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Genetic Variation in the Oxytocin Receptor Gene is Associated With a Social Phenotype in Autism Spectrum Disorders

Ashley J. Harrison,[1]* Ece D. Gamsiz,[2,3] Isaac C. Berkowitz,[4] Shailender Nagpal,[4] and Beth A. Jerskey[2]

[1]Department of Educational Psychology, College of Education, University of Georgia, Athens, Georgia

[2]Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, Rhode Island

[3]Developmental Disorders Genetics Research Program, Emma Pendleton Bradley Hospital, Riverside, Rhode Island

[4]Department of Molecular Biology, Cell Biology and Biochemistry and Institute for Brain Science, Brown University, Providence, Rhode Island

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Oxytocin regulates social behavior in animal models. Research supports an association between genetic variation in the oxytocin receptor gene (*OXTR*) and autism spectrum disorders (ASD). In this study, we examine the association between the *OXTR* gene and a specific social phenotype within ASD. This genotype–phenotype investigation may provide insight into how *OXTR* conveys risk for social impairment. The current study investigated 10 SNPS in the *OXTR* gene that have been previously shown to be associated with ASD. We examine the association of these SNPs with both a social phenotype and a repetitive behavior phenotype comprised of behaviors commonly impaired in ASD in the Simons simplex collection (SSC). Using a large sample to examine the association between *OXTR* and ASD (n = range: 485–1002), we find evidence to support a relation between two *OXTR* SNPs and the examined social phenotype among children diagnosed with ASD. Greater impairment on the social responsiveness scale standardized total score and on several subdomains was observed among individuals with one or more copies of the minor frequency allele in both rs7632287 and rs237884. Linkage disequilibrium (LD) mapping suggests that these two SNPs are in LD within and overlapping the 3′ untranslated region (3′-UTR) of the *OXTR* gene. These two SNPs were also associated with greater impairment on the repetitive behavior scale. Results of this study indicate that social impairment and repetitive behaviors in ASD are associated with genomic variation in the 3′UTR of the *OXTR* gene. These variants may be linked to an allele that alters stability of the mRNA message although further work is necessary to test this hypothesis.

Key words: autism spectrum disorder; social phenotype; OXTR

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INTRODUCTION

The neuropeptide oxytocin has an identified role in social processes in animal models. Specifically, the oxytocin system has been found to be associated with altered social attachment, social affiliation, and social recognition [Bartz and Hollander, 2006; Lim and Young, 2006; Heinrichs and Domes, 2008; Caldwell, 2012]. Translational research has begun to investigate the function of the OXTR gene in the development of social cognition in humans given the mounting research within animal models demonstrating that altering oxytocin receptor functioning has a negative impact on social functioning such as social recognition and memory and maternal interactions [Lee et al., 2008; Nishimori et al., 2008]. More than 30 single nucleotide polymorphisms (SNPs) have been identified within the *OXTR* gene in humans associated with autism spectrum disorders (ASD) in at least one study. Many of these SNPs demonstrate associations with a variety of phenotypes related to social cognition [Insel, 2010]. This prior research demonstrates

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*Correspondence to:
Ashley Johnson Harrison, University of Georgia, Department of Educational Psychology, 110 Carlton Street, Athens, GA 30602.
E-mail: Ashley.Harrison@uga.edu
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consistent ties between socialization and *OXTR* variability across species.

One approach in human genetic studies has been to test for association between *OXTR* variants and DSM-based diagnoses, such as ASD. A growing body of the literature supports an association between the diagnosis of ASD and a range of *OXTR* SNPs [Yamasue, 2013]. For example, several studies have identified that *OXTR* rs2254298 [Wu et al., 2005; Jacob et al., 2007; Liu et al., 2010] and rs53576 [Wu et al., 2005; Liu et al., 2010; Wermter et al., 2010] were associated with ASD. An additional study demonstrated an ASD-associated haplotype including rs2254298 along with four other SNPs (rs237897, rs13316193, rs237889, and rs2268494; [Lerer et al., 2008]). Another individual study found an association between ASD and *OXTR* rs2268493 [Yrigollen et al., 2008]. More recently, a meta-analysis examined the 16 different *OXTR* SNPs previously found to be associated with ASD and revealed a significant association between ASD and four *OXTR* SNPs: rs7632287, rs237887, rs2268491, and rs2254298 [LoParo and Waldman, 2015]. This literature base indicates that polymorphisms in *OXTR* convey risk for ASD; however, one limitation with these studies is the utilization of relatively small sample sizes to investigate candidate associations. Furthermore, these studies have primarily examined associations between *OXTR* and ASD, a disorder comprised of heterogeneous impairments in social communication, as well as restricted and repetitive behaviors. As a result, studies investigating the association between *OXTR* polymorphisms and a broad ASD phenotype leave many questions remaining about which specific symptoms or behaviors *OXTR* SNPs may impact.

As an alternative to testing for association of variants to DSM diagnoses, researchers have begun to investigate specific symptom domains, or specific phenotypes of ASD, such as repetitive behaviors, or socialization atypicalities, particularly whereby these phenotypes may reflect the underlying biology more directly [Abrahams and Geschwind, 2008]. Given the hypothesized specificity of oxytocin to social impairment within animal models, the most prudent domain for an initial investigation is the social phenotype within ASD. Contemporaneously, researchers within ASD sought to define clearly the features or behaviors that may comprise the social phenotype [Klin et al., 2002; Bartz and Hollander, 2006]. An understanding that *OXTR* variants are contributing specifically to social impairment, rather than other domains of impairment among individuals with ASD, may help to identify specific behavioral targets for oxytocin-based biological treatments. More specifically, if we know what specific social behaviors are related to *OXTR* variants, we may be able to identify individuals with those specific impairments that may most benefit from such treatments.

Preliminary findings have identified an association between a specific *OXTR* SNP, rs7632287, and social functioning as assessed by the social responsiveness scale [Campbell et al., 2011]. This study including 2,333 individuals with ASD collected by the Autism Genetics Resource Exchange (AGRE) consortium and several other sites (independent of the Simons simplex collection [SSC]) was well powered. Furthermore, using two different sets of twin data, Walum et al. [2012] found that in their samples of female twins, rs7632287 was associated with early childhood social problems as assessed with the childhood behavior checklist (CBCL) and the Autism-Tics, AD/HD, and other comorbidities inventory (A-TAC). Similarly, Wermter et al. [2010] investigated whether social domains assessed using a commonly used diagnostic metric (autism diagnostic interview – revised [ADI-R]; Lord et al., 1994) were related to *OXTR* SNPs among 100 individuals. Results from this study revealed that no single markers were significantly related to socialization as assessed with the ADI-R after correcting for multiple statistical tests. In a haplotype analysis conducted by Wermter et al. [2010], participants with the specific haplotype (rs237851-rs6791619-rs53576-rs237884) demonstrated significantly more impairment in multiple social domains assessed with the ADI-R (e.g., A1: failure to use nonverbal behaviors to regulate social interaction; A2: failure to develop peer relationships; A4: lack of socio-emotional reciprocity; and B2: relative failure to initiate or sustain conversation). Finally, Rodrigues et al. [2009] demonstrated that allelic variation in *OXTR* relates to impaired emotion recognition, empathy, and heightened stress reactivity. In sum, these studies provide promising evidence for a specific social phenotype associated with variation in the *OXTR* gene.

The current study aimed to replicate and extend past research investigating genetic correlates of a social phenotype in ASD. *OXTR* SNPs with prior evidence of association with ASD were identified in the literature and examined to determine if they were related to a more specific social phenotype within ASD. Similar to past research, socialization was assessed with the social responsiveness scale (SRS; Constantino and Gruber, 2005). However, the current study also examined the relation between the *OXTR* SNPs and joint attention (JA), a commonly impaired social behavior among individuals with ASD. We utilized a JA subfactor derived from the ADOS based in part on prior studies [Thurm et al., 2007; Maljaars et al., 2012]. We predicted that we would replicate Campbell's findings demonstrating a relation between rs7632287 and SRS scores. In addition, we postulated that this SNP, as well as potentially other *OXTR* SNPs, would show associations with the ADOS-derived JA subfactor.

METHOD

Participants and Genotyping

Participants with phenotypic data included in this analysis were 1,061 children from simplex families derived from the SSC. The SSC database contains phenotypic and genotypic information on individuals diagnosed with ASD in the United States [Fischbach and Lord, 2010]. In the SSC dataset, not all participants had data for each of the SNPs of interest. Table I provides a detailed account of the sample size for each SNP investigated. To meet inclusion criteria for the SSC database participants must: (i) surpass clinical cutoffs for ASD (autistic disorder, Asperger's disorder, or pervasive developmental disorder, not otherwise specified) on either the autism diagnostic observation schedule (ADOS) [Lord et al., 2002] or the autism diagnostic interview-revised (ADI-R) [Lord et al., 1994], (ii) range in age from 4 to 18 years, (iii) not have a number of predefined

TABLE I. Sample Size for Each Examined SNP

	Number of probands
rs237884	997
rs7632287	565
rs4686301	1002
rs237889	1000
rs53576	484
rs237888	1002
rs237897	998
rs2268491	1002
rs2268495	921
rs1042778	1002

medical conditions or complications (for more information see Fischbach and Lord, 2010), and (iv) be the only child affected in the pedigree (i.e., from a simplex pedigree). The phenotypic variables assessed were, in part, derived from ADOS modules 1 and 2; therefore, only SSC participants that completed either of these two modules were included in the current study. Probands included in this study were primarily male (84%), had a mean age of 7.57 years, and mostly identified as Caucasian (65%). Participants also identified as Biracial (18%), Asian (7%), African American (6%), or Native Hawaiian, Native American, or other (2% or less, respectively).

Genotyping was conducted at the Keck Foundation Yale Center for Genomic Analysis using one of three different array versions: Illumina 1Mv1, Illumina 1Mv3 Duo, and Illumina HumanOMNI 2.5. Illumina 1Mv1, and 1Mv3 Duo versions share 1,040,853 probes in common (97% of probes on the 1Mv1 and 87% of probes in the 1Mv3) HumanOMNI 2.5 array has 2,450,000 probes including single nucleotide variants (SNVs) with minor allele frequency down to 1% [Sanders et al., 2011; Gamsiz et al., 2013].

OXTR SNPs to Investigate

In total, seven studies were included that had conducted analyses on 42 unique *OXTR* SNPs to investigate associations with ASD [Wu et al., 2005; Jacob et al., 2007; Lerer et al., 2008; Yrigollen et al., 2008; Liu et al., 2010; Wermter et al., 2010; Campbell et al., 2011]. From these studies, evidence of an association was observed among 21 of the 42 different *OXTR* SNPs. The current study conducted follow-up analyses on a subset of these SNPs. More specifically, of these 21 pre-identified *OXTR* SNPs, within the SSC database genotyping at the allelic level was only available for a subset of 10 of the 21 initially identified SNPs. Associations with the predefined social and repetitive behavior phenotypic profiles were examined among these specific 10 *OXTR* SNPs available in the SSC database with previously demonstrated associations with ASD: rs237884, rs7632287, rs4686301, rs237889, rs53576, rs237888, rs237897, rs2268491, rs2268495, and rs1042778. Within the framework of genetic models of inheritance for association studies, a recessive model was employed [Tansey et al., 2010] with the prediction that one or more copy of the minor alleles within each SNP would convey risk.

Linkage Disequilibrium (LD) Structure

The data were derived from the SSC of 2,616 trios with a child affected by autism. Plink was used to filter out SNPs in the neighborhood of the OXTR gene and imported into Haploview for downstream analysis. SNPs were assessed for quality using Plink. Loci with a minor allele frequency less than 1% were removed, as were those with a Hardy–Weinberg equilibrium *P*-value of less than 0.0001. A Mendelian error threshold was set at 0.0001 for both SNPs and families. This threshold was lowered to ensure that all SNPs examined in this study were included in the linkage disequilibrium (LD) plot, as rs23788 fell below the default parameters threshold. In order to assess LD, we examined the set of SNPs common to the three platforms, in addition to rs7632287, which was genotyped in 54.8% of cases and was included due to prior association with ASD. The minimum genotype percentage was set at 45% to include rs53576 (genotyped at 46.1%). LD was plotted in Haploview (version 4.2), and blocks were defined using the solid spine method, with default parameters.

Social Phenotype Measures

Parents of probands completed the SRS to assess social skill abilities in a range of areas including social awareness, social information processing, reciprocal communication, and social avoidance [Constantino and Gruber, 2005]. The SRS is a 65 item, Likert response scale in which each item is rated from 1 (not true) to 4 (almost always true). The SRS is commonly used to assess social impairment among children with ASD through the generation of an overall standardized score of autistic social impairment (SRS_T-score). In addition to providing an assessment of overall social symptoms, the SRS also generates scores for five clinical subscales: social communication (SRS_Communication), autistic mannerisms (SRS_Mannerisms), social awareness (SRS_Awareness), social motivation (SRS_Motivation), and social cognition (SRS_Cognition). The SRS has demonstrated excellent reliability and validity [Constantino et al., 2003].

Quantification of the JA phenotype was achieved by deriving a JA subscale score from the ADOS calculated for modules 1 and 2; due to the variability of item wording across modules, only these two modules contained items clearly assessing JA by definition (spontaneous initiates joint attention, response to joint attention and showing). Possible scores on items ranged from 0 to 2 (raw scores were converted to algorithm scores). Total JA subfactor scores ranged from 0 to 6. Although this approach to assessing JA has not established formal reliability and validity, the coding of the ADOS itself has demonstrated excellent psychometric properties [Lord et al., 2000; Mazefsky and Oswald, 2006] and previous studies have set the precedent for using such a measure [Thurm et al., 2007; Maljaars et al., 2012].

Repetitive and Stereotyped Behavior Measure

To determine if *OXTR* SNPs demonstrated an association with additional ASD phenotypes, such as repetitive and stereotyped behavior, additional analyses were conducted to examine the association between identified SNPs of interest and the repetitive behavior scale – revised (RBS-R) [Bodfish et al., 2000]. The RBS-R

is a 43-item caregiver-rated questionnaire that assesses repetitive and stereotyped behaviors often conducted by individuals with ASD. Conceptual groups of behaviors assessed with the RBS-R include stereotyped behavior, self-injurious behavior, compulsive behavior, ritualistic behavior, and restricted behavior. The RBS-R has demonstrated good reliability and validity for use among populations with ASD [Lam and Aman, 2007; Mirenda et al., 2010].

Statistical Analysis

We ran correlational analyses to understand how the social (JA and SRS) and repetitive (RBS) phenotypic variables are related to one another. Considering the data collected included missing values, we used pair-wise correlation analysis, which is more robust than the conventional list-wise deletion analysis [Little and Rubin, 2002]. Associations were examined between 10 *OXTR* SNPs and the social phenotype variables using multivariate general linear modeling analysis in IBM SPSS statistical software version 22. In the analyses, *OXTR* SNPs were grouped by LD block as depicted in Figure 1 to account for the correlated nature of SNPs in LD. Seven distinct genotype groups (i) LD block 1: rs237884 and rs7632287, (ii) No LD block: rs1042778, (iii) LD block 2: rs237888 and rs4686301, (iv) No LD block: rs2268491, (v) LD block 3: rs237889, (vi) LD block 4: rs53576, and (vii) LD block 5: rs2268495 were included as fixed factors. The first set of models was run with these seven genotypes groups and all social variables assessed including standard total SRS score, SRS subscale scores (communication, mannerisms, awareness, motivation, and cognition), and the ADOS-derived JA score. All social variables assessed demonstrated a normal distribution. The second set of models again used the seven genotype groups as fixed factors but examined scores from the RBS (overall and subfactor scores) as dependent variables. RBS variables exhibiting a skewed distribution were transformed.

To account for population stratification, all analyses were run including race as a covariate. Stratification is a complex issue [Burnett, 2006]. Although questions have been raised as to the reliability of self-reported race, a review by Barnholtz-Sloan et al. [2008] found that self-report aligns with ancestral population of

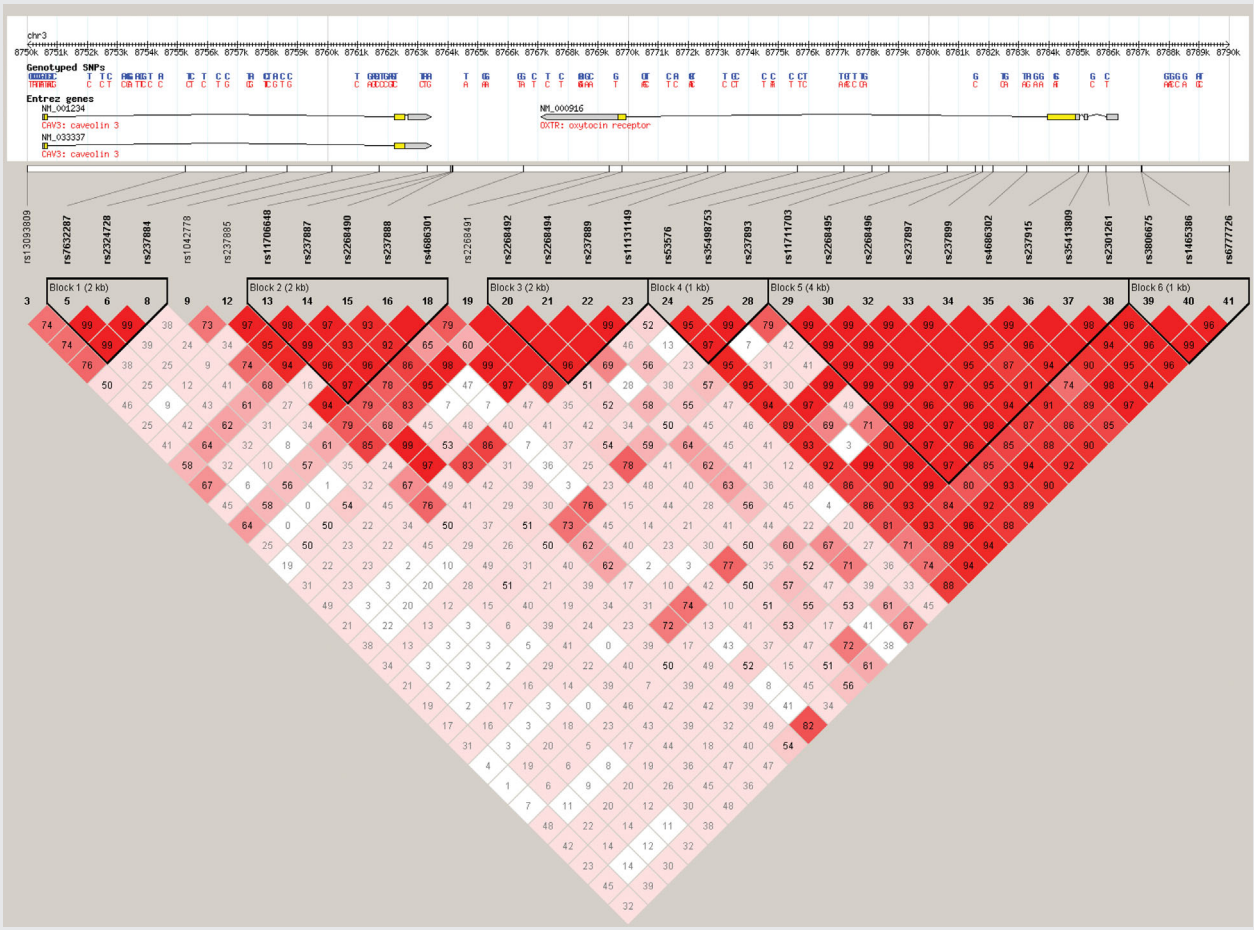

FIG. 1. Plot showing linkage disequilibrium in the region of OXTR. LD values are shown in r2 but D' coloration is used to present both data. Markers shown are those genotyped in all three platforms included in the SSC database using default parameters. The annotation tracks displayed at the top of the diagram were downloaded separately from Hapmap (browser release #28, genome build 36). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb]

origin. As a result, this well-established method can be effectively used to account for much of the effect of stratification [Liu et al., 2011]. Given the relatively low frequency of probands homozygous for the minor allele, individuals with one or two copies of the minor allele were compared to probands homozygous for the major allele.

RESULTS

Linkage Disequilibrium (LD) Structure

An examination of LD in the region of *OXTR* reveals three separate blocks (Fig. 1). Block overlaps with the 3′ untranslated region (UTR) and contains rs7632287, which has prior evidence for association to a social phenotype within ASD [Campbell et al., 2011]. SNP rs7632287 is 649 base pairs beyond the currently annotated 3′UTR of the *OXTR* gene (build 36). Of note, rs237884 is another investigated SNP in this study and is shown to be in strong LD with rs7632287 ($r^2 = 0.90$), making LD block 1 of particular interest. SNP rs237884 resides within the predicted 3′UTR of the *OXTR* gene. Given the *CAV3* gene maps 3.5 kb downstream of OXTR and previous research demonstrating LD between the *OXTR* and *CAV3* genes [Campbell et al., 2011], the current LD diagram includes several of the *CAV3* SNPs located near the *OXTR* gene genotyped in the current database.

Association of OXTR SNPs With a Social Phenotype

The preliminary correlational examination of the variables comprising the social phenotype revealed that JA, the SRS *t*-score, and the five SRS subscale scores were all significantly correlated with one another at an alpha level of $P < 0.001$. Similarly all component of the repetitive phenotype (overall RBS score and five RBS subscale scores) were all significantly correlated with one another at an alpha level of $P < 0.001$. More variability was observed in the correlations between the social and repetitive phenotype components (see Table II). Whereas overall and subscale scores from the RBS and SRS were significantly positively correlated, the ADOS-derived JA score was only significantly correlated with RBS ritualistic and stereotyped behavior subscales (see Table II).

Multivariate models examined the relation between seven distinct genotype groups and social phenotype variables. The regression analyses revealed multiple associations between the social phenotype and 3 of the 10 *OXTR* SNPs at a $P < 0.05$ alpha level. Two of these SNPs were located in the *OXTR* 3′UTR, in genotype group 1 within the LD block 1 and these SNPs were presumed to be in LD (see, Fig. 1). More specifically, we observed that a polymorphism in rs237884 from the A to G allele was associated with greater impairment in the overall SRS *t*-score, $F(1, 542) = 8.16$, $P = 0.004$, and greater impairment in the following SRS subscales, social communication, $F(1, 542) = 5.51$, $P = 0.02$, autistic mannerisms, $F(1, 542) = 4.97$, $P = 0.03$, and social cognition, $F(1, 542) = 6.49$, $P = 0.01$ (see, Table III). Within the same LD block and, therefore, within the same model, a polymorphism in rs7632287 from the G to A allele was also associated with greater impairment in the overall SRS *t*-score, $F(1, 542) = 6.51$, $P = 0.01$, in the social cognition SRS subscale, $F(1, 542) = 5.73$, $P = 0.02$, and in JA as assessed

TABLE II. Variable Correlation Matrix (* indicates significant at a $P < 0.001$ level)

	ADOS_JA	SRS: *t*-score	SRS: social comm.	SRS: autistic mannerisms	SRS: social awareness	SRS: social motivation	SRS: social cognition
RBS: total	r = 0.03, $P = 0.343$	r = 0.52**, $P < 0.001$	r = 0.43**, $P < 0.001$	r = 0.43**, $P < 0.001$	r = 0.60**, $P < 0.001$	r = 0.43**, $P < 0.001$	r = 0.50**, $P < 0.001$
RBS: compulsive behavior	r = 0.04, $P = 0.211$	r = 0.35**, $P < 0.001$	r = 0.28**, $P < 0.001$	r = 0.25**, $P < 0.001$	r = 0.39**, $P < 0.001$	r = 0.28**, $P < 0.001$	r = 0.36**, $P < 0.001$
RBS: restricted behavior	r = 0.01, $P = 0.647$	r = 0.34**, $P < 0.001$	r = 0.28**, $P < 0.001$	r = 0.28**, $P < 0.001$	r = 0.43**, $P < 0.001$	r = 0.28**, $P < 0.001$	r = 0.35**, $P < 0.001$
RBS: ritualistic behavior	r = −0.14**, $P < 0.001$	r = 0.25**, $P < 0.001$	r = 0.17**, $P < 0.001$	r = 0.17**, $P < 0.001$	r = 0.33**, $P < 0.001$	r = 0.18**, $P < 0.001$	r = 0.26**, $P < 0.001$
RBS: stereotyped behavior	r = 0.19**, $P < 0.001$	r = 0.47**, $P < 0.001$	r = 0.41**, $P < 0.001$	r = 0.41**, $P < 0.001$	r = 0.51**, $P < 0.001$	r = 0.38**, $P < 0.001$	r = 0.42**, $P < 0.001$
RBS: sameness behavior	r = −0.03, $P < 0.276$	r = 0.43**, $P < 0.001$	r = 0.34**, $P < 0.001$	r = 0.34**, $P < 0.001$	r = 0.48**, $P < 0.001$	r = 0.38**, $P < 0.001$	r = 0.40**, $P < 0.001$

TABLE III. LD Block 1: rs237884 (AA vs. AG/GG) and rs7632287 (AA vs. AG/GG) Adjusted for Ethnicity (* indicates $P < .05$ and ** indicates $P < .01$)

	rs237884		rs7632287	
	F	*P*-Value	F	*P*-Value
Social behaviors				
ADOS_JA	3.55	0.060	4.77	0.029*
SRS: *t*-score	8.16	0.004**	6.51	0.011*
SRS: social communication	5.51	0.019*	4.31	0.038*
SRS: autistic mannerisms	4.97	0.026*	3.86	0.050
SRS: social awareness	0.95	0.349	0.16	0.690
SRS: social motivation	2.32	0.129	2.00	0.158
SRS: social cognition	6.49	0.011*	5.73	0.017*
Repetitive behaviors (RBS - R)				
Total	4.26	0.015*	3.57	0.029*
Compulsive behavior	4.26	0.015*	3.68	0.026*
Restricted behavior	1.98	0.140	1.53	0.217
Rituatlistic behavior	4.78	0.009**	4.34	0.014*
Stereotyped behavior	3.15	0.044*	2.62	0.074
Sameness behavior	0.54	0.581	1.90	0.150

with the ADOS-derived JA composite, $F(1, 542) = 4.77$, $P = 0.03$ (see, Table III). A significant interaction effect was observed between rs237884 and rs7632287 for the ADOS-derived JA score, $F(1, 543) = 4.37$, $P = 0.04$, but follow-up analyses examining the nature of this interaction were not significant. Within genotype group 2, one other significant association was observed revealing a polymorphism in rs237888 was associate with greater impairment on the ADOS-derived JA subfactor, $F(1, 977) = 4.45$, $P = 0.04$ (see, Table IV). No significant main effects were observed between the social phenotype and any of the other remaining seven SNPs investigated (see, Tables V–IX).

Association of OXTR SNPs With a Repetitive Behavior Phenotype

Multivariate general linear models were also conducted to examine if polymorphisms were related to repetitive behaviors as assessed by the RBS overall score and subscale scores (restricted, ritualistic, stereotyped, sameness, compulsive). Again, race was included in the regression analyses as a controlling variable and we ran seven different models to account for the seven different genotype groups. Again, the analyses revealed multiple associations between the repetitive behavior phenotype and the two *OXTR* SNPs in genotype group 1 within the LD block 1 (see, Fig. 1). More specifically, we observed that a polymorphism in rs237884 from the A to G allele was associated with greater impairment in the total RBS-R score, $F(1, 543) = 4.26$, $P = 0.02$, and greater impairment in the following RBS-R subscales: compulsive behavior, $F(1, 543) = 4.26$, $P = 0.02$ and ritualistic behaviors, $F(1, 543) = 4.78$, $P = 0.01$ (see, Table III). Within the same LD block and, therefore, within the same model, a polymorphism in rs7632287 from the G to A allele was also associated with greater impairment in the total RBS-R score, $F(1, 543) = 3.57$, $P = 0.03$, and again, in the compulsive behavior, $F(1, 543) = 3.68$, $P = 0.03$, and ritualistic behavior, $F(1, 542) = 4.34$, $P = 0.01$, RBS-R subscales (see, Table III). No associations were observed between the repetitive behavior phenotype and any of the other six genotype groups including the remaining eight SNPs investigated (see, Tables VI–IX).

DISCUSSION

The current study provides additional support for an association between a symptom subset and genetic variation in the *OXTR* receptor, as opposed to investigating the singular DSM diagnosis. This is important further evidence supporting an association

TABLE IV. No LD Block: rs1042778 (TT vs. TG/GG) Adjusted for Ethnicity (* indicates $P < .05$ and ** indicates $P < .01$)

	rs1042778	
	F	*P*-Value
Social behaviors		
ADOS_JA	1.39	0.238
SRS: *t*-Score	0.28	0.598
SRS: social communication	2.88	0.090
SRS: autistic mannerisms	0.14	0.710
SRS: social awareness	0.29	0.589
SRS: social motivation	0.19	0.664
SRS: social cognition	2.31	0.129
Repetitive behaviors (RBS - R)		
Total	1.10	0.294
Compulsive behavior	0.09	0.768
Restricted behavior	0.07	0.768
Rituatlistic behavior	1.94	0.164
Stereotyped behavior	3.04	0.820
Sameness behavior	1.12	0.291

TABLE V. LD Block 2: rs237888 (TT vs. TG/GG) and rs4686301 (TT vs. TG/GG) Adjusted for Ethnicity

	rs237888		rs4686301	
	F	*P*-Value	F	*P*-Value
Social behaviors				
ADOS_JA	4.45	0.035*	0.00	0.957
SRS: *t*-score	0.09	0.763	0.08	0.776
SRS: social communication	0.27	0.607	0.14	0.713
SRS: autistic mannerisms	0.18	0.676	0.30	0.584
SRS: social awareness	0.00	0.963	0.28	0.599
SRS: social motivation	0.28	0.600	0.17	0.677
SRS: social cognition	0.15	0.697	0.00	0.947
Repetitive behaviors (RBS - R)				
Total	0.10	0.759	1.16	0.282
Compulsive behavior	0.01	0.917	0.19	0.666
Restricted behavior	0.45	0.505	1.80	0.180
Rituatlistic behavior	1.79	0.181	1.01	0.315
Stereotyped behavior	1.91	0.170	1.10	0.295
Sameness behavior	0.07	0.797	0.14	0.706

TABLE VII. LD Block 3: rs237889 (TT vs. TG/GG) Adjusted for Ethnicity (* indicates $P < .05$ and ** indicates $P < .01$)

	rs237889	
	F	*P*-Value
Social behaviors		
ADOS_JA	0.67	0.412
SRS: *t*-score	0.26	0.612
SRS: social communication	0.46	0.498
SRS: autistic mannerisms	0.23	0.628
SRS: social awareness	0.43	0.514
SRS: social motivation	0.01	0.910
SRS: social cognition	2.29	0.131
Repetitive behaviors (RBS - R)		
Total	0.11	0.741
Compulsive behavior	0.00	0.957
Restricted behavior	0.57	0.450
Rituatlistic behavior	2.88	0.090
Stereotyped behavior	0.17	0.685
Sameness behavior	2.27	0.133

between the oxytocin system and ASD-related symptoms. These results suggest that among children with ASD, polymorphisms in the *OXTR* gene may be associated with specific aspects of social impairment. More specifically, similar to past research [Campbell et al., 2011], we observed that a polymorphism in *OXTR* rs7632287 was associated with greater impairment in social skills, specifically joint attention, social communication, social cognition, and overall socialization. Importantly, rs7632287 was one of the SNPs that demonstrated a significant association with ASD in comprehensive meta-analysis examining the relation between *OXTR* and ASD [LoParo and Waldman, 2015]. These results extended this previous work through the finding that an additional SNP from the same *OXTR* LD block, rs237884, exhibited similar relatedness to the SRS including social communication, autistic mannerisms, social cognition, and overall socialization. With this information, we observe that in addition to demonstrating similar patterns of inheritance, it appears as though rs237884 and rs7632287 show similar associations with social behavior. This provides preliminary evidence to

TABLE VI. No LD Block: rs2268491 (TT vs. TG/GG) Adjusted for Ethnicity (* indicates $P < .05$ and ** indicates $P < .01$)

	rs2268491	
	F	*P*-Value
Social behaviors		
ADOS_JA	0.52	0.473
SRS: *t*-score	1.21	0.271
SRS: social communication	0.21	0.645
SRS: autistic mannerisms	1.75	0.186
SRS: social awareness	1.67	0.197
SRS: social motivation	0.00	0.963
SRS: social cognition	0.03	0.853
Repetitive behaviors (RBS - R)		
Total	0.77	0.380
Compulsive behavior	0.53	0.465
Restricted behavior	0.15	0.704
Rituatlistic behavior	0.60	0.439
Stereotyped behavior	2.47	0.116
Sameness behavior	0.09	0.762

TABLE VIII. LD Block 4: rs53576 (GG vs. AG/AA) Adjusted for Ethnicity (* indicates $P < .05$ and ** indicates $P < .01$)

	rs53576	
	F	*P*-Value
Social behaviors		
ADOS_JA	0.43	0.512
SRS: *t*-score	2.48	0.116
SRS: social communication	1.92	0.167
SRS: autistic mannerisms	1.50	0.221
SRS: social awareness	0.04	0.837
SRS: social motivation	1.32	0.252
SRS: social cognition	3.75	0.530
Repetitive behaviors (RBS - R)		
Total	2.84	0.093
Compulsive behavior	3.35	0.680
Restricted behavior	2.97	0.860
Rituatlistic behavior	0.50	0.478
Stereotyped behavior	3.16	0.076
Sameness behavior	0.00	0.966

TABLE IX. LD Block 5: rs2268491 (TT vs. TG/GG) and rs237897(GG vs. AG/AA) Adjusted for Ethnicity (* indicates $P < .05$ and ** indicates $P < .01$)

	rs2268491		rs237897	
	F	*P*-Value	F	*P*-Value
Social behaviors				
ADOS_JA	1.40	0.238	0.17	0.678
SRS: *t*-score	0.04	0.838	3.36	0.670
SRS: social communication	0.51	0.475	2.02	0.016
SRS: autistic mannerisms	0.49	0.484	3.41	0.065
SRS: social awareness	0.03	0.860	0.06	0.809
SRS: social motivation	1.06	0.305	0.02	0.883
SRS: social cognition	0.24	0.627	3.20	0.074
Repetitive behaviors (RBS - R)				
Total	0.03	0.871	2.15	0.143
Compulsive behavior	0.08	0.774	0.26	0.612
Restricted behavior	0.00	0.967	2.30	0.130
Rituatlistic behavior	0.98	0.323	2.23	0.136
Stereotyped behavior	0.41	0.522	0.67	0.415
Sameness behavior	0.15	0.701	0.01	0.929

support that the genetic association in social impairment among children with ASD might be localized to a specific region of the *OXTR* gene. That said, we also observed that joint attention impairment was related to a polymorphism in *OXTR* rs237888 and the association between *OXTR* and behaviors observed among children with ASD was not specific to the social phenotype of ASD. In addition to demonstrating an association with multiple components of the examined social phenotype, we also found that polymorphisms in both rs7632287 and rs237884 were associated with repetitive or restricted behaviors as assessed with the RBS. The current study is the second largest investigation of the relation between *OXTR* candidates and specific ASD phenotypes with n's ranging from 484 to 1002 depending on the SNP of interest (see Table I). With the exception of the study by Campbell et al. [2011], all other studies investigating the association between ASD and *OXTR* SNPs have included between 57 and 282 probands.

In addition to providing evidence for a localized association between ASD symptom impairment and a specific region, or LD block, of the *OXTR*, the current study also took an initial step toward narrowing the social phenotype investigated within ASD by investigating a unitary behavioral construct, such as JA. Within this study, JA was associated with both rs7632287 and rs237888 providing preliminary evidence that JA may be part of a broader social phenotype related to *OXTR* polymorphisms. To date, this is the first known study to investigate the association between *OXTR* polymorphisms and specific social behaviors commonly impaired among individuals with ASD, such as JA, as opposed to examining broader social composites alone. Given the known associations between discrete social behaviors and *OXTR* in animal models [Bartz and Hollander, 2006; Caldwell, 2012], future research among individuals with ASD would benefit from a more targeted examination of the relation between *OXTR* and specific social behaviors with more rigorous behavioral assessment procedures. Identification of these more precise relations may have implications for ASD treatment involving oxytocin.

Oxytocin treatment studies targeting social growth provide additional evidence in support of the relation between oxytocin and ASD. More specifically, several studies have demonstrated that intranasally administered oxytocin results in improved eye contact, social memory, and better use of social information among individuals with high functioning ASD [Hollander et al., 2003; 2007; Andari et al., 2010]. In their review of intranasal oxytocin functional magnetic resonance imaging studies, Bethlehem et al. [2013] posit that oxytocin not only has the ability to modulate activity in brain regions specific to prosocial behavior but also the ability to facilitate communication between these regions [Bethlehem et al., 2013]. Given the heterogeneity that exists in social impairment in ASD, it is important to understand which specific autism-related behaviors may be improved through the use of intranasal oxytocin treatments so we can target individuals and symptoms most likely to benefit from such a treatment. There has been some controversy surrounding the efficacy of such treatments (for reviews, see, MacDonald et al., 2011; Graustella and MacLeod, 2012); however, narrowed phenotypic targets might help to add clarity to this body of research.

Given that the oxytocin system in part regulates hypothalamic–pituitary–adrenal (HPA) axis functioning, a perturbation of oxytocin could have a substantial role in the development of neuropsychiatric disorders. For example, Spratt et al. [2012] found that children with autism expressed an increased reactivity in the HPA under conditions of stress as well as novel stimuli. There continues to be mounting evidence associating *OXTR* polymorphisms with individuals with ASD [Yamasue, 2013]; however, the variability of specific *OXTR* polymorphisms associated with ASD remains likely due to the heterogeneous nature of the disorder. Rather than investigating the genetic underpinnings of wider psychopathological phenotypes such as ASD, more honed investigations of specific social phenotypes may result in the discovery of more robust genetic associations.

Many past association studies have also been limited by relatively small sample sizes (e.g., Wu et al., 2005; Jacob et al., 2007; Lerer et al., 2008; Yrigollen et al., 2008). Future research investigating associations between ASD social phenotypes and *OXTR* candidates would benefit greatly from increased power. In the present study, while some variability existed with regard to sample size between the specific SNPs assessed (see Table I), the majority of the SNPs (8 of 10) investigated were from samples of over 900 probands with only two SNPs with sample sizes closer to 500 (rs7632287: $n = 565$ and rs53576: $n = 484$). This variability in sample size across the SNPs investigated was one limitation of the current study. Future research should emphasize more targeted investigations of specific SNPs and specific phenotypes to minimize the number of analyses conducted.

As an additional limitation to consider, contrary to theoretical claims that maladaptive phenotypes should align with the "at risk" or minor allelic variant (see, Devlinet al., 2011), association studies also frequently reveal phenotypic associations with the major. Although research conducted with *OXTR* reveals consistently points to a relation between ASD and the minor allele of

rs237884, research examining rs7632287 has been less consistent. Although the results from the current study align with the meta-analysis conducted by LoParo and Waldman [2015] indicating that the ASD-related phenotype is associated with a copy of the rs7632287 minor allele (A), other studies have shown that ASD traits are associated with the major allele (G; e.g., Tansey et al., 2010; Campbell et al., 2011). The explanation for these differences is unclear but among *OXTR* association studies within ASD great methodological variability exists with regard to operationalizing examined genotypes and phenotypes. For example, to date, over forty *OXTR* SNPs have been examined but positive associations with ASD have only been observed for 21 and positive associations with specific social phenotypes for far fewer. To help clarify the nature of ASD and *OXTR* associations, there may be a need for more theory-based research with specific *OXTR* SNP and more narrowly defined phenotypes. Although not the focus of the current study, it is important to note the LD observed between *OXTR* and CAV3. Future research may also want to examine the relation between social behavior and variability in the *CAV3* gene. This may provide some insight as to whether behavioral impairment is a function of variability in *OXTR*, *CAV3*, or both.

A final limitation of the current study was the cross-sectional design. The cross-sectional nature of the design allowed for an investigation of genetic correlates of social impairment in ASD; however, little can be gleaned about how *OXTR* candidates may contribute to the development of social deficits in ASD. Furthermore, genetic data processed for the SSC database are predetermined; therefore, some SNPs of potential interest had not been genotyped (e.g., rs2254298) and could not be investigated in this study.

Understanding how genetic variation may impact specific behaviors has important implications for understanding the etiology of ASD and for identifying mechanisms for novel biological treatments. That said, future research would greatly benefit from understanding the biological and molecular mechanisms that confer this gene to behavior disruption [Yamasue, 2013]. Understanding how *OXTR* SNPs results in variable oxytocin function may elucidate mechanisms by which social functioning becomes disrupted in disorders like ASD. At present, identifying a region of the *OXTR* gene that may be especially important in socialization provides a small piece of evidence in support of this mechanism. One hypothesis is that genetic variation in the relevant *OXTR* 3′ UTR may alter the levels of the mRNA and thereby protein levels in relevant parts of the brain. We failed to identify variation in mRNA levels of *OXTR* associated with these SNPS in a publically available dataset of gene expression in peripheral blood (data not shown) [Luo et al., 2012]. Further work in the future will be necessary to determine if these SNPs or other linked variation confer effects on gene expression levels in relevant brain tissues.

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