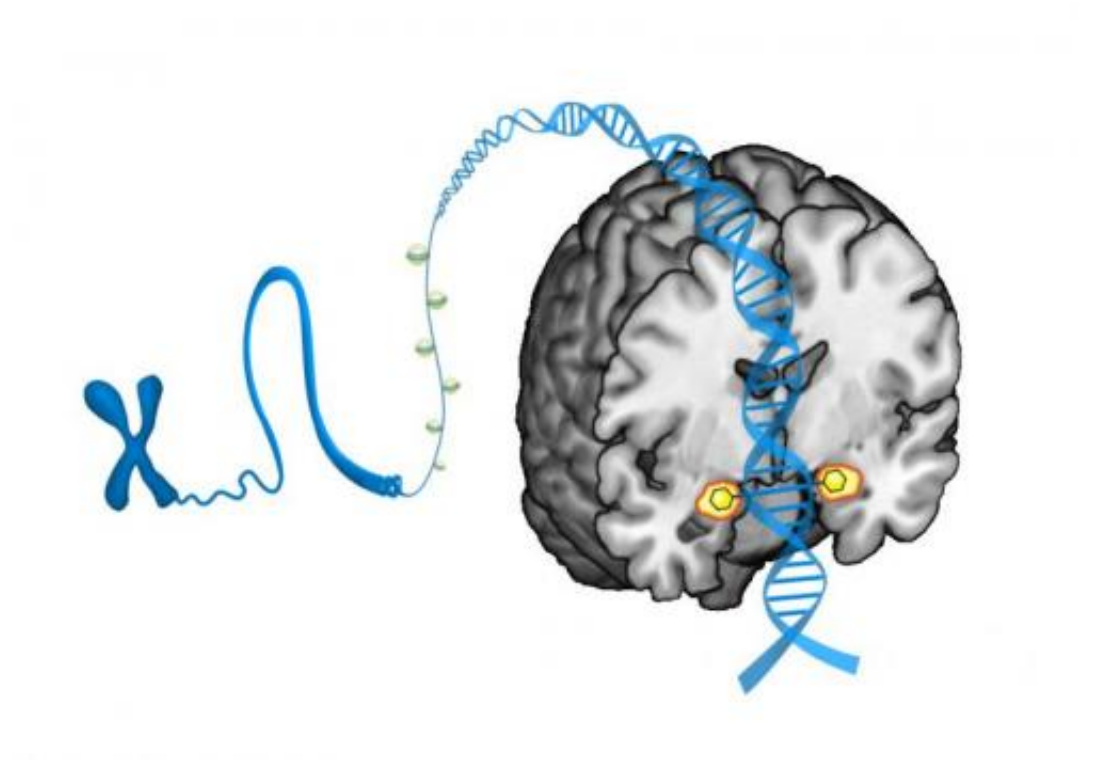
Small DNA modifications predict brain's threat response

August 3 2014



An artist's conception shows how molecules called methyl groups attach to a specific stretch of DNA, changing expression of the serotonin transporter gene in a way that ultimately shapes individual differences in the brain's reactivity to threat. The methyl groups in this diagram are overlaid on the amygdala of the brain, where threat perception occurs. Credit: Annchen Knodt, Duke University

The tiny addition of a chemical mark atop a gene that is well known for its involvement in clinical depression and posttraumatic stress disorder

can affect the way a person's brain responds to threats, according to a new study by Duke University researchers.

The results, which appear online August 3 in *Nature Neuroscience*, go beyond genetics to help explain why some individuals may be more vulnerable than others to stress and stress-related psychiatric disorders.

The study focused on the serotonin transporter, a molecule that regulates the amount of serotonin signaling between brain cells and is a major target for treatment of depression and mood disorders. In the 1990s, scientists discovered that differences in the DNA sequence of the serotonin transporter gene seemed to give some individuals exaggerated responses to stress, including the development of depression.

Sitting on top of the serotonin transporter's DNA (and studding the entire genome), are chemical marks called methyl groups that help regulate where and when a gene is active, or expressed. DNA methylation is one form of epigenetic modification being studied by scientists trying to understand how the same genetic code can produce so many different cells and tissues as well as differences between individuals as closely related as twins.

In looking for methylation differences, "we decided to start with the serotonin transporter because we know a lot about it biologically, pharmacologically, behaviorally, and it's one of the best characterized genes in neuroscience," said senior author Ahmad Hariri, a professor of psychology and neuroscience and member of the Duke Institute for Brain Sciences.

"If we're going to make claims about the importance of epigenetics in the human brain, we wanted to start with a gene that we have a fairly good understanding of," Hariri said.

This work is part of the ongoing Duke Neurogenetics Study (DNS), a comprehensive study linking genes, brain activity and other biological markers to risk for mental illness in young adults.

The group performed non-invasive brain imaging in the first 80 college-aged participants of the DNS, showing them pictures of angry or fearful faces and watching the responses of a deep brain region called the amygdala, which helps shape our behavioral and biological responses to threat and stress.

The team also measured the amount of methylation on serotonin transporter DNA isolated from the participants' saliva, in collaboration with Karestan Koenen at Columbia University's Mailman School of Public Health in New York.

The greater the methylation of an individual's serotonin transporter gene, the greater the reactivity of the amygdala, the study found. Increased amygdala reactivity may in turn contribute to an exaggerated stress response and vulnerability to stress-related disorders.

To the group's surprise, even small methylation variations between individuals were sufficient to create differences between individuals' amygdala reactivity, said lead author Yuliya Nikolova, a graduate student in Hariri's group. The amount of methylation was a better predictor of amygdala activity than DNA sequence variation, which had previously been associated with risk for depression and anxiety.

The team was excited about the discovery but also cautious, Hariri said, because there have been many findings in genetics that were never replicated.

That's why they jumped at the chance to look for the same pattern in a different set of participants, this time in the Teen Alcohol Outcomes

Study (TAOS) at the University of Texas Health Science Center at San Antonio.

Working with TAOS director, Douglas Williamson, the group again measured amygdala reactivity to angry and fearful faces as well as methylation of the serotonin transporter gene isolated from blood in 96 adolescents between 11 and 15 years old. The analyses revealed an even stronger link between methylation and amygdala reactivity.

"Now over 10 percent of the differences in amygdala function mapped onto these small differences in methylation," Hariri said. The DNS study had found just under 7 percent.

Taking the study one step further, the group also analyzed patterns of methylation in the brains of dead people in collaboration with Etienne Sibille at the University of Pittsburgh, now at the Centre for Addiction and Mental Health in Toronto.

Once again, they saw that methylation of a single spot in the serotonin transporter gene was associated with lower levels of serotonin transporter expression in the amygdala.

"That's when we thought, 'Alright, this is pretty awesome,'" Hariri said.

Hariri said the work reveals a compelling mechanistic link: Higher methylation is generally associated with less reading of the gene, and that's what they saw. He said methylation dampens expression of the gene, which then affects amygdala reactivity, presumably by altering serotonin signaling.

The researchers would now like to see how methylation of this specific bit of DNA affects the brain. In particular, this region of the gene might serve as a landing place for cellular machinery that binds to the DNA

and reads it, Nikolova said.

The group also plans to look at methylation patterns of other genes in the serotonin system that may contribute to the brain's response to threatening stimuli.

The fact that serotonin transporter methylation patterns were similar in saliva, blood and brain also suggests that these patterns may be passed down through generations rather than acquired by individuals based on their own experiences.

Hariri said he hopes that other researchers looking for biomarkers of mental illness will begin to consider methylation above and beyond DNA sequence-based variation and across different tissues.

More information: "Beyond genotype: serotonin transporter epigenetic modification predicts human brain function," Yuliya S. Nikolova, Karestan C. Koenen, Sandro Galea, Chiou-Miin Wang, Marianne L. Seney, Etienne Sibille, Douglas E. Williamson and Ahmad R. Hariri. *Nature Neuroscience*, August 3, 2014. DOI: 10.1038/nn.3778

Provided by Duke University