neurons, and subsequently to dementia. Amyloid-b (Ab) and tau are the two pathological hallmarks, and both are known to be dysregulated in AD leading to widespread proteinaceous aggregation in the brain. We now know from tau-deficient animal models that tau does not merely facilitate Ab-induced toxicity but is also essential in that particular signalling cascade. However, a tau-deficient human *in vitro* model has not been available to corroborate the Ab-tau interaction. **Methods:** Here we report generation of the first *MAPT* knockout (tau-KO) human induced pluripotent stem cell (iPSC) lines in order to study Ab-tau interaction in human biological context. We also characterised a versatile and scalable cortical neuron differentiation protocol that successfully produced a heterogeneous population of functional neurons manifesting cortical identity. Furthermore, we extracted brain homogenate from AD patient to serve as a source of Ab. **Results:** Application of brain homogenate, which contains soluble Ab in pM range, in iPSC-derived neuronal culture resulted in neurite degeneration and cytotoxicity within 72 hours. We then asked if the human tau-KO genetic background could exhibit neuroprotective effects upon Ab exposure to the neuronal culture. **Conclusions:** We have initiated an investigation into the interaction between Ab and tau in human iPSC tau-KO cortical neurons utilising patient brain homogenate as the source of Ab to mimic human AD pathology *in vitro*.

P3-145 HEREDITARY SPASTIC PARAPLEGIA AND ALZHEIMER'S DISEASE: CLINICAL AND GENETIC STUDY OF A BRAZILIAN FAMILY

Roberto Rumore[1], Celeste Montecchiani[1,2], Fabrizio Gaudiello[1], Marialuisa Miele[1], José L. Pedroso[3], Orlando G. P. Barsottini[4], Carlo Caltagirone[1], Toshitaka Kawarai[5], **Antonio Orlacchio[1,2]**, *[1]IRCCS Santa Lucia, Rome, Italy; [2]University of Perugia, Perugia, Italy; [3]Universidade Federal de Sao Paolo, Sao Paolo, Brazil; [4]Universidade Federal de Sao Paulo, Sao Paolo, Brazil; [5]University of Tokushima, Tokushima, Japan. Contact e-mail: a.orlacchio@hsantalucia.it*

Background: Mutations in the SPG4/*SPAST* gene are the major cause of hereditary spastic paraplegias (HSPs), a group of genetic disorders leading to progressive spasticity and weakness of the lower limbs. Alzheimer's disease (AD) is a degenerative disorder of the central nervous system. Early-onset familial AD (EOFAD) accounts for 3-5% of all AD cases and denotes families in which onset is reliably before age 60 to 65 years and sometimes before age 55 years. Three SPG4/*SPAST* Italian families and one Japanese family with HSP and AD were previously described by our research team. **Methods:** Whole exome sequencing (WES), Sanger sequencing, Multiplex Ligation dependent Probe Amplification (MLPA) analysis, bioinformatics, neurological evaluation, diagnostic imaging, and pathological assessment. **Results:** One Brazilian man was diagnosed as certainly affected by slowly progressive autosomal dominant HSP, according to the Harding criteria. The age at onset of the first motor symptoms was 36 years. At 55 years, the phenotype was complicated by cognitive impairment; a diagnosis of EOFAD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria was formulated. The case was definite Alzheimer's disease (autopsy proven): the brain pathology showed plaques with a congophilic core and neuritic pathology. Additional four affected subjects revealed the same initial symptoms of dementia and HSP was diagnosed. Additional clinical signs, such as scoliosis and *pes cavus*, were present in the affected individuals. WES revealed in all patients a new heterozygous change in SPG4/*SPAST*. MLPA analysis excluded the presence of deletions/duplications in SPG4/*SPAST*. Bioinformatic analyses and population study confirm a pathogenetic role of such mutation. Screening of *PS1*, *PS2*, and *βAPP* genes did not reveal any coding mutation. No affected subject carried out *APOE* genotype ε4/ε3 or ε4/ε4. **Conclusions:** To our knowledge, this work describes the first Brazilain family with a new SPG4/*SPAST* mutation and association of HSP and EOFAD.

P3-147 APOLIPOPROTEIN E ISOTYPE AND EXERCISE INTERACT IN THE EPIGENETIC REGULATION OF MICRORNA-146A

Bruce Teter[1,2], Mary Jo Ladu[3], Ana Verduzco[4], Sally A. Frautschy[1,2], Gregory M. Cole[1,2], *[1]Veterans Greater Los Angeles Healthcare System, Los Angeles, CA, USA; [2]University of California Los Angeles, Los Angeles, CA, USA; [3]University of Illinois at Chicago, Chicago, IL, USA; [4]Scripps Research Institute, San Diego, CA, USA. Contact e-mail: bteter@ucla.edu*

Background: The apolipoprotein E (apoE) isotype apoE4 can increase systemic and central inflammation, independent of amyloid accumulation. ApoE4 dysregulates innate immune toll-like receptor (TLR) signaling in AD by modulating expression of is major regulator, miR146a, a microRNA enriched in the brain. We examined the effect of apoE isotype and age on brain levels of miR146a, its epigenetic expression regulation by histone acetylation (Hac), and the effect of exercise. **Methods:** ApoE3 and apoE4 targeted replacement mice with and without mutant familial AD (5xFAD) transgenes (E-FAD), at 6 month-old and 13 month-old, were exercised with running wheels for the last 10 weeks, and were compared to sedentary controls. **Results:** In young sedentary mice, apoE4 greatly reduced levels of miR146a compared to apoE3, both in the brain (29%; $p<0.0001$) and plasma (47%; $p<0.05$), which correlated with each other ($r2=0.74$; $p<0.05$). The presence of 5xFAD transgenes increased brain miR146a in both E3-FAD and E4-FAD young mice; however, miR146a levels in E4-FAD mice remained lower than in E3-FAD mice (62%; $p<0.05$), despite increased amyloid and inflammation. ApoE4 brains showed increased expression of interleukin receptor associated kinase-1, IRAK1 (that mediates TLR signaling and is normally downregulated by miR146)(160%; $p<0.05$); IRAK1 mRNA inversely correlated with miR146a levels ($r2=0.637$; $p<0.0001$). ApoE4 is known to induce histone deacetylases which could reduce Hac at the miR146a gene, explaining the lower levels of miR146a. In