Dementia genetics in greece: insights from a large community-based cohort in the island of crete, greece

I. Zaganas, L Mathioudakis, M Bourbouli, K Michaelidou, C Dimovasili
Neurology Laboratory, University of Crete, Greece

Introduction: Apart from the gene mutations associated with familial early-onset Alzheimer's disease (AD) and the *APOE* ε4 allele that predisposes to late-onset AD, there have been no other strong genetic determinants of AD identified. Aim: Aim of this study was to characterize the genetic background of dementia in a cohort of aged adults on the island of Crete, Greece. Methods: Whole exome sequencing (WES) was performed in 201 participants (100 suffering from dementia, of whom 95 with AD, 20 with mild cognitive impairment-MCI and 81 cognitively normal controls) of our cohort. Using WES data, we assessed the genotype of these individuals concerning the early-onset AD associated genes (*PSEN1*, *PSEN2*, *APP*), the *APOE* gene and two genes (*GLUD1*, *GLUD2*) involved in glutamate metabolism. Results: As expected, the *APOE* ε4 allele was more common in dementia (25.0%) patients than in cognitively normal controls (8.6%; p=0.006). In addition, we identified several variants of potential interest in the *APP*, *PSEN1*, *PSEN2*, *GLUD1* and *GLUD2* genes. In a combined sample of 612 individuals (that included an additional local cohort), we found the *GLUD2* Ser498Ala variant in 7 (3.2%) of 220 dementia X chromosomes, 22 (6.0%) of 370 MCI X chromosomes and 27 (6.5%) of 413 control X chromosomes. None (0%) of 50 male dementia patients had the Ser498Ala *GLUD2* genotype, compared to 7 (8.4%) of 83 male controls (p=0.05). Conclusions: In this culturally and genetically homogeneous cohort of aged adults, we identified, using a WES approach, a number of genetic variants of potential clinical significance.