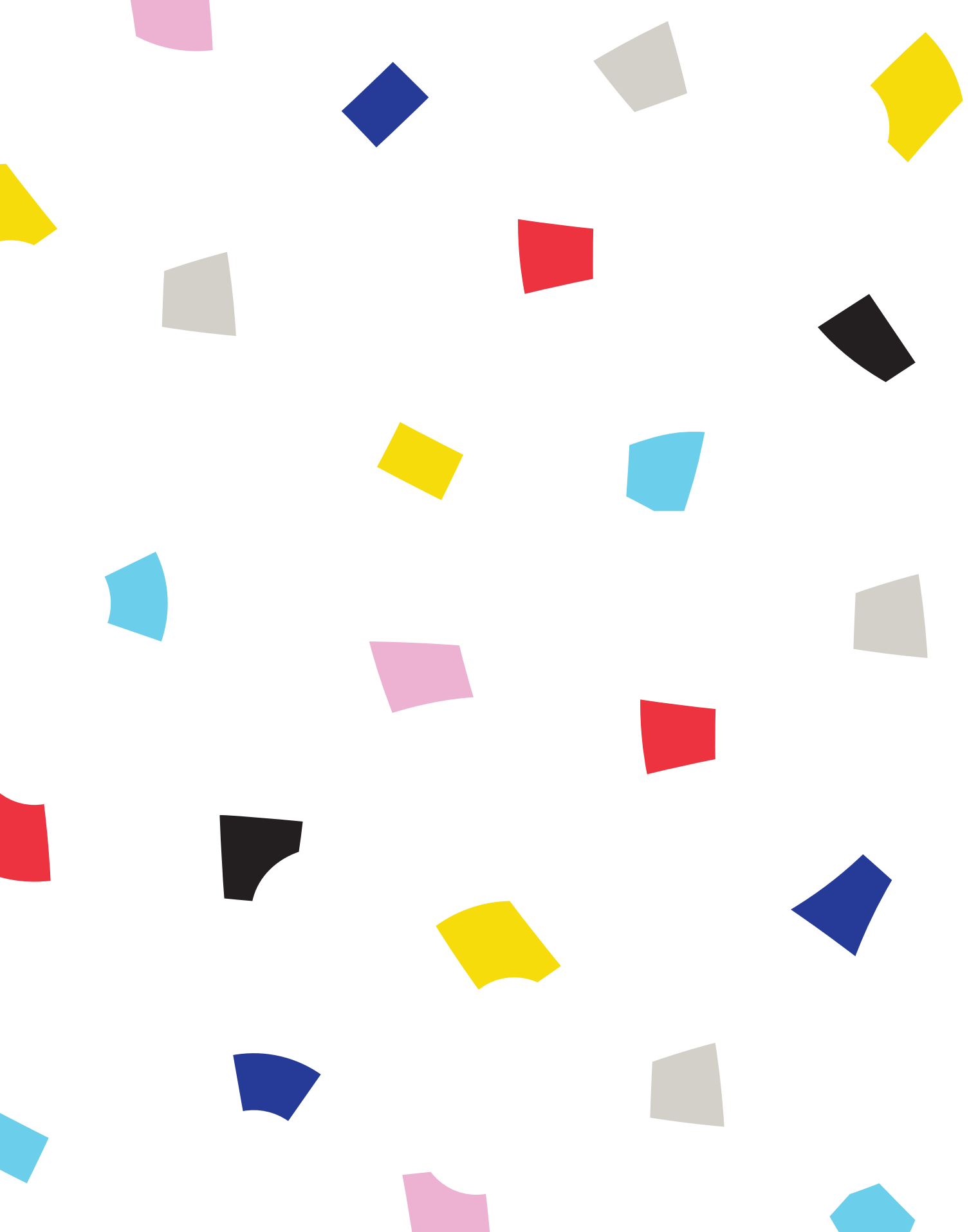


# Tales from Spectrum





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It has been 10 years since *Spectrum* launched with the mission to provide comprehensive news and analysis of advances in autism research. The site started in 2008 as an editorially independent arm of SFARI.org and grew rapidly, spinning off into a separate online entity in 2015.

Lucky for us, the field, too, has expanded dramatically during the past decade, giving us front-row seats to some of the biggest ideas in autism research as they have been revised, revived or rejected entirely.

In this collection of *Spectrum* articles, we wanted to share our unique vantage, revisiting some of the top headlines and discoveries we have covered since we began. The front of the book features important news stories from each year: seminal investigations on gaze, insights into the 'connectivity theory' of autism, observations from studies of infant siblings of autistic children and – more and more each year – revelations about key genetic variants.

The articles toward the end of the book are in-depth explorations of areas that have exploded during the past decade, such as autism genetics, and those that still need attention, such as the pressing healthcare needs of autistic adults. Other stories chart ideas that are being reconsidered – the prevalence of regressive autism, the merits of applied behavioral analysis, how to define autism – as well as newer ideas in the field, including a 'predictive coding' theory of the condition.

We hope you enjoy this look back at the past decade of fast-paced science, and help us celebrate *Spectrum's* 10<sup>th</sup> anniversary.

**Team *Spectrum***



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# 2008

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# Changes in chromosome 16 firmly linked to autism

BY MEREDITH WADMAN

Roughly ten percent of autism cases that occur as part of other clearly defined disorders, such as Rett or fragile X syndromes, have an obvious genetic cause.

What of the other 90 percent?

Mark Daly and his colleagues have hunted down a 593 kilobase 'hot spot' of genetic sequence that, when duplicated or deleted, substantially boosts the risks of autism seen independent of other syndromes.

In a paper published today in *The New England Journal of Medicine*, the researchers have identified a segment containing 25 genes on chromosome 16 that was deleted or duplicated in roughly one percent of children with autism. The results are based on samples drawn from three different populations in three independently conducted studies.

"It's a beautiful paper that demonstrates a clear association between a genetic locus and autism," says Arnold Levine, a molecular biologist who heads the Simons Center for Systems Biology at the Institute for Advanced Study at Princeton University.

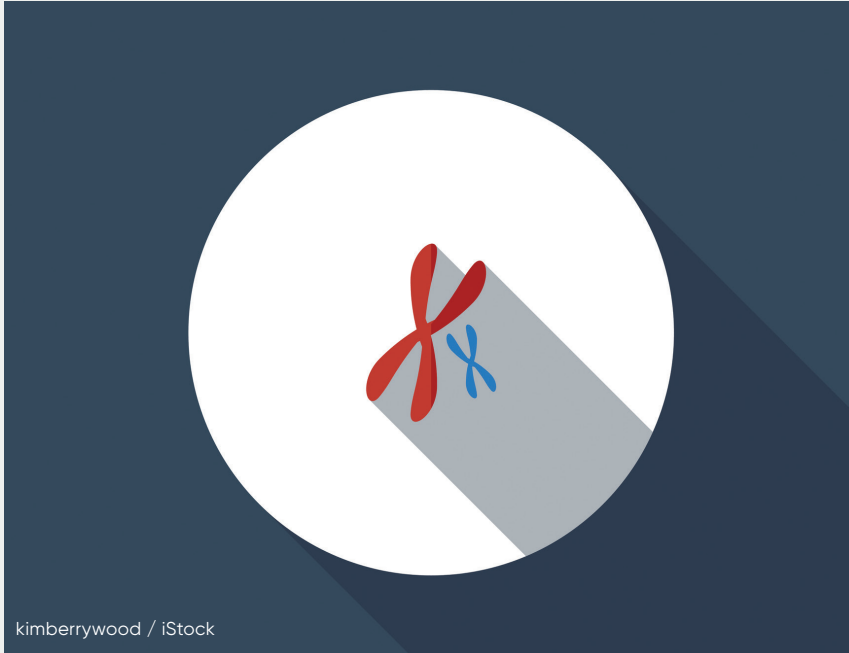
Unlike his predecessors, Daly and his team didn't simply identify a suspect region, but found it in numerous affected individuals, Levine notes. "This paper has been held to a higher standard," Levine

says. "It asked for reproducibility of observations and it got it. That's the power of this paper."

The finding provides unequivocal evidence that these genetic variations are a risk factor for autism, says Daly, assistant professor of medicine at Massachusetts General Hospital and Harvard Medical School and an associate member of the Broad Institute in Cambridge, Massachusetts.

Using sophisticated gene-scanning technology from Affymetrix, Daly hunted for instances in which an individual carries fewer or more than the standard two copies of any given gene. This so-called 'copy number variation' – which boils down to the duplication or deletion of a genetic sequence – became a hot area in autism research following the publication last year of a paper in *Science*. That paper, written by Mike Wigler and Jonathan Sebat at Cold Spring Harbor Laboratory and their colleagues, reported a laundry list of de novo – meaning new or non-inherited – copy number variations in individual children with autism.

Using DNA samples from 1,441 subjects with autism from the Autism Genetic Resource Exchange, Daly found five de novo deletions and seven duplications in that specific region of chromosome 16, a rate of nearly one percent.



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**Chromosome 16 variations not autism specific, company says**

**BY VIRGINIA HUGHES  
7 NOVEMBER 2008**

“The fact that it’s been identified as a de novo event, and that it’s recurrent – that is, that they found it in one percent of patients with autism – is the exciting part,” says Evan Eichler, a Howard Hughes Medical Institute investigator at the University of Washington in Seattle who wrote an accompanying commentary on the Daly paper. “So it’s not a transmitted mutation from grandparents to parents to offspring. This is something that is happening in the germ line.”

**REPEAT OCCURRENCE:**

Daly’s team also examined the DNA from two more sets of cases and controls, one from Boston Children’s Hospital and the other from deCODE genetics in Iceland. The same chunk of chromosome 16 was duplicated or deleted in substantially greater numbers in subjects with autism from these groups than in controls. Among all three groups, deletions and duplications in the region occurred

in roughly one percent of subjects with autism; among controls it was close to zero.

“Because we see this specific event many, many times in many, many patients and hardly at all in the general population, we know specifically that this event has great importance to autism,” Daly says.

Sebat says Daly’s findings further legitimize the notion that although autism is heritable, spontaneous mutations have an important role in causing the disorder. “The kids with the [chromosome] 16p deletions, most of their risk comes from that single, primary insult,” Sebat says. “The six-word message is: ‘heritable’ does not always mean inherited.”

The finding is likely to have immediate, practical implications for diagnosis of autism and for genetic counseling, Sebat says. “If you know a first child is carrying a de novo deletion in this region of chromosome 16, the chance of a second child having the same deletion is low.”

The role of the newly flagged region in autism remains mysterious. Of the 25 genes, ranging from some expressed in the brain to others that are important for the immune system, “there’s nothing obvious,” to autism’s causation, says Daly. Still, they provide a tantalizing way forward. The MAPK3 gene in the region, for instance, codes for a regulatory protein involved in cell growth and brain wiring.

As important as the new results are, however, they are unlikely to yield a one-size-fits-all answer for autism. For instance, five children in four of the families had de novo deletions of the relevant region of chromosome 16. But three other autistic children in the same families did not have the deletion.

“There are going to be other genes and maybe even environmental factors that modify the phenotype,” Levine says. “It isn’t going to be so simple as to say, ‘this gene causes this disease.’” ■

21 APRIL 2008

# Eyes provide insight into autism's origins

BY VIRGINIA HUGHES

The eyes, so goes the ancient proverb, are the window to the soul. Sophisticated machines that track vision suggest that eyes may also be the window to autism.

In the fall of 2002, clinicians at the Yale Child Study Center were testing 15-month-old Helen\*\*\* for developmental disorders. For most of her life, Helen had developed normally: smiling, then crawling, then walking, even saying a handful of words. But when she was about a year old, she stopped speaking. She stopped bringing things to her parents, and ignored new people.

Her parents were especially worried because Helen's 3-year-old brother had been diagnosed with autism a year earlier. Their fears for their daughter were confirmed: after a battery of cognitive and behavioral tests, the specialists at Yale found that Helen, too, is autistic.

In a way, Helen's visit was "serendipitous," says Ami Klin, a psychologist at the center. At the time, clinicians rarely saw an autistic child younger than age 2 or 3, so Helen provided a rare research opportunity.

Klin and his colleague, Warren Jones, began observing the way Helen looked at people. In one experiment, they used infrared cameras mounted on a baseball cap to track her precise

eye movements as she watched a video of a cooing woman's face. Unlike typical babies, Helen focused much more on the woman's mouth than on her eyes.

"That [experiment] generated the hypothesis that this girl could actually be watching somebody's face, but not necessarily experiencing that face as a person," Klin says.

Helen's case study has led to several follow-up experiments with larger groups of children, which have so far produced similar results. Several research groups are using eye-gazing differences to probe how autism might be linked to social cognition.

Because the technology provides one of the cheapest, most quantifiable measures of social cognition, it could routinely be used to diagnose autism, some experts say.

"Eye tracking is one of the few affordable and easily implemented technologies that gives us a real quantifiable way of measuring social cognition," says Michael Spezio, a social neuroscientist at Scripps College in California. The machines needed are much cheaper than those for EEG, fMRI or MEG, but more expensive and labor-intensive than the current gold standard of behavioral tests.

"People are really just feeling out what existing [eye-tracking] paradigms

would be appropriate to use on children of various ages, and then how children with autism will respond," says Sally Rogers, a development psychologist at the University of California, Davis. "We're still at the beginnings of this kind of work."

Eye tracking has long been used in human perception experiments. In 1977, psychologists at the University of Durham in England tracked the eye movements of three healthy adults as they looked at black-and-white photographs of human faces. They found that people tend to gaze mostly on 'core features' of the face – the nose, the mouth, and especially the eyes.

This focus on the eyes "is well-programmed in us," Klin says. Decades of research has shown that even in the first few days of life, babies prefer to look at their mothers, and mothers prefer to look at their babies.

"Out of this mutually reinforcing choreography, a lot that is important in human development seems to emerge," Klin says. Because impaired social development is a characteristic feature of autism, it's logical to study eye movements in people with autism, he adds.

In 2002, researchers at the University of North Carolina published the first eye-tracking study targeting individuals with autism. They tracked the eye movements of five adults with autism looking at photographs of facial expressions, and found that they spent a smaller fraction of time looking at the nose and eyes than did controls.

But still photographs lack the rapid social cues that occur in real social interactions, Klin notes. "Nothing is more challenging for individuals with autism than naturalistic situations," he says. "In the lab, we should be interested in how they can function in the real world."

In 2002, Klin and Jones published a study that used highly emotional

scenes from the film *Who's Afraid of Virginia Woolf?* instead of photos. They confirmed that individuals with autism gaze at the actors' mouths, or even at movements far in the periphery of the scene, as opposed to watching the actors' eyes.

These eye-tracking studies all involved adults or adolescents with autism – until Helen.

### CONNECTING THE DOTS:

Helen was tested on two eye-tracking paradigms. In the first, she watched a video of a woman making friendly cooing noises. Unlike typical babies, Helen focused much more on the woman's mouth than her eyes.

The second paradigm tested Helen's interest in biological motion by using 'point-light animations' of body movement that Klin and Jones had created at an animatronics studio in California. In the studio, they attached small lights to the major joints on an actor's body. Then the actor was taped making a variety of movements – such as playing patty-cake or waving excitedly – in the dark.

The resulting animations, white dots on a black background, look like moving constellations. Normal babies – even as young as two days old – can connect the dots and recognize the animations as human figures.

And typically developing babies in Klin's lab preferred to look at the waving human figure than at the same animation presented upside-down. "Our typically developing kids saw those displays as people. They're imposing social meaning onto these white dots," says Jones.

But Helen didn't make this social connection.

She showed a preference for the right-side-up version of the patty-cake animation only when it was accompanied by clapping noises for every time the actor's hands came together. "She was acutely sensitive

to this physical contingency," Klin says, meaning that she had no trouble recognizing the physical synchrony between movement and sound.

This idea of "physical contingency" might explain why many previous experiments showed that autistic individuals seem to gaze at the mouth, rather than the eyes. The mouth moves more than the eyes do, and produces sounds that are synchronous with these movements.

Klin and his group have expanded their studies to two groups of 2-year-old autistic children. Their results are currently in press. "Let's just say that whatever you read about the 15-month old stands for these larger groups of children," Klin says.

### CENTER OF EMOTION:

Knowing where children with autism are looking, however, doesn't necessarily show whether and how their brains use this visual information.

In 2005, researchers at the California Institute of Technology found that, like people with autism, a patient with unusual lesions to the amygdala – a small region in the temporal lobe that's thought to be the center of emotion – focused less on the area around the eyes when judging emotions. The observation suggested that autism might stem from an abnormal function of the amygdala.

Last year, Spezio reported that when people with autism are shown random parts of a face expressing fear or happiness, they rely on the mouths rather than on the eyes to correctly identify the emotion.

Even when they were shown photos of eyes, they didn't make use of that information to make emotional judgments. From this, Spezio concluded that "the brains of people with autism treat facial information differently."

"What's really interesting is how an autistic person looks at the face as

it unfolds over a minute or two of conversation," Spezio says. These longer "gaze paths", he adds, are likely to show distinct differences between autistic and normal individuals.

In unpublished studies, Klin and Jones are finding abnormal gaze patterns in babies younger than a year old who later develop autism.

But another ongoing study suggests that eye gazing patterns may change drastically during early development.

In 2006, Rogers and her colleagues at the University of California, Davis, tested 6-month-old siblings of children with autism as they interacted with their mothers in real time through a TV monitor. Using a "still-face paradigm," the researchers measured 31 babies' eye movements just after the mothers suddenly froze their faces. They found – just as Klin's group had – that these siblings of autistic kids spent more time looking at their mothers' mouths than their eyes.

As the researchers followed these babies, however, they found that the ones who had gazed longer at their mothers' mouths did not necessarily go on to develop autism.

"The three children who did develop autism, in fact, all had shown a preference for their mothers' eyes," says Rogers. Her group is still analyzing the results but, she says, "The lesson here is that we have to be very careful when extracting a hypothesis from adult studies and taking it down to infancy."

Before using eye tracking as a diagnostic tool, "We'd have to have some reliable markers using eye-tracking that are better than behavioral markers," Rogers says. "It's an exciting time right now, we're all testing new paradigms and new kinds of stimuli. But we're not there yet."

\*\*\* Name has been changed for privacy reasons. ■



# 2009

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BY VIRGINIA HUGHES  
9 FEBRUARY 2009

**Autism mouse model debuts with common genetic flaw**

BY KELLY RAE CHI  
7 JULY 2009

**Genome-wide study fingers first common risk factors for autism**

BY VIRGINIA HUGHES  
28 APRIL 2009

**Mother's age is real factor in autism risk, study says**

BY VIRGINIA HUGHES  
28 SEPTEMBER 2009

21 JULY 2009

# Studies of brain structure boost ‘connectivity theory’ of autism

**BY VIRGINIA GEWIN**

The brains of people with autism have structural abnormalities that disrupt normal connections between brain regions and impede the flow of information across the brain. That’s the conclusion of a 20-year-old theory supported by several new, independent studies.

The most recent report, published in the June issue of the *Journal of Autism and Developmental Disorders*, focuses on the corpus callosum – the thick bundle of nerve fibers that bridges the left and right hemispheres of the brain.

The researchers found that the corpus callosum has seven percent less volume in the brains of people with autism than in those of healthy controls. What’s more, the lower the volume of the corpus callosum, the lower a participant’s score on tests of planning and problem solving.

Another study, published in the May issue of the journal, found that the gyral window – the conduit for nerve fibers running between the corpus callosum and the cortex – is abnormally narrow in autistic brains. This smaller passageway could impinge on normal nerve transmission.

“These papers demonstrate that the field is moving from basic volumetric measures of brain regions to more specific measures

of the structure and shape of multiple brain regions in our search for abnormalities,” says Antonio Hardan, associate professor of psychiatry at Stanford University’s School of Medicine and lead investigator of the first study.

The new findings bolster the so-called ‘cortical connectivity’ hypothesis of autism, which suggests that the disorder stems from impaired long-range circuits and excessive local connections in the brain.

When Nancy Minshew and colleagues began developing the theory almost two decades ago, it focused on reduced connections to and from the cortex, the large outer layer of brain cells responsible for higher brain functions such as reasoning and memory. Newer evidence shows that autistic brains may have connectivity problems between non-cortical regions as well.

“The connectivity hypothesis is so well established, I don’t think it’s a hypothesis anymore,” says Minshew, a behavioral neurologist at the University of Pittsburgh who collaborated with Hardan on the first study.

Other proponents add that no other theory has been put forth to explain both the pathology and the behavioral attributes of autism.

"There are a million theories about autism; the problem is that 99.9 percent of those only try to explain behavior alone," says Manuel Casanova, professor of psychiatry at the University of Louisville and lead investigator of the gyral window study.

The cortical connectivity hypothesis, in contrast, could explain why a person with autism could have impaired language acquisition – which requires connections between far-reaching brain regions – as well as enhanced visual acuity, which is localized to one brain region.

Most of the evidence comes from brain imaging, however, which doesn't directly measure brain structure or neuron signaling patterns. Some autism experts say that more work is needed to better quantify connectivity before putting too much stock in the hypothesis.

"The evidence so far suggests there are problems with cortical connectivity in autism, but the nature of the problem remains a hypothesis to be tested," says Pat Levitt, director of the Zilkha Neurogenetic Institute at the University of Southern California in Los Angeles.

### IMAGING INSIGHT:

Behavioral clues have long suggested that autism is a disorder that affects multiple regions of the brain. For example, people with autism don't typically have sensory deficits, such as blindness or deafness, that stem from one brain region. On the contrary, their complex cognitive and language problems point to abnormalities in regions responsible for integrating sensory information.

In the 1980s, however, no physical evidence could yet prove the idea of distributed brain deficits, Minshew says.

"Twenty years ago, psychologists were looking for a single primary deficit, and assumed it would reside in a single location in the brain, to explain the core features of autism," she says.

In the next decade, after studies found that head circumference and total brain volume are increased in the brains of people with autism, researchers began to search for widespread defects in connectivity.

Using magnetic resonance imaging, they found several intriguing connectivity patterns in autistic brains: compared with healthy controls, children with autism have larger brains and a lower ratio of nerve cells to nerve connections.

In 2002, Casanova conducted a series of imaging studies on postmortem brain tissue that provided the first physical proof that the structural abnormalities could explain observed behavior. The studies showed abnormally narrow and numerous 'minicolumns' – stacked groupings of small neurons – in the cortexes of adults with autism.

Usually, the smaller the neuron, the shorter its connections to other cells. So Casanova suggested that the large number of small cells in people with autism would bias the formation of short connections at the expense of longer ones.

"Casanova's findings were significant because we finally had some pathological evidence of the location of the problems – the cortex," says Minshew.

At the same time, Minshew's colleague Marcel Just, a professor

of psychology at Carnegie Mellon University in Pittsburgh, began developing methods to link brain anatomical differences to cognitive abilities using functional magnetic resonance imaging. This technique allows researchers to observe connectivity associated with performing a task.

In 2004, Just and colleagues found, for example, that the distant cortical areas involved in sentence comprehension are not synchronized in people with autism.

In 2007, his team found decreased synchronization when people with autism try to perform problem-solving tasks that require both the left and right brain hemispheres.

Yet researchers must still determine the degree to which impaired connectivity occurs across the heterogeneous autism spectrum. "I think almost certainly that a significant subset of individuals with autism have reduced connectivity," says Elliott Sherr, a pediatric neurologist at the University of California, San Francisco.

Sherr studies people with defects in the corpus callosum in order to directly trace how losing this nerve highway may disrupt connectivity. He, too, has found structural causes of reduced connectivity. What's more, he has found preliminary evidence that reduced connectivity correlates with poor performance on problem-solving tasks – a common deficit in people with autism.

The corpus callosum isn't the only place where connectivity deficits may occur, nor will anatomic differences alone explain behavior, Sherr notes. Still, "the more we can break down the components of autistic behavior or clinical deficits, the better we can study the underlying biology."

## MYRIAD DIFFERENCES:

Structural changes occurring during brain development may also disrupt connectivity, according to a report by Minshew and Hardan published in the June issue of *Biological Psychiatry*. The team found that over a 30-month period, adolescent boys with autism have more thinning of cortical brain cells than do healthy controls. This age-related shrinking is more profound in boys with severe autism, suggesting that connectivity is most disrupted in this group, say the researchers.

At least one study, however, challenges the idea that structural abnormalities in autistic brains disrupt normal long-range connections.

Last year, Chantal Kemner found that the integration of auditory and visual information, which requires intact long-range connections, is normal in people with autism. The study used electroencephalography – a non-invasive technique that measures brain waves through the scalp – because it can measure fast changes in regional activation.

“If there is normal connectivity, there should be no abnormalities in timing of auditory and visual information – and there weren’t,” says Kemner, a developmental psychologist at the Rudolf Magnus Institute in Utrecht, The Netherlands.

Kemner and others caution that more direct evidence of connectivity is needed both to confirm the hypothesis and to find out more about the mechanisms that underlie these abnormal connectivity patterns. For instance, Levitt is using an animal model of autism to obtain electrophysiological measures of local and long-range brain circuits.

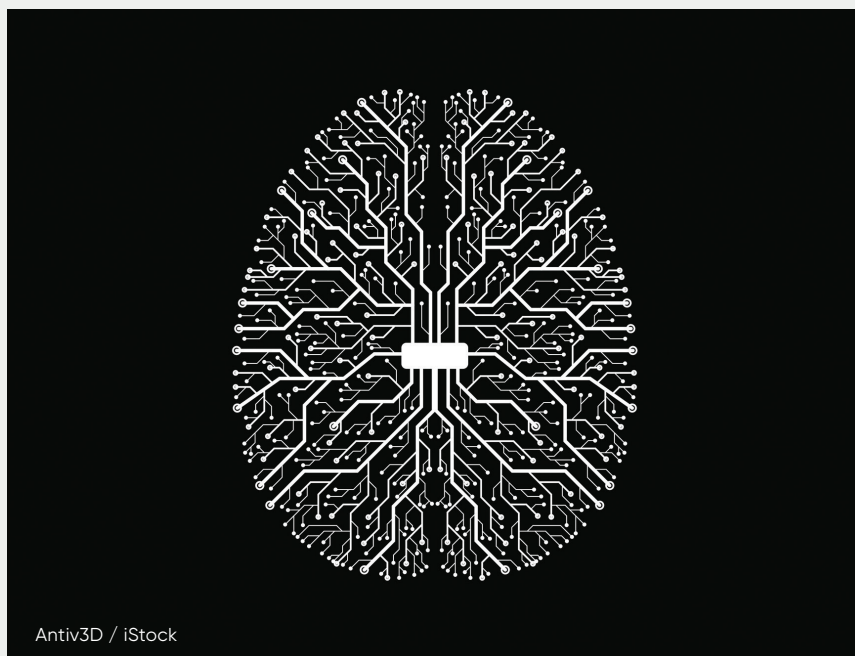
Minshew agrees that the research has to get much more specific, to

probe how structural abnormalities lead to particular behaviors. “We need to work out the interaction between all brain structures for each function,” she says.

By doing so, she says, scientists can determine whether the disruption of specific neural systems explains the variability seen in autism symptoms. For example, she thinks people with autism who have high anxiety will have more cortical connections to the amygdala, the deep brain region that processes emotion.

The biggest unanswered questions involve the myriad differences among people, in both circuitry and genetics. Fortunately, recent technological advances have accelerated work done in imaging, genetics and other areas of autism research. Minshew expects research to continue at the same pace.

“If we can make as much progress in next three to five years as we did in the last three to five years, it will be phenomenal,” she says. ■



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20 NOVEMBER 2009

# Only subset of chromosome 16 variants linked to autism

BY VIRGINIA HUGHES

Deletions or duplications of chromosomal segment 16p11.2 – previously reported as a key autism region – are seen in people with developmental delays and speech and behavioral problems, but not necessarily autism. That’s the finding from two large studies published last week of people carrying these rare genetic variations.

The results suggest that variants in the 16p11.2 region – referred to briefly as 16p – must pair with other genetic or environmental factors to cause the full-blown social deficits and stereotyped behaviors seen in autism, the researchers say.

“We are trying to make it clear that the association with autism is there, but also to be open-minded to other conditions that are associated with this rearrangement,” says Marwan Shinawi, an investigator on one of the studies, led by researchers at Baylor College of Medicine in Houston, Texas.

Published online 12 November in the *Journal of Medical Genetics*, that study analyzed 45 people with 16p variants. The other new report, published online by Spokane-based Signature Genomics the same day in the *Journal of Neurodevelopmental Disorders*, analyzed 77 individuals carrying abnormalities in the region – the largest such group to date.

Both reports found that the most common symptoms in people carrying these variants are speech delay and cognitive impairments.

“It’s probably a bit of a misnomer that this has been flagged as an autism disorder,” says Evan Eichler, an investigator on the Signature study. “If you look at all of the studies, the speech delay issue is pretty much the most highly penetrant feature of this disease, and I think that’s why it gets classified as autism quite frequently.”

Two other studies this year dove into the complicated medical histories of people carrying 16p variants. All of them found that the region is associated with a wide variety of clinical features, and that only a subset of people carrying the variants also have autism.

“There’s been a number of these medical record reviews now and I think we have an overall feel for these individuals,” notes Ellen Hanson, director of the Phenotyping Core at Children’s Hospital Boston, who was not involved in either new study. “But none of the studies has really done any rigorous phenotypic analysis of the patients. It’s a great time to take the next step.”

For a more complete clinical picture, researchers should use more rigorous and standardized psychological batteries, and try to

collect brain imaging data on all participants, she says.

Since the trio of studies that first tied it to autism in early 2008, 16p11.2 has been one of the hottest regions of study in the field.

Those reports showed that deletions or duplications – dubbed ‘copy number variations’ (CNVs) – in the region crop up in about 1 percent of people with autism. But the studies also found these CNVs in a handful of people with schizophrenia, bipolar disorder, depression or no recorded health problems.

Subsequent research told an even more complicated story of the region, which spans 600 kilobases and includes about 25 genes. For example, earlier this year, researchers identified 14 16p deletions in a group of 4,284 people with mental retardation, only one of whom has a confirmed autism diagnosis.

Last month, a study analyzing data from about 6,000 people found that carrying a 16p duplication increases the risk of developing schizophrenia by about 14-fold.

#### MYSTERY SAMPLES:

Signature Genomics, a commercial molecular diagnostic laboratory, based its findings on blood

samples sent in for tests for various health problems, including heart defects, seizure disorders and developmental delay. Most of the samples are from children or teenagers, and about 10 percent of the cases are referred because of suspected autism spectrum disorders (ASD), says Blake Ballif, the company’s director of product development and research.

Analyzing 9,773 blood samples using high-resolution DNA microarrays, the researchers identified 45 deletions and 32 duplications of the 16p region.

Six individuals carrying the deletion and three carrying the duplication have suspected autistic features, autism or Asperger syndrome – that’s about 1.1 percent of the total number of autism cases the company has received, and roughly consistent with previous studies.

But the company also identified 16p variants in 0.76 percent of its non-autism referrals, and in 3.1 percent of samples identified with genetic abnormalities.

Similarly, the other study analyzed blood samples sent to the Medical Genetics Laboratories at Baylor College of Medicine. About 70 percent of the samples are from people who live in Texas, according to Shinawi, who led the clinical work.

#### RELATED STORIES:

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2 OCTOBER 2009

## Chromosome 16 duplications tightly linked to schizophrenia

BY KELLY RAE CHI  
28 OCTOBER 2009

## Autism study zooms in on five-gene strip on chromosome 16

BY VIRGINIA HUGHES  
10 NOVEMBER 2009

Among the roughly 7,400 samples, the researchers picked up 27 deletions and 18 duplications of the 16p region. Only about 20 percent of the people carrying these variations have been diagnosed with autism or autistic features. The final number could be higher, however, because the lab lacks clinical data for most of the samples.

The sheer number of individuals with 16p abnormalities is impressive, but both teams acknowledge that their studies suffer from scattershot clinical descriptions.

When a doctor sends Signature Genomics a sample that's suspected of autism, for example, "there's a wide range of things that could fall under the ASD [label], and it's not entirely clear what those all might be, or whether they had full testing for autism," says Ballif.

The company tried to contact the referring doctor for each of the 77 people carrying 16p CNVs to get additional information, but succeeded in only 28 of the cases.

The Baylor group obtained clinical information for 17 people carrying the deletion and 10 carrying the duplication. Shinawi was able to personally interview and give a physical exam to 11 of these individuals, and 15 had accompanying brain imaging data.

This 'reverse genomics' approach – in which researchers start with a genetic description and work backwards to find a clinical description – is in stark contrast to previous studies of the region, which drew from large cohorts of people diagnosed with autism using standardized behavioral tests, such as the Autism Diagnostic Observation Scale (ADOS).

### DISTINGUISHING FEATURES:

The clinical descriptions published in the studies span a wide range of features, and provide an intriguing contrast between people carrying the deletions and those carrying the duplications.

For example, both studies show that deletions tend to be spontaneous, or *de novo*, rather than inherited. Deletions are more strongly associated with autism than are duplications.

"This tells us that whatever the duplication phenotype is, it's much milder," Eichler says. In contrast, he says, "the deletions must be largely contributed by new mutations in the population, presumably because most of these individuals are not going to marry and reproduce."

Perhaps most interesting, the Baylor team found a statistically significant difference in head size between people carrying each type of variant. Of the 16 carrying the deletion, 11 have enlarged heads. In contrast, 6 of the 10 people with the duplication have heads that are smaller than normal.

These findings agree with previous reports showing that children with autism tend to have large heads, and that people with different types of psychosis, such as schizophrenia, tend to have smaller heads.

"This is an observation that definitely deserves a little bit more attention in the future," says Shinawi, now an assistant professor of pediatrics at Washington University in St. Louis. He points out that head size is associated with CNVs in other chromosomal regions as well, though no one knows why.

For example, people carrying duplications in 1q21.1 have large heads, whereas those with deletions have smaller heads. The 1q21.1 deletion has also been associated with schizophrenia.

Hanson says she is glad to see an emphasis on differences between duplications and deletions of this much talked-about region. "It needs to be very clear, when we start talking to the general population, that the 16p11.2 deletion and the 16p11.2 duplication are really two completely different things," she says. "We're going to have to do analysis on both, and probably start doing separate papers so it's not confusing."

The biggest question to tackle will be why individuals with the same CNV have dissimilar clinical manifestations, Shinawi adds. Because only one copy of the chromosome is deleted or duplicated in these individuals, it could be that point mutations on the second copy affect the ultimate phenotype. Genes on other chromosomes or epigenetic or environmental factors could also be at play.

Shinawi and several other teams are building registries of children with 16p CNVs, aiming to refine the clinical phenotype of each of the variants, as well as find additional mutations that may interact with them. "I'm sure that over the next two years we'll be hearing a lot more about this region," Shinawi says. ■

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6 APRIL 2010

# Autism symptoms emerge in infancy, sibling study finds

**BY SANDEEP RAVINDRAN**

At 6 months of age, babies who will later develop autism begin to lose some of their social skills and continue to regress until age 3, according to a study published in March in the *Journal of the American Academy of Child & Adolescent Psychiatry*.

Unexpectedly, most parents do not notice this decline, suggesting that it happens gradually and without easily detectable dramatic changes.

"The results really, really surprised us," says lead investigator Sally Ozonoff, professor of psychiatry at the University of California, Davis M.I.N.D. Institute.

The study highlights the need for better screening methods to identify children at risk for the disorder as early as possible, the researchers note.

"We don't have any screeners right now that are useful for the 6-to-12 month period," says Sally Rogers, professor of psychiatry at the University of California, Davis MIND Institute. Based on the findings of their study, the researchers are developing new screening tools.

The American Pediatric Association recommends that clinicians screen children for autism twice by age 2. Given the new findings, these guidelines may need to be revised, Rogers adds. "It may

really be that we're going to have to be recommending repeated screenings, maybe at every well-baby checkup, across the infant and pre-school period if we really want to identify everybody."

Rogers' team followed younger siblings of children with autism from 6 months to 3 years of age. Many studies in the past few years have focused on these so-called 'baby sibs', who are 10 to 20 times as likely to develop the disorder as are those without a family history, experts say.

None of these previous studies – which focused mostly on language, motor and sensory skills – found signs of autism in children younger than 6 months.

The same trend holds in the new study, the first to delve more thoroughly into baby sibs' social behaviors. Researchers compared 25 children who would later be diagnosed with autism with 25 healthy controls. Every three months, the scientists evaluated the children on a variety of measures, such as their ability to utter sounds, words or phrases, how often their gaze is directed either at faces or at objects, and how often they smile or laugh.

At 6 months, children who go on to develop autism score no differently than do controls. "This was the most

important finding that we had, and the biggest surprise to us," Rogers says. "We were sure that we would be able to detect decreased social interaction, decreased social interest and decreased eye contact in babies who were going to develop the behaviors of autism – and we could not find that."

### **DIRECT MEASURES:**

The researchers did not detect differences between the two groups until the babies reached 12 months. At that age, baby sibs who go on to develop autism begin to spend less time looking at faces or vocalizing while doing so than do healthy baby sibs.

By 18 months, baby sibs who develop autism show a similar decrease in the amount of time they spend smiling while looking at faces. As they get older, this group of children continues to lose skills and social behaviors.

This study is important because it is one of the first prospective studies to look for early onset of autism, notes Ami Klin, director of the Autism Program at Yale Child Study Center.

Until recently, researchers relied either on retrospective reports or indirect measures, such as movies made by parents, when looking

for early signs of autism. "This is a great advancement, in that people are now observing children directly," Klin says.

Still, he adds that the researchers' conclusions are a bit premature. "This study utilized basically brief observational measures of children obtained in a very constrained environment," he says. More sophisticated and quantifiable measures of behavior that appear early in development could help detect autism even earlier than 6 months, he says.

For example, even 2-day-old healthy infants show a preference for animated depictions of human motion compared with other animations. Klin's studies have shown that 2-year old children with autism show no such preference.

Other experts say they have qualms about the way the researchers measured and analyzed baby behaviors.

Researchers at two sites videotaped the infants while they interacted with adults. For the final analyses, the researchers pooled observational data from both sites. Because some families missed visits and some video clips were unusable, however, the two sites evaluated a different number of infants in each age group.

The lack of a tightly controlled observational setting and the particular statistical analyses used make the data difficult to interpret, notes Mayada Elsabbagh, coordinator of the British Autism Study of Infant Siblings.

"The findings may be robust as group data, but we need to be careful with how valid such measures are in individual children," she says.

### **REGRESSIVE DEBATE:**

The findings about regression are somewhat more controversial. Researchers had previously hypothesized that there are two kinds of autism: one in which symptoms appear early and become more pronounced with age, and another in which children develop normally and then gradually lose skills.

But not all reports agree with the idea of a regressive autism phenotype. For example, a study that analyzed the brain waves of children with autism during sleep found epilepsy-like readings in 14 percent of children who had undergone regression, as opposed to 6 percent of children with early-onset autism. A subsequent study, however, found no difference



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**BY DEBORAH RUDACILLE  
30 SEPTEMBER 2010**

in brain activity between the two groups.

The new study found that 86.4 percent of the infants who later develop autism show a clear decline in social communication. This differs from previous reports, based on which the researchers expected to see regression in only a small proportion of the children.

"When the babies came in before 12 months, parents would say, 'I'm so happy to be sharing my normal baby with you,'" Rogers says. "But then in the next year, that baby developed autism, which was just devastating."

Parents noticed this regression in only 4 out of 19 cases, however. "It was very surprising. It's one of the most interesting things we've learned in these seven years of study," Rogers says.

Rogers previously reported that parents can detect early signs of autism by the time their children are 12 months old. Taken with the new results, this suggests that children with autism lose social skills slowly over the first year. The decline is so subtle and gradual that parents don't notice it, the researchers suggest.

Early-onset and regressive autism are probably part of the same continuum, says Rogers, adding that the timing of autism's onset may be random, with no bearing on the disorder's severity. She compares it to an infant catching a cold for the first time: "You're going to get a cold, and it probably doesn't mean anything whether it's at 6 months or at 15 months."

Researchers will need more intensive follow-up studies using better measures of social development before drawing such

strong conclusions about whether autism is regressive, Klin cautions. That's because social behaviors may serve different purposes at different times of development. For example, at 6 months, a smile could be an instinctive reaction to seeing other people, but at 12 or 18 months, it could indicate that the child is engaging socially with others.

Without understanding the purpose of a specific behavior at a particular age, it's difficult to know whether a child loses social skills, or simply fails to develop them in the first place, Klin says.

To confirm the findings and address some of these limitations, the researchers plan to expand the study to include more children and evaluate them more frequently. They also plan to use different measures of early development, such as eye-tracking. ■

7 MAY 2010

# Rat study sniffs out vasopressin's role in social behavior

**BY VIRGINIA HUGHES**

Neuroscientists have discovered a population of cells in the smell-perception area of the rat brain that express the hormone vasopressin. Blocking vasopressin in this region, called the olfactory bulb, impairs the animals' ability to recognize other rats by smell, the study found.

Vasopressin plays vital roles in many body tissues, such as regulating water absorption in the kidneys and salt content in the blood.

But in the past few years, the hormone has attracted attention for its role in complex social behaviors. For instance, some studies have found that individuals with autism, who have impaired personal relationships, have increased levels of vasopressin in blood plasma compared with healthy controls.

The new rat work, published 18 March in *Nature*, adds to several rodent studies showing that vasopressin and its sister brain chemical, oxytocin, control a range of social and reproductive behaviors, from wooing a mate to caring for pups. After years of striking discoveries in animals, geneticists and neuroscientists are beginning to take a closer look at how the hormones affect human social behavior, according to a review published 25 March in *Neuron*.

Vasopressin and oxytocin differ chemically by only two amino acids, and can bind to each other's receptors. They are both produced primarily in the brain and then travel through blood to the rest of the body. Both hormones are released during stress, and their actions seem inextricably tied: vasopressin elicits an active, fight-or-flight response, whereas oxytocin dials down the resulting anxiety.

A few small genetic and clinical studies have linked both hormones to autism.

For example, a February report described a high-functioning man with autism who is missing both olfactory bulbs.

A couple of other studies have also hinted at a problem with the olfactory system in people with autism. The researchers hypothesize that because olfactory bulbs contain a high density of oxytocin and vasopressin receptors, damage to this region could severely affect social development.

Other groups have reported this year that inhaling oxytocin improves social behaviors in individuals with autism and helps teenage boys with the disorder recognize facial emotions. But scientists know relatively little about how these hormones affect neural circuits.



The new study begins to unpack the complicated molecular interactions of vasopressin in the brain, which could lead to additional autism treatments, researchers say. Nasal sprays are not ideal, because researchers don't know how the hormones get into the brain, nor which specific regions they act on.

"Maybe in the future, one way to help would be to activate these vasopressin cells in the olfactory bulb by a trick we don't know yet," says lead investigator Mike Ludwig, professor of neurophysiology at the University of Edinburgh.

### RECEPTOR ROOTS:

The vasopressin protein fits into the oxytocin receptor, but it binds most strongly to three different receptors, one expressed in the kidneys and two – AVPR1a and AVPR1b – in the brain.

Human studies have tied the gene that encodes AVPR1a to a wide variety of behaviors, from creative dance performance to having troubled romantic relationships. Studying 552 twin pairs and their spouses, one group found that men who carry certain common alleles in AVPR1a are less likely to be married or, if they are married, more likely to have marital problems, than are controls. Other researchers have reported links between AVPR1a variants and age of first sexual experience and altruistic tendencies.

Since 2002, five studies have found that common variants of AVPR1a are

more likely to arise in individuals with autism than in healthy controls. All of these studies had small sample sizes, however, and fingered variants in different parts of the gene.

"It's somewhat disturbing that none of the studies exactly replicate any of the others," notes Richard Ebstein, professor of psychology at Hebrew University in Jerusalem. His group has investigated AVPR1a's role in autism, eating disorders, stress responses and impulse control.

Although these association studies indicate that variants in the vasopressin receptor are not primary causes of autism, they may influence the severity of an individual's social impairments, Ebstein says.

Because there are few treatments for autism's core social problems, these hormonal pathways deserve more attention, he adds. "In most cases of autism, vasopressin and oxytocin aren't major explainers of illness, but they might still be very good targets for pharmacology."

Animal work suggests that the specific expression patterns of vasopressin receptors in the brain control animals' social and mating behaviors.

For example, researchers at Emory University compared vasopressin receptor coding and expression in the brains of montane voles, which are polygamous, and prairie voles,

which are monogamous. Montane voles carry short sequence repeats in a specific region upstream of the AVPR1a gene, whereas prairie voles carry long repeats, the study found.

What's more, animals carrying long repeats have a high expression of AVPR1a in the olfactory bulb, suggesting that vasopressin signaling in this region is crucial for pair bonding.

### LOCAL CONNECTIONS:

Scientists had assumed that all of the brain's vasopressin is produced in the hypothalamus – the nub of cells in the center of the brain – and then travels to the olfactory bulb to regulate social bonding behaviors.

But the new *Nature* study shows that vasopressin is also produced by a group of cells within the bulb.

"That's what's exciting – the finding that there's a new population of neurons that are producing vasopressin locally, rather than having to diffuse a long distance from the hypothalamus," says Elizabeth Hammock, instructor of pediatrics at Vanderbilt University, who did the vole work as a graduate student.

Ludwig's team engineered a line of rats with green fluorescent protein genetically inserted into a vasopressin pathway. After the rats are born, every brain cell that makes vasopressin glows green. The researchers found that, surprisingly,

one group of these cells sits in the olfactory bulb.

In subsequent experiments, the team used several methods to selectively block the activity of these cells in the olfactory bulb. This severely disrupts the animals' social recognition, causing them to sniff a familiar rat as if it were a stranger. Interestingly, blocking these cells does not affect the animals' ability to recognize objects.

In electrophysiological experiments, the scientists found that these vasopressin cells do not project outside of the olfactory bulb. Instead, they link up to other types of cells inside the bulb, which then project deeper into parts of the limbic system, such as the amygdala and hippocampus, important for processing emotions and forming memories.

Ludwig suspects that when rats smell something new, the odor "primes" the vasopressin cells in the olfactory bulb. The second time the animal smells the odor, vasopressin effectively inhibits connections to these deeper areas, which dampens the rat's emotional response.

### THE NOSE KNOWS:

In people, most sensory input, such as light or touch, gets routed through the brain's relay center, the thalamus, before reaching the limbic areas. The notable exception is smell: odor molecules take a shortcut, going directly from the olfactory bulb to deeper brain structures for processing.

"It has primitive and privileged access to our emotion regulation," Hammock says.

Even so, scientists studying human social behaviors have paid little attention to the olfactory system. That's because, unlike rodents, which are dependent on their smelling ability, the olfactory bulb doesn't take up a huge portion of the human brain. People rely much more on their eyes.

"We don't sniff each other to recognize who is who anymore. Humans have evolved a bit further," Ludwig says.

It's unclear, he says, whether the activity of vasopressin cells in the rat olfactory bulb is reflective of the hormone's workings in the healthy human brain.

Ebstein says that vasopressin signaling in the amygdala, rather than in the olfactory bulb, is more likely to be important in autism. A functional magnetic resonance imaging study last year found that individuals carrying various autism-associated variants of AVPR1a have abnormal amygdala activity – some variants leading to over-active, and others to under-active, amygdalae – when performing a task of matching faces.

In unpublished experiments on college students, Ebstein's team has found that sniffing vasopressin before giving a speech to a panel of judges can increase heart rate and blood cortisol levels – standard measures of stress response. This increased anxiety

doesn't occur when the students make the speech facing a wall.

Ebstein hypothesizes that in the presence of other people, vasopressin stimulates the amygdala, which then sets off a hormonal cascade that results in cortisol release. "Vasopressin needs an audience – it doesn't work well unless you've got that social stress element," he says.

Although the hormone's effect on the brain is uncertain, the mounting genetic and behavioral evidence is prompting more neuroscientists to take note, he says. "Because there are no drugs to treat autism's core social problems, these hormones deserve as much attention as we can give them." ■

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15 AUGUST 2011

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# Study finds high rate of autism in South Korea

BY DEBORAH RUDACILLE

The first comprehensive autism study in South Korea has found that the prevalence of the disorder is more than double the number in the United States.

Three-quarters of the children identified in the study had not previously been diagnosed with autism, and most were attending mainstream elementary schools, according to the report, published Monday in *The American Journal of Psychiatry*.

Researchers aimed to screen the 55,266 children born between 1993 and 1999 in Ilsan, a residential community near the South Korean capital, Seoul. They succeeded in screening less than half that number, possibly due to the extreme stigma attached to an autism diagnosis in the country.

Parents of more than 23,000 children between 7 and 12 years of age enrolled in mainstream schools and of 103 children in special-needs schools filled out a 27-item Autism Spectrum Screening questionnaire.

Of 1,742 children in mainstream schools who screened positive for autism risk, the parents of 785 initially consented to a full diagnostic evaluation. But only 234 of those children returned for the follow-up. This low number may be due to the fact that researchers could not contact some of the parents and others decided not to participate.

Parents of 84 children who were either in the district's disability registry or special schools also provided consent: Of that number, the researchers fully assessed 52.

For the autism diagnosis, the researchers relied on cognitive tests, interviews and the two gold-standard assessment tools – the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised.

Based on these criteria, they diagnosed autism spectrum disorders in 60 percent of 172 children with no history of psychiatric or psychological services and 77 percent of 62 children with a psychiatric history in mainstream schools. They also identified more than 90 percent of the 52 'high-probability' children already registered in special-education schools as having autism.

Extrapolating these numbers to the total school-age population, the researchers calculated a prevalence of 2.65 percent, compared with roughly 1 percent prevalence in the U.S.

"No matter how we calculated the numbers, we came up with this rate that surprised us," says Roy Richard Grinker, professor of anthropology at George Washington University in Washington, D.C. and one of the investigators on the study.



Grinker points out that a total population study of any disease or disorder is likely to turn up a higher rate than previous estimates based only on known cases. "You are leaving no stone unturned, and if you look hard enough, you will find cases," he says.

### **PUZZLING STATISTICS:**

There are few studies of autism prevalence outside of the U.S. and Western Europe, and those have typically found far lower rates than the official U.S. estimate of 1 in 110 children. For example, reports this year found 27.2 cases of autism per 10,000 children in Brazil and 51 per 10,000 children in Western Australia.

Researchers say that lack of awareness about autism and poor medical infrastructure partly explain these low prevalence estimates.

"Crude estimates of autism rates show that a lot of discovery needs to be done," says Peter Bearman, professor of social sciences at Columbia University. "The real incidence is higher than those crude estimates would indicate."

Bearman was not involved in the new study, but has extensively researched social factors driving the 637 percent increase in autism diagnoses in California between 1987 and 2003. His team concluded that the 'autism epidemic' in that state is largely an epidemic of discovery.

The high rate of autism in the South Korea study requires further investigation, Bearman says. "This is an extremely interesting study, but it is one setting," he says.

Grinker acknowledges that the high rates in the study may reflect a sampling bias.

Parents concerned about their child's behavior may have viewed the Ilsan study as an opportunity to gain information and access to services, Grinker says. Meanwhile, those who saw no reason to participate may have opted out, driving up the proportion of affected children.

In South Korea, an autism diagnosis stigmatizes not only the affected individual, but his or her whole family. For that reason, the researchers expected parents not to report problems on the screening questionnaire.

"I thought maybe we wouldn't get that many kids because people would be too frightened of the diagnosis," Grinker says.

To his surprise, parents not only chose to participate but also viewed the focus groups he assembled as a kind of support group. "A lot of them had never talked to another parent of an autistic kid," he says.

His colleagues are already following up with a study of 6,000 children in a second community in Cheonan, a city south of Seoul.

That study, funded by the Simons Foundation, SFARI.org's parent organization, aims to include phenotyping of both the Ilsan and Cheonan groups, characterizing their symptoms in detail. The researchers also plan to reanalyze whole-blood DNA samples from the Ilsan group and collect saliva samples from the Cheonan children.

The researchers found that autism combined with intellectual disability is much more prevalent in the high-probability group – 59 percent compared with 16 percent in the general population – already enrolled in the disability registry or attending special schools. Mean intelligence quotient scores are about 20 points higher in the general population than in this group.

The researchers identified five times as many boys as girls with autism in the high-probability group, but that ratio dropped to twice as many boys as girls in the general population.

Whether a similar study would uncover a significant number of children with undiagnosed autism in the U.S. remains unresolved.

A revised U.S prevalence might not rise to 2.65, "but I think we'd come up with significantly higher rates than 1 in 110," Grinker says. "I can't imagine that anyone would argue that there is a total absence of [undiagnosed] autistic kids in our school system." ■

8 JUNE 2011

# Studies find high rate of rare new mutations in autism

**BY DEBORAH RUDACILLE**

Three new studies analyzing genetic data from families in which just one child has autism have found the strongest evidence yet that rare new mutations contribute to the disorder. The reports appear today in *Neuron*.

The studies use powerful new screening tools to scan for genetic anomalies in affected children, their parents and siblings. They are the largest genetic studies of so-called 'simplex' families to date, covering approximately 4,000 individuals from more than 1,000 families.

Researchers searched for both rare de novo mutations, which occur spontaneously in the individual, as well as rare variants passed down from parents to child. For a variant to be defined as rare, it must appear in less than one percent of the population. Common variants, by contrast, are present in five percent or more of the general population.

In 2007, Michael Wigler and his colleagues at Cold Spring Harbor Laboratory in New York reported that children with autism carry more de novo copy number variations (CNVs) than their siblings do. CNVs are deletions and duplications in stretches of DNA. The de novo mutation rate among affected children in simplex families in that study was ten percent, compared with one percent in controls.

In his new study, Wigler found a de novo mutation rate of 8 percent among affected children compared with 2 percent in unaffected siblings. A second study, led by Matthew State of Yale University, found a rate of 5.8 percent among affected children compared with 1.7 percent in unaffected siblings.

In the third study, a team headed by computational biologist Dennis Vitkup performed a network analysis of the genes identified in Wigler's study. A significant proportion of genes in the identified CNVs are associated with a network involved in the formation of synapses, the junctions between neurons, the researchers found.

"The studies are well-done and very much needed," says Stephen Scherer, director of the Center for Applied Genomics at the Hospital for Sick Children in Toronto, who was not involved with the work. "The most important finding is the validation of the de novo rate."

## **RISKY BUSINESS:**

Wigler's and State's teams both found that de novo CNVs in the affected individuals are larger than those in their siblings, and cover more genes. The studies pinpointed several known autism-related regions, including 16p11.2, 7q11.23 and 15q13.2-q13.3.

The 7q11.23 region is associated with both autism and Williams syndrome, which is characterized by hyper-social behavior combined with intellectual disability. This large stretch of chromosome 7, encompassing 25 genes, is deleted in Williams syndrome, but duplicated in individuals with autism.

"This region is going to be fundamentally important in understanding the social brain," says State, associate professor of psychiatry and genetics at Yale University.

All of the studies relied on samples from the Simons Simplex Collection, a repository of genetic samples and clinical data from simplex families. The collection is funded by the Simons Foundation, SFARI.org's parent organization.

Though the collection now includes 2,712 families, the new studies are based on the first roughly 1,000 families enrolled.

Another study published last month, and based on 20 children and their parents from the collection, found four new de novo point mutations – variations in which a single nucleotide is inserted, deleted or replaced with another – in the children. Two of the four children in that study carry both an inherited variant and a de novo mutation, and are the most severely affected.

Wigler and State used two different array platforms, NimbleGen and Illumina respectively, to scan the sequences of essentially the same individuals, though the State sample is slightly larger, with 1,174 families. In terms of validating the results, "using both platforms is really useful," says Scherer. "In many cases, the de novo CNVs [identified] were the same."

Wigler's team identified 75 de novo events in 68 affected individuals compared with 19 in their 17 unaffected siblings in 915 families.

Most of these mutations appear in unique locations, but 16 overlap at four distinct regions of the genome. The study underscores the importance of the 16p11.2 region in autism, which has repeatedly been implicated in the disorder: ten of the duplications or deletions are in this region, and all but one of those is in a male.

The group also found two de novo and two inherited duplications at 16p13.2, a duplication on 16p13.11 in an affected and an unaffected child from different families, as well as a duplication at 7q11.23.

His data suggest that, overall, CNVs in at least 300 spots in the genome confer risk for autism. "It could be many more," Wigler says. "What that tells us is that we are dealing with a whole host of causes."

### **GENDER BIAS:**

Wigler's study offers compelling evidence that females are more resistant to autism: Even when they carry the same genetic lesions as males, they do not develop the disorder. "You've got a boy and a girl and they both have the same genes, and [only] the boy has autism. That to me is a big puzzle," Wigler says.

His team found that the autism-linked de novo CNVs in girls are also typically larger than those in boys. "It's like a meteor strike, a huge insult to the genome that occurs and when it happens there is very little protection against it," he says.

The researchers also found one instance of a 16p11.2 deletion transmitted by a mother, but overall

did not find higher transmission of rare mutations from mothers than fathers, he says. Other studies have reported inheritance of duplications at 16p11.2, but this is one of the few reports of an inherited deletion at the site.

Because mutations identified in CNV studies are by definition rare, occurring in only a few individuals – and in the case of 'ultra-rare' mutations, a single person or family – it can be difficult to prove that they are culprits in autism.

"Imagine this in terms of a gang," says Vitkup, assistant professor of biomedical informatics at Columbia University. "If every crime is done by a different person, it's very hard to track. Instead, you look to see if the people who are potentially responsible go to the same school or live in the same neighborhood."

He and his colleagues mapped associations between genes perturbed by CNVs identified in Wigler's study. Roughly 40 percent of the genes are part of a functional network needed for synapse formation, neuron movement or the formation of axons, the projections that carry electrical impulses away from the cell.

Vitkup's analysis implicates several pathways, including the neurexin1-neurologin3 pathway that forms the postsynaptic density, key to the proper functioning of the synapse.

In autism, glitches in individual genes are not as significant as perturbation of a critical network, Vitkup says. "The commonality of the disease comes not from the fact that specific mutations are very frequent, but because the number of mutations that could produce the [autistic] phenotype is very large."

## **NUMBERS GAME:**

One of the challenges in CNV studies is calculating the probability of seeing a rare recurrent de novo event at precisely the same spot in the genome in more than two individuals with the disorder.

This is a more sophisticated metric than merely counting the number of rare CNVs observed in cases versus controls, says Matthew State, associate professor of psychiatry and genetics at Yale University School of Medicine in New Haven, Connecticut.

Because the number of potential CNVs in the human genome is so large – even healthy individuals can carry 10,000 or more variants – researchers first need to pinpoint the genomic regions that could plausibly contribute to autism. Based on that estimate, they can compute the statistical likelihood of observing a recurrent CNV in those regions.

He and his colleagues created a method that establishes a statistical threshold for significant de novo events that he says he would like to share with other researchers.

“We want a methodologically rigorous and stringent standard so that people are able to hone in on things that will be associated with autism and not just general observations,” he says.

Using this technique, his group identified two regions that are clearly over-represented in autism – seven deletions and four duplications in the 16p11.2 region and four duplications at 7q11.23. The probability of seeing the same CNV in more than two people is less than five percent, State says.

State’s team also identified four other regions where autism-

associated de novo mutations seem to recur: 1q21.1, 15q13.2-q13.3, 16p13.2 and 16q13.3.

State’s study does not show any direct evidence of gender difference in the size or impact of the CNVs. But he found that in males, large CNVs are associated with a lower intelligence quotient (IQ). “We didn’t find that in females,” State says, “which suggests that females might be protected.”

Still, the study contradicts two pieces of conventional wisdom regarding intellectual disability and CNVs, he says. First, it counters the hypothesis that large CNVs are more common among individuals with lower IQs. “Look at our graph and the CNVs are pretty much evenly distributed across the sample,” State says.

It also challenges the belief that large CNVs may be genetically coding for ‘bad brains’ in general and not specifically for autism. “Our study shows that these large risk events are bona fide risks for autism,” says State. ■



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# 2012

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4 APRIL 2012

# Hundreds of genes involved in autism, sequencing studies say

**BY EMILY SINGER**

The largest set of exome sequencing studies of children with autism and their families to date has identified a handful of genes that may increase risk of the disorder. Such studies analyze the protein-coding region of the genome.

Three studies, published today in *Nature*, encompass more than 600 families and represent the first comprehensive search among children with autism for single-letter DNA mutations that are de novo, meaning that they occur spontaneously rather than being inherited from a parent.

Researchers found strong evidence linking six genes to autism, two of which had not been associated with the disorder before and two of which had only been weakly linked to sporadic, or non-inherited, autism. They also identified scores of candidate mutations to investigate in future studies.

"This is a landmark set of studies for the field," says Patrick Sullivan, professor of genetics at the University of North Carolina School of Medicine, who was not involved in the studies. Sullivan notes that the design of the study — analyzing de novo mutations in families — is particularly important. "In one fell swoop they are taking us farther than any other studies in the past, in autism and in other psychiatric disorders."

But perhaps the most significant result is the evidence of the enormous complexity of autism. Though the disorder is known to be highly genetic, only a small proportion of the overall genetic basis of autism has been identified. Taking into account the new findings, researchers estimate that about 400 to 1,000 genes are involved in the disorder. That means that even larger-scale studies are likely needed to identify all or most of the genetic risk factors.

"It's very exciting but also very sobering," says Aravinda Chakravarti, professor of medicine, pediatrics, and molecular biology and genetics at Johns Hopkins University School of Medicine in Baltimore, who was not involved in the studies.

## **SINGLE LETTERS:**

Previous research on the genetics of autism has focused largely on searching for rare mutations in families with high rates of autism, common single-letter variations identified in genome-wide association studies, and copy number variations — deletions or duplications of stretches of DNA that can encompass multiple genes.

The new studies focus specifically on rare single-letter mutations, also



called single nucleotide variations, or SNVs, that arise spontaneously in a parent's sperm or egg cells. These de novo mutations can be identified by searching for genetic glitches that are present in children with autism but not in their parents.

Given the high rate of variation in the genomes of even healthy people, focusing on these rarer de novo mutations helps to narrow the list of candidates that actually raise risk of disease. The other benefit of identifying single-letter changes over copy number variations is that the latter often contain a number of genes, making it difficult to pinpoint the gene responsible for the variant's effect.

"Getting to the resolution of a single gene is a really important step in being able to understand the specific pathological mechanisms underlying autism," says Matthew State, professor of genetics and psychiatry at Yale School of Medicine.

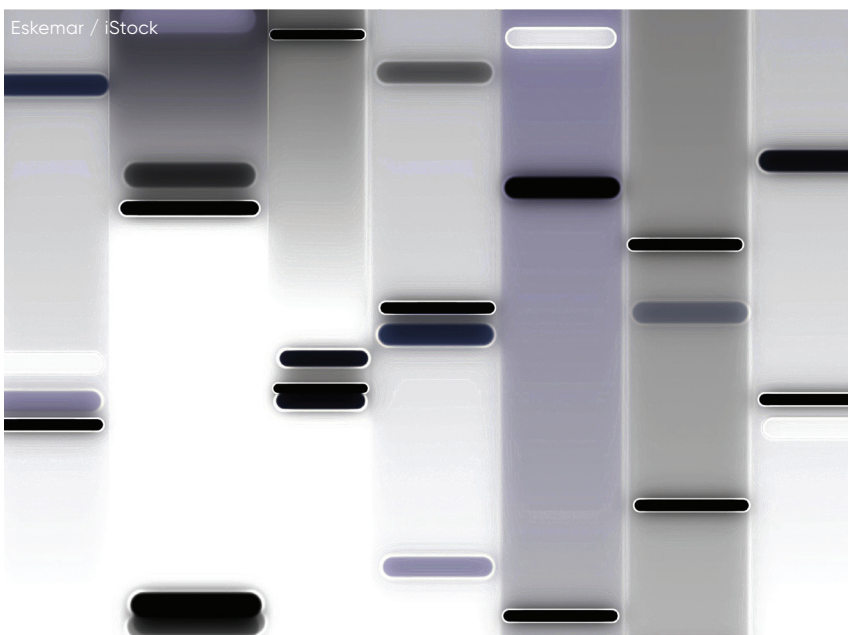
Two of the studies, led by State and Evan Eichler, professor of genome sciences at the University of Washington, are based on data from the Simons Simplex Collection (SSC). The SSC contains genetic and other information, such as cognitive and behavioral data, from 2,700 families that have a single child with autism and unaffected parents and siblings, and is funded by the Simons Foundation, SFARI.org's parent organization. They examined a total of 447 family trios – an affected child and unaffected parents – and 250 unaffected siblings.

The third study, headed by Mark Daly, associate professor of medicine at Harvard Medical School, sequenced exomes from 175 family trios that are part of the Autism Consortium in Boston. Unlike the SSC, this group includes families with a history of autism, but Daly says that 70 percent of the families in this cohort have no family history of the disorder.

Taken together, researchers sequenced the exomes of 622 family trios and 250 unaffected siblings.

Part of the rationale for sequencing the genomes of unaffected siblings is to get a better sense of the baseline mutation rate. "There is so much mutation in the genome, you really need to have data on what mutation looks like in well-matched unaffected people in order to have traction in what's going on in affected people," says State.

All of the studies used newer, cheaper sequencing technologies that have enabled a boom in exome and genome sequencing. "It's the largest-scale application of next-generation sequencing for any complex trait that I know of in my field," says Sullivan.



## RATE OF CHANGE:

Each study identified a number of non-synonymous – meaning those that alter or truncate the structure of the gene – de novo mutations found only in individuals with autism. But determining which of those truly drives an increased risk of the disorder is no easy task.

“The bad news is there is heterogeneity out the ying-yang,” says Eichler.

Considering all the data together, researchers found 18 genes with de novo mutations, some of which have been previously linked to autism. Each of these genes was identified in two unrelated individuals with autism, but not in their unaffected family members. Three of these genes had two loss-of-function mutations, which provides stronger evidence linking them to autism, says State.

According to statistical calculations, two independent instances of a mutation make it much more likely the affected genes are linked to autism, but the association is still not definitive.

“Even when we put all of the mutations observed in the three studies together, we haven’t found any gene hit with more than two de novo mutations, so nothing stands out as a major cause of autism,” says Daly. “But we do see several genes hit twice and have a high degree of confidence these are genuine risk factors.”

Daly’s team took the top candidate genes from State and Eichler’s studies and searched a separate cohort of 935 people with autism and 870 controls for mutations in

these genes only in people with autism. They found additional protein-altering mutations in KATNAL2 (katanin p60 subunit A-like 2) and CHD8, a chromatin remodeling factor, neither of which had been previously linked to autism.

Eichler’s group took a similar approach with several of its top single-hit candidates, searching for autism-specific mutations in 1,703 people with autism and 744 controls. They identified additional hits in GRIN2B, which has been linked to autism and schizophrenia, LAMC3, which has been linked to autism and development of the cerebral cortex, and SCN1A, which has been linked to epilepsy and autism.

Another candidate, SCN2A, a sodium channel gene that has previously been associated with familial autism and seizures, is mutated in two cases in State’s study. Joseph Buxbaum’s lab, part of Daly’s collaborative team, identified a third mutation in this gene in a person with autism while the papers were in press, “providing very strong evidence that this is an autism spectrum disorder risk gene,” says State.

“While the findings were not very rich in terms of the number of harmful variants found, it was clear that they converge on pathways that affect the brain and allow us to estimate the number of genes involved in autism,” says Thomas Lehner, chief of the genomics research branch at the National Institute of Mental Health, which funded some of the research. “For me these are the most exciting findings of the paper.”

The role of the other mutations identified in the studies is not yet



clear, but State estimates that 14 percent of the autism group carries a de novo mutation linked to autism.

Adding this estimate to previous calculations that about 6 to 10 percent of people with autism carry de novo copy number variations, “we have now found in the Simons sample about 25 percent of likely genetic contributors,” State says.

He also estimates that once sequencing of the 2,700 families in the SSC is complete, researchers will identify on the order of 25 to 50 additional autism-linked genes. A third paper analyzing data from the SSC, from Michael Wigler’s group at Cold Spring Harbor Laboratory in New York, is now under review.

Despite the careful controls, it’s still unclear whether the findings will hold up to further scrutiny. “The question all three studies raise is are the mutations they found any more than we would expect by chance?” says Chakravarti. “We don’t know the background rates of mutation in the human genome, so we don’t know what would be surprising.”

The SSC studies tried to control for this by sequencing unaffected siblings as controls, but Chakravarti says even larger numbers are needed to get an accurate sense of both the rate and variability of de novo mutations.

### **SIZE MATTERS:**

In addition to looking for double hits to a single gene, researchers can try to determine the most

likely candidate genes by looking for those that fall into specific molecular networks.

Eichler’s team found that nearly 40 percent of the genes they identified were part of a related molecular network. (Computational simulations showed that such a pattern was highly unlikely to occur by chance.) Researchers did not find a significant number of mutations in the genes in this pathway in 50 unaffected siblings, “confirming its relevance to autism,” says Eichler. “For me, that’s exciting.”

Some of the genes in the network, such as beta-catenin, which is important in early neurogenesis in the brain, have been previously implicated in autism, says Eichler. It also includes a number of genes that weren’t previously implicated but could become important, “such as chromodomain helicases, which are thought to be important in chromatin regulation,” he says. “I think it opens up an entirely new area for people to investigate.”

State’s study did not find this type of network, and Daly’s found some evidence of protein-protein interactions among candidate genes, highlighting how similar studies can come up with very different results.

“It’s interesting and highly provocative, but it’s hard to know how to take them to the bank,” says Sullivan.

Eichler’s group also looked at the parent of origin in a subset of cases in his study and found that de novo mutations are four times more likely

to come from the father than the mother. That’s not surprising – sperm go through many more cell divisions than do eggs, providing more opportunities to make mistakes in replicating DNA – but the finding gives a more accurate number to biologists’ predictions, says Eichler.

In addition, the findings confirm that older fathers are likely to have higher rates of these mutations in their sperm, lending additional support to research that suggests an increased autism risk among children of older fathers.

All scientists interviewed agreed that the new research shows that even larger studies are needed to confirm and advance these results. “It’s a challenge to the field,” says Lehner. “To get some traction on that problem, we need new forms of collaboration and new ways to find families.”

One such collaboration is the Autism Sequencing Consortium, a global consortium of scientists working to unravel the genetics of autism. The three *Nature* papers are the first publications to come out of the program, which encourages researchers to share data prior to publication.

The consortium is working on finding larger groups to study, including several thousand trios available to be analyzed in Europe.

“Only with large numbers will we get unequivocal evidence for key genes that are essential for us to move ahead with functional studies into the causes of autism,” says Daly. ■

15 OCTOBER 2012

# Common variants, en masse, may add up to strong autism risk

BY EMILY SINGER

Individually, common genetic variants confer little risk for autism. But taken together, they may contribute significantly, predicts a statistical analysis published 15 October in *Molecular Autism*.

Common variants are typically defined as those found in more than five percent of the population, and rare variants as those found in less than one percent.

Researchers predict that cumulatively, common variants contribute as much as 40 percent of autism risk in families with one child who has the disorder, and 60 percent in families with more than one affected member.

The report is the result of a sophisticated statistical analysis based on data from about 2,000 families. It is the latest contribution to a long-running debate over whether relatively common diseases such as autism stem from rare mutations that individually have large effects, or from a combination of many common variants that each exert small effects.

The new finding falls squarely in the middle.

"[Autism risk] is neither only rare nor only common," says lead investigator Bernie Devlin, professor of psychiatry at the University of Pittsburgh. "We provide sound

evidence that common variants en masse exert a large effect on risk."

Others are skeptical about the magnitude of risk the model predicts, however.

"Common variants are clearly important, but whether they account for half of the risk, this paper doesn't prove or disprove that," says Hakon Hakonarson, associate professor of pediatrics at the University of Pennsylvania School of Medicine, who has published research on both common and rare variants. "We still need much more data to convincingly show that this is the case."

Still, says Hakonarson, the findings do suggest that common variants are worth studying. "There are so many voices in the field telling us to ignore common variants," he says. "But this gives us more balance."

## SWINGING PENDULUM:

The debate over the relative contributions of common and rare variants has been driven in large part by the technologies available. The advent of gene microarrays nearly ten years ago enabled scientists to quickly and cheaply search the genome for common genetic variants, known as single nucleotide polymorphisms, or SNPs.

That in turn triggered a flood of genome-wide association studies (GWAS), which are designed to detect common variants that occur more frequently in people with a certain disease than in others. But GWAS approaches to autism have been somewhat disappointing.

For example, an analysis published in August of more than 2,700 families who are part of the Autism Genome Project (AGP) found no SNPs that are significantly linked to autism or to symptoms associated with the disorder.

In the new study, rather than look for individual SNPs, Devlin and his collaborators used statistical modeling to determine whether common variants overall contribute to risk. They focused their analysis on GWAS data from two large projects – the AGP, which includes data from multiplex families, in which one or more children are affected, and the Simons Simplex Collection (SSC), a database of families that have a single child with autism and unaffected parents and siblings. The SSC is sponsored by the Simons Foundation, SFARI.org’s parent organization.

Altogether, the researchers compared data from more than 2,000 families with a history of autism and 1,600 control individuals.

In simplified terms, the researchers used the SNP data to calculate the distant relatedness between everyone in the sample, generating a massive pedigree.

“People who are more closely related tend to have autism and those who are more distantly related do not, consistent with the idea that common variation is driving some heritability of disease,” says Andrew Paterson, Canada Research Chair in Genetics of Complex Diseases at the University of Toronto, who was not involved in the study.

The fact that both datasets, which include different types of families, arrive at similar results supports the idea that common variants contribute significantly to autism, says Hakonarson. “But nothing in the paper says this is clearly the case.”

#### **ADDITIVE EFFECT:**

Rather than debate the relative contributions of common and rare variants, the researchers say it’s time to look at how the two types of variants work together.

“As we move forward in sorting this out, it will begin to give us an opportunity to understand the relationship between common variants and rare variants,” says Matthew State, co-director of the Yale Program on Neurogenetics and one of the researchers on the study.

“We don’t know yet how much overlap there will be among different types of risk,” he says. “Overall, this understanding is likely to open important doors to get a handle on things like genetic modifiers.”

Genetic modifiers can influence the outcome of a mutation. For example, rare variants can cause highly variable symptoms, suggesting additional genetic or environmental factors at play. Devlin says common variants may modify the effect of the rare risk variants.

Some companies have already begun to market diagnostic tests that predict an individual’s risk of autism based on a set of SNPs. But Devlin says his findings have little clinical relevance. “[Individual] common variants are going to be very difficult to find,” he says.

There is also little agreement among the experts over the best way to move forward.

Hakonarson favors sequencing DNA from large numbers of individuals with autism – 20,000 to 30,000 – which he says is likely to give a much more accurate estimate of the percentage of risk that can be attributed to common variants. Paterson says larger GWAS are needed, perhaps on the order of tens of thousands.

Devlin suggests better analysis of existing SNP data. “There may be smart ways of looking at data where you might be able to eke out some of the common variants without huge sample sizes,” he says. ■

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28 FEBRUARY 2013

# Twin study suggests girls are protected from autism risk

**BY VIRGINIA HUGHES**

A comparison of autism-like behaviors in nearly 10,000 pairs of fraternal twins suggests that girls are somehow protected from the disorder.

The findings, published 19 February in the *Proceedings of the National Academy of Sciences*, may partly explain why autism is four times more common in boys than girls – one of the oldest and most puzzling statistics in the field.

The study measured autism traits – such as conversational abilities, social preferences and repetitive behaviors – in children in the general population. Among children who have many autism symptoms, girls are more likely than boys to have siblings who also have the traits, the study found.

The findings suggest that girls have a baseline level of protection, and don't display many autism traits unless they're "loaded up to the gills with risk factors," says lead investigator Angelica Ronald, senior lecturer in psychological sciences at Birkbeck, University of London.

Risk factors in these families may include inherited genetic variants, shared environmental influences or some combination of both, she says.

The study does not address the larger question of how this

protective effect might work. It might be rooted in biological differences between the sexes. Or it might not really be a matter of protection at all, but rather the result of bias in how clinicians diagnose the disorder, the researchers say.

For example, the male-to-female ratio in autism becomes even bigger for children with high intelligence quotients, suggesting that clinicians and parents may not notice less severe autism symptoms in girls, or may be more primed to look for them in boys.

"I think the approach to this \$64,000 question would be having a better understanding of sex differences in autism more generally," says co-investigator Elise Robinson, instructor in medicine at Harvard Medical School. "It's very hard to understand differences in the causes of autism between boys and girls if we don't really understand differences in what gets them diagnosed."

## **FAMILY RESEMBLANCE:**

Researchers have long struggled to explain the extreme gender bias in autism. Some have proposed factors, such as high levels of fetal testosterone, that might make boys particularly vulnerable. Others

have suggested that girls may be protected through a genetic mechanism related to their second X chromosome.

Genetic evidence of a possible female protective effect came in 2011, when two studies in *Neuron* showed that girls with autism are more likely to carry rare, spontaneous copy number variations (CNVs) – DNA deletions and duplications – than are boys with autism. What’s more, the CNVs that girls carry tend to be larger, suggesting that they only get autism when exposed to the most powerful genetic hits.

“Those original findings could be taken in two ways,” Robinson says. For example, she says, one explanation is a diagnostic bias. “Sure, the girls show more insults, but it’s just because to get diagnosed with autism as a girl, you generally have to be more impaired.”

The other possibility is that there is a bona fide protective effect in girls, she says.

In the new study, she and Ronald investigated whether girls in the general population are protected from autism risk factors that run in families. The study measured autism traits on a continuum, rather than by categorical diagnoses. For

example, a child might have some repetitive behaviors without being diagnosed as having autism.

The researchers relied on two large samples of fraternal twins: 3,842 pairs from the Twins Early Development Study in the U.K. and 6,040 pairs from the Child and Adolescent Twin Study in Sweden. Both studies used questionnaires to measure autism traits, such as speech delay or difficulty making conversation, in the twins as children.

The researchers focused on pairs in which one of the twins – dubbed the ‘proband’ – scored in the top five percent of autism trait scores. Siblings of female probands showed significantly more autism symptoms than did siblings of male probands, the study found.

That suggests that girls don’t have autism-like behaviors unless they come from families with high risk, whereas boys can have these traits even in low-risk families.

“This female protective effect idea is something that’s tossed around all the time, but really hasn’t had much strong evidence behind it,” says Lauren Weiss, assistant professor of psychiatry at the University of California, San Francisco. “I think this study provides some very good evidence.”

Researchers would have had to study many more twin pairs to reach the same level of statistical power in a study based on autism diagnoses rather than on traits of the disorder, she adds.

#### SERVE AND PROTECT:

Although the data strongly support the 'female protective effect' hypothesis, they don't completely rule out other explanations, Ronald says.

For example, the questionnaires used to measure autism traits are based on ratings from parents, which are susceptible to cultural biases. What's more, many instruments used to assess autism and autism-like symptoms were designed and validated largely in groups of boys, who may manifest the symptoms of autism differently than girls do.

The data are also somewhat puzzling in light of older studies on spontaneous risk factors in girls with autism.

The Neuron studies found that girls with autism are more likely than boys to have spontaneous mutations. Because these mutations are not inherited, it would suggest that the girls' siblings would be less likely to

show autism traits – exactly the opposite of the new findings.

"It struck me that on its surface, there seem to be some kind of a contradiction," says Jeremy Silverman, professor of psychiatry at Mount Sinai School of Medicine in New York, who was not involved in the new work.

However, Robinson says that because spontaneous mutations are rare in the general population, they wouldn't be expected to play a "meaningful role" in this sample.

Robinson and Ronald are next looking at whether specific genetic risk factors for autism and related disorders are more likely to lead to traits of the disorder in boys than in girls. If the female protective effect hypothesis is correct, then "you should see a greater trait burden in boys who carry these risk factors than girls, on average," Robinson says.

Everybody agrees that the autism field would benefit from more studies of girls with the disorder, who have historically been ignored.

"Understanding the sex difference is going to help everyone, boys and girls with autism," Ronald says. "It's part of the whole mechanism by which autism develops." ■

21 MARCH 2013

# Can nutritional supplements help treat some cases of autism?

**BY EMILY SINGER**

The mention of nutritional supplements to treat autism might make some scientists wary. Little rigorous research has been done on their effects, and what research exists is often inconclusive.

In the past year, however, researchers have found specific genetic problems that point toward a metabolic deficiency in some cases of autism. These studies open up the possibility that supplements such as carnitine or certain amino acids may help treat autism.

The findings are exciting because they suggest that some forms of autism may be preventable. But scientists don't yet have data on whether supplementing the diet in these cases can prevent the disorder or improve symptoms. Nor do they know whether the potential benefits will be limited to those with specific genetic deficiencies or be effective more broadly.

Some teams are looking more rigorously at the benefit of supplements across a larger population.

In January, a large-scale study from Norway showed that women who take folic acid supplements during early pregnancy reduce their risk of having a child with autism. And a small, placebo-controlled trial of N-acetylcysteine

(NAC), an antioxidant used to treat acetaminophen overdose, found that the supplement improves irritability in children with autism.

Despite the promise, scientists say it's important to tread carefully and keep expectations in check.

Joseph Gleeson, professor of neurosciences at the University of California, San Diego, published a study in September on a rare metabolic deficiency that may be treatable with certain amino acids. After the publication, he cautioned parents not to give it to their children until there was evidence of if and when it worked.

"We had people tell us, 'I know you said don't start this, but we did,'" he says.

## FOLLOWING THE GENES:

Last May, Arthur Beaudet and his collaborators showed that a small deletion in a gene called trimethyllysine hydroxylase, epsilon (TMLHE), which is involved in synthesizing carnitine, raises autism risk. (Carnitine helps transport fatty acids into the mitochondria, the cell's energy producer, which has also been implicated in autism.)

The study looked specifically at TMLHE, but Beaudet says that common variations in a number



of genes have been shown to influence carnitine levels in the blood. He says environmental factors, such as diet, illness or even the microbes living in the gut, may also alter carnitine and, potentially, the risk of autism.

Beaudet's team is studying children with severe carnitine deficiency, a rare condition, and trying to get carnitine testing implemented on a wider scale.

It's not yet clear how broadly applicable the findings will be. "We already have a lot of patients who take carnitine and don't see striking behavioral effects," says Gleeson, who is not involved in the carnitine study. "Whether it will have a striking effect when used at optimal dosage, I don't know."

Beaudet says he hopes to work with researchers studying infants at high risk of autism – those who have an older sibling with the disorder and a 20-fold higher risk of developing the disorder than does the general population.

"I would like to see if nutritional supplementation from birth can push down this rate," says Beaudet. "But I don't know if I can convince anyone to buy into a trial like this."

It's not yet clear how lack of carnitine affects the brain, but Beaudet's team aims to answer that question by studying animal models – including worms, fruit flies and mice – with abnormal carnitine metabolism.

In September, Gleeson's team published a study identifying rare mutations in a gene called

branched-chain ketoacid dehydrogenase kinase (BCKDK) in a pair of siblings with autism. BCKDK is involved in the breakdown of branched-chain amino acids, a set of molecules that are essential for building proteins.

Gleeson says he doesn't yet have enough people with the mutation to start a clinical trial of supplements. His team has shown, however, that giving the amino acids to mice lacking the enzyme helps restore their brain levels of other amino acids to normal.

To test whether the treatment might work for other forms of autism, his team is testing the amino acids in other mouse models of autism.

#### DIET DILEMMA:

These new studies aren't the first to link metabolic problems and autism. Some children with untreated phenylketonuria, an inherited metabolic condition, or other rare inherited metabolic disorders also show symptoms of autism.

It's unclear how common these disorders are among people with autism. A 2011 study found that only 2 of 274 children with autism tested positive for a metabolic disorder. But Beaudet and Gleeson's studies, as well as ongoing sequencing studies of autism, may expand the number of disorders that fall into this category.

Other researchers are looking at whether supplements can lower autism risk or symptoms generally.

A study of more than 800 children, published in July, found that mothers who take 600 micrograms of folate during the first month of pregnancy are less likely to have a child with autism.

The effect is strongest in women with a mutation in an enzyme called methylenetetrahydrofolate reductase (MTHFR), which is involved in a chemical reaction involving folic acid. MTHFR mutations have been weakly linked to autism.

A second, much larger study, published in January, provides further support that folic acid early in pregnancy can reduce the child's risk of autism by about 40 percent.

The antioxidant NAC has also shown preliminary promise. A study published in June of 31 people with autism, half taking the supplement and half on a placebo, found that those taking the drug improved on a test of irritability. (The only two drugs approved by the U.S. Food and Drug Administration for autism both treat irritability.)

Antonio Hardan, who led the NAC study, says he was inspired to study the supplement in part because parents were already using it, despite little evidence of its benefit. But he says he was also interested in its antioxidant properties.

"There is some evidence to suggest oxidative stress is abnormal in individuals with autism," says Hardan, associate professor of child and adolescent psychiatry at Stanford University School of Medicine in California. NAC also targets a

signaling chemical in the brain called glutamate, which has also been implicated in autism, he says.

The fact that nutritional supplements are available over the counter has both benefits and drawbacks for clinical research. It's often easier to get approval to study these molecules in people. But because they are more loosely monitored than traditional drugs, the quality can vary widely, and researchers often need to do quality control tests themselves.

"We had huge issues over how and where to get NAC, and the quality," says Hardan.

It's also more difficult to find funding for these types of trials, because pharmaceutical companies aren't interested. The NAC study was funded by a private, parent-run foundation. With the promise of the pilot trial under his belt, Hardan is applying for funding for a larger trial from the National Institutes of Health ■



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# Cluster of symptoms reveals gene's link to autism subtype

**BY JESSICA WRIGHT**

CHD8, a gene that regulates the structure of DNA, is the closest thing so far to an 'autism gene,' suggests a study published today in *Cell*.

People with mutations in this gene all have the same cluster of symptoms, including a large head, constipation and characteristic facial features; nearly all also have autism.

Autism is notoriously heterogeneous, perhaps involving mutations in any of hundreds of genes. Typically, researchers begin by studying people with similar symptoms and working backward to identify what causes those symptoms. But that approach has not been particularly productive.

"We've tried for so long to identify subtypes of autism based on behavior alone and we've done abysmally at that," says lead researcher Raphael Bernier, associate professor of psychiatry at the University of Washington in Seattle.

The reverse approach – that is, beginning with people who all have mutations in the same gene and characterizing their symptoms – may prove to be more useful for simplifying autism's complexity.

For example, identifying subtypes of autism may help researchers develop drugs tailored to that particular cause, says Evan Eichler,

professor of genome sciences at the University of Washington, who spearheaded the genetics side of the study. "I think the most important realization is that not all autisms are created equal," he says.

Researchers first linked CHD8 to autism in 2012. They found mutations in the gene in nine people with autism but none of their unaffected family members. Among those in the autism group, more than twice as many people have de novo, or spontaneous, mutations in CHD8 as have de novo mutations in any other gene.

In the new study, researchers sequenced CHD8 in 3,730 children with autism or developmental delay, and found eight more mutations in the gene. They saw no mutations in the gene in nearly 9,000 controls.

An independent team led by Joseph Buxbaum at the Icahn School of Medicine at Mount Sinai in New York City has identified another seven CHD8 mutations in individuals with autism. That team has not yet published the data.

## **OLD-SCHOOL GENETICS:**

With only about two dozen people identified so far, mutations in CHD8 appear to be rare. Still, the gene's link to autism is clear.

"The significance of the mutation is quite high," says Edwin Cook, professor of psychiatry at the University of Illinois at Chicago, who was not involved in the study.

To characterize the symptoms of people with a CHD8 mutation, Bernier and his colleagues invited eight such individuals and their families to spend two days at the University of Washington. The researchers combined their observations of these people with detailed clinical reports about another seven individuals who were not able to come to the university.

Of these 15 individuals, 13 have a well-established diagnosis of autism. The remaining two are a 40-year-old woman who has a diagnosis of intellectual disability and had been institutionalized since she was a child; and a boy diagnosed with intellectual disability and attention deficit hyperactivity disorder.

"These could be cases of autism that were missed," says Bernier, who was not able to diagnose the participants because they live abroad. Adults, in particular, may have undiagnosed autism because there was less awareness of the disorder when they were children, he says. "My take-home is that if you have this [mutation] there's going to be a significant problem, and the vast majority of times it's going to be autism."

Others are more circumspect about the link.

The high proportion of autism in people with a CHD8 mutation

is striking, but the researchers identified nine people with mutations from a database of people known to have autism, notes Cook. The prevalence of autism might go down when researchers look for CHD8 mutations among people with other diagnoses, he says.

In terms of their symptoms, too, the participants share a striking resemblance to each other. The first girl in the study with a mutation has unusual facial features and unequivocal autism symptoms such as lack of eye contact – the kind Bernier refers to as "diagnosis in the lobby." The girl's parents complained of her severe gastric distress and the fact that she would not sleep for days on end.

A few days later, Bernier met the second child with a mutation. This boy also had clear signs of autism, severe constipation and could not fall asleep. His facial features looked remarkably similar to those of the girl. "He could pass as her sibling," says Bernier.

As more people with mutations came in, Bernier's team realized that most of them have wide-set eyes, large ears and broad foreheads and noses. Of the 15, 12 have enlarged heads, 12 have gastrointestinal problems (9 specifically have constipation) and 10 have sleep problems.

Many single-gene brain disorders related to autism are characterized by intellectual disability, but nearly half of the individuals with CHD8 mutations have intelligence quotients in the normal range.

"The subgroup has a remarkably clear phenotype," says Thomas Frazier, director of the Center for Autism at Cleveland Clinic Children's, who was not involved in the study. Clinicians might be able to identify people with this subtype of autism by these features, he says.

To study the mutations further, the researchers blocked expression of the gene in zebrafish embryos. The fish end up with large eyes and take hours longer than controls do to move a fluorescent pellet along their digestive tract. The mutant fish also have about half the number of neurons coating their gut as controls do.

These observations are in line with the high prevalence of digestive issues among people with a CHD8 mutation. "It tells me right away that this is not one quirky thing that happened in 15 people," Frazier says. "This is a real biological phenomenon and we should pay attention to it."

The researchers are looking for more people who have CHD8 mutations. Eichler and his team have access to sequences from nearly 15,000 people worldwide who have autism or other developmental disabilities. They have clinical information from these people and permission to contact them and their families – a rare advantage in large-scale genetics studies.

"The devil is in the details and that's where we need to be – in the trenches and really working with the families," Eichler says. ■

29 OCTOBER 2014

# Massive sequencing studies reveal key autism genes

BY JESSICA WRIGHT

Analyzing the sequences of more than 20,000 people, researchers have unearthed the largest and most robust list of autism genes so far, they reported today in *Nature*.

These 50 'high-confidence' autism genes may help researchers understand the biological underpinnings of autism.

"This is just absolutely thrilling," says Matthew State, chair of psychiatry at the University of California, San Francisco, who was involved in both studies. "For so many years it felt incredibly challenging to figure out how we were going to identify autism genes. Now we can begin to see the biology clarify itself through these papers."

The researchers found these genes by scouring the exomes, the protein-coding regions of the genome, looking for rare genetic glitches unique to people with autism.

One study sequenced members of 2,517 families – a child with autism and his or her unaffected siblings and parents – and pinpoints 27 candidate genes.

The other bears the fruit of an international consortium that has compiled data from nearly 4,000 people with autism from across the world. It highlights 33 autism risk genes.

The two lists share only ten genes, but overall the genes point to two key functions: communication between neuronal junctions, or synapses, and control of gene structure and expression. The latter, virtually unheard of in autism five years ago, is emerging as the strongest pathway involved in the disorder.

"The two studies have complementary but certainly distinctive designs, and they point to basically the same biological processes," says Patrick Sullivan, professor of genetics at the University of North Carolina at Chapel Hill, who was not involved with either study. "It will give some important clues to work from."

## AUTISM GENES:

The family study relied on data from the Simons Simplex Collection (SSC) – a database of families that have one child with autism and unaffected parents and siblings. (The SSC is funded by the Simons Foundation, SFARI.org's parent organization.) This collection is designed to identify *de novo*, or spontaneous, mutations, which are present only in the affected child.

In 2012, three teams of researchers independently analyzed a subset of

more than 800 families from the SSC. In the new study, they collaborated to analyze the exomes of 2,517 people with autism, their 5,034 parents and 1,911 unaffected siblings.

The researchers found 27 genes that have so-called 'loss-of-function' mutations – which abolish function of the corresponding protein – in at least two people with autism. "Around here, we call them killers," says lead researcher Michael Wigler, professor at Cold Spring Harbor Laboratory in New York.

Of the 27 genes, 6 are mutated in three or more people with autism. This makes these six – CHD8, DYRK1A, ANK2, GRIN2B, DSCAM and CHD2 – the strongest autism candidates so far.

Overall, the researchers found 391 killer mutations in 353 genes in children with autism. By looking at the rates of these mutations in unaffected siblings, they estimate that roughly 40 percent of the de novo loss-of-function mutations contributed to autism diagnoses.

In each case, the mutation affects only one copy, or allele, of the gene, which is encouraging, says Wigler. "That means there is at least some hope that symptoms can be lessened by targeting the remaining good allele," he says.

The children with autism also carry another 1,500 de novo 'missense' mutations of unknown significance. Because of the large sample size, the researchers were able to estimate that about 13 percent of these mutations are likely to lead to symptoms, says Wigler. This was impossible in the smaller SSC studies published two years ago, in which the sequences were split among three research groups.

The estimate suggests that missense mutations are less valuable for identifying autism risk

genes than are the killer mutations, says Wigler. "Missense is a sticky ball of wax. We don't know what point mutations are disruptive for a gene, and most are not," he says.

### **FAMILY RISK:**

In their paper, the members of the research consortium looked at mutations whose impact is even more difficult to interpret: mutations inherited from family members. This collaboration of more than 20 teams, called the Autism Sequencing Consortium, has collected sequences from across the globe, including Costa Rica, Finland and the Middle East.

The teams analyzed sequences from 3,871 people with autism and 9,937 controls of the same ancestry. This includes 2,270 children with autism – including 825 from the SSC – whose unaffected parents served as controls.

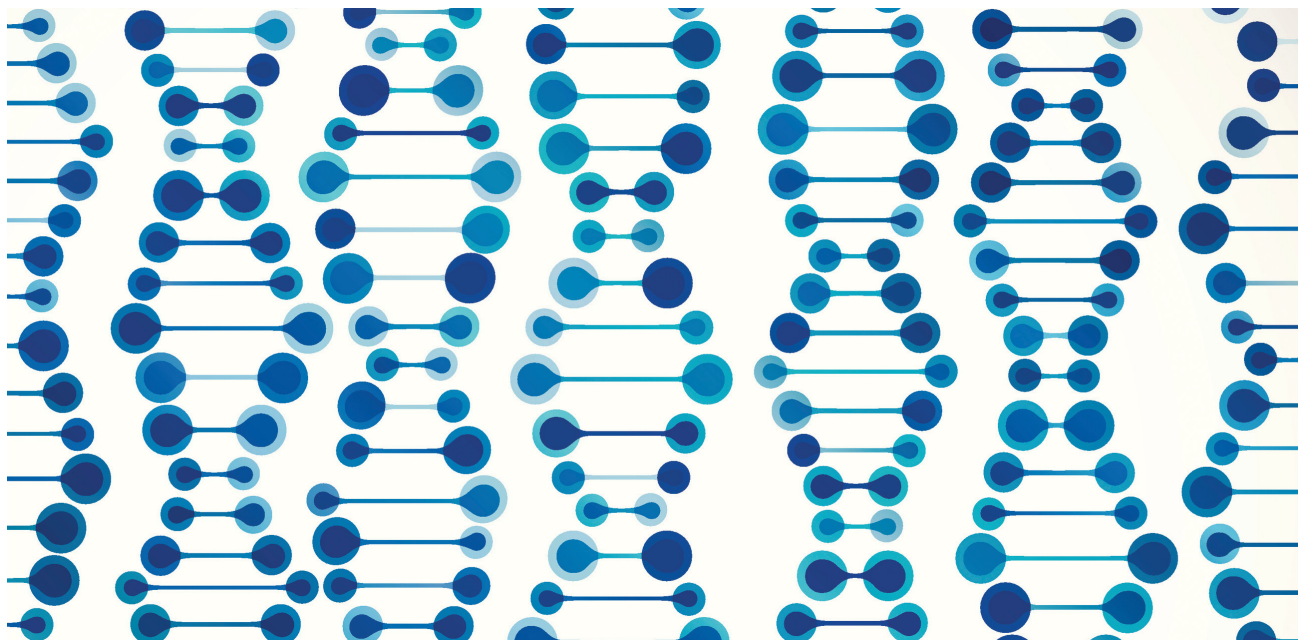
To analyze these mixed data, they used a statistical method called TADA. This approach merges information about inherited and de novo loss-of-function and harmful missense mutations to rate the significance of a particular autism gene.

Using this method, the researchers identified 33 genes that have at least a 90 percent chance of being true autism genes, including 13 genes that have a 99 percent chance or more of being so. The latter list includes ADNP, ANK2, CHD8, DYRK1A, GRIN2B, SCN2A, SYNGAP1 and TBR1. The researchers also uncovered seven genes that have never been linked to autism before.

To further strengthen the genes' link to autism, the researchers looked at their prevalence in males and females with the disorder. Because it takes a bigger genetic hit to



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lead to autism in women than in men, mutations with a true link to autism would be expected to be more prevalent in women with the disorder than in men.

The study found that mutations in the 33 autism genes are more prevalent in females than in males, and increase the risk of autism by at least 20-fold.

"This shows us that these are the uniquely high-impact set," says Mark Daly, associate professor of medicine at Harvard University.

The set of genes is merely the first step to revealing the biology of autism, however. "We want not just to collect genes and genetic variants in a stamp-collecting mode, but to derive potential hypotheses," Daly says.

To find patterns among their data, the researchers used another statistical tool, called DAWN, that identifies genes expressed at the same time and place in the developing brain. This tool points to regulation of the synapse and of gene expression as

key pathways in autism. The strongest signal, the researchers say, comes from genes that modify chromatin, which helps package DNA in the nucleus of the cell.

"It's breathtaking," says Joseph Buxbaum, director of the Seaver Autism Center at the Icahn School of Medicine at Mount Sinai in New York City, of the data linking chromatin-modifying genes to autism. "The entire universe of these genes is less than a couple dozen and I have four of them right in front of me."

The SSC study also identified genes that influence transcription and chromatin modification. Genes important in fetal development and targets of the protein involved in fragile X syndrome also figured in both lists of genes.

Taken together, the studies suggest clear starting points in the search for autism treatments, Buxbaum says. "Genetics is not the end; it's the beginning. Here we're finally coming to the point where we can think about that beginning." ■



# 2015

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29 JANUARY 2015

# Noisy patterns of connectivity mark autism brains

BY ALLA KATSNELSON

A new study may have solved a decade-old debate about whether the brains of people with autism are more or less connected than those of controls: They're both, depending on where in the brain you look. The study, published 19 January in *Nature Neuroscience*, suggests that a mix of abnormally strong and weak brain connections is a hallmark of the disorder.

"In the very same individual, we can see both, depending on spatial distribution," says Marlene Behrmann, professor of psychology at Carnegie Mellon University in Pittsburgh.

Behrmann and her colleagues analyzed functional magnetic resonance imaging (fMRI) scans from 68 adults with high-functioning autism and 73 age-matched controls. As a group, people with autism showed the opposite pattern of connectivity to that seen in controls.

"Those areas that are typically highly connected were less connected in [the autism group], and those areas that are typically less connected were more connected in the autism group," says Behrmann.

On an individual level, however, the researchers found noisier patterns of connectivity in the brains of people with autism than in controls. The more these patterns deviate

from those of controls, the more severe a person's autism symptoms tend to be.

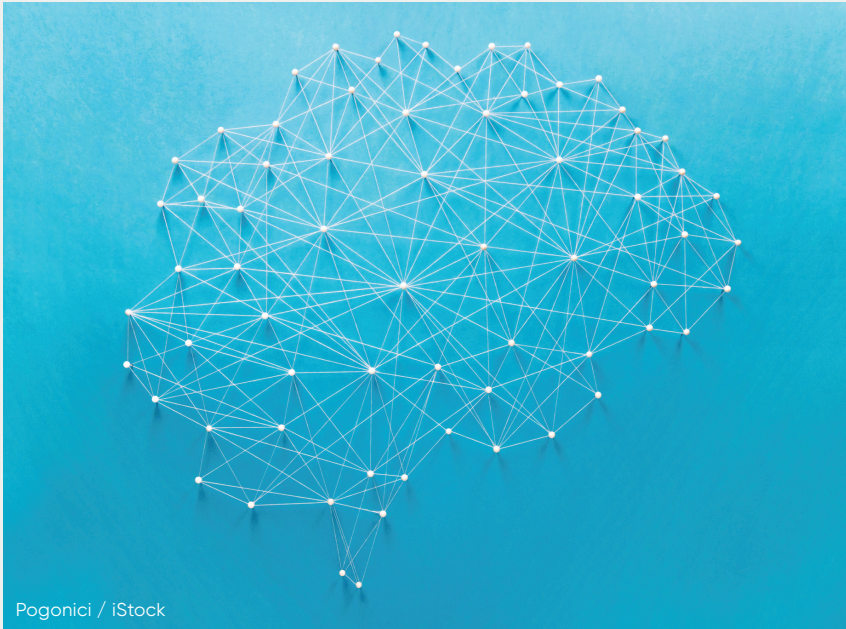
The findings jibe with previous studies from Behrmann's team, which suggest that signaling in the brains of people with autism is more variable than in controls. They may also help to reconcile discrepant findings on brain connectivity that have dogged autism researchers for years.

"They're actually saying that maybe everyone with [autism] is just different from that canonical response or pattern of brain activity," says Dan Kennedy, assistant professor of psychological and brain sciences at Indiana University in Bloomington, who was not involved in the work.

The findings also fit with the growing appreciation of autism's heterogeneity. "We know there are lots of different causes of autism and different developmental trajectories," says Kennedy. "To expect that everyone with autism is going to show some clear biological commonality might be incorrect."

## PARSING PATTERNS:

Most previous studies of brain connectivity in autism had smaller sample sizes and focused on a



Pogonici / iStock

select few regions of the brain. In the new study, Behrmann and her colleagues analyzed data from the Autism Brain Imaging Data Exchange (ABIDE), an open-access repository of more than 1,000 fMRI scans from 17 labs worldwide.

They measured connectivity by mapping the level of synchrony between different brain areas across and within the two hemispheres of the brain. Two areas are considered connected when they light up on the scans simultaneously.

Overall, connections that are strong in controls are weaker in people with autism and vice versa. But these group-level differences do not hold up when the researchers look at individual connectivity patterns, which vary widely within the autism group. This idiosyncrasy tracks with autism severity, so that individuals whose brain connectivity is most different from that of controls score highest on the Autism Diagnostic Observation Schedule, a widely used scale for assessing autism.

Some experts say this should come as no surprise. "We do know that regardless of the psychiatric disorder studied, there's always more variability in patient groups," says Vinod Menon, professor of psychiatry and behavioral sciences at Stanford University in California, who was not involved in the work.

Others say the findings highlight a new way of thinking about altered brain connectivity in autism. "If it's confirmed, it brings up a very new avenue of research," says Adriana Di Martino, assistant professor of child and adolescent psychiatry at New York University's Langone Medical Center. Di Martino was not involved with the study but manages the ABIDE database.

Di Martino and her colleagues also found evidence for both over- and underconnectivity in the brains of people with autism in a 2013 analysis of 763 scans from ABIDE. But their work differed in that it focused on specific brain circuits and contained a more diverse pool of participants, including children.

Expanding the new study to include children will clarify whether noisy connectivity is a cause or effect of autism, according to Menon. "Mapping out the developmental trajectory of these changes is, I think, going to be an interesting and important action for the future," he says.

Behrmann says she plans to study children and hopes other labs will extend the study to people with severe autism.

"The more the field can work together to aggregate big datasets," she says, "it's my opinion that we will be able to uncover patterns that have heretofore been elusive." ■

6 APRIL 2015

# Genes dwarf environment in autism's origins, study says

**BY RACHEL NUWER**

The genetic makeup of an individual plays much a bigger role than environmental factors in whether he or she develops autism, according to one of the largest twin studies to date. The findings, published 4 March in *JAMA Psychiatry*, suggest that genes confer up to 95 percent of the risk for autism – nearly double that of previous estimates.

For example, a 2011 twin study pegged the autism risk from environmental factors at 58 percent. A study last year of more than 2 million people, including 37,570 pairs of twins, found that genetic and environmental factors each confer 50 percent of the risk for the disorder. However, the latter study loosely defined the term 'environment' to include spontaneous, or de novo mutations.

Pinpointing the relative contributions of genetics and the environment is more than just an academic debate. "There is huge concern amongst families and professionals about possible environmental factors that may have a role in the etiology of autism," says Francesca Happé, professor of cognitive neuroscience at King's College

London and lead researcher on the new study. "Genetically sensitive designs like twin studies

are essential to estimate the magnitude of environmental effects in a population."

To parse the source of autism risk, researchers often turn to twin pairs. By comparing autism rates in identical twins, who share all of their DNA, and fraternal twins, who are only as similar as non-twin siblings, they can tease out how strong of a role genetics and shared environmental factors play in autism risk.

## **TAPPING TWINS:**

Studies of autism in twins date back to 1977, when researchers provided the first evidence that autism is heritable rather than springing solely from environmental factors.

A 1995 follow-up of 40 twin pairs found a so-called concordance rate for autism of 92 percent for identical twins and 10 percent for fraternal twins. Several other twin studies have yielded rates that suggest a strong genetic contribution.

The new findings are based on data from the Twins Early Development Study, which follows twins born in England and Wales between 1994 and 1996. The researchers selected participants from hundreds of families in which at least one twin has received a score suggestive of autism on the Childhood

Autism Spectrum Test or has been diagnosed with autism.

From this sample, they found 146 twin pairs in which at least one sibling received an initial autism diagnosis. They then performed in-depth diagnostic tests as well as cognitive assessments during home visits to 129 of these families. Parents also provided reports on each twin's development. From this information, the researchers confirmed 141 cases of autism and identified 40 children who have autism-like traits, or 'broad autism phenotype.'

If one twin has autism, the odds of the other twin having the disorder range from 62 to 94 percent for identical twins and 5 to 61 percent for fraternal twins, the researchers found.

A statistical model then produced an estimate of the relative pull of genetic and environmental factors on autism risk: Genetic influences account for 56 to 95 percent of the risk and environmental factors, such as prenatal exposure to chemicals and parental age at conception, contribute 5 to 44 percent.

This statistical model also supports the idea that autism traits and skills are continuously distributed throughout the general population, with people who have autism at one extreme.

However, the model does not account for interactions between genes and the environment, says Janine LaSalle, professor of medical microbiology and immunology at the University of California, Davis.

"The reality is that there are many known complex gene-environment interactions that have major effects on shaping phenotypic traits in humans, and are beginning to be uncovered in autism spectrum disorders," she says.

LaSalle also points out that 93 percent of the individuals in the new study are Caucasian and all are from the U.K. This homogeneity may explain why the estimate for genetic risk is higher than in the earlier twin studies, she says. "It's pretty clear that environmental exposures vary by race, socioeconomic status, geography and occupation."

One big challenge is to identify which exposures constitute environmental risk, says Joachim Hallmayer, associate professor of psychiatry at Stanford University and lead investigator of the 2011 study. "At the end of the day, we have to find the genes and environmental factors that impact the development of the disorder." ■

# 2016

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BY JESSICA WRIGHT  
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18 FEBRUARY 2016

# Blocking key immune signal prevents autism signs in mice

BY ANN GRISWOLD

Researchers have identified a key immune molecule in pregnant mice that produces autism-like behaviors in their pups. The findings, published 28 January in *Science*, support the theory that infections during pregnancy raise the risk of autism. The study also hints at a way to mitigate the risk.

"Somewhere down the road, if this applies to human physiology, it may be possible to prevent autism by treating women who have elevated levels of [the immune signal]," says lead researcher Dan Littman, professor of immunology at New York University.

An infection during pregnancy raises the risk of having a child with autism by 37 percent; women with an overactive immune system also have a heightened risk. How an immune reaction might spur autism is unclear, but some studies have found elevated levels of interleukin-17 (IL-17) – a signaling molecule that helps to fend off foreign invaders – in children with autism.

Mouse studies also support this theory. Pups born to pregnant mice exposed to a mock virus have autism-like characteristics, such as social deficits and repetitive behaviors.

In the new study, Littman and his colleagues show that blocking

IL-17A – a subtype of IL-17 – in infected pregnant mice prevents these symptoms in their pups.

IL-17 plays a key role in autoimmune diseases such as multiple sclerosis, lupus and rheumatoid arthritis. Women with these conditions have an increased risk of having a child with autism.

"This work provides further evidence for a role of maternal infection and inflammation in autism and suggests potential therapeutic targets in this disorder," says Alan Brown, professor of psychiatry and epidemiology at Columbia University, who was not involved in the research.

## SIGNAL MALFUNCTION:

Littman and his team created mice lacking the cell type that produces IL-17A. They injected these mice, as well as controls, mid-pregnancy with a molecule that mimics a viral infection.

Consistent with previous work, pups born to the control mothers performed poorly on tests of social behaviors (time spent interacting with other mice), communication (number of high-pitched squeaks) and perseveration (time spent burying a marble).

The mice also showed signs of abnormal brain development: The layers of the brain's outer shell, called the cerebral cortex, appear disorganized.

By contrast, pups born to mothers that lack IL-17A performed normally on all of the tests. The researchers saw similar results when they treated controls with antibodies that block IL-17A.

They injected IL-17A directly into fetal mouse brains and found that doing so could produce abnormal cortical layering and autism-like behaviors, even without a maternal infection. This finding suggests that maternal IL-17A leads to autism by acting in the fetal brain, rather than through the mother.

"This is a very elegant study for understanding how important the maternal immune system is for fetal brain development," says Betty Diamond, head of the Center for Autoimmune and Musculoskeletal Disorders at the Feinstein Institute for Medical Research in Manhasset, New York, who was not involved in the study.

#### **ON TARGET:**

Littman says his team was surprised that an immune molecule from the mother binds to a protein in the fetal brain, and that it might shape

fetal brain development as a result. It's possible that the receptor has roles beyond binding IL-17, he says.

"The more we learn about the connection between the immune and central nervous systems, the more we'll understand disorders such as autism that target both of them," says Jonathan Kipnis, professor of neuroscience at the University of Virginia in Charlottesville, who was not involved in the study.

Whether this maternal-fetal immune connection exists in people remains to be seen, however. Researchers still aren't sure which brain cells express the IL-17A receptor in mice, so they don't know whether the same cells express the receptor in people. It's also unclear whether IL-17A levels are elevated in pregnant women who give birth to children with autism.

"It's far too early to determine whether this pathway will apply to humans, but it certainly opens up a potential avenue of research that should be looked at carefully," says Sarah Gaffen, professor of rheumatology and clinical immunology at the University of Pittsburgh, who was not involved in the work. "This is a beautiful and intriguing study." ■



5 SEPTEMBER 2016

# Words say little about cognitive abilities in autism

BY NICHOLETTE ZELIADT

Nearly half of children with autism who speak few or no words have cognitive skills that far exceed their verbal abilities, according to the largest study of so-called 'minimally verbal' children with autism to date. The findings call into question the widespread assumption that children with autism who have severe difficulty with speech also have low intelligence.

"What I think is really interesting is that among children who have very limited levels of language, there is more cognitive variability than you might expect," says lead investigator Vanessa Bal, assistant professor of psychiatry at the University of California, San Francisco.

The study, published 30 July in the *Journal of Child Psychology and Psychiatry*, also reveals that the number of children with autism classified as minimally verbal depends on the test used to identify these children.

"It might seem easy to put these kids in a category because they don't talk, but this paper shows it's not so straightforward," says Isabelle Soulières, associate professor of psychology at the University of Quebec in Montreal, who was not involved in the study. "Depending on the test you choose, you will get very different answers."

Bal and her colleagues analyzed data on language skills for 1,470 children ages 6 to 17 from the Simons Simplex Collection (SSC), an autism registry funded by the Simons Foundation, *Spectrum's* parent organization. Through the SSC, the researchers had access to results from five standardized tests that assess language.

## DIFFICULT DEFINITION:

Two of these tests – the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised – classify children as minimally verbal if they use only single words or simple phrases such as 'want juice.'

The other three tests use various criteria. One classifies children as minimally verbal if they rely primarily on gestures and single words to communicate. Another puts children in that category if they don't use phrases or sentences at all. The third uses a vocabulary of 25 or fewer words as its benchmark.

Of the entire SSC group, 18 percent were minimally verbal according to at least one test. The ADOS flagged nearly 93 percent of these minimally verbal children. By contrast, a test called the Vineland Adaptive Behavior Scales captured only 26 percent.

The researchers found only a partial overlap among the children the different tests identified as minimally verbal: 41 percent of minimally verbal children scored as such on three or more tests and 23 percent met the criteria on two tests. The remaining 36 percent qualified as minimally verbal on only one test.

The discrepancies highlight a challenge for researchers who study minimally verbal children with autism, says Connie Kasari, professor of human development and psychology at the University of California, Los Angeles, who was not involved in the study. "We're struggling with how to define who the minimally verbal kids are," she says.

### INTELLECTUAL DIVIDE:

Inconsistency across measures makes it difficult for researchers to compare results from one study to the next, Bal says.

But no one test can capture all minimally verbal children with autism. "There's huge variability in this population and no definition is going to capture the full range of kids," says Helen Tager-Flusberg, director of the Center for Autism Research Excellence at Boston University, who was not involved in the work.

Bal and her colleagues also examined results from intelligence tests that contain only some questions that require language. Using these results, the researchers compared the children's verbal cognitive skills, such as their ability to name objects, with their performance on nonverbal tasks, such as copying line drawings.

They found that regardless of the method used to classify children as

minimally verbal, 43 to 52 percent of minimally verbal children have significantly higher nonverbal than verbal intelligence scores. By contrast, typically developing children tend to achieve similar scores on the verbal and nonverbal parts of intelligence tests, Bal says.

The findings suggest language difficulties do not necessarily stem from cognitive problems in children with autism. "I think we have to look somewhere else," Soulières says. Some children may have trouble developing language because they have difficulties imitating others or moving parts of their mouth or face, for example.

Minimally verbal children with autism who have relatively strong cognitive skills may benefit from treatments different from those who have lower cognitive ability, Bal says. "Trying to separate those out clinically is important," she says. ■



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# 2017

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15 FEBRUARY 2017

# Rapid brain growth in infancy may signal autism

**BY NICHOLETTE ZELIADT**

The faster the brains of children with autism grow in their first year of life, the more severe their autism features are likely to be at age 2, according to a study published today in *Nature*.

This rapid growth can in fact predict whether a child will later be diagnosed with autism.

The findings point to a possible biomarker that could help doctors identify autism in infants –two to three years before the typical age of diagnosis.

“This is a first step towards something that has tremendous potential for early identification and intervention,” says lead investigator Joseph Piven, Thomas E. Castelloe Distinguished Professor of Psychiatry at the University of North Carolina at Chapel Hill.

The results add to mounting evidence that subtle signs of autism may appear in infancy. For example, some baby boys who are later diagnosed with autism lose interest in looking at others’ eyes during the first 6 months of life.

“It’s showing us that the early postnatal years are critical to study in order to understand autism,” says Mark Johnson, director of the Centre for Brain and Cognitive Development at Birkbeck, University of London, who was not involved in the new work.

The findings also jibe with work in the past decade suggesting that brain overgrowth in infancy occurs in a subset of children with the condition. The new study begins to clarify which brain regions are most affected and hints at the underlying mechanism.

## **GROWING PAINS:**

The researchers used magnetic resonance imaging (MRI) to scan the brains of 148 infants, 106 of whom have an older sibling with autism. These so-called ‘baby sibs’ are about 20 times more likely to have autism than are children in the general population. All of the children in the study are part of the Infant Brain Imaging Study (IBIS), which tracks the development of more than 300 babies with a family history of autism.

The researchers measured the children’s total brain volume at 6, 12 and 24 months of age. They also looked at the surface area and thickness of the cerebral cortex, the brain’s outer layer. They assessed the children’s cognition, daily-living abilities and communication skills. Of the 106 baby sibs, 15 received an autism diagnosis at age 2.

The surface area of the cortex grows significantly faster between the ages of 6 and 12 months in children with autism than in

those without the condition, the researchers found. The expansion occurs primarily in regions that process visual information.

"It's not simply generalized overgrowth," says Gordon Ramsay, director of the Spoken Communication Laboratory at the Marcus Autism Center in Atlanta, Georgia, who was not involved in the study.

Between 12 and 24 months of age, the surface area growth rate evens out in the two groups. At that point, the overall brain volume increases faster in children with autism than in controls. The faster growth is associated with poor performance on tests of social communication.

The findings suggest that surface expansion of the brain precedes overall overgrowth and the emergence of autism features. This sequence is consistent with results in mice.

The molecular mechanisms underlying brain surface area expansion — many of which are known — may also provide clues to how autism unfolds, Piven says.

### **PREDICTIVE POTENTIAL:**

The researchers input measures of surface area, thickness and volume at 6 and 12 months into a machine-learning algorithm to predict which infants would later be diagnosed with autism. The data came from brain scans of 34 baby sibs with autism and 145 baby sibs without the condition, all participants in IBIS.

The algorithm analyzed data from all but 10 of the participants to predict the diagnostic status of the remaining individuals, and repeated the process 10 times. The computer correctly predicted an

autism diagnosis for 81 percent of the children.

Many of the measurements the algorithm relied on most are related to surface area, and came from 6-month-old children. The brain regions involved are different from those that show rapid surface area expansion in autism, Ramsay says. "The fact that they're not consistent suggests that some of the expansion in surface area may actually not be relevant to the detection of autism," he says.

If the findings hold up in a larger, independent sample of children, the algorithm might be a useful tool for predicting autism in baby sibs, Piven says.

But some experts say using brain scans to screen for autism is an impractical proposition; only about one-third of the infants enrolled in IBIS were able to complete brain scans at all three ages, Johnson notes. "It's unlikely that's going to be adopted as a screening protocol."

The researchers acknowledge this limitation. Parents who already have a child with autism may find it particularly difficult to show up for repeated brain scans, Piven says.

It is unclear whether brain growth will be predictive of autism in children without a family history of the condition. Piven says a next step is to compare brain growth patterns in children who have autism with those of children who have other neurodevelopmental conditions. ■

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**BY NICHOLETTE ZELIADT  
7 JUNE 2017**

14 SEPTEMBER 2017

# Sizeable fraction of autism risk traced to 'mosaic' mutations

**BY NICHOLETTE ZELIADT**

Mutations that appear in only some of the body's cells contribute to autism in about 4 percent of people with the condition, an analysis of more than 8,000 sequences suggests.

Mosaic mutations arise spontaneously after conception; the later they appear, the fewer cells of the body they affect.

The findings suggest that these so-called 'mosaic mutations' play a bigger role in autism than previously thought. "This number places mosaic mutations as a whole as having a similar contribution [to autism risk] as other classes of de novo mutations," says lead investigator Brian O'Roak, assistant professor of molecular and medical genetics at Oregon Health & Science University in Portland.

A large study published in July found that 7.5 percent of de novo, or spontaneous, mutations in people with autism occur in a mosaic pattern. The new study found that about 22 percent of de novo mutations are mosaic. The results were published 31 August in the *American Journal of Human Genetics*.

O'Roak's team unearthed another surprise: About 7 percent of spontaneous mutations in people with autism are present in some of their parents' blood cells.

"That's important in terms of genetic counseling," says Anne Goriely, associate professor of human genetics at the University of Oxford in the United Kingdom, who was not involved in the study. Clinicians usually assume that a de novo mutation in a child is a one-off event. "But if you can pick it up at a low level in the blood of one of the parents, then you know the risk [of recurrence] is much higher."

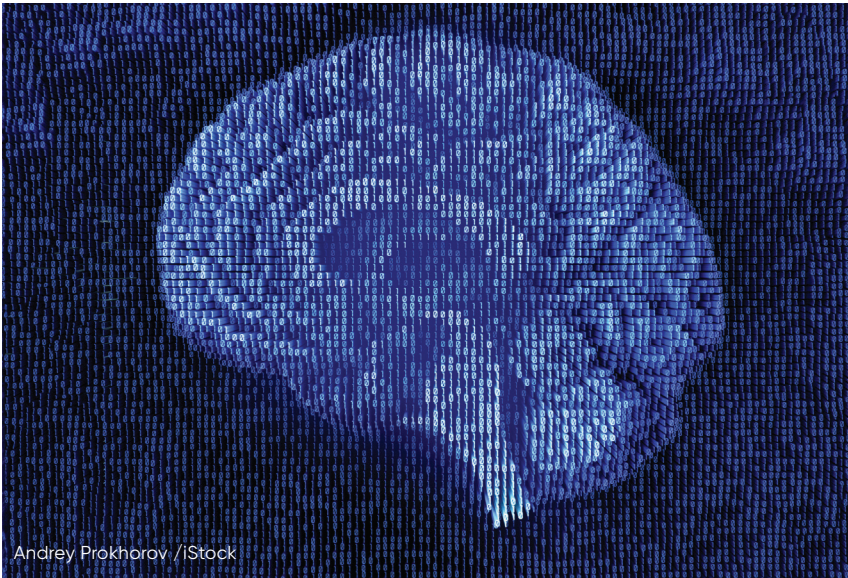
## SEQUENCE SCANS:

O'Roak's team looked for mosaic mutations in 2,506 families that have one child with autism and unaffected parents and siblings. Previous studies revealed a total of 2,996 mutations in the participants with autism and 2,080 in their siblings that do not show up in their parents.

The researchers looked at each mutation's 'allele fraction,' a number based on the proportion of an individual's cells that contain the mutation. A de novo mutation that arises in an egg or sperm shows up in all of a child's cells but affects only one of the two DNA copies, or alleles, yielding an allele fraction of about 50 percent. A mosaic mutation affects fewer cells, so its allele fraction is smaller.

Roughly 11 percent of the de novo mutations in people with autism,





Andrey Prokhorov /iStock

and 10 percent of those in their siblings, have an allele fraction of 35 percent or less, the researchers found. They predict that these mutations are likely to be mosaic, and the rest originated in a parent's egg or sperm.

The researchers sequenced many copies of DNA at the sites of germline and mosaic mutations in 24 of the families for more precise estimates of these mutations' allele fractions. They found that their previous predictions were accurate for 701 of the 965 mutations.

O'Roak's team then identified features that distinguish germline mutations from mosaic ones, and developed a computational method to spot mosaic mutations. They refined their method with 400 additional families until it identified 95 percent of the mosaic mutations.

The researchers then applied the method to 2,264 of the families. They found 2,147 de novo mutations, 470 of which are mosaic, in the people with autism and their siblings. Mosaic mutations occur at about the same frequency in people with autism as they do in their unaffected siblings, the analysis found.

### PIECED TOGETHER:

People with autism have twice as many mosaic mutations that are 'synonymous,' meaning they do not change a protein's amino acid sequence, as their siblings do, however. These mutations are also more likely than those in siblings to land close to 'splice' sites — regions that control how genes are pieced together — and to disrupt these sites.

Another mutation type, called 'missense,' occurs at roughly the same frequency in people with autism as in their siblings. But mosaic missense mutations in people with autism are more likely to occur in genes that are rarely mutated in the general population. They are also more likely to land in genes strongly linked to autism, including *SCN2A*, *SYNGAP1*, *CHD2* and *CTNNA1*.

By comparing the rates of synonymous and missense mosaic mutations in people with autism and their siblings, the researchers estimate that the mutations contribute to 4 percent of autism cases.

"We're starting to get an estimate of another source of contribution to [autism risk], one that might

### RELATED STORY:

## Large study shines spotlight on 'mosaic' mutations in autism

BY NICHOLETTE ZELIADT  
19 JULY 2017

have slipped through our filters and ability to detect with older technology a few years ago," says Michael Ronemus, research assistant professor at Cold Spring Harbor Laboratory in New York. (Ronemus has collaborated with O'Roak but was not involved in the new study.)

The researchers also looked for mosaic mutations in the parents' DNA. They found that up to 11 percent of mosaic mutations in parents also appear in their children. Parents' mosaic mutations account for 6.8 percent of mutations presumed to be de novo in their children.

Studies that compare sequences in different body tissues may reveal additional mosaic mutations, Goriely says.

O'Roak says his team is doing just that, comparing mosaic mutations in blood and brain tissue (collected from epilepsy surgeries) in people with autism. The team is also comparing mutations in blood and saliva from identical twins in which only one twin has autism, to determine whether mosaic mutations contribute to their discordant diagnoses. ■

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29 MAY 2018

# Monkey study bolsters case for brain hormone's role in autism

BY NICHOLETTE ZELIADT

Male monkeys that avoid touching, grooming or playing with others have low brain levels of the hormone vasopressin, according to a new study. Low levels of vasopressin in the brain also characterize boys with autism, the study found.

Vasopressin and the related hormone oxytocin control a variety of social behaviors. Both hormones have been touted as potential treatments for autism.

The findings hint that vasopressin levels are a useful marker for autism. They also support the idea that boosting these levels improves social functioning. The study appeared 2 May in *Science Translational Medicine*.

"This is some preliminary evidence to suggest that vasopressin could be a marker of impaired social function in both monkeys and humans," says lead investigator Karen Parker, associate professor of psychiatry and behavioral sciences at Stanford University in California. "I think the obvious next step would be to say, 'Well, maybe we need to replace vasopressin.'"

In fact, a study published today in *Scientific Reports* indicates that boosting vasopressin levels improves social interactions, at least in monkeys.

Parker's team measured several chemicals in samples of blood and cerebrospinal fluid in the monkeys, and vasopressin alone proved to be the best social gauge.

"Autism is hugely complicated and yet, at least in this one instance, there was one molecule whose concentrations in the central nervous system predicted social function," says Michael Platt, professor of psychology at the University of Pennsylvania. Platt led the study in *Scientific Reports* but was not involved in Parker's study. "I think that's very surprising."

However, the researchers caution that the findings from both studies are preliminary and need to be replicated. It is also unclear whether low vasopressin levels are unique to autism or are a feature of other psychiatric conditions as well.



Michael Warren / iStock

## **MONKEY MARKER:**

The rhesus monkeys in Parker's study live in half-acre corrals, each with up to 221 animals, at the California National Primate Research Center in Davis. The monkeys range in age from 1 to 5 years.

Parker and her colleagues monitored the social behaviors of 42 monkeys for 10 minutes twice a day for 8 days. These monkeys showed a wide range of sociability in tests conducted when they were 3 to 4 months old.

The team identified the 15 most and 15 least sociable monkeys by observing how often they interact by, for example, chasing, wrestling with or grooming others. They drew samples of blood and cerebrospinal fluid and measured levels of vasopressin and oxytocin. They also measured the expression of the receptors for these hormones, as well as molecular activity in two signaling pathways linked to autism, PI3K and RAS/MAPK.

The researchers used a machine-learning algorithm to identify the markers that distinguish the low- and high-social monkeys. The combination of oxytocin and vasopressin levels in cerebrospinal fluid, along with the activity of the PI3K pathway in blood, correctly classified 24 of the 27 monkeys. (The researchers only had complete data for these 27 monkeys.)

Statistical analyses revealed that the level of vasopressin in the cerebrospinal fluid is the most robust marker of sociability in the monkeys. Levels of this hormone are significantly lower in low-social monkeys than in their more social peers.

These findings held up in an independent set of 15 low-social monkeys and 15 high-social ones from the same colony. Levels of vasopressin in cerebrospinal fluid alone correctly classified 28 of these 30 monkeys.

This specificity surprised some experts.

"If I had to guess ahead of time which one would be lower in the

low-social guys, I would have picked oxytocin," says Larry Young, chief of behavioral neuroscience and psychiatric disorders at Emory University in Atlanta, who was not involved in the work. "But I would have been wrong."

## **CAUSE OR CONSEQUENCE:**

Parker and her colleagues then measured vasopressin in the cerebrospinal fluid of seven boys with autism and seven age-matched controls. The samples had been drawn for conditions unrelated to autism, such as cancer.

As a group, boys with autism have lower vasopressin levels than controls do. And the levels predict whether the boys have a diagnosis of autism, with one exception: a boy with autism whose vasopressin level is similar to that of controls.

"That's a really valuable approach, starting with the rhesus macaques and then being able to quickly take a look in a population with a diagnosis," says Elizabeth Hammock, assistant professor of psychology and neuroscience at Florida State University in Tallahassee, who was not involved in the study.

Vasopressin levels in some of the boys with autism overlap with those in the controls. So the hormone may be an indicator of social function in only some people with autism, she says.

One open question is whether low vasopressin levels are a cause or a consequence of low sociability.

"If you were to take some monkeys and separate them so that they can't have social interactions, would they then have lower vasopressin?" Young says.

## **DON'T STARE:**

In the study published today, Platt's team found evidence to suggest that boosting vasopressin levels promotes social interactions.

In this study, seven male rhesus monkeys inhaled either vasopressin,

oxytocin or placebo, and the researchers recorded how much time the animal spends gazing directly at or away from an untreated monkey seated across from it. (Direct gaze is a sign of dominance, and looking away is a sign of submission.)

In pairs of control monkeys, one monkey frequently looks at the other, and the length of its stares increases with time – a sign of dominance. The hormone-treated monkeys remain more relaxed: They do not stare for as long as controls do, the researchers found. This effect is stronger for vasopressin than for oxytocin.

The findings raise the possibility that vasopressin treatment would ease social difficulties in people with autism.

Parker and her colleagues have completed a small clinical trial of an inhaled version of vasopressin as a treatment for autism. Unpublished results of the treatment in 28 children with autism suggest it improves their social communication. The researchers are enrolling 100 children with autism in a phase II clinical trial.

But vasopressin may not always be deficient in people with autism. Paradoxically, researchers at the Swiss drug company Roche have unpublished evidence that blocking the receptor for vasopressin – which would decrease vasopressin signaling – improves social function in men with autism.

In February, the U.S. Food and Drug Administration gave the drug, called balovaptan, 'breakthrough therapy' status, meaning it can move quickly through the approval process. And at the International Society for Autism Research meeting in May, researchers from Roche presented evidence that the drug improves social interactions in mice lacking CNTNAP2, a gene linked to autism. ■

14 DECEMBER 2018

# Analysis spotlights mutations in 'dark' regions of the genome

**BY JESSICA WRIGHT**

Spontaneous mutations in stretches of DNA between genes contribute to autism, a robust new analysis of nearly 8,000 whole genomes suggests. These mutations are present in promoters, the segments that abut genes and control their expression.

The work stops short of identifying individual mutations, but it provides a starting point for further analysis. Researchers published the findings today in *Science*.

Scientists have typically hunted for autism mutations within genes, but the vast majority of human DNA lies between genes. This DNA was once dismissed as unimportant, but over the past five years, researchers have begun to search through it for mutations linked to various conditions, including autism.

Figuring out which mutations in these regions are harmful and why is a big challenge, says lead researcher Stephan Sanders, assistant professor of psychiatry at the University of California, San Francisco. This is because it is difficult to find a relevant variant among the hordes present across the whole genome.

Sanders' team devised a multistep computational approach to clear this hurdle. "The big message is

that this is a tractable problem with current technology," he says.

The team hit upon a promising way to focus on a few regions of interest within the genome, says Lucia Peixoto, assistant professor of biomedical sciences at Washington State University in Spokane, who was not involved in the study.

"You have a problem if you look everywhere, because a huge proportion of the genome is not really going to have a signal," she says.

## **NEEDLES IN A HAYSTACK:**

In May, Sanders' team described a way to link noncoding variants to autism with no prior assumptions about which regions might be important. They came up with about 52,000 possible categories of noncoding variants that could be involved in autism.

They looked for links between variants in these categories and autism in 519 families but did not find a credible signal.

In the new study, they used the same technique in 1,902 families with one autistic child and one typical child. They focused on variants that arise spontaneously, or *de novo*.

Again, they did not find a statistically significant signal. The team then used a machine-learning approach to link variant types to autism.

This new analysis linked 163 types of noncoding variants from the 519 families to autism. Of the 163 categories, 45 include promoters – defined as the 2,000 base pairs closest to the beginning of a gene. Promoters appeared in the categories more than twice as often as would be expected by chance.

A noncoding variant in one of these promoters predicted autism in the remaining 1,383 families. (The team presented some of this work in May at the 2018 International Society for Autism Research annual meeting in Rotterdam, the Netherlands.)

#### **FINDINGS TO FUNCTION:**

The researchers then looked at which of these promoter regions are mutated more often in the children with autism than in their siblings. They found that promoter regions that are preserved across species – that is, conserved throughout evolution – show more mutations among the autistic children.

The genes these promoters control tend to regulate the expression

of other genes or play a role in development. The next step is to narrow these broad functional categories to specific types of genes, including those linked to autism, Sanders says.

The findings make sense because many autism genes are known to control other genes, says Jonathan Sebat, professor of psychiatry and cellular and molecular medicine at the University of California, San Diego, who was not involved in the study.

“[This study is] really drilling down more deeply into the specific interactions,” he says.

In a study published earlier this year, Sebat and his colleagues linked a different type of genetic variant in promoters to autism.

The study is large, but to link specific noncoding variants to autism, researchers will need to analyze thousands more whole genomes, says Yufeng Shen, assistant professor of systems biology and biomedical informatics at Columbia University.

“This highlights the importance of expanding sample size to improve statistical power,” Shen says. ■





# **Evolving ideas in autism research**

10 AUGUST 2016

# The controversy over autism's most common therapy

BY ELIZABETH DEVITA-RAEBURN

Applied behavioral analysis is the most widely used therapy for autism, but some people say its drills and routines are cruel, and its aims misguided.





**ILLUSTRATIONS BY  
SCOTT BAKAL**

When Lisa Quinones-Fontanez's son Norrin was diagnosed with autism at age 2, she and her husband did what most parents in their position do – they scrambled to form a plan to help their child.

Ultimately, they followed the experts' advice. They put Norrin in a school that used applied behavioral analysis, or ABA, the longest-standing and best-established form of therapy for children with autism. They also hired an ABA therapist to direct a home program.

ABA involves as much as 40 hours a week of one-on-one therapy. Certified therapists deliver or oversee the regimen, organized around the child's individual needs – developing social skills, for instance, and learning to write a name or use the bathroom. The approach breaks desirable behaviors down into steps and rewards the child for completing each step along the way.

ABA was tough on everyone at first, says Quinones-Fontanez: "He would cry sitting at the table during those sessions, hysterically cry. I would have to walk out of the room and turn on the faucet to tune it out because I couldn't hear him cry."

But once her son got settled into the routine of it, things improved, she says. Before he began therapy, Norrin did not speak. But within a few weeks, the ABA therapist had Norrin pointing his fingers at letters. Eventually, he learned to write letters, his name and other words on a dry-erase board. He could communicate.

Norrin, now 10, has been receiving 15 hours a week of ABA therapy at home ever since. He is still in an ABA-based school. His therapists help him to practice age-appropriate conversation and social skills, and to memorize his address and his parents' names and phone numbers.



"I credit ABA with helping him in a way that I could not," Quinones-Fontanez says. "Especially in those first few years, I don't even know where we would have been without ABA therapy."

But in recent years, Quinones-Fontanez and parents like her have had cause to question ABA therapy, largely because of a fiercely articulate and vocal community of adults with autism. These advocates, many of them childhood recipients of ABA, say that the therapy is harmful. They contend that ABA is based on a cruel premise – of trying to make people with autism 'normal,' a goal articulated in the 1960s by psychologist Ole Ivar Lovaas, who developed ABA for autism. What they advocate for, instead, is acceptance of neurodiversity – the idea that people with autism or, say, attention deficit hyperactivity disorder or Tourette syndrome, should be respected as naturally different rather than abnormal and needing to be fixed.

"ABA has a predatory approach to parents," says Ari Ne'eman, president of the Autistic Self Advocacy Network and a prominent leader in the neurodiversity movement. The message is that

"if you don't work with an ABA provider, your child has no hope."

What's more, the therapy has a corner on the market, says Ne'eman. Most states cover autism therapy, including, often, ABA – perhaps because of its long history. But in California, for example, parents who want to pursue something else must fund it themselves.

These criticisms haven't made Quinones-Fontanez want to ditch Norrin's ABA therapy, but they confuse her. She says she can see what the advocates are saying on some level; she does not want her son to become a 'robot,' merely repeating socially acceptable phrases on command because they make him seem like everyone else. Sometimes Norrin will approach friendly people on the street and say, "Hello, what's your name?" as he's been taught, but not wait around for the answer, because he really doesn't understand why he's saying it. "He just knows to do his part," she says.

The message that ABA might be damaging distresses her. "I'm trying to do the best I can. I would never do anything to hurt my child," she says. "This is what works for him; I've seen it work."

Whether ABA is helpful or harmful has become a highly contentious topic – such a flashpoint that few people who aren't already advocates are willing to speak about it publicly. Many who were asked to be interviewed for this article declined, saying they anticipate negative feedback no matter which side they are on. One woman who blogs with her daughter who has autism says she had to shut down comments on a post that was critical of their experience with an intensive ABA program because the volume of comments – many from ABA therapists defending the therapy – was so high. Shannon Des Roches Rosa, co-founder of the influential advocacy group Thinking Person's Guide to Autism, says that when she posts about ABA on the group's Facebook page, she must set aside days to moderate comments.

Strong opinions on both sides of the issue abound. Meanwhile, parents like Quinones-Fontanez are caught in the middle. There's no doubt that everyone wants what is right for these children. But what is that?

#### **A NEW VIEW:**

Before the 1960s, when autism was still poorly understood, some children with the condition were

treated with traditional talk therapy. Those who had severe symptoms or also had intellectual disability were mostly relegated to institutions and a grim future.

Against this backdrop, ABA at first seemed miraculous. Early on, Lovaas also relied on a psychotherapeutic approach, but quickly saw its futility and abandoned it. It wasn't until Lovaas became a student of Sidney Bijou, a behaviorist at the University of Washington in Seattle – who had himself been a student of the legendary experimental psychologist B.F. Skinner – that things began to click.

Skinner had used behavioral methodologies to, for instance, train rats to push a bar that prompted the release of food pellets. Until they mastered that goal, any step they made toward it was rewarded with a pellet. The animals repeated the exercise until they got it right.

Bijou contemplated using similar strategies in people, judging that verbal rewards – saying “good job,” for instance – would serve as adequate motivation. But it was Lovaas who would put this idea into practice.

In 1970, Lovaas launched the Young Autism Project at the University of

California, Los Angeles, with the aim of applying behaviorist methods to children with autism. The project established the methods and goals that grew into ABA. Part of the agenda was to make the child as ‘normal’ as possible, by teaching behaviors such as hugging and looking someone in the eye for a sustained period of time – both of which children with autism tend to avoid, making them visibly different.

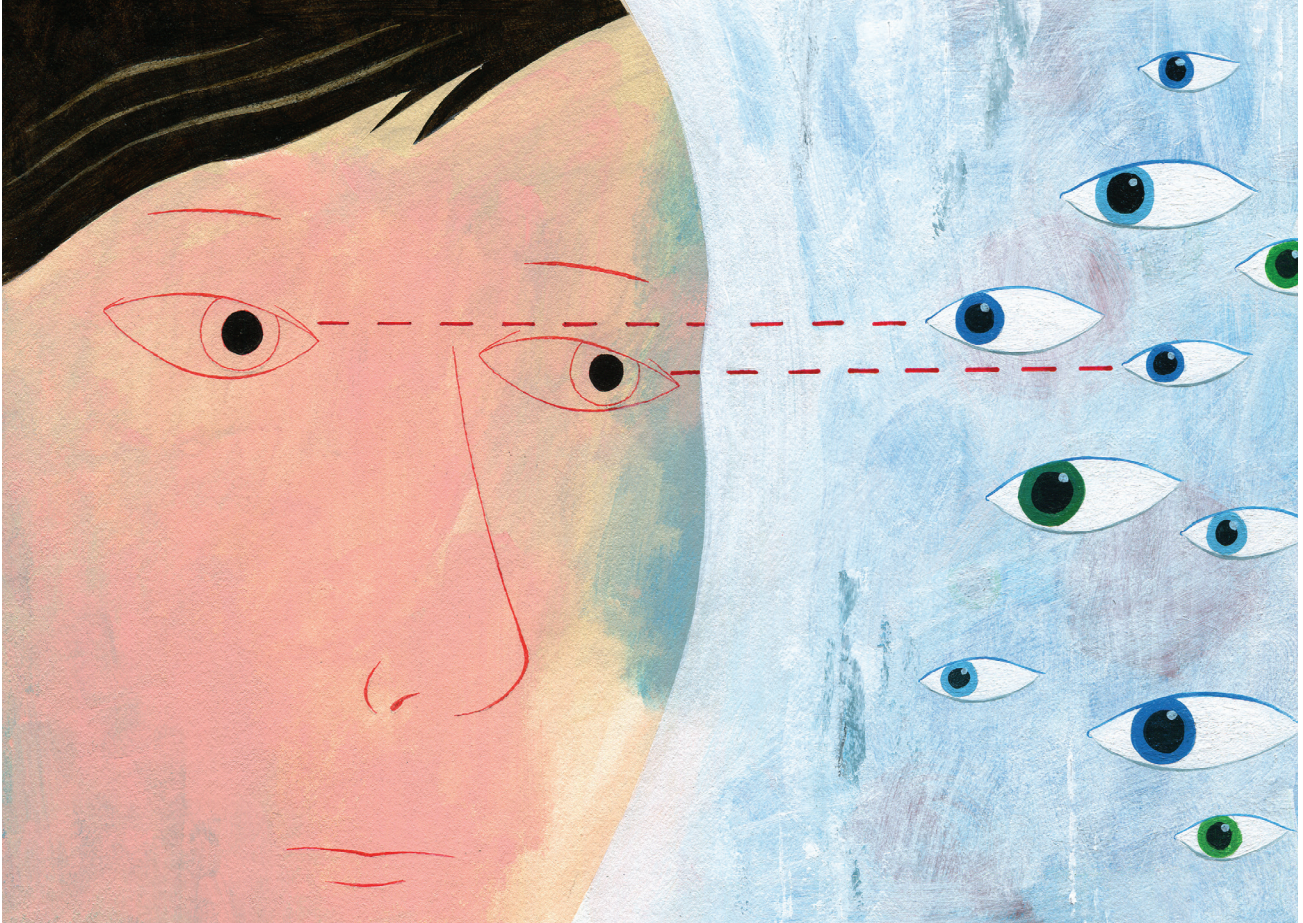
Lovaas’ other focus was on behaviors that are overtly autism-like. His approach discouraged – often harshly – stimming, a set of repetitive behaviors such as hand-flapping that children with autism use to dispel energy and anxiety. The therapists following Lovaas’ program slapped, shouted at or even gave an electrical shock to a child to dissuade one of these behaviors. The children had to repeat the drills day after day, hour after hour. Videos of these early exercises show therapists holding pieces of food to prompt children to look at them, and then rewarding the children with the morsels of food.

Despite its regimented nature, the therapy looked like a better alternative for parents than the institutionalization their children faced. In Lovaas’ first study on

his patients, in 1973, 20 children with severe autism received 14 months of therapy at his institution. During the therapy, the children’s inappropriate behaviors decreased, and appropriate behaviors, such as speech, play and social nonverbal behavior, improved, according to Lovaas’ report. Some children began to spontaneously socialize and use language. Their intelligence quotients (IQs) also improved during treatment.

When he followed up with the children one to four years later, Lovaas found that the children who went home, where their parents could apply the therapy to some degree, did better than those who went to another institution. Although the children who went through ABA didn’t become indistinguishable from their peers as Lovaas had intended, they did appear to benefit.

In 1987, Lovaas reported surprisingly successful results from his treatments. His study included 19 children with autism treated with ABA for more than 40 hours per week – “during most of their waking hours for many years,” he wrote – and a control group of 19 children with autism who received 10 hours or less of ABA.



Nine of the children in the treatment group achieved typical intellectual and educational milestones, such as successful first-grade performance in a public school. Eight passed first grade in classes for those who are language or learning disabled and obtained an average IQ of 70. Two children with IQ scores in the profoundly impaired range moved to a more advanced classroom setting, but remained severely impaired. In comparison, only one child in a control group achieved typical educational and intellectual functioning. A follow-up study six

years later found little difference in these outcomes.

The methods promised parents something that no one else had: hope of a 'normal' life for their children. Parents began to demand the therapy, and soon it became the default option for families with newly diagnosed autism.

#### **A TOUCHSTONE:**

Lovaas' ABA was formulaic, a one-size-fits-all therapy in which all children for the most part started

on the same lesson, no matter what their developmental age.

Michael Powers, director of the Center for Children With Special Needs in Glastonbury, Connecticut, started his career working at a school for children with autism in New Jersey in the 1970s. The therapist would sit on one side of a table, the child on the other. Together, they went through a scripted process to teach a given skill – over and over until the child had mastered it.

“We were doing that because it was the only thing that worked at the time,” Powers says. “The techniques of teaching autistic kids hadn’t evolved enough to branch out yet.” Looking back, he sees flaws, such as requiring children to maintain eye contact for an uncomfortably long period of time. “Five seconds. That was one skill we were trying to establish, as if that was the pivotal skill,” he says. But it was artificial: “The last time I looked someone in the eye for five consecutive seconds, I proposed.”

Doubts grew about how useful these skills were in the real world – whether children could transfer what they’d learned with a therapist to a natural environment. A child might know when to look a therapist in the eye at the table, especially with prompts and a reward, but still not know what to do in a social situation.

The aversive training components of the therapy also drew criticism. Many found the idea of punishing children for ‘bad’ behavior such as hand-flapping and vocal outbursts hard to stomach.

Over the years, ABA has become more of a touchstone – an approach based on breaking down

a skill and reinforcing through reward, that is applied more flexibly. It’s a broad umbrella that covers many different styles of therapy.

Among the many variations now in practice include pivotal response training, a play-based interactive model that sidesteps the one-behavior-at-a-time practice of traditional ABA to target what research shows to be ‘pivotal’ areas of a child’s development, such as motivation, self-management and social initiations. Another is the Early Start Denver Model (ESDM), a play-based therapy focused on children between the ages 1 and 4 that takes place in a more natural environment – a play mat, for example, rather than the standard therapist-across-from-child setup. These innovations have in part stemmed from the trend toward earlier diagnosis and the need for a therapy that could be applied to young children.

Each type of ABA is often packaged with other treatments, such as speech or occupational therapy, so that no two children’s programs may look alike. “It’s like a Chinese buffet,” says Fred Volkmar, Irving B. Harris Professor of Child Psychiatry, Pediatrics and Psychology at the Yale University Child Study Center and lead author of “Evidence-Based Practices and Treatments for Children with Autism,” a book many consider the go-to reference for ABA.

As a result, when asked whether ABA works, many experts respond: “It depends on the individual child.”

Today, Lovaas is viewed with the same kind of respectful ambivalence afforded Sigmund Freud. He’s credited with shifting

**“ABA has a predatory approach to parents.”**

– ARI NE’EMAN



the paradigm from hopeless to treatable. "Lovaas, may he rest in peace, was really on the forefront; 30 years ago, he said we can treat kids with autism and make a difference," says Susan Levy, a member of the Center for Autism Research at the Children's Hospital of Philadelphia. Without his passion, says Levy, many generations of children with autism might have been institutionalized. "He has to get credit for going out on a limb and saying we can make a difference."

### **TESTING ABA:**

Given the diversity of treatments, it's hard to get a handle on the evidence base of ABA. There is no one study that proves it works. It's difficult to enroll children with autism in a study to test a new therapy, and especially to enroll them in control groups. Most parents are eager to begin treating their children with the therapy that is the standard of care.

There is a large body of research on ABA, but few studies meet the gold standard of the randomized trial. In fact, the first randomized trial of any version of ABA after Lovaas' 1987 paper wasn't published until 2010. It found that toddlers who received ESDM therapy for 20 hours a week over a two-year period made significant gains over those who got the usual care available in the community.

That year, a report from the U.S. Department of Education's What Works Clearinghouse, a source of scientific evidence for education practices, found that of 58 studies on Lovaas' ABA model, only 1 met its standards, and another met them only with reservations.

Those two studies found that Lovaas-style ABA leads to small improvements in cognitive development, communication and language competencies, social-emotional development, behavior and functional abilities. Neither of the high-standard studies evaluated children in literacy, math competency or physical well-being.

The following year, the U.S. Agency for Healthcare Research and Quality commissioned a stringent review of studies on therapies for children with autism spectrum disorders, with similar results. Of 159 studies, it deemed only 13 to be of good quality; for ABA-style therapies, the review focused on two-year, 20-hour-a-week interventions.

The review concluded that early intensive behavioral and developmental therapies, including the Lovaas model and ESDM, are effective for improving cognitive performance, language skills and adaptive behavior in some children. The results for intensive intervention with ESDM in children under the age of 2 were "preliminary but promising." There was little evidence to assess other behavioral therapies, the review's authors wrote, and information was lacking on what factors might influence effectiveness and whether improvements could carry over outside of the treatment setting.

Levy, who served on the review's expert panel, says although the evidence in favor of ABA is not all of the highest quality, the consensus in the field is that ABA-based therapy works.

"There is a lot of good clinical evidence that it is effective in helping little kids learn new skills and can appropriately intervene

with behaviors or characteristics that may interfere with progress," says Levy. There are also other types of ABA that might be more appropriate for older children who need less support, she says.

Broadly speaking, the body of research over the past 30 years supports the use of ABA, agrees Volkmar. "It works especially well with more classically challenged kids," Volkmar says — those who may not be able to speak or function on their own. These are, however, exactly the people that anti-ABA activists say need protection from the therapy.

Most experts acknowledge that there is a segment of children for whom ABA might be less appropriate — say, those who don't need much support. One active area of research is scanning the brains of children to try to understand who responds and why. "Probably, as we go further down this path, we'll see kids whose brains don't change in response to treatment. They're going to emerge as an important group," says Volkmar. "We don't know enough about them."

Being able to identify those children who don't have the expected neurological response — or being able to classify those who do into meaningful groups — might make it possible to fine-tune therapy.

"One day, it would be nice to match the treatment approach based on more information from these profiles rather than one-model-fits-all treatment," says Karen Pierce, co-director of the Autism Center of Excellence at the University of California, San Diego, who uses imaging to study people with autism. "If we're more informed, the treatment will be more successful."

### THE PUSHBACK:

In December 2007, a series of signs in the style of ransom notes started appearing around New York City. One read, in part, "We have your son. We will make sure he will not be able to care for himself or interact socially as long as he lives." It was signed "Autism." The sign and others were part of a provocative ad campaign by New York University's Child Study Center.

The campaign unintentionally provoked an onslaught of criticism and rage from some advocacy groups against the center, which offers ABA. Many of the vocal activists once received ABA, and they reject both the therapy's methods and its goals.

Ne'eman, then a college student, was at the forefront of the pushback. One major criticism of ABA: the continued use of aversive therapy including pain, such as electric shock, to deter behaviors such as self-injury. Ne'eman cites a 2008 survey of leaders and scholars in the field of 'positive behavior interventions' — ABA techniques that emphasize desirable behaviors instead of punishing disruptive ones. Even among these experts, more than one-quarter regarded electric shock as sometimes acceptable, and more than one-third said they would consider using sensory punishment — bad smells, foul-tasting substances or loud or harsh sounds, for example. Ne'eman calls these numbers "disturbing."

He and others also reject what they say was Lovaas' underlying goal: to make children with autism 'normal.' Ne'eman says that agenda is still alive and well among ABA therapists, often encouraged by parents who want their children to fit into society. But, "those aren't

**“There is a lot of good clinical evidence that it is effective in helping little kids learn new skills.”**

– SUSAN LEVY

necessarily consistent with the goals people have for themselves," he says.

The core problem with ABA is that "the focus is placed on changing behaviors to make an autistic child appear non-autistic, instead of trying to figure out why an individual is exhibiting a certain behavior," says Reid, a young man with autism who had the therapy between ages 2 and age 5. (Because of the controversial nature of ABA and to protect his privacy, he asked that his full name not be used.) The therapy was effective for Reid. In fact, it worked so well that he was mainstreamed into kindergarten without being told he had once had the diagnosis. But he was bullied and picked on in school, and always felt different from the other children for reasons he didn't understand, until he learned in his early teens about his diagnosis. He had been taught to be ashamed of his repetitive behaviors by his therapists, and later by his parents, who he assumes just followed the experts' advice. He never realized these were signs of his autism.

Reid says he worries ABA forces children with autism to hide their true nature in order to fit in. "It's taken me a long time to not be ashamed of being autistic, and that only came because I got the chance to learn from other autistic people to be proud of who I am," he says.

### **THE MIDDLE GROUND:**

There might be middle ground between critics and supporters of ABA, says John Elder Robison, bestselling author of "Look Me In The Eye," who was diagnosed with Asperger syndrome at age 40.

Because of his late diagnosis, Robison did not receive ABA himself, but he has become involved in the issue on behalf of those who did. He envisions a place for ABA for people with autism – as long as it's done well. That means a focus on teaching skills, rather than efforts toward normalization or suppressing autism-related behaviors: helping a child who could not communicate begin to talk and engage with other kids at school, for instance. "That is life-changing in a good way," he says. Ditto an ABA therapist who helps a high school or college student become more organized. The emphasis should be on learning to function in areas the individual chooses, not on changing who she is, Robison says.

This approach will require oversight from people with autism, says Robison. "ABA programs and practitioners are going to need to accept guidance from adult versions of people they propose to treat," he says. "What was not clear in the past is that we are the clients; we [should] have a say in what happens."

Advocates say scientists also need to be open to the fact that ABA might not work for all. There is increasing evidence, for example, that children with apraxia, or motor planning difficulties, can sometimes understand instructions or a request, but may not be able to mentally plan a physical response to a verbal request.

Ido Kedar, who at 16 published his own memoir, "Ido in Autismland: Climbing out of Autism's Silent Prison" writes on his blog that he spent the first half of his life "completely trapped in silence."



Kedar received 40 hours a week of traditional ABA therapy, in addition to speech therapy, occupational therapy and music therapy. But he still could not speak, communicate nonverbally, follow instructions or control his behavior when asked, for instance, to pick up the correct number of sticks. Kedar understood the request, but was unable to coordinate his knowledge with his physical movement. He was humiliated when the ABA therapist reported that he had “no number sense.”

Many researchers who study ABA welcome input of voices like Kedar’s. “I feel like it is the most wonderful, amazing thing to

be able to talk with adults with autism about their experiences,” says Annette Estes, professor of speech and hearing sciences at the University of Washington in Seattle. “We all have a lot to learn from each other.” Estes led two studies of ESDM for children with early signs of autism. She says the worst stories she has heard are not from people who had traumatizing therapy, but from those who got no therapy at all.

“They have horrible memories of being bullied at school and [having] no one to help them or include them or help them make friends or handle tricky social situations,” she says. “I get letters from people begging us to expand services

to adults to help them learn how to date and be less lonely and isolated.”

There is not likely to be an easy end to this discussion, and in the meantime, parents must do the best they can. Quinones-Fontanez says she understands the anti-ABA argument, but she wonders how much the perspective of those who don’t need a lot of support applies to her son. ABA, she says, works for him: “I don’t find it to be abusive.”

“I am his advocate, and I will advocate for him because he’s not able to do that for himself,” she says. “I try to understand him as best I can.” ■



27 JUNE 2017

# From 0 to 60 in 10 years

BY SIMON MAKIN

After a decade of fast-paced discovery, researchers are racing toward bigger datasets, more genes and a deeper understanding of the biology of autism.



**ILLUSTRATIONS BY**  
**JOHN HERSEY**

It's been 10 years since Michael Wigler had a breakthrough revelation in autism genetics – one that arguably launched the field as we know it.

In April 2007, Wigler and his then colleague, Jonathan Sebat, reported that 'de novo' mutations – those that arise spontaneously instead of being inherited – occur more often in people with autism than in typical people. The mutations they noted were in the form of 'copy number variants' (CNVs), deletions or duplications of long stretches of DNA. CNVs crop up frequently in cancer, an earlier focus of Wigler's work. But his find that they are also involved in autism came as a surprise to those in the field. "Genetics was striking out with other efforts based on transmission and inheritance," Wigler says. "In that vacuum, the new idea was quickly embraced."

The discovery fast led to further advances. Focusing primarily on

de novo mutations, three teams of scientists, including one led by Wigler, began hunting for genes that contribute to autism. Their approach was efficient: Rather than looking at the entire genome, they scoured the 2 percent that encodes proteins, called the exome. And they looked specifically at simplex families, which have a single child with autism and unaffected parents and siblings. The premise was that comparing the exomes of the family members might expose de novomutations in the child with autism. The approach yielded a bumper crop: Based on data from more than 600 families, the teams together predicted that there are hundreds of autism genes. They identified six as leading candidates. Some of the genes identified at the time – CHD8, DYRK1A, SCN2A – quickly became hot areas of research.

In 2014, the number of strong candidates jumped higher. In two

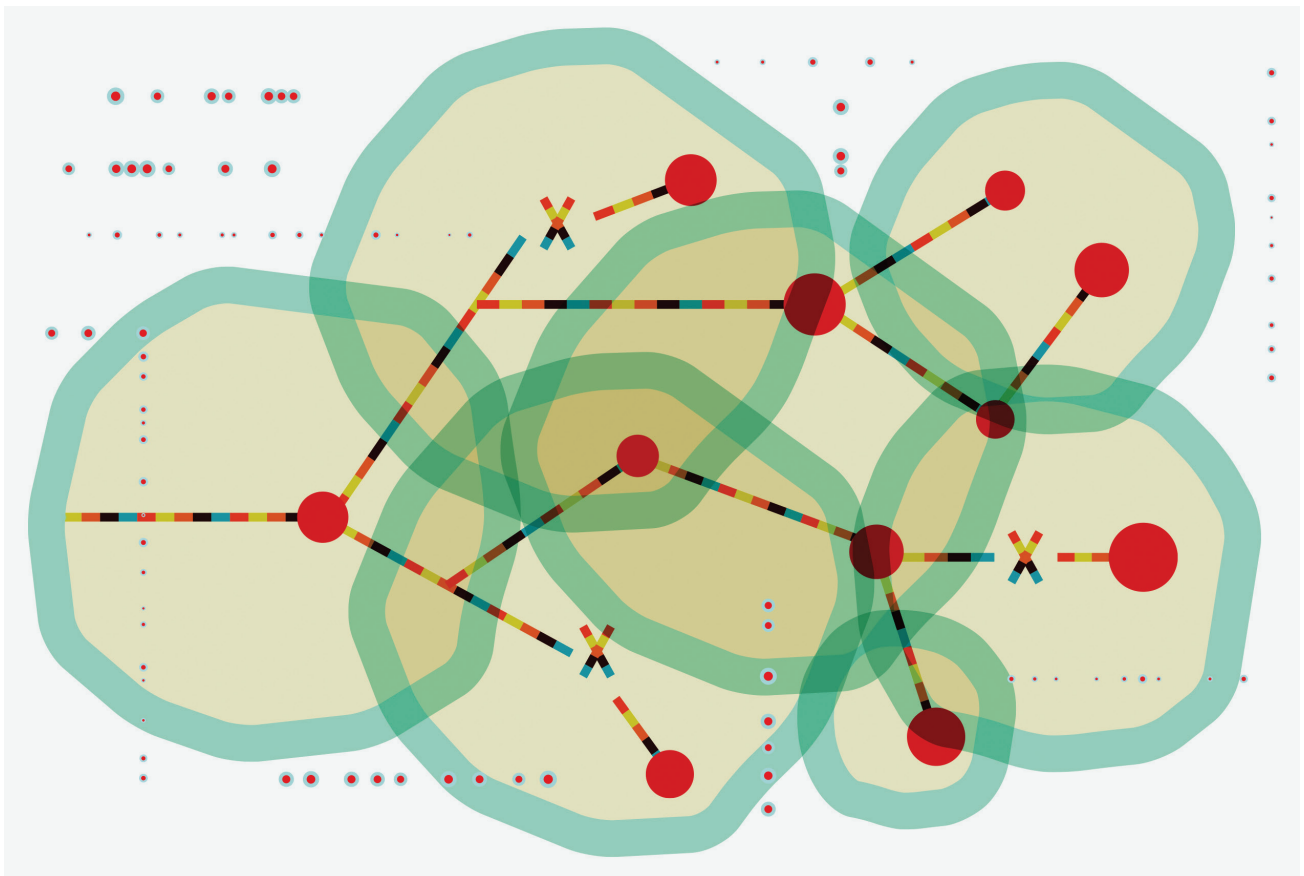
massive studies analyzing the sequences of more than 20,000 people, researchers linked 50 genes to autism with high confidence. Wigler's team looked at simplex families and found rare de novo mutations in 27 genes. In the second study, researchers screened for both inherited and de novo mutations and implicated 33 genes. The two studies identified 10 genes in common.

Two years ago, the tally of autism gene candidates shot up again. Deploying statistical wizardry to combine the data on de novo and inherited mutations, along with CNV data from the Autism Genome Project, researchers pinpointed 65 genes and six CNVs as being key

to autism. They also identified 28 genes that they could say with near certainty are 'autism genes.'

"For so long, we've been saying if we could just find these genes, we'd be able to really make some headway," says Stephan Sanders, assistant professor of psychiatry at the University of California, San Francisco, who co-led the study. "Suddenly, you've got this list of 65-plus genes, which we know have a causative role in autism, and as a foundation for going forward, it's amazing."

These advances establish beyond doubt that autism is firmly rooted in biology. "More and more, we are erasing this idea of autism being a



stigmatizing psychiatric disorder, and I think this is true for the whole of psychiatry," Sanders says. "These are genetic disorders; this is a consequence of biology, which can be understood, and where traction can be made."

This is just the start, however. As scientists enter the next chapter of autism genetics, they are figuring out how to build on what they have learned, using better sequencing tools and statistics, bigger datasets and more robust models. For example, they are looking for common variants – which are found in more than 1 percent of the population but may contribute to autism when inherited en masse. And they are also starting to look beyond the exome to the remaining 98 percent of the genome they have largely neglected thus far.

"Most of the genetic advances fall into a category of large-effect-size de novo variants, which is only one piece of the puzzle," says Daniel Geschwind, professor of human genetics at the University of California, Los Angeles. It's an important piece, but one that still cannot explain why autism clusters in families, for instance, or why close relatives of people with autism often share some of the condition's traits.

### COMMON CORE:

So how much of autism's genetic architecture have scientists uncovered? Current estimates suggest that rare mutations, whether de novo or inherited, contribute to the condition somewhere between 10 and 30 percent of the time. Before the recent spate of discoveries, the proportion of individuals whose autism had a known genetic cause was only 2 to 3 percent –

much of that from rare related genetic syndromes, such as fragile X syndrome and tuberous sclerosis complex, which stem from mutations in a single known gene. These syndromes often involve some core features of autism, along with their own set of characteristic traits, and intellectual disability.

"Two generations ago, at least 75 percent of the time autism was comorbid with severe intellectual disability and other neurodevelopmental abnormalities," says Mark Daly, associate professor of medicine at Harvard University. "It was also a much rarer diagnosis."

The large increase in diagnoses in recent decades "overwhelmingly" reflects cases at the mild end of the spectrum, Daly says, creating a new challenge. "The genetics of autism has us wrestling with the fact that rare mutations, and especially these spontaneously arising ones, are the strongest risk factors," he says. "But at the same time, there's a majority of cases now that don't have any of those high-impact risk factors."

Instead, much of the risk in these instances likely comes from common variants, which have small effects on their own, but can add up to increase overall risk. Researchers have tried to identify those relevant to autism using genome-wide association studies (GWAS), which compare the genomes of people with and without a condition to find differences in single-letter swaps of DNA called single nucleotide polymorphisms.

Because common variants have small effects individually, they are difficult to find, but multiple studies suggest that they play a

**"If you go into a clinic today, there's about a 10 percent chance of you getting a genetic diagnosis."**

– STEPHAN SANDERS

major role in autism risk. In a 2014 study, for instance, researchers used statistical tools to estimate the heritability of autism from the amount of common variation shared by unrelated people with autism. They applied the method to data from more than 3,000 people in Sweden's national health registry. Their calculations indicated that common variants account for 49 percent of the risk for autism in the general population; rare variants, equal parts de novo and inherited, explain 6 percent. Some scientists dispute these figures, but it's clear that common variants, rare inherited variants and spontaneous mutations all play a part in autism.

Wigler says he is skeptical of using GWAS studies for autism precisely because they focus on common variants. "Most of the disorders that will cause pain and suffering and require expensive treatments, if they're genetic, are caused by rare variants that are not going to stay around in the population," he says.

Common variants may turn out to be more relevant at the milder end of the spectrum than in those who are severely affected. "The people who have de novo mutations, en masse, tend to have lower intelligence quotients and more cognitive problems," Sanders says.

Researchers are grappling with how to fit these pieces

together: Finding and diagnosing rare variants linked to severe outcomes is important, but so is unraveling how the core traits of autism relate to other psychiatric conditions and manifest in the general population. "Both goals are important, and they shouldn't be seen as at odds with each other," Daly says. In fact, a study published in May reported that rare and common variants can combine to increase an individual's risk.

The landscape of autism genetics becomes even more complex when considering the sheer number of genes that could be involved – some researchers estimate up to a thousand – and the fact that many high-confidence autism genes are also associated with other conditions, ranging from intellectual disability and epilepsy to schizophrenia and congenital heart disease.


This 'many-to-one' and 'one-to-many' relationship is not surprising, Sanders says. But it does mean there are probably no unique 'autism genes' per se. "But I could flip that round and say we've not found anything which is a pure intellectual disability or schizophrenia gene [either]; on a fundamental level, these disorders seem to be related," he says. "If I was to say, 'Can we find something which contributes more to autism than other disorders?' then I think

the answer's yes." The genes that seem particularly tied to autism could offer important clues about the condition's biology.

#### EXPECT THE UNEXPECTED:


The genes identified so far have hinted at a handful of underlying mechanisms that contribute to autism. Most of them seem to be involved in three broad categories of tasks: maintaining the function of synapses, or the connections between neurons; controlling the expression of genes; and modifying chromatin, structures of DNA wound around protein 'spools' called histones. Chromatin determines which stretches of DNA can be read and so influences gene expression.

The idea of a brain condition originating with atypical neuronal connections made logical sense from the start. "There had been a lot of interest in the synapse," Sanders says. But the candidates that control gene expression only emerged in the genetic studies. Two genes that consistently top the 'high-confidence' lists – CHD8 and SCN2A – were both somewhat of a surprise. CHD8 encodes a chromatin regulator that controls the expression of thousands of other genes. SCN2A codes for a sodium channel and had primarily been associated with infantile seizures.



Using gene expression maps, such as the BrainSpan Atlas, researchers have traced when and where autism genes are active in the brain. They have found that many of the genes, CHD8 and SCN2A included, are expressed in parts of the cortex during mid- to late fetal development – which happens to be the peak period when neurons are forming. “We don’t really understand it yet, but they’re more likely than not to disrupt fetal brain development in mid-gestation,” Geschwind says. That timing suggests they interfere with processes that are critical to setting up the cortex, including which types of cells form and where in the brain they migrate. If the cortex isn’t set up right, he says, you create ongoing problems with how neurons communicate, among other important functions. Within the next few years, he says, researchers will have a refined understanding of the neurons and circuits affected.


Work in animal and cell models reveals similar problems with the genesis, structure and fate of new neurons and the connections between them. In some cell and animal models of syndromic forms of autism, scientists have managed to at least partially correct some of these problems with drugs. The unrealized promise of these findings is that some traits of autism may ultimately prove reversible, even in adults.



“The idea that there’s something plastic here, not set in stone at birth, is very important,” says Matthew State, chair of psychiatry at the University of California, San Francisco, and lead investigator on many of the big autism genetics studies.

In the meantime, genetic discoveries have delivered some immediate benefits for people with the condition. “If you go into a clinic today, there’s about a 10 percent chance of you getting a genetic diagnosis, and I would expect to find evidence which was suggestive in about another 5 to 10 percent,” Sanders says. “We can’t then turn round and say, ‘Here’s your cure,’ but what we can do, at least, is put people in touch with other people with that same mutation.” Becoming part of such a group gives people a better idea about what the future holds for them and provides them with support and understanding.

Advocacy groups can lobby researchers and funding bodies, contribute to research on their condition and help find participants for clinical trials – which, by grouping people according to their underlying genetics, would then have a greater chance of success. “It becomes very empowering,” says Joseph Buxbaum, director of the Seaver Autism Center for Research and Treatment in New York.



**“The idea that there’s something plastic here, not set in stone at birth, is very important.”**

– MATTHEW STATE



Genetic diagnoses can also help families make decisions about family planning and treatment options. For example, deletion of a region on chromosome 17, called 17q12, is associated with autism and schizophrenia, but treating someone who has this CNV with certain mood stabilizers or antipsychotics could be dangerous: It is also associated with renal failure and adult-onset diabetes, which the drugs would exacerbate. What's more, certain mutations increase the risk for some types of cancer. "Knowing those mutations can be very helpful in those cases, not just in treating autism, but in treating the patient more broadly," Geschwind says.

#### THE HUNT FOR MORE GENES:

Debates abound on how best to move the field forward, but one thing most researchers agree on is the need to identify more mutations linked to autism. "There's great benefit now in just doing more exome sequencing," Sanders says. "There's more genes to be found: Those will hopefully help patients; they'll also give us more of an understanding of what autism is."

Much of the variation that predisposes someone to autism, however, may lie in noncoding regions. "If half of the variants are outside of the coding region, we need to know how to interpret them," Wigler says. "For that reason alone, we have to study that region. Plus, we're going to learn an enormous amount of biology in the process."

Noncoding regions make up the 'dark genome,' which is about 98 percent of the whole. Because of the cost and effort involved in sequencing the whole genome, most autism researchers have stayed focused on exomes, until recently. Several teams are now sequencing whole genomes of people with autism, with the aim of identifying risk variants in these noncoding regions. "Whole-genome sequencing inevitably will overtake exome sequencing," Sanders says. "It's just a question economically of whether its moment is now, or in two years, or five years. Right now, that's a hard question to answer."

In March, researchers in Canada reported results from the largest set of whole genomes of people with autism to date. They sequenced the whole genomes of more than 5,000 individuals, about half of whom have autism. Among the 61 variants the researchers identified, 18 had not been firmly linked to autism before. The team found that many of the CNVs in people with autism rest in noncoding regions.

Some teams are applying other resources, such as gene co-expression maps and protein-protein interaction networks, to understanding the underlying biology of the condition. These networks are only likely to become more powerful as researchers uncover more risk genes for autism. "The question is how to integrate all that genetic data with other '-omics' data, and network-type approaches are probably going to be critical there," Geschwind says.



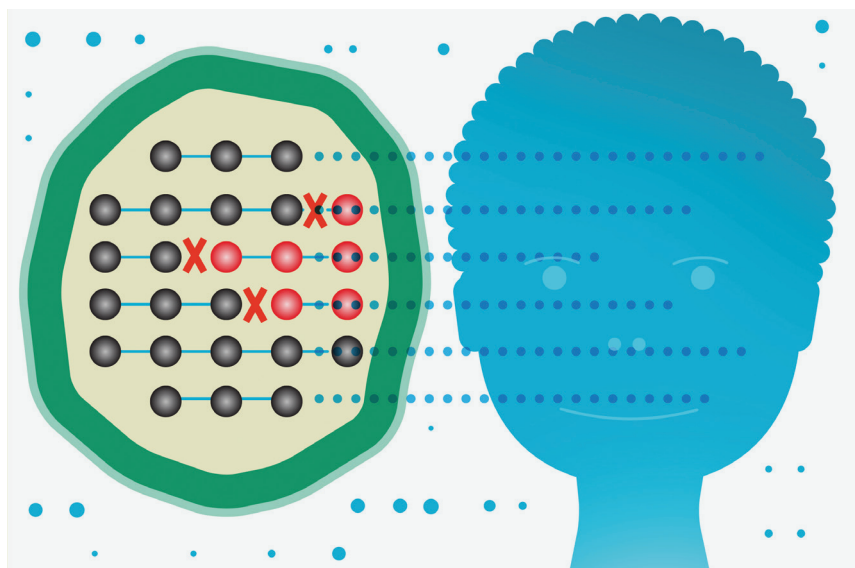
Most autism research arising from gene discovery is focused on repercussions at the molecular and cellular levels, but there's an important gap from there to whole circuits and behavior. "Ultimately, the value of genetics is very likely to play out through an improved understanding of circuit-level function and anatomy," State says.

Stem cells and emerging technologies such as brain organoids – so called 'mini-brains' in a dish – could afford researchers a prime opportunity to study the effects of genetic variation in human neurons. Faced with the limitations of mouse models in studying a condition characterized by behavioral problems, some teams are also turning to monkeys, which enable them to study more complex social interactions. "Something we should be doing for the future is taking the precise mutations we find in humans and making those in primates," Wigler says.

These days, Wigler is on to another big idea: risk modifiers. Rare variants strongly associated with autism also occur in people without autism – especially women. Researchers know that mutations can contribute to autism by amplifying or attenuating the effects of other genes, so it's feasible that two mutations could cancel each other out. But few teams have looked into these combinations as yet. "People talk about autism as being an additive disorder," Wigler says, "but nobody's really looking at additivity."

This idea brings him to a possible experiment: Take two mutations that individually have damaging effects, and introduce them both into mouse or monkey. Having the combination would be predicted to be worse than having either mutation alone. "But what if the net result is correction?" Wigler asks. "Then we know modifiers exist. There's not much of that kind of scientific exploration happening now."

A finding of that nature would herald a whole new wave of advances. It might also help to explain why the mutations identified so far vary in their effect – or what geneticists call 'penetrance' – only sometimes resulting in autism. And it might help researchers develop therapies. "If we ever saw a self-correcting defect in two mutations in autism," Wigler says, "I would stand up and cheer." ■





2 AUGUST 2017

# Rethinking regression in autism

BY DAVID DOBBS

The loss of abilities that besets some toddlers with autism is probably less sudden and more common than anyone thought.



**ILLUSTRATIONS BY**  
**KOUZOU SAKAI**

One of the oldest ideas in autism – as old as the naming of the condition itself – is that it comes in two forms: one present from birth, and one that abruptly emerges in toddlerhood. The latter type, or so the idea goes, announces itself through a rapid loss of skills.

In this classic picture of ‘regression,’ a talkative, curious 2-year-old suddenly withdraws. He grows indifferent to the sound of his name. He begins to speak less than before or stops entirely. He turns from playing with people to playing with things, from exploring many objects and activities to obsessing over a few. He loses many of the skills he had mastered and starts to rock, spin, walk on his toes or flap his hands. It’s often at this point that his terrified parents seek answers from experts.

This dichotomous view of the onset of autism is what Sally Ozonoff long held to be true. The textbooks and papers she read as a student in

the 1980s described regression as a subtype of autism – an exception to the more common ‘early-onset’ version of the condition, which many considered innate. Studying autism, Ozonoff recalls, meant accepting this divide.

But in the decades since, these once-clear boundaries have started to fade. Epidemiological studies have found that anywhere from 15 to 40 percent of autism diagnoses fit the regressive type, with estimates varying wildly depending on how regression is defined. And regardless of the definition, estimates of regression’s prevalence (mainly as measured in the United States) have tended to rise as studies have become larger and more rigorous, Ozonoff says. This variability and expansion have both challenged the prevailing view of regression as an exception.

Today, Ozonoff, professor of psychiatry and behavioral sciences at the University of California, Davis

MIND Institute, is one of a growing cohort of researchers who say the simple split between regressive and non-regressive autism is almost certainly wrong. Their proposal, which has gained momentum over the past 15 years, is that researchers and clinicians should retire the division for good.

"I think most kids with autism lose some skills, but how many they lose – and when they lose and what they lose – varies across kids," says Catherine Lord, director of the Center for Autism and the Developing Brain at New York-Presbyterian Hospital in New York City. "I think classifying them as regressive or non-regressive is a waste of time and a misnomer."

This idea was a major theme – the elephant that kept walking through the room – at a conference on regression that the U.S. National Institutes of Health held last February. One researcher after another described onset patterns of autism that defied the two-category view. Several, for example, reported that the more they scrutinized home videos or other contemporaneous records, such as clinician or caretaker reports from the first year of life in children ultimately diagnosed with regressive autism, the more they saw early signs of the condition.

The strength of these early signs varies, and they're often subtle, but they show up in multiple domains, from movement and eye-gaze patterns to language responses and social interactions. Regression should be seen not as an event but as a process – occasionally sudden but usually protracted, Katarzyna Chawarska, a researcher at the Yale Child Study Center, said at the meeting. Trying to separate the

children who regress from those who don't, she said, "can be like drawing a line in the sand" – an unreliable marker in shifting terrain.

Chawarska's view echoes the findings of numerous studies that reveal a "range of onset patterns," as University of Melbourne autism researcher Amanda Brignell and her colleagues explain in a 2016 paper, from 'early onset' (early developmental delays, no loss of skills) and 'delay and regression' (some early delays, then loss) to 'plateau' (no early delays and no loss, but a failure to gain) and ordinary 'regression' (no delays before a clear loss). These trajectories differ so much in their timing, speed, depth and effects that it requires a tangle of words and parentheticals to try to squeeze them into a binary framework.

Given all this, Ozonoff argues, we should speak not of regression, but of a variety of onsets: The true clinical picture of how autism begins to present is not two-tone or even spectral, but a complex kaleidoscope of possibilities. "I don't even call it regression anymore," she says. "I just think of it as onset: how symptoms start."

### **THE GREAT DIVIDE:**

To understand this shift from the innate-versus-regressive dichotomy, it helps to understand how that split took hold to begin with. It originated, as journalist Steve Silberman's bestselling book "NeuroTribes" describes, in Leo Kanner's seminal 1943 paper describing autism. In that study of 11 children, Kanner claimed to have identified a new developmental syndrome. Although this syndrome,

overlapped heavily with a broadly defined developmental condition others were then calling 'childhood schizophrenia,' Kanner argued it was unique in that it was present "from the very beginning of life" – even if it only became apparent later. By contrast, childhood schizophrenia, he contended, usually occurred only after "at least two years of essentially average development."

Kanner's emphasis on the inborn quality of the 11 children's traits was crucial to his assertion that he had discovered a new syndrome. As Silberman says, "Kanner needed this dichotomy so he could claim his own turf."

Kanner's gambit worked. His paper quickly established autism as a new condition, as well as a new field of study. It also cemented the idea that there are two types of autism, innate and regressive, distinguished by the different onsets and, presumably, different etiologies and developmental pathways. Researchers investigating childhood schizophrenia politely objected, noting that Kanner's 11 children sounded a lot like children they had studied. Later, during the 1950s, Kanner himself noted that the line between innate and regressive autism was fuzzy. But by then, Silberman notes, Kanner could afford this retreat because his reputation had been secured – and deservedly so.

In the meantime, the dichotomy stuck, and the vast literature that rose around it consistently classified autism as either innate or regressive. Although this sharp divide inspired valuable research, it also caused problems. In Kanner's day and after, he and

other researchers, most notably Bruno Bettelheim, cited regression as evidence that unaffectionate 'refrigerator' mothers or working women could somehow warp their children's development. (Kanner eventually retracted this view.) More recently, anti-vaccine groups have pointed to regression, which frequently occurs at an age when children receive several vaccines, as proof that the shots can cause autism – a spurious argument that has contributed to outbreaks of measles (including a recent outbreak in Minnesota), whooping cough and other serious illnesses.

In fact, after 70 years of autism research, there is still no clear definition of what regression is. Psychologists Brian Barger and Jonathan Campbell have wrestled with this problem energetically over the past few years, combing through more than 100 studies. They have concluded that the literature on regression is "without a central conception" and has "no universally agreed-upon central definition."

In one meta-analysis of 85 papers, the pair uncovered a hodgepodge of definitions for virtually every type of regression commonly described in autism research – among them, language regression, social regression, motor regression, 'mixed' regression, 'regression, developmental,' just plain regression and even 'regression, unspecified.' In the case of language regression, for instance, they found no agreement on how many words a child must have had and then lost, or how long she needed to have used them, to qualify as having regressed. "You may have one paper saying it's a single word," Barger says, whereas another would require 20 words or

the use of two- and three-word phrases. One lab might say the child must possess language skills for at least three months before losing them, but another might shorten that window to only a week.

Other definitions were similarly tangled. 'Social regression' referred to the loss of a varying subset of skills from a list including, but not limited to, emotional expressiveness, joint attention, eye contact, play skills and the child's response to her own name. Definitions of 'language-social regression' also included different mixes and measures of language and social-skill loss. 'Mixed regression' definitions encompassed losses of language, social ability or other skills – sometimes specified (such as motor), sometimes unspecified and sometimes hopelessly broad (such as 'developmental'). Possibly the most consistent definition, though hardly the most helpful, was for 'regression, unspecified,' which, of course, almost always went unspecified.

This definitional disaster, Barger and Campbell wrote in a paper last year, has created a "literature marked by conflicting results." Barger says it also helps to explain the huge variations seen in estimates of regression's prevalence. "If you don't have a clear sense of what you're looking for, then you can't clearly prove that what you're looking for looks the same across independent replications." The problem, in short, isn't like comparing apples and oranges; it's more like comparing apples, oranges, pineapples, spinach and chicken salad. It's little wonder Barger





and Campbell concluded that “the research to date should be considered preliminary.”

They and many others say that these sorts of definitional and measurement problems may mask regression’s true prevalence. Regression may be the norm in children with autism, says Campbell, professor of psychology at the University of Kentucky. “I think you have operational definitional problems. You have measurement problems. And the phenomenon itself is difficult,” he says. “[Regression] might be part of a larger, normal development process. Maybe it’s not specific to autism; maybe there are more kids that go through losses and delays and spurts.”

### **STREETLIGHTS AND TINY THINGS:**

One challenge in spotting autism’s onset is what scientists call the streetlight effect: the human tendency to look for things where we can most easily see them (whatever’s visible beneath the proverbial lamppost) even though what we seek may lie elsewhere, off in the proverbial dark.

In the case of regression, researchers and parents both tend to focus on language, which usually appears (and sometimes regresses) in the second year of life. But when they focus too much on this one ability, as important as it is, they may overlook or forget gains or losses made earlier in less

noticeable areas, such as sensory and motor skills. “Most autism likely involves what we are currently calling regression,” says Joseph Piven, professor of psychiatry at the University of North Carolina at Chapel Hill. But he adds that it may occur before speech arises, and in areas other than language, where it is less likely to be spotted and “much harder to call.”

Piven and his colleagues documented this blind spot in a 2015 study. They assessed 210 infant siblings of children with autism (who are at high risk of autism themselves) and 98 babies from families with no history of autism. They took a number of developmental measures every few months, starting at age 6 months. They then used the children’s

scores on several measures at the 24-month mark to sort them into four groups: a low-risk group showing no signs of autism, a high-risk group also showing no signs of autism, and two additional high-risk groups that they further categorized as 'moderate' or 'severe' based on the number and severity of their autism traits.

The study's key finding was that at 6 months of age, the children who would later be diagnosed with autism showed subtle but distinctive sensory and motor characteristics that had gone unnoticed. These signs showed up in areas that standard autism screenings don't assess, and most parents and even professionals might miss them in the absence of other difficulties. The Autism Observation Scale for Infants (AOSI), for instance – which focuses on eye gaze, visual tracking, imitation and other early social-communicative behaviors – picked up no significant differences among the four groups at 6 months. And at 12 months, this same screen detected subtler autism traits only in the group ultimately placed in the 'severe' group at 24 months.

As the researchers say, it would be premature to consider these newly recognized signs definitive harbingers of autism, because they might occur at lower rates in typical children as well, although the researchers did not assess that. The study wasn't meant to generate diagnostic markers. But it does suggest that subtle signs of autism are there early on. "My take on this topic is that regression is a misnomer," Piven says.

Other researchers have found that early social changes are also easily overlooked. In a 2011 study, Ozonoff and her colleagues watched home videos of children with regressive autism throughout their first two years, scoring them on four budding social skills: vocalizing, gazing at faces, sharing smiles and pointing as a way to direct another person's attention. Reviewers attending to these behaviors noticed signs of social regression between 12 and 24 months of age in all of the children later diagnosed with autism, well before the children were diagnosed and before anyone noticed anything amiss. Parents and standard autism screens, such as the Autism Diagnostic Observation Schedule, missed these problems. In two-thirds of the children whose video histories showed some form of social regression, their parents had not picked up on it at the time.

**“I don't even call it regression anymore. I just think of it as onset: how symptoms start.”**

– SALLY OZONOFF

The picture of regression may be even further complicated by some evidence that it occurs in typical children as well. A team led by Brignell and her colleague Angela Morgan, for instance, found that about one in seven typically developing toddlers at some point regresses in eye gaze and in showing emotions, compared

with one in four children who have autism. A key difference, however, is that the children with autism are less likely than the typical children to make up for those losses. The researchers found that 26 percent of typically developing toddlers may also regress in other areas, such as eye gaze, social interest, or smiling or head movement in response to social stimulus, compared with 41 percent of children on the spectrum. "Loss," Brignell says, "is not unique to autism spectrum disorder."

Even with these regressive episodes, both typically developing children and those with autism usually gain skills in all these domains between their first and second years – though most toddlers with autism make their gains more slowly.

#### **IN HINDSIGHT:**

A final but central problem in the regression literature is its heavy reliance on retrospective studies – those that depend on reconstructing events, rather than observing them as they occur. In these studies, researchers ask parents of a child who's already been diagnosed or evaluated for autism to remember their child's development, highlighting any noticeable loss of skills. If the parents recall a typical course of development that suddenly hit a snag, the researchers might deem the child's autism onset regressive. It's only during the past decade or so that Ozonoff and others have used prospective studies or home videos to check

parent recall. Their work has shown that parents' memories, like most human memories, can be astoundingly unreliable.

People tend to misremember things such that they fit their current impressions or beliefs – a form of confirmation bias. As a result, they may remember a troublesome teen as a more ornery toddler than she really was, or forget that an agreeable 10-year-old was, at 2, impossibly impossible. Asking parents to remember the progress of a child showing signs of autism is especially perilous. Along with the difficulty of noticing subtle setbacks (of the sort even researchers miss), these faint cues are also more likely to be forgotten. Compounding the problem, classic recall exercises can easily steer a parent's memory toward her child's biggest, most memorable lapses, creating the illusion of a sudden regression.

This illusion may be further magnified by something called the telescoping effect: The more time that passes after a significant event occurs, the more likely a person is, in remembering that event, to move it forward in time. That is, memory draws distant events closer, like a telescope focused on a distant object.

A 2011 study by University of California, San Francisco researcher Vanessa H. Bal is one of several that show how telescoping encourages a false perception of regression. Bal found that in those instances when children had acquired and then lost skills, parents remembered both the appearance and the disappearance of those skills as happening later – and nearer to the present – than records showed.

Those errors grew in proportion to the amount of time that had passed between event and recall. The parents of an 18-month-old, for example, might accurately remember the appearance of a trait at 13 months. But three years later, they might place that milestone at 18 or 20 months. This telescope effect may have helped to set the purported average age of regression at 18 to 20 months in most studies.

Ozonoff is now working on a paper she calls, tongue half in cheek, "Everyone regresses." Her point is not to say that late regression never occurs, but that an overemphasis on the division between supposedly innate and seemingly regressive autism is a red herring and a distraction. A better approach, she says, is to think instead of multiple factors that could generate a kaleidoscopic range of onsets. "I don't think of onset as two or four categories," she says. "There's not many different things, but one thing that looks different in different cases."

Early overgrowth in the brains of children with autism could explain this diversity. A small 2001 study found that in children with autism, the brain appeared to grow abnormally fast up to 24 months. Later, the brains of these children appear to undergo synaptic pruning – a process that trims back connections among neurons – at faster rates than is seen in typical children. (Many other studies have found that children with autism have too many synapses, rather than too few.)

In 2015, the late neuroscientist Annette Karmiloff-Smith published





**“Most autism likely involves what we are currently calling regression.”**

– JOSEPH PIVEN

a paper consolidating this and other findings into an ‘over-pruning’ hypothesis of onset: Too much growth, followed by too much cutting back, leads to the appearance of autism traits.

Less than two years later, Piven reported that the timing of the overgrowth coincides with the middle of the second year, when social and language problems often appear. When Piven’s team closely examined a series of structural brain scans of 15 children diagnosed with autism, they found a pattern of overgrowth in the children’s brains between 6 and 12 months of age, even in children who did not show any autism traits until around 18 months. This finding nicely supports the idea – key to the over-pruning hypothesis – that behavioral regression appearing in the second year arises from atypical processes that start in early infancy or even before birth.

Karmiloff-Smith and others have suggested that ongoing atypical

development gradually generates enough atypical brain activity to overwhelm the processes driving typical behavior – so that eventually a typically developing circuit, having produced a behavior such as early speech, loses the ability to do so. The seemingly sudden loss is actually long in the making.

The idea “fits perfectly well” with a leading theory of dynamic brain development, says Kevin Mitchell, a neurodevelopmental geneticist at Trinity College Dublin in Ireland. According to this dynamic or ‘neuroconstructivist’ theory, articulated with particular force by Karmiloff-Smith, atypical outcomes such as autism come about not simply because of major genetic faults or distinct environmental insults, but from an aberrant unfolding of complex neurodevelopmental processes. Over time, these processes create the differences, bad and good, that distinguish all of us; in the case of autism, they may simply

create differences that are more noticeable and consequential.

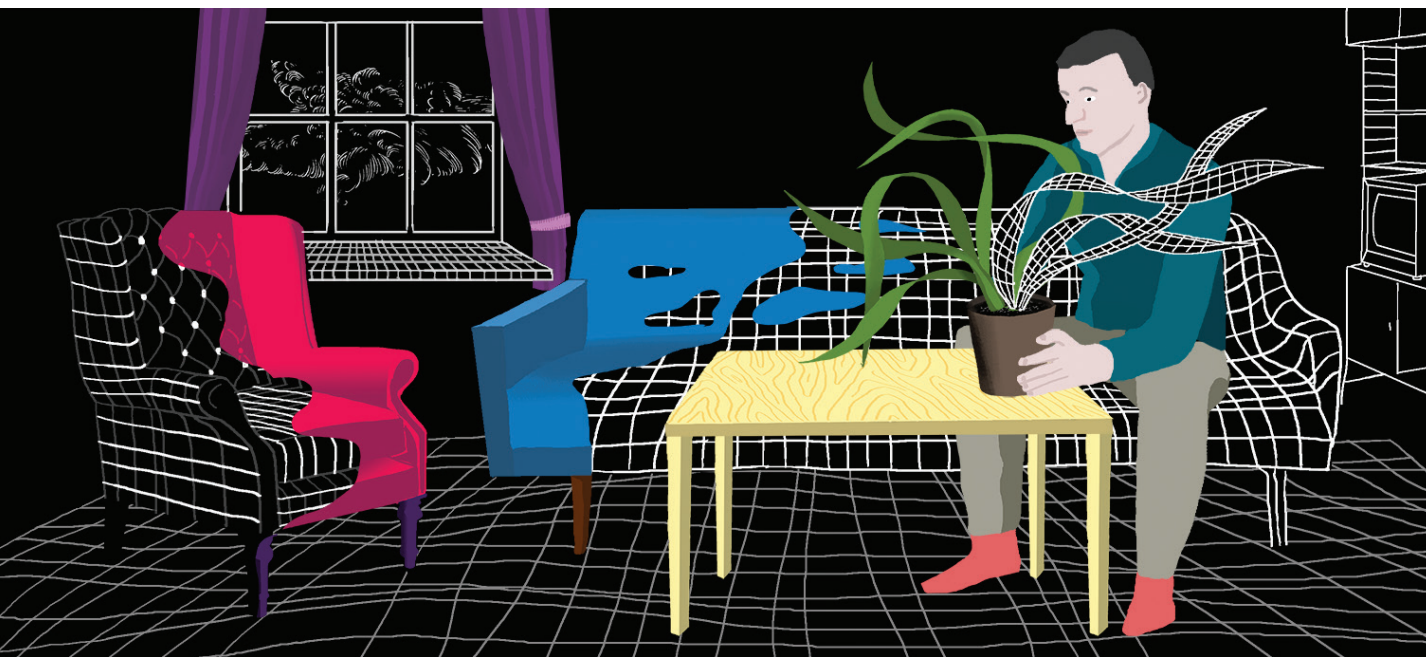
Setting aside Kanner’s innate/regressive dichotomy would open up rich theoretical and experimental terrain for exploring this theory. And it might offer more immediate returns as well. If clinicians recognize that autism typically appears gradually rather than abruptly and learn to spot the signs earlier, they will have more opportunity to help the child and to meet the challenges that atypical development can present. Pediatricians might even start measuring social and perhaps motor skills at routine well-child visits – something, Ozonoff says, that “would require all of us, parents and providers, to think of how autism emerges in a fundamentally different way.” A more dynamic, multifaceted view of brain development might not only be more useful, she notes, it’s also more likely to be true. ■

7 MARCH 2018

# How autism may stem from problems with prediction

BY GEORGE MUSSER

A 'predictive coding' theory of autism suggests that many of the condition's hallmark traits occur when sensory input overrides expectation in the brain.



**ILLUSTRATIONS BY  
ALEXANDER GLANDIEN**

Satsuki Ayaya remembers finding it hard to play with other children when she was young, as if a screen separated her from them. Sometimes she felt numb, sometimes too sensitive; sometimes sounds were muted, sometimes too sharp. As a teenager, desperate to understand herself, she began keeping a journal. "I started to write my ideas in my notebooks, like: What's happened to me? Or: What's wrong with me? Or: Who am I?" she says, "I wrote, wrote, wrote. I filled maybe 40 notebooks."

Today, at 43, Ayaya has a better sense of who she is: She was diagnosed with autism when she was in her early 30s. As a Ph.D. student in the history and philosophy of science at the University of Tokyo, she is using the narratives from her teen years and after to generate hypotheses and suggest experiments about autism – a form of self-analysis called *Tojisha-Kenkyu*, introduced nearly

20 years ago by the disability-rights movement in Japan.

In Ayaya's telling, her autism involves a host of perceptual disconnects. For example, she feels in exquisite detail all the sensations that typical people readily identify as hunger, but she can't piece them together. "It's very hard for me to conclude I'm hungry," she says. "I feel irritated, or I feel sad, or I feel something [is] wrong. This information is separated, not connected." It takes her so long to realize she is hungry that she often feels faint and gets something to eat only after someone suggests it to her.

She has also come to attribute some of her speech difficulties to a mismatch between how her voice sounds to her and how she expects it to sound. "Just after she speaks, her own voice feeds back to her ears, and she tends to notice the difference," says her collaborator Shin-ichiro Kumagaya, a pediatric

neurologist at the University of Tokyo who studies autism using *Tojisha-Kenkyu*. The effect is like the awkward echo on a phone line that makes it difficult to carry on a conversation – except that for Ayaya, it's like that almost all the time.

Ayaya's detailed accounts of her experiences have helped build the case for an emerging idea about autism that relates it to one of the deepest challenges of perception: How does the brain decide what it should pay attention to? Novelty captures attention, but to decide what is novel, the brain needs to have in place a prior expectation that is violated. It must also assign some level of confidence to that expectation, because in a noisy world, not all violations are equal: Sometimes things happen for a reason, and sometimes they just happen.

The best guess scientists have for how the brain does this is that it goes through a process of meta-learning – of figuring out what to learn and what not to. According to this theory, biases in the meta-learning process explain the core features of autism. The theory essentially reframes autism as a perceptual condition, not a primarily social one; it casts autism's hallmark traits, from social problems to a fondness for routine, as the result of differences in how the mind processes sensory input.

Consider what happens when we are new to a situation or a subject. Every detail – every bump on a graph, every change in a person's tone of voice – seems meaningful.

As we gain experience, though, we start to learn what the rule is and what the exception. The minutiae become less salient; the brain shifts its focus to the big picture. In this way, the brain masters one challenge and moves to the next, keeping itself at the cusp between boredom and frustration. Autism might represent a different learning curve – one that favors detail at the price of missing broader patterns.

Unlike other 'unified theories' of autism – those that purport to explain all aspects of the condition – this one builds on a broad account of brain function known as predictive coding. The premise is that all perception is an exercise of model-building and testing – of making predictions and seeing whether they come true. In predictive-coding terms, the brain of someone with autism puts more weight on discrepancies between expectations and sensory data. Whereas the typical brain might chalk up a stray car horn to chance variation in a city soundscape and tune it out, every beep draws conscious attention from the autism brain. "It provides a very parsimonious explanation for the cardinal features of autism," says Karl Friston, a neuroscientist at University College London who helped develop the mathematical foundations of predictive-coding theory as it applies to the brain.

For now, the model is vague on some crucial details. "There's many loose pieces," says Katarzyna Chawarska, an autism researcher at Yale University. And some question whether a single model



could ever account for a condition as heterogeneous as autism. Yet proponents say this very diversity argues for a unified theory. Understanding a fundamental cause might yield treatments that are equally broad in their reach. “If prediction truly is an underlying core impairment [in autism], then an intervention that targets that skill is likely to have beneficial impacts on many different other skills,” says computational neuroscientist Pawan Sinha of the Massachusetts Institute of Technology.

### **PREDICTIVE CODING 101:**

The basic premise of predictive coding goes back to the mid-19th century German physicist and psychologist Hermann von Helmholtz, and arguably to the philosopher Immanuel Kant, both of whom maintained that our subjective experience is not a direct reflection of external reality, but rather a construct. “All experience is controlled hallucination,” says Andy Clark, a cognitive scientist at the University of Edinburgh in Scotland. “You experience, in some sense, the world that you expect to experience.”

One reason we rely so much on expectation is that our perceptions lag behind reality. Much of what we do, from playing sixteenth notes on the guitar to adjusting our stance on a jerking subway train, happens faster than the 80 milliseconds or longer it takes our conscious minds to register input, let alone act upon it. And so the brain must always be anticipating what comes next. It generates a model of the world,

makes decisions on that basis, and updates the model based on sensory feedback. In the language of probability theory, the brain is a Bayesian inference engine, merging prior expectations with current conditions to assess the probability of future outcomes.

**“All experience is controlled hallucination. You experience, in some sense, the world that you expect to experience.”**

– ANDY CLARK

Predicting and updating needn’t be – and usually aren’t – conscious acts; the brain builds its models on multiple subconscious levels. Nearly 20 years ago, researchers showed how the visual cortex works in a hierarchical and predictive fashion. The primary visual cortex generates a prediction for small-scale image patterns such as edges. It refines its prediction to match the incoming signals from the retina, but if this localized fine-tuning is not enough, it passes the buck to the secondary cortex, which revamps its expectations of what larger-scale geometric patterns must be out there. And so it goes up the hierarchy, evoking ever more sweeping changes, until the buck stops at the highest level: consciousness. (Neuroscientists adopted the term ‘predictive coding’ from communications engineering, which in the 1950s developed the

idea of transmitting discrepancies rather than raw data, to minimize the amount of information a network needs to carry.)

When the brain perceives a discrepancy, it can respond by either updating its model or deeming the discrepancy to be a chance deviation, in which case it never swims up into conscious awareness. “You want to attenuate fake news,” Friston says. Or there is a third alternative: Faced with a discrepancy between model and world, the brain might also update the world – say, by moving an arm or flexing a hand to make the prediction come true. “One can reduce prediction errors not only by updating the model but by performing actions,” says Anil Seth, a neuroscientist at the University of Sussex in the United Kingdom. In this way, predictive coding can be not just a system for perception, but also for motor control.

But which of these three responses should the brain take? In the predictive-coding model, the brain decides among them by assigning its predictions a precision – the statistical variability it expects from the input. Precision is the brain’s version of an error bar: High precision (low variance) plays up discrepancies: “This is important. Pay attention!” Low precision (high variance) downplays them: “Just a fluke, never mind.”

Suppose the brain consistently set the precision higher than conditions called for. It would be as if Google Maps understated its uncertainty about a person’s location and drew that approximate blue circle







around them too small. Random variations in the signal that cause the estimated location to jump around would look like real motion. One might well watch it and wonder what could possibly be causing that person to hop around like that: Where others saw noise, you'd see signal.

That same sort of miscalculation may occur in people with autism. "Maybe autism spectrum disorder involves a kind of failure to get that Bayesian balance right, if you like, or at least to do it in the neurotypical way," Clark says.

### **EXTREME PRECISION:**

Although the ideas underlying predictive coding date back at least 150 years, it came of age as a theory in neuroscience only in the 1990s, just as machine learning was transforming computer science — and that's no coincidence. The two fields have cross-fertilized each other.

Many machine-learning systems have a parameter called the

'learning rate' that plays the role of predictive precision, Friston says. An artificial neural network learns by trial and error; if it classifies a puppy as a kitten, it tweaks its internal connections to do better next time, and the learning rate dictates the amount of tweaking. The system can adjust the learning rate to optimize its training and avoid problems such as overfitting the data — recognizing every kitten and puppy it has already encountered, but failing to grasp the general features that distinguish these pets. The learning rate is often high at first but decreases over time. In the predictive-coding model, the typical brain, too, starts with a high precision and gradually dials it down, possibly by adjusting the concentrations of chemical messengers such as norepinephrine and acetylcholine. "The belief is that precision is usually encoded by neuromodulators in the brain — chemicals that change the gain on cortical responses," says Rebecca Lawson of the University of Cambridge in the U.K. When it's time to initiate another round of learning, the brain cranks up the precision again.

In people with autism, however, the precision may have a tendency to jump to a high level or get stuck there – for whatever reason, the brain tends to overfit. This general idea was first put forward in 2010 by Columbia University neuroscientists Ning Qian and Richard Lipkin. Inspired by machine learning, they suggested that the autism brain is biased toward rote memorization, and away from finding regularities or patterns. “We can think about the difficulties of training people with [autism] as a mismatch between the learning style and the tasks,” Qian says.

The following year, another team put forth the first Bayesian model of the condition, proposing that in individuals with autism, the brain gives too little credence to its own predictions and therefore too much to sensory input. In response, two groups – one including Friston and Lawson – suggested that predictive coding could provide the mechanism for the imbalance between predictions and sensations. And in 2014, Sinha and his colleagues proposed that in autism, the brain’s predictions aren’t underweighted but simply inaccurate, which becomes especially apparent in cases where prediction is intrinsically difficult. For example, when one event follows another only slightly more often than expected to by chance, a person with autism might not notice any connection at all. A world that seems at least somewhat predictable to typical people can strike those with autism as capricious – or, as Sinha puts it, “magical.”

Although these groups focused on different parts of the predictive process, they described much the same principle: For a person with autism, the world never stops being surprising. “That is a very common narrative in individuals

with [autism],” Kumagaya says. “They tend to be surprised more frequently than neurotypicals.” In a way, this view of the world facilitates some kinds of learning. For instance, studies show that people with autism do well at tasks that involve sustained attention to detail, such as spotting the odd man out in an image and identifying musical pitches. Also, they are less likely to see visual and multisensory illusions that presume strong expectations within the perceptual system.

**“In autism, rather than being adaptively surprised when you ought to have been surprised, it’s as if there’s mild surprise to everything.”**

– REBECCA LAWSON

But hyperawareness is exhausting. “You’re forever enslaved by sensations,” Friston says. Giving too much attention to the mundane would explain the sensory overload that people with autism commonly report. Some people with autism say they remain acutely conscious of buzzing lamps and rumbling air conditioners, and studies confirm they are slow to habituate to repeated stimuli.

Also in support of the predictive-coding model, people with autism can have trouble with tasks that are predictive by nature, such as catching a ball or tracking a moving dot on a screen. The problem is amplified when dealing with the most unpredictable things of all: human beings. To predict what someone will do in a given context, you may need to make

a guess based on what they or someone like them did under different circumstances. That is hard for anyone, but more so for people with autism. “It’s very common, for example, for [people with autism] to get into social interactions and have difficulty taking what they’ve learned from situation A and bringing it to situation B,” Lipkin says. A lack of predictability can lead to acute anxiety, a common problem in people on the spectrum. Many features of autism, such as a preference for routine, can be understood as coping mechanisms. “When you see most of the repetitive movements, they are actively retreating to shield complexity in the natural world,” says Sander van de Cruys of the University of Leuven in Belgium.

In addition to offering explanations for a range of autism traits, predictive coding might also make sense of the confusing links between autism and schizophrenia. The theory accounts for schizophrenia as, in some ways, autism’s mirror image. In autism, sensory data overrides the brain’s mental model; in schizophrenia, the model trumps data.

Consider schizophrenia’s distinguishing feature: having auditory verbal hallucinations (hearing voices). Last year, Philip Corlett of Yale University and his colleagues studied the origin of these hallucinations by inducing mild versions in 30 people who reported hearing voices on a daily basis (half of whom had been diagnosed with psychosis) and 29 who didn’t. To do so, the researchers borrowed a trick from Russian physiologist Ivan Pavlov. They showed the participants checkerboard images while playing a tone, so that the participants came to expect the two together. Then the researchers stopped playing the tone. The participants who hadn’t reported hearing voices



quickly caught on, but those who were hallucination-prone were more likely to report that they still heard the tone. The team interpreted this difference in terms of predictive coding. "People with auditory verbal hallucinations have very, very precise expectations about the relationships between visual and auditory stimuli in our task, so much so that those beliefs sculpt new percepts from whole cloth," Corlett says. "They make you hear things that weren't actually presented to you."

Autism resembles schizophrenia in some ways, Corlett says. Although hearing voices is not common, people on the spectrum have elevated rates of delusions – fixed beliefs they hold in the face of all evidence to the contrary, such as being manipulated by aliens or paranormal forces. Corlett suggests that these delusions occur when sensory data are given too much weight and install a new set of beliefs, which then become lodged in place.

### LOOKING AHEAD:

There is still much about autism that predictive coding doesn't explain, such as what exactly accounts for the autism brain's hesitancy to dial back predictive precision as the brain gains experience. Researchers are still investigating which is askew: the prediction, the sensory input, the comparison of the two or the use of a discrepancy to force a model update. And what types of predictions are involved – all kinds, or just some? Our brains make predictions on many levels and

timescales. People with autism do just fine with many of them.

Some researchers are skeptical that problems of prediction are the root cause of autism. Psychologist James McPartland, also at Yale, says he is partial to explanations that give primacy to the condition's social traits. If one thing characterizes autism, he says, it's social difficulties, suggesting that researchers should focus on the mental machinery we need to interact with other people, such as face recognition. He says he finds a social explanation no less biologically plausible than a perceptual one. "We have a really clear idea where in the brain faces are processed," he says. He also wonders about the direction of causation: Instead of predictive problems explaining social difficulties, the relationship might work in reverse, because so much of the brain's predictive capacities are developed through social interactions. "Is social information a critical kind of information for the normative development of predictive coding?" he says.

Predictive-coding researchers themselves acknowledge that they are just beginning to test the theory in autism. "Those initial papers, they're sort of just-so stories, in that they are post hoc – explaining data that was already collected," Lawson says. But she and others have been conducting experiments that probe the predictive mechanisms more specifically. Many involve associative-learning tasks, in which people have to figure out the rule that governs some series of images or other stimuli. Every so often, the experimenters

change the rule in a way that's not immediately obvious and see how quickly their participants catch on.

Last year, for example, Lawson and her colleagues brought two dozen people with autism and 25 controls into the lab. They played a high or low beep, showed a picture of a face or house, and asked participants to press a button for 'face' or 'house.' At first, a high tone presaged a house 84 percent of the time, then a low tone did, then tones had only a 50-50 relation to image type, and so on. The controls slowed down whenever a run of violated expectations convinced them that the rule must have changed, but the participants with autism responded at a more consistent rate, which was slightly slower overall. The researchers concluded that the participants with autism responded as if each deviation – a house when the tone augured a face, say – signaled a change of rule, whereas typical people were inclined to write off the first few deviations as probabilistic happenstance.

For about half the participants, the researchers also measured pupil size, because pupils dilate in response to norepinephrine, one of the chemicals thought to encode predictive precision. Interpreting these results was tricky because each person followed a slightly different learning curve and formed different expectations. To determine whether a given event would seem surprising, the researchers had to model each person's pattern of responses individually. The upshot was that the pupils of participants with autism seemed to be on a hair trigger. "In autism, rather than

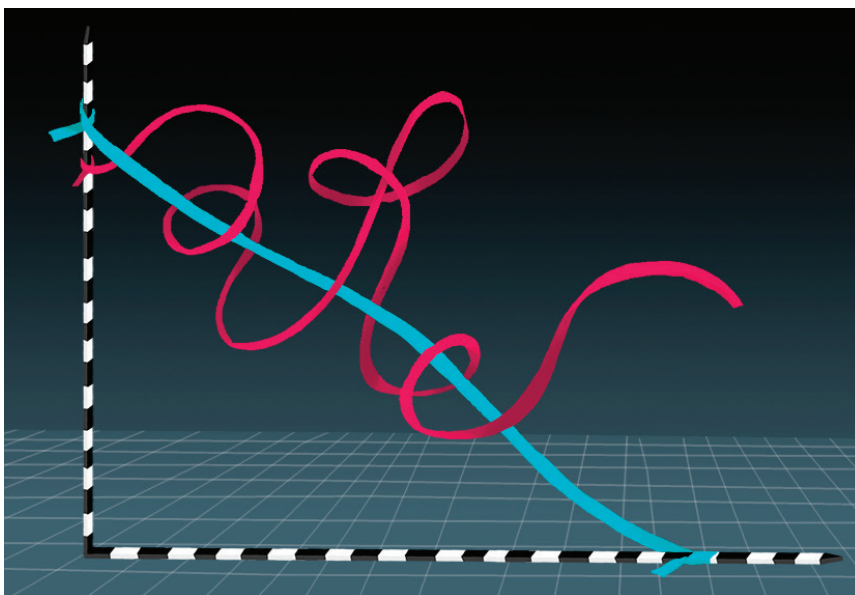
being adaptively surprised when you ought to have been surprised, it's as if there's mild surprise to everything – so, it's sort of saying, well, that was mildly surprising, and that was mildly surprising, and that was mildly surprising, and that was mildly surprising," Lawson says.

One intriguing approach is to build the predictive-coding theory into computer models, even robots. Artificial neural networks that embody theories of brain function could serve as digital lab rats. Researchers could tweak the model parameters to see whether they reproduce the traits of autism, schizophrenia or other conditions. In 2012, computational scientist Jun Tani and a colleague programmed a robot to simulate schizophrenia. By adding noise to the robot controller's calculations, they led it to miscalculate the discrepancy between its expectation and its sensory data. The spurious error – a robotic hallucination, if you will – propagated up the robot's cognitive hierarchy and destabilized its operation. "The robot shows disorganized behaviors," says Tani, professor at the Okinawa Institute of Science and Technology in Japan. He and others are beginning to apply predictive coding to autism in this way.

If predictive coding holds up as a model for autism, it might also suggest new directions for therapies. "Different kids with autism may show impairments in somewhat different parts of that predictive chain," Chawarska says, which might call for a range of clinical approaches. When she meets with parents, she uses the idea of prediction to help them

understand their child's experience of the world, telling them: "Your child really has tremendous difficulties understanding what's going to happen next," she says. "It's something that really comes through, particularly with these very, very young kids. Their anguish and difficulty in relating to events is that they simply don't know where they fit."

If nothing else, predictive coding might offer the insight some young people crave – as Ayaya did when she was a teenager. "I noticed the differences between me and other kids, and I was thinking, why was this going on?" she recalls. As an adult, she says, her anxiety has abated, not just because of the self-knowledge she has achieved, but also because of the awareness shown by her peers and friends. Often, the typical people she spends time with know about her condition, she says. "They know me. [So] I feel more free to ask, 'I got surprised, but didn't you?'" ■



9 MAY 2018

# Why the definition of autism needs to be refined

BY LINA ZELDOVICH

Five years after its latest revision, the manual used to diagnose autism is back under scrutiny, as evidence suggests it excludes some people on the spectrum.



## PHOTOGRAPHS BY PARTY OF ONE

For about six months, starting in late 2012, Valerie Gaus found herself much busier than usual. The New York area psychologist sees adults with autism, and a number of them suddenly seemed to be grappling with a new set of anxieties. They brought up their fears over and over again in their sessions. It seemed, Gaus recalls, as if they felt the sky was falling.

At the heart of their worries lay the impending revision of the “Diagnostic and Statistical Manual of Mental Disorders,” or the DSM-5. This book, the fifth edition of the psychiatric manual, was expected to bring sweeping changes to autism diagnoses, placing what had been separate conditions – autism, Asperger syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS) and childhood disintegrative disorder (CDD) – under a single umbrella: ‘autism spectrum disorder.’

Some of Gaus’ clients were afraid they would lose their insurance coverage and would have to be re-diagnosed. Those concerns were relatively easy to dispel: Gaus explained that many insurance carriers use codes from the International Classification of Diseases (ICD), which still distinguishes between the various conditions. “I would pull out insurance forms to show my clients and say, ‘Look, all along you’ve been coming here, I’ve been billing using ICD codes – which I will continue to do,’” she says.

But many clients had abstract worries that were more difficult to assuage. For instance, people with a diagnosis of Asperger syndrome felt they were being robbed of their identity. Many had been diagnosed late in life after years of unexplained challenges. Receiving the diagnosis had given them feelings of closure and belonging within a community of people with

## Autism prevalence in 2008: 1 in 99

## Autism prevalence in 2018: 1 in 59

similar difficulties. “The diagnosis provided them with a sense of relief, an explanation of what they had struggled with,” Gaus says. Now they were worried they were losing their footing all over again.

As it turned out, the manual’s publication was “anticlimactic,” Gaus says – at least for people like her clients: After it was released in May 2013, no one lost services, and the billing systems continued to work as they always had. Even though ‘Asperger’s disorder’ and ‘PDD-NOS’ faded from clinical use, people formerly diagnosed with those conditions continued to use them socially. They told Gaus the terms helped them preserve what they felt they had gained from those diagnoses.

In the research world, by contrast, opinions about the manual followed a different course: Researchers were also apprehensive about the DSM-5’s proposed changes beforehand – but their initial concerns ignited into a fiery debate that is still smoldering today. One side argued that the DSM-5 criteria represented a move toward standardizing autism diagnoses. The other maintained that the manual was a disastrous mistake that would cut some people off from the help they needed.

The argument launched an avalanche of research, and after five years, the results are starting to trickle in. They show that both camps were right. The DSM-5 did indeed bring about greater

diagnostic consistency: Clinicians at independent sites are now more likely to arrive at the same conclusion. At the same time, though, the criteria appear to exclude certain segments of the autism spectrum: people who are mildly affected, and older adults and girls, who may be better at masking their traits.

“We are missing some of the highest-functioning cases when we apply DSM-5 criteria,” says Thomas Frazier, who, as director of the Cleveland Clinic Center for Autism, conducted studies to validate the DSM-5 criteria. “We are not missing a ton of them, but we are missing some, and it’s a reasonable amount. It raises the question of whether or not we could do better.”

### **EXPERTS DISAGREE:**

By the time the DSM-5’s autism committee began writing the manual’s autism chapter, it was clear that the prior edition’s criteria could stand some improvement. There was growing concern among experts that there was little consistency in how clinicians at different sites distinguished among autism, Asperger and PDD-NOS. The diagnoses people received varied according to their age, address, access to services and even the clinician’s or parents’ comfort levels with a label.

“It was clear that the same child could get a PDD-NOS, Asperger or autism diagnosis from different





people, depending on who diagnosed them,” says Catherine Lord, director of the Center for Autism and the Developing Brain at New York–Presbyterian Hospital, and a member of the DSM-5’s autism committee. “It was also clear that kids could get a different diagnosis at different points of their lives,” Lord says.

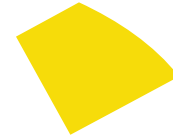
The outcome also depended on the goal. In states such as California that provided services for children with autism but not Asperger syndrome, families pushed for the former diagnosis, Lord says.

In places such as New York City, which provided services for both diagnoses, parents often lobbied for an Asperger diagnosis, worried that the ‘autism’ label would dampen their child’s chances of getting into a top school.

The committee set out to create criteria that would be less subjective and balance sensitivity (identifying anyone who should qualify for a diagnosis) with specificity (excluding those with other conditions). The group planned to set up clear guidelines and definitions for clinicians

and, crucially, to merge the three conditions into one. And because there were overlaps in the descriptions of some traits, the new criteria folded the diagnostic triad of social interaction impairments, social communication difficulties and restricted or repetitive behaviors into a dyad of requirements: social communication problems and restricted interests and repetitive behaviors.

As a result of these revisions, the single diagnosis would encompass the entire spectrum, from nonverbal, intellectually challenged people to those with high



intelligence quotients (IQ) and mild social challenges. To distinguish between these far-ranging degrees of impairment – and the types of services someone should receive – the committee also created a ‘severity table’ that spells out three levels of need.

The new criteria deliberately gave diagnosticians less leeway. For example, the previous version, the DSM-IV, let clinicians pick and choose any 6 items from a list of 12 to make a diagnosis. This flexibility earned the list the nickname ‘the Chinese menu.’ The DSM-5 offers fewer options with firmer rules – among them, the specification that someone show at least two of four restricted and repetitive behaviors.

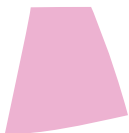
Some scientists – including a few committee members – found the guidelines too stringent. Although the criteria’s specificity was good, they said, the sensitivity was too low and would end up excluding some people on the spectrum. In a 2012 study, committee member Fred Volkmar and his colleagues compared the specificity and sensitivity of the DSM-IV with those of the draft DSM-5 criteria. They reported that only 61 percent of people who met autism criteria under the DSM-IV criteria did so with the DSM-5. The subgroup of people diagnosed with Asperger syndrome showed the greatest discrepancy, with only 25 percent retaining their diagnosis. Overall, the new criteria seemed to discriminate against those with high

cognitive ability. Although anyone who already had a diagnosis of Asperger’s or PDD-NOS was guaranteed an autism diagnosis under the DSM-5, the criteria would exclude those yet to be diagnosed, Volkmar pointed out.

Supporters of the DSM-5 criticized the study, saying it is misleading to compare old test scores with the new criteria. For example, sensory problems are among the four behavioral items clinicians can choose from in the DSM-5, but the DSM-IV criteria did not address sensory sensitivity. Volkmar ultimately resigned from the committee.

But within a few years, several retrospective meta-analyses added weight to his argument. One review considered 25 studies that evaluated various groups using both manuals. The majority of those studies found that only 50 to 75 percent of the people diagnosed under DSM-IV criteria would maintain diagnoses under the DSM-5, and people at the mild end of the spectrum stood an even lower chance. A 2016 meta-analysis came to the same conclusion.

According to Volkmar, the worst is yet to come. He says he views the DSM-5 as a societal time bomb, the results of which will only become apparent in 10 to 15 years, when the children now being overlooked by the DSM-5 grow up. With a diagnosis and adequate support, this group may have stood a





strong chance of succeeding and becoming productive members of society, he says. Without it, their possibilities are dimmed. "I think we have yet to realize the full impact of DSM-5," Volkmar says. "The high-functioning people coming newly to diagnosis are in trouble."

#### FIVE YEARS LATER:

Whether his long-term predictions pan out or not, researchers now have five years' worth of diagnoses to begin to analyze the DSM-5's true effects.

The first such study came out last year. Researchers asked six autism centers to diagnose children using both the DSM-IV and the DSM-5 simultaneously. They found that the DSM-5 does exclude some people – and exactly the groups of people critics of the DSM-5 warned about. In this study, 89 percent of the children who met DSM-IV criteria did so with the DSM-5. "If someone has more ambiguous symptoms, they are probably less likely to meet criteria on DSM-5," says lead researcher Micah Mazurek, associate professor of education at the University of Virginia in Charlottesville. "It seems like children who were referred at an older age and those who have had higher IQ, and girls, had greater discrepancy."

Ironically, the DSM-5 may have made it more difficult to identify girls with autism just as researchers

were beginning to realize that the manuals had excluded them for decades. Like Mazurek, clinical psychologist William Mandy pins this lowered sensitivity on the DSM-5's stricter requirements – particularly for repetitive behaviors, which are more prevalent in males with autism.

**“It was clear that the same child could get a [different] diagnosis, depending on who diagnosed them.”**

– CATHERINE LORD

"There is a fairly solid emerging evidence base that, on average, autistic girls and women score lower on measures of repetitive and stereotyped behaviors than do autistic males," says Mandy, senior lecturer at University College London. "You can begin to see how the move from DSM-IV to DSM-5 may be excluding some females on the basis of their less severe stereotyped behaviors."

Mandy also notes that the DSM-IV had a place for people with social communication difficulties but whose repetitive behaviors didn't meet the diagnostic threshold for classic autism. "That was the PDD-NOS category," he says. Some of those individuals may now be left out.

That kind of adaptation may also be important to consider in college students, says Susan White, co-director of the Virginia Tech Autism Clinic, where she works with young adults and students on the spectrum. Thanks to their intellectual aptitude, skill at camouflaging autism traits or their parents' help, some people on the spectrum remain undiagnosed throughout their childhood. When they start living independently, perhaps on a college campus, they can face great difficulty. "We need, as clinicians and educators, especially in college settings, to be aware that someone could come to college non-diagnosed," White says. The DSM-5 could miss such students, she says.

Some advocates for people at the other end of the spectrum are also unhappy with the DSM-5. The manual's criteria for autism are too inclusive and have made the diagnostic label meaningless, says Alison Singer, president of the Autism Science Foundation, whose daughter has autism and severe intellectual disability. "It's so broad, there are so many people under the big tent of autism, that people in the tent have nothing in common with each other anymore," she says. The media's portrayal of autism is skewed toward the highly capable but quirky genius, and the other end of the spectrum is being forgotten, Singer says.

Overall, however, most people in the autism community say the

good that has come from the DSM-5's changes outweighs the bad. "Before DSM-5, there was a lot of evidence that which diagnosis code you got had more to do with which doctor you saw than any real difference in what your autism or what your disability was like," says Julia Bascom, executive director of the Autistic Self Advocacy Network, a nonprofit organization based in Washington, D.C. "We always felt very strongly that we are one community, regardless of what labels were put on us."

#### **MOVING FORWARD:**

The DSM-5's autism criteria might still be improved in terms of sensitivity and how they convey levels of impairment, some experts say.

One simple fix that was proposed – but abandoned for fear it would artificially inflate prevalence – was to require only one repetitive behavior. Frazier, who is now chief science officer at the New York-based advocacy organization Autism Speaks, while still affiliated with the Cleveland Clinic, came up with the idea in 2012, during the first round of the DSM-5 debates. He wrote an algorithm that mapped children's behavioral traits, as reported by their parents, onto the proposed DSM-5 criteria. He then analyzed those same data requiring only one repetitive behavior for a diagnosis. The results showed that this change would bring the new criteria's sensitivity in line with that of the DSM-IV without losing any specificity. "That was my suggestion to the field – requiring only one repetitive behavior symptom," Frazier says. "Obviously they went with two, but I think the result of going with two is

that specificity is pretty good, but the sensitivity is not quite as high as we'd like it to be."

His suggestion is unlikely to resurface. Frazier says some committee members oppose any move to relax the criteria. "The field is concerned that if you decrease specificity at all, there will be a significant increase in autism cases, and some of these cases won't be true cases," Frazier says. "And in this case, the public will be even more skeptical about the diagnosis."

There are no expected revisions to the DSM-5's autism criteria, but researchers are taking inspiration from the forthcoming edition of the ICD – the ICD-11 – due out later this year. A draft of this manual mirrors some of the DSM-5's big changes – for instance, subsuming Asperger syndrome and PDD-NOS under autism. At the same time, it gives clinicians more flexibility and makes a clearer distinction between autism with and without intellectual disability. Volkmar sees it as a move in the right direction: "They do a very good job of talking about how you can effectively make a differential diagnosis, which I think will make this a very useful book."

The ICD-11 draft also helps to close some of the DSM-5's diagnostic gaps, Mandy says. In particular, it acknowledges that individuals with autism and no intellectual disability may come to clinical attention later in life or be diagnosed first with anxiety or depression. It also puts a greater emphasis on camouflaging, which may bring the phenomenon to the attention of more clinicians. Because later diagnoses and camouflaging are both more common among women with autism,

he says, the additions could help to ensure that more women with autism are identified.

For all the draft does right, however, it doesn't solve the ongoing debate about terminology. "There continue to be questions of whether there should be different terms for people with different skill levels within autism," Lord says. The severity levels included in the DSM-5's criteria are supposed to help determine the level of support an individual needs, but they don't give families a simple way to describe their child's condition. "They feel that if there were a different term for their kids, it would be helpful," she says.

And the disappearance of labels has been a problem for researchers, too. Gaus found that professionals who studied Asperger syndrome before the DSM-5's release have had to get "creative." She says the literature now includes at least seven alternatives to describe individuals previously diagnosed

with Asperger syndrome: autism 'without intellectual disability,' 'with no intellectual impairment,' 'with normative cognitive ability,' 'intellectually able,' 'cognitively able,' 'high-functioning,' and 'cognitively high-functioning.'

It's not clear what will happen when the Asperger label vanishes from the ICD-11 this year – but it's unlikely to upset Gaus' clients as much as the DSM-5's deletion did. "There has not been as much buzz about ICD-11," Gaus says, noting that the draft includes a category – 'autism spectrum disorder without disorder of intellectual development and without impairment of functional language' – that sounds a lot like Asperger syndrome. Nor is she worried that the billing codes for her clients will change any time soon. "[U.S. insurance companies] did not begin using ICD-10 until 2015 even though it was published in 1990," she says. For the time being, it seems, her clients can leave their anxieties behind them. ■

**“If someone has more ambiguous symptoms, they are probably less likely to meet criteria on DSM-5.”**

– MICAH MAZUREK



25 JULY 2018

# The healthcare system is failing autistic adults

BY ALISA OPAR

Adults on the spectrum frequently have a range of other conditions – but they rarely get the help they need.



Photograph by Nick Hagen

**PHOTOGRAPHS BY**  
**NICK HAGEN**  
**KIM RAFF**

Rebekah Hunter lay in the hospital bed, terrified. A nurse had taken Hunter's underwear earlier in the emergency room and warned that an alarm would sound if they got out of bed. (Hunter, who presents as female, identifies as non-binary and uses the pronouns 'they' and 'them.'). If Hunter had to use the bathroom or wanted to walk around the room, they needed to ask the nurse's permission.

Hunter, then 28, was already on edge. They had tried to overdose on ibuprofen and acetaminophen and were being held in the hospital under observation. Anyone would find the experience distressing, but Hunter's distress was magnified by the fact that they are autistic.

Like many people on the spectrum, Hunter suffers from bouts of depression and chronic gastrointestinal problems. At the time, Hunter was also in an abusive relationship. (Some research

suggests that abusive relationships are common among people on the spectrum.)

Hunter had been seeing a therapist but says the sessions weren't helping. "I felt like a lot of the stuff I was going through was dismissed," Hunter, now 30, recalls. "I would tell her that I felt like my partner didn't care about me, that I didn't feel safe; she'd talk me down and say it was fixable. It felt like gaslighting."

The experience was one of many that left Hunter feeling that no one in the medical community was willing to listen to them. And so it was with the nurses in the hospital, too. Scared of angering them, Hunter shut down completely and complied with everything they said. Hunter felt helpless; they couldn't sleep because the lights were on all the time and the hospital gown was itchy. It took about four days of this "sensory torture" before they were released.



Like Hunter, many autistic adults struggle to receive good care from doctors and hospitals. These individuals often find it difficult to communicate with healthcare professionals and are misunderstood or ignored. They're less likely to have their routine health needs met, from dental check-ups to tetanus vaccinations. "I think that as an autistic person, I've had to habituate to other people's rules and comfort levels," Hunter says.

For their part, primary care doctors and mental health providers are often unprepared to treat this population. Many are unaware that adults on the spectrum are at risk for a range of other ailments in addition to their autism: Adults with autism are almost twice as likely as their typical counterparts to have diabetes, high blood pressure and heart disease, for instance. As a result, they die, on average,

16 years earlier than typical adults matched for gender, age and country of residence, according to one study. Making sure people on the spectrum receive routine and preventive care could help bridge that mortality gap.

"A lot of adults with autism feel lost," says Lisa Croen, director of the Autism Research Program at Kaiser Permanente, a managed healthcare provider based in California. "It'd be great if physicians had some more general training and awareness. Just like with any other condition, they really have to take into account that particular person in their office and adjust what they're doing to meet the needs of that patient."

Croen and others are working on a number of potential solutions – including specialty clinics, online tool kits and training programs



for community mental health workers. And some autistic adults, including Hunter, are eager to offer their input.

### **GROWING PAINS:**

More than half of all adults with autism have additional diagnoses. Apart from diabetes, high blood pressure and heart disease, they also tend to have obesity, autoimmune diseases, hearing impairment, sleep disorders and gastrointestinal problems – plus a laundry list of psychiatric disorders, including schizophrenia, depression and attention deficit hyperactivity disorder.

Some of these conditions, such as constipation and sleep problems, are also common in autistic children, says Croen, which may be a consequence of the autism or reflect some common physiologic or genetic ground. But others, including heart disease, more often arise in adulthood.

Still, autism is often erroneously described as a childhood condition, and children are where the vast bulk of research dollars and media attention are focused. The U.S. Centers for Disease Control and Prevention estimates that 1 in 59 children has autism, up from 1 in 150 in 2002. “These kids have been growing up and reaching their adulthood and now need medical care just like anybody,” Croen says. But all evidence suggests that’s not happening. One study last year, for example, analyzed the insurance records of more than 16,000 people with autism, aged 16 to 23, and found that outside of emergency-

room visits, their use of healthcare services dropped significantly with age.

“This is a huge issue; we see adults who still go to their pediatrician because there just aren’t enough providers for general care or psychiatrists who will see adults with autism,” says Julie Lounds Taylor, a developmental psychologist at the Vanderbilt University in Nashville, Tennessee. Lounds Taylor studies the transition of autistic teenagers to adulthood. “The challenge is: Can you find someone who will take you, and can you find someone who will provide competent care?”

## **“A lot of adults with autism feel lost. It’d be great if physicians had some more general training and awareness.”**

– LISA CROEN

Andee Joyce, a former medical transcriptionist in Hillsboro, Oregon, says she has faced numerous barriers in trying to navigate the healthcare system as an adult. She was diagnosed with autism in 2007 at age 44. Thanks to her work, she knows all the diagnostic jargon. Even so, nearly everything about doctors’ appointments has been a challenge, starting with scheduling them, she says. Because telephone conversations often become garbled for her, she always procrastinates. “I only have so many

spoons for phone calls,” she says. (Some people with a disability or chronic illness refer to the

‘spoon theory’ to explain the limited energy they have available for daily tasks.)

Once she has an appointment – to see her therapist about her depression, her endocrinologist about her polycystic ovary syndrome or her primary care physician about sinus issues – arriving on time can be a trial. She has learned to write down in advance everything she wants to discuss with her doctor because, she says, “my mind and my mouth aren’t always in sync.” And she wants details – all of them. In May, for instance, when her doctor prescribed a nasal spray for ongoing sinus issues, she wanted to know exactly why, when and how she should use it, along with any side effects. “I tell doctors, ‘Err on the side of over-explaining,’” she says. Her doctor didn’t mention the spray’s terrible aftertaste, which startled and distressed her.

Joyce finds dental appointments to be the “absolute worst,” between her sensitive gag reflex and the discomfort of having her mouth “stretched open like the Grand Canyon.” Some women on the spectrum find gynecologic visits the most intimidating. Autistic women are significantly less likely to visit a gynecologist and get pap smears, which screen for cervical cancer, than other women of the same age. The gap may be due to a combination of factors: Primary care doctors may assume these women aren’t sexually active, for instance, or the women may



avoid visits because they are hypersensitive to touch.

Few clinics cater to these special needs. The Women with Disabilities Gynecology Clinic at the University of Michigan in Ann Arbor is one of the few that treat women on the spectrum. Unlike a typical women's clinic, it has an array of charts, pictures and anatomically correct dolls, along with tiny speculums, so that the staff can tailor their explanations to their clients, including those with intellectual disability. Women who visit the office are also encouraged to bring advocates with them to help ensure they're as comfortable as possible and receive all the information they require.

For the physicians at the clinic, flexibility is key, says Susan D. Ernst, the gynecologist who directs the clinic. Ernst regularly takes histories while women pace around the exam room; she doesn't force them to sit. She says one woman she sees communicates through a voice output device and requests that Ernst dim the lights so that the exam is less overwhelming. Many women need two or more visits to get through a full exam. It all comes down to accommodating the individual's needs, Ernst says. "These patients really shouldn't have to be seen in a special clinic," she says. "What we really need to do is educate providers so that any physician is able to care for them."

## THE DOCTOR WILL

### SEE YOU NOW:

After Hunter was released from the hospital, they decided it was time to find better care. "I just left and found a new doctor," Hunter says. That might sound straightforward,

but as it is for Joyce, making appointments can be difficult for Hunter. "Phones are scary to me," Hunter says. "It's a deterrent."

Over the next two years, Hunter was prescribed an array of antidepressants by various doctors. Hunter also developed gynecological problems in the form of irregular bleeding and says their doctor largely ignored their questions and didn't take notes during appointments. "At first I thought it was that he was hard of hearing; I speak softly," Hunter says. "But it became a horrible nightmare."

Hunter's doctor's approach is the antithesis of what Ernst and others have found to be effective when treating people on the spectrum. At the Neurobehavior HOME program at the University of Utah, for example, the entire clinic is designed around people who have disabilities. The center is funded entirely by Medicaid and provides medical and mental health care to about 1,200 people with developmental disabilities, 60 percent of whom are autistic adults.

Providers slot a full hour for each appointment, which allows for late arrivals and helps keep the waiting room quiet and uncrowded (crowded spaces are tough for people with sensory sensitivities). Exam rooms are large, allowing people to move around as needed and to bring caregivers along. There's a phlebotomy lab on site, with staff trained to help ease anxiety during a blood draw. And a nutritionist works with clients to manage weight gain, a common side effect of seizure and antipsychotic medications that can contribute to other conditions, such as diabetes and heart disease.

“Being able to very closely integrate our care is huge, and we’re showing it’s leading to much better outcomes for adults with autism,” says Kyle Jones, who directs the primary care team. Although autistic adults have elevated rates of conditions such as diabetes, the clinic has better-than-average rates of controlling those comorbidities and fewer hospitalizations, Jones says.

Most people on the spectrum join the program as they’re transitioning into adulthood and leaving their pediatrician, the structure and routine of school, and other familiar services. “We can help with their needs, with some of those unknowns,” Jones says. For example, in late May, a young woman with autism who was new to the program came in with her father. The father told Jones his daughter had been unable to have a dental exam because he couldn’t find anyone to sedate her; even if

he had, he would have had to pay out of pocket. Jones reassured him that the program pays for dental anesthesia through discretionary funds it receives for each client from the state. “The dad started crying,” Jones recalls. “He said, ‘This has been such a huge frustration.’”

The vast majority of adults with autism don’t have access to anything like the HOME program, however. Other states either haven’t considered or have not been willing to fund similar clinics that provide ongoing care.

In Philadelphia, researchers are working to train community mental health providers to fill some of that unmet need. Last year, clinical psychologist Brenna Maddox and her colleagues interviewed adults with autism and surveyed therapists and case managers who connect them with community-based social services. She is now designing a training program,





which she expects to roll out to clinics next year. One driver for the work, she says, is the fact that there is a dearth of psychiatrists and therapists who treat autistic adults – and those who do often don't take insurance. "Of course, we could bring adults here to Penn, and I could treat them as part of a research study," says Maddox, a postdoctoral fellow working with David Mandell's team at the University of Pennsylvania. "But if we can train the clinicians in the community, they're going to have a much broader and more impactful reach."

#### **BETTER TOOLS:**

For now, most clinicians feel ill-equipped to treat autistic adults. That was the message Croen received when she surveyed hundreds of primary care and mental health providers in 2015. "They told us that they need more resources and training to work with adults with autism," she says.

The study Maddox conducted received similar responses.

"Treating depression and anxiety is their bread and butter – they do that all the time," she says. "But the second it's an adult with autism who has depression and anxiety, they don't feel like they have the comfort level or confidence to work with them."

Awareness is at least growing among the next generation of doctors. Ernst says dental and medical students at the University of Michigan in Ann Arbor are collaborating with a local advertising firm to create and distribute a list of providers who are good at working with people who have disabilities. (Ernst is on a national list compiled by the nonprofit organization Autistic Women & Nonbinary Network.) What's more, she and her colleagues are developing a curriculum for the medical school on caring for people with disabilities, including autism. Educating providers early in their careers, these scientists say, will make treating autistic people less daunting and help them more fully address the needs of people on the spectrum.

Until medical schools incorporate information about autism into their curricula, doctors and autistic adults have another resource to help them communicate and build better relationships. In 2016, scientists developed an online healthcare tool kit that offers a multitude of resources, from medical, legal and ethical information to worksheets that can help autistic people manage appointments. The tool kit is accessible through the Academic Autism Spectrum Partnership in Research and Education (AASPIRE), a research collaboration between several organizations.

The centerpiece of the tool kit is an 'accommodations report' that an autistic adult or her caregiver can fill out and give to a doctor to inform treatments. "Because everybody on the spectrum is going to be different and have different needs, it's really hard for me to tell a provider, 'These are the things you have to do to take care of adults on the spectrum,'" says Christina Nicolaidis, an internist who leads the project. "[The accommodations report] provides really concrete, actionable items that providers would need to know," she says – items such as an autistic person needing to have dimmed lights during an exam or to know how many test tubes of blood the clinician might draw.

Nicolaidis and her colleagues tested the tool kit in 170 adults with autism and 41 primary care doctors in 2016. The participants reported that communication with their doctor improved one month after they received the tool kit. The next step, Nicolaidis says, is to see if the tools can be incorporated into primary care practices, as opposed to something individuals take to their physician. To find out, she's collaborating with three large

healthcare networks, two in Oregon and one in California. (Croen, at California's Kaiser Permanente, is a collaborator.) In January, they launched the two-year study, which includes around 220 people at 12 clinics, about half of which will use the tool kit.

The tool kit incorporates data from interviews with dozens of autistic adults; another six actively helped to create it. Those pages include an extraordinary level of detail. "That comes from our autistic partners saying: 'Wait, wait, wait. Don't just tell me I should make an appointment; I need a script to follow,'" Nicolaidis says. Her team also worked with doctors to streamline the accommodations report so that they could actually use it. "When we first started doing cognitive interviewing with the doctors, it was a disaster: 'This is too long'; 'I can't look at this'; 'It's too much information'; 'You need to make it shorter.'" she recalls them telling her.

**“This is a huge issue; we see adults who still go to their pediatrician because there just aren't enough providers for general care or psychiatrists who will see adults with autism.”**

– JULIE LOUNDS TAYLOR

The tool kit isn't meant to be a substitute for specialized expertise. "I've been focused on autism for years, and I'm still not going to get it all right when I work with an autistic patient," Nicolaidis

says. "But it's a first step to give people a way to try to make those interactions more effective, to help non-autism healthcare providers know enough about autism to be able to do their jobs."

Hunter has learned to self-advocate without the benefit of such a resource. Their new gastroenterologist finally diagnosed Hunter with irritable bowel syndrome and has been patient and communicative about finding a treatment. "He listens to me, takes his time with me, remembers my history," Hunter says. "I get the sense that he cares about me." Hunter has also started seeing a primary care physician who not only listens, but also actively encourages them to explain their needs – something many of the providers Hunter encountered did not support. "It's so much better," Hunter says.

And Hunter is learning to advocate for others these days, too. While taking an abnormal psychology course last year, Hunter met a member of the AASPIRE team. Hunter jumped at the chance to pitch in and began reviewing and coding write-ups that struck close to home: descriptions of people's negative healthcare experiences. In May, Hunter took on a bigger role with AASPIRE, becoming a community council member, offering feedback and creating resources to help others. In that capacity, Hunter will interact with adults on the spectrum and ensure that these individuals' input is incorporated into programs and resources the group develops.

Hunter is in a much better place today than five years ago and eager to put their own negative experiences to use to help others: "I think we're the only ones that know what our lives are like." ■

