ASSESSING THE ROLE OF PLCG2*M28L RISK IN A NOVEL MOUSE MODEL LATE-ONSET ALZHEIMER’S DISEASE
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INTRODUCTION
Alzheimer’s disease (AD) is the most common cause of dementia, and 95% of patients have sporadic Late-Onset AD (LOAD). MODEL-AD has recently characterized mice LOAD1 mice which contain apolipoprotein E4 (APOE4), the greatest genetic risk factor of LOAD, and the R47H variant on the triggering receptor expressed on myeloid cell 2 (TREM2R47H). In addition, GWAS studies have also identified the M28L variant of PLCG2 (PLCG2M28L), which plays a crucial role in signal transduction during phagocytosis, and introduced this variant to LOAD1 (LOAD1.PLCG2M28L). Clinically, environmental risk factors such as diet and exercise can significantly impact overall health including cognition and brain connectivity. Therefore, we hypothesize that combining LOAD risk alleles will result in AD-related cerebral metabolic and blood flow patterns, and that addition of a high fat diet will accelerate AD development. To test this, we measured neurovascular uncoupling and brain connectomics in novel LOAD1 and LOAD1.PLCG2M28L mouse models to assess their alignment human to genetic and environmental risk factors with and without a high fat diet.

METHODS AND MATERIALS
All studies were carried out in accordance with, and approval of, the IACUC of Indiana University School of Medicine and National Research Guide of the Care and Use of Laboratory animals, and were conducted according to the ARRIVE guidelines[1], where mice were randomized by sex and genotypes. APOE4, TREM2R47H, and PLCG2M28L allele were incorporated into C57BL/6J (B6) mice to produce LOAD1 (N=41) and LOAD1.PLCG2M28L (N=71) mice. Mice of both sexes were fed control (male n=33, female n=25) or high fat diet (HFD) (male n=27, female n=27). Mice were administered 3.7-7.4 MBq of 18F-FDG (ip) and were allow 30 min conscious uptake[2], post-isoflurane (2-3%) anesthesia, and high fat diet (HFD). (A) network degree, (B) negative nodal strength.

RESULTS

Figure 2. Representative 18F-FDG PET/CT of LOAD1 and LOAD1.PLCG2M28L mice at 12mo on control diet (left) compared to HFD (right) at bregma targets.

Figure 3. Representative 64Cu-PTSM PET/CT of LOAD1 and LOAD1.PLCG2M28L mice at 12mo on control diet (left) compared to HFD (right) at bregma targets.

Figure 4. Uncoupling analysis bi-directional z-score plots of 28 brain (56 bilateral) regions in male and female mice on diet control or HFD. Post segmentation, subject by region data are subjected to bi-directional uncoupling analysis by comparing p-score relative to the male diet subjects. In a parallel analysis, these same regions are subjected to consensus graph theory analysis, where adjacency matrices are modularized by multi-resolution consensus cluster analysis, subjected to multi-p-value thresholding, and estimates of cluster-coefficients, degree, density, and nodal strength measured. Post-thresholding, statistical analysis of MRCC matrices aligned to the male control diet group, and unaligned ANOVA conducted with sex and diet as factors for the main effect.

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REFERENCES

CONCLUSION
The combination of APOE4, TREM2R47H genes in LOAD1 mice with HFD induced diet-dependent LOAD-relevant neurovascular uncoupling and network changes consistent with LOAD; however, the addition of PLCG2M28L on LOAD2 did not enhance the disease phenotype, suggesting that the TREM2 dependent signaling was impaired when mice were fed a HFD.