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Psychiatric and Occupational Histories in Families of Children with Autism

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1. Introduction

We have consistently found a high incidence of familial major affective disorder, especially bipolar disorder, among relatives of children with idiopathic autism compared to published incidences in the general population. [DeLong and Dwyer 1988] Psychiatric family histories of children with idiopathic autism revealed a dramatically higher incidence of affective disorder than the families of children with symptomatic neurological autism. These findings led us to advance the idea that an important segment of idiopathic autism is etiologically related to familial affective disorder.[DeLong 2004]]

Several subsequent controlled studies found a higher than expected incidence of familial psychiatric disorder, especially major affective disorder, in families of autistic probands, but these findings were minimized or ignored in large part. Larsson et al. [2005] in a careful epidemiological study in Denmark, identified two significant risk factors for autistic spectrum disorder: birth injury and familial affective disorder and psychosis, the second bearing the greater risk.

We have continued to find, in our clinics, a very strong association among idiopathic autism, major affective disorder, and another feature: special intellectual abilities or unusually high achievement, often in mathematical, scientific or computational areas. We have published our clinical observations showing a strong correlation among these three features: idiopathic autism, bipolar disorder and special intellectual abilities in family members in a retrospective open study.[DeLong et al, 2002] We have also pointed out the clinical analogies between idiopathic autism and major affective disorder, as well as the emerging similarities in neurochemistry, pharmacology, neuroimaging, and putative genetic linkages. [DeLong 2004]

The present study was undertaken to compare the family histories of autistic children with a suitable control population, with respect both to psychiatric history and special abilities. We considered that children with genetic or chromosomal disorders which confront their families with an equivalent burden regarding genetic and developmental significance would be a suitable control group. For this, we collaborated with members of the Duke Division of Genetics and Metabolism, who routinely see children with comparable developmental disorders in terms of severity and stress involved to the child's family, and who are accustomed to taking careful and complete family histories. Moreover, the importance of the family history is at least as apparent to the families of children with

genetic/metabolic disorders as to families of children with autism – if not more so – so that their maximal cooperation is likely. We planned to determine the incidence of the same psychiatric disorders in both groups of families, utilizing a controlled prospective blinded study. The prior hypothesis was that relatives of children with idiopathic autism would have a higher incidence of familial psychiatric disorder, especially major affective disorder (bipolar disorder and major depression) than the relatives of children in the comparison group, in whom the incidence was expected to approximate the rates in the population at large. A second objective of the study was to determine and compare the occupational and academic achievements of the parents in the two groups, with the hypothesis that achievement reflecting special intellectual abilities would be higher in the autistic group.

2. Methods

The study was conducted jointly by the Duke University Division of Genetics and Metabolism and the Division of Pediatric Neurology. The control group consisted of families of children with major developmental disorders having diagnoses of defined genetic metabolic disorders, major chromosomal disorders, or neurofibromatosis. (Previous control studies of autism of this kind have uniformly utilized Down's syndrome children, which is subject to the possibility that Down's syndrome families may have a different incidence of psychiatric disorder from that of the general population. Including as controls children with varied diagnoses guarded against distortion by any unrecognized factor in family histories of children of any one diagnostic group.)

For the controls, successive families of children having one of the accepted diagnoses, seen in the clinic of the Division of Genetics and Metabolism, were invited to participate in the study. Participation consisted of taking a detailed and complete family history by the senior genetics fellow (VK), with emphasis on a structured psychiatric history and "special abilities and achievements" history, in the course of a comprehensive clinic visit with the family or during a telephone interview. The Family History Method (in which one or more family members, commonly the mother of the proband, is the informant) was used; this method has been shown to be accurate for major psychiatric illness, tending if anything to underestimate true incidence. Family history taking was structured to ensure uniform coverage of all pertinent relatives and all significant disorders [see Table 1.] and included questioning about first, second, and third order relatives of the probands. The study including the family history protocol was approved by the Duke Institutional Review Board. Thirty-four families participated in this phase of the study.

For the autistic probands, a similar complete family history was taken by a senior clinician (GRD), using the same structured outline, during the course of a comprehensive clinic visit. The study group of families of autistic children consisted of thirty-four successive families seen in the Duke Autism Clinic in whom complete family history was obtainable. All probands were diagnosed as having idiopathic autistic spectrum disorder (using DSM-IV criteria) after appropriate neurological, language and developmental assessments, including ADOS; none had detectable dysmorphic, neurological, genetic or chromosomal abnormalities. History taking utilized the same structured outline and the Family History Method, with mother or another family member – such as father or a grandparent -- as the informant. For some analyses, a larger (78) successive group of families of autistic probands was utilized.

In both the study and control groups, psychiatric diagnoses were made using DSM-IV criteria. Diagnoses were accepted if the history indicated they were made by a psychiatrist

or other physician, if the disorder caused significant chronic or recurrent disability, if appropriate psychotropic medication was used, or if hospitalization occurred. Suicide without other evidence was not taken to indicate a psychiatric diagnosis.

In addition to psychiatric diagnoses, parents' occupations and educational history were recorded. Data were recorded for all individuals in each family by diagnosis. Thus we could calculate the percentage of family members diagnosed with each specific diagnosis for each group (Genetic/Metabolic and Autistic). Data analysis utilized the chi square method to determine whether the incidence of specific disorders differed significantly between the study and comparison groups. (For analyses of the percentage of families who had one or more individuals with major affective disorder, a larger group of successive autism families (78) was utilized.)

1.	**Do you know of any nervous or mental disorder in the family?**
a.	Do you know of any other disorder of development among family members?
b.	Is there any family history of depression, alcoholism (or other substance [drug] abuse)? or extreme anxiety disorder?
c.	Is there any history of mental disorder? Bipolar disorder? Post-partum depression? IF SO: Any psychiatric hospitalization? Diagnosis by a psychiatrist? Use of lithium? Or other psychiatric medications? Duration of disability, if any? Schizophrenia?
d.	Is there anybody with social reclusiveness? With obsessive-compulsive disorder?
2.	**Are there any family members with unusual or special abilities, intelligence or talents? Any one with unusually high achievement?**
a.	Anyone with unusual scholarly or mathematical talents?
b.	Anyone with unusual artistic, musical, or mechanical abilities?
c.	Anyone with unusual memory abilities? E.g. photographic memory
d.	Anyone with strongly focused, narrow, intense interests in something?
3.	**Now go through the family pedigree individual by individual as indicated; e.g.:**
Mother and mother's family:	
a.	Have you been well? Any nervous or mental problems?
b.	Do you have brothers and sisters? Have they all been well? (Any nervous or mental problems?) Do they have children? Are those children well?
c.	How about your parents? Are they well? (Do they have any nervous or mental problems?) Do they have brothers and sisters? Any nervous or mental disorders among them that you know?
d.	Anyone with special abilities or achievement in your family?
Father and father's family: (depending on respondent; here the form of questions assumes it is mother. If father, can use same language as above.)	
a.	Is your husband (or: the child's father) well? Does he have any history of nervous or mental problems? If so, elaborate:
b.	Does father have any brothers or sisters? If so, how many? Are they well? Do they have any children? Are those children well?
c.	Are father's parents well? (Any nervous or mental disorders?) Do they have brothers and sisters? How many? Are they well? (etc.)
d.	On father's side, are there any individuals with unusual talents, abilities or achievement? What is father's employment or profession? What was (is) grandfather's employment or profession?

(Respondent: parent or principal caregiver (in practice, usually mother or both parents)

Table 1. Outline of Family History Questioning

3. Data storage and analysis

Data was transferred from the clinician taking the history directly to the data technician of the Autism Program and stored anonymously. Data compilation was done by a technician blind to the families' names or identifiers (which were discarded before this stage) and naïve as to the purpose of the study, including that she was and remained unaware of the initial hypotheses. Data were analyzed utilizing the following:

a. Presence or absence of bipolar disorder, major depression, schizophrenia; plus suicide, attempted suicide; psychiatric hospitalization; use of psychotropic medications.
b. Presence or absence of special abilities, unusual achievement or talents
c. Re each of the above, the incidence of each: i.e. no. having a specific diagnosis/total no. included in pedigree
d. The family history data from the group of autistic probands were compared with that from the group of control families, looking at:

1. The number of families (and percentage of families) having members with bipolar disorder and other specific psychiatric diagnoses.
2. The aggregate burden of major psychiatric disease in each group (i.e. the proportion of individuals in the aggregated families of each group having a history of major psychiatric disorders).
3. The same foregoing analysis was applied to special abilities and achievements.

Diagnosis of special ability or achievement is not systematized. We so classify anyone having doctoral-level education and/or work in scientific or mathematical fields, or a professional career in the arts (usually music), or masters level education and/or work in computer science, finance, engineering or related highly technical field. In addition, we so consider anyone with demonstrable photographic memory or similar prodigy of memory. These criteria are somewhat arbitrary, but derive from our clinical experience and if anything probably underestimate the true incidence.

4. Results

Incidence of familial psychiatric disorder by group

	Metabolic (n = 761)	Autistic (n = 566)	Chi square
Depression	4.86%	12.36%	$X^2 = 24.7$, $p<0.001$
Suicide	1.31%	1.41%	ns
Bipolar disorder	1.83%	3.71%	$X^2 = 4.3$, $p<0.05$
Psychiatric hosp.	0.26%	4.24%	$X^2 = 28$, $p<0.001$
Psychotropic meds	3.02%	5.65%	$X^2 = 5.6$, $p<0.025$
Schizophrenia	0.53%	1.06%	ns
Attempted suicide	0.26%	0.53%	ns

Table 2. Percentage incidence of psychiatric diagnoses in relatives by group

	Metabolic (n=34)	Autistic (n=78)
Families with bipolar/depression	20	61
Families without " "	14	17

$X^2 = 4.47$, $p<0.05$

Table 3. Families with individuals having major affective disorder by group

Autism group	
Fathers	Mothers
1. Architect	1. Architect
2. PhD computers	2. Psychologist
3. Engineer, civil	3. RN, Nurse
4. PhD law	4. MPH, public health
5. PhD, professor EE	5. *
6. PhD, professor language	6. *
7. PhD, professor, English	7. *
8. Lawyer	8. *
9. MA, CPA	9. BS, BA
10. Special forces, Army	10. MA, education
11. MD, physician	11. MD, physician
12. MA, banker	12. Architect
13. PhD, professor political sci	13. MS
14. BA, dietitian	14. RN, nurse
15. MS, electrical engineering	15. BS
16. Law librarian	16. *
17. BS, computer engineering	17. *
18. MA, English	18. MA, education
19. MS, computer engineering	19. MS, computer engineer
20. BS, science teacher	20. BS
21. BS	21. DDS, dentist
22. Graphic designer	22. Psychologist
23. Sales manager, 1 year college	23. GED
24. BS, civil engineer	24. *
25. Fireman	25. Dental assistant
26. BS, CEO	26. BS
27. Welder	27. Hairdresser
28. *	28. *
29. PhD, statistician	29. *
30. Computer work, music scholar	30. *
31. “high IQ”, no career	31. Counsellor
32. PhD, professor education	32. RN
34. BA, CEO	33. BA, marketing director
35. MD, physician	34. *

Metabolic/genetic Group	
Fathers	Mothers
1. BS, golf course superintendent	1. Pharmacist
2. Marble worker	2. Waitress
3. Factory worker	3. *
4. PhD candidate	4. BA
5. *	5. GED
6. Forklift operator	6. Paramedic
7. Welder	7. Cashier
8. Mechanic	8. High school graduate
9. Roofing worker	9. *
10. *	10. *
11. BS, engineer/manager	11. BA
12. Insurance, project manager	12. Security
13. *	13. *
14. *	14. *
15. *	15. *
16. *	16. *
17. *	17. PhD, pharmacy
18. Cafeteria worker	18. "Slow learner"
19. BS, computer programmer	19. High school graduate
20. *	20. GED
21. Truck driver	21. *
22. Did not graduate high school	22. College, 2 years
23. BS, prison system	23. Dental assistant
24. Optician	24. *
25. *	25. *
26. PhD, music	26. Artist
27. Store manager	27. *
28. High school graduate, printing worker	28. BS
29. BS, mortgage industry	29. BA
30.AA (associate degree)	30.AA, veterinary tech
31. High school graduate, air force	31. College
32. *	32. *
33. Construction work	33. *
34. *	34. *
35. College student: literature and history	35. *

* no data

Table 4. Academic/Occupational Achievements of Parents

5. Discussion

This study confirms once again that the incidence of familial psychiatric disorder, especially major affective disorder, is increased in the families of children with idiopathic autistic spectrum disorder. More strikingly it demonstrates a pronounced increase in the incidence of special intellectual or academic gifts in family members, especially fathers, of children with idiopathic autism. In these respects it corroborates our earlier open studies showing strong correlation among idiopathic autism, familial major affective disorders, and special intellectual ability.[DeLong et al. 2002]

The current study is subject to critique. The family histories were taken by different individuals (VK for the genetic/metabolic families, GRD for the autism families); however, the same objective criteria were utilized by all investigators It may be that the family histories were taken more seriously by the autism families, many of whom were aware of the postulated link between autism and familial affective disorder. However, the families of the genetic/metabolic group were aware that their child had a genetic disorder and thus were presumably motivated to consider family history seriously. As it turned out, the incidences of major affective disorders in the control families approximated published population incidences, thus tending to give greater confidence in the results. In the autism families in the current study, 3.7% of first-, second- and third-degree relatives were reported to have bipolar disorder; this compares to 4.2% in our first study [DeLong and Dwyer, 1988] which included first- and second-degree relatives.

The larger number of relatives in the genetic/metabolic group as compared to the autism group (761 versus 566), for an equivalent number of families is unexplained. It is unlikely to be caused by less intense questioning of the autism families; if anything, we would suspect the opposite. It may be suggested that the higher incidence of familial psychiatric disorder may have the effect of decreasing fertility, or that higher educational status may yield the same result.

The data about academic achievement and occupations of parents, especially fathers, require scrutiny. Although a difference between the two groups was not surprising, the magnitude of the difference was astounding. Several possible contributing factors must be considered: 1) Referral bias: Our Autism Clinic is situated in an area of dense academic and research concentration (Research Triangle Park); but the Genetics clinic is in the same institution. Both clinics draw patients from the same geographic area, and both accept both private and staff patients indiscriminately. Though we have no definite information about this, outside providers may refer children to our Autism Clinic whom they consider to be favorable candidates for pharmacotherapy, which could result in an increased concentration of a certain subgroup of autistic children. Likewise, more educated families may be more insistent on further referral or more vigorous treatment efforts. While these factors may apply to some extent, they seem unlikely to account for all the difference between groups, and seemingly cannot account for the particular, rather narrow, strand of talent represented – primarily engineering, computation, or academic work at professional level. In the Genetic/Metabolic control group, these features are sparsely represented (4 of 24 (17%) compared to 26 of 33 (79%) in the Autism group). 2) Lower than normal ability in the comparison group: Fathers in the comparison group may have lower than expected academic talent or occupational

achievement, possibly by virtue of the same genetic disorder expressed in their offspring. We have no data pertinent to this, and in any event, this would not account for the strikingly high achievements and talents identified in the Autism group. 3) Missing data: data are unavailable for eleven fathers of the control group versus one for the autism group. Even assuming all of those missing fell into the talented category – an unreasonable assumption to be sure – only 15 of 35 (43%) in the control group would be so characterized (versus 79% in the Autism group). 4) Investigator bias in selecting cases: The authors are not aware of such bias. Sequential cases were enrolled. Indeed, such "cherry-picking" of certain cases would have to be massive to account for the great differences found.

Overrepresentation of academic and computational ability in fathers of autistic children has been found and remarked repeatedly. We found a strong correlation among fluoxetine-responsive autism, bipolar disorder, and special intellectual abilities in an earlier study. [DeLong et al. 2002] Various authors have supported [Dor-Shav and Horowitz 1984; Wheelwright and Baron-Cohen 2001] a link between autism and special abilities. Others have not found a correlation of autism with socioeconomic status [Tsai et al 1982, Larsson et al. 2005]; we suggest this may be because special intellectual abilities and socioeconomic status are not correlated in any simple way; or perhaps more importantly, the correlation of special abilities in family members with autism only applies to a subgroup of autistic children, and is diluted if one looks at the entire population of individuals considered as autistic.

Cognitive hyperfunction – greater than normal function in certain areas – is an intrinsic part of autism, as manifested in the autistic child (savant features, increased visuo-spatial abilities)[Caron et al 2004] and in the parents and other relatives (unusual intellectual abilities). Any comprehensive theory of autism must account for this hyperfunction. [see for example Nurmi et al 2003] That is why the finding of increased learning and memory ability in mice with GABRA5 gene knockout is so intriguing.[Collinson et al 2004] GABRA5 has been linked with autism; it has been linked with bipolar disorder; and it has been shown that knocking it out produces increased learning and memory [see DeLong 2007]. We have speculated that the special abilities seen in fathers of autistic children may be due to decreased expression of GABRA5, while the autism itself may result from some further distortion of the expression of the same gene, or that plus other neighboring genes, by imprinting.

6. Summary

This investigation was undertaken to clarify the psychiatric and cognitive characteristics of members of the families of autistic children. We were especially interested in the fathers, because of our experience and that of others suggesting that fathers of autistic children may have unusual intelligence or other cognitive gifts, and/or may have an increased incidence of major affective disorders. A control group was chosen from children referred to genetics clinic with various genetic developmental diagnoses thought to entail an effect on family anxiety and need to investigate family history comparable to that imposed by autism. Detailed family history questioning was carried out according to a structured interview (outlined herein).

Results indicated a significant .increase in incidence of psychiatric disorders in family members in the autism families, especially depression, bipolar disorder, and psychiatric hospitalization. Most striking, however, were the remarkably high academic and occupational attainments of the fathers of the autistic children. 79% of these fathers had high academic or occupational achievement compared to 17% of the fathers from the control group. These results reinforce extensive evidence of an association of high cognitive ability with autism, and must be explained in any comprehensive hypothesis of autism.

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