Medical Xpress

Does brain size really matter?

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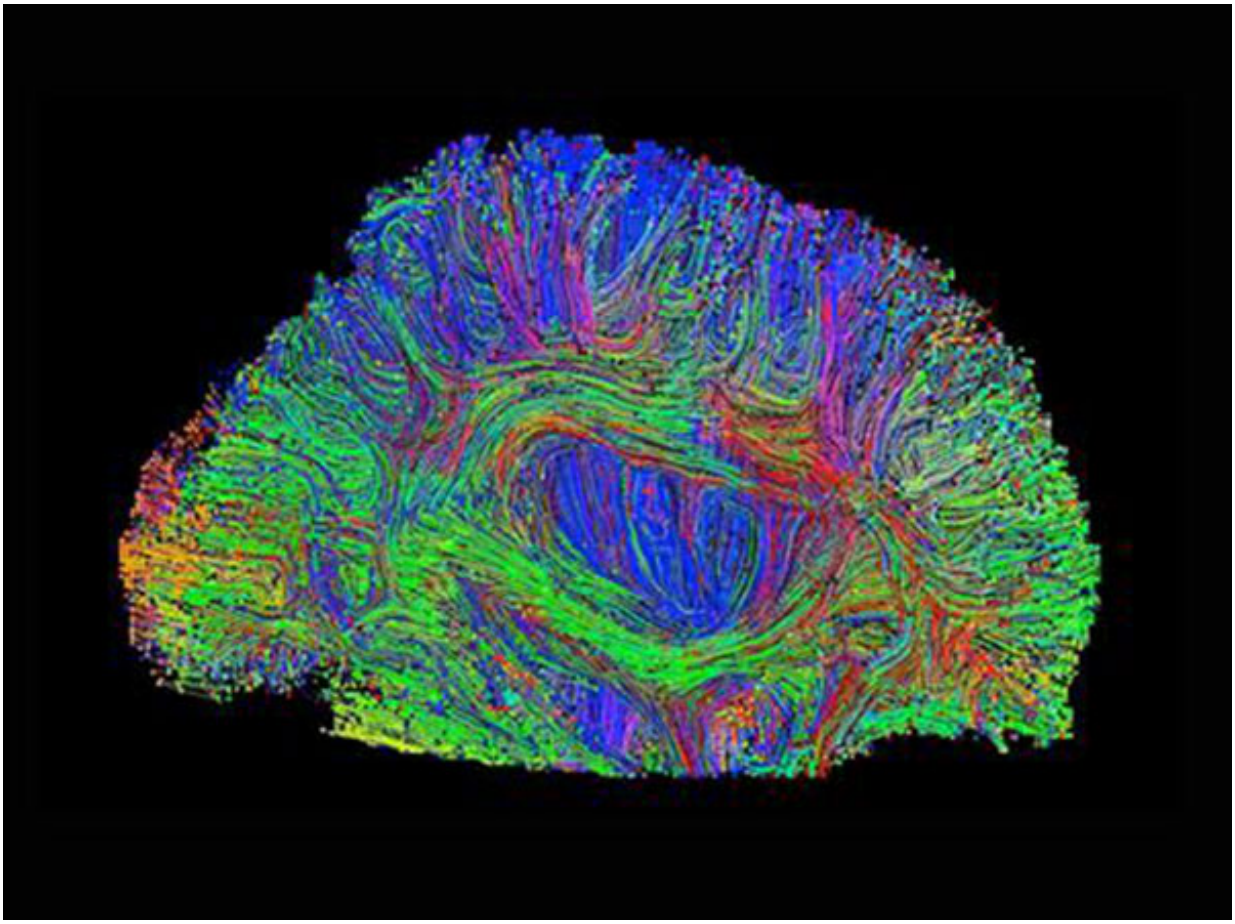

USC researchers lead an international team identifying seven genes that predict ‘intracranial volume’ and Parkinson’s disease. Credit: University of Southern California

Brain size may matter. In the world's largest MRI study on brain size to

date, USC researchers and their international colleagues identified seven genetic hotspots that regulate brain growth, memory and reasoning as well as influence the onset of Parkinson's disease.

Most brain imaging studies evaluate around 100 people, but the *Nature Neuroscience* study published on Oct. 3 examined 32,438 adults, said Paul Thompson, a corresponding author and associate director of the USC Mark and Mary Stevens Neuroimaging and Informatics Institute. The results bring scientists closer to understanding the genetic program that builds the living brain.

"Brain measures from MRI account for about 15 percent of the differences in our cognitive ability—that is, brain-based skills required to perform simple and complex tasks," said Thompson, who led a team of more than 300 international scientists. "The genes underlying brain development have far-reaching effects that extend well beyond the initial years of life. You have genes that are beneficial for you and help build brain structures early in life. Yet some of these are harmful later in life and promote diseases such as Parkinson's."

Parkinson's disease is a progressive disorder of the nervous system that affects movement and often leads to tremors. Like many other degenerative brain disorders, a cure does not yet exist.

Although scientists have not determined an ideal healthy brain size, a brain that is too small (microcephaly) or too big (macrocephaly) can lead to abnormal cognitive development and lifelong challenges. The human brain reaches maximum size around a person's early 20s, Thompson said.

The study used data on subjects from 52 study sites that are part of the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium and Enhancing Neuro Imaging Genetics through Meta

Analysis (ENIGMA) consortium, which is based at USC and led by Thompson. The research supports the notion that brain size could be used as a measure of "brain reserve," meaning brain size can promote resilience to age-related brain diseases.

ENIGMA is part of the USC Mark and Mary Stevens Neuroimaging and Informatics Institute, which aims to enhance discovery through the application of imaging and information techniques in the study of the brain. The institute is a leader in data acquisition, analysis stewardship and computational innovation for the purpose of biomedical research.

Genes and environment come into play

Both genetics and environmental factors affect brain size. Good diet, education and exercise build a healthy brain in young people and protect older people from tissue loss.

"This research is on the leading edge of cracking the brain's genetic code," Thompson said. "Millions of people carry variations in their DNA that help boost or lower their brains' susceptibility to a vast range of diseases. Once we identify these genes, we can target them with drugs to reduce the risk of disease. People also can take preventive steps through exercise, diet and mental stimulation to erase the effects of a bad gene."

The study began seven years ago. Its technique of using brain scans to identify gene hotspots provides more information than the traditional method of collecting DNA samples from patients.

"Now that we can see a gene's imprint in brain scans, it's like capturing a thief red-handed," Thompson said. "You can chase it down brain pathways and circuits and discover what brain cells the gene is damaging. Using brain scans builds a foundation so that scientists in the future can better focus their studies on hotspots of interest."

The seven genes and what they do

Thompson and his colleagues identified five new gene hubs that predict brain growth and confirmed two known hotspots. The genes in these areas provide links between an individual's maximum brain size and processes such as:

- the production of self-renewing stem cells (FOXO3)
- brain degeneration (MAPT)
- bone density (CENPW)
- physical growth (IGF1, HMGA2)
- DNA replication (GMNC)
- the creation of chemical bonds and proteins (PDCD).

Researchers adjusted their data for height and confirmed growth predictions by examining 2,824 children from before birth until age 6.

Of note, one of the areas of the human genome that affects brain size has a normal version and an inverted alphabet variant that evolved some 3 million years ago, Thompson said.

"MAPT is one of the most dangerous genes in this inverted zone," he said. "It is implicated in neurodegenerative diseases such as frontotemporal dementia and Parkinson's, Alzheimer's and Lou Gehrig's disease. Even in the normal brain-size range, brain scans reveal telltale signs of future disease."

Ongoing studies may reveal additional brain conditions that are promoted by the tau-associated MAPT gene, Thompson said.

"The genetic program that builds our brains consists of growth factors, cancer genes, genes that promote dementia and genes that are crucial in helping the brain to form connections," Thompson said. "A complex

interplay of factors makes some genes that are beneficial in early life go rogue later in life. It's extremely important to understand when genes that affect brain size—such as the MAPT gene—are helpful and what parts of the brain they are influencing."

More information: Hieab H H Adams et al. Novel genetic loci underlying human intracranial volume identified through genome-wide association, *Nature Neuroscience* (2016). DOI: 10.1038/nn.4398

Provided by University of Southern California