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#### P1084. Alzheimer's Disease and the Cystatin C gene polymorphism: an association study.

R. Cittadella<sup>1</sup>, F. Condino<sup>1</sup>, N. Romeo<sup>1</sup>, G. Nicoletti<sup>1,2</sup>, V. Andreoli<sup>1</sup>;

<sup>1</sup>Istituto di Scienze Neurologiche, Pianolago di Mangone (CS), Italy, <sup>2</sup>Institute of Neurology, University Magna Graecia, Catanzaro, Italy.

Cystatin C is a cysteine protease inhibitor which is found to colocalize with A $\beta$  in plaques and cerebrovascular deposits in Alzheimer's Disease (AD). Recent studies have reported a genetic association between the 73 G/A polymorphism within exon 1 of the cystatin C gene (CST3), a common Ala/Thr substitution in the signal peptide, and Alzheimer's disease (AD) with conflicting results. To further investigate the proposed association in our population, we analyzed this variant in a clinic and population based group of 171 Italian patients with sporadic AD from southern Italy (Calabria region) and 190 healthy controls subjects from the same geographical area. All 361 subjects were genotyped for CST3 and APOE polymorphisms but our data showed no association between AD and CST3. We therefore stratified our samples based on age (of controls) or age of onset (of cases): <65-69, 70-79, and 80+ years. After this stratification according to age, in older patients (80+ years) the GG frequency resulted over-represented when compared to controls, but far from statistically significant. There was also no evidence of a statistical interaction between CST3 and APOE polymorphisms. In conclusion, our data suggest that the 73 G/A polymorphism within exon 1 of the cystatin C gene is not a susceptibility factor in AD and nor mitigate the effect of the ApoE - $\epsilon$  4 allele in the risk of developing AD in our population but further studies will be necessary to clarify the CST3 polymorphism position among AD risk factors.

#### P1085. Two SNPs in the Fas gene on chromosome 10 are not associated with Italian Sporadic Alzheimer's Disease

V. Andreoli<sup>1</sup>, L. Nicoletti<sup>1</sup>, F. Trecroci<sup>1</sup>, F. Condino<sup>1</sup>, N. Romeo<sup>1</sup>, G. Nicoletti<sup>1,2</sup>, R. Cittadella<sup>1</sup>;

<sup>1</sup>Istituto di Scienze Neurologiche, Pianolago di Mangone (CS), Italy, <sup>2</sup>Institute of Neurology, University Magna Graecia, Catanzaro, Italy.

The TNFRSF6 (Tumor Necrosis Factor Receptor Super Family 6) gene encodes Fas antigen, a cell surface receptor-mediated cell apoptosis situated on chromosome 10q, near the region of linkage to sporadic Alzheimer's Disease (AD). Moreover, elevated levels of Fas have reported in the brain of AD patients. These two criteria, positional and pathobiological, make the Fas antigen an interesting candidate for an association with AD. To address these findings, we have tested two SNPs in the TNFRSF6 gene in a set of 223 Italian patients with non-familial (sporadic) AD from southern Italy and 211 healthy controls subjects: a G to A polymorphism at position (-670) in the enhancer region of the promoter and a single nucleotide change from C to T 74 nucleotides from the beginning of exon 7 in the Fas gene. There was no statistically significant differences in allelic and genotypic frequency distribution between cases and controls or between late and early-onset AD patients. No interactive effect was found between the Fas polymorphisms and the known risk factor of non-familial AD, Apolipoprotein-E  $\epsilon$ 4 allele. We also tested whether these different Fas genotypes were associated with clinical features, such as age at disease onset and disease progression but no significant differences were detected. The present data suggest that the polymorphisms do not represent a risk factor for AD in our population.

#### P1086. Effect of Apolipoprotein E (APOE) genotype and past fertility on age of onset of Alzheimer's disease in women

R. M. Corbo<sup>1</sup>, L. Ulizzi<sup>1</sup>, G. Gambina<sup>2</sup>, E. Broggio<sup>2</sup>, G. Moretto<sup>2</sup>, R. Scacchi<sup>2</sup>;

<sup>1</sup>University La Sapienza, Rome, Italy, <sup>2</sup>Verona Hospital, Verona, Italy, <sup>3</sup>CNR Institute of molecular biology and pathology, Rome, Italy.

Various genetic and non-genetic risk factors have been linked to the development of Alzheimer's disease (AD). In women, having had children is one of the non-genetic factors reportedly associated with an increased risk of AD. Among genetic factors involved in AD susceptibility, the APOE  $\epsilon$ 4 allele has a major role and its presence reduces age at AD onset. But APOE is also thought to influence human reproduction as well, and common APOE genotypes seem to be associated with differential fertility. With this study, we investigated possible relationships between APOE genotype, past fertility, and AD onset age in a sample of 116 women with the sporadic form of the disease. Results from a comparison of APOE genotype distribution

in parous and nulliparous AD women supported previous findings indicating that the  $\epsilon$ 3/ $\epsilon$ 3 genotype was associated with higher fertility and the  $\epsilon$ 4 carrying genotypes with lower fertility. When the combined effects of fertility and APOE genotypes on AD onset age were analysed parity was found to be associated with a significantly lower AD onset age (72.3 $\pm$ 5.9 years) than nulliparity (79.0 $\pm$ 5.6 years; P=0.004) among  $\epsilon$ 3/ $\epsilon$ 3 homozygotes. Since  $\epsilon$ 3/ $\epsilon$ 3 is the most frequent APOE genotype in Europe (0.56--0.70), past fertility may influence AD susceptibility in many women. A similar effect was absent among  $\epsilon$ 4 carriers. Our findings indicate that past fertility may have a relevant effect on AD onset age and that the effect is mediated by APOE genotype.

#### P1087. Complex haplotypes from apo(a) gene locus control regions and correlation to Lp(a) plasma levels

K. Zidkova<sup>1,2</sup>, V. Kebrdlova<sup>2</sup>, L. Zlatohlavek<sup>1</sup>, R. Ceska<sup>1</sup>;

<sup>1</sup>3rd Medical Department, 1st Faculty of Medicine and General Teaching Hospital, Charles University in Prague, Prague, Czech Republic, <sup>2</sup>Institute of Biology and Medical Genetics, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

**Objectives:** High lipoprotein(a), Lp(a), level is an independent risk factor for development of premature atherosclerosis. Apolipoprotein(a), apo(a), is the main determinant of Lp(a) plasma concentration. The aim of our study was to reconstruct haplotypes using five polymorphisms from the apo(a) gene regulatory sequences (promoter, DHIII enhancer) and to compare their distribution in five groups of individuals with different range of Lp(a) level and in a population sample.

**Methods:** The out-patients pool of the 3rd Medical Department was divided into quintiles according to Lp(a) concentration. Population sample was derived from the Institute of Biology and Medical Genetics. Three polymorphisms (TTTTAn repetition, +93C/T, +121G/A) from the apo(a) gene promoter and two polymorphisms (-1617C/A, -1230A/G) from the DHIII enhancer region were detected by the fragmentation analysis (TTTTAn repetition) and by the DGGE method in combination with sequencing in the quintiles and by the RFLP and allele-specific PCR in the population sample.

**Results:** From the 80 possible haplotypes 23 were able to built up all observed genotypes in the quintiles and population sample. Several statistically significant differences were observed in frequencies distribution among quintiles and between each quintile and population sample. Some of the haplotypes were isolated to a narrow range of Lp(a) levels.

**Conclusion:** We conclude from our study that complex haplotypes from apo(a) gene locus could be used as a marker for certain range of apo(a) gene length variants and thus Lp(a) levels.

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#### P1088. Polymorphism of the ApoE locus in the Azores Islands (Portugal)

C. Bettencourt<sup>1</sup>, R. Montiel<sup>1</sup>, C. Santos<sup>1</sup>, M. Pavão<sup>1</sup>, A. Viegas-Crespo<sup>2</sup>, P. Lopes<sup>2</sup>, M. Lima<sup>1</sup>;

<sup>1</sup>University of the Azores, Ponta Delgada - Azores, Portugal, <sup>2</sup>University of Lisbon, Lisbon, Portugal.

The aim of this work was to report on the polymorphism of the ApoE locus in the Azores Islands (Portugal) in order to get insights on the genetic background that influences the lipid profile in this population, ascertained as considerably high in a preliminary study of a sample of healthy subjects (60% of individuals were hypercholesterolemics). One hundred and twenty six Azorean individuals were typed for ApoE polymorphism using standard PCR-RFLP. The allelic frequencies obtained for  $\epsilon$ 2,  $\epsilon$ 3 and  $\epsilon$ 4 were 6.75%, 83.73% and 9.52%, respectively. Genotypic frequencies were in conformity with Hardy-Weinberg expectations. The  $\epsilon$ 3/ $\epsilon$ 3 genotype presented the highest frequency (69.84%), whilst  $\epsilon$ 4/ $\epsilon$ 4 was the least frequent (0.79%). The genotypic and allelic frequencies observed were similar to those reported for other Iberian samples. Furthermore, Nei's gene diversity (0.2864 $\pm$ 0.0351) was similar to the reported for samples from Mainland Portugal. Results obtained did not evidence a particular behaviour of the ApoE locus that could be directly related with the high levels of total cholesterol determined in the Azorean population.