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Dr. Elizabeth Blue, Ph.D., Assistant Professor, Division of Medical Genetics, UW. Variants regulating NCSTN and ZBTB4 are associated with age-at-onset of Alzheimer’s disease

Talk Abstract

The identification of novel genetic modifiers of age-at-onset of Alzheimer’s disease could advance our understanding of AD and provide novel therapeutic targets. A previous genome scan for modifiers of age-at-onset among families affected by early-onset Alzheimer’s disease caused by the PSEN2 N141I variant identified two loci with significant evidence for linkage: 1q23.3 and 17p13.2. Here, we describe the fine-mapping of these two linkage regions, and test for replication in six independent data sets. By fine-mapping these linkage signals in a single large family, we reduced the linkage regions to 11% their original size and nominated 54 candidate variants. Among the 11 variants associated with age-at-onset of Alzheimer’s disease in a larger sample of Germans from Russia, the strongest evidence implicated promoter variants influencing NCSTN on 1q23.3 and ZBTB4 on 17p13.2. The association between ZBTB4 and age-at-onset of Alzheimer’s disease was replicated by multiple variants in independent, trans-ethnic data sets. Our results demonstrate association between age-at-onset of Alzheimer’s disease and both ZBTB4 and NCSTN. ZBTB4 is a transcriptional repressor that regulates the cell cycle, including the apoptotic response to amyloid beta, while NCSTN is part of the gamma secretase complex, known to influence amyloid beta production. These genes therefore suggest important roles for amyloid beta and cell cycle pathways in age-at-onset of Alzheimer’s disease.