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Screening of dementia genes by whole-exome sequencing in early-onset Alzheimer disease: input and lessons

Causative variants in APP, PSEN1 or PSEN2 account for a majority of cases of autosomal dominant early-onset Alzheimer disease (ADEOAD, onset before 65 years). Variant detection rates in other EOAD patients, that is, with family history of late-onset AD (LOAD) (and no incidence of EOAD) and sporadic cases might be much lower.

We analyzed the genomes from 264 patients using whole-exome sequencing (WES) with high depth of coverage: 90 EOAD patients with family history of LOAD and no incidence of EOAD in the family and 174 patients with sporadic AD starting between 51 and 65 years.

We found three PSEN1 and one PSEN2 causative, probably or possibly causative variants in four patients (1.5%). Given the absence ofPSEN1, PSEN2 and APP causative variants, we investigated whether these 260 patients might be burdened with protein-modifying variants in 20 genes that were previously shown to cause other types of dementia when mutated. For this analysis, we included an additional set of 160 patients who were previously shown to be free of causative variants in PSEN1,PSEN2 and APP: 107 ADEOAD patients and 53 sporadic EOAD patients with an age of onset before 51 years. In these 420 patients, we detected no variant that might modify the function of the 20 dementia-causing genes.

We conclude that EOAD patients with family history of LOAD and no incidence of EOAD in the family or patients with sporadic AD starting between 51 and 65 years have a low variant-detection rate in AD genes.

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