's disease & other dementias

**Years:**
2016

**Database Categories:**
N/A

**Database Tags:**
N/A