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Autism, affective and other psychiatric disorders: patterns of familial aggregation

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ABSTRACT

Background. The liability to autism confers a risk for a range of more subtle autistic-like impairments, but it remains unclear whether it also confers a risk for other psychiatric disturbances.

Methods. To investigate this, we studied the pattern of familial aggregation of psychiatric disorders in relatives of 99 autistic and 36 Down's probands, using family history and direct interview measures.

Results. Family history data showed that motor tics, obsessive–compulsive (OCD) and affective disorders were significantly more common in relatives of autistic probands and that individuals with OCD were more likely to exhibit autistic-like social and communication impairments. Direct interview data confirmed the increased rate of affective disorders (especially major depressive disorder) in the first-degree relatives. There was no evidence to indicate significant co-morbidity between affective disorders and the broadly defined phenotype of autism. Moreover, the characteristics of the probands' and the relatives' that were associated with the liability to familiality of the broader phenotype of autism differed from those that predicted the liability to the familiality of affective disorders. Examination of the onset of affective disorders suggested that the increased risk was not confined to the period following the birth of the child with autism.

Conclusions. Overall, the results indicated that OCD, but not affective disorders, may index an underlying liability to autism. They also indicated that the increased risk of affective disorders was not solely the consequence of the stress of raising a child with autism and that further research will be required to clarify the mechanisms involved.

INTRODUCTION

Autism is characterized by qualitative impairments in communication and reciprocal social interaction, along with stereotyped repetitive patterns of interest and activities (World Health Organization, 1994). Identifiable, probably causal, medical disorders are found in some 10% of individuals (Rutter *et al.* 1994). Recent twin and family data have shown that the remaining idiopathic cases of autism are strongly genetically influenced and that the liability to autism also confers a risk for atypical autism, Asperger's syndrome and other pervasive developmental disorders, as well as for more subtle communication and social impairments or repetitive and stereotyped interests and activities occurring alone or in combination (Bolton *et al.* 1994; Bailey *et al.* 1995). 'The broader autism phenotype' is the phrase used to describe the full range of disorders associated with a liability to autism (Fombonne *et al.* 1997) and we will adopt this terminology here. Individuals with autism or Asperger's syndrome may also develop other psychiatric disorders. Thus, Asperger described schizophrenia in one of the 200 subjects he examined (Wing, 1981; Asperger, 1991) and Wolff (1995) in an investigation of 149

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subjects with schizoid disorder of childhood (defined in a way that closely resembles Asperger's syndrome) noted that seven (5%) later developed schizophrenia, and six (4%) committed suicide. Wing (1981) described 34 individuals with Asperger's syndrome: two (6%) developed an unspecified psychotic disorder, and four to eight (12–24%), depending on definitions, an affective disorder. Three (9%) had another unspecified psychiatric disorder. All of the rates of these psychiatric disturbances were greater if one focused solely on the subjects over the age of 16 years. Gillberg & Steffenburg (1987) reported the rate of psychiatric disorders in a series of 23 children with autism and 23 with other forms of pervasive developmental disorder. They found one (4%) of the subjects with autism to have an affective disorder and seven (30%) another unspecified psychiatric condition. In the subjects with other forms of pervasive developmental disorder, the rate of unspecified psychiatric disorders was 26% (6 cases). Tantam (1988) in a study of 60 subjects who exhibited marked social eccentricity found one (2%) with schizophrenia, three (5%) with another unspecified psychotic disorder, and ten (17%) with an affective disorder. A further three (5%) had unspecified psychiatric disturbances. All these findings suggest that there may be significant co-morbidity between autism/Asperger's syndrome and other psychiatric disorders. However, they have a number of methodological limitations, including problems over the diagnosis of psychopathology in people with communication disorders (Lainhart & Folstein, 1994), that preclude any firm conclusions being drawn about the extent and nature of co-morbidity.

There is rather better evidence to suggest that the relatives of individuals with autism may be at increased risk for affective disturbances. For example, Delong & Dwyer (1988) reported on the rates of psychiatric disorders in 196 parents and siblings of 51 individuals with autism or Asperger's syndrome. They found schizophrenia in 0·5%, affective disorders in 7% (including a rate of manic depression of 5%) and other unspecified psychiatric disorders in 19%. Unfortunately, there was no comparison group, but the rate of manic-depression seemed unusually high and was predominantly found in families of probands without any significant neurological disorder (DeLong & Nohria, 1994). Piven *et al.* (1991) reported the lifetime rates of psychiatric disorders according to modified Research Diagnostic Criteria, in the parents of autistic and Down's syndrome probands. They found a significantly increased rate of anxiety disorders in the parents of the autistic children (23·5% *v.* 2·9%; $P = 0{\cdot}02$) and a non-significant tendency for the rate of alcoholism and major depression to be elevated (27·2% of the parents of the autistic children compared with 14·8% of the Down's syndrome parents suffered from a major depressive disorder and 12·3% of the autistic parents *versus* 0% of the Down's syndrome parents from alcoholism). Smalley *et al.* (1995) compared the lifetime rates of psychopathology according to DSM-III-R-criteria, among first-degree relatives of autistic probands *versus* control probands who suffered from either tuberous sclerosis complex or an unspecified seizure disorder. They found major depression (32·3 *v.* 11·1%; $P = 0{\cdot}013$), social phobia (20·2 *v.* 2·4%; $P = 0{\cdot}016$) and substance abuse (22·1 v. 0%; $P = 0{\cdot}002$) to be significantly more common in the first-degree relatives of the autistic probands. Studies using depression questionnaires have also reported significantly higher rates of affective disturbances in the parents of children with autism compared to the rates in parents of children with Down's syndrome (Dumas *et al.* 1991).

There are three possible explanations for these findings. First, the burden of caring for an autistic child and the stresses stemming from dealing with the maladaptive behaviours associated with autism may act as provoking agents for psychopathology. Clearly, this explanation could only account for the increased rates of psychopathology in the relatives of children with autism compared with the rates in relatives of children with other forms of handicap, if the stress arising from raising a child with autism was greater than that arising from the care of children with other forms of disability. Secondly, affective disturbances may constitute part of the autism phenotype or there may be shared genetic risk factors linking the two conditions. For example, autism was first described in Kanner's (1943) report as an innate disturbance of affective contact, and several

investigations into the psychological impairments associated with autism show that affective and socio-emotional deficits characterize the condition (Hobson, 1986*a*, *b*; Hobson *et al*. 1988). Furthermore, individuals with autism and their relatives have been found to show abnormalities in serotonin levels (Cook *et al*. 1994), perhaps indicating abnormalities in the systems regulating affect. Lastly, the raised rates of the psychiatric disturbance may reflect a form of gene–environment correlation (Simonoff *et al*. 1994). Thus, the social communication impairments that are the hallmarks of the broader phenotype may act as risk factors for affective disturbances, because they interfere with the formation of supportive confiding relationships that protect against the development of affective disturbances (Brown & Harris, 1978). Of course, these explanations are not mutually exclusive and they may operate in combination.

In order to address some of these issues, we have analysed data on all first-, second- and third-degree relatives collected as part of a large family study on autism (Bolton *et al*. 1994).

METHOD

Sample selection

The sample selection and assessment procedures are described in detail elsewhere (Bolton *et al*. 1994). Briefly, 99 randomly selected Maudsley clinic probands with idiopathic autism, aged between 5 and 36 years, and stratified by sex and IQ, were group matched using the multivariate distribution of age, sex, social class, birth order and maternal age, with 36 Down's syndrome children drawn from a large community sample.

There were 498 first-degree relatives in these families. Excluding subjects younger than 18 left 416 relatives (195 parents and 97 sibs of autistic probands, and 72 parents and 52 sibs of the Down's probands). Including second- and third-degree relatives there were 2400 relatives in total (1654 autism relatives and 746 Down's relatives).

Proband assessments

Standardized diagnoses of autism were made according to ICD-10 criteria, using the Autism Diagnostic Interview (ADI) and the Autism Diagnostic Observation Schedule (ADOS) (Le Couteur *et al*. 1989; Lord *et al*. 1989). The ADI data were used to determine the symptom severity of autism (by summating the number of ICD-10 symptoms of autism that were endorsed) and also to construct a measure of behavioural and developmental disturbances (the Behavioural Abnormalities Score – BAS) that previous research had suggested were stressful to parents (Bebko *et al*. 1987; Konstantareas & Homatidis, 1989; Freeman *et al*. 1991) and which, on clinical grounds, we predicted should index the burden of raising a child with autism. The score was made up from a number of taxing maladaptive behaviours and developmental abnormalities that were considered to be the most worrying and demanding for parents. They included aggression, self-injury, hyperactivity, intrusive and disruptive rituals, embarrassing socially inappropriate behaviour, incontinence, epilepsy and marked tics and stereotypies. The BAS and the symptom severity score correlated 0·36 ($P = 0{\cdot}001$).

Obstetric histories were obtained from mothers, using a specially devised investigator-based Obstetric Enquiry Schedule (OES) (Bolton *et al*. 1997). Details from the OES were then used to construct an optimality score, that indexed the degree of obstetric adversity. This score has been shown to correlate well with data from contemporaneous birth records (Bolton *et al*. 1997). The optimality score correlated 0·21 with the symptom severity score ($P = 0{\cdot}04$) and 0·26 with the BAS ($P = 0{\cdot}01$).

Apart from confirming the diagnosis of trisomy 21 and the absence of autism, no other assessments of the Down's probands were conducted.

The assessment of psychopathology in relatives

All available, consenting, adult first-degree relatives were interviewed by trained researchers using the Maudsley version of the SADS-L, to assess the lifetime prevalence rates of psychopathology. The Maudsley SADS-L is a semi-structured investigator-based version of the original SADS-L (Spitzer & Endicott, 1978; Harrington *et al*. 1988). The schedule had been modified to include diagnoses not covered in the original schedule (e.g. eating disorders), and had been shown to have substantial agreement with the more structured respondent version of the

SADS-L across most research diagnostic criteria (Harrington *et al.* 1988). Except for eating disorders where DSM-III criteria were employed, diagnoses were made according to the Research Diagnostic Criteria (RDC) (Spitzer & Robbins, 1978), with revisions as described by Mazure & Gershon (1979). These revised diagnostic criteria are equivalent to the criteria of Spitzer & Robbins (1978) except that the diagnosis of major depression required 4 weeks duration of symptoms, rather than 2 weeks. In addition, simple phobias limited to circumscribed areas of a subject's life, and not associated with significant impairment, were not included in the diagnosis of phobic disorder. Whenever there were coding queries, these were discussed by the research group and consensus coding and diagnosis made. It was not possible for the research interviews to be conducted without knowledge of proband diagnosis.

Family history data

In addition to the SADS-L interviews, family history data were collected at parent interview using a specially devised Family History Interview (FHI). This reliable investigator-based standardized instrument documents the presence of developmental disorders of speech, reading and spelling, as well as abnormalities in socio-emotional development, and psychiatric disorders (Bolton *et al.* 1994; Fombonne *et al.* 1997). Following the FHI, a case vignette was compiled for any first-, second- or third-degree relative who might have had problems in one of the above areas. These vignettes were subsequently rated by four researchers, without knowledge of the subject's family of origin and relationship to the proband. The scores on the coded items from the FHI were combined to produce a working definition of the broader autism phenotype. The definition required evidence of clear-cut impairments in areas conceptually linked to autism (i.e. communication impairment, social dysfunction or stereotyped and repetitive patterns of interests and behaviours) according to an operationalized set of criteria. To meet the criteria for the broader phenotype, diagnosis required the presence of either communication *or* social impairments *or* restrictive patterns of interest and activities. Further details of the operationalized criteria can be found in the report of the case–control family history study (Bolton *et al.* 1994). During the development of the schedule it was evident that it was not possible to obtain adequately reliable information for the separation of anxiety disorders, major and minor depression, and agoraphobia. Consequently, these diagnostic groups were amalgamated and one item in the schedule documented the presence of an affective disorder associated with social impairment or treatment. Separate codings were made for bipolar disorders, attempted and completed suicide. As we had both information from the SADS-L interview and the FHI on the first-degree relatives in the study (usually collected at different times by different interviewers), it was possible to compare a comparable amalgamated set of diagnoses made following the SADS-L interview with the diagnosis of affective disorders recorded in the FHI. This indicated an acceptable level of agreement (kappa = 0·65).

Data analysis

Family data may contravene the independence assumptions of standard statistical tests. Consequently, a variety of special procedures were used to correct for this potential problem. The results of the simple bivariate analyses were checked by two methods, the fitting of logistic regression models that allowed for a correlation between relatives by means of a random effect (EGRET, 1990) and also by the calculation of standard errors robust to the lack of independence (White, 1982; Breslow, 1989). Both methods gave essentially identical results to those using the approaches presented here. All significance tests presented are two-tailed. We also performed detailed multivariate analyses focusing on the examination of the pattern of familial aggregation for affective disorders using an approach that exploited variation in the severity of disturbance. For these analyses, an ordinal variable was constructed with four levels of severity of affective disorder, as measured from the SADS-L (none, minor, major, major with onset before age 25 and/or recurrent disorder). An ordinal logistic regression model was fitted to these data using the correlated binary logistic construction first proposed by Snell (1964), the generality of which has recently

been emphasized (Cox, 1995). Using the survey analysis program SUDAAN (Shah *et al.* 1992) the sets of binary logistic responses from each subject were also nested by family to take account of possible dependence of the kind discussed in the previous paragraph (Binder, 1983). For some small number analyses, it was not possible to undertake standard multivariate analyses with confidence. In these circumstances, we performed exact logistic regression using LogXact (Cytel Software Corporation, 1996).

RESULTS

Among the adult first-degree relatives that were eligible for a SADS-L interview, 218 autism relatives (75%) and 87 (70·2%) Down's syndrome relatives consented and were interviewed with the SADS-L. The ages of the autism parents in this sample (50 years, S.D. = 9·0 years) and autism siblings (24 years, S.D. = 5·5 years) were similar to those of the Down's parents (51 years, S.D. = 8·7 years) and siblings (27 years, S.D. = 6·7 years). Furthermore, the subjects who were not interviewed using the SADS-L had a similar rate of psychiatric disorders according to the FHI (15·4%, $N = 124$), compared with those who were interviewed (16·9%, $N = 293$).

Rates of psychiatric disorders in all relatives (Family History Interview data)

Table 1 summarizes the rates of disorder that possibly or definitely met our operational diagnostic criteria, in all first-, second- and third-degree relatives. Clearly, the rates of disturbances in each diagnostic grouping were very low. These low rates partly reflected the stringent criteria adopted in the schedule, partly the fact that these data include some subjects who were still quite young, and hence had lived in the period of risk for relatively short periods of time, and partly the fact that information was gathered from one or two informants about relatives whose life histories were known only to a limited extent. For the most part, the prevalence of psychiatric disorders in the relatives of the autistic and Down's probands were broadly similar. However, there were some striking differences. First, the rate of affective disorder (defined as anxiety, depression, phobia or mixed anxiety and depression that required a course of treatment or was associated with 4 weeks of primary role impairment, or hospitalization) was substantially greater. Moreover, the rate of attempted and completed suicides showed a non-significant tendency to be more common among the relatives of autistic probands. Secondly, the prevalence of definite or possible tics (defined as frequent single motor tics or multiple motor tics or any vocal tics) was significantly higher in the relatives of autistic probands. Thirdly, the rates of possible or definite, obsessive–compulsive disorders were significantly greater in the relatives of individuals with autism. Group comparisons of the rates of definite disorders, as opposed to the rates of possible and definite disorders, showed a significant increase in affective disorders alone. The absolute rates of definite tics and obsessive–compulsive disorders were too low for any test of significance to be meaningful (data not shown).

Detailed evaluation of the pattern of familial aggregation and the extent of their co-morbidity with other conditions was not usually possible for the rare forms of psychiatric disorder. However, highly significant co-morbidity between obsessive–compulsive disorders and the broader autism phenotype was observed. Thus, five of the 106 subjects with communication or

Table 1. *Psychiatric disorders among all relatives of autism and Down's probands* (*family history data: possible and definite disorders*)

	Group				
	Autism		Down's		Exact
Diagnosis	*N*	%	*N*	%	*P*
Subjects aged 7–17	($N = 234$)		($N = 105$)		
Conduct disorder	16	1	6	0·8	0·7
Hyperkinetic disorder	1	0·4	1	1·0	0·5
Tics	11	0·7	0	0	0·02
Clumsiness	9	0·6	1	0·1	0·2
Uncertain childhood disorder	12	0·7	7	1·0	0·6
Eating disorder	6	0·4	3	0·4	1
Subjects aged > 17	($N = 1391$)		($N = 625$)		
Affective disorder	121	8·7	32	5·1	0·005
Suicide	13	0·9	1	0·2	0·08
Obsessive–compulsive disorder	15	1·1	0	0·0	0·005
Schizophrenia	2	0·1	1	0·2	1·0
Bipolar disorder	11	0·8	2	0·3	0·4
Substance abuse	25	1·8	10	1·6	0·8
Uncertain adult disorder	28	2·0	24	3·8	0·2

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Table 2. *Psychiatric disorders among first-degree relatives of autism and Down's probands (SADS-L interview data: RDC criteria)*

	Group				
	Autism ($N = 218$)		Down's ($N = 87$)		
Diagnosis	*N*	%	*N*	%	*P*
Minor depression	37	17	12	13·8	NS
Major depression	43	20	5	5·7	0·004
Bipolar I and II	3	1·4	0	0	NS
Minor/major/bipolar	76	35	16	17·3	0·01
Anxiety	17	7·8	4	4·6	NS
Anxiety with depression	1	0·46	1	1·2	NS
Panic	4	1·8	3	3·5	NS
Phobias	17	7·8	5	5·7	NS
OCD	3	1·4	0	0	NS
Schizophrenia	1	0·46	1	1·2	NS
Anorexia	1	0·46	1	1·2	NS
Alcohol/drugs	5	2·3	0	0	NS

social impairments suffered from obsessive–compulsive disorders, compared with 10 of the 2249 remaining relatives ($\chi^2 = 20{\cdot}1$; $P = 0{\cdot}00001$).

Rates of disorders among first-degree case and control relatives (SADS-L data)

Table 2 shows the rates of psychiatric disorder in the first-degree relatives of the autism and Down's probands following a SADS-L interview and using the modified RDC criteria. The rate of major depression and a more broadly defined form of affective disorder, made up from any combination of minor and major depression and bipolar disorder, were significantly elevated in the autism relatives. It was noteworthy that the rates of schizophrenia, anorexia nervosa, phobias, anxiety disorders and alcohol and drug abuse were not significantly different in the two samples.

The severity of affective disorder

Table 3 shows the rates of major depression in the two groups of relatives according to the severity of the disorder, as indexed by the type of disorder (minor or major depression) the number of episodes (single or recurrent) and the age of onset (before or after age 25). Information regarding age of onset and number of episodes was not available on the total sample, so the number of subjects in this analysis was fewer than the number reported in Table 2. It was evident that a substantial minority of the autism relatives suffered from a severe recurrent disorder that began early in adult life. The analysis in SUDAAN testing for higher levels of more severe depression in the autism group confirmed that the rate was significantly increased (df = 1 adjusted $\chi^2 = 7{\cdot}86$, $P = 0{\cdot}01$). A test for homogeneity of effect across severity levels (the addition of a level by group interaction) was non-significant.

Table 3. *Rates and severity of depression*

	Group	
Diagnosis (SADS-L)	Autism ($N = 198$) %	Down's ($N = 81$) %
Unaffected	70·7	85·2
Minor depression	9·1	8·6
Major depression	8·6	3·7
Major depression + early onset or recurrent	11·6	2·5

Rates of affective disorder by sex and relationship to the proband

Comparison of the rates of major depression according to the sex of the relative revealed that 9·6% of the male relatives of autistic probands, compared with 4·8% of the male relatives of Down's probands, suffered from major depression (odds ratio 2·13, $P = 0{\cdot}3$). Among female relatives, the rate of major depression was 31·1% in the relatives of autistic probands and 9·6% in the relatives of Down's probands (OR 5·88, $P = 0{\cdot}002$). Ordinal logistic regression models were fitted to the four-level SADS-L response. Covariates included group (autism/Down's), subjects' age and sex, and whether the relative was a parent or sibling. As expected, female relatives were at higher risk than males ($P < 0{\cdot}01$), but the association of group (autism) with frequency and severity of depression remained highly significant after controlling for these variables. Clearly, the pattern of association between the risk of depression and the characteristics of the relatives was quite different from the pattern observed for the broader autism phenotype, where the risk was greatest in males.

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The onset of affective disorders in relation to the probands' birth

We examined the numbers of subjects with depression according to the onset of the first episode in relationship to the birth of the proband, with the expectation that if the demands of raising an autistic child were responsible for the raised rate of depressive disorders in the parents of autistic individuals, the group differences should not apply to depression with an onset before the birth of the autistic child, but should instead be confined to the period following their birth. The rate of major depression before the birth of the proband was 6% in the autism group and 0% in the Down's syndrome group: after the proband's birth the rates were 17 and 8% respectively. The comparable figures for all cases of depression (i.e. pooling major and minor varieties) were 13·2 *versus* 6·2% and 20·8 *versus* 25%. Whichever definition is used, the profile of rates before and after the proband's birth did not differ significantly between the two groups. Thus, it is clear that the rates of depression in the parents of autistic individuals were as much raised before, as after the birth of the proband.

Features associated with SADS-L diagnosis of affective disorder

We next turned to an examination of the relationship between the nature of the probands' disorder and the risk in relatives of major depression (the severity of depression that most distinguished first-degree case and control relatives) and the broader autism phenotype. We first examined the proband characteristics that predicted major depression testing the impact of the symptom severity score, the Behavioural Abnormalities Score (BAS) and the optimality score, while controlling for various characteristics of the relatives (age, sex and parent *versus* sib status). Also included in the logistic model was an indicator variable for proband speech that previous analyses had indicated was a possible marker of heterogeneity (Bolton *et al.* 1994). Whether entered individually or jointly, the BAS was the only measure that significantly increased the risk for depression ($P = 0{\cdot}01$ individually, $P = 0{\cdot}02$ jointly). The joint analysis suggested an odds ratio for major depression of 2·03 (95% CI = 1·14–3·61) for families one standard deviation apart on the BAS. The corresponding estimates for the symptom severity and optimality scores were 0·97 (CI = 0·55–1·72) and 0·72 (CI = 0·44–1·19) respectively. Both effect size and significance increased when the analyses were restricted to parents. The BAS remained a significant predictor of affective disturbance, when the outcome criteria were relaxed to include minor depression. The sex of the proband was unrelated to the risk of major depression in relatives. By contrast, the analyses showed that the BAS was not related to the risk of a relative exhibiting the broader phenotype ($P = 0{\cdot}6$; standardized OR = 0·85, CI = 0·48–1·48). Instead, consistent with previous findings (albeit in this reduced sample), the symptom severity score predicted the occurrence of the broader phenotype ($P = 0{\cdot}03$, standardized OR = 2·13, CI = 1·09–4·16), with a lesser contribution from the optimality score (standardized OR = 1·27, CI = 0·81–1·99; $P = 0{\cdot}3$).

Table 4. *Rates of depression according to the presence of the broader autism phenotype*

Severity of depression (SADS-L)	Status of relatives: Unaffected *N*	Unaffected %	Broader phenotype *N*	Broader phenotype %
Unaffected	181	75·1	28	73·7
Mild	20	8·3	5	13·2
Moderate	17	7·1	3	7·9
Severe	23	9·5	2	5·3

We also looked for evidence of an association between the occurrence of major depression and the broader phenotype in relatives. Table 4 summarizes the rates of depression according to the presence of the broader phenotype in a relative. There was no evidence of co-morbidity between the two conditions (exact test, $P = 1{\cdot}0$). We also examined the question at the level of the family. Thus, we classified families according to whether any first-degree relative had the broader phenotype (broader phenotype families) and/or depression (depression families). There was no association at the level of the family between these two phenotypes with 12 out of the 32 broader phenotype families having a relative

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Table 5. *Rates of affective and other psychiatric disorders according to genetic relationship to proband*

Genetic relationships/group	Other psychiatric disorders		Affective disorders		Odds ratio (D *v.* A)	*P*
	N	%	*N*	%		
Second-degree relative						
Down's (D) ($N = 291$)	9	3·1	12	4·1		
Autism (A) ($N = 708$)	20	2·8	52	7·3		
					1·84	0·07
Third-degree relative						
Down's (D) ($N = 211$)	4	1·9	3	1·4		
Autism (A) ($N = 390$)	6	1·5	8	2·1		
					1·43	0·9

with depression, compared with 18 out of 45 of the non-broader phenotype families (OR = 0·90, CI = 0·32–2·51; $P = 1·0$).

The rates of affective disorders in second- and third-degree relatives

We have previously reported that the second- and third-degree relatives of the autistic probands were at increased risk for the broader phenotype (Pickles *et al.* 1995). We also examined the rates of psychiatric disorder in these relatives. In view of the low sensitivity of the family history method for depression, Faraone & Tsuang (1995) recommend using less stringent criteria for caseness than would be the rule with direct interview data. Table 5 gave the rates of disorder by group using the FHI equivalent of minor depression. The reported rates of depression appeared somewhat higher in second-degree ($P = 0·07$, OR = 1·84, CI = 0·95–3·85) and third-degree autism relatives ($P = 0·9$, OR = 1·43, CI = 0·34–8·48). An exact test stratified by degree of relative estimated the exact odds ratio as 1·77 (CI = 0·98–3·39) which was just significantly higher ($P = 0·05$). However, the inclusion of a term in the analysis to account for the possibility of reporting bias (i.e. informants with a history of affective disorder may be more likely to report affective disorders in their relatives), reduced the significance of this difference ($P = 0·1$).

The familiality of disorders in second- and third-degree relatives according to the characteristics of the proband and the type of disorder in first-degree relatives

We next focused on the relationship between the characteristics of the probands disorder and the risk of a second- and third-degree relative suffering from an affective disorder, in order to determine whether the relationship between the BAS and risk of a first-degree relative having an affective disorder was also present in more distant relatives. Logistic regression with sex, age, parental status, degree of relative and language level gave a significant association between affective disorder and the BAS ($P = 0·04$). This association was again less significant ($P = 0·07$) following the inclusion of the term to account for possible reporting bias.

As both the broader phenotype and affective disorders were familial, we examined the association between the phenotypes shown by first-degree relatives with the phenotypic rates reported among second- and third-degree relatives. These analyses were undertaken to determine whether an increased risk of affective disorders in first-degree relatives was associated with an increased risk in more distant relatives of affective disorders alone or affective disorders and the broader phenotype. Similarly, we looked to see if the risk for the broader phenotype in first-degree relatives was related to the risk in more distant relatives of the broader phenotype alone or the broader phenotype and affective disorders. Diagnoses of affective disorders were made in first-degree relatives using SADS-L, and when these were missing, FHI data. The diagnosis of the broader phenotype was made using FHI data.

The associations proved quite specific. Using logistic regression to control for the age, sex, parental status and degree of genetic relationship (second- or third-degree), there was a strong association between the rate of depression reported in second- and third-degree relatives and the presence of depression in first-degree relatives ($P = 0·02$, OR = 1·96, CI = 1·13–3·41) but no association with the presence of the broader phenotype in first-degree relatives ($P =$

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0·9, OR = 1·03 CI = 0·59–1·81). Correspondingly, there was no association between the reported rate of the broader phenotype among second- and third-degree relatives with the presence of depression among first-degree relatives ($P = 0·4$, OR = 1·28, CI = 0·71–2·31), but there was an association with the presence of the broader phenotype ($P = 0·04$, OR = 1·82, CI = 1·01–3·28).

DISCUSSION

Our Family History Interview results suggested that tics, obsessive–compulsive disorders (OCD) and affective disorders aggregate in relatives of children with autism. The evidence for an increased risk of tics was weak, in so far as the difference in rates only became significant when cases of possible as well as definite tic disorder were included in the analyses. When this is considered along with various other points (namely, that the rate of tic disorder was unrealistically low; and that there were no relatives with Tourette syndrome or any association with the broader phenotype), it seems probable that the finding was due to the likelihood of occasional spurious associations when undertaking multiple tests. The position regarding OCD is somewhat different. It is true that, as with tic disorder, the association only emerged after including cases of possible OCD in the analyses and that the same concerns regarding multiple tests apply. However, we found OCD to be strongly associated with communication and social impairments and this was not evident with tics. This suggests that the finding may be meaningful and it supports our decision to include obsessive–compulsive disorders as one of the indicators of the broader autism phenotype (Bolton *et al*. 1994).

The increased rate of affective disorder was confirmed among first-degree relatives following face to face interviews with subjects using the Maudsley version of the SADS-L. The pattern of familial aggregation was inconsistent with the notion that affective disorders constitute part of the autism phenotype. Thus, there was no evidence that the two co-occurred at the individual or family level. Moreover, the characteristics of relatives that were associated with a predisposition to the broader phenotype (male, siblings) differed from those associated with a predisposition to affective disorders (female, parents). Likewise, the proband characteristics that predisposed relatives to the broader phenotype (symptom severity of autism, optimality score), differed from those proband characteristics that predisposed relatives to affective disorders (the Behavioural Abnormalities Score). However, the correlation between the symptom severity and behavioural abnormalities scores made it difficult to identify clearly separate predictive relationships. Furthermore, the fact that both the broader phenotype and affective disorders were familial, yet the liabilities to their familiality were not correlated, adds further weight to the view that affective disorders do not constitute part of the broader phenotype of autism. In combination, these findings indicate that some explanation for the elevated familial aggregation of affective disorders in relatives of autism families other than depression being part of a broader autism phenotype needs to be sought.

The hypothesis that the burden of caring for an autistic child could account for an elevated rate of affective disorders is only tenable, if the burden of raising an autistic child is greater than that arising from raising a child with Down's syndrome. Questionnaire studies of the impact of raising a handicapped child on family life have suggested that parents of children with autism may experience higher levels of stress than parents of Down's children and that the greater stress seems to account for increased rates of dysphoria (Dumas *et al*. 1991). There is also evidence that the burden of care seems to fall principally on the mother (Holmes & Carr, 1991) and that mothers are the most likely to experience stress and dysphoria (Moes *et al*. 1992). In addition, the risk of a sibling developing dysphoria seems to be related to the difficulties the mother has in coping with the handicapped child (Gold, 1993), the behavioural disturbance of the handicapped child and the quality of the marriage (Gath & Gumley, 1987). In this study, the only finding supportive of the burden hypothesis was the statistically significant association between the level of behavioural abnormalities in the autistic proband and the rate of affective disorder in first-degree relatives. However, the relevance of

this finding is weakened by the equivocal evidence of a similar association in second- and third-degree relatives (which would not be expected on the basis of the burden hypothesis). It should be added that our measure of burden was indirect (although it had some face validity – Bebko *et al*. 1987; Konstantareas & Homatidis, 1989; Freeman *et al*. 1991) and was unavailable in the Down's syndrome probands.

Despite this one weakly supportive finding there are three findings that suggest the burden hypothesis should be rejected as a sufficient explanation for the raised rate of affective disorders in the families of individuals with autism. First, and most crucially, there was no indication that the raised rate of depression in parents was confined to the period after the birth of the proband. The same applied to the study by Smalley *et al*. (1995), although methodological limitations prevent firm conclusions. Secondly, the increased risk for affective disorders applied to the more severe, recurrent early onset forms of disorder, rather than only to milder forms of mood disturbance, a finding that seems out of keeping with the burden hypothesis. The findings on personality function in these families, however, indicated that parents of autistic children are more prone to being 'tense' and that the likelihood of suffering from tension was related to the Behavioural Abnormalities Score (Murphy *et al*. 1997). Thirdly, there was weak evidence to suggest that the second- and third-degree relatives of the autistic probands also showed higher rates of affective disturbances, although this may have reflected a reporting bias, as the effect was attenuated when we attempted to control for this.

Taking the evidence as a whole, it may be that the burden of raising a child with autism plays some contributory role in a vulnerability to depression, but it cannot account for the overall raised rate of affective disorder in the relatives. That leaves open the need for some alternative explanation. Our results take the research forward in their incompatibility with both the burden hypothesis and the hypothesis that depression is part of a broader autism phenotype. The search for the true basis for the association needs, however, to continue. Such research will have to pay careful attention to the methods of sample ascertainment. That is important because clinic samples may bias family studies if the likelihood of referral is influenced by mental disorder in the parent (see Shepherd *et al*. 1971). Groups to be compared should also be assessed for stress/burden. The element that is likely to be most useful, however, in defining which types of psychopathology constitute part of the same genetic liability is the identification of susceptibility genes for autism (see Rutter & Plomin, 1997). The several molecular genetic studies of autism currently in progress are likely to provide such identification over the course of the next few years.

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REFERENCES

Asperger, H. (1991). Autistic psychopathy in childhood. (Translated by U. Frith) In *Autism and Asperger's Syndrome* (ed. U. Frith), pp. 37–92. Cambridge University Press: Cambridge.

Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E. & Rutter, M. (1995). Autism as a strongly genetic disorder: evidence from a British twin study. *Psychological Medicine* **25**, 63–77.

Bebko, J. M. Konstantareas, M. M. & Springer, J. (1987). Parent and professional evaluation of family stress associated with characteristics of autism. *Journal of Autism and Developmental Disorders* **17**, 565–576.

Binder, D. A. (1983). On the variances of asymptotically normal estimators from complex surveys. *International Statistical Review* **51**, 279–292.

Bolton, P. F., Macdonald, H., Pickles, A., Rios, P. Goode, S., Crowson, M., Bailey, A. & Rutter, M. (1994). A case–control family history study of autism. *Journal of Child Psychology and Psychiatry* **35**, 877–900.

Bolton, P. F., Murphy, M., Macdonald, H., Whitlock, B., Pickles, A. & Rutter, M. (1997). Obstetric complications in autism: consequences or causes of the condition. *Journal of the American Academy of Child and Adolescent Psychiatry* **36**, 272–281.

Breslow, N. (1989). Score tests in over dispersed GLMs. In *Proceedings of Statistical Modelling*, *Trenta*, *Lecture Notes in Statistics 57* (ed. A. Decarli, B. Francis, R. Gilchrist and G. Seeber), pp. 64–74. Springer: Berlin.

Brown, G. W. & Harris, T. (1978). *Social Origins of Depression*. Tavistock Publications: London.

Cook, E. H. Jr., Arora, R. C., Anderson, G. M., Berry Kravis, E. M., Yan, S. Y., Yeoh, H. C., Sklena, P. J., Charak, D. A. & Leventhal, B. L. (1993). Platelet serotonin studies in hyperserotonemic relatives of children with autistic disorder. *Life Sciences* **52**, 2005–2015.

Cook, E., Charak, D. A., Arida, J., Spohn, J. A., Roizen, N. J. M. & Leventhal, B. L. (1994). Depressive and obsessive–compulsive symptoms in hyperserotonemic parents of children with autistic disorder. *Psychiatric Research* **52**, 25–33.

Cox, C. (1995). Location-scale cumulative odds models for ordinal data: a generalized non-linear model approach. *Statistics in Medicine* **14**, 1191–1203.

Cytel Software Corporation (1996). *LogXact*. Cytel Software Corporation: Cambridge, MA.

Delong, R. & Dwyer, J. T. (1988). Correlation of family history with specific autistic subgroups: Asperger's syndrome and bipolar affective disease. *Journal of Autism and Developmental Disorders* **18**, 593–600.

Delong, R. & Nohria, C. (1994). Psychiatric family history and neurological disease in autistic spectrum disorders. *Developmental Medicine and Child Neurology* **36**, 441–448.

Dumas, J. E., Wolf, L. C., Fisman, S. N. & Culligan, A. (1991). Parenting stress, child behaviour problems, and dysphoria in parents of children with autism, Down syndrome, behaviour disorders, and normal development. *Exceptionality* **2**, 97–110.

Faraone, F. V. & Tsuang, M. T. (1995). Methods in psychiatric genetic research. In *Textbook in Psychiatric Epidemiology* (ed. M. T. Tsuang, M. Tohen and G. E. P. Zahner), pp. 81–134. Wiley: New York.

Fombonne, E., Bolton, P. F., Prior, J., Jordan, H. & Rutter, M. (1997). A family study of autism: cognitive patterns and levels in parents and siblings. *Journal of Child Psychology and Psychiatry* **38**, 667–684.

Freeman, N. L., Perry, A. & Factor, D. (1991). Child behaviours as stressors: replicating and extending the use of the cars as a measure of stress: a research note. *Journal of Child Psychology and Psychiatry* **32**, 1025–1030.

EGRET (1990). *EGRET Manual*. Statistics and Epidemiology Research Corporation: Seattle, Washington.

Gath, A. & Gumley, D. (1987). Retarded children and their siblings. *Journal of Child Psychology and Psychiatry* **28**, 715–730.

Gillberg, C. & Steffenburg, S. (1987). Outcome and prognostic factors in autism and similar conditions: a population-based study of 46 cases followed through puberty. *Journal of Autism and Developmental Disorders* **17**, 273–287.

Gold, N. (1993). Depression and social adjustment in siblings of boys with autism. *Journal of Autism and Developmental Disorders* **23**, 147–163.

Harrington, R., Hill, J., Rutter, M., John, K., Fudge, H., Zoccolollo, M. & Weissman, M. M. (1988). The assessment of lifetime psychopathology: a comparison of two interviewing styles. *Psychological Medicine* **18**, 487–493.

Hobson, R. P. (1986*a*). The autistic child's appraisal of expressions of emotion. *Journal of Child Psychology and Psychiatry* **27**, 321–342.

Hobson, R. P. (1986*b*). The autistic child's appraisal of expressions of emotion: a further study. *Journal of Child Psychology and Psychiatry* **27**, 671–680.

Hobson, R. P., Ouston, J. & Lee, A. (1988). Emotion recognition in autism: co-ordinating faces and voices. *Psychological Medicine* **18**, 911–923.

Holmes, N. & Carr, J. (1991). The pattern of care in families of adults with a mental handicap: a comparison between families of autistic adults and Down syndrome adults. *Journal of Autism and Developmental Disorders* **21**, 159–176.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child* **2**, 217–250.

Konstantareas, M. M. & Homatidis, S. (1989). Assessing child symptom severity and stress in parents of autistic children. *Journal of Child Psychology and Psychiatry* **30**, 459–470.

Lainhart, J. E. & Folstein, S. E. (1994). Affective disorders in people with autism: a review of published cases. *Journal of Autism and Developmental Disorders* **24**, 587–601.

Le Couteur, A., Rutter, M., Lord, C., Rios, P., Robertson, S., Holdgrafer, M. & McLennan, J. (1989). Autism diagnostic interview: a standardized investigator-based instrument. *Journal of Autism and Developmental Disorders* **19**, 363–387.

Lord, C. Rutter, M. Goode, S., Heemsbergen, J., Jordan, H., Mawhood, L. & Schopler, E. (1989). Autism diagnostic observation schedule: a standardized observation of communicative and social behaviour. *Journal of Autism and Development Disorders* **19**, 185–212.

Mazure, C. & Gershon, E. S. (1979). Blindness and reliability in lifetime psychiatric diagnosis. *Archives of General Psychiatry* **36**, 521–525.

Moes, D., Koegel, R., Schreibman, L. & Loos, L. M. (1992). Stress profiles for mothers and fathers of children with autism. *Psychological Reports* **71**, 1272–1274.

Murphy, M., Bolton, P. F., Pickles, A. & Rutter, M. (1997). Personality traits of relatives of autistic probands. (Submitted.)

Pickles, A., Bolton, P., Macdonald, H., Bailey, A., Le Couteur, A., Jordan, H., Sim, C.-H. & Rutter, M. (1995). Latent class analysis of recurrence risks for complex phenotypes with selection and measurement error: a twin and family history study of autism. *American Journal of Human Genetics* **57**, 717–726.

Piven, J., Chase, G. A., Landa, R., Wzorek, M., Gayle, J., Cloud, D. & Folstein, S. (1991). Psychiatric disorders in the parents of autistic individuals. *Journal of the American Academy of Child and Adolescent Psychiatry* **30**, 471–478.

Rutter, M. & Plomin, R. (1997) Opportunities for psychiatry from genetic findings. *British Journal of Psychiatry* **171**, 209–219.

Rutter, M., Bailey, A., Bolton, P. & Le Couteur, A. (1994). Autism and known medical conditions: myth and substance. *Journal of Child Psychology and Psychiatry* **35**, 311–322.

Shah, B. V., Barnwell, B. G., Hunt, N. P. & Levange, L. M. (1992). *Sudaan User's Manual Release 6.0*. Research Triangle Institute, PO Box 12194, Research Triangle Park, NC 27709-2194, USA.

Shepherd, M., Oppenheim, A. N. & Mitchell, S. (1971). *Childhood Behaviour and Mental Health*. University of London Press: London.

Simonoff, E., McGuffin, P. & Gottesman, I. I. (1994). Genetic influences on normal and abnormal development. In *Child and Adolescent Psychiatry: Modern Approaches*, 3rd edn (ed. M. Rutter, E. Taylor and L. Hersov), pp. 129–151. Blackwell Scientific Publications: Oxford.

Smalley, S. L., McCracken, J. & Tanguay, P. (1995). Autism, affective disorders, and social phobia. *American Journal of Medical Genetics* **60**, 19–26.

Snell, E. J. (1964). A scaling procedure for ordered categorical data. *Biometrics* **20**, 592–607.

Spitzer, R. L. & Endicott, J. (1978). *Schedule for Affective Disorders and Schizophrenia*, 3rd edn. Government Printing Office: Washington, DC.

Spitzer, R. L. & Robbins, J. (1978). Research diagnostic criteria. *Archives of General Psychiatry* **35**, 773–782.

Tantam, D. (1988). Asperger's syndrome. *Journal of Child Psychology and Psychiatry* **29**, 245–253.

White, H. (1982). Maximum likelihood estimation of misspecified models. *Econometrics* **50**, 1–25.

Wing, L. (1981). Asperger's syndrome: a clinical account. *Psychological Medicine* **11**, 115–129.

Wolff, S. (1995). *Loners: The Life Path of Unusual Children*. Routledge: London.

World Health Organization (1994). *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. World Health Organization: Geneva.