

NEWS

Fragile X symptoms don't add up to autism, studies suggest

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Fragile X syndrome is an inherited form of intellectual disability often linked to autism: About one-

third of people with **fragile X syndrome** also have an autism diagnosis.

Several studies in the past few months, however, suggest that the set of autism-like symptoms seen in people with fragile X syndrome only superficially resemble those of the classic definition of autism^{1,2}.

Fragile X syndrome results from mutations in a single gene, **FMR1**. The fragile X protein also influences the expression of **several autism-linked genes**. With this known entry point, research into treatments for the syndrome has **surged ahead**.

In contrast, autism is genetically complex, and as a result is diagnosed based primarily on behavioral symptoms. Many children with well-characterized genetic disorders, fragile X syndrome included, show some of the symptoms associated with autism, and often merit a diagnosis of the disorder — some researchers have begun referring to these subtypes of the disorder as “autisms.”

But what is labeled as autism in these individuals may in fact be a distinct condition.

This has implications for treatments. Some treatments being developed for fragile X syndrome are **also being tested for autism** but may not have any benefits for the latter.

“I started off thinking that it didn’t really matter. If kids with fragile X syndrome met diagnostic criteria for autism, it was autism and that was the end of the story,” says **Leonard Abbeduto**, director of the University of California, Davis MIND Institute in Sacramento.

“I’ve come to appreciate that that’s not a fruitful approach,” Abbeduto says. “They are not exactly the same thing and I think that’s really important for treatments.”

Social anxiety:

One key distinction between the disorders, for example, is in social interactions. Children with autism and those with fragile X syndrome both shy away from social contact, have trouble making friends and avert their gaze when people look at them.

But children with fragile X syndrome often sneak a peek when the other person turns his back, researchers say. Children with autism, in contrast, seem mostly uninterested in social interactions.

“Children with fragile X syndrome all have very severe social anxiety that plays a big role in the perception that they have autism,” says **Stephen Warren**, professor of human genetics at Emory University School of Medicine in Atlanta. “They are actually interested in their environment; they are just very shy and anxious about it.”

Likewise, children with autism and those with fragile X syndrome both show **repetitive behaviors** —

a **core diagnostic feature of autism** — but the nature of the repetitive behaviors differs between the two disorders. Children with fragile X syndrome show basic repetitive behaviors such as hand-flapping, whereas children with autism can have one or more of a range of behaviors, including compulsive organizing of their toys and restricted interests³.

“We have someone who has hand movements and slaps their face, compared with someone who doesn’t have any of this and just likes to line their toys up,” says **Joseph Piven**, professor of psychiatry at the University of North Carolina, Chapel Hill. “We lump them into the same domain, but they’re really different phenomena.”

Fragile X syndrome is also distinct from autism in that nearly all boys with the disorder have low intelligence quotients (IQs). This intellectual disability leads to poor language skills and communication, which can easily be mistaken for autism, experts say.

Intellectual disability may also worsen the social deficits or repetitive behaviors associated with fragile X syndrome, making them more likely to be picked up by tests used to diagnose autism, says **Scott Hall**, assistant professor of psychiatry at Stanford University School of Medicine in California⁴. “As the IQ goes down, they are going to start to hit more and more on particular impairments that are designed to categorize kids with autism,” he says. In line with this hypothesis, low IQ seems to accompany the social symptoms seen in fragile X syndrome⁵. In autism, by contrast, social deficits dominate even in children of average intelligence.

Careful comparison:

One way to avoid IQ confusing the results is to only compare children who have fragile X syndrome with children who have autism and comparable IQs, says Warren.

In two studies published this year, Abbeduto and his colleagues followed just this approach. They found that at a given IQ level, children with fragile X syndrome have fewer inherent social deficits than do children with autism.

For example, boys with fragile X syndrome are **more likely to smile at** and to try to engage others than are boys with autism. They are also more anxious and hyperactive, perhaps causing them to avoid social situations.

Imaging studies also suggest that there are **structural differences** between the brains of children with autism and those with fragile X syndrome⁶.

In particular, several studies point to an enlarged caudate nucleus in children with fragile X syndrome⁷. This region organizes brain circuits that are primarily involved in movement. By contrast, the brains of children with autism are larger overall than those of controls, but have a caudate nucleus of average size⁸.

Brain imaging studies may be an objective measure for classifying children with autism or fragile X syndrome, instead of relying on superficial behaviors, says Piven.

For example, in a study published in April, Piven and his colleagues found that a group of boys with fragile X syndrome who have an enlarged caudate are also the most likely to have low IQs and severe autism symptoms⁹.

Ultimately, understanding how fragile X syndrome and autism are alike and different may help scientists treat the disorders.

“It’s sort of a plodding-along process; it feels like peeling an onion,” he says. “We need to do better and do more than just lump all these things together as the ‘autisms.’”

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