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Oral communications
OC9- Genome-wide characterization of a cohort of Alzheimer’s patients from Iberia: a focus on rare variants

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Aims/Context: To perform a genetic characterization of a cohort of late-onset Alzheimer’s disease (LOAD) patients from Northern Portugal and Spain focusing on the spectrum of genome-wide rare variants (MAF). Methods: DNA was extracted from saliva and buccal swab samples and genotyped with Axiom Spain Biobank Array, which provides high coverage of whole-genome common and low frequency variation as well as Mendelian and functional alleles that are specific to Spanish. This analysis comprised 128 LOAD patients from Northern Portugal and from the Spanish autonomous community of Castile and León with a clinical diagnosis of AD. In addition, 59 controls (individuals over 65 years old with no signs of dementia or other brain disorders) from both regions were also analyzed. Rare variants in genes relevant for AD and with highly deleterious potential as assessed by CADD were prioritize for detailed annotation. Gene- based tests using SKAT-O and different models were performed to examine the aggregate effect of risk and protective variants. Results: In spite of the modest sample size, we detected a suggestive enrichment of rare variants in cases in several genes with functional links to AD. Overall, 16 AD genes harbored very rare pathogenic/likely pathogenic variants in our sample (cases and controls), thus making these variants much more frequent in our cohort than in control populations from GnomAD and ExAC. Conclusions: This study provides a characterization of genome-wide rare variation in AD in Castile and Léon and in Northern Portugal, the latter a region where dementing diseases are highly prevalent but still understudied. Even in a small sample of patients we were able to identify rare pathogenic variations and an excess of rare variants in cases in genes likely relevant to AD etiology, making this a valid approach to identify genes contributing to AD burden.