Autism Families with a High Incidence of Alcoholism

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To determine the significance of neuropsychiatric disorders in autism families, we analyzed 167 pedigrees ascertained through an autistic child; 39% had alcoholism in patterns consistent with transmission of a genetic trait. Children from high alcoholism families were more likely to have the onset of their autistic behavior occur with a loss of language (52.5% vs. 35.8%, $p = 0.04$). This occurred primarily in families where the mother was alcoholic (80% vs. 40%, $p = 0.05$), suggesting an association between maternal alcoholism and regressive onset autism. Children from high alcoholism families were less likely to be macrocephalic (14.7% vs. 40.6%, $p = 0.0006$). Children from high alcohol and low alcohol families did not differ in dysmorphology status, IQ, sex ratio or sib recurrence risk.

KEY WORDS: Autism; alcoholism; genetics.

INTRODUCTION

Autism is a neurodevelopmental disorder characterized by a triad of persistent social and language deficits and stereotypic behaviors. Family studies have noted that neuropsychiatric disorders including depression, manic depression, obsessive compulsive disorder, alcoholism, substance abuse, social phobia, anxiety disorders and motor tics tend to cluster in the relatives of autism probands (DeLong & Dwyer, 1988; Piven *et al.,* 1991a; Abramson *et al.,* 1992; Piven & Palmer, 1999; Smalley *et al.,* 1995; Bolton *et al.,* 1998). This apparent genetic overlap between autism and other neuropsychiatric disorders suggests that familial psychopathology may characterize certain types of autism and eventually lead to an understanding of common biochemical and genetic aberrations.

Lobascher *et al.* (1970) compared the family histories of 23 autistic children with normal controls and found a greater incidence of alcoholism (35%), psychiatric illness (35%), and mental retardation (26%) in the parents of autistic children. DeLong and Dwyer (1988) reported that 55% of their 51 autism families had a first or second degree relative with alcoholism though the overall incidence rate of alcoholism among all 929 first and second degree relatives was only 6.5%. Piven *et al.* (1991a) reported that 12.3% of 81 parents of autistic children were alcoholic compared with 0% of 34 Down syndrome parents; the difference was not statistically significant. In a study of 36 autism families, Smalley *et al.* (1995) compared the lifetime rates of psychopathology based on direct SADS-LA interviews of parents and adult siblings of autism probands versus controls who had either tuberous sclerosis or an unspecified seizure disorder. They found that 47% (17/36) of the autism families had a first degree relative with substance abuse, including alcoholism, versus none in the 21 control families. And 22% of first degree relatives reported substance abuse compared to none in the controls ($p = 0.002$). They also found increased rates of depression (32.3% vs. 11.1%; $p = 0.013$) and social phobia (20.2% vs. 2.4%; $p = 0.016$).

Not all family studies have reported increased rates of alcoholism. Bolton *et al.* (1998), using direct SADS-L interviews to assess the lifetime prevalence rates of psychopathology found a significant increase in major depression in first degree relatives of an individual with autism but no significant increase in other psychiatric disorders including alcoholism and drug abuse.

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In our study, families ascertained through an autistic child were queried using the family history method (Andreasen *et al.,* 1986; Orvaschel *et al.,* 1982; Yuan *et al.,* 1996; Thompson *et al.,* 1982; Rice *et al.,* 1995; Davies *et al.,* 1997) to determine the prevalence and pedigree configuration of alcoholism and related neuropsychiatric disorders and to determine whether a family history of alcoholism correlates with any identifiable subset of individuals with autism.

METHOD

Subjects

The study sample consisted of 167 unrelated patients with infantile autism referred to the Autism Center at the University of Missouri-Columbia Hospitals and Clinics between 1994 and 2000. Of 333 consecutive patients referred to the Autism Center, 68 percent (227/333) met DSM-IV (American Psychiatric Association, 1994) and CARS (Childhood Autism Rating Scale) (Schopler *et al.,* 1986) criteria for the diagnosis of an autistic disorder. Autism spectrum diagnoses include 213 with infantile autism, 14 with Aspergers and 41 with PDD-NOS. Of the 227 patients with infantile autism or Aspergers, 167 had a complete family history and were included in this study.

Because this is the only comprehensive Autism Center in Missouri, patients were drawn from the entire state for diagnosis, medical management and recommendations for behavioral and school placement. There was no recognizable ascertainment bias toward more or less phenotypically abnormal, mentally retarded or multiplex subjects, and no exclusion of any individuals who met autism diagnostic criteria specified by DSM-IV, and CARS criteria. Each patient was evaluated by the Autism Center directors using our center based version of the ADI and ADOS scoring protocol and only those meeting criteria were included in the study. Independent diagnostic evaluations were conducted by a child psychiatrist and a neuropsychologist. The results were compared and in any case where there was a disparity, the individual was discussed jointly to reach a conclusion. A subset of patients were evaluated by the ADI-R (Lord *et al.,* 1994), and ADOS-G (Lord *et al.,* 1998) and in all cases the ADI-R and ADOS-G confirmed the previous diagnosis.

Clinical Evaluation

The Autism Center diagnostic evaluation utilized a standard data set for the collection of historical data including prenatal, teratogen exposure, perinatal, developmental, language, behavior, health history including allergies and traumas, medication, dietary, metabolic, neurologic and family history. All pertinent records including school, therapy, and IEP reports as well as psychological, developmental, and medical testing were reviewed. A detailed history of the onset of autistic symptoms was obtained including the age of onset of each symptom and whether delays and or losses occurred in language, gross motor, fine motor, activities or social interactions. Laboratory tests included G banded chromosomes, DNA for fragile X, urine metabolic screen, organic acids, urine and serum amino acids, short chain fatty acids, thyroid profile, CMP, heme profile and differential and lead level. Brain MRI and EEG were performed on 60% of the probands. Neurological and physical examinations were performed including standard morphologic measurements of the head, face, hands, feet, body proportions and dermatoglyphic analysis (Aase, 1990; Hall *et al.,* 1989; Jones, 1997). The skin was also examined with a Woods lamp. Parents and other available relatives were examined and family photographs were reviewed. Based on the physical examination, each proband was classified as having normal, abnormal or equivocal morphology; those with syndromes were considered separately. The method used for phenotypic classification has been described previously (Miles, & Hillman, 2000). Socioeconomic status was assessed using the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975). All study data were entered into a fully searchable relational database.

Family History Interview

Family history was obtained by direct semistructured interviews using the family history method (Andreasen *et al.,* 1986; Orvaschel *et al.,* 1982; Yuan *et al.,* 1996; Thompson *et al.,* 1982; Rice *et al.,* 1995; Davies *et al.,* 1997). All participants were sent a detailed history questionnaire prior to the initial evaluation so that information could be verified from available resources including baby books, journals and relatives. In the personal interview each informant was asked about each first, second and third degree relative individually and asked if that individual had medical, psychological/psychiatric or alcohol problems. The interview questions were based on the *Schedule for Affective Disorders and Schizophrenia Lifetime Version (SADS-L)* (Endicott & Spitzer, 1978; Harrington *et al.,* 1988), the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz *et al.,* 1994, 1995) and

the short computer interview for psychiatric diagnoses (Bucholz *et al.,* 1996) expanded for our protocol. For first degree relatives, if a diagnosis was unclear, medical and psychiatric records were requested. History was generally obtained from parents and grandparents (mothers = 151/167 (90.4%), fathers = 62/167 (37.1%), and grandparents = 8/167 (4.8%)).

Alcoholism Designation and High Alcohol Family Designation

Alcoholism was defined as excessive use of alcohol, tolerance to high amounts of alcohol consumption and/or negative consequences to family, jobs or health. During the family history interview, if a family member was said to have "alcoholism" or "problems with alcohol" or was reported to "drink too much," the informant was asked direct questions about the amount of alcohol consumed, the frequency of alcohol consumption, tolerance level, age of onset, treatment and outcome. Adult family members were rated as "unequivocally affected," "probably affected," "unknown," "unaffected" or "recovered." Individuals who did not consume alcohol either because of concern about the family history or for religious reasons, were coded "unknown." If individuals reported consuming alcohol but had no symptoms of alcohol abuse or dependence they were coded "unaffected." For this analysis, individuals rated as "unequivocally affected," "probably affected," or "recovered" were counted in the alcoholism group. Alcohol questions were derived from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz *et al.,* 1994, 1995) and the short computer interview for psychiatric diagnoses (Bucholz *et al.,* 1996).

Alcoholism prevalence ascertained through family history interviews resembles lifetime prevalence since family members were asked whether each family member had alcoholism currently or in the past. It is however an underestimate since some family members will be unaware of alcoholism in the family and because the individuals were not striated by age. In addition, the family history method does not distinguish between abuse and dependence since in most instances the informant would not be as aware of the dependence criteria, especially for second and third degree relatives. Since the majority of our study population are young children, sibling and cousin rates were not obtained.

In addition to counting the number of relatives with alcoholism, we developed a set of rules to distinguish between families whose family pedigrees revealed a "substantial genetic distribution of the alcoholism phenotype," consistent with an inheritance pattern, and those with scattered or only occassional affected relatives. A family history was rated as having "high alcoholism in a genetic distribution" if the proband had 1) a first degree relative with alcoholism (manifesting prior to concerns about the health of the proband), 2) a second degree relative plus at least two additional individuals in the same family branch in a pattern suggesting mendelian inheritance, or 3) alcoholism in at least four individuals all in the same branch of the family. Analogous analyses were done for autism, cognitive, language and affective disorders, dyslexia, ADHD and seizures.

Ruling Out Fetal Alcohol Syndrome

Due to reports of autism in children diagnosed with Fetal Alcohol Syndrome (FAS) (Aronson *et al.,* 1997; Harris *et al.,* 1995; Nanson, 1992), we needed to be certain we were not looking at a direct teratogenic effect of alcohol. Each autism proband was examined for features of FAS including microcephaly, increased height to weight ratio, smooth philtrum, long philtrum, thin upper lip, micrognathia, distal digital hypoplasia including small fingernails and excess fingertip arches, camptodactyly and hirsutism. None fit diagnostic criteria for FAS. There were two microcephalic individuals, neither of whom had other sentinel features of FAS. There was no significant difference in the common dysmorphic features observed in the probands from high vs. low alcoholism families. In fact, dysmorphic features generally were less frequent in the high alcoholism subgroup. One mother reported drinking heavily during her pregnancy and that child did not show features of FAS.

IQ Assessment

Each patient was assigned an IQ/DQ score based on the most recent and comprehensive neuropsychological evaluation. Children were evaluated by the Autism Center's neuropsychology team or recent results from the schools or other centers were used. When more than one set of test results were available, nonverbal IQ scores were used with the order of preferred testing being the Leiter-R (Roid, 1997), the WISC-III (Wechsler, 1991), and the Stanford Binet (Thorndike *et al.,* 1986). For younger children, developmental quotients, specifically standard scores from the Vineland (Sparrow *et al.,* 1984) were used. Children assessed by the neuropsychologist as untestable were classified as "unknown."

Statistical Analysis

Fisher's Exact Test or a Chi Square test of homogeneity was employed to compare proportions from the high and low alcohol groups. Chi square tests of independence were employed to investigate the relationship between autism, affective disorder and alcoholism. The Wilcoxen rank sum test was used to compare the female to male ratios in the low and high alcohol groups.

RESULTS

A high prevalence of alcoholism was reported in the 167 family study population; 13.5% of the first degree relatives and 13.6% of second degree adults were reported to have alcoholism including, 6.6% of mothers, 20.4% of fathers, 8.4% of grandmothers, and 27.5% of grandfathers (Table I). Men were significantly more likely to have a history of alcoholism than women (20.3% vs. 6.6%) $\chi^2(1) = 74.1$, $p < 0.0001$. Alcoholism rates in the autism ascertained families were compared to a control population of 22 families ascertained through a child with Down syndrome and to lifetime alcohol prevalence data reported by three large United States alcoholism epidemiological studies, including a Missouri rural and suburban cohort (Eaton *et al.,* 1989; Robins *et al.,* 1984; Kessler *et al.,* 1994; Grant, 1997). The Down syndrome families reported significantly less alcoholism in all family members ($p < 0.0001$), comprising 0% (0/44) of first degree relatives and 0.4% (l/234) of second degree relatives, 0% (0/22) of mothers, 0% (0/22) of fathers, 0% (0/44) of grandmothers, and 2.3% (1/44) of grandfathers. Compared to the 15.2% lifetime prevalence of alcoholism reported for suburban, small town and rural Missouri (Robins *et al.,* 1984), the overall 13.7% rate of alcoholism reported by the autism families was similar, $\chi^2(1) = 1.7$, $p = 0.19$. The women in our population, however, were significantly more likely to report alcoholism than all women in Missouri (6.6% vs. 4.3%); $\chi^2(1) = 7.1$, $p = 0.008$.

The 167 autism families were then separated into two groups based on the pattern of the alcoholism in each family. In 39% of the families (65/167) alcoholism followed a pattern consistent with our definition of a genetic trait; the remainder had sporadic alcoholism. Families and children whose pedigrees revealed an apparent genetic distribution of alcoholism (designated high alcoholism families) were compared with those

Table I. Alcoholism in Relatives of Autism Probands: Compare High and Low Alcoholism Families

Relatives	Relatives from all 167 families			Relatives from 65 high alcoholism families			Relatives from 102 low alcoholism families		
	Total N	Alcoholism		Total N	Alcoholism		Total N	Alcoholism	
		N	%		N	%		N	%
Mothers	167	11	6.6%	65	11	16.9%	102	0	0.0%
Fathers	167	34	20.4%	65	34	52.3%	102	0	0.0%
First degree adults	334	45	13.5%	130	45	34.6%	204	0	0.0%
Aunts	417	22	5.3%	157	22	14.0%	260	0	0.0%
Uncles	461	69	15%	182	54	29.7%	279	15	5.4%
Maternal aunts	198	10	5.1%	71	10	14.1%	127	0	0.0%
Maternal uncles	224	26	11.6%	93	18	19.4%	131	8	6.1%
Paternal aunts	219	12	5.5%	86	12	14.0%	133	0	0.0%
Paternal uncles	237	43	17.7%	89	36	40.4%	148	7	4.7%
Aunts/uncles	878	91	10.4%	339	76	22.4%	539	15	2.8%
Grandmothers	334	28	8.4%	130	23	17.7%	204	5	2.5%
Grandfathers	334	92	27.5%	130	56	43.1%	204	36	17.6%
Maternal Gmothers	167	10	6.0%	65	9	13.8%	102	1	1.0%
Maternal Gfathers	167	45	26.9%	65	27	41.5%	102	18	17.6%
Paternal Gmothers	167	18	10.8%	65	14	21.5%	102	4	3.9%
Paternal Gfathers	167	47	28.1%	65	29	44.6%	102	18	17.6%
Grandparents	668	120	18.0%	260	79	30.4%	408	41	10.0%
Second degree adults	1546	211	13.6%	599	155	25.9%	947	56	5.9%
Second degree females	751	50	6.7%	287	45	15.7%	464	5	1.1%
Second degree males	795	161	20.2%	312	110	35.2%	483	51	10.6%
First degree & second degree adults	1880	258	13.7%	729	200	27.7%	1151	56	4.9%
First degree & second degree females	918	61	6.6%	352	56	15.9%	566	5	0.9%
First degree & second degree males	962	195	20.3%	377	144	38.2%	585	51	8.7%

that did not (low alcoholism families) (Tables I to V). Probands from the two groups had similar ages, CARS scores, socioeconomic status (SES) and fulfilled DSM-IV criteria (Table II). However, the high alcoholism families did have a significantly higher proportion of affected (alcoholic) females. In the high alcoholism families, the number of female alcoholics was 18 times the number in the low alcoholism families, whereas males were only 4 times more likely to be alcoholic (15.9% vs. 0.9% females; 38.2% vs. 8.7% males) (Table I). For statistical analysis, the fraction of

alcoholic females was compared to the fraction of alcoholic males in each family. The ratio of female to male alcoholics was significantly higher in the high alcoholism families compared to the low (0.46 vs. 0.052, $p = 0.0001$). Compared with unselected Missouri families (Robins *et al.,* 1984), the females in our autism ascertained population were 1.5 times more apt to be alcoholic and females from the high alcohol families were 3.7 times more apt to be alcoholic.

Autistic children from the high alcoholism families were similar to those from low alcoholism families

Table II. Proband Characteristics

	High alcoholism families N = 65 (39%)		Low alcoholism families N = 102 (61%)	
Mean age at ascertainment	7.7 ± 6.1		8.6 ± 7.2	
Age range	(1.1–39.8)		(1.0–41.2)	
Socioeconomic status				
Group I & II	18/50	36.0%	45/89	50.6%
Group III	14/50	28.0%	23/89	25.8%
Group IV & V	18/50	36.0%	21/89	23.6%
DSM-IV avg # criteria met	8.0		8.0	
Mean CARS score	37.2		37.9	

Table III. Phenotypic and Clinical Features

	High alcoholism families N = 65		Low alcoholism families N = 102		*p* value
Dysmorphology category					
Nondysmorphic	50/65	76.9%	70/102	68.6%	NS
Equivocal	7/65	10.8%	15/102	14.7%	NS
Dysmorphic	4/65	6.2%	11/102	10.8%	NS
Syndromes	4/65	6.2%	6/102	5.9%	NS
Head circumference mean (SD)[a]	0.47 (1.2)		0.75 (1.4)		0.0591
Macrocephalic[a]	9/61	14.7%	39/96	40.6%	0.0006
Normocephalic[a]	50/61	82.0%	50/96	52.1%	0.0001
Microcephalic[a]	2/61	3.3%	7/96	7.3%	NS
Onset with regression[b]	31/59	52.5%	34/95	35.8%	0.04

[a]Comparisons exclude probands diagnosed with an autism related syndrome.
[b]2 probands in high alcoholism group and 1 in the low group have unknown onset status.

Table IV. Outcome Measures[a]

Outcome measures	High alcoholism families N = 61		Low alcoholism families N = 96		*p*
IQ > 70	26/48	54.2%	25/68	36.8%	0.063
IQ 55–70	11/48	22.9%	24/68	35.3%	NS
IQ < 55	11/48	22.9%	19/68	27.9%	NS
Total with IQ ≤ 70	22/48	45.8%	43/68	63.2%	0.063
Mean IQ (SD)	70.4 (25.3)		67.5 (24.8)		NS
IQ range	25–131		20–160		NS
Seizures	17/61	27.9%	16/96	16.7%	0.093

[a]Comparisons exclude probands diagnosed with an autism related syndrome.

Table V. Genetic Features[a]

Genetic features	High alcoholism families N = 61		Low alcoholism families N = 96		All families N = 157		High vs. low alcoholism p value
Male : female ratio	52:9	5.8:1	76:20	3.8:1	136:31	4.4:1	NS
Recurrence in sibs of true autism	4/71	5.6%	4/138	2.9%	8/209	3.8%	NS
Recurrence in sibs of broad autism phenotype[b]	10/71	14.1%	11/138	8.0%	21/209	10.0%	NS
Latter sib method of true autism	2/25	8%	2/65	3.1%	4/90	4.4%	NS
Latter sib method of broad autism phenotype[b]	3/25	12%	7/65	10.8%	10/90	11.1%	NS
Significant family history[c]							
Autistic disorder	15/61	24.6%	14/96	14.6%	29/157	18.5%	NS
Alcoholism	61/61	100%	0/96	0%	61/157	38.8%	—
Affective disorder	31/61	50.8%	23/96	24.0%	54/157	34.4%	0.0006
Cognitive disorder	21/61	34.4%	27/96	28.1%	48/157	30.6%	NS
Language disorder	17/61	27.9%	22/96	22.9%	39/157	24.8%	NS
Dyslexia	5/61	8.2%	7/96	7.3%	12/157	7.6%	NS
ADHD	14/61	22.9%	14/96	14.6%	28/157	17.8%	NS
Seizures	9/61	14.7%	8/96	8.3%	17/157	10.8%	NS

[a]Comparisons exclude probands diagnosed with an autism related syndrome.
[b]Broad phenotype includes infantile autism, PDD-NOS, Aspergers and significant autistic traits.
[c]Significant family history designation follows classification rules outlined in the methods section.

in dysmorphology status, IQ distribution, occurrence of seizures, sex ratio and sib recurrence risks. However, they differed in two aspects. First, children from the high alcoholism families were much less likely to be macrocephalic than children from low alcoholism families (14.7% vs. 40.6%), $\chi^2(1) = 11.76$, $p = 0.0006$ (Table III). Second, children from the high alcoholism families were more apt to have experienced a regressive onset (52.5% vs. 35.8%) $\chi^2(1) = 4.19$, $p = 0.04$. This was found predominately in families where the mother was alcoholic (80% vs. 40%) $\chi^2(1) = 5.36$, $p = 0.05$ (Table IV). There was no correlation with paternal alcoholism. Similar analyses were done for each of the physical and genetic features and outcome measures and in no other instance, did the results diverge depending on which parent was alcoholic.

Our third observation was that high alcoholism families had more relatives with affective disorders, also distributed in a familial pattern (50.8% vs. 24%), $\chi^2(1) = 11.93$, $p = 0.0006$ (Table V). This is consistent with previous studies of alcoholism which report an association between alcoholism and affective disorders in families (Kendler *et al.,* 1993; Bierut *et al.,* 1998; Tsuang *et al.,* 1998). A significant family history of alcoholism did not associate preferentially with any other family history categories (cognitive, language, dyslexia, ADHD or seizures). Because having a significant family history of affective disorders was almost

as common as alcoholism (Table V), separate analyses were performed to see whether the children from families with high vs. low frequencies of affective disorders differed in their physical features, genetic features or outcome measures (data not shown). The 54 families (34%) with a significant family history of an affective disorder showed no difference in the frequency of regressive autism, macrocephaly or other features.

To look for evidence of genomic imprinting of a putative alcohol/autism gene, each of the 65 pedigrees was scored as consistent or inconsistent with paternal or maternal imprinting (maternal grandfathers affected but not the mothers = possible male imprinting; maternal grandfathers and mothers affected = inconsistent with male imprinting; paternal grandmother affected but not the father = possible maternal imprinting; paternal grandmother and father affected = inconsistent with maternal imprinting). Pedigrees where male imprinting was ruled out (both the mother and her father were alcoholic) had more probands with regression (71.4% vs. 47.4%) than when male imprinting was possible.

DISCUSSION

Autism and alcoholism are both highly heritable but heterogeneous disorders for which there is biochemical

and clinical evidence of some shared genetic causes. Dysregulation of the major neurotransmitter systems for serotonin and dopamine occur in autism (Anderson, 1987; McBride *et al.,* 1990; McBride *et al.,* 1998; Gordon *et al.,* 1993; Cook *et al.,* 1993; Cook & Leventhal, 1996; Robinson *et al.,* 2001) and in alcoholism (Lovinger, 2000, 199l; Zhou & Lovinger, 1996; Di Chiara & Imperato, 1988; Koob, 1992; Wise & Bozarth, 1987; Hemby *et al.,* 1997; Bloom & Morales, 1998; Barnes & Sharp, 1999; Sander *et al.,* 1998; Heinz *et al.,* 2001). Empirically, there is some overlap of the drugs used in the treatment of autism and alcoholism, especially the selective serotonin reuptake inhibitors which modify the craving for alcohol (Johnson & Ait-Daoud, 2000; Pettinati *et al.,* 2000) and decrease or attenuate some autism symptoms (Awad, 1996; Cook *et al.,* 1992; Cook & Levanthal, 1996; McDougle *et al.,* 1998; Posey *et al.,* 1999; McDougle *et al.,* 2000). There may be some overlap of candidate gene areas on chromosomes 1p, 7p, 16p and 19p identified though genome-wide screens of both disorders (Risch *et al.,* 1999; Reich *et al.,* 1998; Liu *et al.,* 2001; Valdes *et al.,* 1999; Foroud *et al.,* 1998; Nurnberger *et al.,* 2001). And finally, previous studies have also found that alcoholism occurs frequently in autism families ranging from 12.3% of parents to 22.1% of first degree adults (Piven *et al.,* 1991a; Abramson *et al.,* 1992; Smalley *et al.,* 1995; Piven & Palmer, 1999). These associations support our hypothesis that these two discrete neuropsychiatric disorders share one or more genes that predispose to both disorders.

We have documented high alcoholism rates in families ascertained through a child with autism, with a very high prevalence in the subset of families where alcoholism appears to be segregating as a highly penetrant genetic disorder. To verify that the autism families have higher than average rates of alcoholism, we compared our results with a number of control populations. An internal control population was recruited specifically for this study, composed of families whose children were referred to the Down Syndrome Clinic. This population was selected because of certain similarities to the autism families; both had been referred and chose to bring their child to a University Clinic and both sets of families experienced stresses coincident to having a child with special needs. The families were recruited with the instruction that they must be willing to disclose all instances of behavioral and neuropsychiatric disorders in their families. Nevertheless, the reports of alcoholism in the Down syndrome ascertained families were unreasonably low in all categories with only 4% (l/22) of the families having a history of

any alcoholism, with 0% of first degree relatives and 0.4% of second degree relatives affected. We also enumerated the control family data reported in the autism literature (Lobascher *et al.,* 1970; Piven *et al.,* 1991a; Bolton *et al.,* 1998; Abramson *et al.,* 1992; Smalley *et al.,* 1995; Piven & Palmer, 1999); the frequency of alcoholism in first degree relatives of control probands was, again, much less than in our study population (0% [0/166] vs. 13.5% [45/334]); $\chi^2(1) = 24.58$, $p < 0.001$. Though both these comparisons support our assertion that families ascertained through a child with autism have significantly more alcoholism, we think that Down syndrome family histories are not comparable to autism family histories and thus don't provide satisfactory or acceptable controls. Parents of children with autism are often aware that autism may be associated with other neuropsychiatric disorders in family members, and, therefore are more likely to reveal that information in the family history interview. By contrast, the families of children with Down syndrome are counseled early and often that trisomy 21 is a chance event over which they had no control and which is unrelated to anything else in the family history or anything that happened in the pregnancy. Thus, even if they are asked about alcoholism, Down syndrome parents are likely to discount the importance of the information and not report it. Also, in our autism clinic the parents are aware of the research activities of our center and know that we are trying to ascertain information that may eventually be useful in the treatment of autism. Consequently, they make every effort to provide accurate and complete family histories. For these reasons, we think that the differences between the autism and Down syndrome families introduce a strong and unacceptable bias which makes family history data comparisons moot.

To obviate these difficulties, we compared alcoholism rates in the autism families to alcoholism prevalence data reported by three large United States epidemiologic studies (Eaton *et al.,* 1989; Robins *et al.,* 1984; Kessler *et al.,* 1994; Grant, 1997; Dawson & Grant, 1998). Each of the studies reported a lifetime prevalence rate defined as the proportion of the sample who had ever experienced alcoholism. Though the epidemiologic studies differed by whether they attempted to diagnose alcohol dependence or abuse, their results were remarkably similar. The Epidemiologic Catchment Area (ECA) program, reported by Robins *et al.* (1984), was of interest to us because it ascertained alcoholism in Missouri. In the Missouri population, they reported 15.7% (±0.9) lifetime prevalence of either alcohol abuse or dependence with the highest rate (19.4% [±2.1]) in the central city, 15.9% [±1.1] in the

suburban population and 14% [±1.7] in small towns and rural areas. Our finding of 13.7% alcoholism in autism families was not significantly different from that reported by Robins for rural and suburban Missouri populations. The more recent NLAES study (Grant, 1997) reported a 13.3% lifetime dependence. The National Comorbidity survey (Kessler *et al.,* 1994) reported abuse and dependence separately and their additive result was higher than our alcoholism rate and higher than the rates reported in the ECA and NLAES studies. Male predominance was reported in all studies.

Comparing our data to the epidemiologic studies requires certain adjustments. Epidemiologic studies, which utilize direct face-to-face interviews, are expected to detect significantly higher histories of alcoholism than a family history study which uses only one reporting source for the entire family. On the other hand, the family history method offers advantages. In the clinical setting, the family history method is relatively inexpensive. And, the specificity rates for psychiatric disorders have been shown to be high, particularly for major psychiatric illnesses, including alcoholism and affective disorders (Thompson *et al.,* 1982; Rice *et al.,* 1995; Davies *et al.,* 1997). The principal disadvantage is the lower sensitivity. An alcohol family study by Yuan *et al.* (1996) used methods analogous to ours and reported a 94% specificity for detecting alcoholism with a sensitivity of 68%. The conclusion is that data obtained through the family history method will always be an underestimate because the family reporter either may not be aware of the diagnosis in family members or may not reveal that information. If we assume the same sensitivity of 68% in our autism families, the estimated prevalence of alcoholism would be 22% for adults, 30% for men, and 10% for women, which is significantly higher than the lifetime prevalence data obtained by Robins *et al.* (1984). Thus, we conclude that the similarity of our alcoholism prevalence rates to that reported from the epidemiologic studies, is evidence that alcoholism is more prevalent in relatives of children with autism than in the general population.

Since alcoholism, like autism, is an etiologically heterogeneous disorder (Johnson *et al.,* 2000; Babor *et al.,* 1992; Brown *et al.,* 1994; Litt *et al.,* 1992; George *et al.,* 1999), we wanted to distinguish families with strongly genetic alcoholism from those with only sporadic or occasional cases that might be more environmentally induced. Using strict rules to pick out the families with clusters of alcoholism, we classified 39% (65/167) of the families as having probable genetic alcoholism. These 65 families had a high percentage of affected relatives in all categories, with 17% of mothers, 52% of fathers, 14% of maternal grandmothers, 41% of maternal grandfathers, 21% of paternal grandmothers and 45% of paternal grandfathers reported as alcoholic (Table I). The remaining 102 families reported scattered individuals with alcoholism in unrelated branches of the family (less than 1% of females and less than 10% males). Comparing families with apparent genetic alcoholism to those with sporadic alcoholism revealed a significant increase in alcoholism rates in each relative category ($p < 0.001$ for all, except maternal uncles which was $p < 0.005$). Though higher raw alcoholism rates were anticipated in these families since the procedure for designating familial clusters required that one to four family members have alcoholism, the distinction based on the pedigree structure split the families clearly into high and low alcoholism incidence groups. The alcoholism rate in the high alcohol families was 27.7% (202/729), which is twice the lifetime prevalence reported for rural Missourians (Robins *et al.,* 1984) and 5.7 times that in the low alcoholism families. In the low alcoholism families, the rate was 4.9%, which is comparable to the rate of alcoholism in the Down syndrome control families. We believe that this association between autism and high rates of alcoholism indicates that there is a type of alcoholism that is both genetically mediated and highly penetrant and which predisposes to the development of autism.

In this study we attempted to begin to define the nature of both the alcoholism and the autism that cosegregates in these families. The primary distinction between alcoholism in the autism families and in control populations was the higher proportion of affected women. Women from autism families had significantly higher rates of alcoholism than those reported by the ECA Missouri epidemiologic study (6.6% [61/918] vs. 4.3% [77/1802]; $\chi^2(1) = 7.1$, $p = 0.008$) (Robins *et al.,* 1984). This was accentuated in the high alcoholism families, where women alcoholics were 3.8 times more common than in Missouri generally; the rate for male alcoholics was only 1.3 times the rate for Missouri men (Robins *et al.,* 1984).

Comparisons between the high and low alcoholism families did not reveal significant differences in the age of the autistic proband, socioeconomic status, DSM-IV criteria met, CARS scores, dysmorphology status, IQ distribution, seizures, sex ratio or recurrence risks. This suggests that, whatever the effects of the presumed alcoholism gene(s), the autism phenotype is not conspicuously changed. Subtle differences in language, social relatedness or repetitive behaviors, however,

can't be ruled out, since this study did not explore variations in the autism behavioral phenotype.

We found, however, two phenotypic differences between the autism probands from the high and low alcoholism families. First, children from the high alcoholism families were 2.8 times *less likely* to be macrocephalic (14.7% vs. 40.6%, $\chi^2(1) = 11.76$, $p = 0.0006$). Macrocephaly, defined as a head circumference greater than the 98th centile, is an important physical feature in autism, which occurs in about 20% of autistic individuals (Bolton *et al.,* 1994; Bailey *et al.,* 1995; Davidovitch *et al.,* 1996; Stevenson *et al.,* 1997; Woodhouse *et al.,* 1996; Lainhart *et al.*, 1997; Fombonne *et al.,* 1999; Miles *et al.,* 2000). We had noted this inverse relationship between macrocephaly and alcohol family histories in our previous study of head circumference and autism (Miles *et al.,* 2000), as only 20.7% of macrocephalic probands had strong histories of addictive disorders, compared with 37.2% of the normocephalic probands. In that study we also observed that macrocephaly in autism was highly familial with 45% of the macrocephalic autistic children having at least one macrocephalic parent. This is consistent with studies in non-autistic families which show that parental head circumference is the major predictor of head circumference in children (Schreier *et al.,* 1974; Weaver & Christian, 1980). We concluded from that data that there must be gene(s)which cause macrocephaly and also predispose to autism, and that non-autistic macrocephalic parents may be carrying gene(s) that put them at risk for having a child with autism. Recently, Bolton *et al.* (2001) confirmed our observation, reporting that infantile macrocephaly was associated with an increased risk of developing an autistic disorder with an odds ratio of 5.44. Our present data indicate that the gene(s) that cause macrocephaly and autism are different and operate independently from the gene(s) that cause alcoholism and autism. Future analy-

ses of sibling risks in these families will determine whether alcoholism and macrocephaly are independent, additive risk factors for developing autism.

The type of autism onset, with or without a loss of language, is a key feature of autism (Kurita, 1985, Tuchman & Rapin, 1997; Shinnar *et al.,* 2001, Lainhart *et al.,* 2002). We reported previously that children with "essential autism," defined as having a normal morphologic examination, non-microcephalic head circumference and structurally normal brain by MRI, were more apt to present with loss of language (44% vs. 28%, $p = 0.035$) (Miles *et al.,* 2001). In the current study, we found that the autistic children from high alcoholism families were also more likely to develop regressive autism than children from the low alcohol families (52.5% vs. 35.8%, $p = 0.04$) (Table III). In addition, the development of regressive autism correlated with the parental origin of the alcoholism (Table VI). When the mother was alcoholic, the children were more apt to develop regressive autism [mother alcoholic 8/10 (80%) vs. mother not alcoholic 20/50 (40%)], $\chi^2(1) = 5.36$, $p = 0.05$. This raised the question of a direct teratogenic effect of alcohol on the developing fetus, however, only one mother with a history of alcoholism reported drinking during the pregnancy. And in all of the children, fetal alcohol syndrome was ruled out by careful physical examinations. A second possibility which was considered, was male imprinting of a autism/alcoholism gene. However, in the pedigrees where male imprinting was ruled out (both the mother and her father were alcoholic) there were more probands with regression (71.4% vs. 47.4%) than when male imprinting was possible. This suggests that, in these families, male imprinting of the putative autism/alcoholism gene does not lead to regressive autism. The third possibility was that regressive autism was more common when both parents were alcoholics. This could not be completely ruled out since in 9 out of 10 families with

Table VI. Regressive Autism Related to the Sex of the Alcoholic Parent[a]

	Significant family history of alcoholism N = 61		Mother affected N = 11		Mother not affected N = 50		Father affected N = 31		Father not affected N = 30		Mother only affected N = 1		Father only affected N = 21		Both parents affected N = 10	
Regressive autism	28/59[c]	47.5%	8/10	80%	20/50	40%	13/31	41.9%	15/30	50%	1/1	100%	6/21	28.6%	7/9	77.8%
				$p = 0.05$[b]					NS							

[a]Comparisons exclude probands diagnosed with a known autism syndrome.
[b]Fishers Exact Test.
[c]Two individuals with unknown onset history.

an alcoholic mother, the father was also alcoholic. However, since regressive autism occurred in just 28.6% of families with only paternal alcoholism, a stronger maternal effect remains more likely. Theoretically, a maternal factor is of interest since recent studies have reported that autism is associated with the maternal dopamine β-hydroxylase alleles and that there is sib concordance for maternal, but not paternal alleles, linked to dopamine, serotonin and norepinephrine transmitters (J. J. A. Holden, personal communication, 2003; Robinson *et al.,* 2001). Clarification of our association between regressive autism and maternal alcoholism will depend on replication of the studies in a larger sample of families. Nevertheless, it does recommend that for autism, like other complex disorders (Labuda *et al.,* 2002) parental genotypes should be considered as possible risk factors.

Our third observation was that the high alcoholism families also had strong family histories of affective/depressive disorders. This is consistent with previous family studies of alcoholism which report a 0.50 genetic correlation between alcoholism and affective disorders (Kendler *et al.,* 1993; Bierut *et al.,* 1998; Tsuang *et al.,* 1998). Autism families also have been reported to have significant depression ranging from 2% to 33% first degree relatives (Smalley *et al.,* 1995; Bolton *et al.,* 1998; Miles *et al.*, 1999; Piven & Palmer, 1999; DeLong, 1999; Murphy *et al.,* 2000). Piven *et al.* (1991a), found no significant comorbidity between major depression and alcoholism in parents of 42 autistic probands.

Our data provide some information on the nature of this association between autism, alcoholism, and depression. Numerous family, adoption, twin and population based studies have investigated the genetic predisposition toward depression and alcoholism and their comorbid occurrence (see reviews in Bukstein *et al.,* 1989; Cloninger *et al.,* 1979; Hill, 1993; Merikangas & Gelernter, 1990; Dawson & Grant, 1998, Prescott *et al.,* 2000). Of our 167 autism families, 34% reported a history of depressive disorders, compared to 39% for alcoholism. The families with alcoholism were more apt to also have a family history of affective disorders (50.8% vs. 23.5%, $p = 0.0005$). If the association between depression and alcoholism were independent, 13% (.39 × .34) would be expected to have both. Rather, 21% had family histories of both disorders, indicating a significant genetic overlap between alcoholism and depression. We concentrated on the relationship between autism and alcoholism, since in family history studies, alcoholism can be documented with higher specificity and sensitivity than depression. Future work, perhaps utilizing more sensitive measures

of major depression, will be necessary to clarify the genetic association between autism and alcoholism with and without depression.

With this clear observation of alcoholism in autism families, it is surprising that there is no mention in the alcohol literature of an association with autism. The most likely explanation is that the incidence of alcoholism is so much greater than autism that the study size would have to be very large to consistently detect an appreciable number of children with autism. The association could also be missed if studies were directed toward determining correlations with adult disorders. Moreover, the prevalence of autism in families ascertained on the basis of any proband with alcoholism may be quite low if only a subgroup of alcoholism is caused by the genes which also contribute to autism.

In summary, in a large population, ascertained on the basis of a child with autism, 39% of families had a high incidence of alcoholism in patterns consistent with genetic inheritance. Families with an apparent genetic cluster of alcoholism were more apt to have children with a normal head circumference (not macrocephalic) and with regressive onset autism. Regressive autism was associated with maternal alcoholism, supporting the hypothesis that there is a maternal effect on the development of autism. Moreover, we have put forth a model that can be tested in the laboratory, which postulates that the parental genotype is an important factor in autism development.

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