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# First-degree relatives of young children with autism spectrum disorders: Some gender aspects

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ABSTRACT

Prenatal risk factors, with special focus on gender distribution of neurodevelopmental and psychiatric conditions were analysed in first-degree relatives in a population-based group of young children with autism spectrum disorders (ASD). Multiple information sources were combined. This group was contrasted with the general population regarding data from the Swedish Medical Birth register. In the ASD group, information was also obtained at parental interviews focusing on developmental and psychiatric disorders in the family. Compared to the general population, fathers of children with ASD were older and parents more often of non-European origin. Mothers of children with ASD had an increased rate of antidepressant and psychoactive medication use, and of scheduled caesarean sections. Fathers and brothers of children with ASD had high rates of ASD including the broader phenotype. Mothers of children with ASD had high rates of depression and other psychiatric disorders. These findings, hypothetically, could reflect a different ASD phenotype and difficulties diagnosing ASD in females or be an example of the close genetic relation between ASD and other psychiatric disorders. The results suggest that, in clinical and research settings, the familial background in ASD should be reviewed with a broader approach, and not be restricted to "looking out" only for diagnoses and symptoms traditionally accepted as being part of or typical of ASD. The high rate of parents of non-European origin has been noted in many Swedish studies of ASD, but the reason for this association, remains unclear.

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## 1. Introduction

The aim of the present study was to analyse certain prenatal risk factors, with special focus on gender distribution of neurodevelopmental and psychiatric conditions in first-degree relatives in a population-based group of young children with ASD, by combining multiple information sources.

Autism spectrum disorders (ASD) represent a heterogeneous group of conditions with respect to aetiology and clinical manifestations. Genetic factors play a major role in the etiological panorama (Coleman & Gillberg, 2012). Microdeletion and

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microduplication syndromes have been increasingly recognized as important background factors as have copy number variations (CNVs) causing mutations in alleles regulating synaptogenesis and synaptic function ((Abrahams & Geschwind, 2008; Jamain et al., 2003; Persico & Bourgeron, 2006; Pinto et al., 2010; Sebat et al., 2007; Shen et al., 2010; Toro et al., 2010). Genetic findings using high resolution microarray-based comparative genomic hybridization and other new methods indicate that genomic imbalances found in children with ASD can also be identified in childhood onset epilepsy, intellectual disability (Betancur, 2011; Cook & Scherer, 2008; Ropers, 2010), and attention-deficit/hyperactivity disorder (ADHD) (Rommelse, Franke, Geurts, Hartman, & Buitelaar, 2010; Williams et al., 2010). In a proportion of the identified genetic abnormalities there is also overlap with psychiatric conditions such as schizophrenia and bipolar disorder (Guilmatre et al., 2009; Morrow, 2010; Sebat, Levy, & McCarthy, 2009). The broader phenotypes of ASD and schizophrenia share several characteristics (King & Lord, 2011; Lugnegard, Hallerback, & Gillberg, 2011a; Lugnegard, Hallerback, & Gillberg, 2011b). Higher penetrance of de novo mutations in males than in females – and mutations on the X-chromosome – may contribute to the higher ASD incidence in boys (Zhao et al., 2007). Due to variable expressivity, and/or incomplete penetrance, parents carrying heritable susceptibility genes for ASD may have a milder/broader phenotype with autistic traits/speech and language delays, other neurodevelopmental impairments or may present with psychiatric symptoms (Coleman & Gillberg, 2012).

The shared genetic relationships between ASD, epilepsy, intellectual disability and psychiatric conditions are partly explained by genomic imbalances affecting cell adhesion molecules and synaptic function such as the neurexin/neuroligin complex including the SHANK3 gene (Ching et al., 2010; Dhar et al., 2010; Durand et al., 2012; Gauthier et al., 2009; Herbert, 2011; Kim et al., 2008).

Parental psychiatric history has been associated with increased risk for ASD in the offspring in several epidemiological studies (Daniels et al., 2008; Larsson et al., 2005; Lauritsen, Pedersen, & Mortensen, 2005; Piven et al., 1991; Yirmiya & Shaked, 2005). Affective disorders appear to be significantly more common in probands with autism as compared with other groups (Bolton, Pickles, Murphy, & Rutter, 1998; Lugnegard et al., 2011b; Piven & Palmer, 1999). In mothers (but not in fathers) of children with ASD depression and personality disorders have been found to be more common than in mothers of typically developing children (Daniels et al., 2008).

Results from a recent very large population twin study of mono- and dizygotic ASD twins indicates that a variety of neuropsychiatric disorders, including ADHD, developmental coordination disorder, and tic disorders seem to have shared genetic aetiology with ASD (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010).

High rates of comorbid psychiatric disorders in children with ASDs (social anxiety disorder 29%, ADHD 28%) and of bipolar disorder in adolescents and young adults with high-functioning ASD have been reported by different authors (Munesue et al., 2008; Simonoff et al., 2008).

Several studies have reported sub-threshold autistic traits and broader phenotype characteristics among relatives of probands with ASD (Constantino et al., 2006; Murphy et al., 2000). In a study by (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010), the recurrence rate of ASD in siblings was 11% but "an additional 20% of non autism-affected siblings had a history of language delay, one half of whom exhibited autistic qualities of speech".

In a recent meta-analysis it was demonstrated that most perinatal and neonatal factors examined, have shown inconsistent results, and the preponderance of findings overall have not been statistically significant (Gardener, Spiegelman, & Buka, 2011). The strongest prenatal factors that was associated with an increased risk for autism included advanced maternal and paternal age at birth, maternal gestational bleeding, gestational diabetes, being first born versus third born or later, maternal prenatal medication use, and maternal birth abroad.

Caesarean section (emergency and elective/scheduled) has been identified as an independent ASD risk factor in some studies (Glasson et al., 2004; Hultman, Sparen, & Cnattingius, 2002; Maimburg & Vaeth, 2006). In the above mentioned meta-analysis, caesarean delivery did not reach statistical significance ($p = 0.06$)(Gardener et al., 2011).

## 2. Participants and methods

### 2.1. Participants

The study included 208 children with a diagnosis of ASD. They were drawn from a population-based group of 313 children with ASD diagnoses in Stockholm County. This group of 313, 20–54-month-old, children (all with birth years 2002–2006) had been registered with a clinical diagnosis of ASD between 2005 and 2008 in the county (approximately 28,000 births per year). Twenty-five of them were catered for at general habilitation centres (extremely severely and multiply additionally impaired children with ASD) but in some cases for geographical reasons. Of the remaining 288 children, project financial and staff resources limited the participation invitation rate to 92% (264 children). Thirty-seven families declined participation, and 15 further families were excluded because their ability to communicate in either Swedish or English was insufficient. Another two children moved abroad, leaving 210 for participation in a prospective follow-up study of children receiving intervention for ASD at a specialized Autism Centre for Young Children in Stockholm. However, two of the 210 were referred to general habilitation centres because they were found to have very complex needs in addition to ASD.

The remaining 208 children (176 boys and 32 girls) were included in the study. Details regarding diagnostic assessments in this group (Time 1, T1) have been reported in a previous publication (Fernell et al., 2010).

At follow-up by the research team, two years later (Time 2, T2), 198 of the 208 children had been systematically re-assessed (Fernell et al., 2011). Autistic disorder was diagnosed in 105 (53%) children, atypical autism in 58 (29%), Asperger

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