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Pragmatic Language in autism and fragile X syndrome: Genetic and clinical applications

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Abstract

Evidence suggests a strong genetic basis to autism. Our research program focuses on identifying genetically meaningful phenotypes in autism, through family-genetic and cross-population methods, with a particular focus on language and social phenotypes that have been shown to aggregate in families of individuals with autism. In this article, we discuss recent findings from family study research implicating particular language and personality features as markers for genetic liability to autism and fragile X syndrome and *FMR1*-related variation in relatives. We conclude with consideration of the clinical implications of such findings.

Keywords

Autism; Fragile X Syndrome; Broad Autism Phenotype; *FMR1* Premutation; Pragmatic Language

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders that are characterized by impairments in communication and social reciprocity, as well as a pattern of restricted interests and repetitive behaviors (American Psychiatric Association, 1994). Autistic disorder, Asperger's syndrome, and pervasive developmental disorder–not otherwise specified (PDD-NOS) comprise ASD. While the specific diagnostic criteria for each ASD differ slightly, all are characterized by core impairments in social communication, including pragmatic language deficits. In this article we will use the term "autism" to denote any ASD, unless otherwise specified. Autism is exceedingly common, with an estimated 1 in 110 children diagnosed with the disorder (CDC, 2009; Fombonne, 2009; Kawamura, Takahashi, & Ishii, 2008; Yeargin-Allsopp et al., 2003), and some reports suggesting the prevalence may be as high as 2.6 in 100 (Kim et al., 2011).

One of the most striking characteristics of individuals with autism is their difficulties with the pragmatic aspects of language, such as narrative (i.e., storytelling) and conversation. This impairment is observed universally in all individuals with autism, even among high-functioning individuals who otherwise have no expressive language delay or intellectual disability (Landa, 2000; Tager-Flusberg, Paul, & Lord, 2005). During storytelling tasks, individuals with autism consistently produce poorer quality, less cohesive narratives that are

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characterized by less complex grammatical constructions and limited use of storytelling devices to engage the listener and enrich the narrative (e.g., discussing the thoughts and emotions of characters, using attention-getting language to direct the listener's attention) (Capps, Losh, & Thurber, 2000). Individuals with autism also use less causal language to explain the actions and emotions of the characters (Capps et al., 2000; Diehl, Bennetto, & Young, 2006; Losh & Capps, 2003; Tager-Flusberg, 1995) and are more likely to include irrelevant or inappropriate statements during narrative tasks (Diehl et al., 2006; Loveland, McEvoy, & Tunali, 1990). Similarly, naturalistic conversation of individuals with autism is characterized by a reduced use of causal frameworks to describe their own emotional experiences and difficulty in communicating understanding of complex emotions (Losh & Capps, 2006).

There is significant behavioral overlap between autism and fragile X syndrome (FXS), the most common known inherited cause of intellectual disability and most common single-gene disorder associated with autism (Cohen, Pichard, & Tordjman, 2005; Hagerman, 2008). About 2-6% of individuals with autism have FXS (Hagerman, 2006) and about 25-52% of males with FXS meet diagnostic criteria for autism (Clifford et al., 2007; Hatton et al., 2006; Rogers, Wehner, & Hagerman, 2001). In a study of conversational abilities among school-aged boys with FXS and comorbid autism, FXS without autism, Down syndrome, and younger boys with typical development of similar mental age, we found that boys with FXS and comorbid autism showed more off-topic or tangential language than all other groups (Roberts et al., 2007), suggesting that the pragmatic language difficulties seen in FXS may be associated with comorbid autism.

In what follows, we briefly present evidence for the genetic basis of autism. We then describe results of our studies which suggest that mild, but qualitatively similar language and personality features are evident among relatives of persons with autism as well as parents of children with FXS. We conclude with a discussion of clinical implications of these findings.

Genetic Basis of Autism

Strong evidence supports a genetic basis of autism (Geschwind, 2009; O'Roak & State, 2008). First, twin studies examining concordance of autism in monozygotic versus dizygotic (i.e., identical and fraternal) twins show high heritability. Monozygotic twins, who share nearly all of their genes, are much more likely to both receive a diagnosis of autism than dizygotic twins, who share roughly half of their segregating genes. Reports vary according to classification methods and sample characteristics, but findings show that 36%-96% of identical twins will both be classified as having autism, as opposed to 0%-31% of fraternal twins, which supports strong heritability and a substantial genetic component in autism (Ronald & Hoekstra, 2011).

Further evidence supporting a genetic etiology comes from studies of the recurrence of autism within families, recently estimated at nearly 20%, which is significantly greater than the general population risk (Chakrabarti & Fombonne, 2001; Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Lauritsen, Pedersen, & Mortensen, 2005; O'Roak & State, 2008; Ozonoff et al., 2011; Ritvo et al., 1989). This recurrence rate is even higher among families who have multiple children with autism, with 32-35% of later-born siblings from families who already have two or more children with autism also developing autism themselves (Ozonoff et al., 2011; Ritvo et al., 1989). Furthermore, siblings of children with autism, even those that do not go on to be diagnosed with autism, often demonstrate a multitude of developmental differences and delays early in life (see Tager-Flusberg, 2010, for review), and many continue to exhibit cognitive and language deficits well into childhood (e.g.,

Bishop, Maybery, Wong, Maley, & Hallmayer, 2006; Gamliel, Yirmiya, & Sigman, 2007; Yirmiya, Gamliel, Shaked, & Sigman, 2007).

The Broad Autism Phenotype

Despite evidence that autism is a genetically based disorder, specific “autism genes” have not yet been conclusively identified. The genetic cause of autism is thought to be extremely complex, involving multiple genes that may interact together and with the environment (Geschwind, 2009). This genetic complexity, combined with the heterogeneous clinical presentation of autism, has hindered efforts to identify autism genes. One approach for simplifying this complex clinical and etiological picture is through the study of family members who are at increased genetic liability, and who, although clinically unaffected, may show subtle characteristics qualitatively similar to features observed in autism. Through the study of such features among family members, the aim is to identify traits that are simpler in clinical presentation than autism, and which may be more closely linked to underlying genes.

Mild characteristics sharing qualitative similarities to features of autism in family members have been described as constituting a broad autism phenotype (BAP). The term ‘phenotype’ refers to observable characteristics (clinical-behavioral, neuropsychological, biochemical, etc.) that are the result of underlying genes and gene-environment interactions. The BAP is characterized by specific personality and language traits that resemble the core symptoms of autism, but are much more subtle in presentation and are not generally associated with impairment. For example, multiple studies have found that parents of individuals with autism demonstrate increased rates of specific personality features, including social reticence, rigidity, and perfectionism, and particular patterns of pragmatic language use (see Losh, Adolphs, & Piven, 2011 for review). Features of the BAP are thought to be linked to underlying genes, with families who have higher genetic susceptibility showing increased expression of these traits. Support for this hypothesis comes from findings that parents from multiple-incidence families (with two or more children with autism) are more likely to demonstrate social reticence, rigid personality, fewer/lower quality friendships, and increased rates of pragmatic language violations than parents with only one child with autism or control parents of children with Down syndrome (Losh, Childress, Lam, & Piven, 2008).

Pragmatic language differences that are milder, but nonetheless similar in quality as those seen in autism, are well-documented among parents of individuals with autism (Landa et al., 1992; Piven, Palmer, Landa, Santangelo, & Childress, 1997; Ruser et al., 2007). Parents of individuals with autism are more likely to produce narratives that are more tangential and less thematically cohesive than control groups’ (Landa, Folstein, & Isaacs, 1991). Similarly, studies of elicited conversations have documented among parents of individuals with autism a tendency to contribute more tangential language, verbosity, and topic preoccupation (Landa et al., 1992; Piven et al., 1997; Ruser et al., 2007). Furthermore, parents from families with multiple cases of autism are more likely to show such features than parents from single-incidence families or control parents of children with Down syndrome, which supports a genetic role in pragmatic language ability (Losh et al., 2008). Because pragmatic language impairment is a central feature of autism, these mild, but qualitatively similar language features observed in relatives are believed to reflect the influence of genes associated with autism. Our research group and others have focused on understanding the neuropsychological underpinnings of these language profiles, and associated features of the BAP among relatives as a tool for investigating the genetic basis of autism.

The Broad Autism Phenotype among FMR1 Premutation Carrier Parents

In current work, our research group is extending this family-based approach to parents of individuals with FXS, who are carriers of the gene that causes FXS in its premutation state. FXS is caused by a mutation in the *Fragile X Mental Retardation 1* (*FMR1*) gene on the X chromosome, which causes the gene to shut down and fail to produce a critical protein expressed in the brain (Hagerman & Hagerman, 2002). FXS is an X-linked disorder, transmitted maternally when the mutation on *FMR1* gene expands from its unstable permutated state (i.e., CGG trinucleotide repeat length between 55-200) to a fully mutated state (>200 repeats) (Tassone, Hagerman, Taylor, Mills, & Harris, 2000). The *FMR1* full mutation (i.e., FXS) is the most common monogenetic disorder associated with autism (Cohen, Pichard, & Tordjman, 2005; Hagerman, 2008), the *FMR1* premutation also appears to confer risk of autism among carrier relatives of individuals with FXS (Aziz et al., 2003; Clifford et al., 2007; Farzin et al., 2006; Goodlin-Jones, Tassone, Gane, & Hagerman, 2004; Tassone, Hagerman, Mills, & Harris, 2000).

The *FMR1* premutation is estimated to occur in 1 in 250 females (Rousseau, Rouillard, Morel, Khandjian, & Morgan, 1995) and in 1 in 813 males (Dombrowski et al., 2002). Although carriers were once thought to be asymptomatic, we now know that a proportion of premutation carriers are affected by fragile-X associated conditions. For example, symptoms of fragile X-associated tremor ataxia syndrome (FXTAS) are seen in over one-third of male premutation carriers by mid-life, with prevalence increasing with age (Jacquemont, Hagerman, Hagerman, & Leehey, 2007; Jacquemont et al., 2004). Fragile X-associated premature ovarian insufficiency, characterized by infertility and menopause before the age of 40, affects up to 20% of women with the premutation (Allingham-Hawkins et al., 1999; Mollolas et al., 2001; Wittenberger et al., 2007). In addition to these neurological symptoms, carriers may also be at increased risk for social anxiety and panic disorders (Franke, Leboyer, Gansicke, & Weiffenbacj, 1998), and somewhere between 29% and 49% of female carriers have major depressive disorder (Franke et al., 1998; Reiss, Freund, Abrams, Boehm, & Kazazian, 1993; Roberts et al., 2009; Thompson, Rogeness, McClure, Clayton, & Johnson, 1996). Symptoms consistent with autism and the BAP are also seen among *FMR1* premutation carriers. Autism is significantly more common among carriers than among individuals of the general population, with about 14% of male carriers meeting criteria for ASD (Clifford et al., 2007). Milder social differences are also seen among carriers, including difficulty recognizing emotional states from facial expression and eye gaze (Cornish et al., 2005). Several reports have also noted symptoms of shyness, social reticence, heightened interpersonal sensitivity, and gaze aversion among *FMR1* premutation carriers (Franke et al., 1998; Hagerman & Hagerman, 2004; Johnston et al., 2001; Sobesky, Hull, & Hagerman, 1994). Evidence from brain imaging studies also points to differences in social functioning, with male carriers showing atypical activation of the limbic system, a set of structures which modulate emotional processing (Hessl et al., 2007).

In current research, we are investigating the presence of the BAP among *FMR1* premutation carrier parents, as a parallel method for studying overlapping symptoms of autism and FXS among a population of individuals who are more mildly affected. In a sample of mothers who were *FMR1* premutation carriers, mothers of individuals with autism, and mothers of typically developing children, we found that both premutation carrier mothers and mothers of individuals with autism showed a similar number of pragmatic language violations during a naturalistic conversational sample, that was significantly greater than the mean number of violations committed by control mothers. Furthermore, mothers of children with autism and mothers of children with FXS showed overlapping *types* of pragmatic language difficulties, which included features such as interrupting, differences in volume modulation, topic preoccupation, and overly-detailed, tangential narratives (Losh et al., in review). We have

also detected increased rates of rigid or inflexible personality features (characterized by difficulty adjusting to minor changes and resistance to novel experiences) among *FMR1* premutation carrier mothers and an expanded sample of parents of individuals with autism, in comparison to control parents (Losh et al., in review). Together, these findings may implicate a particular gene (*FMR1*) in personality and language characteristics associated with the BAP. Such findings also reveal intriguing insights into the genetic basis of the complex human traits of language and personality.

Clinical Implications

Given its high prevalence, clinicians working with pediatric populations will likely have children with autism on their caseload, and therefore should have knowledge of the communication profile associated with autism. Difficulties communicating experiences in narrative form (i.e., story-telling) and general difficulties with social language impose considerable barriers to successful communication among even the highest functioning individuals with autism. Clinicians should be aware that many children with autism who perform within age-limits on standardized measures of structural language (e.g. vocabulary, grammar) will nonetheless show significant difficulties with pragmatic language. Therefore, pragmatic language ability should be a deliberate focus of speech and language evaluations for children with autism. While standardized assessments for pragmatic language provide useful information regarding performance relative to peers, it is helpful to supplement such assessments with observation during naturalistic social contexts, such as during unstructured conversation with the clinician or with a peer. Naturalistic assessment techniques are useful in building a picture of how a child normally communicates during everyday activities, which may not be apparent during more structured contexts. For example, conversational and story-telling activities allow for evaluation of the child's ability to incorporate the listener's perspective and shared knowledge, which is a critical skill that may not be sampled during more structured evaluations. Many checklists of pragmatic language skills are available online or as part of broader language assessment tools, and these can serve as a useful guide for outlining behaviors that should be observed when evaluating pragmatic language in natural contexts, and can also be helpful in providing targets for intervention.

Basic knowledge of the cause of autism and its implications for families is important for clinicians working with families of individuals with autism. Siblings of children with autism are at a significantly increased risk for autism or other developmental differences. Therefore, it is essential that clinicians monitor siblings of children with autism for early signs of language delay, social impairment, and intellectual disability. Considering the high recurrence rates of autism within families, clinicians should also be prepared to refer families who are concerned about reproductive options for genetic counseling, as appropriate.

Clinicians should be cognizant of the significant behavioral overlap of autism and FXS. Because FXS is the leading monogenetic condition associated with autism, it is important that genetic testing (e.g. karyotyping and fragile X testing) is included as part of the diagnostic process for all clients who have autism, and particularly when clients present with dysmorphic features, neurological symptoms, or with a family history of intellectual disability or other learning difficulties (Lintas & Persico, 2009). Similarly, clients with FXS should be evaluated for autism. Children FXS and comorbid autism may present with clinical-behavioral characteristics that are distinct from those in FXS only, and as such warrant additional consideration when tailoring intervention approaches. Moreover, families of children with FXS may have a variety of fragile X-associated health concerns that extend beyond the immediate care of the child with FXS. Clinicians working with families of individuals with FXS should be aware of the range of fragile X-associated symptoms that

families may be facing, and be prepared to refer families for psychiatric, neurological, and genetic counseling services as appropriate.

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