ELUCIDATING THE COMPLEX ROLE OF ABCA7 IN LATE-ONSET ALZHEIMER’S DISEASE

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ABSTRACT

Background: Genome-wide association studies (GWAS) identified a locus containing the ATP binding cassette subunit A7 (ABCA7) gene as increasing risk for Alzheimer’s disease (AD). (PANEL 1). ABCA7 proteins transport various molecules across extra and intra-cellular membranes. ABCA7 is a part of the JAX strain and has high expression in hematopoietic lineage cells including natural killer cells and macrophages. More recently, ABCA7 expression has been shown in brain cells including neurons, astrocytes, microglia, endothelial cells and pericytes. However, the mechanisms by which variations in ABCA7 increase risk for AD are not known.

Methods: The IU/JAX/PITT MODEL-AD Center prioritized the ABCA7 variant in ABCA7 (Abca7*A1527G) as a putative LOAD risk factor. CRISPR/Cas9 was used to introduce Abca7*A1527G variant on to B6.APOE4.Trem2*R47H (termed LOAD1, PANEL 2) and transcriptional profiling of brain hemispheres from mice at 12 mos using an established phenotyping pipeline to LOAD2. Abca7*A1527G was then incorporated into B6.TREM2*A1527G mice (termed LOAD3) to further evaluate the contribution of Abca7*A1527G to LOAD (PANEL 4). Female and male LOAD2, Abca7*A1527G and control mice are being characterized using a combination of a cross-sectional and longitudinal design.

Results: Brain transcriptional profiling at 12 mos showed Abca7*A1527G induced gene expression changes that are similar to some of those observed in human AD (PANEL 3). Enriched pathways included insulin receptor signaling, and granulocyte and neutrophil migration that include Tsf2m, Trem1, CNTF, and endothelial (Pecam-1) related genes (PANEL 3). LOAD2, Abca7*A1527G mice showed no cognitive deficit at 12 mos but an uncontrolled brain glycine and regional perfusion was observed in a sex and age dependent manner (PANEL 4.6). Consistent with the uncontrolled phenotype, 6, 11, 10, and TNFs were elevated in plasma. Interestingly TNFα, primarily expressed by microglia in the brain, was decreased. Also, by 12 mos, the density of neurons, astrocytes and microglia were reduced. Additional timepoints (18-24 mos), and assessment of LOAD2, Abca7*A1527G mice fed a high-fat diet, are in progress.

Conclusions: Data support Abca7*A1527G as a risk for LOAD that exerts its effect through interactions between cerebrovasculature, microglia and peripheral immune cells.

PANEL 1: GENOME WIDE ASSOCIATION STUDIES IDENTIFY ASSOCIATION BETWEEN ABCA7 LOCUS AND ALZHEIMER’S DISEASE

A missense variant (rs3735224, p.Gly1527Ala, OR = 1.2) was identified in a large-scale GWAS at a genome-wide significance level (p-value = 5.0×10−7) [2]. This eQTL (https://gexplot.org/home/snp/rs3735224) variant encodes a glycine to alanine substitution at amino acid position 1527 in exon 32 of the canonical transcript and is associated with decreased expression of ABCA7, transcripts in multiple brain regions.

PANEL 2: CREATION AND VALIDATION OF THE Abca7*A1527G ALLELE

The Abca7*A1527G allele was introduced into the LOAD1 mouse strain (B6.APOE4.Trem2*R47H, LOAD1) from JAX strain (stock no. 029709) by utilizing CRISPR/Cas9 endonucleases in mediated genome editing. Based on human to mouse RNA and protein alignments, the equivalent amino acid in mouse is 1541 in exon 32. For consistency and ease of comparison, we refer to this variant as Abca7*A1527G. Cohorts of male and female LOAD1, Abca7*A1527G, LOAD1 and B6 controls mice were aged to 3 months and Abca7*A1527G expression levels in brains assessed by RNA-seq.

PANEL 3: Abca7*A1527G MODIFIES GENES RELEVANT TO LOAD AT 12 MONTHS

Cohorts of male and female LOAD1, Abca7*A1527G mice were aged to 4, 8 and 12 months and LOAD1 relevant genes assessed in the brains using a Nanostring panel. Alignment to human AD data show Abca7*A1527G causes changes in AMP-AD clusters relating to the immune system, cell cycle, organelle biogenesis and cellular stress response.

PANEL 4: PHENOTYPING LOAD2, ABCA7*A1527G

To further evaluate the role of Abca7*A1527G in LOAD, we created a quadruple homozygous strain B6.APOE4.Trem2*R47HAbca7*A1527G (LOAD2, Abca7*A1527G, available as JAX Stock No. 036243). Cohorts of male and female LOAD2, Abca7*A1527G and LOAD2 controls are being characterized using a combination of a cross-sectional and longitudinal design.

PANEL 5: PET/CT REVEALS Abca7*A1527G DRIVES UNCOUPLING OF GLUCOSE UPTAKE AND BLOOD FLOW

Glucose uptake (18F-FDG) and tissue perfusion (64Cu-PTSM) were determined in 4mo and 12mo female (red) and male (blue) LOAD2 (A-C) and LOAD2, Abca7*A1527G (D-F) for all brain regions. Uncoupling analysis (B,E,F) of 28 brain (56 bilateral) regions in male (blue) and female (red) mice in 12mo vs 4mo for LOAD2 (B) and LOAD2, Abca7*A1527G (E). Univariate statistical modeling of the regions to the 4 mo controls are shown at 3 bregma targets for LOAD2 (C) and LOAD2, Abca7*A1527G (F). Data are presented as means±SD, and show type 1 uncoupling (quadrant 4) for LOAD2 and Type 2 uncoupling (quadrant 2) for LOAD2, Abca7*A1527G.

CONCLUSIONS

- Transcriptional profiling predicts the Abca7*A1527G variant increases risk for LOAD through perturbations in a variety of processes including immune, vascular, cell stress responses, insulin signaling, and granulocyte function.
- The combination of APOE4, Trem2*R47H, H2Aj, and Abca7*A1527G variants induced sex-, age-, and genotype-dependent LOAD-relevant neuropathological uncoupling which is accelerated relative the LOAD2 base strain.
- See P4-003 (Rizzo et al) for more details on LOAD2

FURTHER INFORMATION

- gareth.howell@iu.edu and pttrito@iu.edu
- MODEL-AD: model-AD.org
- AD Knowledge portal: acknowledgeportal.org
- AD Data Explorer: modeladexplorer.org

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ADDITIONAL INFORMATION

- **SUPPORTING INFORMATION**
  - **[Supporting Information](#)"