UC Irvine

UC Irvine Previously Published Works

Title

Autism and tuberous sclerosis.

Permalink

<https://escholarship.org/uc/item/0k7463tx>

Journal

Journal of autism and developmental disorders, 22(3)

ISSN

0162-3257

Authors

Smalley, SL
Tanguay, PE
Smith, M
et al.

Publication Date

1992-09-01

DOI

10.1007/bf01048239

Copyright Information

This work is made available under the terms of a Creative Commons Attribution License, available at
<https://creativecommons.org/licenses/by/4.0/>

Peer reviewed

Autism and Tuberous Sclerosis¹

Susan L. Smalley and Peter E. Tanguay

Department of Psychiatry, University of California-Los Angeles

Moyra Smith

Department of Pediatrics, University of California-Irvine

Griselda Gutierrez

Department of Psychiatry, University of California-Los Angeles

Autism is a behavior disorder with genetic influences indicated from twin and family studies and from the cooccurrence of autism with known genetic disorders. Tuberous sclerosis complex (TSC) is a known genetic disorder with behavioral manifestations including autism. A literature review of these two disorders substantiates a significant association of autism and TSC with 17–58% of TSC subjects manifesting autism and 0.4–3% of autistic subjects having TSC. In initial data collected on 13 TSC probands and 14 autistic probands in our family study of autism and TSC, we identified 7 TSC subjects with autism. The seven TSC autistic probands are similar to non-TSC autistic probands on the Social and Communication domains of the Autism Diagnostic Inventory (ADI) (Le Couteur et al., 1989), but show fewer Repetitive Rituals. There are more male TSC probands with autism than female, despite an equal sex ratio among TSC probands. The TSC probands with autism have significantly more seizures and mental retardation than those without autism; however, the extent and etiology of associations require further study. Our preliminary findings suggest that a fruitful approach for delineating genetic influences in autism may come from further investigation of possible mechanisms underlying the association of autism and TSC.

¹This work was supported by an NIMH grant #1RO1MH44742-01 and by NIH grant #2RO1HD23745. We acknowledge Cathy Lord for her advice regarding the ADI and Robin Gilson for her help in data collection. We also thank all the family members who have participated in this project for their commitment and enthusiasm for this research.

Autism is a pervasive developmental disorder with onset in infancy or childhood characterized by severe impairments in social interactions, verbal and nonverbal communication including imaginative activity, and restricted activities and interests (American Psychiatric Association, 1987). Family and twin studies in autism support genetic involvement but a single mode of genetic transmission is unlikely (Folstein & Rutter, 1988; Rutter, 1991; Smalley, Asarnow & Spence, 1988). Genetic heterogeneity in autism is indicated from the cooccurrence of autism with known genetic disorders including fragile X, untreated phenylketonuria, and tuberous sclerosis (Reiss, Feinstein, & Rosenbaum, 1986). The present investigation reviews the literature regarding the association of autism with tuberous sclerosis, presents new data regarding the cooccurrence of autism with this genetic disorder, and discusses possible mechanisms underlying this association.

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by benign tumors (hamartomas) and malformations (hamartias) of one or more organs, most notably, the central nervous system, skin, retina, kidneys, and the heart (Gomez, 1988, 1991). Genetic heterogeneity is evident in TSC from linkage studies suggesting genes on the long arms of chromosome 9 and possibly chromosome 11 (for review, see Johnson & Gomez, 1991). There is a great deal of phenotypic variation in TSC; however, no specific clinical criteria have been identified, as yet, that differentiate genetically homogeneous subgroups.

There are numerous case reports of autism and other behavioral problems occurring in patients with TSC. We searched the TSC literature for all case reports in which behavior problems *other than mental retardation and seizures* were noted. Fifty cases were identified and a summary of the behaviors noted is listed in Table I. Behavioral categories listed in Table I represent the most often used label for different behaviors. For example, AGG includes behaviors described as aggressive as well as destructive, abusive, violent, delinquent, and assaultive.

Three behavioral problems seem to predominate in TSC based on these case reports: (a) autism or autistic-like behavior (36%), (b) hyperactive or impulsive behavior (26%), and (c) aggressive or destructive behavior (48%). The estimated frequencies of these behaviors based on case reports (rather than a systematic study) are probably biased due to variations in behavioral diagnoses and case reporting, as suggested from the higher proportion of mental retardation (64%) and the unequal sex ratio compared with epidemiological TSC samples (Osborne, Fryer, & Webb, 1991). The frequency of mental retardation may be underestimated in these case reports because we only denote the presence of mental retardation in Table I; the absence of mental retardation in some cases may reflect the failure of the author to discuss cognitive functioning in the case report. There

Table 1. Summary of Behavior Problems in TSC Based on Case Reports^a

Reference	Case no.	Age	Sex	AUT	AUTL	SI	HYP	IMP	AGG	UNC	IRR	SHY	SCZ	STE	OTH	LAN	MR	SZ
Finlayson, 1955	1	8	F						X	X							X	X
	2	8	M				X			X						X	X	X
	3	10	F					X	X	X		X					X	X
	4	14	M												X	X	X	X
	5	19	M												X	X	X	X
	6	28	M												X	X	X	X
	7	10	F						X	X				X			X	X
Jordan, 1956	8	8	M			X	X			X				X	X	X	X	X
	9	8	M											X	X	X	X	X
	10	39	F											X	X	X	X	X
	11	16	F						X	X			X	X			X	X
Cares, 1958	12	14	M						X	X		X	X					X
	13	42	M															X
	14	12	M		X		X			X	X	X	X		X	X	X	X
Dick & Ziegler, 1967	15	6	F				X			X								X
	16	12	F											X			X	X
Tiwari, Srivasta, & Agarwah. 1968	17	7	F				X									X	X	X
	18	<1	F								X							X
Roth & Epstein, 1971	19	4	F									X			X			X
	20	4	F		X					X		X			X	X	X	X

Table 1. Continued

[illegible]

were twice as many males than females in the pooled sample of case reports suggesting that either behavioral problems are more common among TSC males or there is more case reporting of behavioral problems in TSC which are more common among males (e.g., autism and hyperactivity) in the general population.

There are five published *systematic* studies of behavioral problems in TSC, to our knowledge. Critchley and Earl (1932) examined 29 subjects with TSC (the sex of subjects was not specified) in which 28 had mental retardation and a variety of behavioral problems including psychoses, echolalia, perseverative speech, and hand and finger stereotypies. Individual behaviors were described for some of the cases but no clinical diagnoses were made; however, the authors suggested that psychopathology may represent a *forme fruste* or variation in expression of a TSC gene based on the substantial psychopathology identified in the TSC patients and their relatives. Hunt (1983a) collected questionnaire data on 97 tuberous sclerosis subjects (47 male, 50 female) ranging in age from 1 to 51 years in Great Britain. Of these TSC subjects, 82 had seizures and 66 of these had their onset in infancy. The authors reported behavioral problems in 71% of the 82 TSC patients with seizures, 81 of whom were also mentally retarded (Hunt, 1983b). Information regarding autism was not collected in this study. Hyperactivity was reported in 27% and destructive and/or aggressive behavior in 22% of the subjects. Screaming (17%), temper tantrums (11%), and sleeplessness (8%) were among other behavior problems noted in the sample. Unfortunately, the authors did not report on the sex of the TSC patients with behavioral problems.

In a second evaluation of TSC patients, Hunt and Dennis (1987) collected questionnaire- and interview-based data on autism in 90 TSC subjects. Although the sex of these subjects was not specified, families were identified in a previous study where there were approximately equal numbers of males and females (Hunt, 1983a). A 321-item interview schedule was used as well as medical records to obtain information on family life, clinical signs of TSC, and behavior. Social impairment and autism, based on Rutter's criteria, were assessed using 13 questions tapping specific behaviors (e.g., "How does X get along with other children," "Does X stay aloof in a group," "Is X very attached to one object?"). A cutoff score of 7 was used to indicate possible autism with diagnoses confirmed by medical records. Among the 90 TSC subjects, 69 (77%) had reported infantile spasms with onset prior to 17 months of age. Using these 69 subjects, the authors found that 58% met criteria for autism at age 5, although three of the cases no longer met criteria for autism in adolescence. This frequency of autism is substantially greater than the 12.5% observed in a sample of 192 subjects (8 of whom had TSC) with infantile spasms (Riikonen

& Amnell, 1981). The proportions of TSC males and females with these problems were not reported.

Riikonen and Simell (1990) reported the frequency of autism, hyperkinetic behavior, and other behavioral problems in 24 TSC patients (sex not specified) identified from a sample of subjects ascertained because of infantile spasms. They found that among these 24 TSC patients with infantile spasms and mental retardation, 17% were autistic, 21% hyperactive, and 4% (i.e., 1 case) had poor social contact and extreme shyness. Curatolo et al. (1991) reported behavioral problems in 34 (17 male, 17 female) TSC patients ranging in age from 5 months to 18 years. All subjects had seizures with 88% of the patients having seizures beginning in the first year of life. Of 23 subjects 5 years and older, 70% had mental retardation based on an IQ score < 69. The investigators found 26% of these 23 subjects met criteria for infantile autism defined as a score of 10 or greater on the 13-item questionnaire used by Hunt and Dennis (1987). In addition, 34% were hyperactive (including 3 cases with autism), and 7% had aggressive and obsessive behavior.

These studies support a significant association of autism and TSC based on the increased frequency of autism among TSC subjects (frequencies vary from 17 to 58%) compared with the general population (frequency approximately 0.05%) and compared with a population having infantile spasms but not TSC (approximately 12%, based on the Riikonen and Amnell, 1981, sample *excluding* 8 TSC subjects in that sample). If autism and TSC are associated, there should also be an increased frequency of TSC subjects among autistic subjects compared with the general population frequency of TSC of 0.01% (Gomez, 1988; Osborne et al., 1991).

There are seven systematic studies of autism (five epidemiologically based and two clinically based), to our knowledge, in which the frequency of TSC among autistic populations has been reported. Creak (1963) found 1 case of TSC in 100 cases (1%) of psychoses in children. Lotter (1967) reported 1 case of TSC among 32 autistic subjects (3%) identified in an epidemiological study in England. Olsson, Steffenburg, and Gillberg (1988) found 1 case of TSC among 35 children with infantile autism (2.8%) identified in an epidemiological study of autism in Sweden. Ritvo et al. (1990) found only 1 case among 233 cases of autism (0.4%) in their epidemiological study of autism in the State of Utah. Gillberg, Steffenburg, and Schauermann (1991) found 1 TSC subject among 55 individuals with autistic disorder (1.89%) identified in an epidemiological study of autism in western Sweden. Riikonen and Amnell (1981) identified 24 autistic subjects among 192 subjects with infantile spasms, identified in their study of infantile spasms. Two of these 24 autistic subjects had TSC, a frequency of 8%. Gillberg (1991) found 14% of 66 autistic subjects *with* seizures to have TSC.

These six reports substantiate an association of autism and tuberous sclerosis based on the increased frequency of TSC among autistic populations (i.e., 0.4 to 3%) compared with the frequency in the general population (i.e., 0.01%) (Osborne et al., 1991). Furthermore, if a subset of autistic subjects with seizures are examined, the frequency of TSC is even greater, estimated at 8–14%.

Even though the frequency of TSC among autistic samples is significantly greater than the population frequency of TSC, these frequencies (0.4–3%) may be underestimated for two reasons. First, TSC cases in these studies are primarily identified through medical records or, as in the case of Lotter (1967), identified via an autopsy report. Given the great degree of phenotypic variation in TSC, there may be cases that are not identified because an ultraviolet light examination and CT or MRI scans are not routinely done in autism. Second, autistic subjects with TSC may be underrepresented in autistic samples identified in population-based studies of autism because a medical diagnosis, such as TSC, may replace a diagnosis based only on behavior sequelae and such cases may be missed in the screening procedures.

Nevertheless, these reports substantiate a significant association of autism and tuberous sclerosis given that the expected joint frequency is 5×10^{-8} based on the relative frequency of each disorder, 5/10,000 and 1/10,000, respectively. Investigations into putative mechanisms underlying this association may improve our understanding of both disorders. Several potential mechanisms include (a) similar CNS dysfunction, for example, cell migrational abnormalities, localization of hamartomas, or seizure foci in CNS; (b) similar timing of CNS delays or insults in neurodevelopment; and (c) linkage disequilibrium of closely linked loci.

We are currently investigating each of these potential mechanisms in an ongoing family study of autism and tuberous sclerosis at UCLA and UC-Irvine. Families in this study are ascertained either through a TSC proband, an autistic proband, or through a non-TSC, nonautistic control. In this report, we present initial data on the frequency of autism in our TSC subjects and compare behaviors in autistic subjects with and without TSC.

METHODS

Subjects

Studies of 27 probands, 14 autistic and 13 TSC, have been completed to date. Ten of the TSC probands are sporadics based on physical examinations of the parents including ultraviolet light and, in some cases, MRI

and/or CT scans. The 3 familial cases provided 5 additional TSC subjects, 2 siblings, 1 parent, 1 niece, and 1 nephew.

Subjects were identified through several sources. Fifteen (7 autistic probands, 8 TSC probands) families responded to announcements in newsletters of national or regional autism organizations (e.g., the Advocate) or the National Tuberous Sclerosis Association (i.e., NTSA newsletter). The requests were tailored for each association and no mention of the alternative diagnosis (e.g., autism or TSC) was made in the announcement. Ten families (5 autistic probands, 5 TSC probands) were identified through UCLA and/or UC-Irvine affiliated hospitals or clinics. Two families (each with an autistic proband) were identified through a newsflyer circulated through the Los Angeles Unified classrooms for children with autism.

Measures

All mothers of probands are administered the Autism Diagnosis Interview (ADI; Le Couteur et al., 1989) by P.T., who is kept blind to any information on the proband prior to the interview; however, by virtue of several questions contained in the ADI, a diagnosis of TSC is often elicited early in the interview. Additional information collected on subjects includes a behavioral assessment (probands only), a battery of neuropsychological tests (probands and relatives), including the Vocabulary and Block Design subtests of the WAIS-R (Wechsler, 1981) or WISC-R (Wechsler, 1974) to estimate Full-scale IQ, and psychiatric evaluations (probands and relatives) using the SADS-LA (Mannuzza, Fyer, Klein, & Endicott, 1986) or KSADS-E (Weissman et al., 1987). The Vineland Social Maturity Scale (Sparrow, Balla, & Cicchetti, 1984) is used to assess mental age if a subject cannot be administered standardized IQ tests.

A detailed family history interview assessing medical, social, and emotional problems is conducted with at least two family informants when possible. A series of screening questions for autism and/or social deficits are asked within the family history interview based on those used in the family studies by Rutter and colleagues (M. Rutter, personal communication). If social deficits and/or autism is suggested in any first-degree relative based on the family history interview, an ADI is administered to the parent of that subject as well (if available) and a behavioral assessment is conducted. If a second- or third-degree relative is reported by family informants to have social deficits and/or autism, that individual and their first-degree relatives are contacted to participate as well. Approximately 15-20 ml of blood are drawn for establishing cell lines and blood typing of red cell proteins, serum enzymes, molecular markers, and fragile X typing (autistic probands only).

All TSC subjects and their first-degree relatives undergo a physical examination, including ultraviolet light, to evaluate TSC affection status, if medical records are insufficient. All autistic subjects are seen by S.S. and a medical geneticist at the UCLA Genetics Clinic or by M.S. at UC-Irvine to evaluate the subject for TSC

Analyses

Data management and analyses are done using PCSAS (1987) on an IBM compatible 486 personal computer.

RESULTS

Demographic information on the 13 tuberous sclerosis probands and 14 autistic probands are shown in Table II. Although age, IQ status, and the presence of speech, were similar in the two groups, seizures were more common among TSC probands than autistic probands and there were more male autistic probands than male TSC probands, consistent with epidemiological findings in TSC (Gomez, 1988, Osborne et al., 1991) and autism (for review, see Smalley et al., 1988). We are currently collecting data on non-TSC, nonautistic controls matched to these samples for sex, age, IQ status, and seizure presence as well as age of seizure onset.

Seven of the TSC probands (54%) met ICD-10 (World Health Organization, 1987) criteria for autism based on the ADI algorithm (C. Lord, personal communication). Since TSC probands may be more severely af-

Table II. Demographic Information on All Probands

	TSC probands	Autistic probands
<i>n</i>	13	14
<i>n</i> male	5(38%)	12(86%)
Mean age (<i>SD</i>)	10.1(7.4)	8.9(4.0)
IQ > 70	6(46%)	5(36%)
50 < IQ < 70	0	3(21%)
IQ < 50	7(54%)	6(43%)
Seizures ^a	11(85%)	1(7%)
No speech	5(38%)	5(36%)
Sporadic	10(77%)	14(100%)

^aAt least two nonfebrile.

fected than their relatives, we included the 5 TSC-affected relatives in the total sample of TSC subjects to perhaps better reflect the frequency of autism in the general TSC population. Including 5 TSC-affected relatives in the TSC proband sample ($n = 18$) gives a frequency of autism among TSC subjects of 39%. The algorithm cutoff scores for diagnosing autism on the revised ADI (used in our study) are still in the process of being validated; however, currently the cutoff score for the Social domain is between 11 and 15 (11 is used in this report), for nonverbal communication a score of 8, for verbal communication a score of 10, and for repetitive rituals a score of 3. In addition, to meet criteria for autism, the onset of symptoms must occur by 30 months of age. The mean ADI subscale scores for the 7 TSC probands and the 14 autistic probands are shown in Table III.

As shown in Table III, the TSC autistic probands are similar to non-TSC autistic probands on Social ($t = 1.37$, $p = .02$) and communication domains, Verbal ($t = 0.81$, $p = .4$) and Nonverbal ($t = 1.6$, $p = .17$), respectively. In contrast, TSC autistic probands scored lower on the Repetitive Ritual domain ($t = -3.2$, $p = .005$) than their non-TSC autistic controls. Given the small samples in this report, the lack of differences may be due to a lack of power. However, the trend present on Social and Communication domains is for the TSC autistic probands to score *higher* than non-TSC autistic probands.

To examine the specific behaviors which differed in these groups accounting for the mean difference on the Repetitive Rituals domain, we compared the proportion of subjects scoring 1 or greater on individual items shown in Figure 1.

As shown in Figure 1, fewer TSC autistic probands had preoccupations, compulsions, or unusual attachments to objects than autistic probands without TSC although they did show similar frequencies of hand and finger stereotypies and unusual sensory responses.

We next compared the 7 TSC autistic probands with the 6 TSC nonautistic probands for age, sex, IQ status, seizure onset, and activity level,

Table III. Mean Scores on ADI Domains in Autism and TSC + Autism Groups

ADI domains	TSC + autism			Autism		
	<i>n</i>	Mean	SD	<i>n</i>	Mean	SD
Social	7	44.4	14.8	14	38.4	12.8
Nonverbal communications	5	16.6	2.3	5	13.8	3.4
Verbal communication	2	20.5	0.7	9	18.7	3.5
Repetitive rituals	7	6.0	2.4 ^a	14	11.7	3.3

^a $p < .01$.

Fig. 1. Repetitive Ritual items from ADI.

as assessed by two questions on the ADI, to identify specific factors that might contribute to the occurrence of autism in TSC. There were no differences in age or activity level between the groups; however, there were significant differences in the sex ratio and frequency of mental retardation. Significantly more male TSC probands (5/5) had autism than female probands (2/8) (Fisher's Exact test, two-tailed, $p = .002$). There was also significantly more mental retardation present among TSC autistic probands (i.e., 6/7) than nonautistic TSC probands (i.e., 1/6) (Fisher's Exact test, two-tailed, $p = .029$). Although nonsignificant, there were more TSC subjects with seizures among the TSC autism group (7/7) than among the nonautistic TSC probands (4/6). These differences remained even when the 5 TSC-affected relatives (none of whom have autism) were included with proband sample (i.e., $n = 18$). Among the 7 TSC autistic subjects, the frequency of mental retardation, (86%), seizures (100%), and males (71%) was greater than that observed in the 11 nonautistic TS subjects (9% mental retardation, 39% seizures, 27% male).

DISCUSSION

Identifying genetic influences in autism has proven to be an elusive task in spite of considerable evidence for genetic involvement based on twin and family studies (Rutter, 1991). One approach to accomplish this goal has been to systematically investigate populations with fragile X, a known genetic disorder, in which autism frequently occurs (Blomquist et al., 1985; Brown et al., 1982b, 1986). Through the molecular elucidation of fragile X (Montanaro et al., 1991), a better understanding of the biology of behaviors associated with it may emerge (Cohen et al., 1991). We believe this approach may be fruitful to elucidate the mechanism(s) underlying the association of tuberous sclerosis and autism as well.

In a review of the literature, the association of autism and TSC is strongly supported. Estimated frequencies of autism among TSC subjects range from 17–58%, whereas the frequencies of TSC among autistic subjects is in the order of 0.4–3%. Furthermore, in a subgroup of autistic subjects *with seizures*, the estimated frequencies of TSC are much greater, 8 and 14%, from two studies reported to date (Gillberg, 1991; Riikonen & Simell, 1990).

In preliminary data from our ongoing family study, we identified 7 TSC probands with autism among 13 TSC probands (54%). Including 5 TSC-affected relatives, ascertained through a TSC proband, the frequency of autism is 39%. This is the first study of TSC and autism, to our knowledge, in which a thorough diagnostic interview and standard diagnostic criteria for autism have been used. The TSC autistic probands look very similar to the 14 non-TSC autistic probands on Social and Communication domains measured by the ADI but show fewer Repetitive Rituals suggesting that the behaviors leading to a diagnosis of autism in TSC subjects are those considered “core” deficits (i.e., social and language deficits) more than motoric behaviors such as hand and finger stereotypies, which are also commonly found in populations with mental retardation.

Although the sex ratio among TSC subjects is approximately equal, we found more TSC males than females with autism. The sex ratio for autism observed among TSC patients, if replicated in larger samples, suggests sex-influenced expression (at least behavioral) of TSC genes or possibly that a closely linked (sex-influenced) gene involved in autism may be present. Gomez (1988, 1991) has suggested that TSC and mental retardation as well as profound behavioral problems such as autism may result from seizure foci and subsequent CNS damage. This is based on the finding that TSC subjects with mental retardation invariably have seizures and that cognitive impairment and age at seizure onset are strongly correlated (Gomez, 1988, 1991). Curatolo and Cusmai (1987) suggested that specific

CNS location of TSC hamartomas may lead to autism based on their sample of 8 TSC cases in which 3 subjects *with* autism had right parietotemporal MRI lesions, whereas 5 TSC subjects without autism did not.

In this preliminary sample of subjects, we found a strong association of seizures, mental retardation, and autism; however, not all autistic TSC subjects are mentally retarded (we have identified a male autistic TSC subject with an estimated IQ of 106). Furthermore, although all autistic TSC subjects had seizures with onset in the first year of life, so did 3 of 4 of nonautistic TSC subjects with seizures as well. If seizures and or cortical tuber positioning account for the presence of autism, one would predict a sex difference to emerge on seizure activity or localization of hamartomas in the CNS. To our knowledge, there is no report of a sex difference in either of these variables although the latter has not been examined systematically.

In conclusion, autism and TSC are associated and the mechanism(s) of this association remains to be elucidated; however, the association appears to be, in part, independent of seizure onset at 1 year of life and mental retardation. Interpretation of these data regarding the extent of association of autism and TSC needs to be made with caution. First, our samples are clinically, not epidemiologically, based and thus may provide a somewhat biased estimate of the frequencies of behavioral problems. Second, the samples are very small at this point and these findings require replication in larger samples with non-TSC, nonautistic, IQ, age, sex, and seizure-matched controls. Third, these findings are based on the parental report of development using the ADI; later reports will be made on our observational assessments using the ADOS (Lord et al., 1989). In summary, identification of the mechanisms underlying the association of autism and TSC, we believe, may help identify genetic influences in autism and will certainly benefit families with TSC members by improving our understanding (and counseling risks) of behavioral manifestations in this disorder.

REFERENCES

- American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.
- Barakat, A. Y., & Cochran, W. E. (1978). Tuberous sclerosis: Report of nine cases and a review. *Clinical Pediatrics*, 17, 875-879.
- Blomquist, H. K., Bohman, M., Edvinsson, S. O., Gillberg, C., Gustavson, K. H., Holmgren, G., & Wahlstrom, J. (1985). Frequency of the fragile X syndrome in infantile autism. *Clinical Genetics*, 27, 113-117.
- Brown, W. T., Jenkins, E. C., Friedman, E., Brooks, J., Wisniewski, K., Raguthu, S., & French, J. H. (1982). Autism is associated with the fragile X syndrome. *Journal of Autism and Developmental Disorders*, 12, 303-307.

- Brown, W. T., Jenkins, E. C., Cohen, I. L., Fisch, G. S., Wolf-Schein, E. G., Gross, A., Waterhouse, L., Fein, D., Mason-Brothers A., and Ritro, E. (1986). Fragile X and autism: A multicenter study. *American Journal of Medical Genetics*, 23, 341-352.
- Clarke, D. J. Buckley M. E., and Burns B. H. (1987). Epilepsy and psychosis—Ask the family. *British Journal of Psychiatry*, 150, 702-703.
- Cares, R. M. (1958). The tuberous sclerosis complex. *Journal of Neuropathology and Experimental Neuropathology and Experimental Neurology*, 17, 247-254.
- Cohen, I. L., Sudhalter, V., Pfadt, A., Jenkins, E. C., Brown, W. T., & Vietze, P. M. (1991). Why are autism and the fragile X syndrome associated? Conceptual and methodological issues. *American Journal of Human Genetics*, 48, 195-202.
- Creak, E. M. (1963). Childhood psychosis: A review of 100 cases. *British Journal of Psychiatry*, 109, 84-89.
- Critchley, M., & Earl, C. J. C. (1932). Tuberous sclerosis and allied conditions. *Brain*, 55, 311-346.
- Curatolo, P., & Cusmai, R. (1987). Autism and infantile spasms in children with tuberous sclerosis. *Developmental Medicine and Child Neurology*, 29, 550-551.
- Curatolo, P., Cusmai, R., Cortesi, F., Chiron, C., Jambeque, I., & Dulac, O. (1991). Neuropsychiatric aspects of tuberous sclerosis. In W. G. Johnson & M. R. Gomez (Eds.), *Tuberous sclerosis and allied disorders* (Vol. 615, pp. 8-16). New York: New York Academy of Sciences.
- Dick, A. R., & Ziegler, D. K. (1967). Tuberous sclerosis: A report of two cases. *Journal of Kansas Medical Society*, 68, 102-116.
- Entwistle, C., & Sim, M. (1961). Tuberous sclerosis and fatishism. *British Medical Journal*, 2, 1688-1689.
- Finlayson, A. (1955). Tuberous sclerosis. *American Journal of Mental Deficiency*, 59, 617-628.
- Fisher, W., Kerbeshian, J., Burd, L., & Kolstoe, P. (1987). Tuberous sclerosis and autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, 26, 700-703.
- Folstein, S. E., & Rutter, M. L. (1988). Autism: Familial aggregation and genetic implication. *Journal of Autism and Developmental Disorders*, 18, 3-21.
- Gillberg, C. (1991). The treatment of epilepsy in autism. *Journal of Autism and Developmental Disorders*, 21, 61-77.
- Gillberg, C., Steffenburg, S., & Schaumann, H. (1991). Is autism more common now than ten years ago? *British Journal of Psychiatry*, 158, 403-409.
- Gomez, M. R., Kuntz, N. L., & Westmoreland, B. F. (1982). Tuberous sclerosis, early onset of seizures, and mental subnormality: Study of discordant homozygous twins. *Neurology*, 32, 604-611.
- Gomez, M. (1988). *Tuberous sclerosis*. New York: Raven.
- Gomez, M. R. (1991). Phenotypes of the tuberous sclerosis complex with a revision of diagnostic criteria. In W. G. Johnson & M. R. Gomez (Eds.), *Tuberous sclerosis and allied disorders*. New York: New York Academy of Sciences.
- Greenstein, M. A., & Cassidy, S. B. (1986). Is tuberous sclerosis a cause of autism? [letter]. *New England Journal of Medicine*, 314, 449.
- Hunt, A. (1983a). Tuberous sclerosis: A survey of 97 cases, I: Seizures, pertussis immunisation and handicap. *Developmental Medicine and Child Neurology*, 25, 346-349.
- Hunt, A. (1983b). Tuberous sclerosis: A survey of 97 cases, III: Family aspects. *Developmental Medicine and Child Neurology*, 25, 353-357.
- Hunt, A., & Dennis, J. (1987). Psychiatric disorder among children with tuberous sclerosis. *Developmental Medicine and Child Neurology*, 29, 190-198.
- Johnson, W. G., & Gomez, M. R. (Eds.). (1991). *Tuberous sclerosis and allied disorders*. New York: New York Academy of Sciences.
- Jordan, W. M. (1956). Familial tuberous sclerosis. *British Medical Journal*, 2, 132-135.
- Khanna, R., & Border, M. (1989). Mania in a five-year-old child with tuberous sclerosis. *British Journal of Psychiatry*, 155, 117-119.
- Lawlor, B. A., & Maurer, R. G. (1987). Tuberous sclerosis and the autistic syndrome. *British Journal of Psychiatry*, 150, 396-397.

- 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, 363-386.
- Lord, C., Rutter, M., Goode, S., Heemsbergen, S., Jordan, J., Mawhood, L., & Schopler, E. (1989). Autism Diagnostic Observation Schedule: A standardized observation of communicative and social behavior. *Journal of Autism and Developmental Disorders*, 19, 185-212.
- Lotter, V. (1967). Epidemiology of autistic conditions in young children: Some characteristics of the parents and children. *Social Psychiatry*, 1, 163-173.
- Mannuzza, S., Fyer, A. J., Klein, D. F., & Endicott, J. (1986). Schedule for affective disorders and schizophrenia—Lifetime version modified for the study of anxiety disorders (SADS-LA): Rationale and conceptual development. *Journal of Psychiatric Research*, 20, 317-325.
- Mansheim, P. (1979). Tuberous sclerosis and autistic behavior. *Journal of Clinical Psychiatry*, 40, 97-98.
- Matthews, K. L. (1981). Familial Gilles de la Tourette's syndrome associated with tuberous sclerosis. *Texas Medicine*, 77, 46-49.
- Miller, V. S., & Bigler, E. D. (1982). Neuropsychological aspects of tuberous sclerosis. *Clinical Neuropsychology*, 4, 26-34.
- Montanaro, V., Casamassimi, A., D'Urso, M., Yoon, J.-Y., Freije, W., Schlessinger, D., Muenke, M., Nussbaum, R. L., Saccone, S., Maugeri, S., Santoro, A. M., Motta, S., & Della Valle, G. (1991). In situ hybridization to cytogenetic bands of yeast artificial chromosomes covering 50% of human Xq24-Xq28 DNA. *American Journal of Human Genetics*, 48, 183-194.
- Noel, L. P., & Clarke, W. N. (1982). Self-inflicted ocular injuries in children. *American Journal of Ophthalmology*, 94, 630-633.
- Oliver, B. E. (1987). Tuberous sclerosis and the autistic syndrome (letter). *British Journal of Psychiatry*, 151, 560.
- Olsson, I., Steffenburg, S., & Gillberg, C. (1988). Epilepsy in autism and autisticlike condition: A population-based study. *Archives of Neurology*, 45, 666-668.
- Osborne, J. P., Fryer, A., & Webb, D. (1991). Epidemiology of tuberous sclerosis. In W. G. Johnson & M. R. Gomez (Eds.), *Tuberous sclerosis and allied disorders*. New York: New York Academy of Sciences.
- Rakoff, J. (1981). Tuberous sclerosis in the aetiology of the so-called idiopathic epilepsies and psychoses. *South African Medical Journal*, 60, 574-578.
- Reiss, A. L., Feinstein, C., & Rosenbaum, K. N. (1986). Autism and genetic disorders. *Schizophrenia Bulletin*, 12, 724-738.
- Riikonen, R., & Amnell, G. (1981). Psychiatric disorders in children with earlier infantile spasms. *Developmental Medicine and Child Neurology*, 23, 747-760.
- Riikonen, R., & Simell, O. (1990). Tuberous sclerosis and infantile spasms. *Developmental Medicine and Child Neurology*, 32, 203-209.
- Ritvo, E. R., Mason-Brothers, A., Freeman, B. J., Pingree, C., Jenson, W. R., McMahon, W. M., Petersen, P. B., Jorde, L. B., Mo, A., & Ritvo, A. (1990). UCLA -University of Utah epidemiologic survey of autism: Etiologic role of rare diseases. *American Journal of Psychiatry*, 147, 1614-1621.
- Roth, J. C., & Epstein, C. J. (1971). Infantile spasms and hypopigmented macules: Early manifestations of tuberous sclerosis. *Archives of Neurology*, 25, 547-551.
- Rutter, M. (1991). Autism as a genetic disorder. In P. McGuffin & R. Murray (Eds.), *The new genetics of mental illness*. Oxford: Butterworth-Heinemann.
- Smalley, S. L., Asarnow, R. F., & Spence, M. A. (1988). Autism and genetics: A decade of research. *Archives of General Psychiatry*, 45, 953-961.
- Sparrow, S. S., Balla, D. A., & Cicchetti, D. V. (1984). Interview edition survey form manual: Vineland adaptive behavior scales. Circle Pines, MN: American Guidance Service.
- Taft, L. T., & Cohen, H. J. (1971). Hypsarrhythmia and infantile autism: A clinical report. *Journal of Autism and Childhood Schizophrenia*, 1, 127-336.
- Tiwari, A. K., Srivastava, B. N., & Agarwal, S. (1968). Further observations on Bourneville's disease. *Journal of the Indian Medical Association*, 50, 373-374.

- Uchiyama, A., Nomura, Y., and Segawa M. (1988). Trial of a minimum dosis of L-Dopa (0.5 mg/kg/day) on intractable epilepsy associated with tuberous sclerosis. *Japanese Journal of Psychiatry and Neurology*, 42, 584-585.
- Wechsler, D. (1974). Manual for the Wechsler Intelligence Scale for Children-Revised. New York: Psychological Corp.
- Wechsler, D. (1981). WAIS-R Manual: Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corp.
- Weissman, M. M., Wickramaratne, P., Warner, V., John, K., Prusoff, B. A., Merikangas, K., & Gammon, G. D. (1987). Assessing psychiatric disorders in children. *Child Psychiatry*, 44, 747-753.
- World Health Organization. (1987). *ICD-10 1986 draft of chapter 5 categories F00-F99. Mental, behavioural and developmental disorders*. Geneva, Switzerland: Author.
- Zlotlow, M., & Kleiner, S. (1965). Catatonic schizophrenia associated with tuberous sclerosis. *Psychiatric Quarterly*, 39, 466-475.