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Pathogenic mechanism of Alzheimer's disease

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Our current understanding of the pathogenic mechanism of Alzheimer's disease (AD) is based mainly on rare variants with large effect size, however the identification of such variants remains elusive. To identify novel genes and variants with large effect size, we performed exome-sequencing in 14 families with late-onset AD, identifying and following-up all the variants that showed perfect segregation. A rare variant in PLD3 (rs145999145; V232M) segregated with disease status in two independent families, and showed large effect size for AD risk (OR=3.48; p=8.9×10-8). This variant was present in 0.8% of the sequenced samples in the EVS and 0.43% of healthy elderly population (4/922). We have also followed up all the genes that segregated with disease status in 400 AD cases and 1080 controls. A total of 60 genes (DFNB31, NFATC1, LRP4, CACNA1G, CALCR, ZNF30, DMRT2, KIF1A, ZNF341, LRP4, PRKD2) were selected. As replication, the most interesting genes were re-sequenced in additional 800 cases and 400 controls. In order to analyze the association of the selected genes in disease risk we performed gene-based test stratifying by minor allele frequency (MAF), and by analyzing variants that were unique to cases or controls. One gene showed a significant gene-based association (variants MAF<1%) with AD risk after multiple testing (OR=1.97, p=2.51x10-4). The analyses indicated that additional genes harboring low-frequencies risk variants exist, and that, family-based studies could help identify such genes and variants. We are currently performing additional sequencing and functional analyses to validate our findings.

Biography

Carlos Cruchaga is an Assistant Professor of Psychiatry at Washington University School of Medicine. He received his doctoral studies on Biochemistry and Molecular Biology at the University of Navarra (Spain). After his doctoral studies, he became interested in the genetics of neurodegenerative disease. He completed his postdoctoral training at Alison Goate's laboratory. His interests are focused on the identification and characterization of genetic variants implicated in Alzheimer's disease (AD).

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