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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.