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First Drug to Treat Fragile X?

The first drug to treat the underlying disorder instead of the symptoms of Fragile X, the most common cause of inherited intellectual disability, shows some promise according to a new study published in the January issue of Science Translational Medicine. Researchers from Rush University Medical Center helped design the study and are now participating in the larger follow-up clinical trial.

The data from the early trial of 30 Fragile X patients, found the drug, called AFQ056, made by Novartis Pharmaceuticals, helped improve symptoms in some patients. Patients who had the best response have a kind of "fingerprint" in their DNA that could act as a marker to determine who should get treatment.

"This is an exciting development. It is the first time we have a treatment targeted to the underlying disorder, as opposed to supportive treatment of the behavioral symptoms, in a developmental brain disorder causing intellectual disability. This drug could be a model for treatment of other disorders such as autism," said Pediatric Neurologist Dr. Elizabeth Berry-Kravis, a study author and director of the Fragile X Clinic and Research Program and the Fragile X-Associated Disorders Program at Rush.

The drug is designed to block the activity of mGluR5, a receptor protein on brain cells that is involved in most aspects of normal brain function, including regulation of the strength of brain connections, a key process required for learning and memory. Fragile X patients have a mutation in a single gene, known as Fragile X Mental Retardation-1 or FMR1. The mutation prevents FMR1 from making its protein, called FMRP, such that FMRP is missing in the brain. FMRP normally acts as a blocker or "brake" for brain cell pathways activated by mGluR5. When FMRP is missing, mGluR5 pathways are overactive resulting in abnormal connections in the brain and the behavioral and cognitive impairments associated with Fragile X.

The research team, led by Sebastien Jacquemont of Vaudois University in Switzerland in collaboration with Baltazar Gomez-Mancilla of Novartis, found no significant effects of treatment, when the entire group of 30 patients was analyzed. However, in a subsequent analysis, seven patients who had a fully methylated gene, a gene that was fully shut down, presumably resulting in no FMR protein in the blood or brain, showed significant improvement in behavior, hyperactivity and inappropriate speech with the treatment compared to placebo.

"The treatment period in this pilot study was very short and longer treatment might have been needed to see improvement in the whole group of patients. Importantly, the drug was well-tolerated and there were no safety problems," said Berry-Kravis.

A larger study of the drug is now underway that will recruit 160 patients worldwide and test the effects of a longer period of treatment. Rush University Medical Center is one of the participating sites.

Fragile X affects 1 in 4000 males and 1 in 6000 females of all races and ethnic groups. It is the most common known single gene cause of autism or "autistic-like" behaviors. Symptoms also can include characteristic physical and behavioral features and delays in speech and language development. The impairment can range from learning disabilities to more severe cognitive and intellectual disabilities.

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