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Handful of genetic changes led to huge changes to human brain

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Changes to just three genetic letters among billions led to evolution and development of the mammalian motor sensory network, and laid the groundwork for the defining characteristics of the human brain, Yale University researchers report.

This networks provides the direct synaptic connections between the multi-layered neocortex in the human brain responsible for emotions, perception, and cognition and the neural centers of the brain that make fine motor skills possible.

A description of how a few simple changes during the early development of mammals led to the creation of complex structures such as the human brain was published May 31 in the journal *Nature*.

"What we found are the genetic zip codes that direct cells to form the motorsensory network of the neocortex," said Nenad Sestan, associate professor of neurobiology, a researcher for the Kavli Institute for Neuroscience, and senior author of the paper.

The paper investigated the genetic changes that occur during the early stages of development of an embryo and that direct cells to take on specific functions. Bits of DNA that do not code for proteins, called cis-regulatory elements, have been previously identified as critical drivers of evolution. These elements control the activation of genes that carry out the formation of the basic body plans of all organisms.

Sungbo Shim, the first author, and other members of Sestan's lab identified one such regulatory DNA region, which they named E4, that specifically enhances development of the corticospinal system. E4 is conserved in all mammals, indicating its importance to survival, the scientists explain. The lab also discovered how SOX4, SOX11, and SOX5 – sections of DNA called transcription factors — control the expression of genes and operate cooperatively to shape this network in the developing embryo. The changes in the genetic alphabet needed to trigger these evolutionary changes were tiny, note the researchers.

By manipulating only three genetic letters, scientists were able to functionally "jumpstart" regulatory activity in a zebrafish.

The authors also show that SOX4 and SOX11 are important for the layering of the neocortex, an essential change that led to increased complexity of the brain organization in mammals, including humans.

"Together, our fine motor skills that allow us to manipulate tools, walk, speak, and write, as well as our cognitive and emotional abilities that allow us to think, love, and plan all derive from these changes," Sestan said.

Sestan's lab is also investigating whether other types of changes in these genes and regulatory elements early in development might lead to intellectual disability and autism.

Provided by Yale University