Common Variation in Gene Linked to Structural Changes in the Brain

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An international group of researchers is the first to show that common variations in a gene – previously shown to be associated with Retts Syndrome, autism, and mental retardation – are associated with differences in brain structure in both healthy individuals and patients with neurological and psychiatric disorders. Their findings will be published in the early online edition of the *Proceedings of the National Academy of Sciences* the week of August 17.

"We studied not only the gene itself – a gene called MECP2, which is known to have a big effect on brain development – but also the regions surrounding the gene, sometimes known as junk DNA," said principle investigator Anders M. Dale, PhD, professor of Neurosciences and Radiology at the University of California, San Diego School of Medicine. "Looking at this 'bigger window' of genetic data, we discovered that common variations in the MECP2 region result in changes to brain structure, even in healthy individuals." Anders explained that these effects do not seem to be population or disease-specific.

The link between genetics and brain structure is a hotly debated area of research. According to the research team, past studies investigating the link between gene variations and human brain structure haven't used the types of refined brain measurements provided by the structural MRI scans and software developed at UC San Diego, or the and full genetic coverage included in the *PNAS* study.

A team led by Ole A. Andreassen at Ullelvål University Hospital and Institute of Psychiatry in Oslo, Norway, provided data on one cohort – a sample from the Thematic Organized Psychosis (TOP) research group. This data was compared to a sample from the Alzheimer's Disease Neuroimaging Initiative (ADNI), the largest Alzheimer's disease study ever funded by the National Institutes of Health, in studies conducted at UC San Diego. The researchers looked at 289 healthy and psychotic subjects from the TOP study, and 655 healthy and demented patients, largely with Alzheimer's disease, from the ADNI study.

"The most statistically significant association between the two groups involved a minor allele of a single polymorphism, an inherited genetic variation that is found in more than one percent of the population," said co-author Nicholas J. Schork, PhD, of the Scripps Translational Science Institute. "This variation resulted in structural brain changes, such as reduced surface area in the brain's cortex, the area that plays a key role in memory, attention, perceptual awareness, thought and language." Although expressed in all cells, the MECP2 gene is developmentally regulated and exists in two different genetic transcripts within the brain's neuronal cells. Changes in brain structure caused by this gene are specific to males, since the variation is found on the X chromosome, but the functional, cognitive consequences aren't yet known.

The fact that broader, common variations in the area surrounding the MECP2 gene also resulted in changes to the brain structure suggests that this gene may be a promising candidate gene for further study, according to Dale. "Since each individual genetic mutation causes only small changes, the so-called 'junk DNA' may be where the action is," he said. These regions may not change the gene or the protein it encodes, but change the regulation of the gene, he added.

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