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Multiple neurodevelopmental disorders have a common molecular cause

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Neurodevelopmental disorders such as Down syndrome and autism-spectrum disorder can have profound, lifelong effects on learning and memory, but relatively little is known about the molecular pathways affected by these diseases. A study published by Cell Press October 9th in the *American Journal of Human Genetics* shows that neurodevelopmental disorders caused by distinct genetic mutations produce similar molecular effects in cells, suggesting that a one-size-fits-all therapeutic approach could be effective for conditions ranging from seizures to attention-deficit hyperactivity disorder.

"Neurodevelopmental disorders are rare, meaning trying to treat them is not efficient," says senior study author Carl Ernst of McGill University. "Once we fully define the major common pathways involved, targeting these pathways for treatment becomes a viable option that can affect the largest number of people."

A large fraction of neurodevelopmental disorders are associated with variation in specific genes, but the genetic factors responsible for these diseases are very complex. For example, whereas common variants in the same gene have been associated with two or more different disorders, mutations in many different genes can lead to similar diseases. As a result, it has not been clear whether genetic mutations that cause neurodevelopmental disorders affect distinct molecular pathways or converge on similar cellular functions.

To address this question, Ernst and his team used human fetal brain cells

to study the molecular effects of reducing the activity of genes that are mutated in two distinct autism-spectrum disorders. Changes in transcription factor 4 (TCF4) cause 18q21 deletion syndrome, which is characterized by intellectual disability and psychiatric problems, and mutations in euchromatic histone methyltransferase 1 (EHMT1) cause similar symptoms in a disease known as 9q34 deletion syndrome.

Interfering with the activity of TCF4 or EHMT1 produced similar molecular effects in the cells. Strikingly, both of these genetic modifications resulted in molecular patterns that resemble those of cells that are differentiating, or converting from immature cells to more specialized cells. "Our study suggests that one fundamental cause of disease is that neural stem cells choose to become full brain cells too early," Ernst says. "This could affect how they incorporate into cellular networks, for example, leading to the clinical symptoms that we see in kids with these diseases."

More information: The *American Journal of Human Genetics*, Chen et al.: "Molecular convergence of neurodevelopmental disorders." www.cell.com/ajhg/abstract/S0002-9297(14)00396-6

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