

## **Autism: Familial Aggregation and Genetic Implications**

**Susan E. Folstein<sup>1</sup>**

*Johns Hopkins University*

**Michael L. Rutter**

*Institute of Psychiatry, London*

*A review of the current literature suggests that genetic factors play an important role in the etiology of autism. It is likely that the etiology of currently idiopathic cases of autism will be shown to be heterogeneous, just as the few known etiologies are both environmental and genetic. Moreover, we would speculate that within the group of cases shown to have genetic etiologies, more than one genetic locus will be found. Some evidence suggests that quite often it is not autism itself that is inherited but rather some genetic abnormality of language or sociability that interacts with other factors to produce autism.*

Autism is a syndrome (Kanner, 1943) defined not by etiology or pathology but by particular behaviors and a characteristic natural history (Rutter & Schopler, 1986). While a single pathology or pathophysiology may be discovered that will account for all cases of autism, it is clear that there is no single etiology. Although the etiology is still unknown in most cases, evidence from both biological and epidemiological studies demonstrates two principles about etiology of autism. First, there are many etiologies of autism, as would be expected in a syndrome defined only by its clinical features. At present, however, it is known whether the majority of cases among those currently idiopathic will eventually be shown to have a single cause or whether we will continue to "chip away" small number of cases,

<sup>1</sup>Address all correspondence to Susan E. Folstein, Division of Psychiatric Genetics, Department of Psychiatry, Johns Hopkins University, Baltimore, Maryland.

with no single etiology accounting for the bulk of cases. The second principle is that the etiologies of autism are organic, rather than psychosocial in nature. Among the rare cases of autism for which an etiology is apparent, there are examples of both physical-environmental (especially infections and perinatal trauma) and genetic causes. This discussion will present the evidence for the existence of one or more genetic factors in the etiology of the bulk of autism where the cause is unknown, and will review the evidence that autism can be associated with particular single gene disorders.

### CHARACTERISTICS OF AUTISM

Before discussing the evidence for genetic factors in the etiology of autism, it is helpful to consider some characteristics of the syndrome that may enable us make reasonable hypotheses about etiology.

First, the age of onset is in infancy. Abnormalities may be evident from the 1st year and are almost always noticeable by 30 months. Unlike schizophrenia, with which autism has been commonly grouped, there is no prolonged period of relatively normal development before symptoms begin. Similarly, the distribution of the ages of onset of autism and schizophrenia do not overlap; with but few exceptions, there is at least a 5-year gap between the latest onset of autism and the earliest onset of adult-type schizophrenia (Kolvin, 1971; Rutter, 1974). These facts, along with the failure to find an excess of schizophrenia in the families of autistic children and the essential differences in the clinical features, make it unlikely that there is any etiological or pathophysiological connection between schizophrenia and autism. The age of onset also implies that some pathophysiological mechanism is operating at birth, if not before. Age at onset does not, however, help us predict the nature of etiology. Infections can have either immediate effects (as in congenital rubella) or delayed effects (as in postencephalitic Parkinsonism). Similarly, the manifestations of genetic conditions can begin at any time during life.

Second, although autism is strongly associated with mental retardation, the accompanying risks and neurological findings are different. Like mental retardation, autism is associated with an increased rate of pre- and perinatal abnormalities, but the increase is mainly in minor abnormalities, rather than the major abnormalities found in association with mental retardation (Deykin & MacMahon, 1980; Finegan & Quadrington, 1979; Gillberg & Gillberg 1983). There is also difference in the pattern of seizure development. While most children with severe mental retardation develop seizures in infancy or early childhood (Richardson, Koller, Katz, & MacLaren, 1980), autistic children who develop seizures commonly do so

around the time of puberty (Deykin & MacMahon, 1979). Also while severe mental retardation is almost always associated with some kind of fairly obvious neuropathology (Crome & Stern, 1972), the few autopsy studies of autism either have revealed no detectable abnormalities or have shown rather subtle abnormalities that are not easily interpretable (Darby, 1976; Williams, Hauser, Purpura, DeLong & Swisher, 1980; Bauman & Kemper, 1985; Coleman, Romano, Lapham, & Simon, 1985).

In addition, while autism is associated with disorders that also cause mental retardation, cases are not evenly distributed among those disorders; i.e., some disorders commonly cause both mental retardation and autism (eg., infantile spasm—Riikonen & Amnell, 1981; and congenital rubella—Chess, Korn, & Fernandez, 1971; Chess, Fernandez, & Korn, 1978), while other conditions that are usually associated with intellectual impairment rarely give rise to autism (eg., Down's syndrome and cerebral palsy—Wing & Gould, 1979).

These different associations suggest that while there is some overlap in the specific disorder known to cause the two conditions, that overlap is quite small. It seems likely, therefore, that we must look for different etiologies of autism from those we have found for mental retardation. However, as will become clear below, we do not wish to suggest that the *types* of etiologies need be different. Single gene disorders may cause autism and single gene disorder may cause mental retardation, but the differences in the clinical features of these two syndromes lead us to hypothesize that the specific genes that are eventually found to explain autism will be different from the genes that, when abnormal, lead primarily to mental retardation.

Third, the cognitive deficits in autistic children, even in those who are not mentally retarded, tend to follow a distinctive and highly unusual pattern. Generally, they do poorly on tasks requiring sequential skills, conceptualization, and abstraction, and well on strictly nonverbal visual-spatial tasks (Rutter, 1979, 1983). In addition, they are impaired in their ability to discriminate social and emotional cues (Rutter, 1983). This distinctive pattern of cognitive deficits, present across IQ groups, suggests a common pathophysiology; whether it also implies a common etiology is less certain.

Finally, as suggested above, there is huge variation in the severity of the cognitive handicaps seen in autism. The IQ ranges from profoundly retarded to above average. Language development varies from virtually absent to nearly normal. The upper end of cognitive variability is extended even further if Asperger's syndrome (Wing, 1981) and the possibly equivalent schizoid disorder of childhood (Chick, Waterhouse, & Wolff, 1979; Wolff & Barlow, 1979; Wolff & Chick, 1980) are included in the definition of autism. In these conditions, IQ is normal and there are no

serious delays in language development. Deficits are virtually limited to social relationships that are strikingly similar to the social deficits in autism. Despite these deficits, persons with Asperger's syndrome often attain a degree of social independence in adult life. There is the possibility, therefore, that lesser variants of autism may exist that have not been readily recognized. If these exist, the phenotype of autism used for genetic studies may need redefinition.

Such a wide variation in cognitive capacity usually implies etiologic diversity. Even when cases originally included in a phenotype with a wide IQ range all have genetic causes, multiple mutations have often been discovered (McKusick, 1969; Laird & Schimke, 1979). For example, the mucopolysaccharidoses were originally lumped together as "gargoylism" or "Hurler's syndrome," on the basis of their similar physical characteristics. Within this original syndromic designation, intelligence ranged from normal to profoundly retarded. The IQ range within the current subgroups, defined by recessive mutations at particular loci, is quite narrow (McKusick, 1983). Similarly, the Marfan syndrome, caused by at least one autosomal dominant mutation, and homocystinuria, caused by autosomal recessive mutations at several loci (Valle, Pai, Thomas, & Pyeritz, 1980), were originally thought to be one disorder with a wide range in IQ. It was not until homocystine was found in the urine of a subset of the cases that the subtle differences in the physical features and IQ ranges of the two syndromes were appreciated.

On the other hand, a single etiology can result in a wide variation of handicap. A nongenetic example is congenital rubella. Within genetic disorders there are examples among both recessive and dominant conditions. Patients with sickle cell anemia who also have persistent fetal hemoglobin have significantly less severe clinical manifestations of sickle cell anemia (Dover, & Pembrey, 1981). Affected patients within individual kindreds (all necessarily having the same mutation) of neurofibromatosis, tuberous sclerosis, or Joseph's disease (Rosenberg & Pettegrew, 1980) can show wide variations in the severity of symptoms. This phenomenon is called variable expressivity. In addition, some family members who "must" have the affected gene, given family patterns of inheritance, have no detectable symptoms. Disorders where this occurs are said to have incomplete penetrance. Milder manifestations of recessive conditions, both autosomal and X-linked, are sometimes seen in carriers. Mild mental retardation can be seen in the female carriers of fragile X and will be further discussed in that section. In some disorders that appear to be genetically determined, but appear not to transmit in a Mendelian fashion (eg., Tourette's syndrome and stuttering—Kidd & Pauls, 1982), variable expressivity has been used as evidence for multifactorial etiology (i.e., the interaction of some unknown

number of genes and environmental factors). However, it must be said that multifactorial inheritance has yet to be demonstrated for a human disorder at the molecular level. And evidence is mounting that some of the conditions consistent with multifactorial models, such as Tourette's syndrome, could be inherited as Mendelizing traits with incomplete penetrance and variable expressivity.

Thus, on the basis of clinical features alone, it is hazardous at best to make specific predictions about whether there is one etiology or many. Similarly, it is impossible to predict, without additional data, whether a major etiology is more likely to be traumatic, infectious, or genetic. And finally, the symptoms alone do not allow us to confidently postulate a particular type of genetic transmission. Nevertheless, the data to suggest that it is necessary to search for etiologies that are not synonymous with those for schizophrenia or mental retardation, that organic causes are likely to predominate among the etiologies, and that the etiologies of autism associated with severe mental handicap may differ from that of autism in the presence of normal intelligence. With these considerations in mind, we will review the available evidence for genetic contributions to the etiology or etiologies of autism. As noted above, these data will be divided into two sections: first, the evidence for genetic factors in currently idiopathic autism, and second, a review of a few genetic disorders for which an association with autism has been reported.

### **EVIDENCE FOR GENETIC FACTORS IN AUTISM DERIVED FROM FAMILY AND TWIN STUDIES OF CASES OF UNKNOWN ETIOLOGY**

The first step when investigating a syndrome for the possibility of genetic etiology is to look at familial aggregation of the disorder and patterns of disorder in twins. These studies include only cases where the etiology is unknown—i.e., in cases not associated with any etiologically defined disorder.

Interpretation of twin and family data is fraught with hazards, and several factors must be borne in mind when examining such data. First, family and twin data are prone to sampling biases. Unless sampling is systematic, "interesting families" with several affected members are more likely to be reported than those with just one affected child. Similarly, monozygotic twin pairs are more likely to be reported than discordant ones. Second, whenever diagnostic methods and criteria are less than fully objective, there is wide scope for bias in diagnosing secondary cases in the family. Great caution is needed in the interpretation of studies where the diagnosis

of family members (secondary cases) was not independent of, and blind to, the diagnosis of the proband (the case by which the family was identified). If the investigator making the diagnosis knows that the case is a member of a family with another affected member, he may be tempted to apply less stringent criteria. Similar cautions apply to studies where the diagnostic criteria are not fully specified.

However, cases with "similar" phenotypes are not to be overlooked or dismissed as irrelevant. As discussed earlier, genetic influences may apply to some deficit that is broader than the autism phenotype as strictly defined, so that investigation of familial aggregation of a range of disorders is warranted. The hazard here is in the interpretation of such familial aggregation: Learning disorders and developmental delays in speech and language are common (Silva, 1986; Yule & Rutter, 1985), so that such investigations must include systematic measurements and the use of a comparison group.

A final hazard in the interpretation of twin and family data concerns the methods of genetic analysis. As already noted, genetic heterogeneity must be presumed at this stage of our knowledge, and analyses that assume that any sample of autism represents an etiologically homogeneous population can be misleading.

### *Family Studies*

Mostly epidemiological studies of autistic children have not included cases with known (or presumed) genetic etiologies, such as phenylketonuria or hypsarrhythmia. Even without the inclusion of these cases, some familial aggregation of autism has been noted. Very approximately, some 2% of families have two autistic children (Rutter, 1967; Folstein & Rutter, 1977; August, Stewart, & Tsai, 1981). While this number is small, it is 50 to 100 times what would be expected by chance according to the accepted prevalence rate of autism (2-4 per 10,000 school-aged children; Lotter, 1966, 1967; Wing, O'Conner, & Lotter, 1967; Treffert, 1970; Wing, Yeates, Brierley & Gould, 1976). These estimates of rates in sibs are, however, in need of replication using standardized methods of assessment (Hanson & Gottesman, 1976; Gottesman & Shields, 1982). With the exception of August et al. (1981), none of the investigators systematically examined the secondary cases in the families in the same way as the probands. So it may be that these are mentally retarded children or perhaps mildly autistic children who would not meet the same criteria as those by which their proband autistic sibs were ascertained. While August et al. examined all the secondary cases, the authors do not state whether these diagnoses were blind to that of the proband.

It appeared in August's case series that familial cases were also mentally retarded, and other data to be described below suggest that it may not be autism so much as mental retardation that is familially aggregated. One exception is the report of Burgoine and Wing (1983) of triplets with Asperger's syndrome. We have also observed familial aggregation of Asperger's syndrome in a male proband, in his maternal uncle, and in his mother's male first cousin. As discussed earlier, Asperger's syndrome is probably equivalent to autism without mental retardation (Wing, 1981). It may be that different kinds of questions must be asked when inquiring about the family history if familial aggregation of the milder variants of autism is to be detected.

*Twin Studies.* Even if the 1 to 3% rate of autism in sibs can be confirmed, familial aggregation does not necessarily imply genetic etiology. Infectious conditions can show familial aggregation and there may be a tendency for mothers to have repeated complications of pregnancy and birth (Stanley & Alberman, 1984).

Better evidence for the importance of genetic factors has come from the study of twins. First came a number of reports of individual pairs of twins (reviewed by Rutter 1967; Folstein & Rutter 1977; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985). The great majority of these pairs was reported to be concordant for autism. However, no definite genetic inferences could be made from these case reports for several reasons (discussed in detail by Gottesman & Shields, 1982). First, the number of reported monozygotic pairs far exceeded the number of reported dizygotic pairs, indicating a reporting bias. In the population, dizygotic pairs are twice as common as monozygotic pairs; when only same-sexed pairs are considered, the proportions are about equal (Mittler, 1971). Second, for reasons described above, the proportion of concordant pairs in reports of individual pairs was overestimated. Third, some publications failed to specify diagnostic methods and criteria. And finally, there was a failure in some cases to confirm the appearance of monozygosity by blood typing or dermatoglyphics and to describe the nature of the physical dissimilarities on which dizygosity was based. Twins who are similar in appearance are usually monozygotic, but like siblings, dizygotic pairs can look quite similar. The documentation of dizygosity is somewhat easier—if the pair differs in physical characteristics such as color and texture of hair, ear form, and eye color, dizygosity is virtually certain and need not be confirmed by other methods. However, dissimilarities in these characteristics must be marked in order to be sure of dizygosity. Twins who are actually monozygotic may be thought by friends and family to be dizygotic twins because they are easily distinguished by their demeanor and facial expression. This is particularly true if one of the twins is autistic.

For all these reasons, it was necessary to study a total population sample of twins before drawing any conclusions about possible genetic influences in the etiology of autism. In 1977 Folstein and Rutter reported a study of English autistic twins who were systematically ascertained through multiple sources. We specifically urged the reporting of dizygotic as well as monozygotic pairs and emphasized that we were equally interested in discordant and concordant pairs. According to our checks, our final sample of 21 pairs meeting diagnostic criteria appeared to be a reasonably complete sample, within the school-aged range (Folstein & Rutter, 1977). Zygosity was checked by multiple blood group analyses (or, as in one case, by dermatoglyphics) in all pairs who were not clearly dizygotic by a systematic inspection of physical features. The diagnostic criteria were consistent, and final diagnoses were made blind to zygosity and twin pair membership.

In this total population of 21 pairs of same-sexed twin pairs, the concordance rate for autism was 36% in the monozygotic pairs and 0% in the dizygotic pairs. The concordance could not be explained by complications of pregnancy or delivery or by postnatal illness, and the results therefore supported the hypothesis that autism could be inherited. However, a twin study cannot indicate whether there is one genetic etiology or many, or whether there is one or more genetic mechanism of transmission. Nor is the absolute proportion of concordant monozygotic pairs related to the proportion of "genetic cases" in the population, because of the postconception environmental differences that occur in monozygotic twins.

The concordance rate for monozygotic pairs was considerably lower than would have been predicted from an analysis of the individual twin reports and also lower than that recently reported by Ritvo, Freeman et al. (1985), who claimed 95.7% concordance in MZ pairs and 23.5% in DZ pairs. Although the authors purported to use methods similar to those of Folstein and Rutter, they in fact relied largely on voluntary replies from families to announcements of the study placed in the newsletter of the National Society for Autistic Children, along with a few local case referrals. As expected from the methods of case ascertainment, the sample contains a marked excess of monozygotic pairs. The report (Ritvo, Freeman, et al, 1985) stated that the proportion of MZ to DZ pairs was equal, but because opposite-sexed pairs are included, there should have been twice as many DZ as MZ pairs for the sample to be representative with respect to zygosity. The inclusion of opposite-sexed pairs added to the difficulties in interpretation because of the very different rates of autism in males and females. Although the authors criticized other studies for failing to confirm dizygosity by blood grouping, most of their zygosity determinations were based on parental report. Finally, no mention was made of any attempt to diagnose autism in the twins, blind to pair membership. In short, this study adds little to our



knowledge about genetic factors in autism, and furthermore, it is misleading in its assertions and conclusions.

While the data from the twin studies and the familial aggregation noted in case series indicate that genetic factors are likely to be important in autism, these kinds of studies tell us little about the nature of the genetic defect, or whether there is one defect or many. All these investigations took place before the discovery of the association of autism with fragile X. How much of the familial aggregation of autism in sibs or how much of the twin concordance could be thus accounted for is unknown.

*Other Disorders in Family Members.* Even more striking than the familial aggregation of autism is the aggregation of disorders of general intelligence and of reading and language in families of autistic children. This was first noticed by Bartak, Rutter, and Cox (1975), where a family history of reading or language disabilities was found in at least one first-degree relative of 5 of the 19 families (26%) studied. In these families, ascertained through an autistic child with an IQ above 70, no excess of mental retardation was noted, although this was not systematically studied. This familial aggregation of reading and language disorders in family members is not likely to be accounted for by fragile X because the autistic children had high IQs, an uncommon occurrence with fragile X.

Folstein and Rutter (1977) reported similar findings in their twin study. The concordance rate for disorders of cognition and language was considerably higher than the concordance rate for autism. Nine of the 11 monozygotic pairs (82%) were concordant for language or cognitive disorder, compared with only 1 of the 10 dizygotic pairs (10%). The severity of the disorders varied from rather mild (as evidence by the need for tutoring in reading and grammar) to moderately disabling exemplified by one cotwin with an IQ of 55 who needed special schooling).

The data on birth complications suggested an explanation for the findings. While the nonautistic but cognitively disabled monozygotic cotwin had normal or nearnormal birth histories, their autistic cotwins did not. Several had suffered significant perinatal problems. This suggested that while autism itself was sometimes inherited (as evidenced by the four monozygotic pairs who were concordant for autism), it appeared that more often a language or cognitive deficit was inherited, which, when combined with an environmental insult such as birth difficulties, resulted in autism. This conclusion does not necessarily apply to autism in general because twins are more prone than single births to birth injuries, and the injuries reported in case series of nontwin autistic children have been relatively mild. On the other hand, it is possible that a mild birth injury could have a greater impact in a child who was genetically predisposed to abnormal language or cognitive development.

Cognitive abnormalities among the siblings of autistic children were also reported by August et al. (1981). These investigators tested all the sibs of 41 autistic probands using standard IQ tests and tests of reading, spelling, and math. The age-matched siblings of children with Down's syndrome served as the comparison group. The rate of cognitive abnormalities was 15% in the sibs of the autistic probands, compared with 3% among the sibs of the Down's controls. All of the cognitively disabled children came from 8 of the 41 families, and all the probands in these 8 families were mentally retarded, suggesting that often it may not be autism but mental retardation that is familially aggregated. The familial aggregation of cognitive disabilities in this study could not all have been due to fragile X because 3 of the 8 families with cognitively disabled sibs were ascertained through female autistic probands. Baird and August (1985) have recently confirmed their earlier findings in another sample and did find one family where aggregation was accounted for by fragile X (August & Lockhart, 1984).

Another study of siblings using only IQ tests (Minton, Campbell, Green, Jennings, & Samit, 1982) also found a high rate of mental retardation among the siblings of autistic probands. In this study, the verbal scores of the siblings were significantly lower than performance scores, a pattern also seen in autistic children and in children with developmental language disorders.

*Segregation Analysis.* For several years, Ritvo and his group have been accumulating volunteer families with autism in two or more siblings. In collaboration with Spence (Rivo, Spence, et al., 1985), an attempt was made at segregation analysis—i.e., the investigation of possible genetic mechanisms for inheritance in autism using mathematical analysis of the case material. The authors reported that their data were consistent with autosomal recessive inheritance, and not consistent with multifactorial models. While they used analytic methods that controlled for the bias of sample ascertainment through multiple-case families, the methods presumed that the same segregation ratio was operating in the nonascertained families—that is, that the sample was homogeneous with respect to genetic mechanism. While this result is intriguing, it is somewhat confusing in light of the great excess of affected males and of male-male sib pairs in their sample. This is typical, of course, of autism samples, but it is not ordinarily expected in autosomal recessive inheritance, where the sex ratio should be equal. Clearly, even if all of autism was inherited as single gene disorders, either some families would have to be X-linked to account for the excess of males or some powerful modifying factor must be postulated that somehow inhibits expression in females.

Autosomal recessive inheritance, or a mixture of autosomal and X-linked recessives, is by no means impossible in autism. One would expect

somewhat more familial aggregation (McKusick, 1969), but that may be less than expected under certain circumstances. If family size is small, if the phenotype inhibits further reproduction, or if there is variable expressivity so that not all cases are detected, familial aggregation may be quite minimal.

*Linkage Analysis.* Using 34 families from this same sample, the same investigators (Spence et al. 1985) undertook a limited linkage analysis. The purpose of genetic linkage analysis is to investigate whether a trait or disorder (e.g., autism) is systematically associated with some marker that is known to be the product of a single genetic locus. A positive result provides evidence for single gene transmission and for the association of a particular disorder with a particular genetic locus. The finding of a genetic linkage between a disorder and a marker does not imply that the marker, such as a blood group or an HLA pattern, is related to the cause of the disorder, but simply that the gene for the trait or disorder under test and the gene for the marker are close neighbors on a particular chromosome.

On the assumption that there is a unique chromosomal location for some gene for autism, Spence et al. looked for linkage to HLA (chromosome 6) and 19 other autosomal markers in 34 families with two or more autistic children. One family with fragile X was omitted. No other markers located on the X chromosome were checked. No convincing linkages to the autosomal markers were found, and there was some suggestion of differences between families with only boys and families with one or more girls.

One should by no means conclude that Mendelian inheritance is thus ruled out. More complex analyses are needed to take into account the likely etiological and genetic heterogeneity, even in autism samples chosen for having more than one affected case. Linkage studies need to be undertaken using the more numerous and more informative markers that are now available in the form of highly polymorphic anonymous DNA fragments. (For a discussion of this method of genetic linkage analysis, see Gusella et al., 1984.)

### *Single Gene Disorders Associated with Autism*

Up to this point, we have been considering the evidence for genetic factors in the etiology of autism that is idiopathic in terms of current knowledge. Cases of autism are occasionally found that are not discernibly different from idiopathic autism, but for which an etiology is apparent. And there are a few etiologicaly defined conditions that may be associated with autism more often than expected by chance. Genetic etiologies include

fragile X, and possibly tuberous sclerosis and phenylketonuria. The best-documented association with an infectious disease is that between autism and congenital rubella (Chess et al., 1978).

There are several difficulties in interpreting reports of such associations. First, reports are seldom based on systematically collected samples, so that the strength of the association with autism is not clear. That is to say, how many cases of autism are associated with the condition, and how many cases with the condition are also autistic? Second, many of the cases reported are not described well enough for one to be able to determine whether or not they meet currently accepted diagnostic criteria. (Some cases clearly do not meet criteria.) Third, it remains a puzzle what pathophysiological mechanism might unite these diverse etiologically defined conditions that are associated with autism. There is no obvious common pathophysiology among such diverse conditions as congenital rubella (an infection), hypsarrhythmia (a particular EEG pattern), recessively inherited phenylketonuria, and the X-linked fragile X condition. However, investigations that might answer that question, such as PET scanning or postmortem neurochemical investigations of autistic children with known etiologies, have never been attempted.

With the possible exception of fragile X, such cases represent a tiny proportion of all cases of autism, but it is worthwhile reviewing these often cited associations to see just how much evidence there is for them, and because they may suggest clues about the etiology of idiopathic cases.

*Phenylketonuria.* Historically, the first genetic condition to be reported in associated with autism was phenylketonuria. Phenylketonuria (PKU) is an inborn error of metabolism, inherited as an autosomal recessive disorder (Folling, 1934, and usually, but not universally, associated with mental retardation. Most newborns in the United States are now screened for PKU, and a phenylalanine-free diet is instituted within the first weeks of life. The diet substantially diminishes the cognitive behavioral handicap, although Stevenson and colleagues (Stevenson et al., 1979) found a high rate of behavioral deviance in an unselected school-aged sample with PKU that had been treated from infancy. None were autistic or had other behaviors common to autistic children.

From the few reports that describe the behavior of children with PKU prior to the availability of early treatment, it is clear that in addition to (and sometimes independent from) mental retardation, the children's behavior was severely deviant. In more than half the cases, the children were unfriendly, were often mute, and had repetitive behaviors. This literature is reviewed in an often quoted paper by Friedman (1969), who asserts that most children with untreated PKU are autistic. However, it is not entirely

clear from his paper how autism was conceptualized. In most of the papers referred to be Friedman, the behavioral descriptions were not sufficiently detailed (Kratzer, 1959; Leland, 1957; Bjornson, 1964; Sutherland, Berry, & Shirkey, 1960) to provide convincing evidence that the children actually met criteria for autism, although in most cases at least one autistic symptom was described.

It is of interest that not all socially unresponsive children with PKU were mentally retarded by IQ testing (Sutherland et al., 1960; Blainy & Gulliford, 1956; Cowie, 1951; Bjornson, 1964), and reports from the 1950s and 1960s suggest that when dietary treatment was instituted after infancy, IQ showed no improvement, but that autistic symptoms frequently disappeared (Lewis, 1959; Bickel et al., 1954; Berry, Sutherland, Guest, & Umbarger, 1958; Armstrong & Tyler, 1955; Armstrong, Low, & Bosma, 1957; Blainy & Guillford, 1956; Woolf, Griffiths, & Moncrieff, 1955).

In his review, Friedman concluded that autism and mental retardation were separate manifestations of PKU, as evidenced by the presence of autistic symptoms in normally intelligent children with PKU and by the improvement of autistic symptoms, but not mental retardation, when a phenylalanine-free diet was begun after infancy.

Untreated PKU and PKU treated after infancy provide a useful illustration of the separability of autistic symptoms, if not autism, and mental retardation within a single condition, and within a single case. This observation supports the hypothesis that on a pathophysiological level, autism and mental retardation have different mechanisms.

*Tuberous Sclerosis and Neurofibromatosis.* There may also be specific association between autism and tuberous sclerosis, a neurocutaneous disorder inherited as an autosomal dominant trait. In severe cases the manifestations include mental retardation that is not present from birth but gradually worsens, facial nevi or adenoma sebaceum (also absent in younger children) commonly seen in a "butterfly" distribution over the cheeks, and epilepsy (Rosenberg & Pettergrew, 1980). The disease is transmitted by an affected parent who has milder manifestations or may represent a new mutation. The most common type of EEG pattern in epileptic infants with tuberous sclerosis is hypsarrhythmia (Hunt, 1983a, 1983b, 1983c), and the reported association with autism is not with tuberous sclerosis itself but rather with hypsarrhythmia, which can have other etiologies (Taft & Cohen, 1971; Riikonen & Amnell, 1981). The cases reported both by Taft and Cohen and by Riikonen and Amnell were well described and typically autistic. The prevalence of autism in a case series of children with tuberous sclerosis has not been reported, so that the strength of the association with autism is unknown. In her series of 97 children with

tuberous sclerosis, Hunt (1983c) alluded to a high prevalence of communication disorders, especially in those children with hypsarrhythmia, but did not report specific psychiatric diagnoses.

Another neurocutaneous disorder, neurofibromatosis, also inherited as an autosomal dominant with variable severity of symptoms, was recently reported in association with autism. Neurofibromatosis, also called von Recklinghausen's disease, is characterized by flat, pigmented nevi, tumors (neurofibromas) of the cranial and peripheral nerves and skin, and a predisposition to other tumors. Gillberg and Forsell (1984) reported neurofibromatosis in 6% of autistic children who were ascertained through a community survey. While it is only a single report and needs confirmation, it warrants follow-up because of the systematic nature of the sample. It is somewhat surprising that the association has not been noted previously, but without systematic family histories and physical examinations on each case, the diagnosis could easily be missed. The manifestations in parents are usually mild, and even in severe cases, signs accumulate only with age so that young children may have few stigmata.

Even if there is no specific association with autism, the neurocutaneous disorders may be useful in the investigation of the neuropathology or pathophysiology of autism. Both neurofibromatosis and tuberous sclerosis have brain lesions that are variable in location, so that neuropathological studies comparing cases with and without associated autism may suggest brain areas central to the pathophysiology of autism.

These single gene disorders reported in association with autism are autosomal disorders, and thus the sex ratio of affected persons would be expected to be equal, while the sex ratio in autism is about 4:1 males (see Lord & Schopler, 1987). It is not clear from the various case reports whether the children with autosomal disorders who are also autistic are for some reason more likely to be boys, but in the few reports where sex is mentioned, the ratio of boys to girls appears to be equal. For the most part, these disorders have not appeared in association with "pure" autism but rather with autism accompanied by severe mental retardation, although exceptions are reported. It does appear that the sex ratio among severely retarded autistic children is somewhat less skewed to males (Lord, Schopler, & Revick, 1982), so that it is possible that among the severely retarded autistic population autosomal recessive conditions may have some numerical importance.

*Fragile X.* One single gene disorder, fragile X, has recently been discovered that is X-linked, is found predominantly in males, and appears to have a specific association with autism. The clinical features are somewhat variable, but in its most severe form, the affected males are mentally retarded after puberty, have enlarged testicles. They tend to be hypotonic and

to have somewhat long faces and large ears, but as children they do not appear particularly dysmorphic (Brondum-Nielsen, 1983). This syndrome of X-linked mental retardation was clinically recognized before the discovery of its association with fragile X and was known as the Martin-Bell syndrome (Martin & Bell, 1943).

Males with the genotype vary in IQ. Most are severely retarded, but a few are normally intelligent and have offspring (Sherman, Morton, Jacobs, & Turner, 1984; Varley, Holm, & Eren, 1985). Female carriers are occasionally mildly mentally retarded, possibly related to whether their normal or their fragile X is inactivated (Turner, Brookwell, Daniel, Selikowitz, & Zilibowitz, 1980; Knoll, Chudley, & Gerrard, 1984). In one report (Largo & Schinzel, 1985), IQ was reported to vary inversely with age, suggesting that damage to the brain is progressive. There are a few reports of prominent language impairment, but beyond the physical stigmata and mental retardation, the phenotype has yet to be characterized in a large sample.

The association of the Martin-Bell syndrome with a fragile site at the end of the long arm of the X chromosome was first reported by Lubs (1969), but the association was not confirmed until Sutherland (1977) discovered that demonstration of the fragile site required folate-poor tissue culture media. Even under optimal growing conditions, only a minority of the cells show the fragile site, and it cannot always be demonstrated in female carriers. The prevalence of fragile X is still uncertain, but it is probably the second (after Down's syndrome) most common genetic cause of mental retardation. Estimates of incidence vary between 1 and 3 per 1,000 live births (Herbst & Millner, 1980; Blomquist, Gustavson, Holmgren, Nordenson, & Sweins, 1982; Blomquist, Gustavson, Holmgren, Nordenson, & Palsson-Strae, 1983).

Fragile sites on chromosomes are areas that appear thinner than the rest of the chromosome when observed in metaphase preparations, as if that length of the chromosome were fragile and could easily break apart. Fragile sites have been observed on several chromosomes, but except for the site at Xq27 associated with the Martin-Bell syndrome, they have not been associated with any specific disorder (Sutherland, 1985).

Even though fragile X is transmitted in a Mendelian fashion, the genetics and the genetic counseling are complex (Fryns, 1984; Sherman et al., 1985). For example, in families with fragile X, evidence suggests that the mothers of sporadic male cases are highly likely to be carriers, implying that new mutations occur most often in males (the maternal grandfather) at spermatogenesis. Recurrence rates of mental retardation in subsequent male offspring may be less than the theoretical 50% because not all males with fragile X are retarded; also, there is some risk for mild mental retardation to female offspring of carriers (Sherman et al., 1984; Hagerman & McBogg, 1983).

The first case descriptions of autism in association with fragile X appeared simultaneously in 1982 (Brown et al., 1982; Meryash, Szymanski, & Gerald, 1982). Meryash et al. described a 6-year-old boy with a long face, hypotonia, delayed motor development, severe mental retardation, and autistic features. Brown's cases were not described individually but were retarded and had large testes. The autistic children reported subsequently (August & Lockhart, 1984; Blomquist et al., 1985; De Arce & Kearns, 1984; Fryns, 1984; Gillberg, 1983; Jorgensen, Nielsen, Isager, & Mouridsen, 1984; Kerbeshian, Burd, & Martsoff, 1984; Largo & Schinzel, 1985; Levitas et al., 1983; McGillivray, Dill, Sandercock, Herbst, & Tischler, 1984; Watson et al., 1984) have all been males, and most appear from the case descriptions to have considerable mental retardation, although few IQ scores have yet appeared. In Blomquist's series, two children had IQs above 70 (Blomquist et al., 1983).

While some reports include clinical descriptions of autistic children, others simply state that the children met either DSM-III (American Psychiatric Association, 1980) or Rutter's criteria (Rutter, 1967). Two authors provide some details. Among six fragile X autistic children reported by Levitas et al. (1983), one did not meet the criterion for language deviation and none had pronoun reversal, but all were socially deviant and had repetitive and stereotyped behaviors. Five of the six were self-abusive. Largo and Schinzel (1985) reported 13 boys from three fragile X families, with no apparent selection for autism. These cases are less well described, but most had some autistic symptoms, and several would meet criteria for autism. Five were self-abusive, and an additional four were aggressive to others. From these limited clinical descriptions, it appears that some, and possibly most, fragile X males have some autistic symptoms and a portion are classically autistic. Although based on small numbers, they may tend to have less pronoun reversal and more self-abuse than average for autism.

It is not yet clear how many autistic boys have fragile X. Watson et al. (1984) reported a rate of 5%. The rate was 10% among their cases who were living in institutions. McGillivray et al. (1984) found fragile X in 12% of an institutionalized sample of autistic children, and Blomquist et al. (1985) found fragile X in 16% of autistic children ascertained through a variety of sources. In a sample ascertained because of severe language disability, Jorgensen et al. (1984) diagnosed autism in 11 of 23 children. One of the 11 autistic children had fragile X. At the other extreme, some investigators have found *no* fragile X among their autistic samples (Goldfine et al., 1985; Venter, Hof, Coetzee, Van der Walt, & Retief, 1984; Pueschel, Herman, & Groden, 1985). The reasons for this variation are not yet clear, but they may have to do with diagnostic criteria for autism and possibly with the methods used to detect fragile X. The procedure is by no means routine,



and methods used to increase the expression of the fragile site may lead to false positives (Hargerman & Mcbogg, 1983; De Arce & Kearns, 1984).

Given the uncertain prevalence of fragile X and of autism, both of which vary widely depending on the diagnostic criteria (Gottesman & Shields, 1982; Wing & Gould, 1979), and given the uncertain rate of fragile X in autism populations and the unknown rate of autism among boys with fragile X, it is impossible to say at the present time how strong the association is between autism and fragile X. Both are relatively common conditions and both are associated with mental retardation, so that some association would be expected by chance. Further studies are needed that address the rate of autism in an unselected fragile X population, and that compare the rate of fragile X in autistic samples according to their clinical features.

Nearly all the genetic studies of idiopathic autism described in earlier sections of the chapter were carried out before the reports of the association between autism and fragile X. Could the concordance of twins or familial aggregation in sibs be accounted for by the fragile X mutation? Most of the concordant twin pairs and sib pairs have been male (Folstein & Rutter 1977; Ritvo, Freeman, et al. 1985), so the possibility exists. However, among Ritvo's 34 families with autism in two or more sibs discussed above, only 1 fragile X family was found (Spence et al., 1985). Also as mentioned above, Baird and August (1985) found fragile X in only one of their familial cases. Therefore, it is clear that fragile X will account for some but not all of the familial aggregation of autism. At present, we can only conclude that some children with autism have fragile X, but how many have it, or whether their autistic features are always typical is not clear. From a practical viewpoint, the diagnostic evaluation of an autistic boy should include a karyotype for fragile X, preferably carried out in a laboratory experienced with the procedure.

*Biochemical Abnormalities:  
Their Relationship to Single Gene Disorders*

Over the years many investigators have reported autism in association with abnormal levels of various metabolites (for reviews, see Coleman, 1972; Young, Kavanagh, Anderson, Shaywitz, & Cohen, 1982). Often it has not been possible to replicate the results (e.g., Boullin, Coleman, O'Brien, & Rimland, 1971, Boullin et al., 1982; Gillberg, Trygstad, & Foss, 1982; LeCouteur, Trygstad, Howlin, Robertson, & Rutte 1986), and sometimes the reported cases are not clearly autistic (e.g., Jaeken & Van den Berghe, 1984).

Even when the findings have been replicated, as in the finding of elevated serotonin in about a third of autistic children (Young et al., 1983),

the meaning of the finding has not been clear. First, similar elevations are often found in nonautistic retarded children (Rutter, 1978). While this is certainly reason for pause, it does not necessarily render the finding meaningless. Different metabolic abnormalities, associated with different phenotypes, can result in similar abnormalities in bodily fluids.

The second reason that the findings are confusing is that surprisingly few attempts have been made to study family patterns. Abnormal metabolites are most often due to some recessively inherited disorder, which can be confirmed by finding similar abnormalities in other affected family members, or finding intermediate levels in parents who would be obligate carriers in the case of autosomal recessive inheritance. In the only systematic study of serotonin levels in parents and sibs (Kuperman, Beeghly, Burns, & Tsai, 1985), there was a tendency for levels to aggregate in families, but there was no reported relationship of levels to clinical abnormalities in other family members.

Histidenemia has also been reported in a few autistic children. Studies of other family members have in this instance clearly documented that the association is by chance (Folstein & Rutter, 1977; Kotsopoulos & Kutty, 1979).

## **GENETIC EVALUATION AND COUNSELING FOR FAMILIES WITH AN AUTISTIC CHILD**

The evaluation of every newly diagnosed autistic child should include a medical work-up for genetic disorders, beginning with a thorough family history, a history of perinatal injury and other illnesses, an examination looking for physical stigmata of genetic and neurological disorders, and some screening tests for the genetic disorders that may be associated with autism.

### *Taking a Family History*

In taking the family history, it is important to ask not only about autism and mental retardation but also about problems with reading and language, and about social eccentricities. However, it must be cautioned that we are currently uncertain if and how these milder conditions contribute to the risk for recurrence of autism. The family should be systematic, asking in turn about each first- and second-degree relative, and should be extensive enough to be able to detect X linkage or autosomal dominant patterns where not all heterozygotes are severely affected, as in fragile X, tuberous sclerosis, or neurofibromatosis. A family history that

included only first-degree relatives (parents, sibs, and children of the proband) would not reveal the pattern of X-linked inheritance.

A family pattern is consistent with X-linkage if no male-to-male transmission is found. Affected cases should all be males, although carrier females may occasionally have mild symptoms, at least in the case of fragile X. This may also be true for other X-linked forms of cognitive disability. New mutations do occur in fragile X, and the failure to find other affected family members does not rule out the need for a karyotype. Figure 1 shows a pedigree for a fragile X family.

In autosomal recessive disorders, there are not usually any other affected family members, and any other cases will be found among siblings. Affected sib pairs are equally likely to be same-sexed or opposite-sexed, and the proband either male or female. Sometimes there is consanguinous mating, although this may have occurred several generations earlier. If the parents' families came from the same isolated community, investigation of the ancestors for consanguinity may be indicated. Figure 2 shows a family with phenylketonuria, an autosomal recessive condition, with only one affected child. In autosomal recessive disorders, the risk to subsequently conceived sibs of the proband is 25%. However, the risk to offspring of normal sibs is very small. Even if the sib is a carrier, the probability of marrying

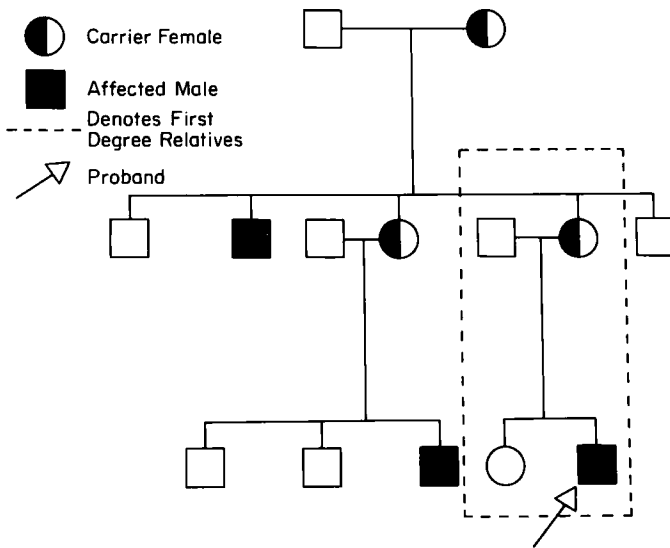
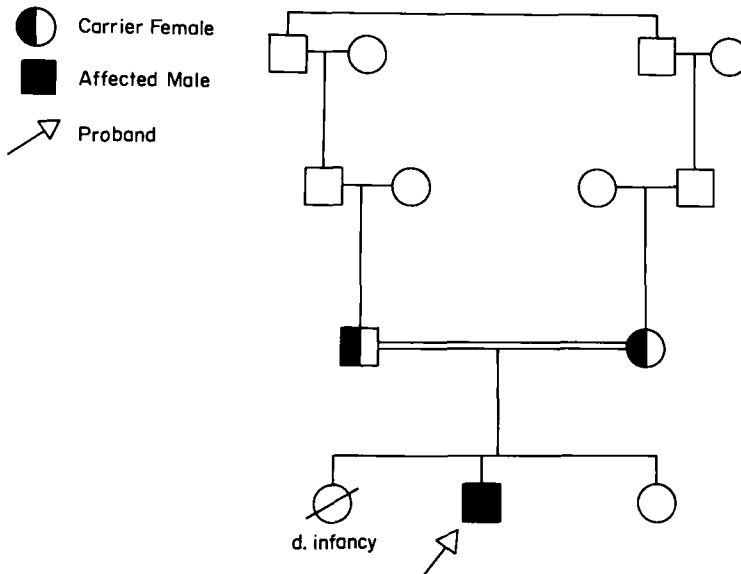


Fig. 1. This pedigree demonstrates X-linked recessive inheritance, with only males affected and no male-to-male transmission. Note that no familial aggregation would be discovered if our information was limited to first degree relatives (enclosed by box).



**Fig. 2.** This pedigree demonstrates autosomal recessive inheritance with normal carrier parents and one affected child. The recurrence risk for subsequent children is 25%. The double line indicates consanguinity. The parents are related through their grandparents.

another carrier is small unless the family lives in an inbred, isolated community.

In autosomal dominant inheritance, one expects cases over several generations and in several collateral lines, but usually only in one parental line. However, not all affected persons will necessarily show the complete phenotype for the condition, so it is necessary to be familiar with the range of symptoms in order to take an accurate pedigree. The only autosomal dominant disorders that are known to be associated with autism are quite rare.

### *History of Early Injury and Illness*

In a genetic evaluation for autism it is equally important to look for detectable nongenetic causes. At present, this endeavor is limited to history taking. A detailed history of complications of pregnancy and delivery, as well as serious illness or accidents within the first 3 years of life, is needed. If there is any suggestion of trouble, the medical record should be carefully reviewed. Sometimes the situation in the delivery room is minimized to the mother, but accurately documented in the record.

Because of the possible interaction between genetic predisposition and mild pre- and perinatal difficulties, it is not possible to discount a risk of recurrence of autism based on a mildly abnormal birth history or mild illness early in life. Also, parents often search their memories for possible explanations for their child's disorder and put undue emphasis on minor events in their attempt to find a cause. However, if there is a documented serious condition such as intracranial hemorrhage, perinatal hypoxia followed by seizures in the neonatal period, or some other severe insult, it is most likely an adequate explanation for the autism syndrome.

### *Physical Examination and Tests*

The physical and neurological examination must be thorough, with the child undressed, so that abnormalities of pigmentation seen in the neurocutaneous disorders can be observed, and so that testicular size can be examined. Testicular size before puberty may be in the normal range in fragile X. Ear size, which may be large in children with fragile X, should be noted, and minor congenital anomalies (Waldrop & Halverson, 1971) systematically documented.

Blood should be sent for amino acid screening, karyotyping, specifically requesting fragile X testing for males, and if there is a history of gradual decline or suggestive findings on the physical examination, appropriate examinations for mucopolysaccharidoses and other storage diseases may be indicated. These more specialized examinations should be undertaken in consultation with a specialist in medical genetics.

### *Genetic Counseling*

The purpose of genetic counseling as it applies to autism is to provide to the parents, and occasionally the adult sibs, of an autistic child information about the risk for recurrence of autism in subsequent pregnancies. As information about possible genetic contributions to autism are disseminated, we expect that more families will request counseling.

At the present time, accurate predictions of risk are possible only a small minority of cases with some detectable single gene disorder (such as the fragile X). In these cases, the risk is linked with that for the medical disorder with which the autism is associated. Referral to medical geneticist is indicated in such instances in order both to carry out the investigations of other family members needed for an accurate appraisal of risk and to provide the knowledge needed for skilled genetic counseling.

In the cases where autism is associated with a clear history of severe perinatal or postnatal trauma giving rise to neurological complications at

the time, and where there is no family history of autism or cognitive disabilities, it may be inferred that the risk of recurrence is probably very low.

The more usual circumstance, however is of autism for which there is no known single gene disorder and no known nongenetic cause. In these cases the recurrence risk for autism has never been estimated. We estimate that about 1 to 3% of families have two autistic children and that 10 to 15% of the families have children with cognitive disabilities (including both persistent mental retardation and transient language handicaps). However, even if these figures are accurate, they cannot be translated into a risk for recurrence of autism in a subsequent pregnancy. In samples of families where the affected child is frequently an *only* or *lastborn* child (as is often the case for autism), familial aggregation will be usually, even if the recurrence risk for a subsequent pregnancy is actually high.

## CONCLUSIONS

Family and twin studies of idiopathic autism have shown that autism is occasionally aggregated in families and that disorders of cognition and language are found commonly among the family members of autistic probands. While there are no firm data about the aggregation of social eccentricities in the families of autistic probands, such as found in Asperger's syndrome, clinical experience suggests that it may well occur. The actual prevalence of such disorders in first-degree relatives is not known. No studies have tested parents and few studies have tested sibs systematically for cognitive and language disorders. No studies of any kind have tested family members for social deficits similar to those seen in autism.

These limited data are open to numerous possible explanations and interpretations. It may be that many different etiologies will be found for autism, some of which will surely be genetic. It is equally possible that the bulk of classically diagnosed cases will share a single etiology, perhaps an inherited deficit in social and language processing that interacts with a variety of mild environmental insults that together result in the full autism syndrome. With respect to genetic mechanisms, there are also numerous possibilities that are not mutually exclusive, ranging from one or more single gene mutations to complex multifactorial determinations.

Several different kinds of studies are needed in order to sort out the various possibilities. A detailed family study based on a systematically ascertained sample is perhaps the most pressing need. In addition to a detailed clinical and laboratory examination of each autistic proband, all first-degree relatives should be examined and tested for social and cognitive

deficits, and detailed pedigrees of the extended families should be collected. Such a family study population would provide a systematically ascertained, diagnosed, and examined sample, appropriate for use in a variety of genetic and biochemical analyses. Rates and patterns of family transmission and their relationship to the clinical features of the autistic proband could be studied. The sample could be tested for its compatibility with a variety of models of inheritance. Families could be screened for fragile X and other genetic disorders, and families appropriate for detailed molecular genetic study could be found. This could include both biochemical and state-of-the-art genetic linkage analyses that have become possible through advances in molecular genetics.

## REFERENCES

- American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington D.C.: Author.
- Armstrong, M. D., Low, N. L., & Bosman, J. F. (1957). Studies on phenylketonuria, IX. Further observations on the effect of phenylalanine-restricted diet on patients with phenylketonuria. *American Journal of Clinical Nutrition*, *5*, 543-554.
- Armstrong, M. D., & Tyler, F. H. (1955). Studies on phenylketonuria, I. Restricted phenylalanine intake and phenylketonuria. *Journal of Clinical Investigation*, *34*, 565-580.
- August, G. J., & Lockhart, L. H. (1984). Familial autism and the fragile X chromosome. *Journal of Autism and Developmental Disorders*, *14*, 197-204.
- August, G. J., Stewart, M. A., & Tsai, L. (1981). The incidence of cognitive disabilities in the siblings of autistic children. *British Journal of Psychiatry*, *138*, 416-422.
- Baird, T. D., & August, G. J. (1985). Familial heterogeneity in infantile autism. *Journal of Autism and Developmental Disorders*, *15*, 315-321.
- Bartak, L., Rutter, M., & Cox, A. (1975). A comparative study of infantile autism and specific developmental receptive language disorder. I. The children. *British Journal of Psychiatry*, *126*, 127-145.
- Bauman, M., & Kemper, T. L., (1985). Histoanatomic observations of the brain in early infantile autism. *Neurology*, *35*, 866-874.
- Berry, H. K., Sutherland, B. S., Guest, G. M., & Umbarger, B. (1958). Chemical and clinical observations during treatment of children with phenylketonuria. *Pediatrics*, *21*, 929-940.
- Bickel, H., Gerrard, J., & Hickmans, E. M. (1954). The influence of phenylalanine intake on the chemistry and behavior of a phenylketonuric child. *Acta Paediatrica* *43*, 64-77.
- Bjornson, J. (1964). Behavior in phenylketonuria: Case with schizophrenia. *Archives of General Psychiatry*, *10*, 65-70
- Blainy, J. D., & Gulliford, R. (1956). Phenylalanine-restricted diets in the treatment of phenylketonuria. *Archives of Disease in Childhood*, *31*, 452-566.
- Blomquist, H. K., Bohman, M., Edvinsson, S. O., Gillberg, C., Gustavson, K-H., Holmgren, C., & Wahlstrom, J. (1985). Frequency of the fragile X syndrome in infantile autism. A Swedish multicenter study. *Clinical Genetics*, *27*, 113-117.
- Blomquist, H. K., Gustavson, K-H., Holmgren, G., Nordenson, I., & Palsson-Strae, U. (1983). Fragile X syndrome in mildly mentally retarded children in a Northern Swedish county. A prevalence study. *Clinical Genetics*, *24*, 393-398.
- Blomquist, H. K., Gustavson, K-H., Holmgren, G., Nordenson, I., & Sweins, A. (1982). Fragile site X-chromosomes and X-linked mental retardation in severely retarded boys in a northern Swedish county. A prevalence study. *Clinical Genetics*, *21*, 209-214.

- Boullin, D. J., Coleman, M., O'Brien, R. A., & Rimland, B. (1971). Laboratory predictions of infantile autism, based on 5-hydroxy-tryptamine efflux from blood platelets and their correlation with the Rimland E2 scores. *Journal of Autism and Childhood Schizophrenia*, 1, 63-71.
- Boullin, D. J., Freeman, B. J., Geller, E., Ritvo, E., Rutter, M., & Yuwiler, A. (1982). Toward the resolution of conflicting findings (Letter to the editor). *Journal of Autism and Developmental Disorders*, 12, 97-98.
- Brondum-Nielsen, K. (1983). Diagnosis of the fragile X syndrome (Martin-Bell syndrome). Clinical findings in 27 males with the fragile site at Xq<sup>28</sup>. *Journal of Mental Deficiency Research*, 27, 211-226.
- Brown, W. T., Jenkins, E. C., Friedman, E., Brooks, J., Wisniewski, K., Raguthu, S., & French, J. (1982). Autism is associated with the fragile X syndrome. *Journal of Autism and Developmental Disorders*, 12, 303-308.
- Burgoine, E., & Wing, L. (1983). Identical triplets with Asperger's syndrome. *British Journal of Psychiatry*, 143, 261-265.
- Chess, S., Fernandez, P. B., & Korn, S. J. (1978). Behavioral consequences of congenital rubella. *Journal of Pediatrics*, 93, 699-703.
- Chess, S., Korn, S. J., & Fernandez, P. B. (1971). *Psychiatric disorders of children with congenital rubella*. New York: Brunner/Mazel.
- Chick, J., Waterhouse, L., & Wolff, S. (1979). Psychological construing in schizoid children grown up. *British Journal of Psychiatry*, 135, 425-430.
- Coleman, M. (1972). Studies of the autistic syndromes. In R. Katzman (Ed.), *Congenital and cognitive disorders*. New York: Raven Press.
- Coleman, P. D., Romano, J., Lapham, L., & Simon, W. (1985). Cell counts in cerebral cortex of an autistic patient. *Journal of Autism and Developmental Disorders*, 15, 245-255.
- Cowie, W. A. (1951). An atypical case of phenylketonuria. *Lancet*, 272-273.
- Crome, L., & Stern, J. (1972). *Pathology of mental retardation* (2nd ed.). Edinburgh: Churchill Livingstone.
- Darby, J. K. (1976). Neuropathologic aspects of psychosis in children. *Journal of Autism and Childhood Schizophrenia*, 6, 339-352.
- De Arce, M., & Kearns, A. (1984). The fragile X syndrome: The patients and their chromosomes. *Journal of Medical Genetics*, 21, 84-91.
- Deykin, E. Y., & MacMahon, D. (1979). The incidence of seizures among children with autistic symptoms. *American Journal of Psychiatry*, 136, 1310-1312.
- Deykin, E. Y., & MacMahon, B. (1980). Pregnancy, delivery and neonatal complications among autistic children. *American Journal of Disease of Children*, 134, 860-864.
- Dover, G. J., Boyer, S. H., & Pembrey, M. E. (1981). F-cell production in sickle cell anemia: Regulation of genes linked to beta-hemoglobin locus. *Science*, 211, 1441-1444.
- Finegan, J., & Quadrington, B. (1979). Pre-, peri-, and neonatal factors and infantile autism. *Journal of Child Psychology and Psychiatry*, 20, 119-128.
- Folling, A. (1934). Phenylpyruvic acid as a metabolic anomaly in connection with imbecility. *Zeitschrift für Physiologische Chemie*, 224, 169-176.
- Folstein S., & Rutter, M. (1977). Infantile autism: A genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry*, 18, 297-231.
- Friedman, E. (1969). The "autistic syndrome" and phenylketonuria. *Schizophrenia*, 1, 249-261.
- Fryns, J. P. (1984). The fragile X syndrome: A study of 83 families. *Clinical Genetics*, 26, 497-528.
- Gillberg, C. (1983). Identical triplets with infantile autism and the fragile X syndrome. *British Journal of Psychiatry*, 143, 256-260.
- Gillberg, C., & Forsell, C. (1984). Childhood psychosis and neurofibromatosis—More than a coincidence? *Journal of Autism and Developmental Disorders*, 14, 1-8.
- Gillberg, C., & Gillberg, I. C. (1983). Infantile autism: A total population study of nonoptimal, pre-, peri-, and neonatal conditions. *Journal of Autism and Developmental Disorders*, 13, 153-166.



- Gillberg, C., Trygstad, O., & Foss, I. (1982). Childhood psychosis and urinary excretion of peptides and protein-associated peptide complexes. *Journal of Autism and Developmental Disorders*, *12*, 229-241.
- Goldfine, P. E., McPherson, P. M., Heath, G. A., Hardesty, V. A., Beauregard, L. J., & Gordon, S. (1985). Association of fragile X syndrome with autism. *American Journal of Psychiatry*, *142*, 108-110.
- Gottesman, I. I., & Shields, J. (1982). *Schizophrenia: The epigenetic puzzle*. Cambridge: Cambridge University Press.
- Gusella, J. F., Tanzi, R. E., Anderson, M. A., Hobbs, W., Gibbon, K., Raschtchian, R., Gilliam, T. C., Wallace, M. R., Wexler, N. S., & Conneally, P. M. (1984). DNA markers for nervous system diseases. *Science*, *225*, 1320-1326.
- Hangerman, R. J., & Mc Bogg, P. M. (1983). *The fragile X syndrome, diagnosis, Biochemistry, and intervention*. Dillon, Colorado: Spectra.
- Hanson, D. R., & Gottesman, I. I. (1976). The genetics, if any, of infantile autism and childhood schizophrenia. *Journal of Autism and Childhood Schizophrenia*, *6*, 209-234.
- Herbst, D. S., & Miller, J. R. (1980). Non-specific X-linked mental retardation. II. The frequency in British Columbia. *American Journal of Medical Genetics*, *7*, 461-469.
- Hunt, A. (1983a). Tuberous sclerosis: A survey of 97 cases. I: Seizures, pertussis immunization handicap. *Developmental Medicine and Child Neurology*, *25*, 346-347.
- Hunt, A. (1983b). Tuberous sclerosis: A survey of 96 cases. II: Physical findings. *Developmental Medicine and Child Neurology*, *25*, 350-352.
- Hunt, A. (1983c). Tuberous sclerosis: A survey of 96 cases. III: Family aspects. *Developmental Medicine and Child Neurology*, *25*, 353-357.
- Jaeken, J., & Van den Berghe, G. V. (1984). An infantile autistic syndrome characterised by the presence of succinylpurines in body fluids. *Lancet*, 1058-1061.
- Jorgensen, O. S., Nielsen, K. B., Isager, T., & Mouridsen, S. E. (1984). Fragile X Chromosome child psychiatric patients with disturbances of language and social relationships. *Acta Psychiatrica Scandinavica* *70*, 510-514.
- Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child* *2*, 217-250.
- Kerbeshian, J., Burd, L., & Martsoff, J. (1984). A family with fragile X syndrome. *Journal of Nervous and Mental Disease* *172*, 549-551.
- Kidd, K. K., & Pauls, D. L. (1982). Genetic hypotheses for Tourette syndrome. In T. N. Chase & A. J. Friedhoff (Eds.), *Gilles de la Tourette syndrome*, *Advances in Neurology*, *35*, 243-249.
- Knoll, J. H., Chudley, A. E., & Gerrard, J. W. (1984). Fragile (X) X-linked mental retardation. II. Frequency and replication pattern of fragile (X) (q28) in heterozygotes. *American Journal of Human Genetics*, *36*, 640-645.
- Kolvin, I. (1971). Psychoses in childhood—A comparative study. In M. Rutter (Ed.), *Infantile autism: Concepts, characteristics and treatment*. London: Churchill Livingstone.
- Kotsopoulos, S., & Kutty, K. M. (1979). Histidinemia and infantile autism. *Journal of Autism and Developmental Disorders*, *9*, 55-60.
- Kratter, F. E. (1959). The physiognomic, psychometric, behavioral and neurological aspects of phenylketonuria. *Journal of Mental Science*, *105*, 421-427.
- Kuperman, S., Beeghly, J. H. L., Burns, T. L., & Tsai, L. Y. (1985). Serotonin relationships of autistic probands and their first-degree relatives. *Journal of the American Academy of Child Psychiatry*, *24*, 186-190.
- Laird, G. J., & Schimke, R. N. (Eds.). (1979). *Clinical genetics: A source book for Physicians*. New York: Wiley.
- Largo, R. H. & Schinzel, A. (1985). Developmental and behavioural disturbances in 13 boys with fragile X syndrome. *European Journal of Pediatrics*, *143*, 269-275.
- LeCouteur, A., Trygstad, O., Howlin, P., Robertson, S., & Rutter, M. (1986). *Urinary peptide findings in autism: a non-replication*. Manuscript in preparation.
- Leland, H. (1957). Some psychological characteristics of phenylketonuria. *Psychological Reports*, *3*, 373-376.

- Levitas, A., Hagerman, R. J., Braden, M., Rimland, B., McBogg, P., & Matteus I. (1983). Autism and the fragile X syndrome. *Journal of Developmental and Behavioral Pediatrics*, 3, 151-158.
- Lewis, E. (1959). The development of concepts in a girl after dietary treatment for phenylketonuria. *British Journal of Medical Psychology*, 32, 282-287.
- Lord, C., & Schopler, E. (1987). Neurobiological implications of sex differences in autism. In E. Schopler & G. B. Mesibov (Eds.), *Neurobiological issues in autism* (pp. 191-211). New York: Plenum Press.
- Lord, C., Schopler, E., & Revicki, D. (1982). Sex differences in autism. *Journal of Autism and Developmental Disorders*, 12, 317-330.
- Lotter, V. (1966). Epidemiology of autistic conditions in young children. I. Prevalance. *Social Psychiatry*, 1, 124-137.
- Lotter, V. (1967). Epidemiology of autistic conditions in young children. II. Some characteristics of the parents and children. *Social Psychiatry*, 1, 163-173.
- Lubs, H. A. (1969). A marker X chromosome. *American Journal of Human Genetics*, 21, 231.
- Martin, J. P., & Bell, J. (1943). A pedigree of mental defect showing sex-linkage. *Journal of Neurology and Psychiatry*, 6, 154-157.
- McGillivray, B. C., Dill, E. J., Sandercock, J., Herbst, D. S., & Tischler, B. (1984). Infantile autism—An occasional feature of X-linked mental retardation. *American Journal of Human Genetics*, 36.
- McKusick, V. A. (Ed.). (1969). *Human genetics*. Englewood Cliffs, New Jersey: Prentice-Hall.
- McKusick, V. A. (1983). *Mendelian inheritance in man. Catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes* (6th ed.). Baltimore: Johns Hopkins University Press.
- Meryash, L., Szymanski, L. S., & Gerald, P. S. (1982). Infantile autism associated with the fragile X syndrome. *Journal of Autism and Developmental Disorders*, 12, 295-301.
- Minton, J., Campbell, M., Green, W., Jennings, S., & Samit, C. (1982). Cognitive assessment of siblings of autistic children. *Journal of the American Academy of Child Psychiatry*, 213, 256-261.
- Mittler, P. (1971). *The study of twins*. Harmondsworth: Penguin.
- Pueschel, S. F., Herman, R., & Groden, G. (1985). Brief report: Screening children with autism for fragile X syndrome and phenylketonuria. *Journal of Autism and Developmental Disorders*, 15, 335-343.
- Richardson, S. A., Koller, H., Katz, M., & McLaren, J. (1980). Seizures and epilepsy in a mentally retarded population over the first 22 years of life. *Applied Research in Mental Retardation* 1, 123-138.
- Riikonen, R., & Amnell, G. (1981). Psychiatric disorders in children with earlier infantile spasms. *Developmental Medicine and Child Neurology*, 23, 747-760.
- Ritvo, E. R., Freeman, B. J., Mason-Brothers, A., Mo, A., & Ritvo, A. M. (1985). Concordance for the syndrome of autism in 40 pairs of afflicted twins. *American Journal of Psychiatry* 142, 74-77.
- Ritvo, E. R., Spence, M. A., Freeman, B. J. Mason-Brothers, A., Mo, A., & Marazita, M. L. (1985). Evidence for autosomal recessive inheritance in 46 families with multiple incidences of autism. *American Journal of psychiatry* 142, 187-192.
- Rosenberg, R. N., & Pettegrew, J. D. (1980). Genetic disease of the nervous system. In J. M. Dietschy & R. N. Rosenberg (Eds.), *The science of clinical medicine. Neurology*, 5, 165-242. New York: Grune and Stratton.
- Rutter, M. (1967). Psychotic disorders in early childhood. In A. Coppen & A. Walk (Eds.), *British Journal of Psychiatry*, Special publication No. 1, Ashford, Kent: Headley Bros.
- Rutter, M. (1970). Autistic children: Infancy to adulthood. *Seminars in Psychiatry*, 2, 435-450.
- Rutter, M. (1974). The development of infantile autism. *Psychology Medicine*, 4, 147-163.
- Rutter, M. (1978). Serotonin, platelets and autism (Editorial). *British Medical Journal*, 1, 1651-1652.
- Rutter, M. (1979). Language, cognition and autism. In R. Katzman (Ed.), *Congenital and acquired cognitive disorders*. New York: Raven Press.
- Rutter, M. (1983). Cognitive deficits in the pathogenesis of autism *Journal of Child Psychology and Psychiatry*, 24, 513-531.

- Rutter, M., & Schopler, E. (1986). Autism and pervasive developmental disorders: Concepts and diagnostic issues. In M. Rutter, H. Tuma, & I. Lann (Eds.), *Assessment, diagnosis, and classification in child and adolescent psychiatry*. New York: Guildford Press.
- Sherman, S. L., Jacobs, P. A., Morton, N. E., Foster-Iskenius, U., Howard-Peebles, P. N., Nielson, K. B., Partington, M. W., Sutherland, G. R., Turner, G., & Watson, M. (1985). Further segregation analysis of the fragile X syndrome with special reference to transmitting males. *Human Genetics*, *69*, 289-299.
- Sherman, S. L., Morton, N. E., Jacobs, P. A., & Turner, G. (1984). The marker (X) syndrome: A cytogenetic and genetic analysis. *Annals of Human Genetics*, *48*, 21-37.
- Silva, P. A. (1986). Epidemiology, longitudinal course, and some associated factors: An update. In M. Rutter, W. Yule, & M. Bax (Eds.), *Language development and disorders* (Series in clinics and Developmental Medicine). London: Spastic International/Blackwell Scientific.
- Sparkes, R. S., & Freeman, B. J. (1985). Gene mapping studies with the syndrome of autism. *Behavior Genetics*, *15*, 1-13.
- Spence, M. A., Ritvo, E. R., Marazita, M. L., Funderburk, S. J., Sparkes, R. S., & Freeman, B. J. (1985). Gene mapping studies with the syndrome of autism. *Behavior Genetics*, *15*, 1-13.
- Stanley, F., & E. Alberman (Eds.). (1984). *The epidemiology of the cerebral palsies (Clinics in Developmental Medicine, No. 87)*. London: Blackwell Scientific/Philadelphia: J. B. Lippincot.
- Stevenson, J., Hawcroft, J., Lobascher, M., Smith, I., Wolff, O. H., & Graham, P. J. (1979). Behavioural deviance in children with early-treated phenylketonuria. *Archives of Disease Childhood*, *54*, 14-18.
- Sutherland, B. S., Berry, H. K., & Shirkey, H. C. (1960). A syndrome of phenylketonuria with normal intelligence and behavior disturbances. *Journal of Pediatrics*, *57*, 521-525.
- Sutherland, G. R. (1977). Fragile sites on human chromosomes: Demonstration of their dependence on the type of tissue culture medium. *Science*, *197*, 265-266.
- Sutherland, G. R. (1985). Heritable fragile sites on human chromosomes. XII. Population cytogenetics. *Annals of Human Genetics*, *49*, 153-162.
- Sutherland, G. R., Turner, G., & Watson, M. (1985). Further segregation analysis of the fragile X syndrome with special reference to transmitting males. *Human Genetics*, *69*, 289-299.
- Taft, L. T., & Cohen, H. J. (1971). Hypsarrhythmia and infantile autism: A clinical report. *Journal of Autism and Childhood Schizophrenia*, *1*, 327-336.
- Treffert, D. A., (1970). Epidemiology of infantile autism. *Archives of General Psychiatry*, *22*, 431-438.
- Turner, G., Brookwell, R., Daniel, A., Selikowitz, M., & Zilbowitz, M. (1980). Heterozygous expression of X-linked mental retardation and X-chromosome marker fra(X) (q27). *New England Journal of Medicine*, *303*, 662-664.
- Valle, D., Pai, G. B., Thomas, G. H., & Pyeritz, R. E. (1980). Homocystinuria due to cystathionine beta-synthase deficiency: Clinical manifestations and therapy. *John Hopkins Medical Journal*, *146*, 110-111.
- Varley, C. K., Holm, V A., & Eren, M. O. (1985). Cognitive and psychiatric variability in three brothers with fragile X syndrome. *Developmental and Behavioral Pediatrics*, *6*, 87-90.
- Venter, P. A., Hof, J. O., Coetzee, D. J., Van der Walt, C., & Retief, A. E. (1984). No marker (X) syndrome in autistic children. *Human Genetics*, *67*, 107.
- Waldrop, M. F., & Halverson, C. F. (1971). Minor physical anomalies and hyperactive behavior in young children. In J. Helmuth (Ed.), *Exceptional infant: studies in abnormalities* (Vol.2). New York: Brunner/Mazel.
- Watson, M. S., Leckman, J. F., Annex, B., Breg, W. R., Boles, D., Volkmar, F. R., Cohen, D. H., & Carter, C. (1984). Fragile X in a survey of 75 autistic males. *New England Journal of Medicine*, *310*, 1462.
- Williams, R. S., Hauser, S. L., Purpura, D., DeLong, R., & Swisher, C. N. (1980). Autism and mental retardation: Neuropathological studies performed in four retarded persons with autistic behavior. *Archives of Neurology*, *37*, 749-753.

- Wing, J. K., O'Connor, N., & Lotter, V. (1967). Autistic conditions in early childhood: A survey in Middlesex. *British Medical Journal* 3, 389-392.
- Wing, L. (1981). Asperger's syndrome: A clinical account. *Psychological Medicine*, 11, 115-130.
- Wing, L., & Gould, J. (1979). Severe impairments of social interactions and associated abnormalities in children: Epidemiology and classification. *Journal of Autism and Developmental Disorders*, 9, 11-30.
- Wing, L., Yeates, S. R., Brierley, L. M., & Gould, J. (1976). The prevalence of early childhood autism: Comparison of administrative and epidemiological studies. *Psychological Medicine* 6, 89-100.
- Wolff, S., & Barlow, A. (1979). Schizoid personality in childhood: A comparative study of schizoid, autistic and normal children. *Journal of Child Psychology and Psychiatry*, 20, 19-46.
- Wolff, S. & Chick, J. (1980). Schizoid personality in childhood: A controlled follow-up study. *Psychological Medicine*, 10, 85-100.
- Woolf, L. I., Griffiths, R., & Moncrieff, A. (1955). Treatment of phenylketonuria with a diet low in phenylalanine. *British Medical Journal*, 1, 57-64.
- Young, J., Kavanagh, M. E., Anderson, G. M., Shaywitz, B. A., & Cohen, D. J. (1982). Clinical neurochemistry of autism and associated disorders. *Journal of Autism and Developmental Disorders*, 12, 147-166.
- Yule, W., & Rutter, M. (1985). Reading and other learning difficulties. In M. Rutter & L. Hersov (Eds.), *Child adolescent psychiatry: Modern approaches* (2nd ed., chap. 27). Oxford: Blackwell Scientific.