Microcephaly genes associated with human brain size

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A group of Norwegian and American researchers have shown that common variations in genes associated with microcephaly - a neuro-developmental disorder in which brain size is dramatically reduced - may explain differences in brain size in healthy individuals as well as in patients with neurological and psychiatric disorders.

The study, which involved collaboration between researchers from the University of Oslo, the University of California, San Diego and Scripps Translational Science Institute in La Jolla, California, will be published on line the week of December 21 in the *Proceedings of the National Academy of Science*.

In relation to body size, brain size has expanded dramatically throughout primate and human evolution. In fact, in proportion to body size, the brain of modern humans is three times larger than that of non-human primates. The cerebral cortex in particular has undergone a dramatic increase in surface area during the course of primate evolution.

The microcephaly genes have been hot candidates for a role in the evolutionary expansion of the human brain because mutations in these genes can reduce brain size by about two-thirds, to a size roughly comparable to our early hominid ancestors. There is also evidence that four of the genes - MCPH1, ASPM, CDK5RAP2 and CENPJ - have evolved rapidly and have been subject to strong selective pressure in recent human evolution.

"It is obvious that such anatomical changes must have a basis in genetic alterations, said Lars M. Rimol, a research fellow at the University of Oslo. "Until now, little has been known about the molecular processes involved in this evolution and their genetic underpinnings. Now we have a piece of that genetic puzzle."

Several previous MRI studies have attempted to demonstrate a link between single polymorphisms (an inherited genetic variation that is found in more than one percent of the population) in these genes and brain size in healthy human adults, all of them unsuccessful. According to the research team, the success of the current study is likely due to two unique characteristics: first, by using a whole genome scan, the scientists could access an unprecedented number of polymorphisms, including non-coding regions outside of the gene itself; second, they were able to estimate cortical surface area, using software that reconstructs the cortical surface, based on volumetric MR scans, allowing for highly precise measurements of cortical thickness and areal expansion.

The software was developed by Anders Dale, PhD, professor of Radiology and Neurosciences at the UC San Diego School of Medicine, who headed the American branch of the research team. "The most statistically significant associations were consistently found with the areal expansion measure, which has implications also for future studies," said Dale.

The initial discovery was made in a sample of 289 psychiatric patients and controls from the Norwegian Thematically Organized Psychosis research project (TOP), led by Ole Andreassen from the University of Oslo, principal investigator of the Norwegian branch of the international research team. The most significant findings were then replicated in a sample of 655 healthy and demented patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI), the largest Alzheimer's disease study ever funded by the National Institutes of Health. The Norwegian

sample was ethnically homogenous; the ADNI sample was ethnically diverse. According to the researchers, the fact that reported associations were found across two independent studies, including healthy controls and various patient groups, shows that these effects are likely to be independent of population or disease.

Highly significant associations were found between cortical surface area and polymorphisms in possible regulatory regions near the gene CDK5RAP2. This gene codes for a protein involved in cell-cycle regulation in neuronal progenitor cells - cells that migrate to the cerebral cortex during the second trimester of gestation and eventually become fully functioning neurons. The cerebral cortex is the outer layer of the brain, often referred to as "gray matter." The most highly developed part of the human brain, the cerebral cortex is responsible for higher cognitive functions, such as thinking, perceiving, producing and understanding language, some of which is considered uniquely human.

Similar but less significant findings were made for polymorphisms in two other microcephaly genes, known as MCPH1 and ASPM. All findings were exclusive to either males or females but the functional significance of this sex-segregated effect is unclear.

"One particularly interesting feature of this new discovery is that the strongest links with cortical area were found in regulatory regions, rather than coding regions of the genes," said Andreassen. "One upshot of this may be that in order to further understand the molecular and evolutionary processes that have determined human brain size, we need to focus on regulatory processes rather than further functional characterization of the proteins of these genes. This has huge implications for future research on the link between genetics and brain morphology."

Provided by University of California - San Diego