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Language impairment and dyslexia genes influence language skills in children with autism spectrum disorders

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Abstract

Language and communication development is a complex process influenced by numerous environmental and genetic factors. Many neurodevelopment disorders include deficits in language and communication skills in their diagnostic criteria, including autism spectrum disorders (ASD), language impairment (LI), and dyslexia. These disorders are polygenic and complex with a significant genetic component contributing to each. The similarity of language phenotypes and comorbidity of these disorders suggest that they may share genetic contributors. To test this, we examined the association of genes previously implicated in dyslexia, LI, and/or language-related traits with language skills in children with ASD. We used genetic and language data collected in the Autism Genome Research Exchange (AGRE) and Simons Simplex Collection (SSC) cohorts to perform a meta-analysis on performance on a receptive vocabulary task. There were associations with LI risk gene *ATP2C2* and dyslexia risk gene *MRPL19*. Additionally, we found suggestive evidence of association with *CMIP*, *GCFC2*, *KIAA0319L*, the DYX2 locus (*ACOT13*, *GPLD1*, and *FAM65B*), and *DRD2*. Our results show that LI and dyslexia genes also contribute to language traits in children with ASD. These associations add to the growing literature of generalist genes that contribute to multiple related neurobehavioral traits. Future studies should examine whether other genetic contributors may be shared among these disorders and how risk variants interact with each other and the environment to modify clinical presentations.

Keywords

language; autism spectrum disorders; *ATP2C2*; *MRPL19*; dyslexia; language impairment

Introduction

The development of adequate communication and language skills is an important milestone in child development. There are numerous neurodevelopmental disorders, including autism spectrum disorders (ASD), language impairment (LI), and dyslexia, that include specific language deficits in their diagnosis and symptomology. Typically, children with ASD lack

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coherence in conversation and verbal utterances, have difficulties in manipulating language with the proper syntax, show delays or regressions in speech and language skills, and are unable to comprehend and follow the language of others (Bishop 2010, Leyfer et al. 2008, Pennington & Bishop 2009). The language deficits observed in children with ASD have similarities to the ones seen in children with LI (Bishop 2010). In fact, there are a subset of children with ASD that are categorized as having comorbid LI (Bishop 2010, Kjelgaard & Tager-Flusberg 2001). Children with LI have difficulties in the development of comprehension and utilization of verbal language (Pennington & Bishop 2009). A primary deficit observed in children with LI is difficulty in phonological processing and awareness (Gathercole & Baddeley 1990, Pennington & Bishop 2009). However, these deficits in phonology are not unique to LI, as children with dyslexia typically have difficulties in these same phonological domains (Catts 2005, Pennington & Bishop 2009). In fact, children with LI are more likely to develop dyslexia later in childhood than their peers (Pennington 2006). The degree of similarity between language traits in ASD and LI, as well as LI with dyslexia, suggests that these disorders may share core communication deficits and determinants. Nonetheless, clinical or phenotypic similarities or comorbidities between dyslexia and ASD have not been noted in the literature.

In addition to similarities and comorbidity in clinical presentation, there are also similarities in the genes implicated in ASD, LI, and dyslexia. Heritability studies have demonstrated that LI and ASD share substantial genetic components (Bartlett et al. 2004, Bartlett et al. 2012, Bartlett et al. 2014). Unfortunately, the relative low number of LI candidate genes has made the interrogation of specific shared genetic associations somewhat difficult. However, both *FOXP2* and *CNTNAP2* are associated with LI and ASD, with the functional link that *FOXP2* regulates the transcriptional activity of *CNTNAP2* (Vernes et al. 2008, Vernes et al. 2011). There is also evidence that *FOXP2* contributes to dyslexia as well (Wilcke et al. 2012). There is less evidence suggesting that dyslexia and ASD may share genetic components. In fact, there are no known reports examining the heritability of shared genetic components between the two. However, there is limited evidence that dyslexia and ASD share genetic contributors. *FOXP2* has further been linked to dyslexia and reading-related traits (Kaminen et al. 2003, Peter et al. 2011, Wilcke et al. 2012). The axon guidance gene *ROBO1* has been implicated in both dyslexia and ASD, although with limited evidence supporting the association of *ROBO1* to each (Anitha et al. 2008, Bates et al. 2011, Tran et al. 2014). Nonetheless, the shared genetic associations of dyslexia and LI as well as LI and ASD suggest all three disorders may share genetic contributors.

Therefore, the overall goal of this study is to examine whether genes previously implicated in dyslexia, LI, and/or language-related traits are also associated with language skills in individuals with ASD. To accomplish this, we specifically assess associations with performance on a receptive vocabulary task in two family-based ASD cohorts: the Autism Genome Research Exchanges (AGRE) and Simons Simplex Collection (SSC). We hypothesize that both dyslexia and LI risk genes also contribute to language phenotypes observed in children with ASD.

Methods

AGRE (www.agre.org) and SSC (www.sfari.org) are family cohorts recruited based on a clinic diagnosis of ASD in a family member. The AGRE is a collection of well-characterized multiplex and simplex families with a large amount of phenotypic and genotypic data (Geschwind et al. 2001, Weiss et al. 2009). Following enrollment in AGRE, diagnosis of ASD was confirmed using the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 1994, Lord et al. 1989). The SSC is a more recent study, where, similar to AGRE, probands were recruited along with unaffected parents and siblings across 12 participating sites in the United States (Abrahams et al. 2013, Fischbach & Lord 2010). Each affected proband completed a wide range of neurobehavioral measures including the ADI-R and ADOS (Lord et al. 1994, Lord et al. 1989). Informed consent was completed under the guidance of each site's institutional review board. De-identified data were obtained by the authors for analysis.

Subjects completed a language measure, the Peabody Picture Vocabulary Test (PPVT), in both the AGRE and SSC cohorts. The PPVT is a measure of receptive vocabulary (Dunn & Dunn 1997). Subjects are verbally prompted with a word and four pictures. The subject chooses the picture that most closely matches the meaning of the prompted word. Raw scores are converted to a quantitative standard score corrected for age norms. This test quantitatively measures the ability of the subject to process verbally presented language and to connect it to a concrete meaning. In total, 941 and 1048 individuals with genetic information completed the PPVT in the AGRE and SSC cohorts, respectively.

The AGRE cohort was genotyped with the Illumina 500K SNP chip, while the SSC cohort was genotyped with the Illumina 1M and 1M Duo chips. The difference in genotyping chips resulted in increased marker coverage on average for the SSC sample when compared to the AGRE cohort. However, the use of the same manufacturer ensured that there was substantial overlap among the genotyped markers in the two samples. Markers within the risk LI and dyslexia genes and/or loci listed in Table 1 were selected for association analyses. Genes were selected based on prior evidence of association or linkage to dyslexia and/or LI. Notably, we excluded markers in *CNTNAP2*, as the relationship of this gene with language has already been characterized in the AGRE sample (Alarcon et al. 2008), and markers within *ZNF385D* and *ROBO1*, as the sheer size of these genes would have overwhelmed the marker composition in our study design. Markers with a minor allele frequency <0.05, call rate <0.85, Mendelian errors, were not in Hardy-Weinberg equilibrium ($p<0.0001$) or had more than 2 alleles were excluded from the analysis. In total, there were 2022 and 904 markers within these risk genes and loci in the SSC and AGRE cohorts, respectively. Of these, 805 genotyped markers were in common between the two samples.

Genetic associations with quantitative performance, as measured by standard score, on the PPVT were performed with PLINK using the QFAM function with 100,000 permutations to correct for family structure (Purcell et al. 2007). The association results of the 805 shared markers in each individual cohort were then used in a meta-analysis using METAL (Willer et al. 2010). To conservatively correct for multiple testing, we used a statistical Bonferonni threshold of 6.21×10^{-5} ($p = 0.05 / 805$ shared markers tested). Associations from the meta-

analysis with p<0.001 are presented in the main text to present suggestive associations (Table 2). Full association results are available upon request.

Results

Results for the meta-analysis of performance on the PPVT in the AGRE and SSC cohorts are presented in Table 2, with the top results in individual cohorts presented in Supplemental Tables 1-2. There were two associations that survived correction for multiple testing: rs11149652 in *ATP2C2* ($p=5.00\times10^{-6}$) and rs7588016 in *MRPL19* ($p=3.90\times10^{-5}$) (Table 2). Three other markers within *ATP2C2*, rs12446219 ($p=6.44\times10^{-5}$), rs4782624 ($p=2.34\times10^{-4}$), and rs8059665 ($p=8.56\times10^{-4}$), showed suggestive associations. Another LI risk gene located within the SLI1 Locus on chromosome 16, *CMIP*, showed suggestive evidence of association ($p=1.79\times10^{-4}$). No other markers in *MRPL19* showed suggestive associations in these cohorts; however, there were suggestive associations with a marker in *GCFC2*, rs17011662 ($p=1.09\times10^{-4}$), which is located in the same DYX3 locus on chromosome 2. In the SSC sample, there were multiple associations with markers in *KIAA0319L* ($p=1.00\times10^{-5}$) (Supplemental Table 2), with suggestive evidence in the meta-analysis ($p=1.52\times10^{-4}$) (Table 2). There were other notable suggestive associations with markers in *DRD2* and several genes in the DYX2 locus including *ACOT13*, *GPLD1*, and *FAM65B*. However, in the meta-analysis, we found no evidence of association for other language genes such as *DCDC2*, *KIAA0319*, *FOXP2*, *DYX1C1* and *CYP19A1* in the DYX1 locus, *RCAN3*,and *ABCC13*. However, there was suggestive evidence in the association results in the individual cohorts (Supplementary Tables 1-2).

Discussion

In this study, we examine whether genes previously implicated in dyslexia, LI, and/or other language related traits are also associated with language skills in children with ASD. We aimed to determine whether genes identified with related communication traits may also contribute to language deficits observed in children with ASD. There were associations of *ATP2C2* and *MRPL19* with performance on a measure of receptive vocabulary. In addition, we found suggestive evidence for other language-related genes, including *CMIP*, *GCFC2*, *DRD2*, and *KIAA0319L*, as well as several DYX2 genes (*ACOT13*, *GPLD1*, and *FAM65B*). These results demonstrate that genes that contribute to other communication disorders also influence language traits in children in ASD.

ATP2C2 is one of two risk genes, the other being *CMIP*, in the SLI1 locus on chromosome 16. The SLI1 locus was first identified in genome-wide linkage studies (SLI Consortium 2002 and 2004) of LI, with subsequent association studies implicating *ATP2C2* and *CMIP* in LI and phonological short-term memory deficits in children with LI (Newbury et al. 2009, Newbury et al. 2011). Phonological short-term memory is a common endophenotype for LI, while receptive vocabulary typically is a marker of general verbal cognition (Bishop 2010, Pennington & Bishop 2009). The association of *ATP2C2* with a more general language measure expands its role for one solely in LI to now also include language deficits in ASD. Further supporting a more general neurocognition role of *ATP2C2* is the previous association of *ATP2C2* with attention deficit hyperactivity disorder (ADHD), a condition

commonly comorbid with dyslexia and LI (Lesch et al. 2008). The evidence here implicating *ATP2C2* in language skills in children with ASD further suggests that the SLI1 risk genes contribute to general language and neurobehavioral traits and not specifically to LI.

The other gene for which we found substantial evidence for association, *MRPL19*, is located within the DYX3 locus on chromosome 2. *MRPL19* was initially implicated in dyslexia through family-based studies (Anthoni et al. 2007, Fagerheim et al. 1999, Kaminen et al. 2003, Paracchini et al. 2011, Peyrard-Janvid et al. 2004). Markers in this locus have been associated with Verbal IQ (Scerri et al. 2012). Receptive vocabulary measures, including the PPVT, are sometimes used to estimate Verbal IQ, indicating that here we expand the association of *MRPL19* from Verbal IQ performance in the general population and dyslexia cases to include ASD cases. Additionally, Roberts et al. recently reported a deletion including this locus in a case with ASD (Roberts et al. 2014). The DYX3 locus has shown repeated associations with overall language skills, as measured by Verbal IQ and receptive vocabulary tasks, in multiple sample types (general population, dyslexia, and ASD), suggesting that DYX3 genes (e.g., *MRPL19*) influence general language and communication traits.

Our associations of dyslexia and LI associated genes with language skills in ASD add to the growing literature showing that genes appear to contribute to multiple related neurobehavioral, neurocognitive, and language traits, as opposed to specific disorders (e.g. a specific dyslexia gene, a specific ASD gene, or a specific LI gene). Risk variants of associated genes whether common or rare alter a cellular process, such as calcium transport with *ATP2C2* or neuronal migration with *DCDC2*/*KIAA0319* (Meng et al. 2005, Paracchini et al. 2006, Xiang et al. 2005). These alterations either individually, as seen in syndromic and rare variants, or interactively with other genetic variants or environment, including both common and rare variants, yield the nuanced clinical presentations of these disorders. Discerning how these variants and/or environmental factors interact to cause specific types of clinical presentations will be vital to determining the etiologies of these disorders and to improving remediation of language skills.

Our study is subject to several limitations including (1) selection bias of genetic markers included in the analyses based on the current literature of dyslexia and LI, (2) differences in genotyping chips used in the AGRE and SSC samples limiting our coverage of the genes examined, and (3) the use of only a receptive vocabulary measure in assessing language skills in both cohorts. However, we hope the results of our study prompt the expansion of language batteries used in studies of individuals with ASD as well as highlight the importance of resources with large amounts of genetic and behavioral data such as AGRE and SSC.

In conclusion, our study shows that the LI associated gene *ATP2C2* and dyslexia associated gene *MRPL19* also contribute to language skills in children with ASD, linking language and communication process in these three disorders. For example, genetic associations shared between dyslexia, LI, and ASD likely influence general language skills, as measured by tasks similar to receptive vocabulary measures used in this study. On the other hand, genes

associated with dyslexia and LI, but not ASD, may influence phonological processes, known to be important in dyslexia and LI, but not necessarily in ASD. Genes associated with language and behavior appear to be associated with general communication and behavior phenotypes as opposed to specific disorders or traits. Future studies should further interrogate the degree to which these and other related disorders share genetic factors and begin to examine how these factors may interact to bring about individual conditions, marking a beginning of personalized medicine in polygenic, complex disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ASD	autism spectrum disorders
LI	language impairment
AGRE	Autism Genome Research Exchange
SSC	Simons Simplex Collection
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Scale
PPVT	Peabody Picture Vocabulary Test
GWAS	genome-wide association study
PING	Pediatric Imaging Neurocognition Genetics
ADHD	attention deficit-hyperactivity disorder

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Table 1

List of genes previously associated with LI, dyslexia, and/or language-related traits examined in AGRE and SSC

Gene	Location	# in AGRE	# in SSC	Gene	Location	# in AGRE	# in SSC
RCAN3	1p35.3-1p33	8	20	*ANKK1/ DRD2***	11q23	26	59
KIAA0319L	1p34.2	6	66	*DYX1C1*	15q21.3	11	37
GCFC2	2p12	9	20	*CYP19A1*	15q21.1	36	258
MRPL19	2p11.1-q11.2	17	30	*CMIP*	16q23	111	183
DYX2*	6p22	260	657	*ATP2C2*	16q24.1	88	128
FOXP2	7q31	69	151	*ABCC13*	21q11.2	21	36

Abbreviations: # in AGRE, number of markers examined in AGRE; # in SSC, number of markers examined in SSC

* DYX2 refers to the dyslexia risk locus DYX2 on chromosome 6, which contains 12 genes including risk genes *DCDC2* and *KIAA0319*

** *ANKK1* and *DRD2* are located adjacent to one another on chromosome 11 and therefore grouped together

Table 2

Associations (p<0.001) with performance on the Peabody Picture Vocabulary Test from meta-analysis of AGRE and SSC.

Marker	Ch	BP	Gene	Allele 1	Allele 2	Dir.	AGRE P-value	SSC P-value	Combined P-value
rs11149652*	16	84414399	*ATP2C2*	A	G	− −	1.47×10^{-2}	7.00×10^{-5}	5.00×10^{-6}
rs7588016*	2	75649214	*MRPL19*	T	C	++	2.64×10^{-2}	3.70×10^{-4}	3.90×10^{-5}
rs12446219	16	84415015	*ATP2C2*	T	C	− −	2.70×10^{-3}	7.76×10^{-3}	6.44×10^{-5}
rs17671350	6	24898628	*FAM65B*	T	C	− −	9.10×10^{-3}	2.43×10^{-3}	6.45×10^{-5}
rs6928074	6	24680062	*ACOT13*	A	G	− −	1.10×10^{-2}	3.41×10^{-3}	1.06×10^{-4}
rs17011662	2	75691522	*GCFC2*	T	C	++	1.51×10^{-2}	2.46×10^{-3}	1.09×10^{-4}
rs12039012	1	35472284	*KIAA0319L*	A	G	− −	2.23×10^{-2}	2.26×10^{-3}	1.52×10^{-4}
rs2966099	16	81516843	*CMIP*	T	C	++	2.85×10^{-2}	2.03×10^{-3}	1.79×10^{-4}
rs12562622	1	35439579	*KIAA0319L*	T	C	− −	2.23×10^{-2}	3.60×10^{-3}	2.29×10^{-4}
rs4782624	16	84431560	*ATP2C2*	A	G	++	6.90×10^{-2}	8.20×10^{-4}	2.34×10^{-4}
rs2242592	11	113408708	*DRD2*	T	C	++	1.92×10^{-2}	4.50×10^{-3}	2.40×10^{-4}
rs793671	6	24428434	*GPLD1*	A	G	++	4.10×10^{-3}	2.16×10^{-2}	2.71×10^{-4}
rs2927332	16	81475688	*CMIP*	T	G	++	9.26×10^{-3}	1.41×10^{-2}	3.53×10^{-4}
rs12596138	16	81457144	*CMIP*	T	C	− −	3.40×10^{-2}	3.67×10^{-3}	3.61×10^{-4}
rs2734849	11	113399438	*ANKK1*	T	C	− −	1.46×10^{-2}	1.02×10^{-2}	3.94×10^{-4}
rs4581480	11	113453752	*DRD2*	T	C	++	3.72×10^{-3}	5.20×10^{-2}	6.59×10^{-4}
rs9393532	6	24164229		A	G	++	1.85×10^{-2}	1.47×10^{-2}	6.97×10^{-4}
rs8059665	16	84429583	*ATP2C2*	T	G	− −	1.39×10^{-1}	1.42×10^{-3}	8.56×10^{-4}
rs2927321	16	81481164	*CMIP*	T	C	++	2.48×10^{-2}	1.47×10^{-2}	9.17×10^{-4}

Abbreviations: Ch, chromosome; BP, base pair; Dir, direction of effect

*Survived correction for multiple testing