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Genetic variations tied to brain size for first time

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By Mark Schrope

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Using advanced brain imaging and genomics technologies, an international team of researchers co-led by Scripps Research Institute scientists has shown for the first time that natural variations in a specific gene influence brain structure. By establishing this link, the researchers have opened the door to a range of potential research efforts that could reveal gene variations responsible for a number of neurological conditions such as autism.

The work was reported in an advance, online Early Edition of the Proceedings of the National Academy of Sciences (PNAS) the week of August 17, 2009.

The research grew out of a larger project called the Thematic Organized Psychosis (TOP) study, led by Ole Andreassen at Ullelvål University Hospital and Institute of Psychiatry at the University of Oslo in Norway. TOP called for using extensive magnetic resonance imaging (MRI) scanning of hundreds of patients, including many with severe mental disorders, in collaboration with Anders Dale of the University of California, San Diego (UCSD), School of Medicine. Recognizing the potential of genetic studies conducted in conjunction with the braining imaging, the team reached out to include Nicholas Schork, a genetics expert at Scripps Research.

In deciding a first target, the group decided to focus on a gene known as MECP2 because it plays major roles in controlling brain development. Past studies with mice have shown that MECP2 regulates the activity of a wide range of other genes important in brain development. Substantial mutations in the gene also cause the rare disease Retts syndrome, in which brain growth slows, leading to a range of debilitating neurological problems and mental retardation. MECP2 has also been linked to autism.

Given its obvious import, says Schork, "This was a logical gene to target."

Making the Connection

In the new research, the team explored whether common variations likely to have small effects individually in the MECP2 and surrounding region in the DNA of patients could be tied directly to the way a patient's brain develops. They found that indeed some of these variations, known as single-nucleotide polymorphisms (SNPs), did correlate well with various measures of a patient's brain, though there was no identifiable tie between the variations and the mental disorders.

The closest connection they found was between two specific SNPs and lower surface area folds of the outer layer, or cortex, of the brainthe "grey matter," which plays critical roles in thinking, language, memory, and other functions. "So, those sorts of common variations actually do have some functional consequences that are dictating variations in brain size," says Schork. Interestingly, and for reasons not yet clear, the pattern was only seen in males.

With the direct correlation reliably identified in the patients from the TOP study, the research team then needed

to show its findings were not a fluke. This proved a challenging task, because the extensive brain imaging used for TOPsand essential for finding the SNP-cortical area correlationsis not commonly used. The researchers finally found what they needed in another study already under way called the Alzheimer's Disease Neuroimaging Initiative (ADNI), an ongoing public-private project supported primarily by the National Institutes of Health (NIH) with pharmaceutical and related industries and not-for-profit organizations providing support.

The researchers then set to work examining the MECP2 variations in the hundreds of patients involved in that study. "Lo and behold, it replicated," says Schork. The very same connection was found between the two SNPs and the lower cortical area, providing confidence that the correlation is quite real. Again, no tie was spotted between brain structure and disorder, in this case Alzheimer's disease.

No such correlation has ever before been established between natural genetic variations and brain volume. Though brain size has long been tied to various neurological conditions, defining such connections has been difficult, in part because of previous limitations in brain imaging technologies and techniques.

Expanding the Search

Schork and the rest of the team are now excited about the potential for additional related work. Because MECP2 has been linked to autism, there is a very real possibility that studying SNPs in autistic patients might reveal one or more that link to brain development problems. This could even illuminate possible paths for autism treatments. The group is also looking at possible connections between variations in other key genes and various brain regions.

Besides overall brain size, researchers believe that some neurological conditions might be tied to increases in the size of certain brain components, perhaps due to unidentified genetic mutations. This could prevent other components from growing to their full size due to the limited space inside a skull, preventing proper functioning.

"Who knows?" asks Schork, "This opens things up considerably. Now we can cast a much wider net and maybe rope in genes nobody had a clue about and discover something that otherwise wouldn't have been known."

Other authors of the paper, titled "A common MECP2 haplotype associates with reduced cortical surface area in humans in two independent populations," include first author Alexander Joyner, a UCSD graduate student and Scripps Research Scholar; Cinnamon Bloss, Trygve Bakken, and Eric Topol, from Scripps Research; Cooper Roddey and Anders Dale, from UCSD; and Lars Rimol, Ingrid Melle, Ingrid Agartz, Srdjan Djurovic from the University of Oslo.

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