Progress in Identifying the Genetic Roots of Autism

By Melinda Beck

Updated Sept. 24, 2012 at 7:45 pm ET

One of the most agonizing questions that parents of children with autism ask is—why?

Now, a growing number of genetic tests are providing some answers.

Scientists say that roughly 20% of autism cases can be linked to known genetic abnormalities, and many more may be discovered.

Pinpointing a genetic explanation can help predict whether siblings are likely to have the disorder—and even point to new, targeted treatments. Last week, for example, researchers reported that an experimental drug, arbaclofen, reduced social withdrawal and challenging behaviors in children and adults with Fragile X syndrome, the single most common genetic cause of autism.

Cari Wheeler of Madera, Calif., says her 11-year old son, Max, who has both Fragile X and autism, used to get "sensory overload" just sitting in a restaurant, and had to withdraw into himself or a DVD player. Now, he can order food, look at the waiter and greet people with "What's up?" says Ms. Wheeler. "These are things he never did, ever."

A cheerleading mascot for the local youth football team, Max is now even comfortable having the entire stadium yell, "How's it going, Max?" to which he responds, "I feel good—like a Hawk should."

Autism spectrum disorder (ASD) is a collection of conditions that can range in severity from the social awkwardness and narrow interests seen in Asperger's to severe communication and intellectual disabilities. ASD now affects 1 in every 88 U.S. children—

nearly double the rate in 2002—according to the Centers for Disease Control and Prevention.

No single blood test or brain scan can diagnose autism spectrum disorders—in part because environmental factors also play a major role. But once a child is diagnosed, on the basis of symptoms and behavioral tests, researchers can work backward looking for genetic causes.

Both the American Academy of Pediatrics and the American College of Medical Genetics recommend that all children diagnosed with ASD be tested for Fragile X Syndrome and other chromosome abnormalities. The newest tests, called chromosomal microanalysis, can identify submicroscopic deletions or duplications in DNA sequences known to be associated with autism. Together, these tests find genetic explanations for more than 10% of autism cases.

Experts estimate that 400 to 1,000 individual genes may play a role in the complex neurological issues involved in autism. Tests are proliferating that look for mutations in some of those genes, thanks to new technologies that let scientists sequence many genes at once.

Mount Sinai School of Medicine in New York City, for example, is offering a new blood test that examines 30 different genes for mutations known to be associated with autism or other developmental delays.

Some autism-related genetic disorders also carry a high risk of cancer, seizures, heart

disease or other health problems, so knowing about them allows families and physicians to be vigilant for such issues.

Identifying genetic causes can also help families find support groups, research programs and potential treatments tailored to their child's specific needs. For example, one of the abnormalities Mount Sinai tests for is the SHANK3 mutation on chromosome 22. It causes an autism-spectrum disorder and Phelan-McDermid Syndrome, in which communication between nerve cells is disrupted, impairing learning and memory. Researchers at Mount Sinai found that an insulin-like growth factor could reverse that disruption in mice and are now testing it in children aged 5 to 17 with SHANK3 mutations.

"Once you know the genetic cause of an intellectual disability and understand the effect on the brain," says Alex Kolevzon, clinical director of the Seaver Autism Center at Mount Sinai, "you can start to think about targeted treatments."

At Mount Sinai School of Medicine's Seaver Autism Center, Lisa Edelmann, director of genetic testing, and Alex Kolevzon, clinical director, lead an effort to test for autism-related gene mutations. ILLUSTRATION: BRIAN HARKIN FOR THE WALL STREET JOURNAL

If a genetic mutation is found, researchers can also test the parents' DNA to see if the problem was inherited or if it occurred spontaneously, in which case the risk of having another child with autism is no greater than in the general population.

Another possible outcome: The test could find no abnormalities in those 30 genes—or find "variations of unknown significance." That would mean "we aren't certain what it means,

but we may know more in the future—and at least this will be in the patient's records," says Lisa Edelmann, director of the genetic testing lab at Mount Sinai.

Several other academic medical centers offer their own gene-sequencing tests for autism, looking at different suspect genes. The tests typically cost about $2,000 and generally are covered by insurance.

Other kinds of genetic tests may predict the likelihood that a child will develop autism before a clinical diagnosis is made.

Researchers at the University of Melbourne, Australia, have developed a test that looks for 237 genetic markers called single-nucleotide polymorphisms (SNPs). Some are thought to raise the risk of autism; others seem to protect against it. The test correctly predicted autism with more than 70% accuracy in people of Central European descent, but only 54% in those of Chinese descent, according to a study in the journal Molecular Psychiatry this month.

In April, IntegraGen Inc., a Cambridge, Mass., biotech company, announced a test, called ARISk , that predicts the likelihood that children aged 6 to 30 months who have older siblings with autism will develop the disorder themselves. The company is also developing a test to assess the risk of autism in children with no family history of the condition.

The goal of such tests, says IntegraGen general manager Larry Yost, is to have children at very high risk for autism referred to specialists for a definitive diagnosis earlier. Studies show that early intervention can significantly improve a child's IQ, language ability and social skills. But many children aren't diagnosed until after age 4, according to the CDC.

Autism experts say the disorder should never be diagnosed based on gene tests alone; some studies suggest that environmental factors may play an equally important role.

The largest-ever study of twins with ASD—192 pairs—reported last year that when one identical twin has autism, there is only a 70% chance that the other twin will, despite their identical genetic makeup.

Among fraternal twins, the likelihood that a second twin will have autism is 35%—nearly twice the risk other siblings face, the study found. "That suggests there was something

about their shared prenatal environment that really increases the risk," says Clara Lajonchere, vice president of clinical programs for Autism Speaks, a nonprofit science and advocacy group.

Environmental factors—premature delivery, low birth weight, maternal infections and maternal nutrition—have been implicated in autism, as well as advanced parental age. Some experts suspect that the older the father, the greater the chance for spontaneous genetic errors in sperm.

Most cases of autism probably involve some combination of genetic and environmental factors, experts say, and research is burgeoning.

More than 2,000 families with two or more affected children have donated DNA samples to the Autism Genetic Resource Exchange, funded by Autism Speaks, which makes the information available to researchers around the world.

And the Autism Sequencing Consortium hopes to collect DNA samples from 20,000 subjects for genome-wide association studies, and identify 100 more genes linked to autism in the next three years.

"We feel pretty good in autism these days," says consortium founder Joseph Buxbaum, director of Mount Sinai's Seaver Autism Center. "It was once the most intractable disorder in genetics and we're making progress."

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