

## GENETICS

# Endophenotypes of Late-Onset Alzheimer's Disease in Mouse Models Expressing IL1RAP Risk Alleles

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**Abstract**

**Background:** It is estimated that by 2050 the number of Alzheimer's disease (AD) patients will exceed 12 million, 95% of which are sporadic, late-onset AD (LOAD). Without novel therapeutics, unlike other age-related disorders, LOAD mortality will continue to increase. But as next-generation-sequencing technologies improve, human disease risk factors are emerging, correlated to the prevalence and severity of disease. Alterations in the *IL1RAP* gene are found to be a strong risk factor for amyloid accumulation in LOAD patients. IL1RAP is a membrane-bound IL-1 $\beta$  receptor expressed in most tissues, including CNS-specific astrocytes, microglia, and neurons, relaying immune signals via NF- $\kappa$ B and MAPK transcription factors. Further, a neuron-specific isoform, *IL1RAPb*, has been identified and found to disrupt MYD88 scaffolding. As a suspected regulatory mechanism for IL-1 $\beta$  vulnerability, IL1RAP may prove to be a potential target for intervention against AD.

**Methods:** Mouse models of LOAD are underutilized and in short supply. Most popular AD strains express amyloid-related, familial AD transgenes and fail to address the heterogeneous dysregulation observed in human disease. For better preclinical models of LOAD, MODEL-AD has developed novel mouse strains incorporating genetic and environmental risk factors identified from human data sets. To investigate how IL1RAP specifically impacts disease, we have designed two strains expressing loss-of-function *Il1rap* transcripts- a whole body *Il1rap* knockout and a neuron-specific *Il1rapb* conditional knockout.

**Results:** We generated mouse strains on a LOAD-relevant genetic background (*APOE $\epsilon$ 4*, *Trem2\* $R47H$* , and humanized *App*) and knocked-out *Il1rap* or *Il1rapb* transcripts which produced gene expression signatures in the brain more similar to those seen in human AD patients. To exacerbate this phenotype, we utilized sterile-infection and high-fat diet insults which produced normal immune responses

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evidenced by increases in plasma TNF $\alpha$ , IL-6, and IL1RAP agonist, IL-1 $\beta$ . Both strains also showed an increase in peripheral biomarker neurofilament light chain (NfL), suggesting downstream neuronal injury. More detailed, CNS-specific characterization of the many aspects of IL1RAP function are still in progress.

**Conclusion:** Here we present two novel mouse strains of LOAD, expressing human-relevant genetic backgrounds aimed at investigating IL1RAP function as a model of human disease and potential target for therapeutic intervention against neurodegeneration.