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BRIEF REPORT

Brief Report: Relationship Between Non-verbal IQ and Gender in Autism

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Abstract It has been proposed that females at risk for autism are protected in some way, so that only those with the greatest genetic liability are affected. Consequently, affected male siblings of females with autism should be more impaired than affected male siblings of male probands. One hundred and ninety-four (194) families with a single child with autism (simplex, SPX) and 154 families with more than one child with autism (multiplex, MPX) were examined on measures of severity, including non-verbal IQ. Among SPX families, girls had lower IQ than boys, but no such differences were seen among MPX families. Similarly, the affected brothers of girls with autism were no different from affected brothers of male probands. These data suggest that MPX and SPX families differ with respect to the relationship between gender and IQ.

Keywords Autism · IQ · Gender · Genetic

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Introduction

One of the most well established findings in the genetic epidemiology of autism is that the disorder has a male predominance by about 4 to 1 (Fombonne 2003). It is also often stated that when females are affected by autism, they exhibit a more "severe" form of the disorder, at least when severity is defined in terms of lower IQ, more impairments in adaptive functioning (Volkmar et al. 1993) or more autistic symptoms (Tsai and Beisler 1983). This is clearly demonstrated in many epidemiological studies which show that the gender ratio approaches equality at the level of severe intellectual disability and becomes more extreme (favoring boys) in the normal IQ range (see Bryson et al. 1988; Wing 1981; Yeargin-Allsopp et al. 2003). Differences in severity of autistic symptoms are not as consistently reported as differences in adaptive functioning and IQ, especially at the higher functioning end of the spectrum (Holtmann et al 2007) or when different stages of development are assessed (McLennan et al 1993). For example, Carter et al (2007) have shown that for very young children with ASD, boys show better language and motor skills and more advanced social development, while girls show better visual receptive skills.

The specific mechanisms underlying male predominance and sex-related phenotypic differences in autism remain a mystery. One possible explanation of these findings of lower risk and greater severity among females is to hypothesize that the genetic liability for autism is normally distributed in the population and that males and females have a different genetic threshold (Ottman 1987). If females have a higher threshold, those with less genetic load are protected in some way and so do not become autistic. Females need a higher genetic load than males to presumably overcome that protective effect and become

affected. If the genetic factors that influence risk also affect severity of symptoms or cognitive impairment, a higher genetic load might also explain their greater severity than males. This model presumes that variation in autism susceptibility and phenotypic severity share a common origin. If this were true, we expect that in pairs of autistic siblings, male siblings of female probands will possess a similarly high genetic load as their sisters. As a consequence, they might also show greater severity, at least as measured by lower IQ or adaptive functioning scores or more symptoms, similar to their sisters. In contrast, male siblings of male probands also diagnosed with autism will possess a greater range of genetic loads (including milder doses of genetic liability), and as such will demonstrate less cognitive and adaptive functioning impairment and possibly less symptom severity as well.

Methods

Sample

Single incidence (or simplex, SPX) and multiple incidence (multiplex, MPX) families were recruited systematically from parent support groups and mental health and social service agencies across Canada that serve children with developmental disorders. The SPX families all had at least one unaffected sibling and MPX families had at least two or more siblings with any form of autism spectrum disorder (ASD). No restriction was placed on ASD subtype or on non-verbal IQ levels. The following additional inclusion criteria were applied if the child received a diagnosis of pervasive developmental disorder (PDD) by DSM IV criteria: (a) age greater than 3 years for the child who was first diagnosed. The affected sibling could, however, be younger than 3 years but was older than 2 years; (b) and no neurological disease or known chromosomal disorder. The autism diagnostic interview—revised (ADI R) (Lord et al. 1994) and the autism diagnostic observation schedule (ADOS) were used to collect information to make a more definite diagnosis. Those administering the ADI-R and ADOS were trained to research standards. Clinical records were obtained and an independent blind best-estimate diagnosis was then made, according to DSM IV criteria, using all available information by three clinicians (a pediatrician, a psychologist, and a psychiatrist) with an average of 15 years experience in the assessment of children with autism (the ADI-R algorithms were not used but agreed highly with the best-estimate diagnoses; see Risi et al 2006). The Leiter IQ scales and the Vineland adaptive behaviour scales (VABS) were also completed on affected children. There were 50 SPX families with an affected girl, and 144 families with one affected boy. There were 154 families with at least two affected children, 48 containing an affected girl (the female proband; if there was more than one affected female in the family, one was randomly selected to be the female proband) and 106 families with only affected boys (one of which was selected at random and termed the "male proband"). There were 156 affected male children of these MPX male and female probands; 109 from male–male sib pairs and 47 from male–female sib pairs. The age of all affected girls with ASD was 9.19 years (SD = 5.64 years), and the mean age of all affected boys with ASD was 9.38 years (SD = 5.76 years). There was no difference in the mean age of affected brothers of the female probands (7.23 years) versus affected brothers (8.55 years) of male probands ($t = -1.46$, $p = 0.15$).

Instruments and Measures

Autism Diagnostic Interview-Revised (ADI-R; Lord et al. 1994)

This is an investigator-based interview administered by interviewers trained to research standards to the primary care giver(s) of the child. It is designed to obtain detailed descriptions of behaviours necessary for the diagnosis of ASD, especially autism. The interview focuses on the key diagnostic features described in the International Classification of Diseases-10th edition (ICD–10) and DSM-IV. The questions are designed to distinguish qualitative impairments from developmental delays by assessing behaviours at an appropriate age, identifying behaviours that would be considered deviant at any age and examining current and most abnormal behaviours for those strongly influenced by maturational age.

Leiter Performance Scales (Levine 1986)

This is the standard measure of nonverbal problem solving and learning ability. It is especially appropriate to this population of ASD children because it does not require verbal instructions or responses for administration and correlates highly with Wechsler intelligence scale for children—revised (WISC-R) IQ. It is commonly used with ASD and other language impaired children. Both the old and the newer versions of the Leiter were used. All scores from the older version were adjusted to be equivalent to the new version according to the formula in the manual. Sixty percent of the boys received the original version compared to 62% of the girls.

The Vineland Adaptive Behaviour Scales

The Vineland Adaptive Behaviour Scales (survey version) is a semistructured interview administered to a parent. This

scale is designed to assess adaptive behaviour in the domains of socialization, language and communication, motor and daily living skills (Sparrow et al. 1984). The communication and socialization scores, and their relation to parameters such as IQ, are seen as very sensitive measures of adaptive functioning impairment in children with ASD (Carter et al. 1998). We report here on the socialization and communication scales which are standardized to a mean of 100 and a standard deviation of 15, with high scores indicating better adaptive behaviour skills.

Analysis

In a preliminary analysis, we determined that the SPX children had different scores than MPX children. This was especially true among MPX and SPX girls on non-verbal IQ (75.82 vs. 50.21; $t = 4.47$; df = 95; $p < .001$). So we conducted all sex difference analyses separately by MPX/SPX status. In the first analysis, the female probands from MPX families were compared with the male probands from MPX families. Second, the affected female children from SPX families were compared with affected male SPX children. The third analysis focused on the other affected children in the MPX families; the affected male children in families with an affected female proband and the affected male children in families with an affected male proband. All analyses were conducted using *t*-tests.

Results

In the first analysis, we focused on the MPX families and compared the female probands (randomly selected if more than one affected female in the family) and one randomly selected affected male child (the male "proband"). There were no significant differences between males and females on any measure of severity; ADI-R, non-verbal IQ or VABS (see Table 1). In fact, the scores were virtually identical. If we now look at the differences among males and females in the SPX families, it is clear that there are differences on ADI-communication score, on non-verbal IQ, and VABS communication scores (females have lower scores on all measures, see Table 2). If we use IQ as a co-variate on the ADI and VABS measures, the significant differences disappear. This suggests that non-verbal IQ is the key difference among male and female SPX affected children.

To identify in which IQ range SPX females might be over-represented, the sample was stratified into IQ below 50, 51–70, and 71 and above and compared by gender. Females appeared to be over-represented in the IQ group below 50. Almost fifty-five percent (54.8%) of females fell in this category compared to 20.3% of males (chi-square = 21.4; $p < .001$) (see Table 3). The gender ratio varied widely by IQ stratum; it was roughly equal in the IQ <50 group and 8.3 to 1 in the typical IQ group (IQ > 70). This was not true in MPX families where there was no association between female gender and IQ <51 (chi-square = 0.99; $p = 0.61$). The ratio of male to female probands was roughly equal across all IQ strata; 2.8–1 in the <51 group, 2.0–1 in the 51–70 group and 1.9–1 in the >70 group.

The next analysis focused on the MPX families only and looked at the affected male siblings of male and female probands. In this comparison, there was no significant difference in IQ, ADI-R communication behaviours, or adaptive behaviour scores between male siblings of female probands and male siblings of male probands (Table 4). The male sibs of affected girls had slightly lower ADI socialization scores compared to male sibs of male probands. However, this difference was in the opposite direction than predicted by the multiple threshold model. In general, variation in severity as defined by IQ and autistic behaviours among males with ASD did not differ by whether or not there was an affected girl in the family.

Table 1 Measures of autistic behaviours, cognition, and adaptive functioning scores in male and female MPX probands

Measure	Number		Mean	Std. deviation	*t*-value	*t*-test significance
ADI: social total	Female	48	23.06	4.61	−.38	0.71
	Male	106	23.39	5.08		
ADI: communication verbal/non-verbal total	Female	48	15.19	4.99	.55	0.58
	Male	106	14.74	4.01		
ADI: repetitive behaviours total	Female	48	5.75	2.41	−1.04	0.30
	Male	106	6.18	2.34		
Leiter IQ	Female	45	74.76	30.36	1.04	0.30
	Male	95	68.87	31.83		
VABS communication	Female	47	64.40	22.18	.22	0.83
	Male	103	63.46	25.74		
VABS social	Female	47	58.98	15.64	−.61	0.54
	Male	103	60.82	19.79		

Table 2 Measures of autistic behaviours, cognition, and adaptive functioning scores in male and female SPX probands

Measure	Number		Mean	Std. deviation	*t*-value	*t*-test significance
ADI: social total	Female	50	24.00	4.10	.83	0.41
	Male	144	23.32	5.30		
ADI: communication verbal/non-verbal total	Female	50	15.58	4.04	−2.22	0.03
	Male	144	17.18	4.52		
ADI: repetitive behaviours total	Female	50	6.62	2.10	−1.60	0.11
	Male	144	7.22	2.35		
Leiter IQ	Female	42	50.21	22.80	−5.22	<0.001
	Male	133	76.15	29.45		
VABS communication	Female	35	51.49	21.92	−2.22	0.03
	Male	112	61.63	28.18		
VABS social	Female	35	51.00	15.67	−.85	0.39
	Male	112	54.18	20.23		

Table 3 IQ range of male and female SPX probands

	IQ Range		
	0–50	51–70	>70
Male			
Number	27	31	75
% within sex	20.3%	23.3%	56.4%
Female			
Number	23	10	9
% within sex	54.8%	23.8%	21.4%

(chi-square = 21.400; df = 2; $p = <0.001$)

Discussion

The results support previous research suggesting that females with autism have lower non-verbal IQ scores than males with autism (Volkmar et al 1993). However, this finding was restricted to the SPX families. Among presumably "genetically loaded families", (that is, those with more than one affected child) this difference was not apparent. This lack of difference in IQ among boys and girls in MPX families was first reported several years ago by Spiker et al (2001) but that paper did not include a comparison with SPX probands. This suggests that the variables that influence variation in IQ among MPX and SPX children are somewhat different, at least among females. SPX females appear to be over represented in the severe intellectual disability range, compared to the mild intellectual disability and typical range. However, there was no difference in the number of autistic symptoms or the mean scores on adaptive skills when IQ was used as a co-variate, suggesting that the effect of gender on IQ is specific and not generalizable across various aspects of severity.

Our original hypothesis was based on a model proposing different thresholds and a normally distributed genetic liability (see Ottman 1987). This model would predict that

Table 4 Measures of autistic symptoms, cognition, and behaviour scores in male siblings of female probands and male siblings of male probands

Measure	Number		Mean	Std. deviation	*t*-value	*t*-test significance
ADI: social total	Males with *male* affected sibling	109	23.74	4.82	−1.98	.05
	Males with *female* affected sibling	47	21.96	5.89		
ADI: communication verbal/non-verbal total	Males with *male* affected sibling	109	16.18	4.29	−1.38	.17
	Males with *female* affected sibling	47	15.17	4.00		
ADI: repetitive behaviours total	Males with *male* affected sibling	109	6.39	2.35	.34	.73
	Males with *female* affected sibling	47	6.53	2.62		
Leiter IQ	Males with *male* affected sibling	102	70.87	28.47	0.70	.48
	Males with *female* affected sibling	41	74.78	33.75		
VABS communication	Males with *male* affected sibling	109	61.65	25.58	1.19	.24
	Males with *female* affected sibling	47	67.11	27.89		
VABS social	Males with *male* affected sibling	109	60.11	20.33	0.20	.84
	Males with *female* affected sibling	47	60.77	16.08		

the affected male siblings of affected girls would show lower IQ than other affected male individuals. However, we found no difference in IQ between male siblings of male probands and male siblings of female probands. As well, we were unable to detect any other difference on adaptive functioning. The small difference in the ADI socialization scores is in the opposite direction, just reached significance and is probably due to chance. Perhaps the lack of differences in severity on metrics of symptoms, IQ and adaptive functioning is not surprising since we did not find differences in IQ between MPX females and males but the idea that females need a "greater genetic load" to push them "over the threshold into ASD" could still result in a situation where we might see no differences in their IQ but a measureable difference on other measures in their male siblings. The bottom line is that the variation in IQ among MPX females does not appear to be due to a greater genetic liability than males (if it were, their male siblings should be more severely affected).

The major limitation of the study is the difference in sample size between the males and females. This will reduce power for sure. But a review of the raw data suggests that the differences on ADI-R and VABS data are so small that we suggest an equal sample size would make little difference to statistical significance. In a post hoc analysis (available from the authors), we re-did the analysis so that there were equal numbers (matching based on age) but that did not change the results on any of the analyses.

These data suggest at least three possibilities; either the differential threshold model is wrong, the genetic factors affecting risk do not also affect severity of non-verbal IQ, or the factors that affect variation in IQ among SPX girls are different than those affecting IQ among the MPX group. It is also possible that the measures of adaptive functioning and autistic symptoms are not sensitive to detect differences by gender. After all, the ADI-R scores are largely based on behaviours present at 4–5 years of age and it may be that gender exerts its effect either earlier or later.

It would be first important to know if the risk of autism in relatives is greater if the proband is female rather than male. The community data from Utah suggest this (7% in relatives of male probands vs. 14.5% in relatives of female probands) but the difference was not significant (Ritvo et al 1989). More recent data from Goin-Kochel et al (2007), suggest no increase risk of autism by sex of proband. If the risk of the broader autism phenotype in relatives instead is used as the outcome measure, there is still no difference by sex of proband (Pickles et al 2000; Szatmari et al 2000). Another possibility is that the genetic factors affecting risk are different than those affecting severity in general, or cognitive impairment in particular. In this case, the difference in cognitive impairment between SPX males and females with ASD might be due to an in utero environmental effect that is either hormonal or epigenetic in nature (Schanen 2006) or due to some sporadic event. It is important to note that in typical children there is little or no hormonal effect on IQ (Azurmendi et al. 2005) so other mechanisms should be considered. We believe the most likely possibility is the existence of etiologic heterogeneity between SPX and MPX cases; more specifically, possibly a greater frequency of genomic risk factors among SPX families, especially girls. Recent data suggest that de novo copy number variants are more common in SPX than in MPX families and perhaps more common in affected girls than boys (Sebat et al 2007; Marshall et al. 2008). Perhaps SPX females with ASD are more likely to have a de novo copy number variant that not only serves as a risk factor for ASD but is also associated with lower non-verbal IQ than SPX males who might have more commonly a familial form of ASD with higher IQ. A focus on the genetics of girls with ASD could illuminate several unanswered questions about the factors that influence variation in severity. Stratification on both gender and MPX/SPX status in whole genome association studies would seem to be a prerequisite if more common genetic variants associated with ASD exist and are to be discovered.

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