Top Ten Autism Research Advances of 2012

Autism Speaks annual "best of" features progress in environmental science, adult support, medicines development and more

In 2012, autism dominated headlines as never before. Public awareness skyrocketed with new updates on autism's estimated prevalence (1 in 88) and costs to society ($137 billion per year nationally). Controversy roiled around proposed changes to how autism spectrum disorder (ASD) will be diagnosed in the years ahead.

Behind the headlines – or at least off the front page – the field of autism research experienced a significant growth in the number of publications and scientists entering the field. In recent years, the field has drawn hundreds of talented scientists from other areas of science. In 2012, we saw many of these teams publishing important findings that confirmed and built on the pioneering discoveries of previous years.

We think you'll see this growth on the pages of this, our fourth annual "Top Ten" report. Instead of isolated breakthroughs, many of this year's top advances represent broad progress in areas of autism science and involve multiple research teams at sites across the nation and the world.

Some of these advances helped solidify relatively new fields of autism research such as environmental science and translational research. We saw a deeper understanding of possible links between environmental exposures, genetic vulnerability and autism risk. We saw real progress in safely moving promising medicines out of the laboratory and into clinical trials.

The year likewise brought progress in more established areas of autism science, including genetics and behavioral therapies. This included evidence that intensive early intervention can change autism's underlying brain biology and new insights into the complexity of autism genetics. Some of these genetic discoveries also held promise for identifying new targets for treating autism's core symptoms.

As always, our choice of the year's most important advances in autism research was guided by the expertise and perspective of Autism Speaks dedicated Scientific Advisory Committee and its science department leadership. In no way is it meant to be exhaustive.

We hope you'll enjoy this update. It represents a step forward in a process that we hope to accelerate through our research funding at Autism Speaks.

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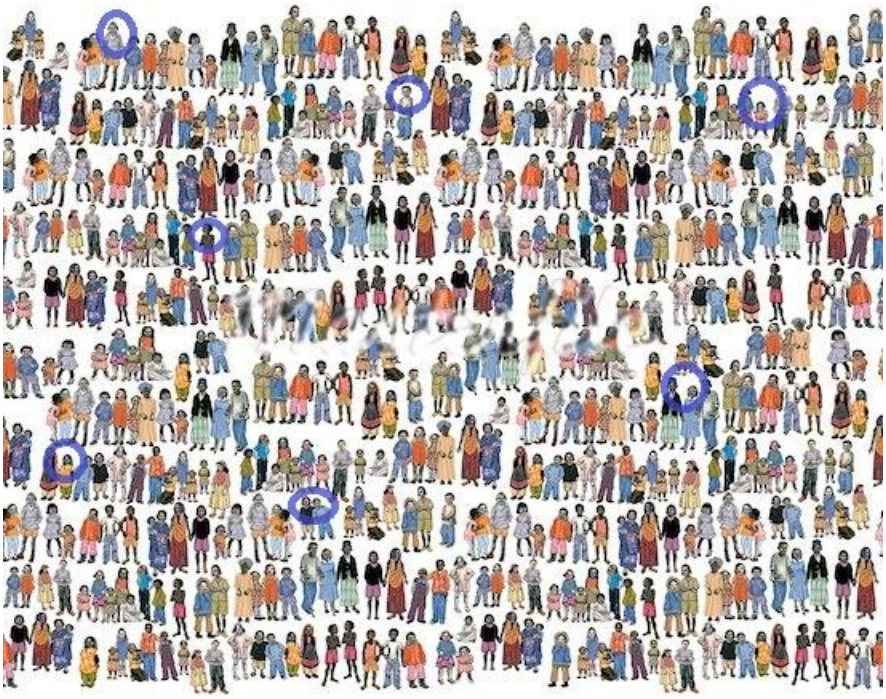
CDC Revises Estimate of Autism Prevalence: 1 in 88

Continuing increase in prevalence reaffirms public-health crisis



In March, the Centers for Disease Control and Prevention (CDC) significantly revised the estimated prevalence of autism in the United States. The new number – 1 in 88 children.

This represents a 23 percent increase from the CDC's previous estimate of 1 in 110 children, reported in 2009. It's a 78 percent increase over the agency's 2007 estimate of 1 in 150. Consistent with previous estimates, the updated numbers remained heavily skewed toward boys – affecting an estimated 1 in 54, compared with 1 in 252 girls.

"The CDC's new estimates of autism prevalence demand that we recognize autism as a public health emergency warranting immediate attention," said Autism Speaks Chief Science Officer Geraldine Dawson, Ph.D. "It is a crisis of epidemic proportions – and not just among children." (See related Top Ten story: "Mounting Evidence of Critical Need for Adult Transition Support.")

The CDC analysis comes from its Autism and Developmental Disabilities Monitoring Network, with sites in 14 states. The researchers reviewed the health and special education records of tens of thousands of 8 year olds in the 14 communities. They looked for a diagnosis of autism spectrum disorder (ASD) or the symptoms that would add up to one.

As in previous CDC reports, prevalence figures varied widely between sites – suggesting possible differences in screening programs and the availability of records. The researchers also found evidence of a persistent but narrowing gap between white and minority children. The estimated prevalence for white children was 1 in 83. This compared with 1 in 127 for Hispanics

and 1 in 98 for African Americans. Here, too, the findings may reflect differences in community screening and services – rather than true differences in prevalence.

More research is needed to understand the situation and address persistent gaps, said Michael Rosanoff, M.P.H., Autism Speaks associate director of public health research and scientific review.

“More attention must be paid, not only to the increasing number of identified cases, but also to the cases still being missed,” he explained. “Autism Speaks is committed to closing the gap in access to early detection and early intervention services, particularly among ethnic minorities and other underserved communities.”

Evidence suggests that autism’s true prevalence in the United States may be considerably higher, he added. A 2011 South Korean study, for example, directly screened grade-schoolers for ASD rather than relying on medical or educational records. It found a prevalence of 1 in 38 among the schoolchildren, two-thirds of whom had previously gone undiagnosed. As such, they would have been missed by the records-review approach the CDC currently uses in its estimates.

Autism Speaks funded the South Korea study and is now funding a similar direct-screening study in South Carolina. It is doing so in collaboration with the CDC’s monitoring site in that state. “This project aims to not only improve the accuracy of autism prevalence estimates, but also to understand the factors that influence why we may be missing diagnoses,” Rosanoff said. Such factors may include differences in community awareness and access to autism screening and services.

“More than ever, these numbers compel us to redouble our investment in the research that can provide more accurate estimates in the US and help us understand the causes of the increases in prevalence we have witnessed,” Dr. Dawson concluded.

Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators. Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill Summ*. 2012; 61(3): 1-19.

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Field Trials Suggest New Criteria for Diagnosing Autism 'Reliable'

American Psychiatric Association approves DSM-5 changes; autism advocates call for further study

Autism experts and families have long been concerned about inconsistencies in how clinicians diagnose autism spectrum disorders (ASD). Though U.S. doctors and therapists use the same checklist of symptoms, they tended to vary in how they applied them. What one clinician diagnosed as autistic disorder, another would call Asperger syndrome or pervasive developmental disorder not otherwise specified (PDD-NOS). Some clinicians misdiagnosed autism in children with related conditions such as language disorder, or vice versa.

So the American Psychiatric Society assembled a committee of experts to improve the criteria used to diagnose ASD. The committee developed a diagnostic definition of autism that they judged to be less subjective and more reliable. Those changes are now slated to become part of the fifth edition of the *Diagnostic Statistical Manual of Mental Disorders* (DSM-5), scheduled for publication in May 2013.

The proposed revision – which generated tremendous public comment throughout 2012 – introduced two fundamental changes.

* First it collapsed previously distinct autism subtypes – including autistic disorder and Asperger syndrome – into one unifying diagnosis of ASD.

* Second, the current three symptom domains of social impairment, communication deficits and repetitive/restricted behaviors were folded into two – social communication impairment and repetitive/restricted behaviors.

"The changes have a strong scientific rationale," said Autism Speaks Chief Science Officer Geraldine Dawson, Ph.D. "However, they are more than an academic exercise. They will impact how ASD is diagnosed, can affect access to services and will influence how the prevalence of ASD is measured."

In 2012, DSM-5 studies began to address the concerns of parents and autism advocacy groups (Photo courtesy the CDC)

Indeed, some research suggested that certain individuals currently diagnosed with ASD might lose their diagnosis under the new system. For this reason, the National Institutes of Health (NIH) and Autism Speaks funded studies to better gauge the effects of the proposed changes. (See Autism Speaks DSM-5 study grants, here.)

In October, the *American Journal of Psychiatry* published the results of the first NIH study to analyze a large number of records of individuals diagnosed with ASD using the DSM-IV. It explored whether the cases examined would retain their diagnosis of ASD based on the DSM-5. While preliminary, the results were reassuring.

The study involved an expert review of more than 5,000 case files of children who had been evaluated for ASD under the DSM-IV criteria. The team, led by psychologist Catherine Lord, Ph.D., of New York's Weill Cornell Medical College, applied the DSM-5 criteria to the symptoms recorded in the children's records. This included both children diagnosed with autism and some who were not.

The study found that the new DSM-5 criteria did not miss a significant number of previously diagnosed children. However, the study was based on a retrospective analysis of medical records. Still needed was a prospective study – with clinicians applying both old and new criteria to the diagnosis of actual children.

November brought the results of the first DSM-5 field trial. The three-part report likewise appeared in the *American Journal of Psychiatry*.

This field trial involved the evaluation of 63 school age children in Massachusetts and California. It, too, found diagnoses using the DSM-5 criteria to be reliable. When one clinician diagnosed a child with ASD using the new criteria, the second clinician was very likely to do so as well. The study also showed that the large majority of children who met the DSM-IV criteria for a disorder on the autism spectrum would retain a diagnosis of ASD.

The results are promising, but more studies need to be conducted to ensure that affected individuals don't lose access to services, Dr. Dawson said. "This is a relatively small sample of school age children from largely Caucasian backgrounds," she noted. "Adults with autism were not included, so we don't know how the proposed diagnostic criteria might affect them. We also don't know how the proposed changes will affect diagnosis of very young children."

Dr. Dawson and other autism experts agree it's crucial to gain a better understanding of how the DSM-5 criteria will affect autism prevalence estimates – which in turn could influence the nation's public health priorities. Autism Speaks is currently funding a study, in collaboration with the Centers for Disease Control and Prevention (CDC), to better address this issue.

"As these new diagnostic criteria come into use, we need to closely monitor how they affect people in our communities," Dr. Dawson concluded. "At Autism Speaks, we remain committed to getting answers to these questions and ensuring that all individuals receive the interventions and services they need."

Huerta M, Bishop SL, Duncan A, Hus V, Lord C. Application of DSM-5 Criteria for Autism Spectrum Disorder to Three Samples of Children With DSM-IV Diagnoses of Pervasive Developmental Disorders. *Am J Psychiatry*. 2012; 169(10): 1056-64.

Regier DA, Narrow WE, Clarke DE, et al. SM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses. *Am J Psychiatry.* Advance online 30 Oct 2012.

Narrow WE, Clarke DE, Kuramoto SJ, et al. DSM-5 Field Trials in the United States and Canada, Part III: Development and Reliability Testing of a Cross-Cutting Symptom Assessment for DSM-5. *Am J Psychiatry*. Advance online 30 Oct 2012.

Clarke DE, Narrow WE, Regier DA, et al. DSM-5 Field Trials in the United States and Canada, Part I: Study Design, Sampling Strategy, Implementation, and Analytic Approaches. *Am J Psychiatry*. Advance online 30 Oct 2012.

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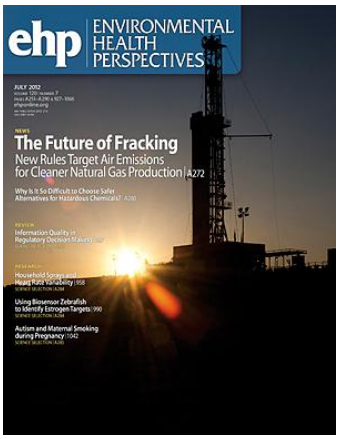
Deeper Understanding of Link between Chemical Pollutants and Autism

The year brought advances in understanding whether and how chemical pollutants affect brain development in ways that may predispose to autism

Most scientists agree that autism involves early changes in brain development. Decades of research have clearly implicated genes that regulate how brain cells and networks develop and interconnect. This year brought increased evidence that chemical pollutants may similarly affect brain development in ways that increase autism risk.

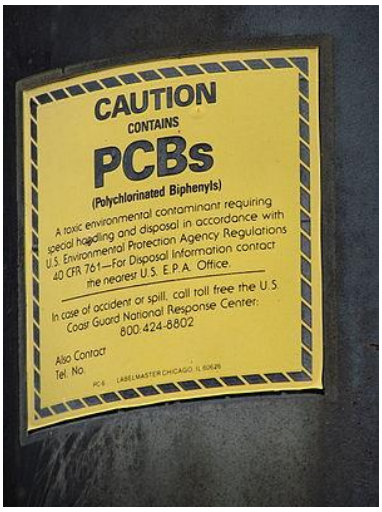
"Environmental studies have been historically underfunded," said Alycia Halladay, Ph.D., Autism Speaks senior director of environmental and clinical sciences. "This year we saw a greater emphasis on studies that examine the link between chemical pollutants and autism. Taken together, they show that exposure can affect the developing brain in ways that may lead to autism."



The July issue of the journal *Environmental Health Perspectives* featured five articles exploring how exposure to certain pollutants may contribute to the development of autism spectrum disorder (ASD).

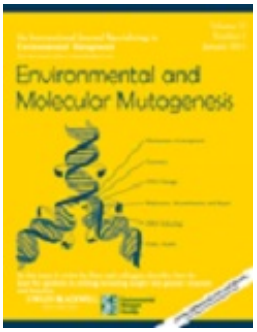
In "Tipping the Balance of Autism Risk," scientists with the University of California's MIND Institute reviewed past research on pesticide exposure, brain development and ASD. They concluded that evidence strongly suggests that certain pesticides can increase the risk for autism. They noted, however, that too little is known about how the timing or dose of exposure influences risk – or the biological mechanisms involved.

Three of the issue's research reports helped address these questions. Two focused on polychlorinated biphenols (PCBs). This class of toxic industrial chemicals became widespread in the environment before the U.S. Congress banned their use in 1979. One of the studies used tissue cultures and the other laboratory rats to show how exposure to PCBs can disrupt the development of crucial connections between brain cells. Both studies involved exposure to PCBs at levels still commonly found in the environment.



Another research team examined a possible link between autism and smoking during pregnancy. Based on a large review of birth certificate records, their study included information on more than 3,000 children diagnosed with autism. They found no overall association between smoking during pregnancy and autism. However, they detected a small increased risk for Asperger syndrome. The researchers called for larger and more focused studies to confirm or rule out this possible association. (More on this special issue of *Environmental Health Perspectives* here.)

Following up on the suspected link between PCBs and autism, another MIND Institute research team compared levels of PCBs in the postmortem brain tissue of individuals with autism with those in brain tissue unaffected by autism. They found elevated levels of one PCB – PCB-95 – in the brains of those with a form of autism linked to mutations on chromosome 15. Only those with these mutations showed the increased PCB, for reasons that remain unclear. However, the researchers suggested that the mutation might affect the body's ability to clear PCBs from the body.



The investigators also analyzed the brain tissue for DNA methylation, an epigenetic marker associated with reduced gene activity. They found significant decreases in methylation in the brains with the highest PCBs. This suggested that gene activity may have been abnormally "switched on" in ways that disrupt normal brain functioning. Appearing in the August issue of the journal *Environmental and Molecular Mutagenesis*, the study was made possible by postmortem donations to Autism Speaks Autism Tissue Program.

In yet another landmark environmental study this year, researchers reported some of the first direct evidence of an association between air pollution and autism. A team led by Heather Volk, Ph.D., of the University of Southern California's Keck School of Medicine, associated exposure to high levels of air pollution during pregnancy and the first year of life with a three-fold increase in autism risk. Their report

appeared in a November issue of the *Archives of General Psychiatry.*

Dr. Volk's team looked at air pollution records associated with the geographic location of more than 500 children and their mothers. The families were part of the California-based Childhood Autism Risks from Genetics and the Environment (CHARGE) study. Roughly half of the children had autism.

"This work has broad public health implications," Dr. Volk said. "We've known for a long time that air pollution is bad for our lungs, especially for children. We're now beginning to understand how air pollution may affect the brain." Dr. Volk and her colleagues are currently pursuing a study supported by Autism Speaks that explores how genetic predisposition to autism may increase vulnerability to certain pollutants. (More on Dr. Volk's research here.)

Shelton JF, Hertz-Picciotto I, Pessah. Tipping the Balance of Autism Risk: Potential Mechanisms Linking Pesticides and Autism. *Environ Health Perspect*. 2012; 120(7): 944–951.

Wayman GA, Yang D, Bose DD, et al. PCB-95 Promotes Dendritic Growth via Ryanodine Receptor–Dependent Mechanisms. *Environ Health Perspect*. 2012; 120(7): 997–1002.

Wayman GA, Bose DD, Yang D, et al. PCB-95 Modulates the Calcium-Dependent Signaling Pathway Responsible for Activity-Dependent Dendritic Growth. *Environ Health Perspect*. 2012; 120(7): 1003–1009.

Kalkbrenner AE, Braun JM, Durkin MS, et al. Maternal Smoking during Pregnancy and the Prevalence of Autism Spectrum Disorders, Using Data from the Autism and Developmental Disabilities Monitoring Network. *Environ Health Perspect*. 2012; 120(7): 1042–1048.

Landrigan PJ, Lambertini L, Birnbaum LS. A Research Strategy to Discover the Environmental Causes of Autism and Neurodevelopmental Disabilities. *Environ Health Perspect*. 2012; 120(7): a258–a260.

Mitchell MM, Woods R, Chi LH, et al. Levels of select PCB and PBDE congeners in human postmortem brain reveal possible environmental involvement in 15q11-q13 duplication autism spectrum disorder. *Environ Mol Mutagen*. 2012; 53(8): 589-98.

Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. Traffic-Related Air Pollution, Particulate Matter, and Autism. *Arch Gen Psychiatry*. Published online Nov 2012.

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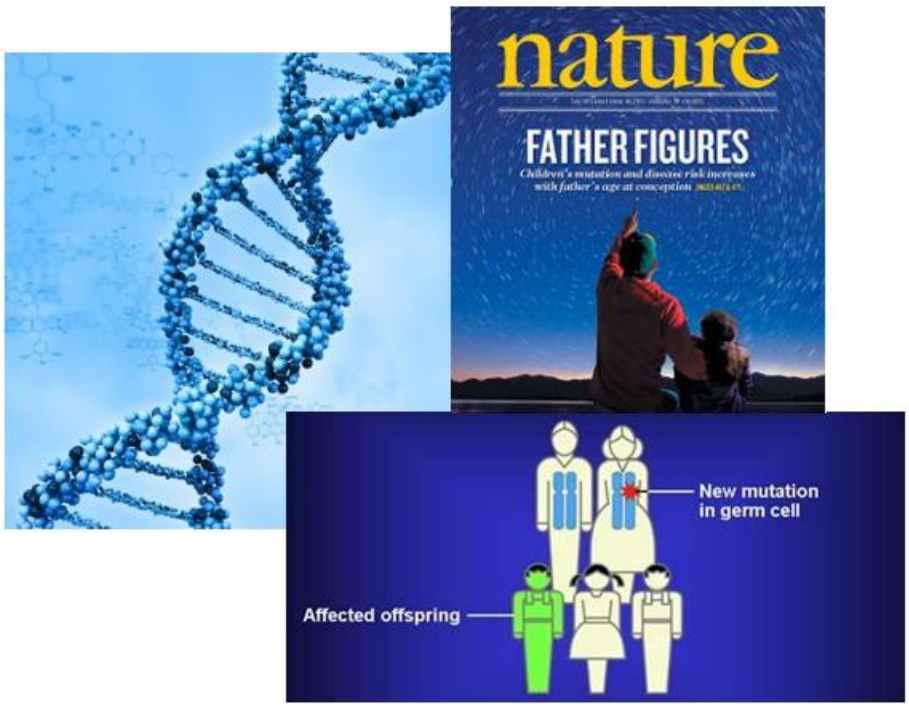
Hundreds of Tiny Mutations Linked to Autism

Many arise spontaneously in germ cells; may explain why autism risk higher among children of older fathers



Over the last 20 years, researchers have uncovered a number of genes that greatly increase the risk of autism. These high-impact genes account for a relatively small percentage of autism cases. Still, scientific evidence remains strong that genes play an important role in the development of autism.

This year, a group of papers helped shed light on what may be autism's missing genetic "dark matter." Together, they show that that hundreds of tiny mutations – not just handful of high-impact genes – may contribute significantly to the development of autism spectrum disorder (ASD).

Any one of these small gene changes is rare. But together with other mutations known to be associated with autism risk, they may be involved in the development of nearly a quarter of ASD cases. Importantly, many are *de novo*, or spontaneous, mutations. They show up in the genes of children but not their parents. Most likely, they arise in sperm, egg or very early embryo development.

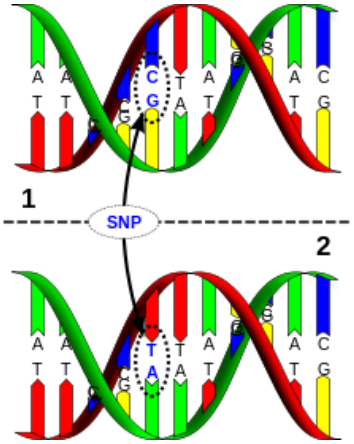
Moreover, the studies found these tiny mutations to be more abundant in children born to older parents – especially older fathers.

In the four papers, published by different research teams in the highly respected journal *Nature,* scientists used DNA sequencing to examine the genomes of families with one child affected by autism. Specifically, they scanned for de novo changes in the active, or protein-coding, part of the genome. This "exome" makes up about 2 percent of our total genome.

All people have some de novo changes in their DNA. Most prove harmless – so long as they do not affect crucial areas of the exome. However, all four *Nature* studies indicated that such mutations were significantly more common in those with autism. This would increase the likelihood that one or more would affect a gene critical to early brain development.

"These findings spotlight a possible gene-environment interaction associated with increased risk of autism," commented Andy Shih, Ph.D., Autism Speaks senior vice president for scientific affairs. "If the children of older fathers have significantly more tiny mutations in their DNA – as these studies suggest – it may be that increased age brings cumulative exposure to influences that produce gene changes in the father's germ cells." These genetic glitches could then end up in a child's DNA.

Such studies also illustrate how scientists are using new tools and approaches to expand the search for autism's genetic risk factors and the environmental factors that may interact with them, Dr. Shih added. "They also shed light on *why* the children of older parents – particularly older fathers – are at higher risk for developing ASD."



A single nucleotide polymorphism (SNP) involves a change in just one nucleotide pair.

The small genetic glitches the studies found include single nucleotide polymorphisms (SNPs) and copy number variations (CNVs). SNPs involve a switch in a single DNA nucleotide pair. (See image at right.) CNVs include duplications or deletions of longer DNA sequences – including entire genes.

In the first of three papers in the April 4 issue of *Nature*, a team of researchers from across the United States identified hundreds of spontaneous mutations in the DNA of children with autism. They also found that the mutations were increasingly frequent in children born to older fathers.

In the issue's second paper, researchers from the University of Washington, Seattle, described their discovery that spontaneous mutations associated with ASD come primarily from the father and increase in frequency with a father's age at time of conception.

In the third paper, another multi-center team of U.S. researchers described sequencing all the protein-coding genes of 175 persons with autism and their parents. They found CNVs in more than a hundred genes previously associated with increased risk of autism.

In *Nature's* August 23 issue, Icelandic scientists likewise reported that children of older men had a greater number of *de novo* mutations than children fathered by younger men. The researchers analyzed the whole genome of 78 trios (mother, father and child). In each trio, the child had been diagnosed with autism or schizophrenia, but neither parent had signs of either disorder. They found that the number of de novo mutations in a child's genome increased with the father's age – by around two per year. The study also found a slight association between a mother's age and these mutations.

"Taken together, these findings are starting to give us a better picture of the biology of autism, of the possible underlying disease mechanisms," said Dr. Shih. "They are one piece of a larger puzzle that is helping us understand the causes of autism."

Kong A, Frigge ML, Masson G, et al. Rate of de novo mutations and the importance of father's age to disease risk. *Nature*. 2012; 488(7412): 471-5.

Sanders SJ, Murtha MT, Gupta AR, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. *Nature*. 2012; 485(7397): 237-41.

O'Roak BJ, Vives L, Girirajan S, et al. Sporadic autism exomes reveal a highly inter-connected protein network of de novo mutations. *Nature.* 2012; 485(7397): 246-50.

Neale BM, Kou Y, Liu L, et al. Patterns and rates of exonic de novo mutations in autism spectrum disorders. *Nature*. 2012; 485(7397): 242-5.

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Insights into Immune Changes & Autism

Researchers produce autism behaviors in mice by mimicking infection during pregnancy; reverse symptoms by resetting offspring's immune system

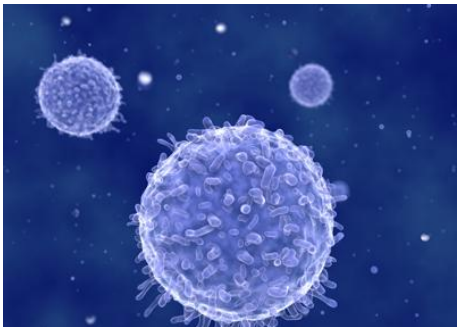
Caltech investigators demonstrated how maternal infection during pregnancy could trigger immune abnormalities and autism behaviors in offspring. (Image by Elaine Hsiao)

Over the last decade, studies have suggested links between autism and immune-system abnormalities. What remained unanswered was whether immune changes played a role in causing autism or resulted *from* it.

Results from a mouse study published this summer provide new insights into how challenges to the immune system may contribute to the development of autism spectrum disorder (ASD).

The researchers mimicked a maternal infection during pregnancy in mice. Doing so produced both an overactive immune system and autism-like behaviors in the offspring. Further, the investigators reversed some of the behaviors by "resetting" the offspring's immune systems with a bone-marrow transplant.

"We have long suspected that the immune system plays a role in the development of autism spectrum disorder," said senior researcher Paul Patterson, Ph.D. "In our studies of this mouse model, we found that the mother's immune system is a key factor in the eventual abnormal behaviors in the offspring."



Inflammation during pregnancy resulted in offspring with reduced levels of inflammation-calming immune cells called T-regulatory cells.

The team's report appeared in the *Proceedings of the National Academy of Science*. It was supported by an Autism Speaks Weatherstone Predoctoral Fellowship for lead researcher Elaine Hsiao.

The investigators injected pregnant mice with a molecule that mimicked viral infection by triggering a similar type of inflammation. "This single insult to the mother translated into autism-related behavioral abnormalities in the offspring," Hsiao explained. These abnormalities included all three of

autism's core symptoms: repetitive behaviors, impaired communication and reduced sociability. The mice compulsively buried marbles and self- groomed, avoided new mice and exhibited reduced and abnormal vocalizations.

A mouse with autism-like symptoms compulsively buries marbles

The mice also had a number of immune abnormalities similar to those seen in some people with autism. These included decreased levels of key immune-calming cells called regulatory T cells. Taken together, the immune abnormalities reflected an immune system in overdrive, Hsiao said.

"We saw these abnormalities in both young and adult offspring of immune-activated mothers," she added. "This tells us that a prenatal challenge can result in long-term consequences for health and development."

In addition, the team directly tested whether the immune problems contributed to the mice's autism-like behaviors. They gave the affected offspring bone-marrow transplants from normal mice. In effect, this reset their immune systems to normal. It also reduced their autism-like behaviors.

"Researchers have studied immune changes in pregnant mothers or in offspring, but have rarely linked the two findings together," commented Alycia Halladay, Ph.D., Autism Speaks senior director of environmental and clinical sciences. "This study is an important contribution to understanding the link between gestational immune dysfunction and outcomes."

Such results in mice can't be directly applied to humans, experts agreed. Nor would a bone marrow transplant be an appropriate treatment for autism. Rather, it was a useful research tool for studying immune system changes in an animal model.

That said, normalizing immune irregularities could be an important target for future treatments, Dr. Patterson said. "By correcting immune problems through safe and proven methods, it might be possible to relieve some of autism's classic developmental delays."

Hsiao is continuing her research on the molecular basis of autism at Caltech, with the aim of developing novel therapeutics for the disorder.

Hsiao EY, McBride SW, Chow J, Mazmanian SK, Patterson PH. Modeling an autism risk factor in mice leads to permanent immune dysregulation. *Proceedings of the National Academy of Sciences*. 2012; 109(30).

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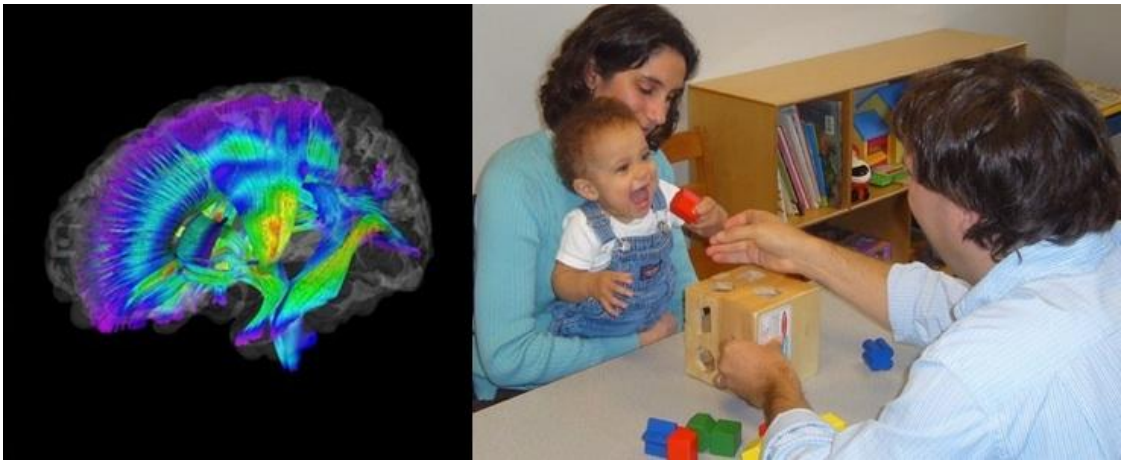
Discovery of Pre-symptom Marker of Autism

Researchers use MRI to reveal differences in the brain's white matter in infants as young as 6 months



Scientists found differences in the early development of major brain pathways in infants who went on to be diagnosed with autism. (images courtesy UNC)

While autism's core behaviors tend to emerge near or after a baby's first birthday, researchers have long searched for earlier signs. A clear biomarker could lead to earlier therapy that promotes brain development in the crucial first year of life. Identifying early differences in brain biology could also increase understanding of what causes autism spectrum disorder (ASD). In some cases, the biomarker itself might become a target of treatment to prevent or ease debilitating symptoms.

This year, researchers found distinctive differences in brain communication pathways in infants who went on to develop ASD. These differences appeared as early as 6 months and continued through 2 years of age.

The study appeared in the June issue of the *American Journal of Psychiatry.* It was led by Joseph Piven, M.D. and Jason Wolff, Ph.D., of the Carolina Institute for Developmental Disabilities at the University of North Carolina, Chapel Hill.

As part of their Infant Brain Imaging Study (IBIS), the researchers followed the early brain and behavior development of 92 infants with an older sibling on the autism spectrum. As such, these children were at an elevated risk of ASD, which frequently runs in families.

The researchers used a special type of magnetic resonance imaging (MRI), called diffusion tensor imaging, to record three-dimensional snapshots of brain development at 6, 12 and 24 months of age. In addition, all the toddlers received a behavioral assessment for autism at 24 months. At that time, 28 of the 92 toddlers met criteria for ASD.

As a group, the children who developed autism showed significant differences in white-matter development compared to those who did not. White matter consists of the nerve fibers that

connect different regions of the brain. The differences seen in the children who developed autism suggested blunted development of this brain wiring during early infancy in advance of core clinical symptoms.

“A very interesting aspect of the findings was that the brain differences change over time,” Dr. Piven said. “The differences we see at 6 months are not the same as the differences we see at 12 and 24 months. This may help us understand emerging evidence that autistic symptoms unfold or emerge over time.”

In addition, Dr. Piven’s team saw the observed pattern of differences in all 15 white matter tracks they examined in the brain. “This suggests a remarkable convergence of evidence and bolsters our confidence in the finding,” he said.

Previous studies have suggested that autism involves abnormal connectivity between different brain regions. In theory, this could explain the impaired communication and social behaviors that are hallmarks of ASD. For example, a typical infant trying to communicate something of shared interest uses a combination of gestures, babbling and eye contact. This requires several brain regions to communicate with each other simultaneously.

It’s too early to tell whether some form of MRI could be used to identify children at risk for ASD in early infancy, Dr. Piven said. But the results could guide the development of better tools for predicting risk and perhaps for measuring whether an early intervention therapy is improving underlying brain biology.

“The discovery of an early biomarker offers the promise of intervening with treatments before behavioral symptoms become obvious,” said co-author Geraldine Dawson, Ph.D. Dr. Dawson is the chief science officer of Autism Speaks and a professor of psychiatry at the University of North Carolina. “Earlier intervention may increase the likelihood that a therapy can reduce, or perhaps even prevent, the development of autism’s disabling symptoms,” she said. (See related Top Ten story, “Early Intervention Program Changes Brain Activity in Children with Autism**.”**)

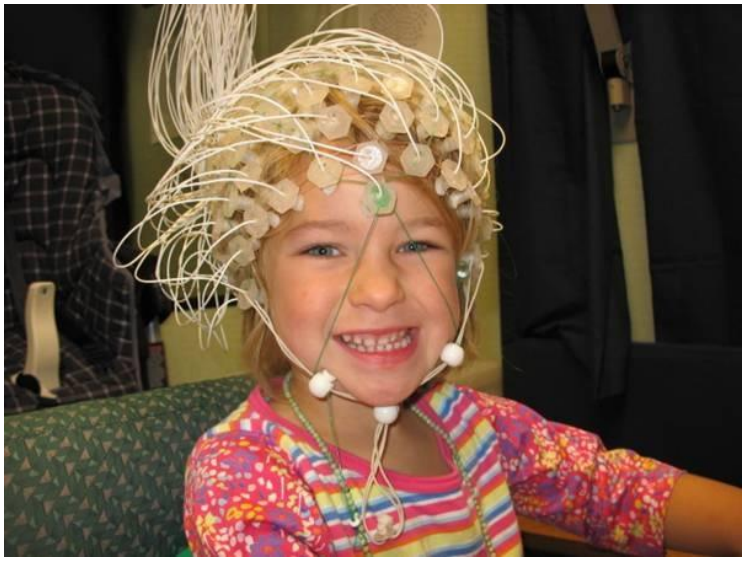
Further research is needed to understand what is causing these differences in early brain development, Drs. Piven and Dawson agreed. This, in turn, could uncover targets for future treatments.

Their study was supported by grants from the National Institutes of Child Health and Development, Autism Speaks, the Simons Foundation, the National Alliance for Medical Image Computing and the National Institute of Biomedical Imaging and Bioengineering. Additional funding from Autism Speaks is enabling the IBIS team to look at genetic and environmental influences on brain and behavior development.

Wolff JJ, Gu H, Gerig G, et al. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatry.* 2012; 169: 589-600.

Early Intervention Program Alters Brain Activity in Children with Autism

Clinical study of Early Start Denver Model intervention improves not only social skills, but also brain responses to social cues

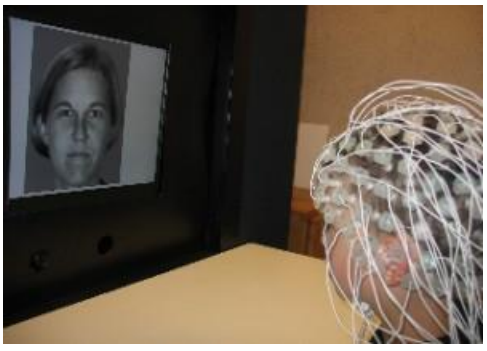


A study participant prepares for noninvasive monitoring of brain activity. (image courtesy University of Washington, Seattle)

Decades of research have shown that behavioral therapies for autism can improve cognitive and language skills. Still, it remained unclear whether behavioral interventions simply reduced autism's symptoms or actually "treated" the developmental disorder. In other words, could an effective behavioral intervention change the brain biology that underlies autism spectrum disorder?

This year, researchers delivered compelling evidence that the Early Start Denver Model (ESDM), an intensive early intervention program for toddlers with autism, improves brain activity related to social responsiveness. The *Journal of the American Academy of Child & Adolescent Psychiatry* published the findings in its November issue.

"This may be the first demonstration that a behavioral intervention for autism is associated with changes in brain function as well as positive changes in behavior," commented Tom Insel, M.D., director of the National Institute of Mental Health.



The young participants viewed images of faces and objects while noninvasive EEG recorded brain responses.

Psychologists Sally Rogers, Ph.D., and Geraldine Dawson, Ph.D., developed the ESDM therapy program in the 1990s. It adapts key techniques from Applied Behavioral Analysis (ABA) for toddlers, with an emphasis on interactive play between children and their therapists and parents. Dr. Rogers is a professor and researcher at the University of California, Davis, MIND Institute. Dr. Dawson was a professor and researcher at the University

of Washington, Seattle, when she and Dr. Rogers developed the program. She is now the chief science officer of Autism Speaks and a professor at the University of North Carolina, Chapel Hill.

Three years ago, Drs. Dawson and Rogers published the first results of a clinical trial comparing ESDM with conventional autism therapy services. They randomly assigned 48 toddlers (ages 18 to 30 months) to receive either ESDM therapy or the early intervention services routinely available in their communities (Seattle). Both groups received roughly 20 hours of weekly therapy for two years. Overall, those in the ESDM group showed greater increases in IQ, language, and adaptive behavior than children in the community-intervention group.

ESDM therapy emphasizes enjoyable interactive play

In this year's report, the research team published their analysis of brain activity monitoring performed on both groups of children at the end of their two years of therapy. For comparison, they also performed the brain activity tests on a group of age-matched children without autism.

Noninvasive electroencephalography (EEG) showed that the children in the ESDM group showed greater brain responses to social information compared to children in the community group. When they viewed women's faces, their brain activity patterns were virtually identical to those of the children without autism. This more-typical pattern of brain activity was associated with improved social behavior including improved eye contact and social communication.

By contrast, children in the community intervention group showed greater brain activity when viewing objects than faces. Previous research has shown that many children with autism have this unusual pattern of brain activity.

"By studying changes in the neural response to faces, Dr. Dawson and her colleagues have identified a new target and a potential biomarker that can guide treatment development," Dr. Insel said.

"So much of a toddler's learning involves social interaction," Dr. Dawson added. "As a result, an early intervention program that promotes attention to people and social cues may pay dividends in promoting the normal development of brain and behavior."

The American Academy of Pediatrics recommends autism screening for all children twice before 24 months. "When families receive a diagnosis, it's vitally important that we have effective therapies available for their young children," Dr. Dawson urged. Currently ESDM is the only early intervention evaluated in clinical trials.

As methods for earlier detection become available, infants flagged at risk for ASD may likewise benefit from early intervention, many experts agree. Research suggests that adults with autism can likewise benefit from interventions that promote social engagement.

Dawson G, Jones EJ, Merkle K, et al. Early behavioral intervention is associated with normalized brain activity in young children with autism. *J Am Acad Child Adolesc Psychiatry*. 2012; 51(11):1150-9.

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Peer Training Outperforms Traditional Autism Interventions

Training classmates produces greater gains in social inclusion than even one-on-one training between therapist and child

Many children with autism attend mainstream classrooms for at least part of the school day. Many struggle socially and are at risk of being isolated or bullied. The most common intervention involves enrollment in social skills training in a clinic or therapist's office. The instructor models appropriate social skills either one-on-one or with a group of socially challenged children. Both types of intervention improve social skills – at least within the clinics and academic centers where they've been studied. Their results in real-world settings have been less clear.

This year, the findings of a landmark study argue for a shift away from relying solely on such standard social-skills training and toward greater emphasis on teaching classmates how to interact with children who have social challenges.

The study was led by educational psychologist Connie Kasari, Ph.D., of the UCLA Center for Autism Research and Treatment. It appeared in the April issue of the *Journal of Child Psychology and Psychiatry*.

The researchers enrolled 60 students with autism spectrum disorder (ASD), in grades 1 through 5. All attended mainstream classes for at least 80 percent of the school day. The researchers randomly assigned them into one of four groups:

- One group received one-on-one training with an adult for six weeks. The provider helped the child practice social skills such as how to enter a playground game or conversation.

- One group didn't receive any social skills training, but had three typically developing classmates learn strategies for engaging children with social difficulties. These classmates did *not* know the

identity of the child with autism.

- One group received both one-on-one and classmate training.

- One group received neither intervention in the first phase of the study and later participated in one of the interventions.

All training sessions lasted 20 minutes, twice weekly for six weeks. During the intervention, observers watched and noted playground behaviors. These observers did not know which children had received which intervention. Three months after training completion, the investigators returned to observe the children with autism and interview them and their teachers.

Those whose classmates received training – including those who themselves received no social skills counseling – spent less time alone on the playground and had more classmates naming them as friends, compared to those who received only one-on-one training or no intervention.

In addition, their teachers reported that the students with autism showed significantly improved classroom social skills following training of their peers. By comparison, the teachers noted no changes in the social skills of children with autism who received one-on-one coaching *without* any training of their classmates. Like the playground observers, the teachers were not told who had received which intervention.

In the situation where classmates were trained, the children with autism continued to demonstrate improved social connectedness even after they changed classrooms and classmates with the new school year.

"I thought working through the peers would be more indirect, and yet we found the exact opposite," Dr. Kasari said of her surprise findings. "The model where an adult works directly with the child with autism just wasn't as effective."

However, the study also highlighted areas of continued concern. For example, while peer engagement lessened isolation on the playground, it did not improve interactions across all areas of playground behavior. Many of the children with autism still struggled with taking turns, engaging in conversations and other joint activities. Also, despite greater inclusion in social circles, the children with ASD did not seem to recognize that they had more friends.

"We found that even if a child with autism is popular, he still has a really tough time on the playground," Dr. Kasari said.

The National Institutes of Health (NIH) sponsored the research. Dr. Kasari has also received several Autism Speaks research grants that build on her work in schools and with underserved populations of children with ASD. Two of her Autism Speaks pilot grants became the basis of larger NIH-sponsored research studies.

"This is ground-breaking work that points to the most effective ways of helping children with autism successfully navigate their social worlds at school," noted Geri Dawson, Ph.D., chief science officer at Autism Speaks. "It is so important that these interventions be tested in real-world settings so we can more easily adapt research findings to the community. That is one of the strengths of this study."

Kasari C, Rotheram-Fuller E, Locke J, Gulsrud A. Making the connection: randomized controlled trial of social skills at school for children with autism spectrum disorders. *J Child Psychol Psychiatry*. 2012; 53(4): 431-9.

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Arbaclofen Shows Promise for Treating Core Symptoms of Autism

Compound advances into larger clinical trials; could pave the way for other future medicines as well

Investigator Randi Hagerman, M.D., and a patient with autism (photo courtesy of UC Regents)

Currently there are no medicines to treat autism's core symptoms of impaired social and communication abilities and repetitive behaviors. This year, two studies – a clinical trial of patients with fragile X syndrome and a mouse study – suggest that arbaclofen could become the first. Both appeared in the September issue of *Science Translational Medicine*.

"Arbaclofen is the most important compound in clinical development in autism today," said Robert Ring, Ph.D., Autism Speaks vice president of translational research. Moreover, arbaclofen derives from the already approved drug baclofen, used to treat muscle spasticity. This means that this class of drugs has already undergone considerable safety testing.

The study of individuals with fragile X syndrome enrolled 63 children and adults. Many but not all had the additional diagnosis of autism. (Around one-third of individuals with fragile X also have autism. Around 5 percent of those with autism have fragile X syndrome.)

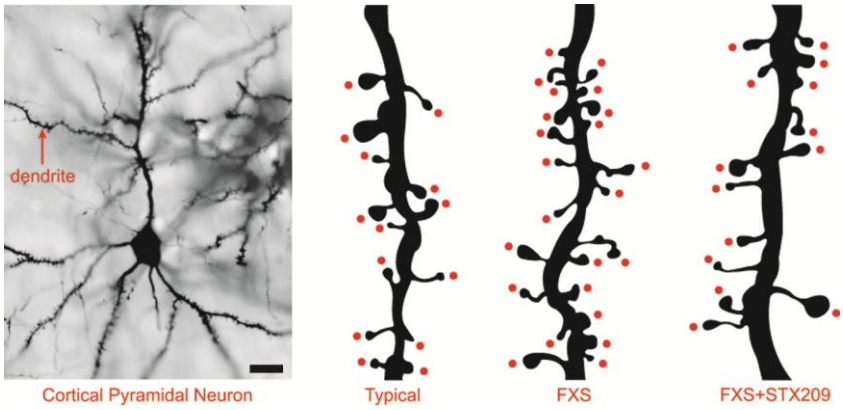
Researchers found a trend in improvements in several areas of social and behavior skills in their first analysis of this clinical trial. However, the trend fell short of significant improvement in most measures. Among the stand-out exceptions was social avoidance.

The investigators then narrowed their focus to look only at participants with severe social impairment. These were also the most likely to have ASD. This group's response to treatment

produced significant reductions in social avoidance and global improvement in problem behaviors and improvement in overall social functioning.

“What’s significant about this study is that the drug had an effect on a core symptom in fragile X that is also a core symptom of autism,” said lead investigator Elizabeth Berry-Kravis, M.D., Ph.D. Dr. Berry-Kravis is a professor of biochemistry, neurological sciences and pediatrics at Rush University, in Chicago. “One would expect that the findings might translate from fragile X to other causes of autism,” she said.

In the animal study, researchers used a mouse model of fragile X syndrome. The mice lacked a working copy of the FMR1 gene. Silencing this gene causes fragile X syndrome. Without it, brain cells lose the ability to respond correctly to a neurotransmitter called glutamate. This in turn, causes the cells to overproduce certain proteins. As a result, malformations arise in the structures (dendritic spines) that connect brain cells. (See illustration below.)



Nerve cells in the brain have branching projections with specialized structures called dendritic spines (red dots) that receive information. These spines are longer, frailer and more abundant in the brains of fragile X mice (center). Treatment with arbaclofen reduced the abnormalities (far right).

Following treatment with arbaclofen, the mice showed evidence of regulated protein production and corrected connectivity in and between their brain cells. In addition, treatment significantly reduced seizures and repetitive behaviors in the mice. Seizures are a symptom of fragile X syndrome and are also associated with other severe types of autism. Repetitive behaviors are a core symptom of all types of autism.

“Because we correct the core pathophysiology in the mouse, we believe that this is a disease modifying treatment,” said Aileen Healy, Ph.D., the study’s lead author and vice president of research for Seaside Therapeutics, the Cambridge, Mass., biotech company developing arbaclofen.

“Together these studies offer important insights that are poised to transform the field of autism medicine development,” Dr. Ring said. “This establishes an important translational bridge between the proverbial bench and bedside by demonstrating that the same experimental agent

can both produce clinically relevant effects in patients and reverse similar endpoints in an animal model of the same disease. With a bridge like this in place, a wave of additional scientific breakthroughs can begin to advance into clinical development."

In November, Autism Speaks non-profit venture affiliate DELSIA (Delivering Scientific Innovation for Autism) announced a partnership with Seaside Therapeutics. Autism Speaks funding will help Seaside discover biomarkers that can help predict which patients are most likely to respond to arbaclofen and which may be at risk of possible side effects.

Henderson C, Wijetunge L, Kinoshita MN, et al. Reversal of Disease-Related Pathologies in the Fragile X Mouse Model by Selective Activation of GABAB Receptors with Arbaclofen. *Sci Transl Med*. 2012; 4(152): 152ra128.

Berry-Kravis EM, Hessl D, Rathmell B, et al. Effects of STX209 (Arbaclofen) on Neurobehavioral Function in Children and Adults with Fragile X Syndrome: A Randomized, Controlled, Phase 2 Trial. *Sci Transl Med*. 2012 19; 4(152): 152ra127.

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Mounting Evidence of Critical Need for Adult Transition Support

Young adults with autism less likely than any other disability group to be employed or enrolled in higher education

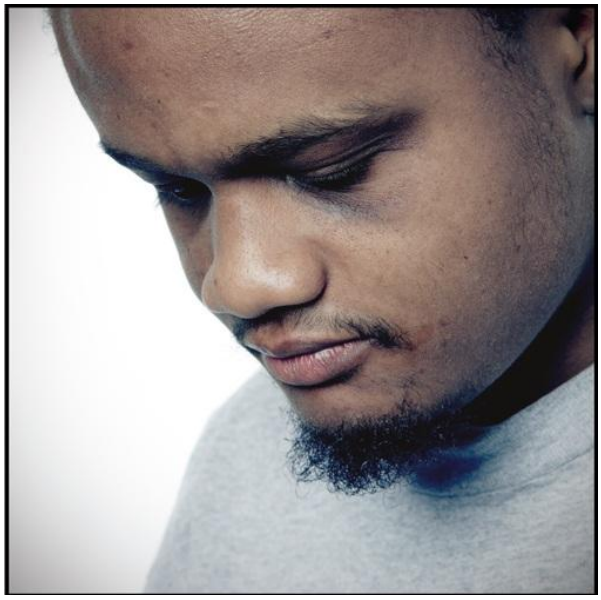

Image courtesy Christopher Gauthier (www.christophergauthier.com)

Approximately 50,000 individuals with autism spectrum disorder (ASD) turn 18 each year in the United States. Yet life beyond the school-age years has largely remained uncharted territory in autism research. This may change following the sobering results of a study tracking young adults with autism over their first six years post-high school.

In the first two years after high school, over half of young adults with ASD had neither held paid employment nor enrolled in vocational training or college. This "no participation" rate was higher than that of any other disability group tracked in the study – including those with intellectual disability. Six years after high school, only a third of young adults with autism had attended college and barely half had ever held a paid job.

"The years immediately after high school are when people create an important foundation for the rest of their lives," said lead investigator Paul Shattuck, Ph.D., of Washington University's Brown School of Social Work, in St. Louis. "Yet many families with children with autism describe leaving high school as falling off a cliff because of the lack of services for adults with ASDs."

Research on autism treatment and support services has long focused on early childhood. On many levels, this is understandable. Early intervention has great potential to improve outcomes, and school systems need to provide appropriate support services.

Yet adulthood makes up the vast majority of a lifespan. To the degree that adults with autism fail to achieve independence, adulthood may also account for autism's estimated lifetime costs of $1.4 million to $2.3 million.

Dr. Shattuck's team examined data from the National Longitudinal Transition Study 2, a nine-year study of youth enrolled in special education classes during high school. They compared the post-high school employment and education of young adults ages 19 to 23 across several disability groups. These included individuals with ASD, intellectual disability, speech-language impairment or learning disability.

Among young adults with autism, employment and education varied with their degree of impairment. The highest rates were seen among those who ranked as "high ability" on a scale of functional life skills. In this group, nearly 60 percent had attended some college. Just over 80 percent had some sort of paid work. By contrast, 11 percent of those on the "low ability" end of the scale had enrolled in postsecondary education. Just 23 percent had ever been employed.

Overall, employment among young adults with autism rose with family income. It ranged from around one in three among families earning less than $25,000 a year to almost three out of four in families earning more than $75,000.

"This suggests that the right support services – such as those made possible by higher family income – can increase the chances for an independent and successful adulthood," Dr. Shattuck said.

In his report, Dr. Shattuck called for research to determine the kinds of services that can best foster a successful transition into adulthood. He also highlighted the need for a special focus on interventions that can help low-income youth overcome barriers to accessing services and achieving fuller participation in society.

The journal *Pediatrics* published Dr. Shattuck's report in its June issue. His research was funded in part by a grant from Autism Speaks.

"Dr. Shattuck's research has played a tremendous role in raising awareness of autism as a lifetime issue," said Autism Speaks Chief Science Officer Geraldine Dawson, Ph.D. "As researchers and advocates for those with ASD, we must increase our emphasis on research that identifies the kinds of services and educational and employment opportunities that can effectively increase independence and quality of life."

Shattuck P, Carter Narendorf S, Cooper B, Sterzing P, Wagner M, Lounds Taylor J. Postsecondary Education and Employment Among Youth With an Autism Spectrum Disorder. *Pediatrics*. 2012; 129 (6): 1-8.