

Autism Research Review

I N T E R N A T I O N A L

A quarterly publication of the Autism Research Institute—www.Autism.org

Reviewing biomedical and educational research in the field of autism and related disorders

Two studies point to “mosaic” mutations as a significant factor in autism spectrum disorders

Mosaic mutations may play a significant role in autism spectrum disorders, according to two recent studies.

Mosaic mutations are not inherited, but rather are caused by an error introduced when a stem cell divides. The mutation is passed only to the cells that descend from it. The earlier a mutation occurs in development, the more cells will carry it.

In the first study, Rachel Rodin and colleagues used whole-genome sequencing to examine post mortem samples of brain tissue from 59 individuals with ASD and 15 controls. The researchers looked for mosaic point mutations, which are alterations in a single “letter” of genetic code. They determined that these mutations are not rare, “with about half of individuals having at least one potentially function-altering somatic mutation somewhere in the cortex.” However, in the brains of people with ASD, mosaic mutations were more likely to affect parts of the genome called “enhancers,” which regulate whether a gene is turned on or off.

Rodin comments, “In the brains of people with autism, mutations accumulate at the same rate as normal, but they are more likely to fall into an enhancer region. We think this is because gene enhancers and promoters tend to be in DNA that’s unwound and more exposed, which probably makes them more susceptible to mutations during cell division.”

The second study investigated copy number variants (CNVs) in individuals with ASD, focusing on CNVs occurring in a mosaic pattern. CNVs are deletions or duplications of whole segments of a chromosome rather than mutations to a single point.

In this study, by Maxwell Sherman and colleagues, the researchers analyzed blood samples from approximately 12,000 people with autism and 5,500 neurotypical siblings, using blood as a proxy for brain tissue. They identified a total of 46 mosaic CNVs in the autism group and 19 in the unaffected siblings. Individuals with autism were especially likely to have very large CNVs, spanning a median of 7.8 million bases compared to 0.59 in controls.

“This is one of the more interesting and surprising aspects of our study,” Sherman

comments. “The kids with ASD had very large CNVs that often hit dozens of genes, and likely included genes important for development. If the CNVs were in all their cells, rather than in a mosaic pattern, they would likely be lethal.”

The study’s results also indicated that the larger the CNVs, the greater the severity of autism. Interestingly, smaller CNVs known to be associated with ASD when they occur in all cells were not associated with autism when they occurred in a mosaic pattern. Study coauthor Christopher Walsh says this suggests that a large number of cells in the brain need to be altered in a significant way for autism to occur.

—
“The landscape of somatic mutation in cerebral cortex of autistic and neurotypical individuals re-

vealed by ultra-deep whole-genome sequencing,” Rachel E. Rodin, Yanmei Dou, Minseok Kwon, Maxwell A. Sherman, Alissa M. D’Gama, Ryan N. Doan, Lariza M. Rento, Kelly M. Girsakis, Craig L. Bohrsen, Sonia N. Kim, Ajay Nadig, Lovelace J. Luquette, Doga C. Gulhan, Brain Somatic Mosaicism Network, Peter J. Park, and Christopher A. Walsh, *Nature Neuroscience*, January 11, 2021 (online ahead of print publication); and “Large mosaic copy number variations confer autism risk,” Maxwell A. Sherman, Rachel E. Rodin, Giulio Genovese, Caroline Dias, Alison R. Barton, Ronen E. Mukamel, Bonnie Berger, Peter J. Park, Christopher A. Walsh, and Po-Ru Loh, *Nature Neuroscience*, January 11, 2021 (online ahead of print publication). Address for both: Maxwell Sherman, maxas@mit.edu.

—and—
“Advances in understanding autism, based on ‘mosaic’ mutations,” news release, Children’s Hospital Boston, January 11, 2021.

Maternal biomarkers identify odds of child having MAR-ASD

Researchers at UC Davis report that they can accurately predict a mother’s risk of having a child with one particular subtype of autism spectrum disorder (ASD).

Alexandra Ramirez-Celis and colleagues focused on maternal autoantibody-related ASD (MAR-ASD), which accounts for approximately 20% of all cases of ASD. In this subtype of autism, a pregnant woman’s autoantibodies (which are antibodies directed against the body’s own proteins) react with her baby’s brain, altering its development.

Ramirez-Celis and colleagues analyzed plasma samples from 450 mothers of children with ASD and 342 mothers of neurotypical children to detect reactivity to eight different proteins that are abundant in fetal brain. Using a machine learning algorithm, they identified three top autoantibody patterns associated with a diagnosis of MAR-ASD: CRMP1+GDA, CRMP1+CRMP2 and NSE+STIP1.

“For example,” senior author Judy Van de Water says, “if the mother has autoantibodies to CRMP1 and GDA (the most common pattern), her odds of having a child with autism [are] 31 times greater than the general population, based on this current dataset. That’s huge. There’s very little out there that is going to give you that type of risk assessment.”

In addition, the researchers found that reactivity to CRMP1 in any of the top patterns significantly increases the likelihood of a child having severe autism.

The study’s authors conclude, “This is the first report that uses machine learning to identify a set of biomarkers that demonstrate an association with MAR-ASD with 100% accuracy.” They say their new findings could potentially lead to pre-conception testing for high-risk women—for instance, those who have previously had a child on the autism spectrum, those who are older than 35 years of age, or those with maternal risk factors associated with ASD (such as metabolic syndrome).

—
“Risk assessment analysis for maternal autoantibody-related autism (MAR-ASD): a subtype of autism,” Alexandra Ramirez-Celis, Martin Becker, Miriam Nuño, Joseph Schauer, Nima Aghaeepour, and Judy Van de Water, *Molecular Psychiatry*, January 22, 2021 (free online). Address: Judy Van de Water, Department of Internal Medicine, Division of Rheumatology, Allergy, and Clinical Immunology, One Shields Avenue, University of California, Davis, CA 95616, javandewater@ucdavis.edu.

—and—
“Biomarkers in mother’s plasma predict a type of autism in offspring with 100% accuracy,” news release, UC Davis, January 25, 2021.

Large numbers of children with autism spectrum disorders have comorbid mental conditions

The majority of children with autism spectrum disorders (ASD) have at least one mental health condition, according to a new study by U.S. and Canadian researchers.

Connor Kerns and colleagues analyzed survey data collected from more than 42,000 caregivers of children, calculating the prevalence of mental conditions in four different groups: children with ASD, children with intellectual disability, children with special health care needs, and children with none of these issues.

The researchers found that nearly 78% of children with ASD had at least one mental

Kerns says, "There's something specific about autism that is increasing this mental health burden, and it's true not only for anxiety, but also for depression, behavior problems, and attention problems. This is a special population that requires special attention."

health condition, and nearly half had two or more. In contrast, only 14.1% of children without ASD had mental health conditions. Children with ASD also had a higher prevalence of mental conditions than children with intellectual disability or special health care needs.

The most common mental health conditions seen in children with ASD were behavior/conduct problems (60.8%), anxiety (39.5%), attention deficit disorder or attention-deficit hyperactivity disorder (48.4%), and depression (15.7%). While mental health

Quotable...

"Lauren Romansky, managing vice president in the Gartner HR practice, said Gartner research shows that a diverse and inclusive workforce is more likely to improve company performance and that organizations are beginning to intentionally include neurodiverse candidates in their recruitment efforts.

"Organizations can benefit from the positive attributes commonly associated with neurodivergence, such as creativity, lateral thinking and a different perspective," she said. "Additionally, neurodiverse individuals have highly specialized skills and consistency in tasks once mastered, all valuable characteristics that can increase organizational innovation."

—"People with autism succeed in IT jobs when companies hire for capabilities not credentials,"
Veronica Combs, *MSN News*,
February 23, 2021

conditions became more prevalent as children with ASD aged, the researchers found that they were already present in nearly 45% of preschool children with ASD.

Kerns says, "There's something specific about autism that is increasing this mental health burden, and it's true not only for anxiety, but also for depression, behavior problems, and attention problems. This is a special population that requires special attention."

She adds, "For a long time, mental health in kids with autism was neglected because the focus was on autism. There's much greater awareness now, but we don't have enough people trained to provide mental health treatments to kids on the autism spectrum. We need to bridge these two systems and the

different sets of providers that tend to treat these children."

It is crucial to detect mental conditions in children with ASD early on, Kerns says, because the longer these problems go untreated, the harder they are to treat. "Right now," she says, "we don't have a great system for that."

"Prevalence and correlates of caregiver-reported mental health conditions in youth with autism spectrum disorder in the United States," Connor M. Kerns, Jessica E. Rast, and Paul T. Shattuck, *Journal of Clinical Psychiatry*, January 2021 (online). Address: Connor Kerns, cmkerns@psych.ubc.ca.

—and—

"Mental health conditions alarmingly high among children with autism, study finds," news release, University of British Columbia, January 19, 2021.

Diesel pollution linked to autism symptoms in study of rats

A new study adds to evidence implicating air pollutants as a factor in autism spectrum disorders (ASD).

In the study, Tin-Tin Win-Shwe and colleagues examined the effects of exposure to a substance called *diesel exhaust origin secondary organic aerosol*, or DE-SOA. This is a pollutant created by chemical reactions between diesel exhaust particles and gases in the atmosphere.

The researchers exposed pregnant rats to clean air or air contaminated with diesel particulates or DE-SOA from gestational day 14 to postnatal day 21. They investigated the behavior of the rats when they were between 10 and 13 weeks old, and later examined the prefrontal cortices of the animals.

The researchers report, "Developmental exposure to DE-SOA induced autism-like behaviors such as poor social interaction, social dominance, and repetitive behavior in male and female rats. These poor social behaviors [were] accompanied by changes of molecular markers such as neurological and immunological biomarkers in the prefrontal cortex."

They comment, "It is possible that the toxic substances from DE-SOA may translocate to the fetal brain via the olfactory nerve route or systemic circulation and induce neuroinflammation. Neuroimmune interaction, synaptic dysfunction, immune dysregulation, and excitatory-inhibitory imbalance are

major contributing factors for the development of ASD in response to environmental pollutant exposure."

The researchers note that their findings are consistent with a number of human studies showing associations between exposure to air pollutants during brain development and ASD.

"Perinatal exposure to diesel exhaust-origin secondary organic aerosol induces autism-like behavior in rats," Tin-Tin Win-Shwe, Chaw Kyi-Tha-Thu, Yuji Fujitani, Shinji Tsukahara, and Seishiro Hirano, *International Journal of Molecular Sciences*, January 2021 (free online). Address: Tin-Tin Win-Shwe, Center for Health and Environmental Risk Research, National Institute for Environmental Studies, Tsukuba 305-8506, Japan, tin.tin.win.shwe@nies.go.jp.

Participants needed for ASD microbiome study

Researchers at Massachusetts General Hospital, Harvard Medical School, and the Autism Research Institute are investigating whether the reason why boys are more affected than girls is related to differences in intestinal bacteria.

We are seeking families to participate in this study who have boy and girl siblings with autism. These families will be mailed stool kits with instructions and will be asked to collect samples. A brief medical history will be taken.

For additional information and enrollment details, please contact Harland Winter, MD by phone, 617-724-2004, or by email at GenderDimorphism@autism.org.

— Autism.Jobs —

A Free Resource for Job Seekers, Families and Caregivers, Job Coaches, and Employers

Visit www.Autism.Jobs

EDITORIAL**Challenging behaviors in adults with autism**

By
Stephen M. Edelson, Ph.D.,
Autism Research Institute
and
Marvin R. Natowicz, M.D., Ph.D.,
Cleveland Clinic and
Case Western Reserve University School
of Medicine

Challenging behaviors such as aggression, destructiveness, and self-injury take a tremendous toll on adults with autism and their caregivers. Each week, the Autism Research Institute receives desperate communications from caregivers seeking help for an adult son or daughter whose behavior is disturbing, dangerous, or even life-threatening. In this editorial, we will look at the scope of this problem, current approaches for treatment, and the steps the autism community can take to help people with autism spectrum disorder (ASD) and caregivers who are struggling with this serious issue.

**The high rate—and high cost—of
 challenging behaviors**

Aggression, destructiveness and self-injury are common among children with ASD, with the Autism Research Institute's E-2 database of more than 2,300 cases indicating that 59% of those with ASD engage in one or more of these behaviors. Other datasets also support the relatively high prevalence rate of challenging behaviors in this population (McClintock et al., 2003; Matson and Rivet, 2008; Rattaz et al., 2018; Steinfeldt-Kristensen et al., 2020). In a recent long-term follow-up study, Laverty et al. found that 44% of individuals with ASD continued to engage in self-injurious behaviors a decade later indicating that this behavior can be persistent and lifelong if not overcome (Laverty et al., 2020).

In children with ASD, challenging behaviors are a significant problem that can interfere with nearly all aspects of daily life. Later, as these children grow into adulthood, their bodies become larger and they become stronger. Consequently, these behaviors can become even more severe, significantly reducing these individuals' quality of life and often endangering the people who care for them.

We hear reports from group home staff members who are "walking on eggshells" when they interact with some of their residents, in fear of unexpected outbursts (reviewed by Barroso et al., 2018). We also hear from parents who feel trapped and isolated in their own homes. They cannot bring their sons or daughters out of the house, and op-

portunities for recreation, employment, and residential placement are limited (see Chen et al., 2015 for a review of issues related to employment). This situation becomes even more dire in situations when there is only one parent or caregiver available to provide support.

To compound the problem, most physicians and therapists have little experience treating adults on the autism spectrum, so there is a dearth of experts who can provide effective support and guidance (Murphy et al. 2016). One common treatment option recommended by professionals is sedation, but sedative drugs can negatively impact cognition, sociability, and motor abilities. In addition, they do not address the underlying problems causing the behaviors.

**Addressing the roots of
 challenging behaviors**

The contributors to aggression, destructiveness, and self-injury can be classified into three categories: a biological basis, a social basis, and an initial biological cause that is later maintained by social consequences.

Examples of biological causes that may predispose to challenging behaviors include high arousal levels, often associated with anxiety (Casanova et al., 2021); medical comorbidities associated with pain or discomfort such as chronic constipation or GERD (Bauman, 2010; Muskens et al., 2017); or environmental sensory input such as certain loud sounds or bright lights (Miller and Misher, 2016).

There also can be social contributors to challenging behaviors. These include a desire for positive or negative attention, a desire to escape or avoid an undesirable task or situation, and a desire to acquire a desired object or situation (Carr, 1977).

In some cases, a challenging behavior may result from an underlying biological problem, usually associated with pain, but individuals learn that their reactions to the problem can result in positive social consequences such as attention. In a well-cited case study by Carr and McDowell (1980), a 10-year-old scratched himself to alleviate the pain from a severe skin allergy. After the initial problem cleared up, his scratching still continued because it was maintained by social attention. May and Kennedy (2010) review studies examining the relationship between organic and social contributors with respect to challenging behaviors.

It is important to mention that some challenging behaviors are associated with an underlying genetic condition (Shirley et al., 2016; Huisman et al., 2018; Kurtz-Nelson et

al., 2020). This does not necessarily mean that the behavior is untreatable. In some instances, the primary metabolic or genetic lesion may be amenable to treatment; in other cases, the challenging behavior may be responsive to

Countless individuals on the autism spectrum and their families worldwide are dealing with challenging behaviors.

Understanding the causes and pathophysiology of these behaviors and developing effective treatments must be a public health priority.

treatment of a co-morbidity that is associated with the genetic condition, such as GI-related pain (Coleman, 2016; Kurtz-Nelson et al., 2020).

There are many assessments that can help shed light on the underlying reasons for challenging behaviors. Types of assessments can include clinical evaluations and laboratory testing, neurodevelopmental and psychological testing, and parent reports. Although many of the behavioral assessments have been validated in studies on children with ASD, most may also be relevant for assessing adults. A thorough multidisciplinary effort may be needed to uncover the underlying cause or causes of a behavior. This may take time to perform, and is variably covered by insurance policies.

Once the underlying reasons for challenging behaviors are uncovered, the most effective treatments may become obvious. In some instances, medical treatments can mitigate the impact of an underlying medical problem such as an infectious, inflammatory, or metabolic process. In other instances, nutritional, sensory, or behavioral interventions can be very helpful. In a number of cases, a combination of approaches may be needed to reduce or eliminate the behavior (Minshaw et al., 2015). For example, if a child engages in head banging, a neurologist might determine that this is due to head pain caused by a specific condition, and treat that condition medically. If this treatment is not completely successful, a therapist might also implement a behavioral strategy to discourage head hitting by teaching the individual alternate behaviors.

**Needed: a coordinated effort
 to understand and treat challenging
 behaviors**

Countless individuals on the autism spectrum and their families worldwide are dealing with challenging behaviors. Understanding
continued on page 6

Research Updates

Biomarkers found in dads of children with ASD

Researchers in Spain and the United States have identified biomarkers in fathers' sperm that may indicate an increased likelihood of having children with autism spectrum disorders (ASD).

Nicolás Garrido and colleagues examined DNA methylation—a chemical process that can turn genes on or off—in 13 men who had fathered children with ASD and 13 who had children without ASD. The researchers were able to use the presence of a set of DNA methylation alterations in sperm samples from the men who had children with ASD to identify with 90% accuracy whether 18 additional men had fathered children with ASD. Study coauthor Michael Skinner says, “We can now potentially use this to assess whether a man is going to pass autism on to his children.”

Skinner notes that it is well established that environmental factors can alter the germline, the sperm or egg, or epigenetics (heritable changes in gene expression caused by factors such as the DNA methylation they studied). If the current findings are confirmed in larger studies, he says, researchers may be able to use the biomarkers seen in men who have children with ASD to determine which types of environmental factors can induce epigenetic changes in autism.

“Sperm DNA methylation epimutation biomarker for paternal offspring autism susceptibility,” Nicolás Garrido, Fabio Cruz, Rocio Rivera Egea, Carlos Simon, Ingrid Sadler-Riggleman, Daniel Beck, Eric Nilsson, Millissia Ben Maamar, and Michael K. Skinner, *Clinical Epigenetics*, January 7, 2021 (free online). Address: Michael Skinner, skinner@wsu.edu.

—and—

“Biomarkers in fathers' sperm linked to offspring autism,” Sara Zaskie, WSU News, January 11, 2021.

Mothers of children with ASD exhibit differences in blood metabolites

Mothers of young children with autism spectrum disorders (ASD) have altered levels of metabolites in their blood, according to a recent study.

Kathryn Hollowood-Jones and colleagues analyzed blood samples from 30 mothers of young children (two to five years of age) with ASD and 29 mothers of neurotypical children. The researchers detected differences in five subgroups of correlated metabolites. Many of the variances were linked to low levels of folate, vitamin B12, and carnitine-

conjugated molecules. While carnitine is present in meat and can be produced by the body, the researchers say there was no correlation between mothers who ate more meat and mothers who had higher levels of carnitine.

Study co-author Juergen Hahn comments that these differences may be related to how some mothers metabolize carnitine. “We had multiple metabolites that were associated with the carnitine metabolism,” he says. “This suggests that carnitine and mothers is something that should be looked at.”

Previously, Hahn and his group identified patterns in metabolites in the blood of children with ASD that can be used to predict diagnosis. Based on their new findings, the researchers are now studying stored blood samples collected during pregnancy to determine if the differences in maternal metabolites are present then.

“Altered metabolism of mothers of young children with autism spectrum disorder: a case control study,” Kathryn Hollowood-Jones, James B. Adams, Devon M. Coleman, Sivapriya Ramamoorthy, Stepan Melnyk, S. Jill James, Bryan K. Woodruff, Elena L. Pollard, Christine L. Snozek, Uwe Kruger, Joshua Chuah, and Juergen Hahn, *BMC Pediatrics*, December 14, 2020 (free online). Address: Jim Adams, School for Engineering of Matter, Transport and Energy, Arizona State University, P.O. Box 879309, ECG 302, 501 E Tyler Mall, Tempe, AZ 85287, Jim.Adams@asu.edu.

—and—

“Mothers of children with autism found to have significantly different metabolite levels,” news release, Rensselaer Polytechnic Institute, January 13, 2021.

Substance abuse risk higher in those with ASD

Individuals with autism spectrum disorders (ASD) have a significantly elevated risk for drug or alcohol abuse, according to a new study from Taiwan.

Jing-Syuan Huang and colleagues analyzed data from 6,599 young individuals with ASD and 26,396 controls. They found that individuals with ASD had a three-fold increased risk for drug use disorder and a two-fold higher risk for alcohol use disorder. Individuals with autism and a substance use disorder had more than a three-fold higher risk of death compared to controls during a follow-up of around 8 years.

The researchers say the risk for substance abuse was highest for individuals with ASD who had certain comorbidities such as a tic disorder or an impulse control disorder. However, people with ASD had a higher risk of substance abuse compared to matched controls with the same comorbidities.

The researchers found that individuals with ASD who took psychotropic agents for the treatment of their autism had a significantly reduced risk of developing a substance abuse. These individuals had a 40% reduced risk if they were taking one medication, and a 63% reduced risk if they were taking more than one. The researchers say future studies should see if non-pharmacological therapies, such as behavioral therapy, can similarly reduce the risk of developing substance abuse.

“Risk of substance use disorder and its associations with comorbidities and psychotropic agents in patients with autism,” Jing-Syuan Huang, Fu-Chi Yang, Wu-Chien Chien, Ta-Chuan Yeh, Chi-Hsiang Chung, Chia-Kuang Tsai, Shih-Jen Tsai, Sung-Sen Yang, Nian-Shen Tzeng, Mu-Hong Chen, and Chih-Sung Liang, *JAMA Pediatrics*, January 4, 2021 (online). Address: Jing-Syuan Huang, Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

—and—

“Untreated autism spectrum disorder tied to alcohol, drug abuse,” Kristen Monaco, MedPage Today, January 4, 2021.

Autism rates elevated in celiac disease

Rates of autism spectrum disorder (ASD) and several other disorders that are often comorbid with ASD are elevated in individuals with celiac disease, according to a recent study.

In celiac disease, an immune system reaction occurs when individuals eat gluten, a protein in wheat and a number of other grains. Symptoms include digestive problems, fatigue, and weight loss.

Motasesm Alkhayyat and colleagues analyzed data collected from 360 hospitals in the United States. Of the approximately 37,500,000 patients included in the database, 112,340 were diagnosed with celiac disease. The researchers say that compared to patients without celiac disease, those with the condition were nearly five times as likely to have ASD. In addition, they were more likely to have a diagnosis of anxiety, depression, bipolar disorder, ADHD, or eating disorders. The researchers conclude that doctors caring for patients with celiac disease need to be aware of these common comorbidities and ensure that they are properly diagnosed and treated.

“Epidemiology and risk of psychiatric disorders among celiac disease patients: a population-based national study,” Motasesm Alkhayyat, Thabet Qapaja, Manik Aggarwal, Ashraf Almomani, Mohammad Abureesh, Omaymah Al-Otoom, Mohammad Zmaili, Emad Mansoor, and Mohannad Abou Saleh, *Journal of Gastroenterology and Hepatology*, February 8, 2021 (online ahead of print publication). Address: Motasesm Alkhayyat, alkhaym@ccf.org.

Research Updates

Kids of “preemie parents” may have higher ASD risk

A new study points to parental premature birth as a possible risk factor for autism spectrum disorders (ASD) in children.

In the study, Jingyuan Xiao and colleagues analyzed the medical registry records of approximately 400,000 parent-child pairs from Denmark. The researchers found that children of men and women who were born at less than 37 weeks or with a low birth weight had an elevated risk of ASD, and that children of parents born very preterm (less than 32 weeks) had a nearly two-fold increase in risk. Other multigenerational factors the researchers explored had only a minimal effect on the risk for ASD.

Zeyan Liew, the study’s senior author, notes that there is increasing evidence that changes in gene activity in response to environmental stimuli can be inherited across generations without changing the underlying DNA sequences, a phenomenon known as epigenetic inheritance. He comments, “These adverse characteristics at birth may act as a proxy measure of possible heritable epigenetic modifications as a result of harmful prenatal exposures affecting early life growth, which could help explain the multigenerational transmission of [ASD] risk we observed.”

“Associations of parental birth characteristics with autism spectrum disorder (ASD) risk in their offspring: a population-based multigenerational cohort study in Denmark,” Jingyuan Xiao, Yu Gao, Yongfu Yu, Gunnar Toft, Yawei Zhang, Jiajun Luo, Yuntian Xia, Katarzyna Chawarska, Jørn Olsen, Jiong Li, and Zeyan Liew, *International Journal of Epidemiology*, January 7, 2021 (online ahead of print publication). Address: Zeyan Liew, Yale Center for Perinatal, Pediatric and Environmental Epidemiology, One Church Street, 6th Floor, New Haven, CT, 06510, zeyan.liew@yale.edu.

“Preemie-born parents linked to children with autism,” news release, Matt Kristoffersen, Yale University, January 11, 2021.

Mitochondrial defects again implicated in ASD

A new study adds to evidence that defects in mitochondria may play a key role in autism spectrum disorders (ASD).

Mitochondria are the “power plants” of cells, and a growing body of research implicates mitochondrial dysfunction as a factor in autism. For example, recent studies have shown that certain variants of mitochondrial DNA (mtDNA) are associated with ASD.

To help determine if mitochondrial defects do make individuals more vulnerable to

ASD, Tal Yardeni and colleagues introduced a mild “missense” mutation in the mtDNA ND6 gene in one strain of mice. The resulting mice exhibited impaired social interactions, increased repetitive behaviors, and anxiety, all of which are common symptoms of autism. In addition, the mice exhibited seizures, electroencephalogram (EEG) abnormalities, and brain-region specific defects in mitochondrial function, despite showing no obvious anomalies in brain anatomy.

Study coauthor Douglas Wallace says, “Our study shows that mild systemic mitochondrial defects can result in autism spectrum disorder without causing apparent neuroanatomical defects. These mutations appear to cause tissue-specific brain defects. While our findings warrant further study, there is reason to believe that this could lead to better diagnosis of autism and potentially treatments directed toward mitochondrial function.”

—
 “An mtDNA mutant mouse demonstrates that mitochondrial deficiency can result in autism endophenotypes,” Tal Yardeni, Ana G. Cristancho, Almedia J. McCoy, Patrick M. Schaefer, Meagan J. McManus, Eric D. Marsh, and Douglas C. Wallace, *Proceedings of the National Academy of Sciences*, February 9, 2021 (free online). Address: Douglas Wallace, WallaceD1@email.chop.edu.

—and—
 “Researchers demonstrate how defects in mitochondria may lead to autism spectrum disorder,” news release, Children’s Hospital of Philadelphia, February 1, 2021.

—In Memoriam— DAROLD TREFFERT, M.D.

Darold Treffert, M.D., passed away on December 14, 2020. The author of *Extraordinary People: Understanding Savant Syndrome and Islands of Genius: The Bountiful Mind of the Autistic, Acquired, and Sudden Savant*, Dr. Treffert was one of the world’s most respected experts on savant syndrome.

Dr. Treffert was on the staff at Agnesian HealthCare, served on the Board of Trustees of Marian University, and was a clinical professor at the University of Wisconsin Medical School and the University of Wisconsin–Milwaukee. In the 1980s, Dr. Treffert (along with Dr. Bernard Rimland) served as a consultant on the film *Rain Man*, starring Dustin Hoffman as an autistic savant.

Jason Padgett, a savant who often spoke in public with Dr. Treffert, says, “He was a force for good. He changed many lives in a positive way and the force of his good will ripple out for a long time to come.”

Case study: folate benefits child at high risk for ASD

Clinicians in India report a case study in which they successfully treated a child at high risk for autism due to a variant in a gene involving the folate pathway.

The child, who was two years old when the doctors saw him, exhibited a number of autistic-like behaviors including speech problems and a lack of eye contact. He was heterozygous for a MTHFR gene mutation called C677T that reduces the ability to convert folic acid into its active form, methylfolate. Previous research has suggested that this mutation may play a significant role in autism.

The clinicians started the child on high-dose folic acid (2.5 mg once a day, given orally) along with behavioral training and speech therapy. They say, “On follow-up three months later, the mother reported improved behavior with the child using words to express his needs, albeit infrequently. He was now making some eye contact when addressed directly. When the Childhood Autism Rating Scale (CARS) was performed six months later at 30 months of age, it was not indicative of any feature of autism.”

They conclude, “Genetic workup for MTHFR gene polymorphism must be considered in children diagnosed with autism spectrum disorder, particularly when basic workup has been noncontributory.”

—
 “Clinical relevance of methylenetetrahydrofolate reductase genetic testing in autism: a case report of successful clinical outcome,” Sufyan Fadila, Praveen Suman, Praveen Kumar, and Faraz Omair, *Cureus*, January 2021 (free online). Address: Sufyan Fadila, sufyanfadila@gmail.com.

ARI Survey: Seniors with Autism Spectrum Disorder

https://www.autism.org/adult_survey

We hope the results from this survey will provide insight about the needs and challenges faced by seniors with autism (ages 50 and older) and their support providers, and better inform the autism community, government agencies, and other welfare and health-related organizations about this population’s quality-of-life issues.

New to autism? If so, the Autism Research Institute has valuable information on seeking appropriate medical care. For a list of important questions to ask a potential medical provider, see:

<https://www.autism.org/finding-a-clinician>

Maternal vitamin D deficiency may increase fetal testosterone

A number of studies implicate low vitamin D levels in utero as a factor in autism spectrum disorders (ASD), and a new study suggests that male children of vitamin D-deficient women have an increased likelihood of having ASD because this deficiency leads to an increase in testosterone in their developing brains.

Research also indicates that fetal testosterone levels are elevated in children who later develop ASD. In addition, the 3-to-1 ratio of males to females in ASD suggests that male hormones play a key role in the condition. However, the new study is the first to link low vitamin D and elevated testosterone.

In the study, Asad Amanat Ali and colleagues, including senior researcher Darryl Walter Eyles, fed female rats a vitamin D-deficient diet before and during pregnancy and then collected tissues from their embryos. The researchers report that maternal vitamin D deficiency led to increases in testosterone

levels in the mothers' blood. In addition, they say, testosterone levels were elevated in the brains of male offspring of the vitamin D-deficient mothers.

Furthermore, Eyles notes, "Our research... showed that in vitamin D-deficient male fetuses, an enzyme which breaks down testosterone was silenced and could be contributing to the presence of high testosterone levels."

Ali and colleagues say their findings provide further support for the prenatal sex steroid theory of ASD.

Levels of testosterone and androstenedione (another sex steroid) were elevated in the amniotic fluid of female but not male fetuses of vitamin D-deficient mothers. However, female fetuses did not exhibit increased testosterone in their brains.

The researchers conclude, "This study is the first to show how an epidemiologically established environmental risk factor for ASD [low vitamin D] may selectively elevate testosterone in male embryonic brains. These findings provide further mechanistic support for the prenatal sex steroid theory of ASD."

"Developmental vitamin D deficiency increases foetal exposure to testosterone," Asad Amanat Ali, Xiaoying Cui, Renata Aparecida Nedel Pertile, Xiang Li, Gregory Medley, Suzanne Adele Alexander, Andrew J. O. Whitehouse, John Joseph McGrath, and Darryl Walter Eyles, *Molecular Autism*, December 2020 (free online). Address: Darryl Walter Eyles, eyles@uq.edu.au.

—and—

"Vitamin D the clue to more autism spectrum disorder in boys," news release, University of Queensland, December 11, 2020.

Coping with COVID-19

To aid individuals with autism and their families during the COVID-19 pandemic, ARI is offering these resources:

- Free presentations offering evidence-based strategies to manage at home during extended school closures
- Social stories and short videos on hygiene and medical procedures.
- Physician resources for supporting patients diagnosed with autism.

To view these, as well as to see first-person stories by families about how they are dealing with this crisis, visit this link:

<https://www.autism.org/covid-19-resources/>

Cannabinoid treatment may reduce behavior problems in children, teens with ASD

Treatment with cannabinoids (compounds found in marijuana) may help to reduce behavior problems in young individuals with autism spectrum disorders (ASD), according to a new study from researchers in Israel and the United States.

In the double-blind, placebo-controlled study, Adi Aran and colleagues tested the effects of a whole-plant cannabis extract and pure cannabinoids on 150 children and adolescents with ASD. Two-thirds of the participants received cannabinoids for 12 weeks (half received the whole-plant extract and half received the purified cannabinoids) while the other third received a placebo. After a four-week washout period, participants were moved to different groups. (Due to a treatment order effect that could impair the validity of their findings, the researchers evaluated efficacy during the first period but not the second. However, data on safety and tolerability were measured in both phases.)

The researchers report that scores on the Clinical Global Impression-Improvement Scale showed that disruptive behavior was either much or very much improved in 49% of participants receiving the whole-plant extract versus only 21% of participants receiving the placebo. In addition, scores on the Social Responsiveness Scale indicated that cannabinoid treatment improved ASD core symptoms. The only common side effects were sleepiness and decreased appetite.

Aran and colleagues say, "Currently, there are no established medications for the core autistic symptoms. Risperidone and aripiprazole have been approved by the U.S. Food and Drug Administration to treat comorbid irritability but these medications often cause obesity and metabolic syndrome. In this study, we have demonstrated for the first time in a placebo-controlled trial that cannabinoid treatment has the potential to decrease disruptive behaviors associated with ASD, with acceptable tolerability. This is specifically important for the many individuals with ASD who are overweight, as cannabinoid treatment was associated with net weight loss in contrast to the substantial weight gain usually produced by antipsychotics."

The researchers note, however, that caution is warranted in interpreting their results due to the study participants' wide range of ages and functional levels.

"Cannabinoid treatment for autism: a proof-of-concept randomized trial," Adi Aran, Moria Harel, Hanoeh Cassuto, Lola Polyansky, Aviad Schnapp, Nadia Wattad, Dorit Shmueli, Daphna Golan, and F. Xavier Castellanos, *Molecular Autism*, February 2021 (free online). Address: Adi Aran, Neuropediatric Unit, Shaare Zedek Medical Center, 12 Bayit Street, 91031 Jerusalem, Israel, aaran@szmc.org.il.

Editorial: Challenging behaviors in adults with autism

(continued from page 3)

the causes and pathophysiology of these behaviors and developing effective treatments must be a public health priority.

It is time for us to create a network to focus on understanding and treating challenging behaviors. This network should consist of all stakeholders in the autism community, including individuals with ASD, family members, clinical professionals, and policymakers. Among other efforts, this network should encourage specialized training for professionals and provide information for caregivers about what they can do at home and where they can find specialists in their area.

Clearly, there are no easy answers to the problem of challenging behaviors in ASD. However, we are stronger when we join forces. By working together, we can provide effective solutions for the millions of people with ASD and their families who are dealing with this difficult issue.

To view the references, visit www.ARRIReferences.org

Need help or information?
The Autism Research Institute maintains a toll-free calling center:
833-281-7165

How just does the world seem to individuals with ASD?

A new study indicates that individuals with autism spectrum disorders (ASD) and neurotypical individuals with high levels of autistic traits are less likely than other individuals to believe that the world is naturally just and that people get what they deserve—a cognitive difference that the study author says has both upsides and downsides for those with ASD.

Alex Bertrams' study involved 588 individuals, 60 of whom had an ASD diagnosis. After assessing participants' reasoning ability and using the Autism Spectrum Quotient to measure their autistic traits, he assessed their global attitude about the justness of the world. In this assessment, participants were asked how strongly they agreed or disagreed with questions such as, "I feel that most people get what they are entitled to have."

A subsample of 388 participants, including all of the individuals diagnosed with ASD, also answered questions designed to assess:

- Their belief that the world was just to them in particular (e.g., "I believe that by and large, I deserve what happens to me").
- Their locus of control (that is, whether events that happened to them were under their own control or externally controlled).
- Their susceptibility to self-deception.

Bertrams' analysis revealed that individuals with ASD or an elevated number of autistic traits had a lower general belief in a just world. Analysis of the subsample showed that this was due to a lower personal belief in a just world, a greater belief in an external locus of control, and lower levels of self-deception.

Bertrams notes that people with a lower belief in a just world are less likely to be socially accommodating and are less biased

by people's group memberships (for instance, their socioeconomic status) when judging them. Similarly, he says, "A tendency toward less diplomacy and less biased information processing has also been found in autistic people or people high in autistic traits."

"Furthermore," he says, "these results point to a crucial autistic strength, namely, the ability to see things in an unbiased, realistic manner." He notes, "The evidence from this study suggests that lower susceptibility to

Bertrams notes that his results "point to a crucial autistic strength, namely, the ability to see things in an unbiased, realistic manner."

some biases is essentially based on a lower tendency for self-deception. This attribute, in combination with their tendency to be undiplomatic, may make autistic people and people high in autistic traits valuable consultants whenever important decisions are made."

However, Bertrams notes, people with a lower belief in a just world are likely to experience a reduced sense of wellbeing because "they deceive themselves too little in a positive direction, that is, they are too realistic." Thus, he says, "In interventions designed to help autistic people, solutions should be sought that appreciate their less-biased view of themselves and the world while still recognizing this as one potential cause of distress."

"Less illusion of a just world in people with formally diagnosed autism and higher autistic traits," Alex Bertrams, *Journal of Autism and Developmental Disorders*, December 2020 (free online). Address: Alex Bertrams, Educational Psychology Lab, Faculty of Human Sciences, Institute of Educational Science, University of Bern, Fabrikstrasse 8, 3012 Bern, Switzerland, alexander.bertrams@edu.unibe.ch.

Free Autism Continuing Education and Webinars

Free Certificates of Participation are available upon passing an online quiz for most webinars. Some events offer Continuing Education Units and/or Continuing Medical Education credits.

—April 21, 2021—

1 p.m. Eastern time

Coping with Transitions During the Pandemic

Amanda Tami, LPC, BCBA

—May 5, 2021—

1 p.m. Eastern time

Neurodiversity in Education and Employment

Lawrence Fung, MD, PhD

Space is limited—watch your email, or visit us on Facebook and Twitter for updates and registration links. You can view previous webinars at <https://www.autism.com/webinars>.

* We are grateful to our friends at the Johnson Center for Child Health & Development for working in partnership to offer presentations.

Positive results reported in study of suramin

A new study adds to evidence that the drug suramin—a hundred-year-old drug used to treat sleeping sickness—may have significant positive effects on the symptoms of autism spectrum disorder (ASD).

In earlier research (see ARRI 2017, No. 2), Robert Naviaux and colleagues administered a single IV infusion of suramin to five boys with ASD, while five boys in a matched placebo group received a single IV infusion of saline. The researchers reported that all five boys who received the suramin infusion showed improvements in language, social behavior, restricted or repetitive behaviors, and coping skills.

In the new study, conducted by the pharmaceutical firm PaxMedica, 52 South African children with moderate to severe ASD were given one of two different doses of intravenous suramin or a placebo at baseline, week 4, and week 8. The researchers conducted a six-week follow-up study after the children received the last dose.

Of the group, 43 children completed the study. One withdrew because of a side effect, and the others withdrew due to COVID-19-related issues or for other reasons.

According to the company's researchers, treatment with suramin led to "marked and sustained" improvement in measures including the Aberrant Behavior Checklist composite score of core symptoms (ABC Core), the Clinical Global Impression of Improvement scale, adapted for autism (CGI-I), and the Autism Treatment Evaluation Checklist (ATEC). They add that participants tolerated both doses of suramin well, although adverse events occurring during treatment included rashes, upper respiratory infection, and vomiting. One child experienced a serious adverse event that resolved with treatment.

According to the researchers, the mechanism by which suramin may improve symptoms of autism is unknown. They speculate that the drug may act to reverse the effects of mitochondrial dysfunction and to reduce neuroinflammation. In the earlier study, Naviaux suggested that suramin works by inhibiting the signaling function of the nucleotide adenosine triphosphate, which is produced by the mitochondria and released from cells to signal danger. He hypothesized that this process can sometimes get "stuck," and that suramin signals that "the cellular war is over, the danger has passed and cells can return to 'peacetime' jobs like normal neurodevelopment, growth and healing."

Editor's note: This research is unpublished. The researchers will present their full findings at an upcoming medical conference.

"Positive topline results for novel autism drug," Megan Brooks, Medscape, February 9, 2021.

Autism Research Institute
4182 Adams Avenue
San Diego, CA 92116
USA

Address Service Requested

NONPROFIT ORG
U.S. POSTAGE
PAID
SAN DIEGO, CA
PERMIT #1

Autism Research Review International Vol. 35, No. 1

*****AUTO

Sample Name
Any Street
Any Street 2
Any City, State Zip_Code



The Autism Research Review International is a quarterly publication of the Autism Research Institute, Stephen M. Edelson, Ph.D., Director.
The Autism Research Institute is a non-profit organization.
Editor: Stephen M. Edelson, Ph.D. • www.Autism.org
Copyright © 2021 ISSN No. 0893-8474

Conducting and sponsoring research on the causes of and best treatments for autism (more than \$280,000 in research grants awarded last year), with a focus on research that can translate rapidly into help for today's autistic children and adults and their families.

- Networking researchers, physicians, and parents to speed the development and dissemination of safe and effective treatment methods.
- Hosting webinars and one of the largest international websites on autism in the world.
- Sponsoring one or two major think tanks a year, involving researchers and experienced clinicians.

ARI's work relies on charitable contributions from individuals and organizations. All donations are tax deductible. We are proud to have earned Charity Navigator's highly respected "Four Star Award" for fiscal management, accountability, and transparency.

ARI'S WORK INCLUDES:

The Autism Research Institute (ARI) is the oldest autism research organization in the world, founded by Dr. Bernard Rimland in 1967.

—About ARI—

Subscriptions

Please send me the *Autism Research Review International* (Four quarterly issues — U.S. \$20; outside the U.S. \$24) (U.S. funds) \$ _____

Advance subscription for _____ 1 yr. _____ 2 yrs. (see rates above) \$ _____

I am enclosing a donation to assist the work of ARI \$ _____

* Federal Exempt Designation 501(c)(3)

NOTE: If you donate \$50 or more to ARI, you will receive a free one-year subscription to the Autism Research Review International!

TOTAL..... \$ _____

NEW SUBSCRIPTION RENEWAL GIFT

I AM DONATING \$50 OR MORE—Start my free one-year subscription!

Name _____ new address

Address _____

Email _____

Phone _____ Fax _____

Credit card: _____ MasterCard _____ Visa _____ Discover _____ Am. Express _____

_____ CVV# _____ Exp. _____

Signature _____

IF THIS IS A GIFT, please list the name and address of the recipient here:

4182 Adams Avenue, San Diego, CA 92116 • 1-833-281-7165 (toll-free)

35/1