INTRODUCTION Tauopathies are characterized by pathologic aggregation of the microtubule-associated tau protein and formation of neurofibrillary tangles (NFTs) and have been linked to neurodegeneration and cognitive decline. Neurochemical measurements can provide unique information on biochemical and pathologic processes during the disease progression. However, the effects of tauopathies on cerebral metabolism reflected in neurochemical level changes are not well described. In this study, we characterized neurochemical alterations associated with the development of tauopathies in a novel animal model of tauopathy, rTg4510 transgenic mice using ultra-short echo time $^1$H MRS at 9.4T.

METHODS rTg4510 mice express a repressible human tau variant and develop progressive age-related NFTs, neuronal loss, and behavioral impairments starting at 5 months of age (mos) [1]. Nine rTg4510 and 10 littermate wildtype (wt) mice were studied at 5, 9 and 12 mos. The $^1$H MRS experiments were performed on a Varian 9.4 T MR system (Agilent Technologies, Santa Clara, CA) and a quadrature surface coil was used. Spectroscopy voxel of 6 $\mu$m (2x1.2x2.4 mm$^3$) was localized in the left hippocampal region (HPL), using T$_2$-weighted MRI (FSE, ETL = 16, echo spacing/TR/TE = 11/4000/11mos, matrix = 256x256, FOV = 2.56x2.56cm$^2$, thk = 0.5mm, NT = 2). Shimming was performed using FASTMAP [2] and the resulting FWHM of water resonances was 13-15 Hz. $^1$H MRS was performed using a spin echo, full intensity acquired localized (SPECIAL) sequence [3] (TR/TE = 4000/3ms). Metabolite concentrations were obtained using the LCMModel [4]. Student t-tests were performed for statistical analysis.

RESULTS AND DISCUSSION Figure 1(a) shows representative $^1$H MR spectra from an rTg4510 mouse, demonstrating longitudinal changes of metabolites indicated by arrows. Reductions in NAA, Glu, and taurine and increase in Ins were clearly visible. Fig 1(b) shows comparisons of metabolite concentrations between rTg4510 and wt groups and longitudinal changes within each group. At 5 mos, Asc (p = 0.035) and taurine (p = 0.004) levels were significantly lower in the HPL of rTg4510 mice compared with those in wt mice. By 12 mos, NAA (p < 0.001), taurine (p < 0.001), Glu (p < 0.001), GSH (p = 0.003), Asc (p = 0.004) and PCr (p < 0.001) levels were significantly lower in the HPL of rTg4510 than those in wt mice; while GPC (p < 0.001), GABA (p < 0.001), Gln (p = 0.005) and Ins (p < 0.001) levels were significantly higher in rTg4510 than those in wt. Changes of Ins (p = 0.003), GABA (p = 0.003), taurine (p = 0.012) were significant at 9 mos compared to 5 mos of rTg4510 mice, indicating disease progression. Changes in Cr (p = 0.026), Ins (p = 0.001), taurine (p = 0.02), GPC (p = 0.02) and NAA (p = 0.016) of rTg4510 mice at 12 mos were also significant when compared to 9 mos indicating these metabolites association with further disease progression.

Figure 2 shows disease progression characterized by selected neurochemical levels (e.g., NAA and Ins) demonstrating gradual separation of rTg4510 from wt mice over 7 months. At 5 mos, wt (●) and rTg4510 (■) mice showed significant overlap of neurochemical levels. However, clear separation of rTg4510 from wt mice started from 9 mos (rTg4510: ● and wt: ○) and was more pronounced at 12 mos (rTg4510: ● and wt: ○), indicating the progression of tau pathology. Neurochemical levels of wt mice remained within a dashed circle over time while those of rTg4510 mice showed gradual and consistent changes marked by solid circles that moved away from the initial data cluster. Longitudinal changes of neurochemical levels in each individual rTg4510 mouse could also be monitored during disease progression (dashed arrows in Fig 2).

In summary, neurochemical changes in the hippocampus started at 5 mos, were pronounced at 9 mos and further progressed at 12 mos, indicating the sensitivity of $^1$H MRS in detecting disease progression with age. The neurochemical profile measured by in vivo $^1$H MRS can provide insights into the neurochemical effect in development and progression of Tau pathology. Asc: ascorbate; GPC: glycerophosphocholine; Cr: creatine; PCr: phosphoryl creatine; GABA: $\gamma$-Aminobutyric Acid; Glu: glutamine; Glu: glutamate; GSH: glutathione; Ins: myo-inositol; NAA: N-acetylaspartate.