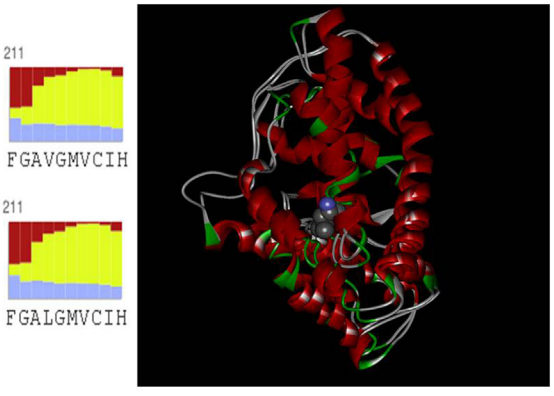
Background: Mutations associated with familial early-onset Alzheimer's disease (AD) were typically found in amyloid precursor protein (APP), and presenilin1 (PSEN1) and presenilin2 (PSEN2). Among them, mutations in PSEN2 are rare, and fewer than 30 different PSEN2 mutations were reported. **Methods:** 89 dementia patients under 60 years of age were screened for AD mutations. A PCR based genetic analysis was performed on above dementia patients and 128 normal controls. Following segments were amplified: the APP exon 16-17; PSEN1 exon 4-8 and 11; PSEN2 exon 4-7 and 12. Two efficient mutation detection methods were used for screening our samples: single strand conformation polymorphism (SSCP) and heteroduplex analysis with mismatch-specific nuclease. For the identification and confirmation of the specific mutations, the PCR products were sequenced. **Results:** A missense PSEN2 mutation, a Val->Leu exchange at codon 214, was found in two unrelated patients. Val214Leu is located at the IVth transmembrane domain of presenilin 2 (PS2). PSEN2 Val214Leu was screened in normal controls, but it was not found in them. In silico modeling of PS2 with Val and Leu at the position 214 was performed to contribute their molecular structures. The theoretical model (Figure below) revealed that this mutation might result significant structural modifications inside the PS2 protein, leading to overproduction of amyloid beta. Novel PSEN2 Val214Leu mutation at codon was found in two patients from unrelated families. One patient suffered from late-onset dementia without family history. The second patient is a 55-year-old woman whose only daughter has osteogenesis imperfecta. Since PS2 is component of the gamma-secretase complex, it could cleave the osteoblast regulator molecules. The mutation was absent in 128 control patients, supporting PSEN2 Val214Leu as a novel mutation for AD. Since Leu is more hydrophobic than Val, it might be possible, that Val->Leu exchange could result extra disturbances in the interactions between the TMIV helix and the membrane layer. **Conclusions:** We predicted the structures of presenilin 2 with native Val 214 residue and Leu 214 mutation, and the results revealed significant structural changes in the region. We found a probable novel mutation in the PSEN2 gene in two patients with Alzheimer's disease from unrelated two families.

***In silico* modeling of PSEN2 with Val and Leu at the position 214**



P1-073 ASSESSMENT OF ALZHEIMER'S DISEASE RISK GENES WITH CSF-BIOMARKER LEVELS

Brit-Maren Schjeide[1], Fran Borovecki[2], Jordi Clarimón[3], Frank Faltraco[4], Vilmantas Giedraitis[5], Martin Ingelsson[6], Harald Hampel[7], Basavaraj Hooli[8], Lena Kilander[6], Julia Kirchheiner[9], Natasa Klepac[2], Alexander Kurz[10], Lars Lannfelt[6], Christina Lill[1], Alberto Lleó[3], Markus Otto[9], Jens Pahnke[11], Robert Perneczky[12], Dan Rujescu[13], Cathrin Schnack[9], Goran Simic[2], Rudolph Tanzi[14], Stefan Teipel[15], Hayrettin Tumani[16], Christine von Arnim[16], Lars Bertram[1], *[1]Max Planck Institute for Molecular Genetics, Berlin, Germany; [2]University Hospital Center Zagreb, Zagreb, Croatia; [3]CIBERNED, IIB-Sant Pau, Barcelona, Spain; [4]Johann Wolfgang Goethe University Frankfurt, Frankfurt, Germany; [5]Uppsala University, Uppsala, Sweden; [6]Uppsala University, Uppsala, Sweden; [7]University of Frankfurt, Frankfurt/Main, Germany; [8]MassGeneral Institute for Neurodegenerative Disease (MIND), Charlestown, Massachusetts, United States; [9]University Hospital, Ulm, Ulm, Germany; [10]Technische Universität München, München, Germany; [11]University and DZNE Magdeburg, Magdeburg, Germany; [12]Technische Universitaet Muenchen, München, Germany; [13]Technische Universität München, Munich, Germany; [14]Massachusetts General Hospital/Harvard Medical School, Charlestown, Massachusetts, United States; [15]University Medicine Rostock and DZNE Rostock, Rostock, Germany; [16]University of Ulm, Ulm, Germany. Contact e-mail: schjeide@molgen.mpg.de*

Background: Recent genome-wide association studies (GWAS) have implicated ten loci as novel Alzheimer's disease risk genes in addition to APOE (see www.alzgene.org). We previously showed that the AD-associated risk alleles near PICALM, but not those near CLU or CR1, correlate with reduced levels of Ab42 in the cerebrospinal fluid (CSF) of AD patients and healthy controls (Schjeide et al [2011] Arch Gen Psychiatry 68(2):207-13). We have now extended the CSF-biomarker analyses to include single-nucleotide polymorphisms (SNPs) in the remaining GWAS loci in a substantially extended dataset. **Methods:** Our sample currently includes a total of 1,111 individuals (732 AD cases, 245 controls, 134 MCI or other dementias) from Germany, Sweden, Spain, and Croatia, in whom we have measured CSF Ab42 and total tau concentrations. These samples were genotyped for disease-associated SNPs in the ten established AD risk genes ABCA7, APOE, BIN1, CD2AP, CD33, CLU, CR1, EPHA1, MS4A6A, and PICALM. These data are currently being extended by genotyping additional AD risk SNPs emerging from GWAS meta-analyses performed by our group, as well as SNPs emerging from independent CSF biomarker GWAS. All signals are compared with data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). **Results:** The currently available genotype data from ten AD susceptibility genes suggest that risk allele dosage of SNPs in APOE, PICALM, and ABCA7 correlates with decreased CSF-Ab42 levels in the complete dataset (P-values ranging from <1x10-15 to 0.08). Conversely, a decrease in CSF-tau concentrations was associated with risk allele dosage in APOE and BIN1 (P-values ranging from <1x10-5 to 0.1). Interestingly, gene ontology analysis reveals that the loci showing association with CSF biomarker levels in our dataset are all linked to "vesicle endocytosis", a process also emerging in similar analyses on other neurodegenerative diseases. **Conclusions:** We have assembled a large dataset including more than 1,100 individuals with CSF-biomarker data relevant for AD. With the exception of APOE, current AD risk genes only show marginal correlations with CSF biomarkers. The loci that emerged as associated with CSF Ab42 or tau are all involved in endocytotic processes. Additional analyses are ongoing and up-to-date results will be presented at the meeting.

P1-074 A SYSTEMATIC ANALYSIS OF GENOMIC CHANGES IN Tg2576 MICE

Lu Tan, *Tongji Medical School, Wuhan, China. Contact e-mail: tanlu_cecilia@yahoo.com.cn*

Background: The pathogenesis of AD is complicated and may involve alterations in a large number of genes/proteins and disruption to their anfractuous interactions, rather than an alteration in a single gene/protein. Several studies, including some microarray analysis, have been performed using Tg2576 mice, and consequently hundreds of differentially expressed genes have been identified, especially regarding plasticity-related genes. However, few studies have focused on the co-expression patterns of associated pathways with their core genes and transcription factors (TF). **Methods:** Published microarray data from Stein's article can be obtained from the Gene Expression Omnibus database, accession No. GSE1556. The data were assessed using the Bioconductor software packages, and genes with a >2.0-fold differential expression were further analyzed by statistical tests. A testing correction method by false discovery rate was applied with a $p < 0.05$ cut-off in our statistical tests. Gene Ontology (GO) analysis, Positional Gene Enrichment (PGE) analysis, and Gene Set Enrichment analysis (GSEA) were performed as previously described. **Results:** Thus, in this study, we applied systematic biology approaches with published microarray