Medical Xpress

# Fragile X protein linked to nearly 100 genes involved in autism

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Doctors have known for many years that patients with fragile X syndrome, the most common form of inherited intellectual disability, are often also diagnosed with autism. But little has been known about how the two diagnoses are related.

Now a collaborative research effort at Duke University Medical Center and Rockefeller University has pinpointed the precise genetic footprint that links the two. The findings, published online in the journal *Nature* on Dec. 12, 2012, point the way toward new genetic testing that could more precisely diagnose and categorize the spectrum of autism-related disorders.

Fragile X syndrome is the most well understood single-gene cause of autism. It results from defects on a small part of the genetic code for a protein that researchers have dubbed the fragile X mental retardation protein, or FMRP.

Normally, FMRP plays an important role controlling production of other proteins in the brain and other organs. It does this by looking for specific genetic patterns located on the messages encoding proteins. When it locates these genetic flags, it attaches to them and, along with other signals, controls where and when protein is made.

In fragile X syndrome, this process breaks down because a defect in the gene causes the body to produce too little, or in some cases, none of the FMRP protein. As a result, additional proteins it would normally

regulate are made in the wrong place and at the wrong time. Until now, little was known about how this process worked in people with the autism.

Using a combination of laboratory experiments and advanced bioinformatics, the research team, led by Thomas Tuschl, PhD, a Howard Hughes Medical Institute investigator at Rockefeller University, and Uwe Ohler, PhD, an associate professor in Biostatistics and Bioinformatics at the Duke Institute for Genome Sciences & Policy, identified both the genetic flags that FMRP is looking for and the genes it targets.

The researchers discovered that FMRP directly controls at least 93 genes that have been independently linked to autism, as well as Angelman, Prader-Willi, Rett and other neurologic syndromes that have overlapping features with autism.

Additional research using a mouse model of fragile X syndrome revealed that the animals had abnormal protein production not only in the brain, but also in the ovary. The findings confirmed that the absence of FMRP protein causes ovarian insufficiency, which is common among women affected by fragile x syndrome.

"We now know not only which genes are linked to FMRP, but we can locate exactly where they interact," said Ohler. "Down the road, this finding could lead to more detailed genetic tests that take into account the subtle ways that genes get turned on and off."

Physicians who work with fragile X patients know that each patient's abilities and challenges are unique. Some individuals have almost no disability, while others have more severe physical and intellectual disabilities. Approximately 2 percent to 6 percent of children with autism are also diagnosed with fragile X and about one-third of fragile X

patients also meet the criteria for autism.

The new discovery should now enable researchers to examine the common molecular pathways leading to all forms of autism. Identification of those pathways could also lead to more targeted treatments for both fragile x and autism.

"We can now look for changes in the FMRP binding sites of genes to identify potential new genetic links to autism-spectrum disorders," said Neelanjan Mukherjee, a Duke post-doctoral scientist who contributed to the research.

Provided by Duke University Medical Center

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