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Researchers identify additional genes that may play a role in Alzheimer's disease

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Researchers from Boston University School of Medicine, in collaboration with scientists from the Rotterdam Study led by professor Monique Breteler; the Cardiovascular Health Study led by professor Oscar Lopez; the AGES-Reyjavik study led by Prof. Lenore Launer; the Mayo AD study led by professor Steve Younkin; the European AD Consortium lead by professor Philippe Amouyel; the Genetic and Environmental Risk in Alzheimer's Disease consortium led by professor Julie Williams and the Fundació ACE study in Barcelona led by professor Merce Boada, have identified two new genes that may be risk factors for the development of late-onset Alzheimer's disease (AD).

The findings, which are reported in the May 12 issue of the *Journal of the American Medical Association*, may lead to new ways to treat, postpone or prevent AD.

It is estimated that one of every five persons aged 65 years will develop AD in their lifetime, and that one in 10 baby boomers will develop the disease before they die. Genetic variants appear to play an important part in the development of the disease since having parents or siblings with the disease increases a person's risk.

Using an intensive, genome-wide association analysis study (GWAS), the researchers identified two new genes at specific locations in the DNA called loci that reached the required genome-wide statistical significance threshold for the first time, thus identifying them as very likely associated with AD. They were found on chromosomes 2 and 19, the

first being close to a gene called BIN1 (Bridging Intergrator 1) on chromosome 2 and the second being close to several genes including EXOC3L2, BLOC1S3 and MARK4 on chromosome 19. These findings were replicated in an independent population.

"Identifying each of these new genes, one on chromosome 2 and a second locus on chromosome 19, points to new biological pathways involved in the development of AD," said senior author Sudha Seshadri, MD, an associate professor of neurology at BUSM and an Investigator at the Framingham Heart Study. "Although such benefits are likely a decade away, studying these pathways should lead to new ways to postpone, prevent and perhaps treat the disease," she added.

Since 1975, the National Heart Lung and Blood Institute (NHLBI) and Boston University's Framingham Heart Study has gathered information on AD and in 2007 obtained extensive genetic data on these persons through the SHARe (SNP Health Association Resource) project. The BUSM researchers then joined with several leading world-wide epidemiological researchers who were also studying AD in population cohorts, notably the Rotterdam study, the Cardiovascular Health Study and the AGES-Reykjavik study to form the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. The researchers combined their data with published data and assembled the largest sample to date, over 35,000 persons of whom over 8,000 developed AD.

"This highly collaborative international effort enabled researchers to build the large sample size needed to identify elusive gene variants that may play a role in this devastating neurological disease," said Marilyn Miller, PhD, of the National Institute on Aging, which funds the collection of AD data in the Framingham study and funded the analysis for this GWAS. "Such collaborations are key to a fuller understanding of the many genetic factors that may contribute to overall risk for late onset

Alzheimer's and how these genes affect the development of the disease."

Provided by Boston University Medical Center