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Secondary Medical Diagnosis in Fragile X Syndrome With and Without Autism Spectrum Disorder

Catalina García-Nonell,[1] Eugenia Rigau Ratera,[2] Susan Harris,[3,4] David Hessl,[4,5] Michele Y. Ono,[3,4] Nicole Tartaglia,[6] Emily Marvin,[4] Flora Tassone,[4,7] and Randi J. Hagerman[3,4]*

[1]PSYNCRON, Barcelona, Spain
[2]Unidad de Neuropediatría, Hospital de Sabadell, Corporació Sanitària Parc Tauli, GIRMOGEN, Sabadell, Spain
[3]Department of Pediatrics, University of California Davis Health System, Sacramento, California
[4]M.I.N.D. Institute, University of California at Davis, Sacramento, California
[5]Department of Psychiatry & Behavioral Sciences, University of California at Davis Health System, Sacramento, California
[6]University of Colorado at Denver Health Sciences Center, The Children's Hospital, Child Development Unit, Denver, Colorado
[7]Department of Biochemistry and Molecular Medicine, University of California at Davis School of Medicine, Sacramento, California

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This study examined whether secondary medical diagnoses that affect CNS function (i.e., seizures, malformations, or genetic disorders), are more likely to occur in individuals with fragile X syndrome (FXS) and autism spectrum disorder (FXS + ASD) or FXS alone. Ninety males (3–25 years) with FXS or FXS + ASD were evaluated for secondary medical diagnoses by medical history and examination. A significant difference in the incidence of medical problems was found between patients with FXS + ASD (38.6%) and FXS alone (18.2%, $P < 0.05$). Medical problems that affect the CNS are more likely to occur in those with FXS + ASD and it is probable that additional brain dysfunction associated with these medical problems enhance the risk of autism in those with FXS. © 2008 Wiley-Liss, Inc.

Key words: fragile X syndrome; autism; PDDNOS; autism spectrum disorder; seizures; Prader–Willi like phenotype

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INTRODUCTION

Fragile X syndrome (FXS) is the most common inherited cause of mental retardation, affecting an estimated 1 in 3,600 males in the general population [Sherman, 2002]. The phenotype of FXS includes intellectual disability, cognitive and behavioral impairments of varying degree, and physical anomalies such as large ears, long face, macrocephaly, and macroorchidism [Lachiewicz et al., 2000; Hagerman, 2002]. Behavior characteristics frequently reported include social avoidance, anxiety, poor eye contact, perseverative behavior, hyperarousal to sensory stimuli, distractibility, irritability, hyperactivity, repetitive motor behaviors, and inflexibility [Hagerman, 2002; Artigas and Brun, 2004; Hatton et al., 2006].

FXS is caused by an unstable mutation in the fragile X mental retardation 1 (*FMR1*) gene. Expansion of a trinucleotide (CGG) repeat (>200) in the 5′ untranslated region of the gene leads to gene silencing and a lack or deficiency of the *FMR1* protein (FMRP), which causes the physical, cognitive, behavioral, and emotional characteristics of FXS [Tassone et al., 1999]. Normal individuals have 5–44 CGG repeats that are stably transmitted to the next generation. Alleles harboring 45–54 CGG repeats are named "gray zone" because instability in transmission to the next generation is common [Nolin et al., 1996]. With CGG repeat sizes in the premutation range (55–200 repeats), the allele usually expands to the full mutation (>200 repeats) when passed from a mother to her children. A mixed pattern of full mutation and premutation alleles is termed mosaicism.

The association between autism and FXS was first reported in 1982 [Brown et al., 1982] and is one of the most recognized behavioral abnormalities observed

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*Correspondence to: Randi J. Hagerman, M.D., Medical Director of the M.I.N.D. Institute; Endowed Chair in Fragile X Research, UC Davis Health System, 2825 50th Street, Sacramento, CA 95817.
E-mail: randi.hagerman@ucdmc.ucdavis.edu

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in males and some females with FXS. Two to six percent of children with autism will have the *FMR1* mutation [Wassink et al., 2001; Estecio et al., 2002; Reddy, 2005] and approximately 30% of children with FXS are diagnosed with autism [Bailey et al., 2001a; Rogers et al., 2001; Kaufmann et al., 2004]. An additional 20–30% of patients with FXS have Pervasive Developmental Disorder—Not Otherwise Specified (PDDNOS) [Harris et al., 2008]. Studies have shown that the presence of autism with FXS is associated with language and social deficits in addition to a lower IQ compared to children with FXS without autism [Bailey et al., 2001a; Kaufmann et al., 2004; Philofsky et al., 2004]. IQ has also been documented to decline with age in most males with FXS [Wright-Talamante et al., 1996]. A decline is also seen in individuals with Down syndrome who develop Alzheimer disease with age [Kittler et al., 2004], but not in the typical population [Zigler et al., 1984].

The autism that occurs in FXS has been hypothesized to be related to a secondary genetic problem because the degree of FMRP deficit does not correlate with the presence of autism when IQ is controlled [Rogers et al., 2001; Loesch et al., 2007]. Some individuals with FXS have a recognizable second genetic abnormality or an additional medical diagnosis, such as epilepsy, that is a known cause of CNS dysfunction. We hypothesize that individuals with FXS and autism will have a higher number of secondary medical diagnoses including genetic disorders that affect the CNS compared to those with FXS alone. A retrospective analysis was conducted to determine if the prevalence of secondary medical diagnoses is different in individuals with FXS and autism spectrum disorder (ASD, including PDDNOS and autism) compared to individuals with FXS alone.

MATERIALS AND METHODS

Participants

Included in this retrospective analysis and chart review were 90 male participants with FXS, ages 3–25 years, who were seen sequentially at the University of California at Davis M.I.N.D. Institute and had an Autism Diagnostic Observation Schedule—General [ADOS-G, Lord et al., 2000] as part of the evaluation between January 2001 and July 2005. Subjects and parents/caregivers signed an IRB approved consent form. All the participants had either a full mutation or mosaicism by *FMR1* DNA testing. Each individual was evaluated for autism or PDDNOS using the ADOS-G and the Diagnostic Statistical Manual—Fourth Edition criteria for Autistic Disorder [DSM-IV, APA, 1994]. Individuals who met the criteria for autism or PDDNOS were considered in the FXS + ASD group. There were 57 individuals with FXS + ASD and 33 individuals with FXS alone. All participants were evaluated for medical or genetic problems through a medical history and a detailed examination for minor anomalies by a developmental and behavioral pediatrician with expertise in genetic disorders and fragile X syndrome (RJH). If asymmetries were seen on neurological examination, an MRI was done. A description of the participants is presented in Table I.

Measures

All patients completed the ADOS-G [Lord et al., 2000] and were evaluated using the DSM-IV criteria for Autistic Disorder [APA, 1994]. When disagreements occurred between the two measures a consensus was reached by a team conference including a developmental and behavioral pediatrician, psychologist, social worker, and genetic associate, who are all experienced in the diagnosis of autism. Patients also underwent one of the following cognitive evaluations (n = 64); Wechsler Intelligence Scale for Children—3rd Edition [WISC-III, Wechsler, 1991], Wechsler Intelligence Scale for Children—4th Edition [WISC-IV, Wechsler, 2003], Wechsler Adult Intelligence Scale—3rd Edition [WAIS-III, Wechsler, 1997], Wechsler Preschool and Primary Scale of Intelligence—3rd Edition [WPPSI-III, Wechsler, 2002], Wechsler Abbreviated Scale of Intelligence [WASI, Wechsler, 1999], Stanford-Binet—4th Edition [Thorndike et al., 1986], and Leiter International Scale of Intelligence-Revised [Leiter-R, Roid and Miller, 1997]. In addition, the parent/caregiver of the patients (n = 62) were administered the Vineland Adaptive Behavior Scales, Interview Edition [VABS, Sparrow et al., 1984] to assess adaptive functioning.

The assessment of the medical and genetic conditions consisted of a clinical history, a review of medical and psychological records including neuroimaging and previous genetic testing, and a medical and neurological examination previously described in Riddle et al. [1998]. Cytogenetic testing was not routinely completed, but was often included in the medical records. *FMR1* DNA testing was performed on all patients. DNA testing was performed on DNA isolated from peripheral blood leucocytes using both Southern Blot and PCR analysis. Details of the methods are previously described in Tassone et al.

TABLE I. Description of Participants

	FXS alone (n = 33)		FXS + ASD (n = 57)	
	M	SD	M	SD
Age (years)	7.75	3.74	9.80	5.74
FSIQ score*	61.00[a]	14.87	52.22[b]	11.54
Vineland score**	52.96[c]	15.14	41.79[d]	14.79

[a]n = 28, [b]n = 36, [c]n = 24, [d]n = 38, *$P < 0.05$, **$P < 0.01$.

[2004] and Saluto et al. [2005]. If the Prader–Willi phenotype in FXS was present (obesity, hyperphagia, and small genitalia), cytoplasmic interacting *FMR1* protein (CYFIP) expression, which is found to be lowered and associated with a higher rate of ASD in this subgroup of FXS, was documented as described in Nowicki et al. [2007].

RESULTS

Autism and PDDNOS

Of the 90 males, 57 (63.3%) met the criteria for ASD according to the ADOS-G and the DSM-IV criteria for Autistic Disorder. Twenty-nine (32%) subjects had autism and 28 (31%) had PDDNOS. The remaining 33 (37%) did not meet criteria for ASD. Those with autism and PDDNOS clinically are on a continuum and since many of the individuals scored at or just below the cut-off for autism; they were combined in our analysis. Often in studies of autism, these two groups are combined into the ASDs category [Harris et al., 2008]. These percentages are quite consistent with our overall numbers for FXS + ASD. In addition, there were no significant differences between the FXS and PDDNOS (FXS + PDDNOS) and FXS and autism (FXS + autism) groups in IQ ($P = 0.92$), VABS score ($P = 0.06$), and age ($P = 0.83$). Combining these groups enhanced statistical power for comparison across those with ASD and those without.

If we compare the presence of secondary medical diagnoses between the FXS and autism group (FXS + autism) and FXS and PDDNOS (FXS + PDDNOS) group we saw that in the FXS + PDDNOS PDDNOS group, 11 (39.3%) had secondary medical diagnoses and in the FXS + autism group, 11 (37.9%) had secondary medical diagnoses. Systematic comparisons between the two groups, FXS + PDDNOS and FXS + autism, showed no significant difference (Chi square = 0.011, df = 1, $P = 0.916$). The presence of secondary medical diagnoses does not differentiate the FXS + PDDNOS from the FXS + autism autism group. Therefore, we combined the group into FXS + ASD for further analysis (Table II).

Mosaic and Full Mutation (FXS)

In the 90 males with FXS that were reviewed, 56 (62.2%) had the full mutation and 34 (37.8%) were mosaic. In the group with FXS + ASD (n = 57), 37 (64.9%) subjects had the full mutation and 20 (35.1%) subjects were mosaic. In the group with FXS alone (n = 33), 19 (57.6%) subjects had the full mutation and 14 (42.4%) subjects were mosaic (Table II). There was no significant difference between the two groups regarding the frequency of the full mutation ($P = 0.14$, Table II) or mosaicism ($P = 0.18$, Table II).

The mean age was 9.80 years (SD = 5.74) in the FXS + ASD group (n = 57) and 7.75 years (SD = 3.74) in the FXS alone group (n = 33). There was no significant difference between the two groups in chronological age ($P = 0.07$, Table I).

Cognitive Ability

In assessing the cognitive ability, 64 individuals completed the WISC-III, WISC-IV, WPPSI-III, WASI, WAIS-III, Stanford Binet 4th Edition, or Leiter-R. The FXS + ASD group (n = 36) had a mean IQ score of 52.22 (SD = 11.54) and the FXS alone group (n = 28) had a mean IQ score of 61.00 (SD = 14.87). There was a significant group difference in IQ ($P = 0.013$, Table I), which has been seen in other studies [Rogers et al., 2001; Bailey et al., 2001b; Kaufmann et al., 2004]. The VABS was completed with a parent/caregiver in 62 of the individuals. Thirty-eight participants from the FXS + ASD group had a VABS mean composite score of 41.79 (SD = 14.79) and 24 individuals from the FXS alone group had a VABS mean composite score of 52.96 (SD = 15.14). There was a significant difference in the adaptive behavior composite score on the VABS ($P = 0.006$, Table I), which has been previously reported by Rogers et al. [2001].

CNS Associated Medical Disorders

Twenty-eight (31.1%) of the 90 subjects were found to have an associated medical disorder that

TABLE II. Medical/Genetic Results of the Two Groups (FXS Alone and FXS + ASD)

	FXS alone (n = 33)		FXS + ASD (n = 57)		Chi-square test (*P*-value)
	n	Percentage	*n*	Percentage	
Full mutation	19	57.6	37	64.9	0.14
Mosaic	14	42.4	20	35.1	0.18
No medical problems	27	81.8	35	61.4	0.04
Seizures	4	12.1	16	28.1	0.15
MRI abnormalities	1	3.0	2	3.5	0.90
Genetic abnormalities	1	3.1	4	7.0	0.43
Total medical problems	6	18.2	22	38.6	0.04

affects the CNS after a detailed medical history, clinical exam, and further testing of a subgroup. Twenty of the subjects had seizures; three had MRI abnormalities, that is, white matter disease, cystic abnormalities, and optic atrophy with microcephaly; and five had genetic abnormalities, four with Prader–Willi like phenotype (PWP) and one with XYY. Age effects were examined between participants with a secondary medical diagnoses and participants without a secondary medical diagnoses using Mann–Whitney *U*-test, and there was no significant group difference ($Z = -1.24$, $P = 0.21$).

In the FXS alone group, 6 (18.2%) subjects had secondary medical diagnoses and in the FXS + ASD group, 22 (38.6%) had secondary medical diagnoses (Table II). Systematic comparisons between the two groups, FXS + ASD and FXS alone, showed a significant difference (Chi squared = 4.064, df = 1, $P = 0.04$). These results indicate that the group with FXS + ASD had approximately twice as many medical problems that affect the CNS than the group with FXS alone (Table II). Age effects were also examined in relation to secondary medical diagnoses within the FXS alone group and the FXS + ASD group using Mann–Whitney *U*-test. There were no significant group differences in age between individuals with a secondary medical diagnoses and individuals without a secondary medical diagnoses in the FXS alone group ($Z = -0.841$, $P = 0.40$) or in the FXS + ASD group ($Z = -0.730$, $P = 0.47$).

Considering seizures only, the FXS alone group had 4 (12.1%) subjects who had seizures and the FXS + ASD group had 16 (28.1%) subjects who had seizures; although more than twice as many had seizures in the FXS + ASD group, this difference was not significant ($P = 0.15$, Table II).

DISCUSSION

Autism occurs in approximately 30% of young males with FXS, but why autism occurs in only this subgroup of patients with FXS is not known. This study demonstrates a higher rate of secondary medical problems in those with FXS + ASD compared with FXS alone. In addition, we found a significantly lower IQ in those with FXS + ASD compared to FXS alone. These results suggest that additional brain dysfunction related to secondary medical diagnoses that affect the CNS can increase the risk for autism for those with FXS. This could be associated simply to more general damage to the brain which could lower IQ or to a secondary medical diagnosis that specifically relates to gene dysregulation, that is, PWP. These results are consistent with the findings of several studies showing lower IQ in those with FXS with autism or ASD compared to those with FXS alone [Rogers et al., 2001; Bailey et al., 2001a; Kaufmann et al., 2004; Loesch et al., 2007]. A number of genetic disorders can lead to autism without FXS including sex chromosome abnormalities, 15q duplication, PKU, and a marker X chromosome [Cohen et al., 2005; Schaefer and Lutz, 2006]. Genetic disorders can be documented in 15–40% of patients with autism with a careful assessment including cytogenetic studies with FISH testing and metabolic studies [Reddy, 2005; Schaefer and Lutz, 2006].

Seizures

The most prevalent secondary medical diagnosis in FXS is seizures, which was first reported by Lubs in [1969]. Other studies have described seizures in FXS and the rate varies between 10% and 40% [Musumeci et al., 1999; Sabaratnam et al., 2001; Berry-Kravis, 2002]. Rates of seizures are increased in the general population with developmental disability, thus FXS is not unique in this regard. We found seizures by medical history in 22.2% of the subjects overall, including 12.1% in FXS alone and 28.1% in FXS + ASD. It is also possible that occult EEG abnormalities occurred more frequently in those with FXS + ASD, but that was not evaluated here. Seizures can occur in 18–29% in those with autism without FXS [Olsson et al., 1988; Rapin and Katzman, 1998]. The underlying neuronal abnormalities leading to neuronal excitability and susceptibility to seizures may be associated with the development of autism in those with FXS. In some cases, prolonged seizures may cause CNS tissue damage which may predispose to autism. The electrical abnormalities associated with seizures may also disrupt connectivity in the brain, which may also predispose individuals with FXS and seizures to autism [Belmonte and Bourgeron, 2006]. If further studies confirm the association between seizures and autism, this would suggest that treating seizure activity in young children with FXS may decrease their risk of having an ASD. In addition, some genes associated with autism may also predispose to seizures such as the ARX gene [Nowicki et al., 2008]. Recently, a mutation in the gene encoding the contactin-associated protein-like 2 (CASPR2) was identified as being associated with childhood onset epilepsy and autism in a sample of Old Order Amish children [Strauss et al., 2006].

Genetic Disorders

The next most prevalent secondary medical problem, in our sample of males with FXS, was genetic disorders. Prader–Willi syndrome (PWS) is a genetic disorder with a 15q deletion and a phenotype that includes severe hyperphagia, significant obesity, hypogonadism, and growth hormone deficiency, demonstrating hypothalamic dysfunction. The Prader–Willi phenotype (PWP) in FXS is not due to a 15q deletion, but consists of

obesity, hyperphagia, hypotonia, and often hypogonadism [de Vries et al., 1993; de Vries and Niermeijer, 1994; Nowicki et al., 2007]. The PWP was seen in four patients described here, all with ASD, and we consider this an additional genetic abnormality because a decrease in the expression of cytoplasmic interacting *FMR1* protein (CYFIP) has been seen in boys with FXS and PWP [Nowicki et al., 2007]. The gene for CYFIP is located at 15q [Chai et al., 2003]. Patients with PWP do not have short stature, as seen in PWS, but hyperphagia and obesity are present and approximately 50% have small genitalia or delayed puberty as reported in Nowicki et al. [2007].

We found a low rate of secondary cytogenetic abnormalities, with just one patient with XYY syndrome; although cytogenetic studies were not routinely carried out in our patients. The association of sex chromosome abnormalities with FXS has been reported in the past, primarily FXS with XXY [Chudley, 1990; Kupke et al., 1991; Milunsky et al., 1993]. Two cases of 46,XY and 47,XYY mosaicism in association with FXS have been reported [Bodurtha et al., 1993; Milunsky et al., 1993]. Although there have been some reports of autism in males with XYY syndrome [Nicolson et al., 1998; Geerts et al., 2003], ASD was not seen in our case of XYY + FXS.

This study suggests that secondary medical diagnoses that affect the CNS should be examined in patients with FXS and autism or ASD. These abnormalities may occur silently and include differences in gene expression, such as *CYFIP* expression in patients with FXS and the PWP. Another example of gene expression changes in autism is the low expression of *MeCP2* in the brains of individuals diagnosed with autism but without Rett Syndrome or fragile X. Although the MeCP2 protein regulates the *FMR1* gene expression, we do not know the expression of MeCP2 in the brains of individuals with FXS, either with our without autism.

Our findings are consistent with the hypothesis that children with FXS and ASD are more likely to have a secondary medical problem compared to those with FXS alone. It is important to note that there may have been a sample bias since it is probable that more of the FXS + ASD participants who were more severe in presentation to their doctors might have been more likely to be referred for evaluation of the secondary medical diagnoses, that is, EEG studies. In other words, it is probable that not every participant was equally screened for a secondary medical diagnosis. Our research suggests that clinicians should be careful to rule out seizures or EEG abnormalities in individuals with FXS + ASD. Treatment with an anticonvulsant in those with seizures may help subsequent social development in those with autism with or without FXS. Although additional genetic problems such as Down syndrome or the Prader–Willi phenotype are recognizable by their physical phenotype, some may involve occult expression abnormalities of genes such as *MeCP2*, *CYFIP*, or other yet unidentified genes. The search for additional gene dysregulation associated with autism in FXS may also be pertinent to individuals with autism of unknown etiology.

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REFERENCES

APA. 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington DC: American Psychiatric Association.

Artigas J, Brun C. 2004. Se peude atribuir el fenotipo conductual del sindrome X fragil al retraso mental y al trastorno por deficit de atencion/hiperactividad? Rev Neurol 38:7–11.

Bailey DB Jr, Hatton DD, Skinner M, Mesibov GB. 2001a. Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome. J Autism Dev Disord 31: 165–174.

Bailey DB Jr, Hatton DD, Tassone F, Skinner M, Taylor AK. 2001b. Variability in FMRP and early development in males with fragile X syndrome. Am J Ment Retard 106:16–27.

Belmonte MK, Bourgeron T. 2006. Fragile X syndrome and autism at the intersection of genetic and neural networks. Nat Neurosci 9:1221–1225.

Berry-Kravis E. 2002. Epilepsy in fragile X syndrome. Dev Med Child Neurol 44:724–728.

Bodurtha J, Jackson Cook C, Maddalena A, Piserchio J, Waller R. 1993. 46XY/47XYY mosaicism and fragile X [letter]. Clin Genet 44:109–110.

Brown WT, Jenkins EC, Friedman E, Brooks J, Wisniewski K, Raguthu S, French J. 1982. Autism is associated with the fragile-X syndrome. J Autism Dev Disord 12:303–308.

Chai JH, Locke DP, Greally JM, Knoll JH, Ohta T, Dunai J, Yavor A, Eichler EE, Nicholls RD. 2003. Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. Am J Hum Genet 73:898–925.

Chudley AE. 1990. Sex chromosomal and autosomal aneuploidy in the fragile X syndrome. Birth Defects Orig Artic Ser 26:257–265.

Cohen D, Pichard N, Tordjman S, Baumann C, Burglen L, Excoffier E, Lazar G, Mazet P, Pinquier C, Verloes A, Heron D. 2005. Specific genetic disorders and autism: Clinical contribution towards their identification. J Autism Dev Disord 35: 103–116.

de Vries BB, Niermeijer MF. 1994. The Prader-Willi-like phenotype in fragile X patients: A designation facilitating clinical (and molecular) differential diagnosis. J Med Genet 31:820.

de Vries BB, Fryns JP, Butler MG, Canziani F, Wesby-van Swaay E, van Hemel JO, Oostra BA, Halley DJJ, Niermeyer MF. 1993. Clinical and molecular studies in fragile X patients with a Prader-Willi-like phenotype. J Med Genet 30:761–766.

Estecio M, Fett-Conte AC, Varella-Garcia M, Fridman C, Silva AE. 2002. Molecular and cytogenetic analyses on Brazilian youths with pervasive developmental disorders. J Autism Dev Disord 32:35–341.

Geerts M, Steyaert J, Fryns JP. 2003. The XYY syndrome: A follow-up study on 38 boys. Genet Couns 14:267–279.

Hagerman RJ. 2002. Physical and behavioral phenotype. In: Hagerman RJ, Hagerman PJ, editors. Fragile X syndrome: Diagnosis, treatment and research 3rd edition. Baltimore: The Johns Hopkins University Press. p 3–109.

Harris SW, Goodlin-Jones B, Nowicki ST, Hessl D, Tassone F, Barabato I, Ferranti J, Rogers S, Hagerman RJ. 2008. Autism Profiles of Young Males with Fragile X Syndrome. Am J Med Genet Part A (in press).

Hatton D, Sideris J, Skinner M, Mankowski J, Bailey DB Jr, Roberts J, Mirrett P. 2006. Autistic behavior in children with fragile X syndrome: Prevalence, stability, and the impact of FMRP. Am J Med Genet Part A 140A:1804–1813.

Kaufmann WE, Cortell R, Kau AS, Bukelis I, Tierney E, Gray RM, Cox C, Capone GT, Stanard P. 2004. Autism spectrum disorder in fragile X syndrome: Communication, social interaction, and specific behaviors. Am J Med Genet Part A 129A:225–234.

Kittler P, Krinsky-McHale SJ, Devenny DA. 2004. Sex differences in performance over 7 years on the Wechsler Intelligence Scale for Children—Revised among adults with intellectual disability. J Intellect Disabil Res 48:114–122.

Kupke KG, Soreng AL, Muller U. 1991. Origin of the supernumerary X chromosome in a patient with fragile X and Klinefelter syndrome. Am J Med Genet 38:440–444.

Lachiewicz AM, Dawson DV, Spiridigliozzi GA. 2000. Physical characteristics of young boys with fragile X syndrome: Reasons for difficulties in making a diagnosis in young males. Am J Med Genet 92:229–236.

Loesch DZ, Bui QM, Dissanayake C, Clifford S, Gould E, Bulhak-Paterson D, Tassone F, Taylor AK, Hessl D, Hagerman R, Huggins RM. 2007. Molecular and cognitive predictors of the continuum of autistic behaviours in fragile X. Neurosci Biobehav Rev 31:315–326.

Lord C, Risi S, Lambrecht L, Cook EH Jr, Leventhal BL, DiLavore PC, Pickles A, Rutter M. 2000. The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 30:205–223.

Lubs HA. 1969. A marker X chromosome. Am J Hum Genet 21:231–244.

Milunsky A, Huang X, Amos JA, Herskowitz J, Farrer LA, Wyandt HE. 1993. 46: XY/47,XYY male with the fragile X syndrome: Cytogenetic and molecular studies. Am J Med Genet 45:589–593.

Musumeci SA, Hagerman RJ, Ferri R, Bosco P, Dalla Bernardina B, Tassinari CA, De Sarro GB, Elia M. 1999. Epilepsy and EEG findings in males with fragile X syndrome. Epilepsia 40:1092–1099.

Nicolson R, Bhalerao S, Sloman L. 1998. 47: XYY karyotypes and pervasive developmental disorders. Can J Psychiatry 43:619–622.

Nolin SL, Lewis FA III, Ye LL, Houck GE Jr, Glicksman AE, Limprasert P, Li SY, Zhong N, Ashley AE, Feingold E, Sherman SL, Brown WT. 1996. Familial transmission of the FMR1 CGG repeat. Am J Hum Genet 59:1252–1261.

Nowicki ST, Tassone F, Ono MY, Ferranti J, Croquette MF, Goodlin-Jones B, Hagerman RJ. 2007. The Prader-Willi phenotype of fragile X syndrome. J Dev Behav Pediatr 28: 133–138.

Nowicki ST, Hansen RL, Hagerman RJ. 2008. X-linked intellectual disabilities. In: Accardo PJ, editor. Neurodevelopmental Disabilities in Infancy and Childhood (Third Edition): The Spectrum of Neurodevelopmental Disbilities (Volume 2). Baltimore: Paul H. Brookes Publishing Co. p 331–351.

Olsson I, Steffenburg S, Gillberg C. 1988. Epilepsy in autism and autistic-like conditions. A population-based study. Arch Neurol 45:666–668.

Philofsky A, Hepburn SL, Hayes A, Hagerman RJ, Rogers SJ. 2004. Linguistic and cognitive functioning and autism symptoms in young children with fragile X syndrome. Am J Ment Retard 109:208–218.

Rapin I, Katzman R. 1998. Neurobiology of autism. Ann Neurol 43:7–14.

Reddy KS. 2005. Cytogenetic abnormalities and fragile-X syndrome in Autism Spectrum Disorder. BMC Med Genet 6:3.

Riddle JE, Cheema A, Sobesky WE, Gardner SC, Taylor AK, Pennington BF, Hagerman RJ. 1998. Phenotypic involvement in females with the FMR1 gene mutation. Am J Ment Retard 102:590–601.

Rogers SJ, Wehner EA, Hagerman RJ. 2001. The behavioral phenotype in Fragile X: Symptoms of autism in very young children with Fragile X syndrome, idiopathic autism, and other developmental disorders. J Dev Behav Pediatr 22:409–417.

Roid GH, Miller LJ. 1997. Leiter International Performance Scale-Revised. Lutz: Psychological Assessment Resources, Inc.

Sabaratnam M, Vroegop PG, Gangadharan SK. 2001. Epilepsy and EEG findings in 18 males with fragile X syndrome. Seizure 10:60–63.

Saluto A, Brussino A, Tassone F, Pappi P, Arduino C, Hagerman PJ, Migone N, Brusco A. 2005. An enhanced polymerase chain reaction assay to detect pre- and full mutation alleles of the fragile X mental retardation 1 gene. J Mol Diagn 7:605–612.

Schaefer GB, Lutz RE. 2006. Diagnostic yield in the clinical genetic evaluation of autism spectrum disorders. Genet Med 8:549–556.

Sherman S. 2002. Epidemiology. In: Hagerman RJ, Hagerman PJ, editors. Fragile X syndrome: Diagnosis, treatment and research. 3rd edition. Baltimore: The Johns Hopkins University Press. p 136–168.

Sparrow SS, Balla DA, Cicchetti DV. 1984. Vineland adaptive behavior scales survey form manual. Circle Pines: American Guidance Service.

Strauss KA, Puffenberger EG, Huentelman MJ, Gottlieb S, Dobrin SE, Parod JM, Stephan DA, Morton DH. 2006. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. N Engl J Med 354:1370–1377.

Tassone F, Hagerman RJ, Iklé DN, Dyer PN, Lampe M, Willemsen R, Oostra BA, Taylor AK. 1999. FMRP expression as a potential prognostic indicator in fragile X syndrome. Am J Med Genet 84:250–261.

Tassone F, Hagerman RJ, Garcia-Arocena D, Khandjian EW, Greco CM, Hagerman PJ. 2004. Intranuclear inclusions in neural cells with premutation alleles in fragile X associated tremor/ataxia syndrome. J Med Genet 41:e43.

Thorndike RL, Hagen E, Sattler J. 1986. Stanford-Binet Intelligence Scale. 4th edition. Itasca: Riverside Publishing.

Wassink TH, Piven J, Patil SR. 2001. Chromosomal abnormalities in a clinic sample of individuals with autistic disorder. Psychiatr Genet 11:57–63.

Wechsler D. 1991. Wechsler Intelligence Scale for Children, Third Edition (WISC-III). San Antonio: The Psychological Corporation.

Wechsler D. 1997. Wechsler Adult Intelligence Scale-Third Edition: Administration and Scoring Manual. San Antonio: Harcourt Assessment, Inc.

Wechsler D. 1999. Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio: Harcourt Assessment, Inc.

Wechsler D. 2002. Wechsler Preschool and Primary Scale of Intelligence. 3rd edition. San Antonio: The Psychological Corporation.

Wechsler D. 2003. Wechsler Intelligence Scale for Children—Fourth Edition. San Antonio: Harcourt Assessment, Inc.

Wright-Talamante C, Cheema A, Riddle JE, Luckey DW, Taylor AK, Hagerman RJ. 1996. A controlled study of longitudinal IQ changes in females and males with fragile X syndrome. Am J Med Genet 64:350–355.

Zigler E, Balla D, Hodapp R. 1984. On the definition and classification of mental retardation. Am J Ment Defic 89:215–230.