# Experiment takes aim at genetic learning disorder

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Shawn Helbig, 27, who has Fragile X syndrome, visits Emory University's Department of Human Genetics, where he is taking part in a clinical trial to find a treatment for the genetic condition, Thursday, Jan. 28, 2010, in Atlanta. Krista Charen, a clinical trial coordinator with the genetic department, administers a electrocardiogram (EKG) to Helbig. (AP Photo/Rich Addicks)

(AP) -- A pill to ease a type of mental retardation? An experiment is under way to develop one, aimed at a genetic disorder that might unravel some of the mysteries of autism along the way.

Chances are you've never heard of the target - Fragile X syndrome - even though it's the most common inherited form of intellectual impairment, estimated to affect almost 100,000 Americans. It's also the most common cause of autism yet identified, as about a third of Fragile X-affected boys have autism.

Now a handful of drug makers are working to develop the first treatment for Fragile X, spurred by brain research that is making specialists rethink how they approach developmental disorders.

"We are moving into a new age of reversing intellectual disabilities," predicts Dr. Randi Hagerman, who directs the MIND Institute at the University of California, Davis, a study site.

Fragile X, more common in males than females, ranges from learning disabilities to severe cognitive impairment, along with emotional and behavioral problems. The genetic defect disrupts a basic foundation of learning: How brain cells respond to experiences by forming connections between each other, called synapses. Those structures aren't destroyed - they're too immature to work properly.

"The process of learning is just that much more difficult but not impossible, because there's nothing wrong with the synapse," says Dr. Stephen Warren, an Emory University geneticist who led the discovery of Fragile X's mutated gene.

The experimental drugs have an unwieldy name - mGluR5 antagonists (pronounced EM-gloo-ahr). But they aim to get the brain back on track by simply blocking an overactive receptor that plays a key role in weakened synapses. The goal is to strengthen synapses, to make learning easier and behavior more normal.

These are early-stage studies, beginning in adults to look for side effects. Specialists expect, if they work, any effect would be bigger in children's still-developing brains.

Scientists are watching closely because "this looks like a really promising pathway" for some types of autism, too, says Dr. Andrea Beckel-Mitchener of the National Institute of Mental Health which, along with

the patient advocacy group FRAXA, helped fund the underlying research.

Researchers don't expect a cure: Drugs can't turn back adults' decades of cognitive impairment, Warren cautions.

"I would be very surprised if this has some overwhelming rescue," he says, "but I think you can hope for at least some improvement."

In Alpharetta, Ga., 27-year-old Shawn Helbig is Emory's first test patient. He can read only small words, but first thing each morning Helbig races to swallow the experimental pill and cross off the day's dose on a special calendar. He's excited, his mother says, to be helping.

"I've always pushed him to be everything that he could be," says Sandy Britt, describing her son as higher-functioning, holding a part-time job at a pet store, for example.

Britt hopes for an easing of Helbig's ability to express himself, saying parents watch that frustration boil over into Fragile X's hallmark meltdowns.

"You look at anybody that's got Fragile X and you know they're there. It's like you ask them something and they kind of get lost in their thought," Britt says. "You still have people in this world that, when they see an adult that looks normal ... but they still have very childlike behaviors and sometimes very childlike responses, they poke fun."

What goes wrong in Fragile X? That mutated gene on the X chromosome shuts off production of a brain protein called FMRP. Boys are usually more affected than girls, because they have only one X chromosome while girls have two.

FMRP puts the brakes on other brain proteins. Among other things, its absence allows too much activity by that mGluR5 receptor. Some drug companies already had been exploring drugs to tamp down mGluR5 because it may play a role in anxiety, too.

Now in the Fragile X pipeline:

-New Jersey-based Hoffman-La Roche just began a Phase II trial at Emory, UC-Davis and three other hospitals comparing its candidate to a dummy pill in 60 adults with Fragile X.

-Hagerman says results are due soon from Swiss drug maker Novartis' similar study in Europe.

-Massachusetts-based Seaside Therapeutics - co-founded by Massachusetts Institute of Technology's Dr. Mark Bear, who made the mGluR5 link - is testing one drug thought to indirectly affect mGluR5 and will open trials of a more targeted one soon.

What's the evidence? The approach worked in mice bred with the Fragile X gene. More startling, when Hagerman gave a single dose of one experimental drug to 12 patients, she measured brain or behavior changes that lasted until the dose wore off in half of them.

Eye contact and language improved, Hagerman recalls; one young man even asked the nurse for a date. "That got us pretty jazzed."