Pilot Study of Maternal Autoantibody–Related Autism

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ABSTRACT: ***Objective:*** **The objective of this study was to investigate the presence of maternal autoantibody–related autism spectrum disorder (MAR-ASD) in 2 geographically distinct DBPNet clinical sites (Pennsylvania and Arkansas). MAR-ASD is a biologically defined subtype of ASD that is defined by the presence of autoantibodies specific to proteins in the fetal brain and present in approximately 20% of a Northern California sample but has not been studied in other states.** ***Methods:*** **Sixty-eight mothers of children with ASD were recruited from 2 DBPNet clinics and provided blood samples. Mothers also completed behavioral questionnaires about their children, and data from the child's clinical diagnostic assessment were abstracted.** ***Results:*** **The mean age of mothers was 38.5 ± 6.1 years, and the mean age of children was 8.3 ± 2.7 years. MAR-ASD was present in 24% of the sample and similar across sites. Children of +MAR mothers had more severe autism symptoms as measured by Autism Diagnostic Observation Schedule comparison scores ($W = 3604$; $p < 0.001$) and the Social Communication Questionnaire ($W = 4556$; $p < 0.001$). There were no differences in IQ, adaptive function, or aberrant behavior.** ***Conclusion:*** **MAR-ASD is a subtype of autism that is present in similar frequencies across 3 states and related to autism severity.**

(*J Dev Behav Pediatr* 00:1–7, 2022) **Index terms:** autism, maternal autoantibodies, antifetal brain autoantibodies, immune, prenatal and perinatal risk factors.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects 1 in 44 children in the United States.[1] The cause is still unknown; however, there are likely multiple biologic, genetic, and environmental causes that contribute to ASD risk.[2–4] There is significant heterogeneity within ASD, and at least 1 meaningful subgroup involves the maternal gestational immune environment.[5–7]

Maternal autoantibody–related ASD (MAR-ASD) is a subtype of ASD that is characterized by maternal reactivity to specific autoantigens present in the developing brain.[8–12] Animal studies suggest that the presence of these maternal antibodies produces ASD hallmark behaviors in offspring, such as repetitive behaviors, communication difficulties, and atypical social behaviors.[13–15] In humans, maternal autoantibody reactivity against 8 proteins highly expressed in the developing brain has been identified, along with ASD-specific patterns of reactivity (for 2 or more proteins) that are present only in mothers of children with ASD and not in mothers of children with typical

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development or developmental delay.[16,17] These maternal autoantibody patterns may be a biomarker of risk for approximately 20% of children with ASD.[16] In addition, reactivity to one of these proteins, collapsin response mediator protein 1 (CRMP1), is associated with more severe Autism Diagnostic Observation Schedule (ADOS) scores.[16]

Autism spectrum disorder prevalence varies greatly across the United States, with a range of 1 in 61 (1.65%) in Missouri to 1 in 25 (3.9%) in California based on records from 11 states.[1] Our MAR-ASD studies have predominantly been conducted with samples from mothers in Northern California. Therefore, we conducted a pilot study using 2 sites from Developmental-Behavioral Pediatrics Research Network (DBPNet) to inform a future larger study involving more sites across the network. We report preliminary data on the frequency of MAR-ASD in these 2 geographically diverse populations and the association of these antibody patterns with child behaviors, including ASD severity.

METHODS

Participants

Participants included biological mothers of children aged 2 to 12 years diagnosed with autism spectrum disorder (ASD) through developmental-behavioral pediatrics (DBP) clinics at 2 DBPNet sites, the Children's Hospital of Philadelphia (CHOP) and the Arkansas Children's Hospital and Research Institute (ACHRI). DBPNet is a multicenter research network involving DBP programs at 16 academic medical centers.

All procedures were approved by the Institutional Review Board at CHOP through the DBPNet Network Coordinating Center, and all participants provided informed consent before inclusion in the study.

Mothers were recruited from the 2 DBP clinics if their child underwent clinical evaluation for ASD, was diagnosed with ASD using the *DSM* criteria, and had Autism Diagnostic Observation Schedule (ADOS)[18,19] scores above the ASD cutoff. Five-hundred and twenty-two eligible mothers (CHOP: 314; ACHRI: 208) were contacted through e-mail or (mailed) letters to participate in this study. Of those invited, 97 mothers (CHOP: 51; ACHRI: 46) responded, with 68 participants enrolled. Exclusion criteria included the presence of a known genetic disorder or sensory/motor impairments (e.g., visual/hearing deficits) that precluded standardized assessment.

Study procedures included a research study visit for the collection of a blood sample from the mother and completion of additional questionnaires, including the Social Communication Questionnaire (SCQ),[20] the Early Development Questionnaire,[21] and the study demographic form, which included information about the family history. Data were abstracted from a chart review of the child's ASD diagnostic evaluation from DBP clinics, including ADOS scores, IQ/cognitive scores, adaptive functioning scores (Vineland Adaptive Behavior Scales-II),[22] and scores from the Aberrant Behavior Checklist (ABC).[23] The ADOS is a semistructured standardized diagnostic assessment of ASD symptoms that is available in 5 modules (module 1, 2, 3, 4, and Toddler) depending on an individual's developmental level and language abilities. Each module has a separate algorithm that yields a total score that can be classified into 1 of 3 categories: autism, ASD, or nonspectrum. An ADOS comparison score (also known as calibrated severity score) can be calculated on a 1 to 10 scale and measures autism severity across modules. Although all clinic notes documented that an ADOS was performed and that scores were above the cutoff for ASD, some encounters did not report specific ADOS items needed to calculate an ADOS comparison score. Owing to the variation in clinical assessments across ages and sites, cognitive scores were predominantly obtained from the Stanford Binet-5,[24] although other assessments included the Wechsler Intelligence Scale for Children-IV,[25] Differential Ability Scales-II,[26] and Mullen Scales of Early Learning.[27] Cognitive scores were categorized as average or above (>85), low average (70–84), or extremely low (<69) given the variety of assessments performed.

Sample Collection and Preparation

Maternal blood was collected in citrate dextrose (BD Diagnostic), and plasma was separated, labeled, aliquoted, and stored at −80°C. Before use, samples were thawed at room temperature (RT), vortexed, and centrifuged at 13,000 RPM for 10 minutes. This collection protocol was identical to the previous studies.[16]

Enzyme-Linked Immunosorbent Assay

IgG antibody reactivity of plasma samples against each antigen was determined by enzyme-linked immunosorbent assay (ELISA) using commercially available proteins, and the assay conditions were optimized for each protein as previously described.[28] Briefly, microplates were coated with 100 μL of antigen in carbonate coating buffer pH 9.6, incubated overnight at 4°C, washed 4 times with Phosphate Buffered Saline Tween-20 (PBST) 0.05%, and blocked with 2% SuperBlock (Thermo Scientific, Rockford, IL) for 1 hour at RT. One hundred microliters of diluted sample was added to each well and incubated for 1.5 hours at RT, followed by 4 washes with PBST 0.05%. Goat anti-human IgG-HRP (Kirkegaard & Perry Laboratories, Inc, Gaithersburg, MA) was diluted at 1:10,000 in PBST 0.05%, incubated for 1 hour at RT, and washed 4 times. Finally, 100 μL of BD OptEIA was added, and the reaction was stopped with 50 μL of 2N HCl after 4 minutes. The absorbance was measured at 490 to 450 nm using an iMark Microplate Absorbance Reader (Bio-Rad, Hercules, CA).

After plate-plate normalization, a positive cutoff was established for each antigen using a ROC curve and Youden's index as previously described. The positive control samples used to create the ROC were not

included in the analysis. Mothers with maternal autoantibody-related (MAR) positivity are referred to as "+MAR," whereas those without the presence of maternal autoantibodies are described as "−MAR."

Data Analysis

Descriptive statistics are presented for demographic characteristics and MAR positivity (+MAR) prevalence. Nonparametric analyses (Wilcoxon rank sum) were used to compare group differences because of the presence of skewed data. A Fisher exact test was used to compare categorical data.

RESULTS

Demographic characteristics are presented in Table 1. In total, 68 mothers participated and provided samples for analysis. On average, mothers were aged 38.5 years and slightly older at the Children's Hospital of Philadelphia (CHOP) (40.5 years vs 36.8 years; $p = 0.014$). At diagnosis, children were an average of 8.25 years of age, with a range of 2.5 to 14 years, and were similar in age across sites.

Maternal Autoantibody–Related Autism Spectrum Disorder Prevalence Across Sites

Maternal autoantibody–related (MAR) positivity was similar across sites, with an overall prevalence of 23.5% (16 of 68 samples). At CHOP, 21% (7/33) of mothers demonstrated MAR positivity (+MAR), whereas 26% (9/35) of Arkansas Children's Hospital and Research Institute (ACHRI) mothers were +MAR (n.s.). There were no significant differences in mothers' age based on MAR positivity (Wilcoxon rank sum $W = 365$, $p = 0.7$). Children of +MAR mothers ranged from 3.4 to 11.25 years of age and did not differ in age from children of −MAR mothers (Wilcoxon rank sum $W = 495$, $p = 0.3$). Ten of the 16 +MAR mothers had other children at the time of blood draw based on the demographic questionnaire; of those, 3 had other children with autism spectrum disorder (ASD) and 2 more had other children with developmental delay. The oldest child (11.25 years) of a +MAR mother in this sample also had a 9-year-old sibling with a diagnosis of ASD. In −MAR mothers, 37 of 52 had other children at the time of blood draw; 5 had other children with ASD, whereas 3 others had other children with developmental delay.

Figure 1 describes the known MAR-ASD patterns that are composed of a combination of 2 or more antigens. Five mothers had positivity for CRMP1 + GDA (4 from ACHRI) and 3 for CRMP1 + CRMP2 (2 from ACHRI), including 1 mother who was positive for CRMP1 + CRMP2 + GDA.

Behavioral Characteristics Associated with Maternal Autoantibody–Related Autism Spectrum Disorder Reactivity

Autism Symptoms

Although clinical records indicated that all children had total Autism Diagnostic Observation Schedule (ADOS) scores above the ASD cutoff, ADOS comparison scores were only available for 53 children (11 children of +MAR mothers; 42 children of −MAR mothers). Seventeen children received module 1, 20 received module 2, and 16 received module 3. ADOS severity was significantly different between the groups (Wilcoxon rank sum $W = 3604$, $p < 0.001$). ADOS comparison scores ranged from 3 to 10 for children in the −MAR group, whereas ADOS comparison scores ranged from 6 to 10 for children in the +MAR group (Fig. 2A).

Total Social Communication Questionnaire scores (Fig. 2B) were available for 67 children (16 +MAR; 51 −MAR) and significantly higher in children of +MAR mothers than children of −MAR mothers ($W = 4556$; $p < 0.001$).

IQ and Adaptive Function

Cognitive abilities (FSIQ or GCA) were available for 56 children (13 children of +MAR mothers; 43 children of −MAR mothers) (Table 2). Adaptive scores were available for 44 children (10 in +MAR; 34 in −MAR). There were no significant differences in IQ, global adaptive function, or any of the adaptive subscales between the 2 groups. In addition, verbal and nonverbal IQ did not differ based on mothers' MAR positivity.

Other Behaviors

Behaviors from the ABC (Table 2) were available for 38 children (9 in +MAR; 29 in −MAR). There were no

Table 1. Demographic Characteristics

	CHOP, n = 33	ACHRI, n = 35	Total = 68	*p*
+MAR	7/33 (21%)	9/35 (26%)	16/68 (23.5%)	0.75 (Fisher's) OR 0.78; 95% CI (0.21; 2.77)
Mothers' age at the time of blood draw (yrs)				
Mean (SD)	40.5 (6.2)	36.8 (5.4)	38.5 (6.1)	0.014
Range	26–54	27–47	26–54	
Child age (yrs)				
Mean (SD)	8.3 (3)	8.2 (2.4)	8.3 (2.7)	n.s.
Range	2.6–14.1	3.2–11.8	2.6–14.1	

ACHRI, Arkansas Children's Hospital and Research Institute; CHOP, Children's Hospital of Philadelphia; MAR, maternal autoantibody related; n.s., not significant.

ID	CRMP1	CRMP2	GDA	STIP1	YBOX	LDHA	NSE
210C26	CRMP1		GDA	STIP1			
210C16	CRMP1		GDA		YBOX		
210403	CRMP1		GDA				
210424	CRMP1		GDA				
210C07	CRMP1	CRMP2				LDHA	
210C08	CRMP1	CRMP2				LDHA	
210C31		CRMP2	GDA				
210135		CRMP2	GDA				
210C22			GDA		YBOX		NSE
UK010	CRMP1	CRMP2	GDA				NSE
HZ633		CRMP2	GDA				
YY521		CRMP2	GDA				
GH784		CRMP2	GDA				NSE
PT573		CRMP2	GDA			LDHA	NSE
TW646			GDA		YBOX		
CC095					YBOX	LDHA	

Figure 1. MAR-ASD patterns observed. CRMP1, collapsin response mediator protein 1; CRMP2, collapsin response mediator protein 2; GDA, guanine deaminase; LDHA, lactate dehydrogenase A; MAR-ASD, maternal autoantibody–related autism spectrum disorder; NSE, neuron-specific enolase; STIP1, stress-induced phosphoprotein 1; YBOX, Y-box binding protein 1. Gray shaded subjects are from the ACHRI cohort.

significant differences in irritability, stereotypy, hyperactivity, or other atypical behaviors.

DISCUSSION

Findings from this pilot sample document the presence of maternal autoantibody–related autism spectrum disorder (MAR-ASD)–specific patterns in 2 geographically distinct DBPNet sites, in addition to Northern California. MAR-ASD pattern positivity may be associated with more severe ASD behaviors, which is supported by 2 measures of ASD symptomatology, the Social Communication Questionnaire (parental report) and Autism Diagnostic Observation Schedule (ADOS) (clinician assessment). There were no differences in IQ, adaptive function, or aberrant behaviors based on MAR status. The existence of these antibodies in various geographical areas and the association with ASD severity in this pilot study support the potential usefulness of +MAR autoantibodies as biomarkers of ASD risk. This may have future implications for better understanding ASD cause and the development of potential treatment for this subtype of ASD in a subset of cases.

The overall prevalence was similar to the Northern California site (~20%),[16,17] although specific MAR patterns varied slightly. The most common MAR pattern observed was CRMP1 + GDA and CRMP2 + GDA; these proteins are independently involved in axon and neurite development.[17,29,30] Interestingly, CRMP2 + GDA was a low-frequency MAR-ASD pattern in the California study (n = 3)[16]; however, in this small study, it was present in 7 samples (5 from CHOP). None of the samples were positive for NSE + STIP1, which is another fairly common pattern associated with ASD.[16]

Consistent with previous studies, ADOS scores were significantly higher in children of +MAR mothers.[16] However, there were no differences in aberrant behaviors, such as stereotypies, based on MAR status, which is inconsistent with other work.[17] IQ and adaptive function were not associated with MAR status, and previous studies have not reported this either. One possible explanation for the association with ASD, but not IQ or adaptive function, may relate to individual proteins affecting early ASD-specific pathways independent from cognitive and adaptive pathways.[16] For example, the presence of CRMP1 has been associated with ASD.[16] We have ongoing, larger studies to address this, and pattern differences for subphenotypes of ASD (such as ASD + intellectual disability) are emerging (manuscript in preparation).

The oldest child of a +MAR mother in the sample was aged 11.25 years, and he had a 9-year-old sister with ASD. The sample tested in this study was obtained after the diagnosis of the sibling. Ten of the +MAR mothers had more than 1 child; half of them had other children with ASD or DD. Further study is required to ascertain why mothers develop these antibodies and how long these antibodies may persist.

One limitation is that plasma samples were collected up to 14 years after birth, so it is unknown whether MAR antibodies were present while these mothers were pregnant, and prospective studies are currently underway to investigate this. If these antibodies are in fact present during pregnancy, based on the oldest child (aged 11 years) of a +MAR mother in our sample, it is possible that MAR antibodies can last for many years, especially because the mother's last pregnancy (also a child with ASD) was 9 years before sample collection. There do not seem to be associations with MAR positivity and IQ/developmental function, aberrant behaviors, or adaptive function in these associative studies. This, however, is limited by our small sample size in this

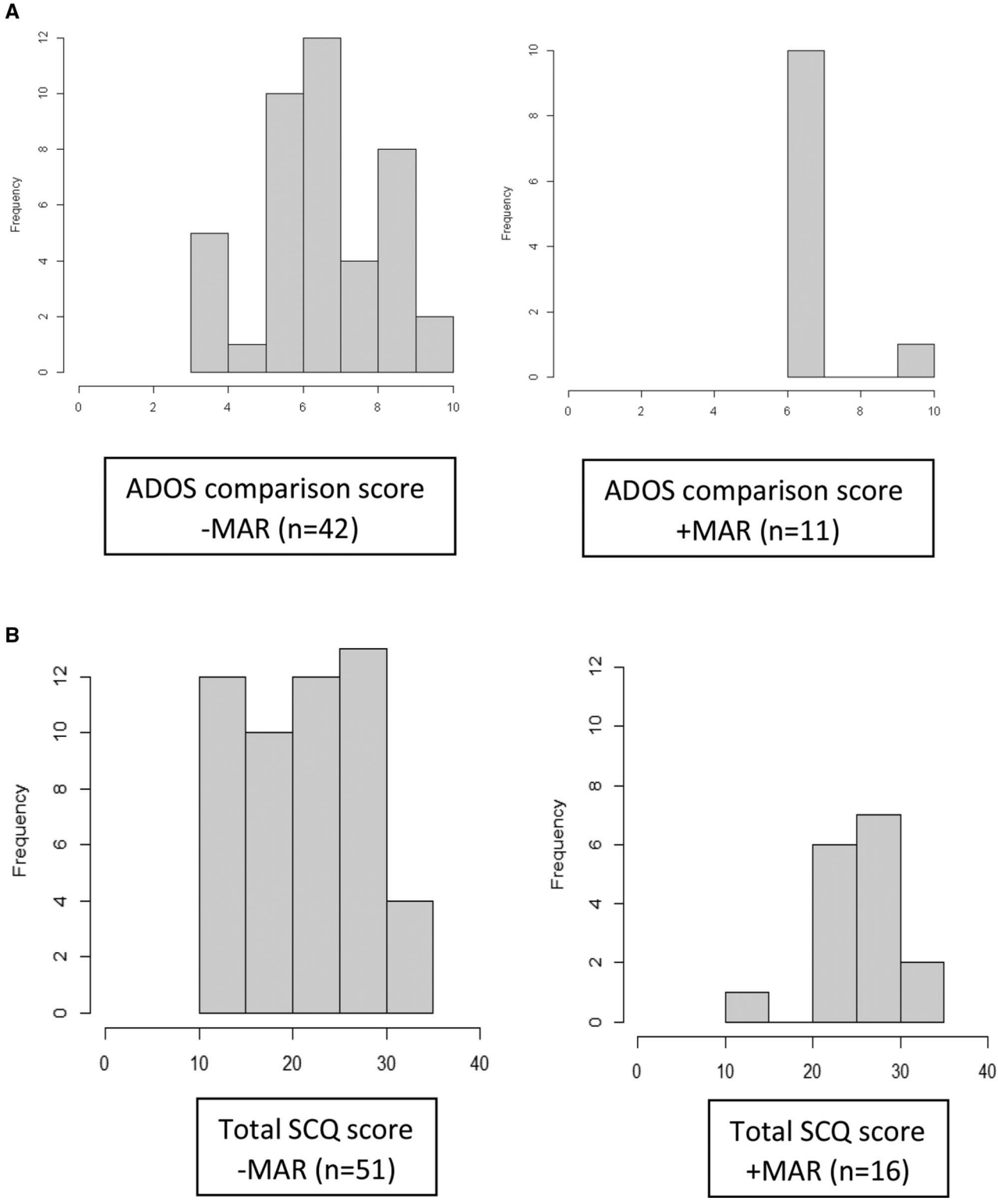

Figure 2. A and B, ADOS comparison and SCQ scores in −MAR and +MAR groups. ADOS, Autism Diagnostic Observation Schedule; MAR, maternal autoantibody related; SCQ, Social Communication Questionnaire.

pilot study, so we may be underpowered to assess these developmental characteristics. Another limitation is our reliance on a clinical sample. Owing to practice variations in clinical diagnostic assessments, data were not collected or were missing for various assessments, such as the ABC. In addition, we cannot prove that the observed MAR-ASD patterns are indeed ASD specific because this study did not include mothers of typically developing or developmentally delayed children without ASD as a comparison. Our small sample also limited our ability to look at behavioral characteristics related to specific MAR autoantibody patterns.

Table 2. IQ, Adaptive Function, and Aberrant Behaviors

IQ	−MAR (n = 43 of 52)	+MAR (n = 13 of 16)	Fisher exact *p*
FSIQ or GCA			0.93
Average or above (≥85)	18 (42%)	6 (46%)	
Low average (70–84)	12 (28%)	4 (31%)	
Extremely low (≤69)	13 (30%)	3 (23%)	
Vineland	**−MAR (n = 34)**	**+MAR (n = 10)**	**Wilcoxon *p***
Adaptive Behavior Composite	70.3 ± 9.4	67.7 ± 9.1	0.42
Communication	75.1 ± 12.3	72.2 ± 15.5	0.57
Daily living skills	72.4 ± 11.4	67.9 ± 11.3	0.16
Socialization	68.2 ± 11	67.8 ± 9	0.89
Motor	78.7 ± 9.5	77.3 ± 10.2	0.85
Aberrant Behavior Checklist	**−MAR (n = 29)**	**+MAR (n = 9)**	**Wilcoxon *p***
Total	50.9 ± 33.6	38.2 ± 17	0.51
Irritability	12.8 ± 9.9	7.1 ± 4.8	0.16
Lethargy	9.4 ± 10	7.7 ± 7.3	0.88
Stereotypy	5.9 ± 5	5.4 ± 4	0.95
Hyperactivity	18.7 ± 11	14.3 ± 6.9	0.27
Inappropriate speech	4 ± 3.7	3.6 ± 2.9	0.93

FSIQ, full-scale intelligence quotient; GCA, general conceptual ability.

One strength of our study is that all children were diagnosed with ASD in a standardized manner (*DSM* and ADOS, along with expert clinical judgment). Another strength of this study is geographic diversity of the sample groups and utilization of the DBPNet.

Future endeavors will include investigation of the clinical utility of including MAR autoantibody patterns as part of the etiologic evaluation of children clinically diagnosed with ASD and as a secondary screening tool for young children with developmental/behavioral concerns who have not yet been referred for diagnostic evaluation or targeted screening for younger at-risk siblings of children with ASD. Our data also support the possible association of MAR positivity with ASD severity ratings and an established protocol for uniform data collection across sites for a larger multisite study in the future. Further investigation is needed to better understand the mechanistic processes related to MAR pathogenicity on neuronal development, and preclinical models are currently underway. In summary, we have preliminarily identified the presence of MAR-ASD in 2 distinct geographic locations (in addition to California) and found associations with ASD severity that support MAR-ASD as a meaningful subtype of ASD likely present across a variety of geographic areas.

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