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Background: Familial Alzheimer's disease associated with PSEN1 mutations has a wide spectrum of clinical presentations. Cognitive deficits are the dominant features; however, other signs and symptoms can be seen including some associated with movement disorders. **Methods:** Affected individuals from a family were studied clinically (2), genetically (3), and neuropathologically (1). **Results:** The proband, a female, reportedly began to have seizures, headaches and psychiatric problems at age 14. She attempted suicide and was considered to have conversion disorder at age 15. Her seizure disorder was treated with phenytoin and carbamazepine at age 19. Also, she was diagnosed by a psychiatrist as having adolescent adjustment reaction and reactive depression. Her family noted episodes of confusion and memory difficulty at age 27. Her memory worsened, speech became dysarthric and spasticity developed in the lower extremities at age 29. A diagnosis of spinocerebellar degeneration was considered at that time. Her condition progressed until she died at age 36. The proband's mother was reported to have had ataxia and spasticity at age 18, dementia by 30 and died at 55. The proband's sister developed a gait disorder at age 21, dementia at 25 and died at 47 after having been in a vegetative state for 9 years. The proband's brother was known to have a gait disorder at age 28, but was lost to follow-up. Genetic analysis of the proband and two siblings identified a single nucleotide substitution (C for T) in exon 6 in the PSEN1 gene leading to a proline for leucine substitution at codon 166 (L166P). Autopsy of the proband showed corticospinal tract degeneration with atrophy of the cerebral hemispheres, pons, cerebellum, and rostral spinal cord. Histopathology revealed advanced stage neurofibrillary tangle and neuritic plaque pathology accompanied by prominent amyloid-β (Aβ) deposition as well as "cotton wool" plaques and severe amyloid angiopathy. **Conclusions:** This mutation in PSEN1 results in one of the earliest onsets of symptoms and most "malignant" clinical courses reported to date. This report underscores the importance of close clinical, genetic, and neuropathologic studies to diagnose atypical presentations of a neurodegenerative disease.

P4-091 FOLLOW-UP OF THE FIRST AMERICAN REPORT OF FAMILIAL ALZHEIMER'S DISEASE

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Background: Lowenberg and Waggoner in 1934 reported 5 members from 2 generations of a Michigan family with onset of dementia early in the 4th decade of life. Although the published pathology appeared to indicate AD, affected members had several unusual features, including unsteady gait, seizures, spasticity, and extensive neuritic plaques in the basal ganglia, raising uncertainty about the appropriate classification of this family. Two affected individuals studied clinically at the University of Michigan during the 1990s were identified as being descendents of that family. Both individuals were found to have a PSEN1 gene mutation (I143T). **Methods:** Two affected siblings of this kindred were studied clinically, neuroradiologically, and neuropathologically using established protocols and procedures typically used in NIA-funded Alzheimer's disease centers. PET imaging studies were carried out using 18 F-2-fluoro-2-deoxy-D-glucose (18 F-FDG). **Results:** Affected individuals presented personality changes and memory loss beginning in the middle of the fourth decade of life. Seizures were also common. The disease duration ranged from 2 to 7 years. We identified metabolic abnormalities with PET scanning including typical pattern of temporoparietal hypometabolism and cerebellar hypometabolism. Neuropathologic studies of both siblings revealed numerous Aβ-immunopositive neuritic and cotton wool plaques in the cerebral cortex. Abundant Aβ deposits were also present in subcortical nuclei and cerebellum. Amyloid deposits were seen in the subcortical white matter. Amyloid angiopathy was severe in the cerebral and cerebellar cortices. Immunohistochemical studies using a panel of antibodies raised against several amyloid β epitopes suggest that there is deposition of truncated amino-terminal Aβ fragments. Tau-immunostaining revealed neurofibrillary tangles and neuropil threads in the neocortex, hippocampus and some subcortical nuclei. **Conclusions:** The clinical and neuropathologic phenotypes of familial Alzheimer's disease association with mutation PSEN1 I143T are described. The original description by Lowenberg and Waggoner and the current results are of interest in defining the natural history of the disease. In two families, one reported in Belgium and one in Sweden, the clinical phenotype appears similar to that seen in the individuals reported here.

P4-093 MIRNA REGULATION OF APP, BACE1 AND NICASTRIN AND THE EFFECT OF 3'UTR POLYMORPHISMS

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Background: It is becoming increasingly acknowledged that polymorphisms in microRNA (miRNA) target sites (PolymiRTS) may influence neurological disorders, including Parkinson's disease and frontotemporal dementia. A number of PolymiRTS in the 3' untranslated region (3'UTR) of AD related genes such APP, BACE1 and nicastrin have been identified, some of which are found exclusively in patients suffering from Alzheimer's disease (AD). Given recent findings, we hypothesize that PolymiRTS could contribute significantly to risk for AD by affecting miRNA binding and increasing the expression of genes like APP involved in the amyloid cascade. **Methods:** Using various bioinformatics logarithms, we established a detailed list of potential miRNA binding sites in the 3'UTRs of APP, BACE1 and Nicastrin. The corresponding miRNAs were tested through luciferase reporter assays as well as by Western blotting for their potential to alter APP, BACE1 and Nicastrin expression. In order to further establish whether the 3'UTR PolymiRTS affect the function of the identified miRNAs, mutagenesis of the 3'UTR of these genes and subsequent luciferase reporter assays were performed. **Results:** We have identified novel miRNAs that regulate APP, BACE1 and Nicastrin expression. Our results suggest that certain polymorphisms influence miRNA binding and therefore expression. **Conclusions:** These data could help to focus future association studies aimed at identifying novel risk factors for AD. The identification of novel miRNAs involved in the physiological regulation of APP may provide novel targets for potential future diagnostics and therapy purposes.

P4-094 DUPLICATIONS IN CHR15Q11 ARE ASSOCIATED WITH LATE-ONSET ALZHEIMER'S DISEASE IN THE CAUCASIAN POPULATION

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Background: A number of large scale GWA studies of Late Onset AD (LOAD) have collectively identified a score of single nucleotide variants that might increase risk of developing LOAD. Some of the estimated heritability, however, remains not accounted for. It has been calculated that occurrence of structural variants, including Copy Number Variations (CNVs), inversion, and translocation, can be as high as 1000 times the rate at which single nucleotide variants occur. Furthermore, that many individuals with Down syndrome, or trisomy 21, who therefore most likely carry three copies of APP, exhibit AD symptoms by their 40s suggests that CNV may contribute to the etiology of AD. **Methods:** We set out to investigate CNV association to AD susceptibility using ADGC ADC1 and ADC2 cohorts genotyped using Illumina 660W Quad BeadChip. We adopted a conservative approach for CNV calling:1) precluding the samples that failed the various quality control measures applied in ADGC's SNP GWA study (Naj et al. 2011).2) We uplifted the hg18 coordinates of Illumina 660W probes to hg19, and eliminated ambiguous probes whose sequences can be mapped to multiple loci in the genome.3) Only CNVs called by both PennCNV and cnvPartition were used for further analyses. **Results:** In the 2141 AD case and 618 control subjects of Caucasian ancestry, we found many more deletions than duplications. In both genome-wide and across 17