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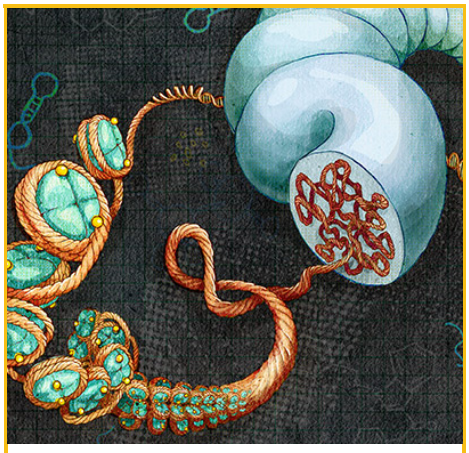
Autism gene may be key to discovering new candidates

Jessica Wright
19 May 2014



Master regulator: CHD8 regulates how the DNA in many autism risk genes winds around its support proteins.

CHD8, a gene that has emerged as one of the strongest risk factors for autism, regulates the expression of more than half of a set of 'high-confidence' risk genes for the disorder. The unpublished data were presented Saturday at the 2014 International Meeting for Autism Research in Atlanta.

The results suggest that there may be more unidentified autism risk factors among the list of CHD8 targets. "CHD8 binding itself may provide additional power to find and detect [autism] risk genes," says James Noonan, associate professor of genetics at Yale University, who presented the work.

CHD8 dampens the expression of genes by regulating how tightly DNA winds around support proteins, called histones. In a 2012 study, researchers found spontaneous mutations in CHD8 in nine people with autism and none of nearly 800 controls[1]. They estimated that mutations in this gene might account for 0.4 percent of cases of autism.

In the work presented Saturday, Noonan and his team looked at neurons from three sources to map all the spots in the genome at which CHD8 binds. They looked at human stem cells induced to become neurons and at neurons taken either from human postmortem fetal brains or from the developing mouse brain. Overall, CHD8 binds to sites at which genes are actively expressed, supporting its key role in gene regulation.

The researchers then looked at a set of 116 autism risk genes, including 9 'high-confidence' genes, meaning that they believe them to have a strong link to autism. CHD8 regulates significantly more of these than one would expect to find by chance, they found.

CHD8 binds to 17 of 30 high-confidence risk genes (most of which are as yet unpublished) for which researchers have found at least two examples of a spontaneous, harmful mutation in an individual with autism. CHD8's targets in this list include FOXP1, DYRK1A and ADNP.

The researchers then grew neuronal stem cells that make little to no CHD8. This significantly changes the expression of CHD8's targets, and in particular the autism risk genes, they found.

"This is really pointing to a very strong regulatory role of CHD8 in the biology of other risk genes for autism," says Noonan.

For more reports from the 2014 International Meeting for Autism Research, please click here.

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Rats with mutant SHANK genes show autism-like behaviors

Jessica Wright
15 May 2014

Treat pursuit: Rats with a mutation in the SHANK2 gene press a lever for a reward about a hundred times more than controls before giving up.

Researchers have engineered two new rats with mutations in a family of genes that function at neuronal junctions, or synapses, they reported today at the 2014 International Meeting for Autism Research in Atlanta.

The rat models have a mutation in either one or both copies of SHANK2 or SHANK3. Rats are generally considered to be better than mice for modeling neurological disorders such as autism because they show complex play and other social behaviors. They also have larger brains than mice do, permitting a more finely tuned investigation of their neural pathways.

"We built a SHANK3-deficient rat model to understand the neural basis of autism," says Hala Harony-Nicolas, an instructor in psychiatry at the Icahn School of Medicine at Mount Sinai in New York, who presented the SHANK3 work.

The rats with SHANK3 mutations have trouble remembering their peers and focusing on a task. Those with SHANK2 mutations show persistent repetitive behaviors and tend not to interact with other rats. Treatment with oxytocin, a neurotransmitter famous for enhancing some social skills, fixes many of the deficits seen in the SHANK3 rats. The researchers did not test the effect of oxytocin on the SHANK2 rats.

"The oxytocin results are really intriguing," says Jacqueline Crawley, professor of psychiatry at the University of California, Davis, who was not involved in the study.

Drop anchors:

SHANK2 and SHANK3 sit at the receiving ends of synapses and mediate neuronal signaling. Researchers have identified multiple mutations in these genes in people with autism, making them — and SHANK3 in particular — strong candidate genes for the disorder.

The SHANK3 rats lack the region of the protein that anchors it to the synapse. They show problems with attention: They are less accurate than controls when choosing between five touch screens that release a treat when lit, for example. They also tend to forget, after about one day, a rat that they've already met. But the rats still prefer the company of another rat to an object, and play normally when young.

The researchers also placed electrodes into the rats' brains to measure signals between two distant brain regions, the hippocampus and the medial prefrontal cortex. The rats' brains show defects in the way they regulate the strength of the signals, the researchers found.

They also express several proteins at different levels than in controls. In particular, genes are expressed differently in the hippocampus and medial prefrontal cortex, which regulate cognitive function and memory, and in the striatum — a brain region that helps regulate and coordinate movement. The affected genes in the hippocampus and cortex are involved in fetal development, whereas those in the striatum tend to be expressed during early childhood.

“SHANK3 may pose its effect in different brain regions during different developmental periods, and may be affecting different mechanisms,” says Harony-Nicolas.

In contrast to rats with mutant SHANK3, those with mutations in both copies of SHANK2 play less than controls do when young and are less likely to interact with other rats as adults. Meera Modi, a neuroscience postdoctoral fellow at Pfizer in Cambridge, Massachusetts, presented the results.

The most significant features of the SHANK2 rats, however, are movements that resemble the repetitive behaviors seen in autism. The rats tend to repeatedly rear up in their cages and almost all of them circle incessantly.

To investigate the motivation driving these behaviors, the researchers tested how often the rats would press a lever for a treat. Once taught that pressing this lever leads to a reward, most rats press it multiple times, but give up eventually. The SHANK2 mutant rats press the lever about 100 times more for the same treat than controls do. Blocking the chemical messenger dopamine in the SHANK2 mutant rats stops this behavior.

The next step is to read the rats’ brain activity using electroencephalography during this test, Modi says. That would reveal whether behavioral training or drugs normalize the activity.

For more reports from the 2014 International Meeting for Autism Research, please click here.

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Autism development may be obscured by parents' memory

Jessica Wright
17 May 2014

Clear questions: Parents may be better able to assess their children's abilities when asked detailed questions that provide examples.

Parents may notice a loss of skills in their children as it is happening, but do not recall it clearly later on. The unpublished research, presented yesterday at the 2014 International Meeting for Autism Research in Atlanta, hints at a fatal flaw in diagnostic tools for autism that rely on parents' memory.

Regular screening by pediatricians would be a more reliable way to pick up early signs of autism, says Sally Ozonoff vice chair for research in psychiatry and behavioral sciences at the University of California, Davis MIND Institute, who presented the findings.

Another study presented yesterday suggests that parents' assessments better match those of clinicians if they answer detailed questions, rather than give ratings for abstract ideas.

Autism is usually diagnosed around 2 to 3 years of age, when problems with social skills and language become most apparent. The findings presented at the meeting suggest that most children with autism show a gradual decline in their social skills in their first two years of life, rather than a sudden loss of skills at that age.

"This kind of regressive onset or declining behaviors is more the rule than the exception in autism," says Ozonoff. "It isn't just the experts who can see it. The parents see it if they're rating that day in real time."

Missed memory:

Ozonoff and her colleagues have been following the development of infant siblings of children with autism, or baby sibs. These infants have a 20 times higher chance of developing autism than the general population.

At the meeting, Ozonoff presented data from 20 baby sibs, all of whom developed autism, along with 40 typically developing controls.

The children came into the clinic six times in the first two years of their life. At each visit, clinicians rated the children's social behavior -- for example, whether they looked or smiled at the examiners or responded to their own names. Parents also filled out the Autism Diagnostic Interview-Revised (ADI-R), a widely used diagnostic tool, at each visit.

Overall, the researchers found that 86 percent of the children showed declining social skills over the

first two years. The data from the parents is similar: Nearly three-quarters of the parents had noted a loss of social skills in their children when the researchers analyzed the parent assessments from each visit.

Surprisingly, however, only 6 of these same 20 parents said that their children had lost skills when they were asked this a year later. Relying on the ADI-R may mischaracterize the type of regression seen in these children, says Ozonoff. “This is a little scary for using the ADI-R, which is our only option once children are already diagnosed,” she says. “The majority are being classified into the wrong group.”

In a similar study, Suzanne Macari showed data comparing parent ratings on the First Year Inventory with in-depth clinical diagnosis using the Autism Diagnostic Observation Schedule, another popular diagnostic tool. The study included 95 baby sibs and 66 controls.

Overall, parent assessments differed significantly from those made by clinicians. For example, parents reported fewer problems with babbling, communication and gestures than the clinicians did. This may be because the children are more likely to interact with their parents at home than with an examiner in a clinic, says Macari, associate research scientist at the Yale Child Study Center in New Haven, Connecticut.

The parents’ ratings better matched those of the clinicians when the researchers changed the questions to be more specific. For example, asking “What do you have to do to get your child to turn towards you?” got more accurate responses than “Does you child answer to his name?”

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Some infants at risk of autism show improvements at 9 months

Jessica Wright
17 May 2014

Kay Hinton

Eye gaze: As they grow older, infants with autism spend less time looking at a woman's eyes in a video clip.

Some infant siblings of children with autism initially behave like children with the disorder, but show improvements in their social skills around 9 months of age. The unpublished research, presented yesterday at the 2014 International Meeting for Autism Research in Atlanta, suggests that these children possess a "resilience" that keeps them from developing autism.

"By understanding this phenomenon, we may get many more children who are at higher genetic risk to also end up unaffected," says Ami Klin, director of the Marcus Autism Center in Atlanta, who presented the findings. The 9-month mark may prove to be the ideal time for early interventions, he says.

So-called baby sibs of children with autism are at up to a 20-fold higher risk of autism compared with the general population. Many research groups track the development of baby sibs to identify early signs of autism.

Klin and his colleagues discovered this intriguing finding when following up on the results of an eye-tracking study published in November. The study made a splash in the popular media, reporting that baby boys later diagnosed with autism lose interest in others' eyes between 2 and 6 months of age.

The study assessed 11 baby sibs who developed autism and 25 typically developing controls ten times from 2 to 24 months of age. To measure early symptoms of autism, the researchers outfitted the infants with an eye-tracking device and noted how often they looked at the eyes of a friendly woman in a recorded video. "Eyes are not only the window to the soul, they are also the window to social neuroscience," says Klin.

At the meeting yesterday, Klin reported analysis from a few more children. As they grew up, 29 typically developing infants looked at the woman's eyes the same amount or more, he said. By contrast, 13 infants who were eventually diagnosed with autism focused on the eyes less and less with age.

This drop in eye contact may relate to when babies stop looking at eyes reflexively and start actively seeking them out as a form of communication, says Klin.

Klin also reported new findings from 28 baby sibs who do not have autism. Ten of these siblings have some symptoms of autism, however — a condition called the broad autism phenotype (BAP).

Of the 28 siblings, 16 have eye-tracking patterns that are nearly indistinguishable from those of controls. All but one of these siblings show no signs of autism.

The other 12 siblings showed a decline in eye contact in the first six months of life, similar to the infants who went on to be diagnosed with autism; 9 of these 12 siblings have BAP.

The findings suggest that these 12 siblings started off on a course toward autism, but at some point switched trajectories and started to improve, says Klin.

The researchers found that these siblings start to look more at eyes starting at 18 months of age, but that this "course correction" in fact begins at 9 months. This suggests that interventions for autism may need to start around the 9-month mark, says Klin. "We have a lot of nice treatment trials around 12 months," he says. "But maybe we are already starting a little bit too late."

For more reports from the 2014 International Meeting for Autism Research, please click here.

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Adults with autism may have high burden of health problems

Jessica Wright
17 May 2014

Aging in autism: Men over 50 with autism look old for their age and may move particularly slowly, with a rigid gait.

Adults with autism may suffer from various health problems, ranging from psychiatric conditions to motor symptoms that resemble Parkinson's disease, according to two studies presented Thursday at the 2014 International Meeting for Autism Research in Atlanta.

Some of the conditions may stem from people with autism feeling like outsiders in society, says Lisa Croen, director of the Autism Research Program at Kaiser Permanente, an integrated healthcare delivery system in California. Croen led one of the studies, which documents the health status of more than 2,000 adults with autism.

"From our experience, inclusion and feeling part of society really does impact on health status," says Croen. "It's very important to include adults with autism in all sections of society."

The findings are also of concern given the rising numbers of children diagnosed with autism, the researchers say. They highlight how little is known about adults with autism, many of whom may be misdiagnosed with other conditions.

"There is almost no literature on older adults with autism in the field, so we have virtually no knowledge base," says Joseph Piven, professor of psychiatry at the University of North Carolina at Chapel Hill, who presented the second study.

Piven and his colleagues pursued a "boots-on-the-ground approach," sending queries to nearly 14,000 households and contacting several health agencies in North Carolina. After three years of searching, they found 20 men with autism who were over 50 years old.

"I think the main finding is how hard it was for Joe Piven's group to find people," says Catherine Lord, director of the Center for Autism and the Developing Brain at New York-Presbyterian Hospital. Lord has followed children with autism over long periods of time, but was not involved in either new study.

Hidden adults:

Most of the men in Piven's group have markedly low intelligence quotients: 40 percent have IQs under 35 and about 60 percent have IQs below 50. This is probably because to be diagnosed with autism decades ago — when there was much less awareness about the disorder — they would have had

to have severe symptoms, says Piven.

One of the men in the study was among the first group of 11 people to be diagnosed by Leo Kanner in 1943. Some of the others received a diagnosis for the first time during the course of the study and had instead been diagnosed with disorders such as schizophrenia or bipolar disorder. “One of the big stories here is that there are people out there who are misdiagnosed. We just can’t find them,” Piven says.

A 2012 study found, for example, that about 10 percent of adult patients in a state psychiatric hospital have undiagnosed autism[1].

Of the 20 men in Piven’s group, 17 look older than their age, with a stooped posture, and about half have at least one symptom associated with Parkinson’s disease, including tremors, slow movement and rigid gait. About one-quarter of the group has two or more of these symptoms.

One of the men was already undergoing treatment for Parkinson’s disease, and the researchers referred two more for therapy. This is a possible prevalence of 3 in 20, which is much higher than the 1 in 1,000 rate of Parkinson’s in the general population, notes Piven.

“One of the big stories here is that there are people out there who are misdiagnosed. We just can’t find them.”

However, the results are preliminary, he cautions, and may be affected by the men’s medical history. Drugs for epilepsy, which commonly co-occurs with autism, can cause motor deterioration, for example.

Lord notes that many older adults with autism have spent time in institutions, where they might have received strong courses of drugs.

Motor deficits are also a common feature among children with autism, says Stewart Mostofsky, director of the Laboratory for Neurocognitive and Imaging Research at the Kennedy Krieger Institute in Baltimore, who was not involved in the study. Slow movement and rigid gait are more common than tremors, he says.

“It’s certainly possible that at least some of these features were present for many, many years, and possibly even in childhood,” Mostofsky says.

There may also be an underlying genetic overlap between autism and Parkinson’s disease, says Emanuel DiCicco-Bloom, professor of neuroscience at the Robert Wood Johnson Medical School at Rutgers University in New Jersey. A family of chemical messengers called monoamine neurotransmitters, which include serotonin and dopamine, are implicated in both disorders.

Health registry:

Piven and his colleagues are collecting detailed life histories for each of the participants, aiming to understand how the disorder manifests throughout a lifetime. In contrast, Croen’s study began with medical records to find and study a large number of adults with autism. She and her colleagues found 2,108 adults with autism enrolled in Kaiser Permanente.

They compared these adults — about 1,000 of them are over 30, and 300 are over 50 — with ten times as many controls matched for age and sex.

Overall, the adults with autism are more than twice as likely as controls to have depression, anxiety or

bipolar disorder, and to attempt suicide, the study found. They are also more likely to have diabetes, gastrointestinal disorders, epilepsy, sleep disorders and high blood pressure.

Interestingly, only the women with autism have a higher chance of having immune disorders than controls do. The rate of cancer is the about the same as in controls, despite the overlap between some autism and cancer genes.

People with autism are also half as likely as controls to use alcohol and to smoke, the researchers found. “The smoking [finding] is quite interesting,” says Lord. This may be because smoking and drinking are social activities and people with autism are less susceptible to peer pressure, she says.

Although health registries are rich with information, Piven warns against relying solely on their diagnosis of autism, which is based on insurance codes. When trying to find adults with autism in North Carolina, his team quickly found 20 people through a health registry — but later discovered that they had a form of dementia that leads to social deficits.

These individuals were diagnosed with autism only after their dementia set in, he says. “I think when you dig into these databases, you’re going to find all this crazy stuff.”

For more reports from the 2014 International Meeting for Autism Research, please click here.

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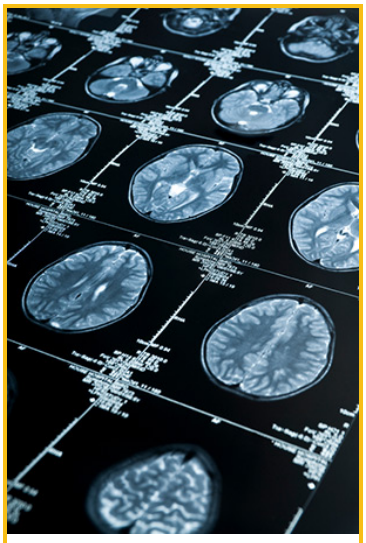
Autism-linked chromosomal region regulates brain size

Jessica Wright
16 May 2014



Growth area: Children with a deletion of the 16p11.2 autism-linked region have increased surface area in the outer folds of their brains.

The genes in 16p11.2, the autism-linked region on chromosome 16, may directly affect brain size early in development, according to unpublished research presented Thursday at the 2014 International Meeting for Autism Research in Atlanta.

Deletion of the region, which leads to autism in about 20 percent of people, results in enlarged brain size, a feature often seen in autism. The duplication results in an equivalent reduction in brain size.

The 16p11.2 region is a 600-kilobase stretch that encompasses 29 genes. About 1 percent of people with autism have a duplication or deletion, or copy number variant (CNV), of this region. Although only some people with the CNV have autism, all have psychiatric and neurological symptoms.

To unravel the importance of 16p11.2 in neurological disorders, researchers are thoroughly characterizing individuals with the deletion or duplication. So far, the project, dubbed the Simons Variation in Individuals Project (Simons VIP), has evaluated 113 people with a deletion and 107 with a duplication in the region. (The Simons VIP is funded by the Simons Foundation, SFARI.org's parent organization.)

One arm of this venture is using magnetic resonance imaging (MRI) to scan the brains of all participants who are older than 8 years and can tolerate brain imaging. The researchers presented results Thursday from 17 adults, 19 to 54 years of age, with a duplication and 25 children, 8 to 17 years of age, with a deletion. They compared these data with those from 33 and 29 age-matched controls, respectively. Four of the children with a deletion and one adult with a duplication have autism.

The deletion boosts overall brain size by 9 percent, whereas the duplication decreases it by the same amount, the study found. This change is seen consistently across all brain regions, with almost symmetrical changes from the duplication and deletion in each case. For example, the amygdala is about 3 percent larger in children with the deletion and 3 percent smaller in adults with the duplication.

Interestingly, the changes in brain size are also present in brain regions that form early in development, such as the thalamus, brainstem and cerebellum. This suggests that 16p11.2 may be involved in early embryonic development, says Abid Qureshi, a postdoctoral associate in Randy Buckner's lab at Harvard University.

Similarly, changes to the cortex suggest an early developmental role for 16p11.2. The cortex is the outermost layer of the brain, and is involved in most higher-order cognitive functions. As the cortex forms during fetal development, it first folds upon itself, building a large surface area. General thickening of the area tends to take place later.

Most of the brain size changes in the cortex were the result of alterations to the surface area, not volume, the researchers found. In children with the deletion, about 90 percent of the increase can be attributed to more surface area whereas in adults, roughly 80 percent of the decrease is the result of a smaller surface area.

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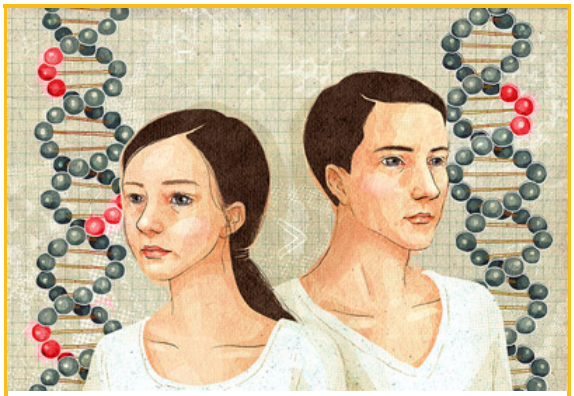
Distinct differences mark male, female autism brains

Jessica Wright
20 May 2014



Julia Yellow

Brain protection: Some brain regions that distinguish girls with autism may be linked to their ability to compensate for their problems.

Male and female preschoolers with autism have distinct sets of brain regions that distinguish them from typically developing controls, according to unpublished research presented Saturday at the 2014 International Meeting for Autism Research in Atlanta.

The findings suggest that differences in brain structure may underlie autism's gender bias. The disorder is four times more common in males than it is in females. Girls with autism tend to have more autism-linked mutations than do boys with the disorder. This has led some researchers to suggest that girls are somehow protected from autism, and need a heavier mutational burden than boys do to develop the disorder.

The data presented Saturday suggest that part of this protection may originate from differences in brain structure. Some of the brain regions that differ between girls with autism and female controls also generally distinguish typical girls from typical boys. These changes to 'female' brain regions also seem to track with the ability to adapt in girls with autism.

"These regions may not be associated with autism severity, but rather with some compensatory or adaptive function," says Christine Nordahl, assistant professor of psychiatry at the University of California, Davis MIND Institute, who presented the results.

Nordahl and her colleagues scanned the brains of 22 girls with autism and 27 age-matched female controls, as well as 134 boys with autism and 54 male controls. The researchers scanned the children while they slept to assess their brain structures. The children were all about 3 years of age and have similar intelligence quotients and autism severity.

The researchers divided the cortex — the outer layer of the brain, responsible for most higher-order functions — into 68 regions. They looked for differences in the size of these regions between the groups.

The boys and girls with autism each have brains that differ from those of their respective control groups, with changes in regions relevant to autism. Surprisingly, however, the changes in boys with autism are completely different from the changes in the girls with autism.

In girls, changes to the volume of the left superior temporal gyrus — a region critical for language

processing — are associated with greater autism severity. In boys, this is true for the left anterior cingulate, which has been linked to empathy and emotion.

Although the results are preliminary, the researchers hypothesize that the brains of girls with autism show evidence of compensatory mechanisms. Nordahl says she aims to recruit at least 90 more girls to balance the number of males and females in the study.

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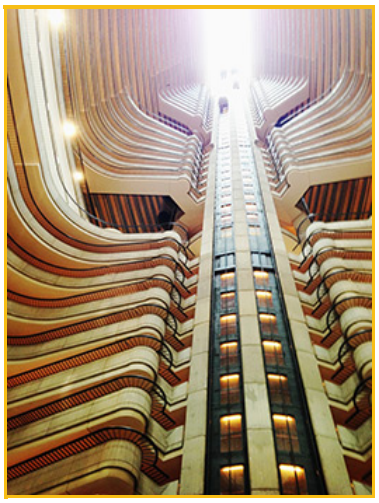
Takeaways from IMFAR 2014

Greg Boustead
22 May 2014



My final glass-elevator descent into the belly of the world's second largest atrium at Atlanta's Marriott Marquis — site of this year's International Meeting for Autism Research (IMFAR) — gave me a bird's-eye view of the hotel staff as they broke down the poster stands in the main conference hall.

The 50-floor trip also gave me a moment to reflect on some of the major themes addressed over the past several days.

One trend that dominated the presentations was a propensity for numbered lists. There were the five critical areas of focus Fred Volkmar outlined, the ten things IMFAR Advocate of the Year winner Peter Bell said researchers can do better, and the David Letterman-style 'Top ten ways to make it harder for us to give you money,' outlined by the Autism Science Foundation's Alison Singer.

In this spirit, I offer my three quick takeaways from IMFAR 2014:

1. Autism is growing up:

Judging from the topic of Friday morning's keynote address by Marsha Mailick, director of the Waisman Center at the University of Wisconsin-Madison, the new epidemiological data two sets of researchers released on the health of adults with autism, and the focus of two of the conference's scientific panels, it seems evident that researchers are taking an increasingly closer look at adults with autism.

"The biggest theme is adult outcomes," Jeremy Veenstra-VanderWeele, associate professor of psychiatry at Vanderbilt University in Nashville, Tennessee, said during our Twitter Q&A. "This year is a coming out party for grownups."

In another way, the field itself is growing up. The record turnout at this year's conference and the unprecedented amount of money going toward autism research underscores the field's increasing maturity.

Still, autism is a relatively new area of study. Yale University's James McPartland put this in perspective with his take on the conference: "It's amazing to think that, despite how much we have yet to learn, everything we know about autism has been learned in a person's lifetime."

2. The future looks promising:

On Wednesday, a large portion of IMFAR's approximately 500-strong student and postdoctoral members assembled for a hands-on grant-writing workshop. After an overview of research priorities

by funding agencies, groups of students were matched with senior investigators to fine-tune grant proposals and get candid feedback.

An oft-emphasized priority of this year's meeting was to engage early-career autism researchers and connect them with quality mentorship opportunities.

"The enthusiasm and passion of the students here is an inspiration," Francesca Happé, president of the International Society for Autism Research, tweeted during our Q&A chat.

The organizers suggest that the workshop will be a permanent and perhaps expanded fixture of the IMFAR program in future years.

3. Scientists get social:

On Friday afternoon, we hosted a Twitter Q&A chat as a way to generate an open dialogue among researchers, clinicians and stakeholders about the current state of autism research and how to move it forward.

According to Keyhole, an analytics service that tracks social media statistics, the chat involved more than 1,300 posts appearing in the feeds of more than 300,000 Twitter users.

Singer suggested that the biggest breakthrough of the meeting was, perhaps, "dozens of scientists, on Twitter chat, communicating directly with public."

A full transcript of the discussion can be found here, and I've highlighted a handful of threads from the chat below.

Twitter Q&A summary:

What are the most important autism findings that came out this year?

> **William Mandy, University College London**: "In terms of diagnosis, the Huerta et al. study did a lot to calm fears about the impact of DSM-5."
>
> **Peter Bell, Eden Autism Services**: "I'm most encouraged to see more attention being devoted to adult services and lifespan issues of those living with autism."
>
> **Pamela Feliciano, SFARI**: "I am really interested in all of the work that EU-AIMS is doing to promote viable objective clinical trial outcome measures."
>
> **John Elder Robison, author of *Look Me in the Eye***: "I am happy to see more of the research focused on the deliverable end of the range, as opposed to basic research. Basic science is good but we need to always deliver value to our community if we want to build their support."

How can advocacy groups contribute to autism research and what can researchers learn from stakeholders?

> **James McPartland, Yale Child Study Center**: "Stakeholders can guide our priorities and help us understand what matters to those living with ASD."

Michael Rosanoff, Autism Speaks: “Common theme of IMFAR 2014: individuals, parents and communities must be partners — not subjects — in autism research.”

Feliciano: “We need science communicators to help dispel myths. Parents’ first question to me should not be about vaccines.”

Kevin Pelphrey, Yale Child Study Center: “I consult with a person with autism every day. Very helpful, and keeps me honest.”

What do think is the best emerging biomarker that could identify subgroups of autism?

McPartland: “Integrating multimodal biomarkers — EEG, eye-tracking, fMRI — is key for identifying subgroups.”

Jeremy Veenstra-VanderWeele, Vanderbilt University: “We need to start looking at the edges of distributions, rather than total ASD versus control comparisons.”

Mandy: “Weak central coherence [is] not a biomarker, but a cognitive endophenotype that may delineate a subgroup.”

Robison: “We have to be careful with biomarkers; the same marker could portend crushing disability or eccentric geekiness. How to tell?”

The Centers for Disease Control and Prevention released new numbers estimating that 1 in 68 have autism. What do you tell people when they ask about an 'epidemic'?

Chris Gunter, Marcus Autism Center: “I get asked about 'epidemic' very often. I explain that our diagnosis and ascertainment has continued to improve over time.”

Mandy: “I think the expectations we place on children's social skills and behavior continue to rise — which means more get labeled.”

Pelphrey: “I tell them an epidemic is 'a widespread occurrence of an infectious disease in a community at a particular time.'”

Robison: “The rising autism prevalence numbers show that we are a formerly invisible army, emerging into the light.”

How can we address the shortage of brain tissue donated from people with autism, and how might such tissue help research?

David Amaral, MIND Institute at the University of California, Davis: “We need ambassadors to spread the word that lack of donated postmortem brain is holding up progress. Help us!”

Francesca Happé, King's College London: “We'll look back and laugh to think we hoped to understand ASD with so few brain samples. Great new initiative.”

What kind of autism research would you like to see this coming year?

Veenstra-VanderWeele: “Continuing trend for research that carefully studies defined subgroups that may respond to treatments.”

Happé: “I want to know whether the women with ASD who fly 'under the radar' are coping or suffering in silence.”

Pelphrey: “Test claims of early indicators in a population sample to have a better sense of true predictive value.”

Robison: “Most studies are still focused on failures. It's worth researching how to develop our strengths.”

Reactions from IMFAR 2014

Greg Boustead
16 May 2014

We checked in from Atlanta, Georgia, where the 2014 International Meeting for Autism Research ran 14-17 May. Read below for daily posts about the conference and initial reactions from the attendees.

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17 May 2014: Final Morning

Saturday brought the lone purely genetics-focused oral session of the conference, with new work suggesting that one of autism's strongest risk genes may lead to the discovery of a large set of more 'high-confidence' risk genes. Our on-site reporter, Jessica Wright, covered the finding here, along with many other breaking reports from the conference, all of which can be found in our IMFAR 2014 section.

Overall, this year packed an ambitious agenda into a precious two-and-a-half day window. Hats off to the organizers for making key adjustments to the program format. For instance, tweaking the timing of the poster sessions (and adding a cash bar!) to make them more social and interactive proved a much-appreciated change, according to the attendees I spoke with. Similarly, the early-career workshop was a real hit with both the trainees and mentors who participated.

See reactions from attendees below, and you can find my final meeting wrap-up here.

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16 May 2014: Day Two

David Mandell
Director, Center for Mental Health Policy and Services Research, University of Pennsylvania Perelman School of Medicine

Good news, bad news: "This morning's keynote by Marsha Mailick was both depressing and inspiring. Her finding that adults show such great decline in middle age, on average, is depressing. On the other hand, it was exciting and surprising to see that symptom profile continues to change in adulthood."

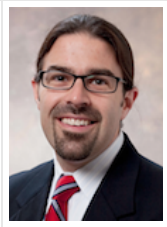
Not just children: "This suggests continued brain plasticity during this period and speaks to the urgent need to develop interventions and community supports for this group with the same intensity and rigor that we apply to interventions for young children. Particularly striking was that adults in

structured day settings, including jobs, showed continued reductions in autism symptoms."

David Skuse
Chair, Behavioural and Brain Sciences, University College London

Diagnosis as guide: "So far, a highlight for me was the panel organized by Eric London, on 'Characterising autism: a re-examination of the diagnosis and the phenotype.' London suggested adoption of a meta-structure of neurodevelopmental disorders where the 'disorders' are characterized in multidimensional terms. The diagnosis of autism should be seen as a tool to inform clinical and educational decision-making, rather than a phenotype that reflects a valid disorder with a discrete biological substrate."

Patient view: "With regard to the discussion of the National Institutes of Health's Research Domain Criteria (RDoC), specifically, Ann Wagner said that diagnostic categories such as autism spectrum disorder were never intended to reflect biological reality. But there was a concern expressed by others that as the biological processes envisaged by the RDoC project may take decades to be elucidated, what are the likely benefits to patients of the project going to be in the meantime?"



James McPartland
Director, Yale Developmental Disabilities Clinic

So far: "Marsha Mailick opened her outstanding keynote by reflecting on the fact that the 8-year-olds in Leo Kanner's original study would now be 79 on average. It's amazing to think that, despite how much we have yet to learn, everything we know about autism has been learned in a person's lifetime. Not bad."

Road ahead: "Marsha's talk also highlighted a few key targets for progress. Given the evidence that successful vocational experience predicts behavioral improvement, the attrition of women from vocational settings must be addressed. Why are women more likely to participate for fewer hours over time? The poorer trajectory for lower-income families transitioning out of high school makes clear the need for more publicly funded services at this transition."

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15 May 2014: Day One

Helen Tager-Flusberg
Director, Research on Autism & Developmental Disorders, Boston University

Machine diagnosing: "One really provocative presentation today was by Colleen Chen and her colleagues at San Diego State University on using resting-state functional magnetic resonance imaging (fMRI) data to predict autism classification. They used data from the Autism Brain Imaging Data Exchange (ABIDE)— a collaborative database — which allowed them to analyze data using very cool machine-learning algorithms from large numbers of participants with autism and age-matched controls. Their analysis looked at connectivity between regions of interest, and this approach led to over 90 percent correct classification, which is pretty impressive!"

Surprising connections: "Of greatest interest to me was the fact that the connections that were most significant in the prediction algorithm involved somatosensory and motor regions and the default network, even though we might have expected that social regions would have also been significant predictors. This new approach to fMRI data from people with autism, made possible by the ABIDE data repository, allowed the researchers to begin analyses based on much larger sample sizes

than we have seen before."

Joseph Piven
Professor of Psychiatry, University of North Carolina School of Medicine; Director of the Carolina Institute for Developmental Disabilities,

Euro-vision: "Of all I heard today, what stood out was the keynote of Declan Murphy. What I found so inspiring was the level of organization and cooperation in Europe between multiple (14!) academic centers, Autism Speaks and industry under the umbrellas of the Innovative Medicines Initiative and the EU-AIMS project. I think this is extraordinary and what will be required to launch the various pipelines of translational research — from cells to services — that are our best hope to move forward with effective treatments.

Back home: "The follow-up experiment? I think we need to figure out how to raise the level of interdisciplinary collaboration in the U.S."

Catherine Lord
Director, Center for Autism and the Developing Brain, Weill Cornell Medical College, Columbia University

Pointed questions: "I attended a very good session today (Gesture, Speech and Social Communication) that addressed many aspects of communication in children with autism and raised fascinating questions about which aspects of communication are inherently entwined or linked with each other or other factors — for example, general intelligence and social motivation — and which represent separate systems. New findings presented during the session show that the use of pointing gestures — but not other gestures — predicts acquisition of vocabulary, and that deaf children with autism use fewer person-related but not object-related pointing gestures."

Hand to mouth: "Such results, coupled with other associations discussed, between heart rate variability when listening to speech and later language development in autism, suggest that we need to consider different pathways to language development and delays."

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14 May 2014: Live Twitter chat from #IMFAR2014 on Friday

On **Friday, 16 May, at 2 p.m. Eastern**, we'll host a moderated Q&A via Twitter, live from the floors of the 2014 International Meeting for Autism Research in Atlanta. The chat will appear on @SFARIorg with the hashtag #IMFARchat.

The discussion will gather key researchers, stakeholders and journalists at the conference and from around the world to react to some of the major themes and open questions that emerge during the meeting.

Some of the participants confirmed to join us so far include Francesca Happé, president of the International Society for Autism Research; Kevin Pelphrey, director of the Child Study Center at Yale University School of Medicine; Alison Singer, president of the Autism Science Foundation; David Amaral, director of research at the MIND Institute at the University of California, Davis; leading members of the research and advocacy organization Autism Speaks and many more.

To join the conversation, log into Twitter at the scheduled time and follow @SFARIorg and hashtag #IMFARchat. If you prefer more of a chat-room experience, you can also participate in the

#IMFARchat discussion room found here.

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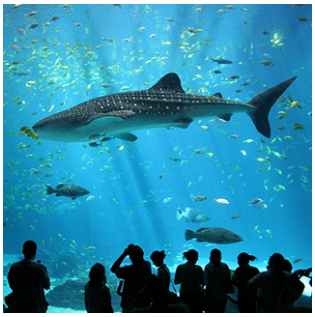
13 May 2014: Heading to Atlanta

Tomorrow night kicks off the 13th International Meeting for Autism Research (IMFAR), with an opening reception among beluga whales and bottlenose dolphins at the Georgia Aquarium in downtown Atlanta.

As far as autism meetings go, IMFAR is the biggest — this year it will host more than 1,500 experts from 40 countries. It's also unique in that it brings basic researchers, clinicians and advocacy groups under one roof — key for a diverse and complex disorder such as autism.

This year's agenda includes an early-career workshop, as well as daily 'Meet the Experts' luncheons for students and trainees — all part of the conference's growing focus on young researchers.



A buzzing metropolis and deep-fried cuisine replace the quaint seaside hills and bar *pintxos*of San Sebastián, Spain (home of last year's IMFAR), as the conference returns to the U.S.

Atlanta makes sense as a host city for the conference. Apart from being a research hub, it is also home to one of three national Autism Centers of Excellence, a consortium of interdisciplinary laboratories focused on investigating the disorder.

Here on SFARI.org, you can expect regular breaking news coverage and analysis of noteworthy findings presented at the meeting. Keep up to date here.

And watch this space for daily reactions from speakers and attendees at the meeting. As we did last year, we'll highlight a range of initial perspectives from the conference floor.

On Friday, we'll host a live Twitter Q&A to reflect on some of the major themes and open questions that emerge during the meeting. The discussion will include, among others, Francesca Happé, president of the International Society for Autism Research.

The chat will take place at 2 p.m. Eastern on 16 May. Find us on Twitter at @SFARIorg and follow along using hashtag #IMFARchat. (I'll post further details on other participants tomorrow.)
