**Sample Extraction:**WT, Abca7-V1599M, 5xFAD and 5xFAD;Abca7-V1599M female and male mice were selected for quantitative biochemical analysis of amyloid beta (Aβ) in the brain and Neurofilament Light Chain (NfL) in the brain and plasma at 4 and 12 months. At the above ages, mice were euthanized via CO2 inhalation. After intracardial blood collection, mice underwent transcardial perfusion with 1X phosphate buffered saline (PBS). Brains were removed and hemispheres separated along the midline. Left hemisphere was dissected and hippocampus and cortex were snap frozen.

**Sample Preparation:** Brain samples were pulverized using a Bessman Tissue Pulverizer kit. Pulverized hippocampal and cortical tissue was homogenized in Tissue Protein Extraction Reagent (TPER). The homogenized samples were centrifuged at 100,000 g for 1 hr at 4°C to generate TPER-soluble fractions. For formic acid-fractions, pellets from TPER-soluble fractions were homogenized in 70% formic acid centrifuged again. Formic acid neutralization buffer was used to adjust pH prior to running ELISAs. Quantitative biochemical analyses of human Aβ soluble and insoluble fraction levels were acquired using the V-PLEX Aβ Peptide Panel 1 (6E10) (K15200G-1; Meso Scale Discovery, Rockville, MD) while analysis of NfL in the brain was done using the R-Plex Human Neurofilament L Assay (K1517XR-2; Meso Scale Discovery, Rockville, MD). Plates were analyzed on the MS2400 imager (MSD).

For plasma NfL quantification, collected blood was centrifuged at 4000 RPM for 20 minutes at 4°C. Plasma was then collected and quantitative biochemical analysis of NfL in plasma was performed using the same R-Plex Human Neurofilament L Assay as for brain samples.

**Analysis:** Protein in the insoluble fraction of micro- dissected hippocampal and cortical tissue were normalized to its respective brain region weight, while protein in soluble fractions were normalized to the protein concentration determined via Bradford Protein Assay. Biochemical data were analyzed using Student’s t- test, one-way ANOVA, or two-way ANOVA via Prism v.9 (GraphPad, La Jolla, CA). Bonferroni- Šídák and Tukey’s post hoc tests were utilized to examine biologically relevant interactions from the two-way ANOVA. Where sex-differences are apparent, a Student’s t-test was used within genotype group. \*p ≤ 0.05, \*\* p ≤ 0.01, \*\*\*p ≤ 0.001, \*\*\*\*p ≤ 0.0001. Data are presented as raw means and standard error of the mean (SEM).