The Relationship Between Autism And Fragile X Syndrome: A Review of the Research

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Abstract

There has been extensive evidence in the literature that people with Fragile X Syndrome (FraX) are at an increased risk of having autism, although it is still unclear how or why these two disorders are related. Even if people with FraX do not fully meet the diagnostic criteria for autism they are very likely to have some typically autistic behaviours such as hand stereotypies, communication abnormalities, and a lack of direct eye contact with others. This paper provides brief descriptions of both autism and FraX, and reviews the behavioural, genetic, and neuroanatomical research on the relationship between the disorders. It is stressed that accurate diagnosis of both autism and FraX are crucial for this type of research. The clinical implications of a relationship between autism and FraX are also described.

Autism

Autism is the most severe of the pervasive developmental disorders (PDD) with primary symptoms of impaired social skills, delayed or non-existent language skills, and the presence of stereotypic, repetitive movements (American Psychiatric Association, 1994). Most people with autism have mild to severe developmental disability, although about 20% of affected individuals have IQs in the normal range (Klinger & G. Dawson, 1996).

Several studies have attempted to find specific neurochemical and/or neuroanatomical deficits in affected individuals but the results have been diverse. There have been reports of cerebellar defects and enlarged fourth and lateral ventricles (Courchesne, Townsend, & Saitoh, 1994), and there is some evidence of increased cell density in the hippocampus of individuals with autism (Saitoh, Courchesne, Egaas, Lincoln, & Schriebman, 1995). However, results from these types of studies have been inconsistent, likely due to the heterogeneity of the disorder and its clinical manifestation. It may be that any finding applies to only a subset of people with autism. One model speculates that impairment in 4 different

neurofunctional mechanisms is involved in the development of autism (Waterhouse, Fein, & Modahl, 1996).

It is widely recognized that autism has a genetic basis. Various studies have examined the familiality of autism and have found that, on average, the probability that a proband's sibling will be diagnosed with autism is 3 - 5% which is substantially higher than the estimated prevalance for the general population (5 - 10 in 10,000; reviewed in Smalley, 1991). In addition, Smalley, Asarnow and Spence (1988) found the pooled concordance rate for monozygotic twins (who share 100% of their genes) to be 0.64 while the concordance for dizygotic twins (who share 50% of their genes) was only 0.09. This genetic liability for autism applies regardless of the proband's IQ level (Starr et al., 2001). A probable, non-Mendelian model for autism is multifactorial inheritance whereby a large number of genes and/or environmental factors contribute to the development of this disorder. Indeed, there is an increased occurrence of minor congenital anomalies in individuals with autism suggesting sub-optimal in utero conditions (A. Bailey et al., 1995). A pattern of particular susceptibility alleles co-occurring with non-optimal environmental conditions may increase susceptibility for the development of autism. This hypothesis can account for the finding that a proband's family members may have an increased probability of being diagnosed with a subtype of PDD, such as Asperger's syndrome, but not necessarily autism itself (Delong & Dwyer, 1988). (See also Joshi, this volume.)

Fragile X Syndrome

Fragile X Syndrome (FraX) is the most common form of inherited developmental disability (DD). It is caused by an expansion of a trinucleotide repeat region in the fragile X mental retardation 1 (FMR1) gene found on the X chromosome, resulting in a fragile site. The trinucleotide repeat region of FMR1 consists of a cytosine-guanine-guanine (CGG) nucleotide sequence that is repeated over and over again. In the general population, the FMR1 gene contains 5 to 50 CGG repeats; however, in FraX, hundreds or thousands of CGG repeats are found (Eberhart & Warren, 1996). As a result, the FMR1 product, the fragile X mental retardation protein (FMRP) is not produced. It is known that this protein is abundant in the neurons of the hippocampus and cerebellum of non-affected individuals, but it is not yet fully understood why the absence of FMRP results in the phenotype of FraX (Eberhart & Warren, 1996). Recent evidence suggests that it may play a regulatory role in protein synthesis in response to synaptic activity (Feng, Gutekunst, Eberhart, Warren, & Hersch, 1997). The FMRP probably has different functions at different stages of brain development (C. Feinstein & Reiss, 1997).

Within families, the disorder is transmitted to other generations by females more often than males. Females who are carriers often have a pre-mutation form of the FMR1 gene which is expanded more than in the normal population, but still produces

the FMRP product (Fu et al., 1991). Females who carry a pre-mutation tend to have a normal level of intellectual functioning, but may be at greater risk for affective disorders (Franke et al., 1996). Males who carry pre-mutations or full mutations transmit only pre-mutations to their daughters; however, their grandchildren are at risk of having full mutations. For the males with the full mutation, the degree of developmental delay varies considerably among individuals. Most have a mild developmental disability although approximately 30% have more severe impairments (Hagerman & Sobesky, 1989; see also Lee and Holden, 1999).

Individuals with FraX from all intellectual levels demonstrate similar behavioural profiles and many of their behaviours are analogous to those seen in people with autism. Almost all of the prepubertal males have attentional problems and are hyperactive (Fryns, Jacobs, Kleczkowska, & van den Berghe, 1984). Hand flapping, tactile defensiveness, poor eye contact/shyness (Lachiewicz, Spiridigliozzi, Gullion, Ransford, & Rao, 1994), and hand biting are common behavioural traits in affected individuals (Hagerman, Jackson, Levitas, Rimland, & Braden, 1986). People with FraX are more shy and less sociable than nonaffected individuals (Kerby & B. Dawson, 1994), and show excessive anxiety when interacting with others such that they often avoid eye contact and turn their bodies away from the other person (Hagerman et al., 1986).

The Relationship Between FraX and Autism

In 1982, two independent reports of a relationship between autism and FraX were published. Meryash, Szymanski, and Gerald (1982) described a 6-year-old boy with mental retardation who was also diagnosed with autism. Subsequent chromosomal analysis showed that he had the Fragile X site in approximately 11% of his cells. Brown et al. (1982) identified 5 males with FraX from a group of 27 males with autism.

These two reports have led to several studies attempting to determine the frequency of autism in people identified as having the Fragile X mutation and/or the frequency of FraX in people diagnosed with autism (see Table 1). The results of these studies have been mixed with some reporting that as many as 47% of participants with FraX met criteria for autism (Demark, Feldman, & Holden, 2002) and others finding no relationship (Einfeld, Molony & Hall, 1989). In research that examined the prevalence of the FraX mutation in people with autism, the numbers ranged from 0% to 12.5% (Goldfine et al., 1985; Fisch et al., 1986). Note that the proportion of males with FraX who also have autism is, on average, about twice that of the males with autism who test positive for FraX (Cohen et al., 1991).

Summary of Results from Research on the Association between Autism and Fragile X Syndrome

*Author(s)**	*Methodology*	*Autism Assessment*	*FraX Criteria*	*Results*
A. Bailey et al. (1993)	Tested for the FraX mutation in 125 individuals with autism	ADI**	4% of cells	1.6% of the sample had the FraX mutation
D. Bailey et al. (1998)	Examined 57 males with FraX for autisic features	CARS**	DNA testing	14 boys (25%) had CARS rating above the cutoff for autism
Blomquist et al. (1985)	Examined 102 children with previously diagnosed autism for the FraX mutation	DSM-III	1% of cells	16% of the boys and 0% of the girls had the mutation
Brown et al. (1982)	Case report of 5 males previously diagnosed with autism who also had the FraX mutation		3% of cells	
Brown et al. (1986)	Multicentre study that examined 614 males with autism for the FraX mutation	DSM-III	Cytogenetic analysis (% not specified)	7.7% of the males were positive for the mutation
Demark, Feldman, & Holden (2002)	Compared 15 children with FraX and 21 children with PDD on behavioural features of autism	CARS	DNA testing	7 (47%) of the children were above the autism cut-off on the CARS

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*Author(s)**	*Methodology*	*Autism Assessment*	*FraX Criteria*	*Results*
Einfeld, Molony, & Hall (1989)	Compared 45 people with FraX to sex-, age-, and IQ-range matched people with other forms of DD	DSM-III, ABC, ADC**	Cytogenetic analysis (% not specified)	Prevalence rates for the groups were not significantly different (9.1% for children with FraX and 8.9% for children with another form of DD
Fisch et al. (1986)	Examined 144 males with autism for FraX	DSM-III	1% of cells	18 (12.5%) of the males had the mutation
Goldfine et al. (1985)	Examined 37 children with autism and 27 matched for IQ for the FraX mutation	DSM-III	3% of cells	None of the children from either group had the mutation
Hagerman et al. (1986)	Assessed 50 males with FraX for autism	DSM-III, ABC, E2**	3% of cells	16% met DSM-II criteria, plus an additional 30% met criteria for Infantile Autism Residual State; 31% met criteria on the ABC; 0% met E2 criteria

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*Author(s)**	*Methodology*	*Autism Assessment*	*FraX Criteria*	*Results*
Ho & Kalousek (1989)	Examined 45 children with autism for the FraX mutation	DSM-III	4% of cells for males, 2% for females	1 (2.2%) boy had the mutation
Mazzocco et al. (1998)	Evaluated 14 males with FraX, 12 females with Rett Syndrome, and 25 individuals with other DDs for autism	DSM-III-R	DNA analysis	3 of the 14 males with FraX met criteria for autistic disorder; 8 of the 12 girls with Rett Syndrome met criteria
McGillivray et al. (1986)	Examined 41 people with autism who were living in an institution for the FraX mutation	DSM-III	Cytogenetic analysis	3 males (7.3%) had the mutation in 20, 35, and 50% of cells
Meryash, Szymanski, & Gerald (1982)	Case report of a 6-year-old boy with autism who also had the FraX mutation in 11% of his cells			
Payton et al. (1989)	Examined 85 males with autism for the FraX mutation	DSM-III	1% of cells	2 people (2.4%) had the mutation

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*Author(s)**	*Methodology*	*Autism Assessment*	*FraX Criteria*	*Results*
Piven et al. (1991)	Examined 75 people with autism for the FraX mutation	DSM-III-R	Cytogenetic analysis	Found 2 people with the mutation in 40% of their cells, and another 2 with the mutation in 1% of their cells
Reiss & Freund (1990)	Examined 17 males with FraX for autism	DSM-III-R	Cytogenetic analysis (% not specified)	3 (17.6%) of the participants met criteria for autism, an additional 10 (58.8%) had PDD-NOS
Rogers, Wehner, & Hagerman (2001)	Compared autistic features in 24 children with FraX, 27 children with autism, and 23 children with other forms of DD	ADI-R, ADOS-G, DSM-IV	DNA testing	8 (33%) of the children with FraX met criteria for autism on at least 2 measures

** See also Wassink, Piven & Patil (2001)*

*** ADI = Autism Diagnostic Interview (LeCouteur et al., 1989); ADI-R = Autism Diagnostic Interview – Revised (Lord et al., 1994); ADOS-G = Autism Diagnostic Observation Schedule – Generic (Lord et al., 1999); ABC = Autism Behaviour Checklist (Krug et al., 1980); E2 = Diagnostic Checklist for Behaviour Disturbed Children (E2; Rimland, 1971); ADC = Autistic Descriptors Checklist (Friedman at al., 1985); and CARS = Childhood Autism Rating Scale (Schopler et al., 1988).*

Potential reasons for conflicting findings of relation between FraX and autism

There are many potential reasons for the discrepancy in findings among studies regarding the relationship between autism and FraX. First of all, assessment of autism can be difficult since there is not yet a biological marker for the disorder, and diagnosis is based solely upon behavioural symptomatology (Klinger & G. Dawson,

1996). The studies of FraX and autism have utilized a variety of measures of autism which vary greatly in terms of their reliability and validity (Parks, 1988). Some researchers may have used inadequate measures such as parent reports, and/or out-of-date, overly stringent criteria, making it difficult to compare results among studies.

The diagnosis of FraX is another crucial factor that may have influenced the results of previous studies. Prior to 1992, FraX was diagnosed using cytogenetic techniques with different thresholds for diagnosis among studies. Some studies diagnosed a person with FraX if they had the fragile site in 1 percent of their cells, while others required 4 percent of cells to have the fragile X site in order to make a positive diagnosis (Piven, Gayle, Landa, Wzorek & Folstein, 1991). After identification of the FMR1 gene in 1992, diagnosis of FraX has been made largely on the basis of DNA analysis. This determines the exact length of the FraX mutation and provides accurate and consistent diagnoses (see Fu et al., 1991 for the specific procedure). These different methods for diagnosing FraX make it difficult to compare between studies.

Age and gender of the study participants may be important. Hessl and colleagues (2001) have emphasized the importance of stratifying for gender in studies of the relation between FraX and autism. These investigators obtained evidence suggesting that for boys with FraX, there might be an association between the quality of the home environment and autistic behaviour, whereas for affected girls, the levels of FMRP were more predictive of behavioural features. Rogers, Wehner and Hagerman (2001) found that a sample of children with FraX (less than 4 years old) had a relatively high freqency of autism (33%) and suggested that this might be due to their young ages and developmental levels. Further research will be necessary to determine if autistic features in people with FraX change as a function of age.

Ascertainment bias (A. Feinstein, 1985) may also result in differing rates of autistic symptoms between groups of individuals with FraX. Several of the studies obtained participants from clinical and residential settings where individuals are more likely to have behavioural difficulties (Piven et al., 1991). Recruiting participants in this manner, rather than using community-based sources, could lead to an increased estimate of autistic behaviours in the FraX population.

Finally, the majority of these studies have not adequately controlled for the degree of developmental delay experienced by many people with autism or FraX. There is evidence that autistic-like behaviours are common among people who have moderate or severe developmental disability (Wing & Gould, 1979). Thus, it is difficult to determine if the autistic symptoms found in a group of individuals diagnosed with FraX are due to FMR1 mutations or simply related to the severity of their developmental disability.

Similarities between autism and FraX

Some studies have indicated that regardless of whether an individual with FraX also meets the diagnostic criteria for autism, they are very likely to display some typically autistic features. Hagerman et al. (1986) reported that while only 16% of the males with FraX in their study fulfilled the DSM III criteria for autism, all of the subjects had delayed motor and speech development; gaze aversion was noted in 90%; 44% showed a pervasive lack of responsiveness as children; 96% had peculiar speech; hand biting, hand flapping and other hand stereotypies were evident in 88% of the subjects; and 44% of the males showed bizarre responses to the environment such as extreme attachment to animate or inanimate objects, or severe mood changes as a result of a minor change in routine.

Another study examined the degree of autistic features in girls aged 6 to 16 years with FraX compared to age- and IQ-matched controls with learning difficulties (Mazzocco, Kates, Baumgardner, Freund, & Reiss, 1997). This study was particularly interesting in that the researchers were able to include people with FraX who had a wide-range of IQ scores, including many with average full-scale scores. Therefore, they could determine whether autistic behaviours occur in people with FraX because of the high likelihood of also having a developmental disability, or because there truly is an increased risk for autism. The researchers found that the girls with FraX displayed more autistic-like behaviours than the control group regardless of intellectual level, and that these behaviours were similar to those expressed by boys with FraX. Only one girl with FraX actually met the criteria for a diagnosis of autism, but the increased difficulties with social play, ability to make friends, communication, stereotyped movements, and a restricted range of interests are very similar to problems that children with autism have.

Differences between autism and FraX

When looking at the cognitive and behavioural profiles of persons with FraX and autism there are many similarities and some striking differences. Both groups display the full range of intellectual abilities with some people having IQs in the normal range (Hagerman & Sobesky, 1989). Both groups also show a discrepancy between their verbal and performance abilities, however individuals with autism do better on the performance tasks and people with FraX are better on the verbal measures (Madison, George, & Moeschler, 1986). Language problems are evident in both autism and FraX, but they are of a different nature and children with autism appear to be more impaired in their communication skills (D. Bailey, Hatton, Mesibov, Ament, & Skinner, 2000). Sudhalter, Cohen, Silverman & Wolf-Schein (1990) compared the conversational skills of males with FraX, Down syndrome (DS) and autism, by analyzing their direct responses, initiation of new material, and topic maintenance. They found that the males with FraX produced more deviant language

than did those in the DS group, but their speech was less deviant than the males with autism. They also noted that the speech differed quantitatively, in that the males with autism produced much more echolalia than did those with FraX, and the boys with FraX were far more perseverative in their speech than were those in the autism group. Further, the males with autism were more deficient in their ability to maintain a conversation than were the FraX participants.

Children with autism are generally more impaired in social relationships than are individuals with FraX (D. Bailey et al., 2000). While people with FraX find eye contact aversive because of social anxiety but do seem to enjoy interacting with others, children with autism do not make eye contact because they do not recognize the social importance of it (Cohen, Vietze, Sudhalter, Jenkins & Brown, 1989). Children with FraX may actually avoid eye contact more than children with autism since the children with autism are as likely to look at another person's eyes as they are to look elsewhere (Dykens, Leckman, Paul, & Watson, 1988).When comparing temperament among boys with FraX or autism to a typically developing reference group, D. Bailey and his colleagues (2000) found that both groups of affected children were rated as less adaptable to change. In addition, both groups of boys were rated by their parents as being less persistent and more likely to withdraw than typically developing children. Boys with autism were described as being less intense and more distractible than were children with FraX. Parents of children with FraX rated them as more active than those of the children with autism.

Neuroanatomical studies of autism and FraX

Although the results of neuroanatomical studies of autism and FraX have yielded conflicting results, there are similarities between the two groups of individuals in terms of neurodevelopment, implying that the people with FraX who demonstrate autistic characteristics may represent a subset of people with autism. A greater understanding of the neurobiology of autism may arise from using the neurobiology of FraX as a model (Mazzocco et al., 1997). In both autism and FraX, there is evidence of enlarged fourth and lateral ventricles (Reiss, Aylward, Freund, Joshi, & Bryan, 1991; Reiss, Abrams, Greenlaw, Freund, & Denckla, 1995), irregular hippocampi (Reiss, Lee, & Freund, 1994), and cerebellar deformations (Saitoh et al., 1995).

There is no relationship between autistic features and the degree of amplification of the FMR1 gene (Tsai et al., 1988; Hallmayer et al., 1994; Holden et al., 1996). However, the fact that the FMR1 gene product, FMRP, is abundant in the hippocampus and cerebellum is another interesting connection between the two disorders. The cerebellum is involved in the processing of sensory information, and moderation of attention and movement (Akshoomoff & Courchesne, 1992), while the hippocampus is thought to function in aspects of learning and memory (Stanton,

2000). Theoretically, individuals who lack FMRP protein would have difficulties with these activities and, indeed, people with either FraX or autism often have attention problems, sensory irregularities, learning disabilities and/or intellectual impairment (Fryns et al., 1984; Hagerman & Sobesky, 1989).

Evidence for a connection between cerebellar malformation and autistic behaviours stems from the finding that girls with FraX are less likely to display severe autistic behaviours than affected boys, and they also have less cerebellar hypoplasia (Mazzocco et al., 1997). The autistic-like behaviours of stereotyped movements, restricted interests, and self-stimulation may be mediated by the cerebellar deficits due to the difficulty with processing sensory stimuli (Mazzocco et al., 1997).

Future Directions

Although the evidence is mixed, many prominent researchers in the field believe that the cognitive, behavioural, and neuroanatomical similarities between autism and FraX cannot be explained by chance alone, nor does the common feature of intellectual impairment account for all of the overlap (C. Feinstein & Reiss, 1998). This relationship suggests many avenues for future investigations focussing on FraX, autism, or both. There is a need for multidisciplinary studies whereby individuals with strengths in the areas of behavioural assessment, diagnosis, genetics, neurobiology, and statistics can pool their resources for an increased understanding of the two disorders in their entirety. Any research in this area may have many benefits other than increasing our knowledge of the relationship between autism and FraX. From such studies we will undoubtedly learn more about the genetics of behavioural disorders, the role of the FMRP protein in both affected and nonaffected individuals, and the structure and functionning of the hippocampus and cerebellum. Moreover, any information that we gain will ultimately assist the affected individuals and their families cope with these devastating disorders.

The finding that the FraX mutation increases the risk of a child developing autistic-like tendencies is important for families and practitioners dealing with affected individuals. Knowledge of the increased tendency for specific problem behaviours (such as poor eye contact, self-injurious behaviours, and limited language skills; Hagerman et al., 1986) will enable practitioners to provide more accurate diagnoses and intervention strategies for children with FraX who display autistic behaviours. Parents of children with FraX can be educated regarding the types of behaviours that they can expect to develop in their children, while practitioners can work on developing specific techniques to reduce the problem behaviours. Although FraX should not be considered a form of PDD (Mazzocco et al., 1998), assessments of autistic behaviours may be useful for people with FraX, in that they could help to identify specific behavioural characteristics of the individual and points for intervention.

References

Akshoomoff, N. A. & Courchesne, E. (1992). A new role for the cerebellum in cognitive operations. *Behavioral Neuroscience, 106,* 731-738.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders.* Fourth edition. Washington, D.C.: Author.

Bailey, A., Bolton, P., Butler, L., LeCouteur, A., Murphy, M., Scott, S., Webb, T. & Rutter, M. (1993). Prevalence of the fragile X anomaly amongst autistic twins and singletons. *Journal of Child Psychology and Psychiatry, 34,* 673-678.

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

Bailey, D. B., Mesibov, G. B., Hatton, D. D., Clark, R. D., Roberts, J. E., & Mayhew, L. (1998) Autistic behavior in young boys with Fragile X Syndrome. *Journal of Autism and Developmental Disorders, 28,* 499-508.

Bailey, D. B., Hatton, D. D., Mesibov, G., Ament, N., & Skinner, M. (2000). Early development, temperament, and functional impairment in autism and fragile X syndrome. *Journal of Autism and Developmental Disorders, 30,* 49-59.

Blomquist, H. K., Bohman, M., Edvinsson, S. O., Gillberg, C., Gustavson, K. H., & Holmgren, G. (1985). Frequency of the fragile X syndrome in infantile autism. *Clinical Genetics, 27,* 113-117.

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., Ritvo, E., Ruttenberg, B. A., Bentley, W., & Castells, S. (1986). Fragile X and autism: a multicenter study. *American Journal of Medical Genetics, 23,* 341-352.

Brown, W. T., Jenkins, E. C., Friedman, E., Brooks, J., Wisniewski, K., & Ragathu, S. (1982). Autism is associated with the fragile-X syndrome. *Journal of Autism and Developmental Disorders, 12*(3), 303-308.

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.

Cohen, I. L., Vietze, P. M., Sudhalter, V., Jenkins, E. C., & Brown, W. T. (1989). Parent-child dyadic gaze patterns in fragile X males and in non-fragile X males with autistic disorder. *Journal of Child Psychology and Psychiatry, 30*(6), 845-856.

Courchesne, E., Townsend, J., & Saitoh, O. (1994). The brain in infantile autism: posterior fossa structures are abnormal. *Neurology, 44,* 214-223.

Delong, G.R., & Dwyer, J.J. (1988). Correlation of family history with specific autistic subgroups: Asperger's syndrome and bipolar affective disorder. *Journal of Autism and Developmental Disorders, 18,* 593-600.

Demark, J. L., Feldman, M. A., & Holden, J. J. A. (2002). Behavioural relationship between autism and fragile X syndrome. Manuscript submitted for publication.

Dykens, E., Leckman, J., Paul, R., & Watson, M. (1988). Cognitive, behavioural, and adaptive functioning in fragile X and non-fragile X retarded men. *Journal of Autism and Developmental Disorders, 18*(1), 41-52.

Eberhart, D. E., & Warren, S.T. (1996). The molecular basis of fragile X syndrome. *Cold Spring Harbor Symposia on Quantitative Biology, 61,* 679-687.

Einfeld, S., Molony, H., & Hall, W. (1989). Autism is not associated with the fragile X syndrome. *American Journal of Medical Genetics, 34,* 187-193.

Feinstein, A. R. (1985). *Clinical epidemiology: The architecture of clinical research.* Philadelphia: W.B. Saunders.

Feinstein, C., & Reiss, A. L. (1997). Autism: the point of view from fragile X studies. *Journal of Autism and Developmental Disorders, 28,* 393-405.

Feng, Y. Gutekunst, C. A., Eberhart, D. E., Yi, H., Warren, S. T., & Hersch, S. M. (1997). Fragile X mental retardation protein: Nucleocytoplasmic shuttling and association with somatodendtritic ribosomes. *Journal of Neuroscience, 17,* 1539-1547.

Fisch, G. S., Cohen, I. L., Wolf, E. G., Brown, W. T., Jenkins, E. C., & Gross, A. (1986). Autism and the fragile X syndrome. *American Journal of Psychiatry, 143,* 71-73.

Franke, P., Maier, W., Hautzinger, M., Weiffenbach, O., Gansicke, M., Iwers, B., Poustka, F., Schwab, S.G., & Froster, U. (1996). Fragile-X carrier females: Evidence for a distinct psychopathological phenotype? *American Journal of Medical Genetics, 64,* 334-339.

Friedman, E., Wolf-Schein, E. G., Cohen, I. L., & Fisch, G. S. (1985). *Autistic Descriptors Checklist (ADC), Parent interview edition and scoring guidelines.* New York: New York State Institute for Basic Research in Developmental Disabilities.

Fryns, J. P., Jacobs, J., Kleczkowska, A., & van den Berghe, H. (1984). The psychological profile of the fragile X syndrome. *Clinical Genetics, 25,* 131-134.

Fu, Y. H., Kuhl, D. P., Pizzuti, A., Pieretti, M., Sutcliffe, J. S., Richards, S., Verkerk, A. J., Holden, J. J. A., Fenwick, R. G., Warren, S. T., Oostra, B. A., Nelson, D. L., & Caskey, C. T. (1991). Variation of the CGG repeat at the fragile X site results in genetic instability: Resolution of the Sherman paradox. *Cell, 67,* 1047.

Goldfine, P. E., McPherson, P. M., Heath, A., Hardesty, V. A., Beauregard, L. J., & Gordon, B. (1985). Association of fragile X syndrome with autism. *American Journal of Psychiatry, 142,* 108-110.

Hagerman, R. J., Jackson, A. W., Levitas, A., Rimland, B., & Braden, M. (1986). An analysis of autism in fifty males with the fragile X syndrome. *American Journal of Medical Genetics, 23,* 359-374.

Hagerman, R. J., & Sobesky, W. E. (1989). Psychopathology in fragile X syndrome. *American Journal of Orthopsychiatry, 59*(1), 142-152.

Hallmayer, J., Pintado, E., Lotspeich, L., Spiker, D., McMahon, W., & Peterson, P. B. (1994). Molecular analysis and test of linkage between the FMR-1 gene and infantile autism in multiplex families. *American Journal of Human Genetics, 55,* 951-959.

Hessl, D., Dyer-Friedman, J., Glaser, B., Wisbeck, J., Barajas, R. G., Taylor, A., & Reiss, A. L. (2001). The influence of environmental and genetic factors on behavior problems and autistic symptoms in boys and girls with fragile X syndrome. *Pediatrics, 108*(5), E88.

Ho, H. H., & Kalousek, D. K. (1989). Brief report: Fragile X syndrome in autistic boys. *Journal of Autism and Developmental Disorders, 19,* 343-347.

Holden, J. J. A., Wing, M., Chalifoux, M., Julien-Inalsingh, C., Schutz, C., & Robinson, P. (1996). Lack of expansion of triplet repeats in the FMR1, FRAXE, and FRAXF loci in male multiplex families with autism and pervasive developmental disorders. *American Journal of Medical Genetics, 64,* 399-403.

Kerby, D. S., & Dawson, B. L. (1994). Autistic features, personality and adaptive behavior in males with the fragile X syndrome and no autism. *American Journal on Mental Retardation, 98*(4), 455-462.

Klinger, L.G., & Dawson, G. (1996). Autistic disorder. In E. J. Mash, & R. A. Barkley, (Eds.). *Child psychopathology*. New York: The Guilford Press.

Krug, D. A., Arick, J. R., & Almond, P. J. (1980). Behavior checklist for identifying severely handicapped individuals with high levels of autistic behavior. *Journal of Child Psychology and Psychiatry, 21*, 221-229.

Lachiewicz, A. M., Spiridigliozzi, G. A., Gullion, C. M., Ransford, S. N., & Rao, K. (1994). Aberrant behaviors of young boys with fragile X syndrome. *American Journal on Mental Retardation, 98*(5), 567-579.

LeCouteur, A., Rutter, M., Lord, C., Rios, P., & Robertson, S. (1989). Autism diagnositc interview: a standardized investigator-based instrument. *Journal of Autism and Developmental Disorders, 19*, 363-387.

Lee, B. A., & Holden, J .J. A. (1999). Chapter 21. Fragile X Syndrome. In I. Brown, & M. Percy (Eds.). *Developmental disabilities in Ontario*. (pp. 295-307). Toronto, Canada: Front Porch Publishing.

Lord, C., Rutter, M., & LeCouteur, A. (1994). Autism diagnostic interview – revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24*, 659-685.

Lord, C., Rutter, M., & DiLavore, P. (1999). *Autism diagnostic observation schedule*. Los Angeles: Western Psychological Services.

Madison, L. S., George, C., & Moeschler, J. B. (1986). Cognitive functioning in the fragile-X syndrome: A study of intellectual, memory and communication skills. *Journal of Mental Deficiency Research, 30*, 129-148.

Mazzocco, M. M., Kates, W. R., Baumgardner, T. L., Freund, L. S., & Reiss, A. L. (1997). Autistic behaviours among girls with fragile X syndrome. *Journal of Autism and Developmental Disorders, 27*, 415-435.

Mazzocco, M. M., Pulsifer, M., Fiumara, A., Cocuzza, M., Nigro, F., Incorpora, G., & Barone, R. (1998). Brief report: Autistic behaviors among children with fragile X or Rett syndrome: Implications for the classification of pervasive developmental disorder. *Journal of Autism and Developmental Disorders, 28*, 321-328.

McGillivary, B. C., Herbst, D. S., Dill, F. J., Sandercock, H. J., & Tischler, B. (1986). Infantile autism: an occasional manifestation of fragile (X) mental retardation. *American Journal of Medical Genetics, 23*, 353-358.

Meryash, D. L., Szymanski, L. S., & Gerald, P. S. (1982). Infantile autism associated with the fragile-X syndrome. *Journal of Autism and Developmental Disabilities, 12*(3), 295-301.

Payton, J. B., Steele, M. W., Wenger, S. L., & Minshew, N. J. (1989). The fragile X marker and autism in perspective. *Journal of the American Academy of Child and Adolescent Psychiatry, 28*, 417-421.

Parks, S. (1988). Psychometric instruments available for the assessment of autistic children. In E. Schopler & G. Mseibov (Eds.), *Diagnosis and assessment in autism*. New York: Plenum Press.

Piven, J., Gayle, J., Landa, R., Wzorek, M., & Folstein. (1991). The prevalence of fragile X in a sample of autistic individuals diagnosed using a standardized interview. *Journal of the American Academy of Child and Adolescent Psychiatry, 30*(5), 825-830.

Reiss, A. L., Abrams, M. T., Greenlaw, R., Freund, L., & Denckla, M. B. (1995). Neurodevelopmental effects of the FMR-1 mutation in humans. *Nature Medicine, 1,* 159-167.

Reiss, A. L., Aylward, E., Freund, L., Joshi, P. K., & Bryan, R. N. (1991). Neuroanatomy of fragile X syndrome: the posterior fossa. *Annals of Neurology, 29,* 26-32.

Reiss, A. L., & Freund, L. (1990). Fragile X syndrome, DSM-III-R, and autism. *Journal of the American Academy of Child and Adolescent Psychiatry, 29,* 885-891.

Reiss, A. L., Lee, J., & Freund, L. (1994). Neuroanatomy of fragile X syndrome: The temporal lobe. *Neurology, 44,* 1317-1324.

Rimland, B. (1971). The differentiation of childhood psychoses: an analysis of checklists for 2218 psychotic children. *Journal of Autism and Childhood Schizophrenia, 1,* 161-174.

Rogers, S. J., Wehner, D. E., & Hagerman, R. (2001). The behavioral phenotype in fragile x symptoms of autism in very young children with fragile x syndrome, idiopathic autism, and other developmental disorders. *Journal of Developmental and Behavioural Pediatrics, 22,* 409-417.

Saitoh, O., Courchesne, M., Egaas, M., Lincoln, A., & Schriebman, L. (1995). Cross-sectional area of the posterior hippocampus in autistic patients with cerebellar and corpus callosum abnormalities. *Neurology, 45,* 317-324.

Schopler, E., Reichler, R. J., & Renner, B. R. (1988). *The Childhood Autism Rating Scale.* Los Angeles: Western Psychological Services.

Smalley, S. L. (1991). Genetic influences in autism. *Psychiatric Clinics of North America, 14,* 125-137.

Smalley, S. L., Asarnow, F. F., & Spence, M. A. (1988). Autism and genetics. *Archives of General Psychiatry, 45,* 953-961.

Stanton, M. E. (2000). Multiple memory systems, development and conditioning. *Behavioral Brain Research, 110,* 25-37.

Starr, E., Berument, S. K., Pickles, A., Tomlins, M., Bailry, A., Papanikolaou, K., & Rutter, M. (2001). A family genetic study of autism associated with profound mental retardation. *Journal of Autism and Developmental Disorders, 31,* 89-96.

Sudhalter, V., Cohen, I. L., Silverman, W., & Wolf-Schein, E. G. (1990). Conversational analyses of males with fragile X, down syndrome, and autism: Comparison of the emergence of deviant language. *American Journal on Mental Retardation, 94*(4), 431-441.

Tsai, L.Y., Crowe, R. R., Patil, S. R., Murray, J., & Quinn, J. (1988). Brief Report: Search for DNA markers on two autistic males with the fragile X syndrome. *Journal of Autism and Developmental Disorders, 18*(4), 681-685.

Wassink, T. H., Piven, J., & Patil , S. R. (2001). Chromosomal abnormalities in a clinic sample of individuals with autistic disorder. *Psychiatric Genetics, 11,* 57-63.

Waterhouse, L., Fein, D., & Modahl, C. (1996). Neurofunctional mechanisms in autism. *Psychological Review, 103,* 457-489.

Wing, L., & Gould, J. (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. *Journal of Autism and Developmental Disorders, 9,* 11-29.