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New discovery in autism-related disorder reveals key mechanism in brain development and disease

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A new finding in neuroscience for the first time points to a developmental mechanism linking the disease-causing mutation in an autism-related disorder, Timothy syndrome, and observed defects in brain wiring, according to a study led by scientist Ricardo Dolmetsch and published online yesterday in *Nature Neuroscience*. These findings may be at the heart of the mechanisms underlying intellectual disability and many other brain disorders.

The present study reveals that a mutation of the disease-causing gene throws a key process of neurodevelopment into reverse. That is, the mutation underlying Timothy syndrome causes shrinkage, rather than growth, of the wiring needed for the development of neural circuits that underlie cognition.

"In addition to the implications for autism, what's really exciting is that we now have a way to get at the core mechanisms tying genes and environmental influences to development and disease processes in the brain," said Dolmetsch, Senior Director of Molecular Networks at the Allen Institute for Brain Science.

"Imagine what we can learn if we do this hundreds and hundreds of times for many different human genetic variations in a large-scale, systematic way. That's what we are doing now at the Allen Institute," Dolmetsch continued.

In normal brain development, brain activity causes branches emanating from neural cells to stretch or expand. In cells with the mutation, these branched extensions, called dendrites, instead retract in response to neural activity, according to this study. This results in abnormal brain circuitry favoring connections with nearby neurons rather than farther-reaching connections. Further, the study identified a previously unknown mode of signaling to uncover the chemical pathway that causes the dendritic retraction.

This finding may have wide-reaching implications in neuroscience, as impaired dendrite formation is a common feature of many neurodevelopmental disorders. Further, the same gene has been implicated in other disorders including bipolar disorder and schizophrenia.

Under Dolmetsch's leadership, the Molecular Networks program at the Allen Institute, one of three major new initiatives announced by the Institute last March, is using similar methods on a grand scale. The Institute is probing a large number of human genetic variations and many pathways in the brain to untangle the cellular mechanisms of neurodevelopment and disease. In addition to identifying the molecular and environmental rules that shape how the brain is built, the program will create new research tools and data sets that it will share publicly with the global research community.

Timothy syndrome is a neurodevelopmental disorder associated with autism spectrum disorders and caused by a mutation in a single gene. In addition to autism, it is also characterized by cardiac arrhythmias, webbed fingers and toes, and hypoglycemia, and often leads to death in early childhood.

More information: Krey, JF et al. (2013) Timothy syndrome is associated with activity-dependent dendritic retraction in rodent and

human neurons. *Nature Neuroscience*, advance online publication January 13, 2013.