Review

Biological Psychiatry

# Autoimmunity, Autoantibodies, and Autism Spectrum Disorder

Elizabeth Edmiston, Paul Ashwood, and Judy Van de Water

**ABSTRACT**

Auism spectrum disorder (ASD) now affects one in 68 births in the United States and is the fastest growing neurodevelopmental disability worldwide. Alarmingly, for the majority of cases, the causes of ASD are largely unknown, but it is becoming increasingly accepted that ASD is no longer defined simply as a behavioral disorder, but rather as a highly complex and heterogeneous biological disorder. Although research has focused on the identification of genetic abnormalities, emerging studies increasingly suggest that immune dysfunction is a viable risk factor contributing to the neurodevelopmental deficits observed in ASD. This review summarizes the investigations implicating autoimmunity and autoantibodies in ASD.

*Keywords:* Autism, Autoimmunity, Immune, Maternal autoantibodies, Neurodevelopmental, Pregnancy

http://dx.doi.org/10.1016/j.biopsych.2016.08.031

Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental disorder characterized by behavioral, social, and cognitive deficits (1). Since its first description nearly 70 years ago, our understanding of the disorder has changed considerably (2). Although the diagnosis always relies on behavioral domains and symptomology, there are likely multiple biologically defined subgroups within the ASD spectrum (3–7). Specifically, growing evidence supports that maternal immune dysfunction may underlie the behavioral abnormalities observed in a subset of children affected with the disorder (8). Several immunologic risk factors have been described, including genetic associations with immune-related genes (9–16), family history of autoimmune disease (15,17–21), maternal inflammation and infection during pregnancy (22–27), and altered immune responses in the children, and are associated with increased impairments in core and associated features of ASD (28). More specific to this review, maternal antibrain autoantibodies, which are thought to access the fetal compartment during gestation, have been identified as a risk factor for developing ASD and are proposed to contribute to early neurodevelopmental perturbations in the developing fetus (29–31).

## THE RELATIONSHIP BETWEEN AUTOIMMUNITY AND ASD

ASD shares many of the features typically recognized in autoimmune disorders; there is a strong familial predisposition and association with immune abnormalities, the genetic predisposition is complex and believed to be polygenic, environmental factors can increase or modulate risk, and there are substantial gender disparities (17,32). Many of the genes implicated in autoimmunity are also clustered within families with ASD. However, although several candidate genes have been implicated in the disorder, replication of the majority of these findings has been elusive and hints that in addition to genetic factors, environmental influences, such as those observed in autoimmune diseases, may be contributing to the disorder in some cases (33). Further, ASD is four times more prevalent in males, and recent studies suggest the prevalence in boys is closer to 1 in 42 (34). The epidemiological links between autoimmunity and ASD are compelling, and the similarities have spurred several investigators to connect biologically rooted autoimmune disorders with behaviorally defined ASD.

The first investigations supporting the idea that autoimmunity could be etiologically relevant to ASD were described in a 1971 case report that presented on a child with ASD who had a strong family history of autoimmune disorders (35). Since that time, numerous other reports of autoimmune or immune-mediated disorders associated with an increased ASD risk have emerged (15,17–19,36,37). In one of the largest studies to date that included close to 700,000 children, an increased risk, as expressed by an increased risk ratio (IRR), for ASD was observed in mothers with rheumatoid arthritis (RA) (IRR: 1.70) and celiac disease (IRR: 2.97). A familial history of type 1 diabetes (IRR: 1.78) was also found to increase the risk for having a child with ASD (18). Similar results were seen in a recent systematic review and meta-analysis performed by Wu *et al.* (20) (2015), which suggested that a family history of autoimmune disease was associated with a higher risk for having an affected child, and a statistically significant association was observed in families with hypothyroidism, type 1 diabetes, RA, and psoriasis. A similar analysis by Chen *et al.* (21) found that children born to mothers with autoimmune disease were 34% more likely to develop ASD. A genetic predisposition in autoimmune diseases is often attributed to specific major histocompatibility complex haplotypes and polymorphisms in



ISSN: 0006-3223

**Table 1. Studies Linking Autoimmunity and ASD**

| Type of Study | Research Group | Year | Findings |
|---|---|---|---|
| Case Study | Money *et al.* (35) | 1971 | Child with ASD had a family history of autoimmune disease |
| Research Study | Warren *et al.* (9) | 1991 | The null allele of the C4B gene and the extended haplotype B44-C30-DR4 is associated with autism |
| | Mostafa and Shehab (14) | 2010 | |
| Research Study | Warren *et al.* (10) | 1996 | The HVR-3 of certain DRP 1 alleles have a very strong association with ASD |
| Research Study | Torres *et al.* (11) | 2006 | The frequency of HLA-A2 alleles was significantly increased in autistic subjects compared with normal allelic frequencies |
| Research Study | Campbell *et al.* (12) | 2008 | The MET promoter variant rs1858830 C allele was associated with ASD |
| Population Study | Atladóttir *et al.* (18) | 2009 | Increased risk for ASD in mothers with rheumatoid arthritis and celiac disease and in families with type 1 diabetes |
| Systemic Review and Meta-analysis | Wu *et al.* (20) | 2015 | A statistically significant association with ASD was observed in families with hypothyroidism, type 1 diabetes, rheumatoid arthritis, and psoriasis |
| Systemic Review and Meta-analysis | Chen *et al.* (21) | 2016 | Children born to mothers with autoimmune disease were 34% more likely to develop ASD |

ASD, autism spectrum disorder; HVR-3, third hypervariable region.

genes involved in establishing self-tolerance and immune regulation (38). Similar polymorphisms and associations have been found in ASD. Most notably, studies have correlated the null allele of the C4B gene (9,14), the extended haplotype B44-C30-DR4, the third hypervariable region of certain DRP 1 alleles (10), and HLA-A2 alleles with an increased susceptibility for ASD (11,39). Interestingly, these alleles and haplotypes are also associated with the same aforementioned autoimmune diseases that are linked with an increased risk for having a child with ASD. Another important functional polymorphism that often clusters in families with ASD is a genetic variant that disrupts transcription of the gene encoding the MET receptor tyrosine kinase (12), which has important roles in both immune regulation and neurodevelopment. The similarities between the findings in ASD and autoimmunity suggest an immune-related subtype of ASD (Table 1).

The notion that immune system dysfunction could be a plausible factor in the cause of ASD is derived from the now-recognized importance of the immune system in healthy neurodevelopment and the ability of immune dysregulation to influence patterns of behavior, especially during gestation (28,39–41). Thus, there is growing recognition that the maternal immune response during critical windows of development has a long-lasting impact on neurodevelopmental outcomes.

## THE DETECTION OF AUTOANTIBODIES IN ASD

The recognition that maternal antibodies may lead to developmental defects in the fetal nervous system is not novel. Experiments performed in the late 1950s demonstrated that when female mice were immunized with a brain emulsion and later mated, subsequent offspring had gross brain abnormalities, which the author attributed to maternal antibodies directed against the brain and nervous system of the embryos (42). This idea gained favor again in the early 1970s when researchers, concerned that maternal environmental exposures could have detrimental effects on fetal nervous system development, discovered that maternal immunoglobulin G (IgG) was present in fetal cerebral spinal fluid and was able to gain access to the brain during gestation and early life because of the permissive nature of the blood-brain barrier during that period (43–45). Succeeding experiments by several groups showed that antibrain antibodies could induce behavioral changes in the exposed offspring (46,47). However, it was not until the 1990s that the first studies implicating maternal antibodies in the cause of ASD emerged.

The earliest study performed by Warren *et al.* (48) (1990) confirmed their hypothesis that maternal autoantibodies reactive to proteins displayed on paternal lymphocytes, which are often found in women with a history of miscarriage, are disproportionately observed in mothers with children with ASD. Although sample sizes of the study were small, it prompted other investigators to conduct similar etiological studies into the role of maternal antibodies and aberrant neurodevelopment associated with ASD. Subsequently, a single sample from the serum of a mother with a child with ASD and developmental delay demonstrated that purified antibodies that reacted to mouse neurons resulted in deficits in the exploratory behaviors in the resulting offspring when injected into a dam during gestation (49).

Acknowledging the importance of these pivotal pilot studies, researchers began to expand these endeavors to include larger clinical populations (Table 1). One of the first expanded case-controlled studies published was performed by Braunschweig *et al.* (50) and included equal numbers of children with autism ($n$ = 61) and mothers of typically developing children ($n$ = 62), along with a subset of mothers who had children with developmental delay ($n$ = 40). This study found a significant correlation between the paired maternal antibody reactivity to fetal brain proteins located within the 37- and 73-kDa molecular-weight bands on a human fetal brain immunoblot and a diagnosis of ASD in the child. Further, this reactivity was only in plasma samples obtained from families affected with ASD because reactivity was not seen in families that had typically developing children or children diagnosed with developmental delay (50). In another small study by Zimmerman *et al.* (51), it was shown by immunoblotting that only antibodies from mothers of autistic children recognized fetal rat brain proteins because no antibody reactivity was detected in the control maternal

group, and they were specific to fetal antigens because they did not bind to proteins derived from postnatal and adult rat brains. These reports were closely followed by a study that examined the serum reactivity of 100 mothers of children with ASD and 100 age-matched control mothers and determined that antibody reactivity to fetal brain proteins observed in mothers of children with ASD significantly differed from the control groups (52).

A similar study using banked midpregnancy (prospective) blood samples also observed that maternal autoantibody binding to antigens near 37 and 73 kDa was only found in women whose children later received a diagnosis of ASD (53). Surprisingly, all the aforementioned reports were unable to find a correlation between a family history of autoimmunity and the presence of maternal antibrain antibodies. However, a later study conducted by Heuer *et al.* (54) reported that 95% of mothers with autoantibodies to both the 37- and 73-kDa fetal brain bands (found only in ASD) possessed the *MET* C allele, which provided the first link between a functional immune-related outcome and an ASD susceptibility gene. In this study population, among the 346 mothers of both children with ASD and typically developing children who were negative for the 37- and 73-kDa bands, 101 (29%) were C/C, 154 (45%) were C/G, and 91 (26%) were G/G. Thus, the *MET* C allele appears to confer susceptibility rather than cause the production of these autoantibodies. Furthermore, because this allelic variant was shown to lead to decreased levels of interleukin 10, a crucial anti-inflammatory cytokine, mothers with this allele are hypothesized to be at increased risk for autoimmunity and autoantibody generation, hinting at a potential mechanism behind the loss of self-tolerance in these mothers. The study conducted by Brimberg *et al.* (55) supports this hypothesis because it found not only that mothers of children with ASD preferentially carried autoantibodies to fetal brain tissue, but that these mothers were also significantly more likely to have antinuclear autoantibodies than mothers of typically developing children and mothers of children with ASD who are antibrain autoantibody negative. Interestingly, it was also discovered that mothers with antibrain autoantibodies had an increased incidence of RA and systemic lupus erythematosus, and conversely, antibrain autoantibodies were detected in women with RA, providing additional evidence that brain-reactive maternal autoantibodies are related to autoimmunity (55). Although the methods for the study by Brimberg *et al.*, in which serum samples were incubated with mouse tissue sections and autoantibodies were detected using immunofluorescence, differed from previous studies using denatured proteins and detecting autoantibodies by immunoblotting, similar results were achieved in that levels of maternal autoantibodies were elevated in mothers of children with ASD. Although the specific maternal antifetal brain antibodies were disproportionately detected in mothers of children with ASD in the earlier studies and were associated with immune dysfunction and autoimmunity, there was still little evidence supporting the notion that maternal autoantibodies could affect behavior at that time.

In order to address the association between maternal autoantibodies and behavior, another large study was conducted by Braunschweig *et al.* (56) that provided further suggestion of a potential role for maternal autoantibodies in ASD behaviors and reported an association between the presence of antifetal brain antibodies in the mother and ASD-related deficits in the child. The study by Braunschweig *et al.* (56) discovered that paired brain (i.e., 37- and 73-kDa bands) reactivity correlated with lower expressive language scores in the child. Additionally, it was noted in a subsequent study that children born to mothers with this antibody-binding pattern also exhibited abnormal brain enlargement when compared with both children with ASD born to mothers who did not harbor antibrain antibodies and typically developing control children (57). Further, reactivity to a band near 39 kDa was later discovered, and paired reactivity to proteins at 39 and 73 kDa correlated with a broader diagnosis of ASD (which was distinct from full autism at that time), as well as increased irritability on the Aberrant Behavioral Checklist scale (56).

In order to understand how these antirain antibodies could potentially lead to aberrant developmental trajectories, the identity of the proteins corresponding to the 37-, 39-, and 73-kDa bands needed to be elucidated. Studies by our laboratory, which used two-dimensional gel electrophoresis followed by tandem mass spectrometry peptide sequencing, determined that the maternal autoantibodies recognize seven developmentally regulated proteins in the fetal brain that include lactate dehydrogenase A (LDH-A) and B (LDH-B), stress-induced phosphoprotein 1 (STIP1), guanine deaminase,

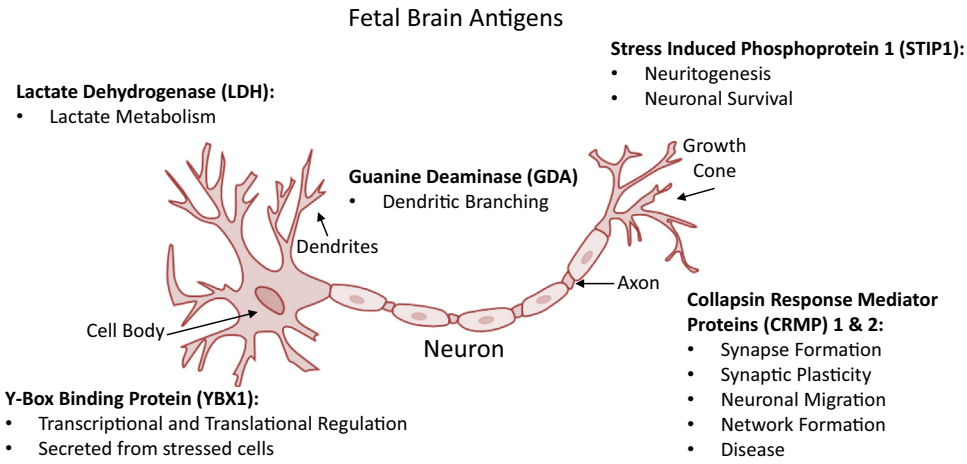


**Figure 1.** Fetal brain antigens. The maternal autoantibodies detected in mothers of children affected with autism spectrum disorder bind to fetal brain antigens that are responsible for a critical process in the developing brain.

collapsin response mediator proteins 1 (CRMP1) and 2 (CRMP2), and Y-box binding protein 1 (Figure 1). The antigens recognized by maternal autoantigens are significant because a number of them are critical for normal brain development, specifically processes essential for neuronal migration and neural network formation; guanine deaminase has an integral role in dendritic branching of hippocampal neurons, whereas STIP1, in combination with the cellular prion protein, is responsible for neuritogenesis and increases neuronal survival (58,59). Further, CRMPs 1 to 5 are necessary for proper growth cone collapse and are required for proper cell migration and axon-dendrite specification (60,61). The effects of Y-box binding protein 1 and LDH in neuronal development are more widespread; Y-box binding protein 1 is involved in almost all DNA and messenger RNA–dependent processes and LDH is essential for energy metabolism (62,63). Subsequent experiments using Western blots containing the purified protein targets confirmed these findings, leading to a finding of a 23% incidence of the highly specific antigen reactivity patterns associated with ASD. Further, we characterized behavioral outcomes in the children of autoantibody-positive mothers that associated with the presence of the most common autoantibody pattern, which included combined reactivity to LDH, STIP1, and CRMP1. Combined maternal antibody reactivity to this autoantigen pattern was found in 7% of mothers with children with ASD and correlated with an increase in stereotypic behaviors in the child (64) (Table 2). Maternal autoantibodies are increasingly implicated in the behavioral and cognitive deficits that characterize ASD, but because these studies have been conducted in human participants, it is impossible to determine the mechanism by which these antibodies lead to the symptoms observed in ASD. In order to understand the potential pathogenic role of maternal antibodies, it was necessary to move to experimental animal studies. Moreover, studies are currently underway to elucidate the peptide epitopes on each fetal antigen recognized by the maternal autoantibody-related ASD antibodies because determining the precise binding site(s) of the autoantibodies may offer insight into the etiology and mechanism by which these antibodies mediate changes in behavior.

## ANIMAL MODELS OF ASD

It is possible that the maternal antibodies represent purely a biological marker of damage that occurred during gestation and may not necessarily underlie the neurodevelopmental dysfunction detected in ASD. In order to determine whether maternal antibodies are clinically significant and not just an immune epiphenomenon, studies were initiated by several research laboratories using animal models. Typically, in autoimmune diseases in which antibodies are suspected to have a deleterious role, passive transfer studies, in which antibodies are transferred from a diseased animal to a healthy animal, are often used to establish a pathogenic capacity (65,66).

### Nonhuman Primate Models

The first animal studies, which used rhesus macaques because of their increased social repertoire and established battery of social tests, demonstrated that the group of monkeys that were prenatally exposed through passive transfer to IgG purified from mothers of children with ASD had significantly more stereotypic behaviors and higher levels of motor activity when placed in a novel social setting than monkeys treated with IgG from mothers with typically developing children (67). Further, these findings were recently replicated in a larger study using nonhuman primates administered targeted IgG from mothers of children with ASD that was specific for the dominant 37- and 73-kDa band pattern (now known to correspond to LDH, CRMP1, and STIP1). In the second nonhuman primate model, it was observed that offspring treated with IgG from mothers of children with ASD had abnormal social behaviors and enlarged brain volume compared with control IgG-treated animals. They also found that the dams receiving the ASD-associated IgG displayed heightened maternal protectiveness toward their progeny (68). Although these studies were not without limitations, they provide insight into the potential pathological significance of maternal autoantibodies in ASD and how their interaction with fetal brain antigens may alter the course of brain and behavioral development.

### Murine Models

Concurrent to the studies conducted in rhesus macaques, researchers revealed similar findings using a murine passive transfer model in which pregnant mice exposed to a single intravenous dose of human maternal plasma predetermined by immunoblotting to be reactive to the 37- and 73-kDa–banding pattern had offspring with increased anxiety and response to stress, along with impaired motor and sensory development (69). This outcome was also seen in a previous study using pooled IgG from mothers of children with ASD, but not based on any 37- or 73-kDa band patterns. The authors determined that the offspring born to dams injected with IgG from mothers with autistic children, and not from mothers with typically developing children, mimicked some of the symptoms seen in ASD, including alterations in sociability and increased activity and anxiety (70). The most recent studies, aiming to further illuminate the mechanism by which maternal autoantibodies alter fetal brain development, transferred human antigen-specific maternal IgG into the cerebral ventricles of embryonic mice. The first of these studies focused on the behavioral outcomes of the exposed offspring. The offspring injected with antibodies reactive to the 37- and 73-kDa–banding pattern had increased stereotypic behaviors and altered social phenotypes reminiscent of the children born to mothers with this brain pattern reactivity (71). In parallel studies, the physiological effects of maternal IgG revealed increased cellular proliferation in the subventricular zone, increased size of adult cortical neurons, and increased adult brain size and weight compared with animals exposed to autoantibody-negative control IgG (72). Although these studies were highly experimental and not representative of a natural exposure, they offer further evidence supporting the role of maternal antibrain antibodies in the incidence of ASD, as well as insight as to the cellular target: radial glial stem cells. Further, because these studies are limited by the passive transfer of IgG during pregnancy at a single time point, our laboratory has recently created an antigen-driven mouse model by breaking tolerance to the specific antigenic

**Table 2. Studies Linking Autoantibodies and ASD**

| Antibody Target | MW | No. in Study | Autoantibody Prevalence in ASD Population | Research Group | Year |
|---|---|---|---|---|---|
| Fetal Rat Brain | Low MW bands and 250 kDa | AU = 11<br>TD = 10 | 45% low MW bands<br>55% 250 kDa | Zimmerman *et al.* (51) | 2007 |
| Fetal Human Brain | 37 and 73 kDa | AU = 61<br>DD = 40<br>TD = 62 | 12% | Braunschweig *et al.* (50) | 2008 |
| Fetal Human Brain | 39 kDa | AU = 84<br>DD = 49<br>TD = 160 | 7% | Croen and Braunschweig (53) | 2008 |
| Fetal Human Brain | 36 kDa | AU = 100<br>TD = 100 | 10% | Singer *et al.* (52) | 2008 |
| Fetal Monkey Brain | 37, 39, and 73 kDa | AU = 201<br>ASD = 71<br>DD = 102<br>TD = 185 | 7% (37 and 73 kDa)<br>4% (39 and 73 kDa) | Braunschweig *et al.* (69) | 2012 |
| LDH, STIP1, CRMP1, GDA, CRMP2, YBX1 | 37, 39, 48, 62, and 68 kDa | ASD = 246<br>TD = 149 | 7% | Braunschweig *et al.* (64) | 2013 |
| Mouse Brain | Undetermined | ASD = 2431<br>TD = 653 | 10.7% | Brimberg *et al.* (55) | 2013 |

ASD, autism spectrum disorder; AU, autism; CRMP, collapsin response mediator protein; DD, developmental delay; GDA, guanine deaminase; LDH, lactate dehydrogenase; MW, molecular weight; STIP1, stress-induced phosphoprotein 1; TD, typically developing; YBX1, Y-box binding protein 1.

determinants of LDHA, LDHB, CRMP1, and STIP1 to create the most clinically relevant animal model in which to study maternal autoantibody-related autism. Behavioral studies are currently underway in these mice.

## AUTOANTIBODIES IN OTHER FORMS OF PSYCHOPATHOLOGY

A number of research groups have established an association with autoimmunity and the presence of antibrain autoantibodies and the incidence of numerous behavioral disorders (73). Antibodies reactive to neuronal tissues have also been detected in schizophrenia (74–77), Tourette syndrome (78–84), and obsessive-compulsive disorder (85–87), seemingly linking these related and often comorbid disorders. Further, antibrain autoantibodies have also been observed in children with ASD (88–94). However, unlike the antibrain autoantibodies observed in mothers of children with autism, the antibrain antibodies observed in children, and in other disorders, have been found to preferentially bind to adult, rather than fetal, brain substrates, suggesting that they are reactive to a different repertoire of protein targets. The variance in diseases associated with these antibrain autoantibodies may be due to their antigen specificity and/or the window of exposure by which they interact with their brain-derived protein targets. There is more support for the etiological relevance of fetal brain–reactive maternal antibodies because maternal antibody exposure overlaps major processes in neurodevelopment, and maternal antibodies have greater access to the fetal brain due to increased permissiveness of the blood-brain barrier during gestation (95). In other forms of psychopathology that arise later in life, autoantibodies may still mediate deleterious effects on the brain leading to aberrations in behavior. Nevertheless, the presence of antibrain autoantibodies postnatally does not necessarily lead to disorders of brain; it is hypothesized that there must be another event that increases barrier permeability, allowing antibodies to traverse the blood-brain barrier and gain access to brain tissue to inhibit and alter neuronal processes (96,97). However, it may be this necessary preliminary event that accounts for the episodic nature of many psychiatric disorders. Although antibrain autoantibodies may represent a common etiological agent leading to related psychopathological disorders such as ASD and schizophrenia, there are likely many other aspects, including genetic predisposition, environmental factors, and timing of exposure during development, that contribute to the differing symptoms and manifestations of non-ASD autoantibody-related neuropsychiatric disorders.

## CONCLUSIONS

Maternal autoantibody-related ASD has been noted by numerous researchers describing the presence of maternal autoantibodies reactive to fetal brain proteins in a subset of mothers of children with ASD. Further, there is now an abundance of evidence supporting their deleterious role in neurodevelopment. For the most part, these studies have described similar experimental outcomes, and given the clinical and biological heterogeneity of ASD, there likely exists a complex relationship between the presence of maternal antifetal brain antibodies and the developmental trajectory of exposed offspring. It is still unclear how and when these maternal autoantibodies arise, but studies currently underway may provide increased insight into their ontogeny. Further, the generation of more

clinically relevant animal models will enable the illumination of the mechanism by which maternal antibodies impair neurodevelopment, resulting in the social and behavioral deficits observed in ASD. Moreover, by determining their mechanism of action, appropriate therapeutic interventions could be implemented, thus raising the optimistic prospect that some future cases of ASD or related neurodevelopmental and psychiatric disorders may be prevented.

## ACKNOWLEDGMENTS AND DISCLOSURES

This study was funded by the National Institute of Environmental Health Sciences (NIEHS) Center for Children's Environmental Health and Environmental Protection Agency (Grant Nos. 2P01ES011269-11 and 83543201, respectively, to JV as PI), the NIEHS-funded CHARGE study (Grant No. R01ES015359 to JV and PA as Co-I), and the National Institute of Child Health and Human Development–funded Intellectual and Developmental Disabilities Research Center 054 (Grant No. U54HD079125 to JV as Co-PI).

We thank the staff of the CHARGE study and the families involved in this research.

There are three patents associated with the work at University of California, Davis noted in this review: A provisional 'Maternal Diagnostic Marker for Autism Risk and Therapeutic Intervention' UC Case No. 2014-467-1. There are two issued patents: The US patent Methods of Diagnosing and Treating Autism, U.S. Patent No. 8,383,360 B2 or Pat. 8,383,360 was filed August 12, 2010, and issued February 26, 2013. The client reference number for this patent is 2009-737-2US. This patent is currently in the process of national filing. The first issued patent is Diagnostic Methods for Detection of Autism Spectrum Disorder, U.S. Patent No. US 7,452,681 B2. This patent was filed May 5, 2006, and was issued November 18, 2008. This patent was filed in the United States only. JVdW received consulting fees from Pediatric Bioscience from January 1, 2015, until October 2015. EE and PA report no biomedical financial interests or potential conflicts of interest.

## ARTICLE INFORMATION

From the Dtivision of Rheumatology/Allergy and Clinical Immunology (EE, JVdW), The M.I.N.D. Institute (EE, PA, JVdW), NIEHS Center for Children's Environmental Health (PA, JVdW), and Department of Medical Microbiology and Immunology (PA), University of California, Davis, Davis, California.

Address correspondence to Judy Van de Water, Ph.D., Division of Rheumatology/Allergy and Clinical Immunology, 451 E. Health Sciences Dr., Suite 6510, University of California Davis, Davis, CA 95616; E-mail: javandewater@ucdavis.edu.

Received Jun 1, 2016; revised Jul 27, 2016; accepted Aug 24, 2016.

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