Journal of Intellectual Disability Research

VOLUME 44 PART 5 pp 562–566 OCTOBER 2000

# Autism in Down's syndrome: a family history study

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## Abstract

Several recent reports have described the occurrence of autism in subjects with Down's syndrome (DS). However, relatively little is known about the family history of these subjects, especially with reference to autism. In order to address this issue, the present author examined 11 subjects with DS and autism (DSM-III-R; nine males), and compared them with seven controls with DS but without autism (DSM-III-R; three males). Details about family psychiatric history were obtained from both groups with an emphasis on autism and related disorders. Subjects with both DS and autism had an excess of first-degree relatives who met the description of the broader phenotype of autism. Seven (64%) of the subjects with autism had an affected parent as against one (14%) of the control group. Similarly, four out of 11 siblings (36%) in the DS with autism group showed features suggestive of the broader autistic phenotype compared to none in the control group. These findings suggest that, at least in some cases, autism-specific genetic factors may be important even when autism occurs in the presence of known medical conditions. Further studies of the mechanism of comorbidity of autism with medical conditions may help clarify the aetiology of the disorder.

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**Keywords** autism, Down's syndrome, family history study

## Introduction

Autism is a neurodevelopmental disorder which is characterized by a distinct pattern of social deficits, communication impairment and rigid ritualistic interests. While the mode of transmission is not clear, it is widely regarded as a genetically heterogeneous syndrome in which several genes acting in combination give rise to an increased vulnerability to the disorder (Rutter 1999). Several recent reports have suggested that first-degree relatives show features consistent with the broader phenotype of autism in a significant number of cases (Bolton *et al.* 1994). According to this view, first-degree relatives of persons with autism may show language-related cognitive deficits, social impairments and stereotypic behaviours without meeting the full criteria for that disorder (Gillberg *et al.* 1992; Bolton *et al.* 1994; Le Couteur *et al.* 1996). However, despite the evidence pointing to a genetic basis of autism, a significant number of autistic subjects show evidence of associated medical conditions (Gillberg & Coleman 1996). Several varieties of medical disorders, ranging from infections to chromosome abnormalities, have been described with autism. Some disorders seem to have a special affinity for autism, such as fragile-X syndrome and tuberous sclerosis, while others do

not appear to be usually associated with autism, such as cerebral palsy and Down's syndrome (DS; Rutter & Schopler 1988). While estimates vary according to the diagnostic criteria and study samples used, at least 10–15% of autistic persons suffer from known medical conditions (Rutter *et al.* 1994; Gillberg & Coleman 1996). Some authorities have suggested that the association of autism with medical conditions reflects nothing more than a chance occurrence, while others have argued that certain discrete agents can play a causative role (see Gillberg & Coleman 1996).

It is possible that autism-specific genetic factors may be important even when autism occurs with known medical conditions. In some cases, this may explain why patients with certain medical conditions present with autism while others with the same conditions do not. The purpose of the present report is to investigate this possibility. Since relatives of autistic probands may show features of the broader autistic phenotype, the present author hypothesized that relatives of autistic patients with known medical conditions will also show similar features. In order to test this hypothesis, he examined the family history of a group of subjects with DS plus autism. The choice of the subject group rested on two reasons. Firstly, there is no known association between autism and DS, as in the case with autism and tuberous sclerosis (Hunt & Shepherd 1993), or the fragile X-syndrome (Hagerman 1990), for example. Secondly, there are no apparent similarities between the behavioural phenotypes of DS and those of autism. In fact, the usual personality profile of DS, i.e. that of a child who is affectionate and outgoing, goes against the behavioural phenotype of autism (Ghaziuddin *et al.* 1992; Howlin *et al.* 1995). In an earlier report, the present author described the occurrence of autistic features in parents of three subjects with autism and DS (Ghaziuddin 1997). The present study compares the family history aspects of 11 subjects with DS and autism with those of seven controls with DS but without autism.

## Subjects and methods

The present study was conducted at the University of Michigan Medical Center, Ann Arbor, MI, USA. A consecutive series of subjects with DS referred to the present author with suspected autism was examined. The series included three patients reported elsewhere (Ghaziuddin 1997). The evaluation process consisted of obtaining a detailed developmental history of the patient and performing a psychiatric examination. School records and reports of previous evaluations were also examined. Diagnoses were based on the DSM-III-R criteria (APA 1987). Cases were personally interviewed by the present author and followed-up for at least 2 years. Family history was obtained from biological parents based on a shorter version of the Family History Schedule (Bolton *et al.* 1994), an investigator-based family history interview designed to identify the presence of developmental disorders, abnormalities of emotional development and psychiatric disorders in first- and second-degree relatives. The interviewer was not blind to the status of the subjects with reference to the diagnosis of autism. To be eligible to participate in the present study, subjects had to be older than 5 years of age and have biological relatives available for interview. The level of intelligence of the subjects was based on case records and clinical judgement and classified as either moderate (full scale IQ = 35–50) or severe (full scale IQ < 35).

Eleven subjects with DS who met the DSM-III-R (APA 1987) criteria for autistic disorder were identified based on the above evaluation process. The sample consisted of nine males and two females with a mean age of 16.5 years (range = 5–29 years). Eight of these subjects had a moderate level of intellectual disability and three had a severe level of intellectual disability. These subjects were compared with seven patients with DS who did not have autistic disorder. The control sample consisted of three males with a mean age of 13 years (range = 6–35 years). Two of these subjects had a moderate level of intellectual disability and five had a severe level of intellectual disability. Since the focus of the present study was to obtain family histories, the subjects were not matched on age, sex or level of intelligence. Also, none of these variables are known to cause autism in DS, although an association may exist between the presence of autism and the degree of mental retardation in DS (see Howlin *et al.* 1995). The control subjects were either referred to the same clinic for an evaluation

of behavioural problems or recruited from a training centre affiliated with a university outreach clinic. Based on a review of case notes and other available information, all the subjects met the DSM-IV criteria for autistic disorder (APA 1994).

## Results

Out of the 22 parents in the DS plus autism group, seven parents (i.e. six fathers and one mother) met the broader autistic phenotype based on the Family History Schedule (see Table 1). One parent (a mother) in the non-autistic group showed marked compulsive traits and ritualistic behaviours with some social deficits consistent with a diagnosis of the broader autistic phenotype. Overall, seven subjects (64%) with DS and autism had a parent who met the criteria of the broader autistic phenotype compared with one (7%) in the control group (Fisher's exact test, one-sided, $P = 0.057$). Out of 11 biological siblings in the autistic group, two had a history of speech problems severe enough to require treatment, two were labelled as having intellectual disability and were placed in special education, and one sibling had DS. Excluding the sibling with DS, four out of the 11 subjects (36%) showed evidence of communication/learning deficits. There were also 11 biological siblings in the non-autistic group, none of whom had a history of communication or social abnormalities severe enough to require special services or other forms of treatment.

## Discussion

The main findings of the present study are that subjects with DS who suffer from additional autism have an excess of relatives who show features consistent with the broader phenotype of autism. These features include marked compulsive traits and rituals, and social deficits. About one-third of parents in the DS plus autism group gave evidence of the broader autistic phenotype (sometimes also known as the lesser variant of autism) compared to 7% in the control group. Overall, seven subjects (64%) with DS and autism had a parent who met the criteria of the broader autistic phenotype compared with one (7%) in the control group. The rates were similarly higher in the siblings of subjects compared to those in controls. Four out of 11 (36%) siblings had evidence of communication/learning deficits in the DS plus autism group compared to none in the controls. Taken together, these findings suggest that autism-specific genetic factors may explain why some patients with a known medical condition, such as DS, show the presence of autism while others do not. Thus, autism-specific genetic factors may be important

**Table 1** Characteristics of the first-degree relatives of subjects with Down's syndrome and autism

| Subject | Sex (M/F) | Age (years) | Level of intellectual disability | Parents* | Siblings |
|---|---|---|---|---|---|
| 1 | F | 20 | Moderate | F: odd, isolative, no friends | One, well |
| 2 | M | 16 | Severe | F: markedly compulsive | Nil |
| 3 | M | 8 | Moderate | Both parents well | Nil |
| 4 | M | 15 | Moderate | Both parents well | Three, one with Down's syndrome |
| 5 | M | 29 | Severe | F: isolative, compulsive | Two, both receiving speech therapy |
| 6 | F | 14 | Moderate | F: odd but talented artist | Two, both with learning problems |
| 7 | M | 20 | Severe | M: marked compulsive trait | Three, all well |
| 8 | M | 7 | Moderate | F: compulsive, odd | Nil |
| 9 | M | 26 | Moderate | F: odd, no friends | Nil |
| 10 | M | 5 | Moderate | Both parents well | Nil |
| 11 | M | 22 | Moderate | Both parents well | Nil |

*Key: (F) father; and (M) mother.

even when autism occurs in the presence of known medical conditions.

Before discussing other aspects of the present study, it is important to comment on the diagnostic validity of autism in DS because it may be argued that the subjects did not suffer from autism but from some non-specific behavioural symptoms. While people with DS have been traditionally described as friendly, affectionate and extroverted (Gibbs & Thorpe 1983), there is evidence that not all patients with DS possess these personality characteristics. Adults with DS show lower prevalence of maladaptive behaviours compared with adults with mental retardation (learning disability) of other causes (Collacott *et al.* 1998). However, clinical experience suggests that some 10–20% of patients show behavioural problems (see Gibson 1978; Flint & Yule 1994). It is possible that the 10–20% of persons with DS with behavioural problems may contain a substantial number of patients with comorbid autism, although the exact numbers are not known (Ghaziuddin *et al.* 1992; Howlin *et al.* 1995). In this context, it is worth noting that a recent epidemiological study estimated the comorbidity of autism in DS to be at least 7% (Kent *et al.* 1999). All the subjects diagnosed with autism in the present study presented with the triad of social deficits, communication impairment and rigid ritualistic interest typical of autism, and met the diagnostic criteria for that disorder. Because the diagnosis of autism is not often suspected in persons with DS, most of the subjects presented later than is usually the case for children with autism without DS. These observations are consistent with recent reports suggesting that autism can be reliably diagnosed in DS and that the association may be more common than generally believed (Wakabayashi 1979; Bregman & Volkmar 1988; Ghaziuddin *et al.* 1992; Howlin *et al.* 1995; Kent *et al.* 1999).

Although the present findings underscore the potential role of genetic factors in cases when autism occurs with DS, it is important to note that other factors may also be important. In four cases with autism plus DS, no evidence of the broader phenotype of autism was noted in the first-degree relatives. This is consistent with recent studies, suggesting that although the disorder is said to be strongly genetic, with a heritability of about 90%, environmental factors may also be important. For example, there is emerging evidence that exposure of the foetus at a critical period of development to a toxic agent, such as thalidomide, may be strongly associated with the later development of autism (Stromland *et al.* 1994). Thus, in the present study, at least in a subgroup of cases, the occurrence of autism may be related to factors other than genetic components. As far as the presence of autism in DS is concerned, the exact nature of these factors is unclear. It is possible that the occurrence of autistic features in DS is influenced by the degree of mental retardation or by the presence of medical complications such as seizure disorder (Howlin *et al.* 1995). However, because of the relatively small number of cases of autism and DS reported in the literature, no firm conclusions can be drawn at this stage.

Clinically, the relatives of autistic individuals should be screened for the traits of autism, even when the subjects show autism with another medical condition. This may have implications for the treatment of the autistic individual and of the family as a whole. Future research should try to investigate the precise genetic and environmental factors which may underlie the association of autism with other medical conditions. While the present study investigated the presence of autism in DS, similar studies can be performed in other patient populations, such as tuberous sclerosis and the fragile-X syndrome. Such studies can not only shed light on the mechanisms underlying the association, but also help tease out the role of genetic and environmental factors in the aetiology of autism.

## Acknowledgements

The author acknowledges the help of Kathy Welch, Mary Poore and the NARSAD Foundation.

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*Received 5 May 1999; revised 22 June 1999*