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Do risk factors for autism spectrum disorders affect gender representation?

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ABSTRACT

To examine the M:F ratio in several known risk factors to demonstrate insights regarding autism spectrum disorders (ASD) etiology and sex. The study included 615 participants aged 18 months to 18 years age (mean = 49.8 months, SD = 28.4 months) diagnosed with ASD. Cognitive, adaptive and assessment of ASD were obtained using standardized tests. Detailed birth, familial, medical and developmental histories were obtained from the parents. Risk factors included ASD in the family (having a first-order family member with ASD); advanced maternal age (≥35 years); advanced paternal age (≥38 years); birth order (first-born *versus* third-born); low birth weight (LBW) (<2500 g); prematurity (gestational age <36 weeks). The M:F ratio (4.4:1) in the LBW group was lower than the M:F ratio (7.1:1) in the >2500 g group; however the difference showed only a statistical trend. No significant differences in M:F ratio were found between the ASD groups with and without the other examined risk factors. It is possible that the absence of a major association between most of the examined risk factors and sex representation points to the relatively minor role of these risk factors in ASD.

1. Introduction

Autism spectrum disorders (ASD) are a group of neurobehavioral disorders defined by social and communication deficits and repetitive and stereotyped behaviors (Johnson & Myers, 2007). The current estimated prevalence of ASD is approximately 1:100–150 (Kogan et al., 2009), which reflects a 15-fold increase from studies published a half-century ago. ASD is a highly heritable disorder, with heritability indices estimated at 60–92% (Bailey et al., 1995), suggesting a major role for genetic factors in the etiology of ASD (reviewed in Schaaf & Zoghbi, 2011). However, the exact cause of ASD is still unknown in most cases. It is now believed that environmental factors may modulate phenotypical expression associated with the genetic predisposition (Johnson & Myers, 2007; Kogan et al., 2009).

Single gene disorders, such as Fragile X syndrome and others, explain only about 5–7% of cases of ASD. In recent years significant genetic etiologies have been discovered. It was found that *de novo* genomic copy number variations (CNVs – gains or losses of genomic material that do not exist in the parents) may explain an additional 7–20% of ASD cases (Schaaf & Zoghbi, 2011). In addition, inherited CNVs may serve as risk factors for ASD. However, the disease etiology is still elusive in the great majority of cases. It is believed that both genetic and environmental risk factors play a role in ASD.

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The association between specific risk factors and ASD has been documented in some studies. Genetic predisposition for ASD as previously described has long been associated with an increased risk for ASD in siblings (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Lintas & Persico, 2009; Ozonoff et al., 2011; Persico & Bourgeron, 2006). Advanced parental age has been documented in many studies as a risk factor for ASD (Grether, Anderson, Croen, Smith, & Windham, 2009; Kolevzon, Gros, & Reichenberg, 2007). Most of the studies that looked at advanced paternal age as a risk factor found an increased risk for ASD with increasing paternal age (reviewed in Guinchat et al., 2012). Several studies described maternal age as a risk factor for ASD but the results are more conflicting than the reports on the effect of paternal age. The biological mechanisms underlying the relationship between parental ages and autism are still unknown, but they may be associated with the increased rate in *de novo* mutations that appears in advanced paternal age. Several studies have reported that higher birth order ($\geq$3rd) might be a risk factor for ASD (Deykin & MacMahon, 1980; Lord, Mulloy, Wendelboe, & Schopler, 1991; Tsai & Stewart, 1983). Low birth weight (LBW) with or without prematurity is a risk factor for many neurodevelopmental disorders, including cerebral palsy and intellectual disability. Inconsistent results were documented regarding the association of LBW ($<$2500 g) and very low birth weight ($<$1500 g) with ASD (Ben-Itzchak, Lahat, & Zachor, 2011; Eaton, Mortensen, Thomsen, & Frydenberg, 2001; Hultman, Sparén, & Cnattingius, 2002; Kolevzon et al., 2007; Schendel & Bhasin, 2008). The main risk factor for ASD is, by far, male sex. Male predominance in ASD has been noted in all epidemiological studies and is a well-established fact in the field of ASD. Male:female (M:F) ratio has been reported in many studies in the range of 4–7:1 (Ben-Itzchak, Ben-Shachar, & Zachor, 2013; Fombonne, 2003; Holtmann, Bolte, & Poustka, 2007; Newschaffer et al., 2007). Moreover, it has been found that, in families having a single child with ASD, the recurrence risk is about 8–21% in male pregnancies but only about 1–7% when the fetus is a female (Miles et al., 2005; Ozonoff et al., 2011).

Interestingly, the M:F ratio in ASD is not constant. For example, in regard to parental age, one of the known risk factor for ASD, it has been reported that a less skewed M:F ratio was observed as the paternal age increased in a cohort of children with ASD. The M:F ratio changed from 6:1 for fathers less than 30 years of age to 1.2:1 for fathers over 45 years (Anello et al., 2009). In addition, it was reported that a low birth weight (LBW $<$ 2500 g) served as a risk factor for autism, with a greater effect in girls (Schendel & Bhasin, 2008). There is no clear explanation for the male predominance in ASD. Given the high M:F ratio and the heritability of ASD, it has been speculated that genetic disorders that are linked to the X or Y chromosomes play a role in the disease etiology. However, so far no X/Y linked disorder can explain more than a fraction of ASD cases. The recent finding that females with ASD and *de novo* CNVs have a higher number of altered genes than males (Levy et al., 2011), implying again that females are more protected from ASD compared to males and need to have a more severe aberration or an increased number of etiological factors in order to show the autistic phenotype.

Recently, we have shown (Ben-Itzchak et al., 2013) that there is an increased representation of females in ASD with additional neurological phenotypes, such as microcephaly, minor neuromuscular deficits, and a history of developmental regression. These findings suggest that ASD in females is associated with a more complicated presentation as compared to males.

The male predominance in prototypical ASD suggests that females are more protected from ASD than males (Levy et al., 2011). Our findings that females with ASD have more neurological phenotypes support this notion, and imply that additional neurological insults may be required in females to have ASD. Therefore, we hypothesized that ASD in females and males are associated with different mechanisms and etiologies, including risk factors for ASD. Because females compose only a small portion of the ASD population, previous research on risk factors for ASD was conducted on the general ASD population and, therefore, represented the effect of these risk factors mainly on males. We hypothesized that risk factors for ASD will therefore occur more frequently in females than in males. In this study we aimed to examine the M:F ratio in several known risk factors in order to demonstrate insights regarding ASD etiology and sex.

2. Methods

2.1. Participants

The study included 615 participants, 532 males and 83 females (M:F = 6.4:1), diagnosed with ASD, with an age range of 18 months to 18 years and a mean age of 49.8 $\pm$ 28.4 months.

2.2. Procedure

Participants were referred to The Autism Center for a comprehensive assessment of a possible diagnosis of ASD. The evaluation included a neurological assessment, and behavioral, cognitive and functional evaluations. Assessments were conducted by a skilled interdisciplinary team. Pediatric neurologists obtained medical, developmental and familial histories from the parents and conducted a comprehensive neurological examination of all the participants.

The diagnosis of autism/ASD was obtained by using two standardized tests, the autism diagnosis interview-revised (ADI-R) (Rutter, LeCouteur, & Lord, 2003) and the autism diagnosis observation schedule (ADOS) (Lord, Rutter, DiLavore, & Risi, 1999) and by meeting criteria for autism/ASD based on DSM-IV criteria (APA, 1994). All the professionals involved in the diagnostic process established reliability as required. Cognitive and developmental abilities (IQ/DQ) were assessed using The Mullen scales of early learning (Mullen, 1995), Bayley scales of infant development (Bayley, 1993), Wechsler preschool and primary scale of intelligence (Wechsler, 1989), Stanford-Binet intelligence scales (Thorndike, Hagen, & Sattler, 1986),