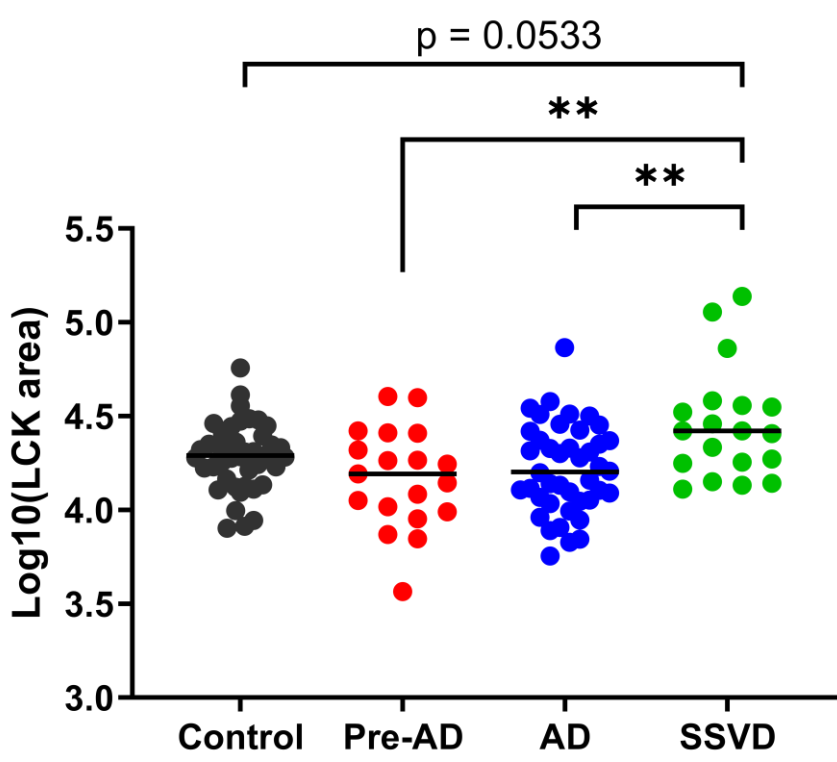
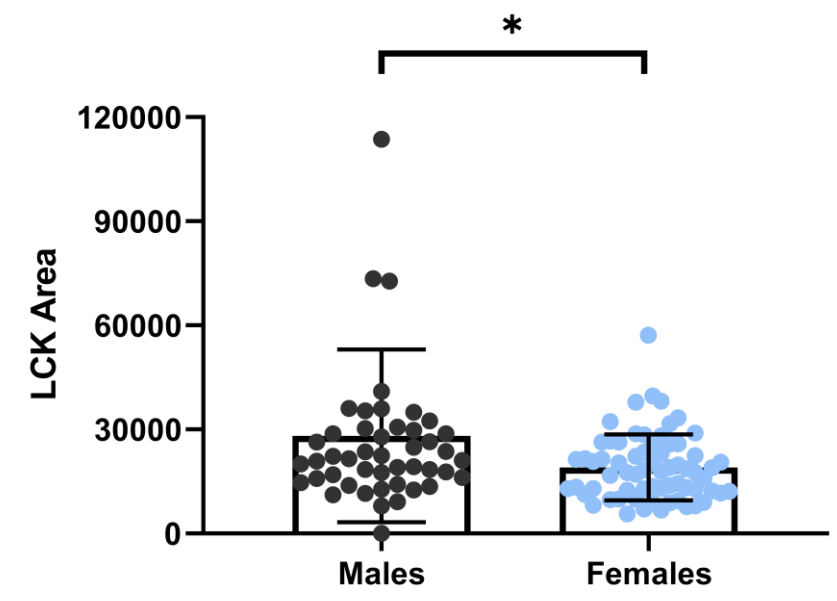
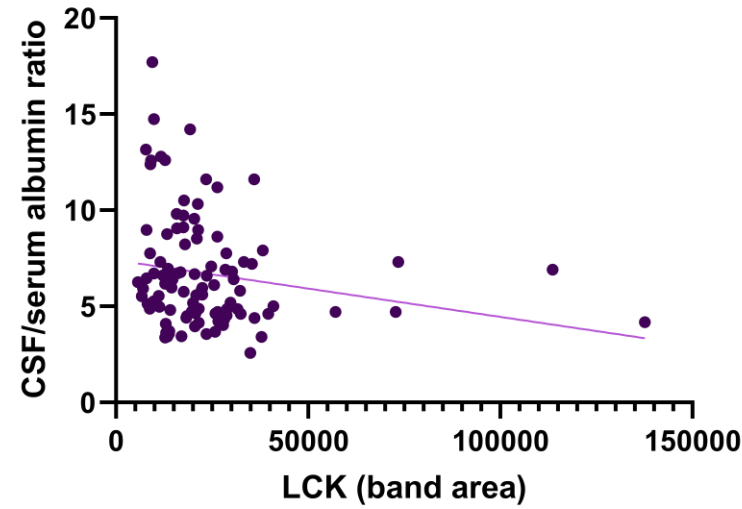
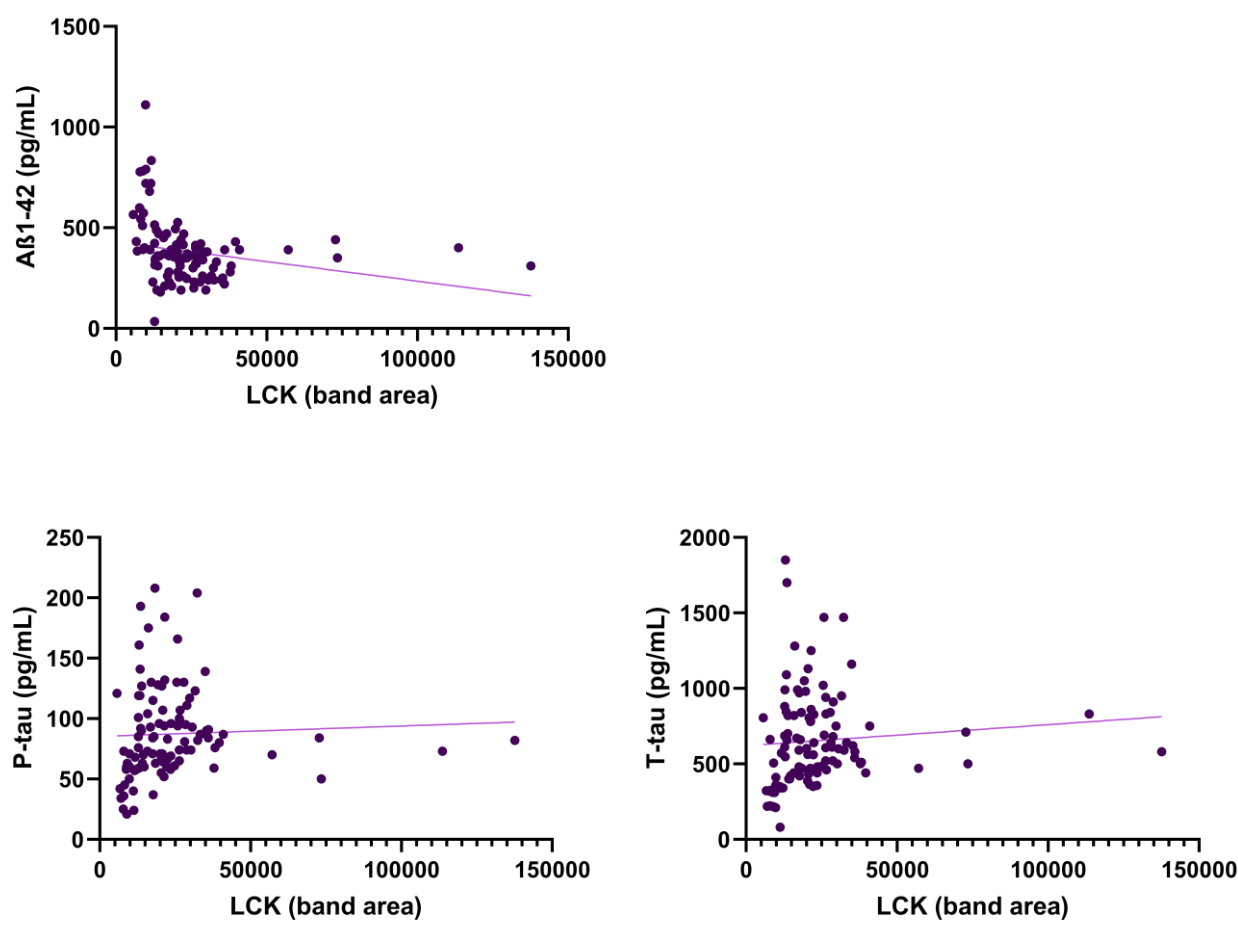
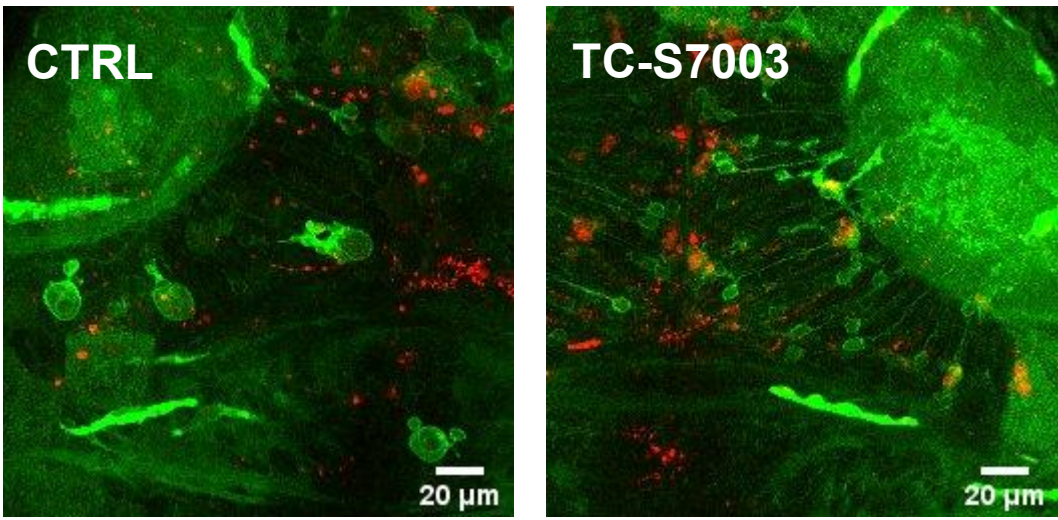
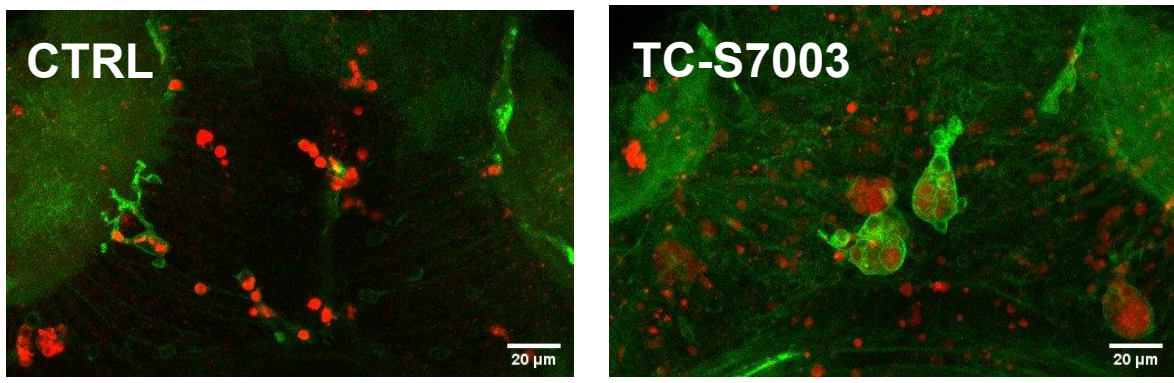


The Role Of The Lymphocyte-specific Protein Tyrosine Kinase In Alzheimer’S Disease - A Translational Study

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INTRODUCTION	METHODS	RESULTS	RESULTS	RESULTS
Microglial dysfunction and neuroinflammation are central to both Alzheimer’s disease (AD) pathology as well as that of cerebrovascular diseases. Lymphocyte-specific protein tyrosine kinase (LCK), a Src-family kinase expressed in microglia and T - cells, regulates inflammatory signaling and has been reported to be downregulated in AD brains [Hata et al., Biochem Biophys Res Commun. 2001;284(2):310-316]. However, its functional role in microglial responses to amyloid-β (Aβ) remains unclear. Furthermore, cerebrospinal fluid (CSF) levels of LCK have not yet been explored in neurodegenerative and vascular cognitive diseases, such as subcortical small-vessel disease (SSVD). The present study aimed to evaluate whether circulating levels of LCK may serve as a biomarker of neurodegenerative and cognitive disorders. In addition, we investigated the potential involvement in disease-related processes by assessing its association with established biomarkers of neurodegeneration. We also explored possible associations with cognitive functions. Finally, we explored how inhibition of lck in zebrafish larvae affects the functions of microglia and their lysosomes.	Patient samples For this experiment, 111 cerebrospinal fluid (CSF) patient samples from the Gothenburg Mild Cognitive Impairment study at the Memory Clinic in Gothenburg were examined. The included patient groups were AD (n=39) and SSVD (n=20). We also measured samples from preclinical patients showing pathological AD CSF biomarkers (pre-AD; n=15), as well as control participants (n=37). We applied the following IWG2 criteria cut-offs for AD pathology in CSF to stratify the cohort: Aβ1-42 < 530 ng/L, t-tau > 350 ng/L, p-tau181 > 59 ng/L. Biomarker analyses LCK was measured in CSF using capillary western blot (Protein Simple). Zebrafish experiments The LCK inhibitor TC-S7003 was used in wild-type (AB) fish and the microglia marker line Tg(<i>apoE:GFP</i>). Fish were injected with Aβ1-42 for cell death and lysosomal analysis and Aβ1-42-TAMRA for microglia analysis. Acridine orange was used to stain dead cells and LysoTracker to stain lysosomes.	1. Comparisons of CSF levels of LCK between patient groups  2. Females have lower CSF levels of LCK than males  3. CSF LCK correlate negatively with the CSF/serum albumin ratio 	4. LCK correlates with core AD CSF biomarkers  The positive correlation with Aβ1-42, and negative correlations with t-tau and p-tau indicate that high CSF LCK levels are beneficial. 5. Block of lck reduces Aβ1-42 phagocytosis by microglia  Microglia in TC-S7003 are shorter and have lower level of Aβ1-42-TAMRA staining than controls.	6. Inhibition of zebrafish lck causes lysosomal dysfunction  Stained lysosomes in zebrafish microglia are larger but with similar acidity as controls.
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