# Function of the TREM2 R47H variant associated with risk of Alzheimers disease

https://www.neurodegenerationresearch.eu/survey/function-of-the-trem2-r47h-variant-associated-with-risk-of-alzheimers-disease/

**Principal Investigators**

HAMERMAN, JESSICA A

**Institution**

BENAROYA RESEARCH INST AT VIRGINIA MASON

**Contact information of lead PI**
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USA

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**Research Abstract**

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is a major clinical problem in the United States and throughout the world. Recent reports from the National Center for Health Statistics state that approximately 5.4 million people have AD in the United States, where it is the 6th leading cause of death. While great strides have been made over the last decades in

understanding the pathogenesis of AD, there are still many unresolved issues and no effective treatments. The identification of genetic associations with AD has led to a greater understanding of the mechanisms involved in disease development. Recently, two studies have independently identified variants in the TREM2 gene with increased risk of late onset Alzheimer's disease. The TREM2 gene encodes a cell- surface receptor expressed on some myeloid cells, including microglia, the macrophage-lineage cells of the brain. Studies in mouse systems have shown that TREM2 can function in microglia and macrophages to inhibit inflammatory responses as well as promote the phagocytosis of apoptotic neurons. As there has been much discussion of whether AD has an inflammatory component, the association of a TREM2 variant with AD supports the idea that increased inflammatory responses of microglia may promote AD development. The predominant TREM2 variant identified as increasing risk of late onset AD encodes a single amino acid change (R47H) in the extracellular portion of the TREM2 receptor. We hypothesize that the TREM2-H47 variant leads to increased inflammation in the brain that promotes late onset AD. Our aim is to test the hypothesis that the TREM2-H47 variant has a reduced ability to inhibit inflammatory responses, promote phagocytosis, and bind sulfated N-acetyllactosamine ligands. We will 1) generate TREM2-Fc fusion proteins of the human and mouse non-risk (TREM2-R47) and risk (TREM2-H47*) variant of TREM2 and determine binding kinetics and specificity using surface plasmon resonance and glycan arrays, 2) express the non-risk and risk variants of human and mouse TREM2 in macrophages and microglia, and compare their ability to inhibit Toll-like receptor induced inflammation, and 3) express the human and mouse non-risk and risk variants of TREM2 in CHO cells and in DAP12-deficient macrophages and compare their ability to bind to and induce phagocytosis of apoptotic cells. Understanding how the R47H variant affects TREM2 function will yield important insights into the role of microglia and inflammation in the pathogenesis of AD. Additionally, the results from these experiments will allow us to better understand how to therapeutically target TREM2 for AD treatment. Therefore this is a high priority area of research in AD centered around the novel finding that TREM2 participates in AD pathogenesis.

**Further information available at:**

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