

The Interagency Autism Coordinating Committee

2009 Summary of Advances

in Autism Spectrum Disorder Research



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ABOUT THE IACC

The Interagency Autism Coordinating Committee (IACC) was established by Congress under the Combating Autism Act of 2006 (CAA) to provide advice to the Secretary of Health and Human Services (HHS) and coordinate all efforts within HHS concerning autism spectrum disorders (ASD).

As mandated by law, the IACC has a membership composed of federal officials from agencies involved in autism research and services and public members, including people with ASD, parents of children and adults with ASD, and members of the autism advocacy and research community. The diversity of the committee ensures that a broad range of views and opinions is reflected and discussed in a public forum.

Under the CAA, the IACC is required to: (1) Develop and annually update a strategic plan for ASD research, (2) develop and annually update a summary of advances in ASD research, and (3) monitor federal activities related to ASD.

In completing the first IACC Strategic Plan for Autism Spectrum Disorder Research in 2009 and releasing the first update of the plan in 2010, the IACC has laid out a framework for the pursuit of critical biomedical and services research. Through activities such as public meetings and workshops, publication of an annual Summary of Advances in ASD Research, dissemination of information regarding ASD research and IACC activities, gathering of public input and coordination of federal activities related to autism, the IACC continues in its effort to provide guidance to the Department of Health and Human Services and to reach out to the broader autism community to find ways to work together to help people with autism and their families.

For more information about the IACC, see: www.iacc.hhs.gov

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THE 2009 IACC SUMMARY OF ADVANCES IN AUTISM SPECTRUM DISORDER RESEARCH

INTRODUCTION:

Each year the members of the Interagency Autism Coordinating Committee identify recent research findings that made the most impact on the field. For the 2009 Summary of Advances, the IACC selected and summarized 20 studies that gave significant insight into the prevalence of autism spectrum disorder, the biology of the disorder, potential risk factors, and possible interventions. These articles were the top selections from a pool of 63 peer-reviewed articles published in 2009 that were nominated by the committee to reflect the most important work in biomedical and services research for ASD during the year — work that is critical to understanding the disorder and addressing the needs of people with ASD and their families. (Articles appear in alphabetical order by first author. A full reference list is included at the end of the document.)

ARTICLES SELECTED FOR THE 2009 SUMMARY OF ADVANCES:

Medication and parent training in children with pervasive developmental disorders and serious behavior problems: results from a randomized clinical trial – Aman, et al. *Journal of the American Academy of Child & Adolescent Psychiatry*. December 2009.

Training parents to use behavior management techniques, in combination with medication, reduces serious behavioral problems in children with ASD and related disorders when compared to medication use alone. Researchers randomly assigned 124 children, ages 4 to 13, into two groups – both groups received the antipsychotic risperidone, but in one group, parents received a structured training program teaching them to manage their children’s severely disruptive and noncompliant behavior. Risperidone has been shown to reduce tantrums, aggression, and self-injury in children with autism; however, the drug can have side effects like significant weight gain and related health problems. The results of the study showed that while both groups of children improved over the six-month trial, the children whose parents had also received training (over an average of 11 sessions) showed a greater decrease in behavioral problems. These children were also taking a lower dose of risperidone at the end of the trial than the children being treated solely with medication (1.98 mg vs. 2.26 mg/daily). The authors noted that the benefits of actively engaging parents in treatment seemed to increase over time, further supporting the power of parent training. Future studies will evaluate whether the benefits of parent training continue into the future and whether younger children benefit as well. Based on the positive findings of this study, it may be beneficial to provide parent training through schools and community clinics.

Association of family history of autoimmune diseases and autism spectrum disorders – Atladóttir, et al. *Pediatrics*. August 2009.

Mothers with rheumatoid arthritis or celiac disease, both classified as autoimmune disorders, are more likely to have children with ASD, based on a study of about 690,000 Danish children. Children with a family history of type 1 diabetes, another autoimmune disorder, are also more likely to have autism that is recognized in infancy. Researchers confirmed the results of earlier studies showing that family autoimmune disorders – disorders caused by an abnormal immune response against the body's own cells -- are linked to autism risk. While maternal rheumatoid arthritis and family history of type 1 diabetes were both known autism risk factors, the association between celiac disease and ASD was a new finding. Researchers looked at all children born in Denmark between 1993 and 2004 and identified children with an ASD diagnosis using the Danish National Psychiatric Registry. They then assessed the rate and type of autoimmune disorders found in the children's immediate family. To explain their findings, the authors hypothesize that the genes involved in autoimmune disorders may also contribute to ASD. There is also evidence that women with rheumatoid arthritis may produce antibodies during pregnancy that affect fetal brain development. Further research is necessary to explore these hypotheses.

Genome-wide analyses of exonic copy number variants in a family-based study point to novel autism susceptibility genes – Bucan, et al. *PLoS Genetics*. June 2009.

A study of more than 900 families with multiple cases of ASD revealed new autism risk genes and adds to what is known about the genetics of autism. The researchers identified 150 rare genetic variants found in two or more unrelated people with ASD, but not in typically developing individuals. Twenty-seven of these variants were also found in a separate group of people with ASD. These submicroscopic deletions and insertions of DNA, called copy number variants (CNV), were noted in genes that have been identified in other studies, such as neurexin 1 (NRXN1), which encodes a synaptic protein, and genes in the 15q11-q13 region of chromosome 15, including UBE3A, which encodes a ubiquitin-related enzyme. The study also implicated new genes, such as BZRAP1 (benzodiazepine receptor peripheral associated protein), which is involved in regulating the transmission of nerve impulses across the synapse. The researchers additionally noted finding abnormalities in a novel gene called MDGA2 gene in people with ASD (MAM domain containing glycosylphosphatidylinositol anchor 2), which is similar to another neuronal gene that has been implicated in mental retardation and autism. Overall, several of the genes identified produce proteins that allow the synapse – the junction through which neurons communicate – to function. Hundreds of rare genetic variants appeared only once in the study, underscoring the complexity of the genetics involved in ASD. However, greater understanding of

the genetics underlying ASD could eventually lead to therapeutics that target specific genes and their pathways.

Prevalence of autism spectrum disorders – Autism and Developmental Disabilities Monitoring Network, United States, 2006 – Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report (MMWR) Surveillance Summaries*. December 2009.

About one percent of 8-year-olds in the United States have an autism spectrum disorder, according to a CDC study of children in 2006 that was released in December 2009. This is a 57 percent increase from the rate of 1 in 150 children found in 2002 using the same research methods, although it is unclear how much of the increase results from better diagnosis and increased awareness. Similar to previous studies, boys were four times as likely to be affected as girls, with 1 in 70 boys receiving a diagnosis. Black or Hispanic children were less likely to have ASD than their white peers, but more research is needed to determine how much of the disparity may result from lower rates of diagnosis in these communities rather than lower rates of autism itself. Investigators analyzed the available medical records and school records of about 300,000 children across the U.S. at 11 sites in the Autism and Developmental Disabilities Monitoring Network. ASD rates ranged across the sites between a high of 1 in 80 children in Arizona and Missouri to a low of 1 in 240 children in Florida. The study also showed that while children are being diagnosed slightly earlier than in 2002, the majority of children are not diagnosed until 3 ½ to 5 years of age – a significant delay considering that most had concerns about their development documented in their records before their third birthday.

Autism genome-wide copy number variation reveals ubiquitin and neuronal genes – Glessner, et al. *Nature*. May 2009.

In the past few years, scientists studying autism have become very interested in a specific type of genetic variation caused by submicroscopic DNA deletions or duplications. Known as copy number variants (CNV), these mutations seem to occur more frequently in people with ASD and are yielding clues about the genetic basis of the disorder. For example, a 2008 study found that people with copy number variants in a region of chromosome 16 are likely to develop ASD. (This chromosomal region includes genes that appear to be related to neurodevelopment and brain function.) Now, a study of CNVs across the entire ASD genome has identified a cellular pathway known as the ‘ubiquitin pathway’ as potentially playing a role in ASD. This pathway is involved in altering protein function and acts as a ‘filtration system’ by removing unused or damaged proteins from the cell. The study, published in *Nature* in April 2009, also revealed variants in genes that had previously been identified in other studies, such as neurexin 1 (NRX1) and contactin 4 (CNTN4). These genes code for proteins that help neurons adhere to one another

and create synaptic connections, which are necessary for communication between neurons. Other genes with the similar functions, neuroligin 1 (NLGN1) and astrotactin 2 (ASTN2), were also newly implicated. The authors hypothesize that the two different types of gene networks identified in the study (ubiquitin-related and synaptic) may interact within the brain. They also note that while the CNVs found in the study are only present in a small percentage of people with ASD, they reveal important gene networks that may contribute to the disorder. Understanding the genetics of ASD may help researchers to categorize the disorder into subtypes and could eventually lead to the development of therapeutics targeting specific biological pathways.

Genomic and epigenomic evidence for oxytocin receptor deficiency in autism – Gregory, et al. *BMC Medicine*. October 2009.

Oxytocin is a hormone believed to be involved in social behaviors such as recognition, bonding, and trust, as well as anxiety and repetitive behaviors. Acting primarily in the brain, early studies have suggested that oxytocin may play a role in ASD and some have suggested supplementing levels of the hormone as a potential treatment. A study published in *BMC Medicine* further supports the role of oxytocin receptors, which allow oxytocin to bind to neurons, in ASD. After comparing the complete genomes of 119 people who came from families with multiple cases of autism, researchers found one boy with ASD who was missing one copy of the oxytocin receptor gene (OXTR). His mother was missing one copy of the gene as well and showed symptoms of obsessive-compulsive disorder. Although his sibling with ASD was not missing the oxytocin receptor gene, the researchers found evidence suggesting that epigenetic changes —changes which can alter the expression of the gene without changing its basic DNA —could be the cause. These epigenetic changes can be caused by environmental factors and most commonly result from chemical entities called methyl groups attaching to points on the DNA helix. These methyl groups are read and, as a result, the gene is “turned off” (silenced) or “turned on” (activated). After examining levels of methylation in the sibling, it was found that there was increased methylation in a region that regulates the activity of the OXTR gene, suggesting that the gene was effectively silenced. The researchers also found evidence of epigenetic changes to elements that regulate OXTR in the blood and brain tissue of other people with ASD. This research provides more evidence that OXTR and the signaling pathway for oxytocin are involved in the disorder. This could potential give rise to therapeutics in the future, based on what researchers have discovered about the role of oxytocin in ASD.

Risk of autism and increasing maternal and paternal age in a large North American population –
Grether, et al. *American Journal of Epidemiology*. November 2009.

Older mothers and older fathers are more likely to have a child with ASD when compared to younger parents, according to a study of 7.5 million children born in California from 1989 - 2002. While previous studies had shown a link between a father's age and autism risk, studies on the effect of a mother's age were not as conclusive. This study found that for every ten-year increase in a mother's age, her risk of having a child with ASD rose by 38 percent, independent of her partner's age. Each ten-year increase in a father's age raised his risk by 22 percent. This effect was seen in all races and ethnicities and was not affected by the baby's birth weight or gestational age. Parents' age had a greater affect on autism risk in first-born children than children born later. More research is necessary to understand why older parents are more likely to have children with ASD, but the authors hypothesize that a number of factors that impact older women may play a role, including hormonal changes that could affect fetal brain development, increased use of assisted reproductive technologies, age-related genetic changes, and the cumulative effect of exposures to environmental toxins. Older men are known to have accumulated a greater number of spontaneous genetic mutations in their sperm over time, which could increase the chances of having a child with ASD. More research is needed to understand autism risk factors and ultimately to communicate them to the public.

Representation of internal models of action in the autistic brain – Haswell, et al. *Nature Neuroscience*. August 2009.

Whenever a person decides to perform a movement, such as lifting his arm, the brain creates a model to predict what kind of sensory information will result. This model gives the person a sense of how the orientation of his arm will feel in relationship to his body, for example. Researchers have found that people with ASD are over-reliant on this sensory feedback (also called "proprioceptive information"), and that greater reliance is linked to greater levels of social impairment and poorer imitation skills. During the study, children were asked to manipulate a robotic arm to move a cursor to a target, "capturing" animals projected onto a screen if the child was quick and accurate enough. Children with ASD and typically developing children were trained on the robotic arm. After the training round, the handle for the robotic arm was moved, making it necessary for the children to readjust to the new positioning. The study revealed that children with ASD were over-reliant – on their mental model of how their arm should feel in relationship to their body during the task. They were unable to use visual cues and adjust to the new positioning like their typically developing peers. These findings could explain in part why children with ASD often have issues with motor control and imitation, and may help to develop methods for improving motor skills in the future.

Incidence of gastrointestinal symptoms in children with autism: a population-based study – Ibrahim, et al. *Pediatrics*. August 2009.

The first long-term study of gastrointestinal (GI) issues in children with ASD found no difference in the frequency of symptoms when compared with typically developing children. While the issue remains a contentious one, this research adds to a body of evidence that GI disorders are no more frequent in children with ASD than they are in the general population. In the study, researchers tracked all the residents of Olmsted County, Minnesota who were younger than 21 years of age between 1976 and 1997. Within this group, there were 124 children who were diagnosed with ASD. The researchers followed these children, along with typically developing children of the same age and gender, until they were about 18 years old, tracking their gastrointestinal symptoms over many years. They found no difference between the two groups in overall incidence of GI symptoms or specific GI disorders. Although children with ASD were more likely to have constipation or feeding issues such as food selectivity, the authors suggest that these problems resulted from ASD-related behaviors rather than from true GI disorders. They conclude that although there may be subgroups of children with ASD who suffer from concurrent GI disorders that contribute to their behavior, this study suggests that in general, GI disorders are not more common in children with ASD than they are in typically developing children. They caution against the indiscriminate use of restrictive diets, vitamin and mineral supplements, and other related treatments for children with ASD, noting that these alternative treatments should only be used on a case-by-case basis for children with a diagnosed GI disorder.

Diagnostic change and the increased prevalence of autism – King & Bearman. *International Journal of Epidemiology*. October 2009.

While autism prevalence has increased dramatically in the last 30 years, it is unclear how much of the increase can be explained by changes to diagnostic criteria and guidelines. After creating a statistical model based on the analysis of service records, researchers estimated that more than one-quarter (26.4%) of the increase in California since 1992 can be explained by a change in diagnosis among a specific group —people initially diagnosed with mental retardation whose diagnosis was later changed to autism. Researchers examined the case records of more than 7,000 people with ASD born before 1987 who were enrolled with the California Department of Developmental Services between 1992 and 2005. They paid particular attention to a group of patients who were initially diagnosed with mental retardation and then received an alternate or additional diagnosis of autism. After analysis, the researchers found that patients were much likelier to acquire an autism diagnosis after changes to the Diagnostic and Statistical Manual of Mental Disorders (DSM), or other diagnostic guidelines. There have been multiple changes to the DSM definition of autism since 1987, most significantly when the fourth edition was

published in 1994. The authors conclude that changes in practices for diagnosing autism have had a substantial effect on the overall autism rate. While the shift in diagnosis from mental retardation to autism accounts for one-quarter of the increase, the reasons for the remaining 75 percent are still unexplained. Understanding the multiple factors that are influencing the increase in ASD may ultimately help to identify the underlying causes.

Two-year olds with autism orient to non-social contingencies rather than biological motion – Klin, et al. *Nature*. May 2009.

People with ASD tend to fixate on other's mouths when they speak rather than their eyes. Now a study published in *Nature* may explain why – the synchronization between mouth movements and speech are compelling for people with the disorder. In a study of toddlers, when presented with a range of possible cartoons to observe, children with ASD were preoccupied with cartoons where motion synchronized with sound, such as dots colliding to produce a clapping sound. On the other hand, typically developing children were equally interested in cartoons where motion-sound synchrony was not as strong. The researchers studied the toddlers' eye movements while watching animations of people moving that had been reduced to points of light at each joint. Even with only a set of moving dots, young children without ASD are able to identify biological motion, such as a person walking, and are naturally drawn to it. The children with ASD showed no preference for biological motion over other types of movement, but were fascinated by animation where sound and motion synchronized. This is a likely explanation for why people with ASD favor the mouth over the eyes during a conversation. Understanding this tendency may help to develop future interventions.

Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007 – Kogan, et al. *Pediatrics*. November 2009.

A 2007 survey of parents across the U.S., called the National Survey of Children's Health (NSCH), showed a similarly increased rate of ASD as the CDC surveillance study (CDC, 2009) published soon after. Parents who participated in the NSCH were asked whether their child had ever been diagnosed with ASD by a doctor or other health professional. They were then asked if their child currently had ASD. Based on the number of parents who said that their child had been diagnosed and still held the diagnosis, researchers estimated that ASD occurs in about 1 in 91 children in the U.S., slightly higher than the rate of 1 in 110 children found in the CDC study. Similar to other studies, boys were four times as likely to have ASD as girls and white children were more likely to be affected than black or multi-racial children. Interestingly, nearly 40 percent of children who had been diagnosed with ASD in the past no longer had the disorder, according to their parents. Black children were more likely than white children to have

reportedly lost their diagnosis. The authors note that the number of children losing their diagnosis could be inflated —children who were suspected to have ASD but later found not to after subsequent assessments would be included in this group. It is also possible that children with developmental delays, mental retardation, or learning disabilities were initially classified as having ASD to obtain needed services. Unfortunately, these hypotheses cannot be tested using the data collected in this study. This study does give more evidence that the rate of ASD is increasing. Surveillance efforts such as these are critical to determining prevalence and providing information for communities when planning for services.

Racial/ethnic disparities in the identification of children with autism spectrum disorders – Mandell, et al. *American Journal of Public Health*. March 2009.

Studies have shown that ASD is often diagnosed long after symptoms have appeared or is misdiagnosed as another disorder. Unfortunately, these delays and errors seem to be even more frequent in racial and ethnic minorities. A study published in the March issue of the *American Journal of Public Health* revealed that black and Hispanic children with ASD were less likely to have been diagnosed by a medical professional than were white children. This was also true of children who identified their race/ethnicity as “other.” Most of the Asian and Hispanic children who failed to be diagnosed with ASD also had an intellectual disability (IQ<70), which can complicate ASD diagnosis. However, black children were less likely to be diagnosed regardless of whether or not they had an intellectual disability. Researchers screened health care and education records from about 2,600 eight-year-olds at sites across the U.S. involved in the CDC’s Autism and Development Disabilities Monitoring (ADDM) network. Using the records, experienced clinical reviewers assessed whether the child had documented symptoms that met the criteria for ASD and whether an official diagnosis had been made. In total, only 58 percent of children in the study meeting the case definition of ASD had received a diagnosis. In addition to minority groups, girls were also significantly less likely to receive a diagnosis when compared to boys. This was also true of children whose mothers had not completed high school. The authors note that mothers with greater education may be more aware that a diagnosis is necessary to receive educational services. The significant racial and ethnic disparities shown in the study support the need for continued professional education for clinicians to improve ASD identification in children.

Abnormal behavior in a chromosome-engineered mouse model for human 15q11-13 duplication seen in autism – Nakatani, et al. *Cell*. June 2009.

Researchers bred mice to have a genetic abnormality that is analogous to one frequently seen in people with ASD and found that the mice showed similar patterns of inflexible behavior, impaired social skills, and anxiety seen in people with the disorder. The mice were engineered to have a duplication on mouse chromosome 7 that bears strong similarity to a particular region of human chromosome 15 —15q11-13 — which has been linked to autism. In the study, researchers found that animals that had inherited the engineered duplication from their fathers showed behaviors characteristic of ASD. These mice showed impaired social abilities, choosing not to interact when introduced to a stranger mouse, and were less able to adapt to changes in mazes than other mice. They were also more likely to show anxiety or depression, based on their reactions to forced swim tests and their increased distress calls when separated from their mother as pups. These findings give evidence that duplications to this particular genomic region can contribute to the behaviors typical of ASD. In addition, this research represents an advance in the development of animal models of autism that display both genetic and behavioral similarities to the disorder in humans. Animal models such as this one will be critical for future research into the underlying biology of ASD.

Autism and other neuropsychiatric symptoms are prevalent in individuals with MeCP2 duplication syndrome – Ramocki, et al. *Annals of Neurology*. December 2009.

Boys with a rare and potentially fatal brain disorder caused by an additional copy of the MECP2 gene are very likely to also have autism, based on a study published in the *Annals of Neurology*. Genetic variation in the MECP2 gene (methyl-CpG-binding protein 2) is known to cause Rett syndrome, a neurodevelopmental disorder on the autism spectrum that appears in girls. Researchers set out to find if the duplication of this gene would cause autism in males and lesser ASD symptoms in females. MECP2 codes for a protein which is essential for brain development and is thought to be involved in the silencing (“turning off”) of several other genes. Boys with an additional copy of MECP2 develop MeCP2 Duplication Syndrome, a recently discovered disorder marked by severe intellectual disability, muscle weakness, and seizures. Researchers studied eight families with MECP2 duplication (9 males and 9 females) and found that all of the boys had classic autism and mental retardation. Their mothers, who were shown to be carriers of the disorder, all experienced psychiatric symptoms, including anxiety, depression, and compulsive behavior. Four of the seven mothers were on the autism spectrum. This study supports genetic testing for MECP2 duplication in boys with autism and mental retardation. If the disorder is identified, the entire family may benefit from genetic counseling – mothers are likely to be carriers and siblings may also be affected. This study also suggests that since duplication of the MECP2 gene is so strongly linked to development of autism in humans, that study of MECP2 function in animal models may reveal critical new insights into how autism develops.

Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study – Shattuck, et al. *Journal of the American Academy of Child and Adolescent Psychiatry*. May 2009.

A large national study of children with ASD revealed that the median age of diagnosis was nearly 6 years old and more than one-quarter of the children were not diagnosed until age 8. Experienced clinicians can identify autism between 2 and 3 years of age, so these statistics show that diagnosis is significantly delayed in most cases. With later diagnosis, children with ASD miss a critical window for early intervention, which has been shown to have a profound impact on development. Researchers reviewed the medical records and education records, when available, of the approximately 2,600 children included in the 2002 ADDM surveillance study. An analysis of the data showed that boys were more likely to be diagnosed at a younger age, as were children with intellectual disabilities (IQ<70), and those who had experienced regression. The authors noted that the gender differences in diagnosis could stem from cultural biases about what constitutes normal behavior for girls – for, example shyness may be more socially acceptable. There was no difference in age of diagnosis across races after adjusting for other factors. This study shows significant delays between the age at which diagnosis is possible and when it is actually taking place. Researchers need to conduct research to understand the consequences of late identification and develop methods to improve the timing of diagnosis. Future efforts should also focus on identifying ASD in school-aged children who may not have been diagnosed earlier, according to the study authors.

Partial reversal of Rett syndrome-like symptoms in MeCP2 mutant mice – Tropea, et al. *Proceedings of the National Academy of Sciences USA*. February 2009.

Researchers were able to reverse some of the symptoms of Rett syndrome in a mouse model through daily injections of insulin-like growth factor-1 (IGF-1), a hormone involved in childhood growth. Rett syndrome, classified as part of the autism spectrum, occurs almost exclusively in girls and is caused by mutations to the MeCP2 gene on the X chromosome. Researchers bred mice with the same genetic abnormality and, as a result, showed similar symptoms to humans with Rett syndrome: lethargy, abnormal breathing, irregular heartbeat, smaller brains, and shortened lifespan. Researchers also observed that the MeCP2 mutant mice had immature synapses, which are necessary for sending signals throughout the brain. Previous research had suggested that one of the target genes regulated by MeCP2 is brain-derived neurotrophic factor (BDNF), which is a growth factor protein that stimulates growth and differentiation of neurons and synapses. Because BDNF does not easily cross the blood-brain barrier, researchers decided to try to see if another related growth factor called insulin growth factor -1 (IGF-1) might be able to reverse Rett syndrome symptoms in the mouse model. The researchers found that after daily injections of IGF-1, the mice were more active, their breathing and heart rate normalized, and

they lived longer than the MeCP2 mice that did not receive the treatment. Importantly, their brain weight increased and they showed signs that their synapses were maturing — the number of dendritic spines, projections on the neuron used to send and receive electrical signals, also increased. The authors note that while the effects of IGF-1 are significant, the mice still develop the full range of symptoms and die prematurely. More research is needed to understand how IGF-1 works to reduce symptoms of Rett syndrome, but this study has exciting implications for potential treatments.

Common genetic variants on 5p14.1 associate with autism spectrum disorders – Wang, et al. *Nature*. May 2009.

Researchers have identified several genomic variants commonly found in people with ASD near two genes on chromosome 5. The strong association of these variants with cases of ASD suggests that they confer risk for the disorder. While many other genetic variants linked to ASD have been identified to date, individually those variants are rare, accounting for only a fraction of cases. This study is the first to find common variants associated with ASD, and came after examining the full genomes of 10,000 people with ASD, family members, and volunteers. The two genes implicated, cadherin 9 (CDH9) and cadherin 10 (CDH10), code for proteins that are embedded in the surface of neurons and allow them to adhere to one another. The authors believe that the newly identified variants may impact the function of these two nearby genes, disrupting neural connections being formed in the developing brain. This finding converges with other recent studies that have implicated genes with a similar function. Results of the study were replicated in two other sample groups. Genome-wide studies allow an extremely comprehensive look at the genetic risk factors for ASD. Together with studies of environmental risk factors and changes to gene expression, scientists will be better able to understand the basis of ASD, which may ultimately result in new treatments and strategies for prevention.

A genome-wide linkage and association scan reveals novel loci for autism – Weiss, et al. *Nature*. October 2009.

While past studies have had limited success identifying autism risk genes that could account for the majority of cases, new technologies that allow researchers to scan a person's entire genetic make-up are leading to new breakthroughs. One such genome-wide study of more than 1,500 people with ASD revealed that genetic abnormalities at a region on chromosome 5 — 5p15 — are linked to the disorder. A gene in this region, semaphorin-5A (SEMA5A), is involved in guiding the neuron's axon during early brain development (the axon is the projection from the neuron that conducts the impulses used to communicate with other cells). Researchers found decreased levels of the protein produced by SEMA5A in the brains of people with ASD, which

suggests that the gene is involved in ASD. In addition to the region on chromosome 5, two other locations were found to be associated with ASD: regions on chromosome 6 (6q27) and chromosome 20 (20p13). By identifying genetic regions and specific genes related to ASD, researchers may be able to one day conduct genetic screening for the disorder to improve diagnosis and develop targeted treatments.

Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants – Zwaigenbaum, et al. *Pediatrics*. May 2009.

With the increased emphasis on early detection and the recommendations from the American Academy of Pediatrics that all 18- and 24-month-olds be screened for ASD, it is important for clinicians to understand how the diagnostic criteria for ASD can be applied to children in this age group and which methods and tools can be used to provide the most reliable diagnosis. An article published in *Pediatrics* addresses what is known about the early signs of ASD, best practices for diagnosis in very young children, and available interventions. Studies of infants who have an older sibling with ASD show that developmental delays related to the disorder can be detected from 12 to 18 months of age. These signs could include a lack of eye contact, delayed motor skills, repetitive actions with toys, or a lack of babbling. However, doctors are faced with trying to diagnose ASD with assessments that may not be useful for children under two years of age. Research shows that fewer than 1 in 5 children diagnosed with ASD at 20 to 24 months of age were correctly identified by the Checklist for Autism in Toddlers (CHAT) at 18 months. Even if a diagnosis is suspected, clinicians have difficulty recommending appropriate interventions for children less than two years of age. It has not been established whether interventions designed for pre-school age children are beneficial for toddlers. The authors advise clinicians to follow up with parents who express concerns about their toddler's development, referring them for additional evaluation and early intervention services when appropriate. Ongoing research will help to expand the options for diagnosing and treating very young children suspected to have ASD.

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