

Altered Gene Expression and Autism: Small Changes, Big Impact

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Can the development of autism be prevented? Can the symptoms of this complex disorder be reversed? Children's Memorial Research Center's Laura Herzing, PhD, is optimistic that in 5 to 10 years we will have an epigenetically based treatment to help at least a subset of patients with autism, and potentially even prevent autism in some genetically susceptible children.

"One of the most exciting insights in autism research," says Herzing, "is the recognition that very subtle changes in expression of genes at certain points of development may throw off a cascade of gene expression changes that affect how neurons are connecting. These changes are 'epigenetics.' It is not that a gene is missing or mutated. It is misregulated. The effects are not usually to the degree that you can see the abnormality in the brain, but to the degree that you can measure it functionally. This really emphasizes how small changes can have big ramifications."

To understand the behavioral consequences of such small changes in gene regulation, she is studying a region on the maternally inherited copy of chromosome 15 (15q11-q13), which has been implicated in many individuals with autism. Currently she is developing mouse models to examine changes in expression levels of 3 candidate genes – *UBE3A*, *GABRB3*, and *ATP10A* – hoping to connect an increase or a decrease in each gene to specific autistic symptoms.

Herzing and others have found that expression of all 3 of these genes is altered in Rett syndrome, a condition that tends to include autism. When the *UBE3A* gene is completely missing, the outcome is Angelman syndrome, which also often has autism as a component and has overlapping symptoms with Rett syndrome.

"One of our questions," says Herzing, "is what if *UBE3A* is not completely lost? What if there is half as much of it, or twice as much? What does that do?" Herzing has suggestive evidence that a slight change in *Ube3a* gene expression in mice produces impaired social interaction and behavioral inflexibility that are characteristic of autism.



Laura Herzing, PHD

Too much or not enough of the *GABRB3* gene may also lead to autistic features. The *GABRB3* protein is part of the neurotransmitter GABA receptor, and mutations are associated with some types of epilepsy and some forms of cleft palate. "Whereas in the adult brain GABA inhibits signaling, in the neonatal brain it promotes signaling," explains Herzing. "It is involved in synapse formation and activating neurons. So if the GABA process is disrupted in the neonate, the child misses the brief window important to neurodevelopment."

Herzing hypothesizes that the *ATP10A* gene keeps the structural aspects of neurons in order, affecting how the neurons function by keeping synaptic membranes intact.

"We are trying to determine the therapeutic value of altering gene expression levels to prevent or alleviate particular autistic manifestations, and possibly reverse the disease," says Herzing. "By characterizing the behavioral effects of alterations in candidate gene expression levels, we also hope to identify the particular features in certain autism patients that would make them more responsive to gene-specific therapies. Furthermore, if we can establish the specific genetic variants associated with naturally decreased or elevated expression levels, then this could be part of an early screen for one of the predisposing factors that may lead to the development of autism."

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