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Are there differences in the behavioural phenotypes of Autism Spectrum Disorder probands from simplex and multiplex families?

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ABSTRACT

Recent research suggests that different genetic pathways may operate for families with one child affected with Autism Spectrum Disorder (simplex ASD), compared to families that have multiple affected children (multiplex ASD). In this study, we investigated possible differences in the behavioural phenotypes of probands from simplex and multiplex ASD families using parent-report and standardised behavioural measures. Participants were 59 probands from multiplex ASD families (28 families), who were each matched on chronological age and sex with two probands from simplex families. Probands from multiplex families had greater social impairment (measured using the Social Responsiveness Scale) and worse pragmatic language (on the Children's Communication Checklist-2) than probands from simplex families. However, the multiplex children had less severe symptoms than the simplex children on the ADOS-G, and a significantly higher proportion of multiplex children did not meet autism spectrum cut-offs on this measure. These findings indicate that there are behavioural differences in children with ASD from simplex and multiplex families. In addition, the results reveal an important discrepancy between parent-report and clinician observation of autistic-like characteristics in siblings of an affected child, which may have implications for the assessment and diagnosis of ASD.

Autism Spectrum Disorder (ASD) is known to be highly heritable (Bolton et al., 1994; Lauritsen, Bøcker, & Bo, 2005; Pickles & Starr, 2000). The results of early twin studies indicate that there is an 88% concordance for ASD in monozygotic twins and 31% for dizygotic twins (Rosenberg et al., 2009), and the concordance rate for monozygotic twins increases substantially with the inclusion of siblings who exhibit a lesser variant of ASD (Bailey et al., 1995; Folstein & Rutter, 1977). Families with one affected child are more likely to have a second, with a sibling recurrence risk that ranges between 5% and 18%, substantially higher than the population risk for ASD (Constantino, Zhang, Frazier, Abbacchi, & Law, 2010; Ozonoff et al., 2011).

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The familiality of ASD has garnered significant research interest. In particular, several previous studies have investigated the aggregation of ASD traits in simplex (SA) and multiplex (MA) ASD families, as it is hypothesised that there may be different genetic pathways operating for families in which ASD affects only one individual, compared with families with multiple affected individuals. Indeed, while several large-scale linkage studies have found that a large number of Copy Number Variants may be implicated for sporadic cases of ASD (Cho et al., 2009; Iossifov et al., 2012; Sanders et al., 2011; Sebat et al., 2007), Campbell et al. (2006) reported the first common allele implicated in ASD for multiplex families only.

Studies of the behavioural phenotypes of SA versus MA families may provide further insight into the heritability of ASD, and may elucidate subtypes of ASD that have distinct aetiologies. Indeed, investigations of the relatives of individuals with ASD indicate that the familial aggregation of sub-threshold traits of ASD (the broader autism phenotype; BAP) may be more pronounced in MA relative to SA families (e.g. Gerdts, Bernier, Dawson, & Estes, 2013; Szatmari et al., 2000). The results of these studies have revealed significantly higher social (Losh, Childress, Lam, & Piven, 2008; Piven, Palmer, Jacobi, et al., 1997) and communication (Gerdts et al., 2013; Losh et al., 2008; Piven, Palmer, Jacobi, et al., 1997; Piven, Palmer, Landa, et al., 1997) impairments, stereotyped behaviours (Piven, Palmer, Jacobi, et al., 1997), behavioural rigidity (Gerdts et al., 2013; Losh et al., 2008), more limited friendships (Losh et al., 2008; Piven, Palmer, Landa, et al., 1997), and cognitive deficits (Piven, Palmer, Landa, et al., 1997) in MA families than in SA families. In addition, Losh et al. (2008) found a linear expression of BAP traits (language, personality and social behaviour) in MA and SA parents, with the MA parents expressing more features than the SA parents, who in turn exhibited more features than a control group comprising parents of children with Down's Syndrome. While in the majority of MA families both parents exhibited the BAP, SA parents and parents of children with Down's syndrome were likely to have only one or no parent showing the BAP. Bernier and colleagues reported similar findings; while MA parents had significantly more BAP traits (on social motivation, social expressiveness, conversation skills, flexibility/range of interests) than SA and parents of children with other disabilities, the latter two groups did not differ from each other in the extent of the BAP (Bernier, Gerdts, Munson, Dawson, & Estes, 2012). These findings converge in suggesting that there may be quantitative differences in the behavioural phenotypes of MA and SA families, with MA families exhibiting more ASD characteristics than SA families.

Efforts to identify distinct phenotypes associated with multiplex and simplex ASD have also focused on the characteristics of affected and unaffected children from these families. Studies that have used the Social Responsiveness Scale (SRS; Constantino, 2002), a caregiver-report measure of the social impairment of ASD, consistently find differences in the distribution of ASD traits in MA and SA children. For example, Constantino et al. (2006) examined SRS scores in unaffected children from MA and SA families, as well as families of children with psychological disorders unrelated to ASD. These authors reported that MA siblings had significantly greater social impairment SRS scores than SA siblings, who in turn had more of the social characteristics of ASD than siblings of children with other psychological disorders. Virkud, Todd, Abbacchi, Zhang, and Constantino (2009) extended this research to include affected children and found significantly higher SRS scores, indicating greater social impairment, for boys in MA families, compared to those from SA families. Furthermore, while there was a distinct low-scoring cluster of unaffected boys from SA families, no such cluster existed within the MA families, which suggests that there is a continuous distribution of ASD traits for MA but not for SA families. These findings indicate that increased genetic loading for ASD, represented by the MA families, may be associated with more severe social impairments.

Only one previous study has explored the pattern of ASD traits in MA and SA families using standardised diagnostic instruments (Cuccaro et al., 2003). In this study, Cuccaro et al. (2003) compared Autism Diagnostic Interview–Revised (Rutter, Le Couter, & Lord, 2003) domain scores between probands from MA and SA families (Cuccaro et al., 2003). In contrast to the studies using the SRS to measure ASD traits, Cuccaro et al. (2003) found no differences in the three ADI-R domain scores (Social Interaction, Communication, Restricted/Repetitive Interests and Behaviour) between the SA and MA probands.

Previous studies have used either standardised diagnostic instruments (Cuccaro et al., 2003) or parent-report questionnaires (e.g. Constantino et al., 2006; Virkud et al., 2009) to compare the behavioural phenotypes of probands from MA and SA families. While the results of studies using the SRS indicate that affected and unaffected children from MA families have more severe social impairments than those from SA families, findings from studies using the ADI-R have been inconsistent with these results, as Cuccaro et al. (2003) reported no difference between probands from MA and SA families on ADI-R domain scores. No previous studies have used Autism Diagnostic Observation Schedule–Generic (ADOS-G) scores or language phenotypes to compare probands from MA and SA families.

The current study used parent-report measures of social impairment (SRS) and communication (Children's Communication Checklist-2 [CCC-2]; Bishop, 2003), as well as the ADOS-G to explore possible differences in the social, communication, and behavioural profiles of probands from simplex and multiplex ASD families. Based on previous findings of higher SRS scores in affected and unaffected children from MA relative to SA families, as well as studies that have shown that increased genetic liability for ASD is associated with structural and pragmatic language difficulties (Taylor et al., 2013), we expected that the MA probands would have more severe ASD symptoms on the ADOS-G, SRS and CCC-2, compared to the SA probands.

1. Method

1.1. Participants

Participants were part of the Western Australian Autism Biological Registry, which is an ongoing study of children with ASD and their families taking place at the Telethon Kids Institute in Perth, Western Australia (Taylor et al., 2013). Participants