New mutations involved in early-onset forms of Alzheimer disease

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The SORL1 gene that encodes a protein involved in the control of amyloid-beta production, may be involved in autosomal dominant early-onset Alzheimer disease (ADEOAD), according to a study published this week in Molecular Psychiatry. The results imply that additional genetic factors may be involved in the development of ADEOAD.

Mutations in amyloid precursor protein and in the presenilin genes have previously been shown to play a role in ADEOAD, however there is a subpopulation of patients who do not have mutations in either of these genes. Using exome sequencing, Dominique Campion and colleagues found that a subgroup of ADEOAD patients, without mutations on known ADEOAD-associated genes, harbored individual mutations on another gene, SORL1. These mutations were not present in a cohort of 1500 control individuals. Computer analyses further predicted that each of the mutations is likely to decrease the functionality of SORL1. Underexpression of SORL1 has previously been shown to result in an
increase in amyloid-beta production, therefore the authors suggest that mutations in SORL1, as outlined in this work, may also contribute to the development of ADEOAD.

This study identifies many rare variants in SORL1 that are exclusive to ADEOAD patients and suggests that further genetic heterogeneity is present in ADEOAD. Whether these mutations result in fully penetrant ADEOAD or not remains to be established.

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