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Autistic Behavior in Children With Fragile X Syndrome: Prevalence, Stability, and the Impact of FMRP

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We examined autistic behavior in a cross-sectional sample of 179 children with fragile X syndrome (FXS) and a longitudinal subset of 116 children using the Childhood Autism Rating Scale (CARS) to (a) determine a prevalence of autistic behavior in FXS, (b) examine the stability of autistic ratings over time, and (c) assess the association between the fragile X mental retardation protein (FMRP) and autistic behavior. Approximately 21% of the sample of 129 children (25.9% of boys) scored at or above the cutoff for autism. CARS scores increased slowly, yet significantly, over time, and low levels of FMRP were associated with higher mean levels of autistic behavior as measured by the CARS. © 2006 Wiley-Liss, Inc.

Key words: fragile X syndrome; autism; fragile X mental retardation protein

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INTRODUCTION

A number of studies published in the past decade have shown that fragile X syndrome (FXS) is associated with an increased prevalence of autistic behavior and autism diagnosis. These studies have reported prevalence rates ranging from 25% to 47% and have used a variety of diagnostic methods [Cohen, 1995; Turk and Graham, 1997; Bailey et al., 2000; Rogers et al., 2001; Demark et al., 2003; Kaufmann et al., 2004]. Other studies have shown that individuals with both autism and FXS often have poorer developmental outcomes [Bailey et al., 2000; Rogers et al., 2001], lower cognitive abilities [Cohen, 1995; Turk and Graham, 1997; Kaufmann et al., 2004], lower levels of adaptive behavior [Cohen, 1995; Turk and Graham, 1997; Rogers et al., 2001; Hatton et al., 2003; Kau et al., 2004], and more problem behavior [Hatton et al., 2002; Kau et al., 2004] than individuals with FXS and fewer autistic behaviors.

Fragile X syndrome is currently considered the leading inherited cause of intellectual disability, with a prevalence of 1 in 4,000 males and 1 in 8,000 females [Sherman, 2002]. Diagnosis is based on DNA analysis that usually identifies the number of CGG repeats in the fragile X mental retardation 1 gene at the *Xq 27.3* site on the long arm of the X chromosome. Individuals with the full mutation have 200 or more repeats, an expansion that typically is associated with methylation of the promoter region of the gene that results in deficient or reduced protein expression. The fragile X mental retardation protein, or FMRP, is believed to be essential for normal brain development and function and is expressed throughout the body, as evident in connective tissue abnormalities and hyperextensive joints in some individuals with the full mutation. Carriers of FXS typically have the premutation with CGG repeats in the 55–199 range. Although most premutation carriers do not have intellectual disabilities, they may have more subtle features such as shyness and anxiety, and they may also have physical features such as premature ovarian failure and the fragile X-associated tremor/ataxia syndrome [FXTAS; Hagerman and Hagerman, 2004]. FXS is distinct from autism in that diagnosis is based on DNA tests, not behavioral observations. However, some individuals with FXS also meet diagnostic criteria for autism. Many individuals with FXS display some autistic behaviors such as eye-gaze aversion,

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atypical sensory responses, delayed and atypical language, and repetitive behaviors; however, there is longstanding disagreement about whether or not these behaviors truly represent autism [Feinstein and Reiss, 1998].

Prevalence of Autistic Behavior/Autism in Children With FXS

Researchers have reported varying prevalence rates of autism in individuals with FXS. Bailey et al. [1998] found that 25% of a sample of 57 boys (ages 24–84 months) with FXS scored 30 or above on the Childhood Autism Rating Scale [CARS; Schopler et al., 1988], the threshold used to distinguish autism. Using the Autism Diagnostic Interview-Revised [ADI-R; Lord et al., 1994], the Autism Diagnostic Observation Schedule-Generic [ADOS-G; Lord et al., 2000], DSM-IV criteria, and expert clinical opinion, Rogers et al. [2001] found that 33% of a sample of 24 children with FXS (ages 21–48 months) met diagnostic criteria on three or more measures. Kaufmann et al. [2004] reported that 25% of their sample of 56 children with FXS (M age = 4.8 years; SD = 1.2) met diagnostic criteria for autism on the ADI-R. Demark et al. [2003] examined autistic behavior in individuals with FXS using the CARS. In a sample of 15 children with FXS (M age = 11.8 years; SD = 2.6), seven children (47%) had a total score $\geq$30 (autism cut-off).

Correlates of Autistic Behavior in FXS

Genetic status. In a study examining the impact of environmental and genetic factors on behavior problems and autistic symptoms in children with FXS, Hessl et al. [2001], found that FMRP predicted autistic symptoms as measured by the Autism Behavior Checklist [ABC; Krug et al., 1993] in girls with FXS (controlling for IQ), but not in boys. In their sample, quality of the home environment predicted autistic symptoms in boys. There was relatively little variability in levels of protein expression in the boys in this study (M = 2.09; SD = 1.57). However, there was considerably more variability for the girls (M = 51.03; SD = 18.57), probably accounting for the differential impact of FMRP on autistic symptoms. Also, IQ was a control variable in the analysis, and IQ and FMRP are usually highly correlated in males with full mutation FXS. Thus, the impact of FMRP on autistic symptoms in boys may have been obscured through its impact on IQ. Additionally, the ABC may not be a sensitive measure of autistic symptoms in children with FXS. Rellini et al. [2004] found that the ABC did not distinguish individuals with autistic disorders from those with other developmental disorders and that there was little correspondence between ABC and DSM-IV results in their sample. These same authors recommended that the CARS be used to examine autistic behavior in individuals with developmental disorders due to its convergence with DSM-IV criteria.

An intriguing study of autism spectrum disorders (ASD) in six individuals with premutation FXS revealed that ASD was related to level of FMRP and adaptive behavior but not to differences in IQ [Goodlin-Jones et al., 2004]. The finding that ASD was related to FMRP and not IQ in this study is similar to the finding reported by Hessl et al. [2001] for girls with FXS. Interestingly, two of the six individuals with premutation FXS and ASD in the Goodlin-Jones et al. sample were females.

Mazzocco et al. [1997] compared 30 girls with FXS to 31 typically developing girls matched on age and IQ. Only one girl with FXS met DSM criteria for autism, so it was not possible to examine the relations between autism and the genetic measure, activation ratio (percentage of normal cells, rather than cells with FXS, that appear to be randomly activated and therefore producing the FMR protein). However, higher levels of stereotypic/repetitive behaviors were significantly correlated with more impairment in social play, less ability to make peer friendships, lower communication abilities and skills, and more behaviors suggesting a restricted repertoire of activities. Girls with low activation ratios had more repetitive behaviors. As noted earlier, there was no association between IQ and autistic behaviors, suggesting that intellectual disability is not the underlying mechanism for autistic behavior in girls with FXS.

IQ. Despite numerous studies of the association between IQ and autistic behavior in individuals with FXS, controversy remains. Many studies have reported that males with both FXS and autism have lower IQ scores [Hagerman et al., 1986; Cohen, 1995; Turk and Graham, 1997; Kau et al., 2004] or lower developmental levels [Bailey et al., 2000; Roberts et al., 2001b; Rogers et al., 2001] than individuals who have FXS but no autism. However, Reiss and colleagues [Reiss and Freund, 1990, 1992] did not find an association between IQ and autistic behavior in males or in females [Mazzocco et al., 1997] with FXS. Some of the discrepancies noted in IQ scores may be related to the challenges of securing valid IQ scores in individuals with FXS [Dykens et al., 1989; Hay, 1994; Hooper et al., 2000; Skinner et al., 2004].

Interestingly, Mazzocco et al.'s [1997] finding that females with FXS with normal intelligence displayed more autistic behaviors than a control sample matched on IQ, along with Goodlin-Jones et al.'s [2004] recent finding that ASD was not associated with IQ in individuals with the premutation suggests that intellectual disability may not be associated with autistic behavior in some individuals with FXS.

Adaptive behavior. A number of researchers have reported that individuals with both FXS and autism (FXS/autism) scored lower than those with

FXS without autism (FXS/no autism) on measures of adaptive behavior [Cohen, 1995; Turk and Graham, 1997; Rogers et al., 2001; Hatton et al., 2003; Kau et al., 2004]. Results from several studies are converging to suggest that adaptive behavior scores may be a better predictor of autistic behavior in FXS than IQ scores [Rogers et al., 2001; Goodlin-Jones et al., 2004; Kaufmann et al., 2004], probably due to challenges in securing valid IQ scores in individuals with FXS, as noted earlier.

Problem behavior. Two studies suggest that autistic behavior is associated with increased problem behaviors in boys with FXS [Hatton et al., 2002; Kau et al., 2004]. Using the child behavior checklist [Achenbach, 1991a,b], Hatton et al. [2002] found that autistic behavior, as measured by the CARS, was related to higher total problem behavior and more thought problems and social problems. Kau et al. [2004] also found that boys with FXS who met diagnostic criteria for autism on the ADI-R had more total problem behavior. Specifically, boys with FXS/autism had higher levels of withdrawn behavior and more attention problems.

Arousal and social anxiety. A number of neurobiological mechanisms have been posited to account for the increase of autism in FXS. Dysfunction of limbic and autonomic functions, including physiological hyperarousal and/or social anxiety, has been one of the most popular theories described. Specifically, associations between electrodermal activity and sensory reactivity [Miller et al., 1999], salivary cortisol and withdrawn behavior [Hessl et al., 2002], skin conductance and gaze avoidance [Belser and Sudhalter, 1995], and salivary cortisol and gaze aversion [Hessl et al., 2006] have been reported in persons with FXS. All of these behaviors are consistent with descriptions of autistic behavior. In our own work, we found that children with FXS and autistic behavior displayed higher arousal (increased heart rate) than those with FXS only and typical controls [Roberts et al., 2001a].

Factors that distinguish children with FXS, FXS/autism, and autism. In studies that have included children with FXS/no autism, FXS/autism, and autism, children with FXS/autism appear to have poorer developmental or intellectual outcomes and lower levels of adaptive behavior than either children with FXS/no autism or children with autism [Cohen, 1995; Bailey et al., 2000; Rogers et al., 2001; Kaufmann et al., 2004]. Cohen's observation that "the developmental outcome of males with fragile X depends on whether or not they have been diagnosed as having autism" [p. 258] appears to be as accurate today as it was in 1995.

In a series of elegantly designed studies, Rogers et al. [2001] compared young children with autism, FXS/autism, FXS/no autism, and developmental delays (DD) using the ADI-R [Lord et al., 1994] and the ADOS-G [Lord et al., 2000]. These researchers found that children with FXS/autism were similar to children with autism, while children with FXS/no autism were similar to children with DD. In subsequent studies, Rogers et al. found that the imitation skills and sensory characteristics of children with FXS/autism were similar to children with autism, while children with FXS/no autism functioned similarly to a group of children with DD [Rogers et al., 2001; Rogers et al., 2003a,b]. With this same sample, Philofsky et al. [2004] reported that children with FXS/autism were more impaired in nonverbal cognition and expressive language than children with FXS/no autism and children with autism. They suggested that low receptive language skills in young children (M age = 34 months) with FXS may distinguish very young children with autism from those with FXS alone.

Stability of Autistic Behavior in FXS

Although some researchers have suggested that autistic behaviors in FXS may be more severe in preschool aged children [Hagerman et al., 1986; Borghgraef et al., 1987; Reiss and Freund, 1992], most researchers to date have used cross-sectional designs. For example, age was not related to CARS scores in the series of cross-sectional studies on autistic behavior in children with FXS that we previously reported, possibly due to the relatively small sample size and restricted age range of the samples [Bailey et al., 1998; Bailey et al., 2000; Bailey et al., 2001a]. One exception to the use of cross-sectional design is a study by Sabaratnam et al. [2003] that examined autistic behavior in a sample of adults with FXS from an epidemiological study of mental retardation in one district in the United Kingdom. However, those authors did not use actual measures of autism or autistic behavior. Instead the Disability Assessment Schedule [DAS; Holmes et al., 1982] and items from the MRC Schedule of Handicaps, Behaviours and Skills [HBS; Wing, 1980] were used to assess changes in autistic behaviors over a 10-year period in 18 adults with FXS whose mean age was 46.1 years at the time of follow-up. They found that ratings of autistic behaviors were stable over time in this group.

Summary and Research Aims

In summary, autistic behavior in children with FXS and its correlates has been documented by several research groups. In samples ranging from 15 to 56 children with FXS using a variety of measures, researchers have reported a prevalence of autistic behavior/autism of 25% to 47%; however, samples have typically included 50 or fewer individuals with FXS.

With the CARS as a measures of autistic behavior, we have previously reported that autistic behavior in our sample of children with FXS predicted (a) poorer developmental and academic outcomes and slower rates of development [Bailey et al., 2001a; Roberts et al., 2005b], (b) different patterns of development [Bailey et al., 2000], (c) more problem behavior [Hatton et al., 2002], and (d) lower levels of adaptive behavior [Hatton et al., 2003]. Moreover, these findings are consistent with those of researchers who have studied autism in FXS using the ADI-R [Rogers et al., 2001; Kau et al., 2004; Kaufmann et al., 2004] and the ADOS [Rogers et al., 2001]. Consistent findings from multiple researchers in the past 10 years suggest that children with FXS with significant autistic behavior/autism have poorer developmental, behavioral, and functional outcomes than children with less autistic behavior, making the topic of autistic features in FXS of particular relevance. Although clinical reports suggest that autistic behavior may be more prevalent in young children with FXS, there have been no reports to date describing longitudinal evidence regarding the changes in autistic behavior in children. In the few studies examining the relationship between FMRP and autistic behavior in FXS, mixed results have been reported, suggesting, for example, that FMRP is associated with autism in individuals with the premutation and in girls with full mutation FXS, but not in boys with the full mutation.

The purposes of the current study are to (a) expand existing research to describe autistic behavior in a larger cross-sectional sample of 179 children with FXS, (b) examine stability of autistic ratings over time using a subset of 116 children with 396 repeated observations, (c) and examine the impact of FMRP on autistic behavior in a subset of 83 children.

METHOD

Procedures

This study was part of a larger set of longitudinal studies examining development; academic achievement; and attention, memory, and executive function in children with FXS. Assessments were completed twice yearly or annually in children's homes or schools after their parents provided written informed consent for their participation in the study. The research protocol was prospectively reviewed and approved by the Institutional Review Board at the University of North Carolina at Chapel Hill. Following developmental, achievement, or cognitive assessments, trained data collectors scored the CARS based on behavioral observations during a one-half day to two-day assessment session and on parent interviews. Data collectors received training on the CARS and achieved inter rater reliability of 0.80 or above before data collection began. Two data collectors completed CARS ratings and came to consensus on any discrepancies.

Data Processing and Analyses

All data were double entered and verified for accuracy before analysis. After the data were screened for normality, simple descriptive statistics were used to describe autistic behavior in 179 children with FXS at the time of their first CARS rating. Hierarchical linear modeling (HLM; SAS Institute, 2003) was used to examine the stability of CARS scores over time and the impact of FMRP and demographic variables. HLM, sometimes referred to as mixed model regression or multi-level modeling, is particularly suited to these data because repeated assessments of each individual introduces dependence of observation over time. This dependence is controlled by the estimation of random effects [Burchinal and Applebaum, 1991; Raudenbush and Bryk, 2002]. One advantage of HLM is that data can be tied to a specific time line, in this case, chronological age, rather than having to collect data at certain assessment ages [Singer and Willett, 2003]. With low incidence populations such as FXS, the ability to collect data across a range of ages maximizes resources. This flexibility extends to the number of observations per respondent as well. Respondents contribute only to the estimation of the components of the model for which they have data [Singer and Willett, 2003]. For example, an individual with a single data point only contributes to the estimation of the intercept, not to slope estimates.

As the first step in data analysis, data were screened for normality. In the second step, descriptive analyses were completed using cross-sectional data from each participant's first CARS assessment.

In the third step of our analysis, longitudinal data were analyzed using HLM. A baseline model was fit predicting CARS scores from age. This model was used to detect age effects for CARS scores and changes over time. Following the age-only model, a more complex model was fit that included child gender, child ethnicity, and maternal education in addition to age as predictors of CARS scores. The last model included FMRP, child gender, and age using the subset of 83 children with FMRP data. FMRP was not normally distributed, so its log-transform was used as a predictor in the model. An alpha level of $<.01$ was used to determine significance.

RESULTS

CARS Total Scores

Table I presents descriptive statistics by gender. The ages of children in this study ranged from 1.5 to 14.7 years. As shown in Table I, overall total scores

TABLE I. Descriptive Statistics for Variables of Interest by Gender (n = 179)

	Females		Males		Total	
Variable	Mean	SD	Mean	SD	Mean	SD
CARS total score	21.3 (n = 32)	4.8	26.5 (n = 147)	5.6	25.6 (n = 179)	5.8
Chronological age in months	50.7 (n = 32)	36.9	56.5 (n = 147)	33.2	55.4 (n = 179)	33.9
FMRP	40.5 (n = 11)	20.1	9.2 (n = 72)	7.9	13.4 (n = 83)	14.7
	Number, percent		Number, percent		Number, percent	
Ethnicity						
European American	29, 90.6%		124, 84.4%		153, 85.5%	
Maternal education						
High school or less	4, 12.5%		15, 10.2%		19, 10.6%	
Some college	13, 40.6%		46, 31.3%		59, 33.0%	
Bachelor's degree or higher	8, 25%		44, 29.9%		52, 29.1%	

for the first CARS assessment of the 179 children included in this cross-sectional analysis was 25.6 (SD = 5.8). Boys (M = 26.5; SD = 5.6) had higher mean scores than girls (M = 21.3; SD = 4.8). Thirty eight (21.2%) of the 179 children obtained scores of 30 or higher on the CARS, the criterion for autism status. Of these, 36 were male (25.9% of males) and 2 were females (6.3% of girls).

Stability of Autistic Behavior Over Time

A mixed effects HLM was estimated to determine if total scores on the CARS systematically changed with chronological age. Age and CARS scores were centered at the sample mean scores. This analysis included 116 children with two or more CARS observations (396 total). Demographic characteristics for this sample are presented by gender in Table II.

A significant effect for chronological age indicated a slight increase in scores, as children grew older (b = 0.018, df = 1,116, $P < 0.001$). Because age was measured in months, this effect suggests that a child's total score increases about a fifth of a point over the course of each year. Projected over 10 years, a child with a score of 26 at age 2 years would be expected to have a score of about 28 by age 12 years.

We also examined stability of CARS classifications (e.g., not autistic, autistic) for the 116 children with two or more CARS. For the 39 children who scored 30 or above on one or more assessments, 21 (53.8%) had stable categorical classifications across all assessment occasions; 13 (33.3%) had scores that increased over time (initially had scores below 30 but later scored 30 or above), and 5 (12.7%) scored 30 or above initially and later scored below 30. Changes in CARS scores were observed at a variety of chronological ages.

Gender, child ethnicity, maternal education level, and location of CARS observations were used in HLM to determine if these factors had any impact on the continuous CARS scores. Gender was the only significant predictor (see Table III). The age effect, although not significant, was similar to that observed in the first HLM, and there is also an effect for gender, mean difference = −5.4 (Cohen's d = 1.07). Girls, on average, had CARS scores that were five points lower than boys.

Impact of FMRP on Autistic Behavior

A final HLM model was run on 83 children for whom FMRP data were collected, and the demographic variables for this subset of children are

TABLE II. Descriptive Statistics by Gender for Longitudinal Analysis (n = 116)

	Females		Males		Total	
Variable	Mean	SD	Mean	SD	Mean	SD
CARS total score	21.1 (n = 17)	4.9	26.3 (n = 99)	5.3	25.5 (n = 116)	5.6
CARS observations	2.5	0.8	2.9	1.1	2.9	1.1
Time between CARS observations	20.0 months	10.9	26.6 months	15.9	25.9 months	15.6
Chronological age in months	49.4 (n = 17)	25.3	51.9 (n = 99)	27.9	51.6 (n = 116)	27.4
FMRP	43.4 (n = 9)	19.1	9.2 (n = 67)	7.8	13.2 (n = 76)	14.7
	Number, percent		Number, percent		Number, percent	
Ethnicity						
European American	16, 94.1%		89, 89.9%		105, 90.5%	
Maternal education						
High school or less	1, 5.8%		11, 11.1%		12, 10.3%	
Some college	7, 41.1%		32, 32.3%		39, 33.6%	
Bachelor's degree or higher	6, 35.3%		31, 31.3%		37, 31.9%	

TABLE III. Effects and Tests of Predictor Variables in Longitudinal Analysis (n = 116)

Effect	Estimate	Std Err	DF	t-value	Pr > |t|
Intercept	27.94	1.28	173	21.89	<0.0001
Age	0.016	0.01	115	2.51	0.0133
Gender (female)	−5.39	0.98	104	−5.47	<0.0001*
Ethnicity	−0.56	1.20	104	−0.47	0.6396
Mother's education (High school)	0.48	0.93	104	0.52	0.6058
Mother's education (Some college)	−1.24	0.96	104	−1.29	0.1986*

*$P < 0.01$.

presented in Table IV. In addition to FMRP, gender and age were included in this model. Although FMRP was collected on only one occasion, there were multiple CARS observations for children in this subset. All effects are presented in Table V. FMRP was significantly and negatively associated with CARS total scores. Specifically, children with more FMRP had lower CARS scores. Figure 1 illustrates the association between the untransformed FMRP values and predicted CARS scores, while Figure 2 illustrates the association between the log of FMRP and predicted CARS scores. Age was a small, but significant, predictor of autistic behavior. Note that gender was no longer a significant predictor. Given the expected association between gender and FMRP, this finding was not unexpected.

DISCUSSION

The purpose of this study was to examine autistic behavior in a relatively large sample of children with FXS, the stability of autistic behavior over time, and the association of FMRP to autistic behavior. We used the largest sample of children with FXS reported to date to address prevalence, and this article presents the only longitudinal description of autistic behavior in children with FXS. Our examination of the impact of FMRP on autistic behavior will be only the third such reported study.

Autistic Behavior

We found that 21.2% (n = 38) of our sample scored 30 or above on the CARS on their first assessment. For boys, the percentage was 25.9%, while only 6.3% (n = 2) of the girls in this study scored 30 or above. The 25.9% prevalence in boys is very similar to the 25% to 30% prevalence rates that we have reported in previous studies of the development, behavior, and achievement of boys with FXS [Bailey et al., 1998, 2001a; Hatton et al., 2002; Hatton et al., 2003; Roberts et al., 2005b]. Although this percentage is a little lower than that reported by Rogers et al. [2001], it is consistent with the prevalence reported by Cohen [1995], Kaufmann et al. [2004], and Turk and Graham [1997].

Interestingly, the overall prevalence of autistic behavior in our sample of children with FXS (21.2%) is considerably lower than the 47% reported in another study that used the CARS [Demark et al., 2003]. These differences are probably due to differences in sample sizes (179 vs. 15) and in the age of children in the samples. The mean age of children in our cross sectional sample was 3.5 years (SD = 0.5), while the mean age of the Demark et al. sample was 11.8 years (SD = 2.6 years). Our longitudinal finding that autistic behavior as measured by the CARS increases slowly but significantly over time could explain the higher prevalence of autistic behavior in Demark et al.'s much older sample of children with FXS.

Considering that researchers have used different measures of autism, the similarity in prevalence rates is surprising and impressive. At a recent research symposium on this topic, data from four different research groups suggested remarkably similar percentages (approximately 25%) of children meeting criteria for autism despite the fact that different measures were used [Cody-Hazlett et al., 2005; Hatton et al., 2005; Hennon et al., 2005; Roberts et al., 2005a].

Only 2 out of the 32 (6.3%) girls in our sample had a CARS score of ≥30, consistent with Mazzocco et al.

TABLE IV. Demographic Characteristics of Children With FMRP (n = 83)

	Females		Males		Total	
Variable	Mean	SD	Mean	SD	Mean	SD
CARS total score	21.7 (n = 11)	5.9	26.0 (n = 72)	5.3	25.5 (n = 83)	5.6
CARS observations	2.5	1.1	3.0	1.3	2.9	1.3
Time between CARS observations	23.2 months	12.2	28.9 months	15.9	28.3 months	15.6
Chronological age in months	53.4 (n = 11)	23.4	54.1 (n = 72)	27.9	54.0 (n = 83)	27.2
FMRP	40.6 (n = 11)	20.1	9.2 (n = 72)	7.9	13.4 (n = 83)	14.7
	Number, percent		Number, percent		Number, percent	
Ethnicity						
European American	11, 100%		64, 88.9%		75, 90.4%	
Maternal education						
High school or less	1, 9.1%		11, 15.3%		12, 14.5%	
Some college	5, 45.5%		24, 33.3%		29, 34.9%	
Bachelor's degree or higher	2, 18.2%		14, 19.4%		16, 19.3%	

TABLE V. Effects and Tests of Age, Gender, and FMRP on CARS Scores (n = 83)

Effect	Estimate	Std Err	DF	t-Value	Pr > |t|
Intercept	25.8	0.72	79	35.9	<0.0001
Age	0.02	0.01	75	3.00	0.0038*
Gender (female)	−1.87	1.70	87	−1.10	0.2746
Mother's Education (Some college)	2.20	0.96	87	2.29	0.0243
FMRP	−1.80	0.62	87	−2.92	0.0045*

*$P < 0.01$.

[1997] who did not have any girls who met diagnostic criteria for autism. Mazzocco et al. did find that girls with FXS had more autistic behaviors than an IQ matched sample, however, and that repetitive behaviors were predicted by activation ratio. More in depth study of autistic behavior in girls with FXS is warranted. Girls have greater phenotypic and genotypic variability than boys with FXS; therefore, more subtle findings may emerge in research that includes larger numbers of girls.

Stability of CARS Scores Over Time

Although some clinical literature suggests that autistic behavior in children with FXS may appear more severe in the preschool years, there have been no longitudinal research data to support that observation. In our sample, scores on the CARS slowly but significantly increased over time, a new finding. The fact that CARS scores increase by only one point over the course of 5 years also reflects relative stability over time. This slight increase in scores seems reasonable. As children age, they face more demands for social interactions and age-appropriate behavior. Children who have difficulty in relating to others, poor imitation skills, and problems with emotional responses will have difficulty with their peers and teachers during preschool and the early elementary grades. Although preschoolers who engage in strange body posturing and repetitive behaviors and who use objects inappropriately and repetitively may be overlooked, these behaviors are much more obvious and more socially isolating in elementary school aged children. Therefore, this knowledge that autistic behaviors in children with FXS appear to increase slowly over time can be helpful to families and teachers as they implement behavior management strategies aimed at decreasing inappropriate behaviors while also encouraging socially acceptable interactions and appropriate behavioral responses.

When examining factors associated with autistic behavior, we found that FMRP predicted mean scores on the CARS, but not change over time. This finding must be viewed cautiously, however,

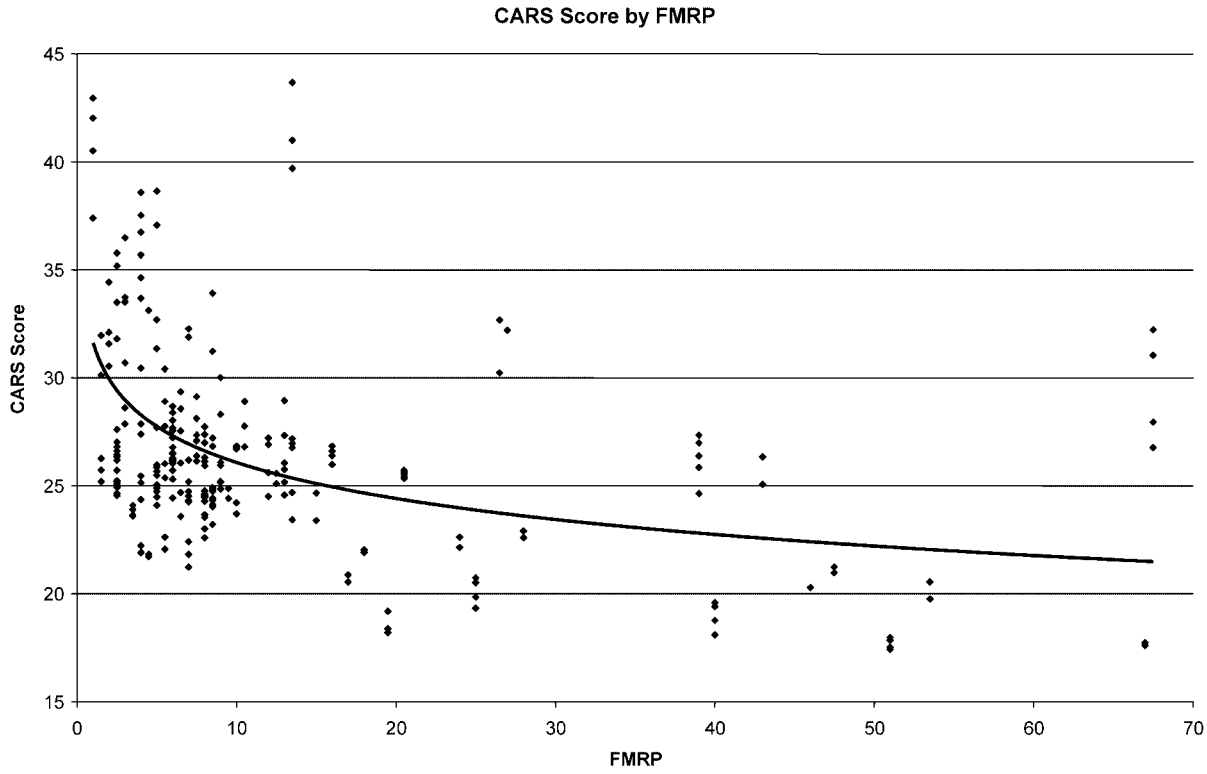

FIG. 1. Relationship between FMR protein expression (not transformed) and CARS scores. X-axis: Percentage of lymphocytes expressing FMRP. Y-axis: Total CARS scores. Points on graph represent individual CARS scores. FMR, fragile X mental retardation. FMRP, fragile X mental retardation protein. CARS, childhood autism rating scale.

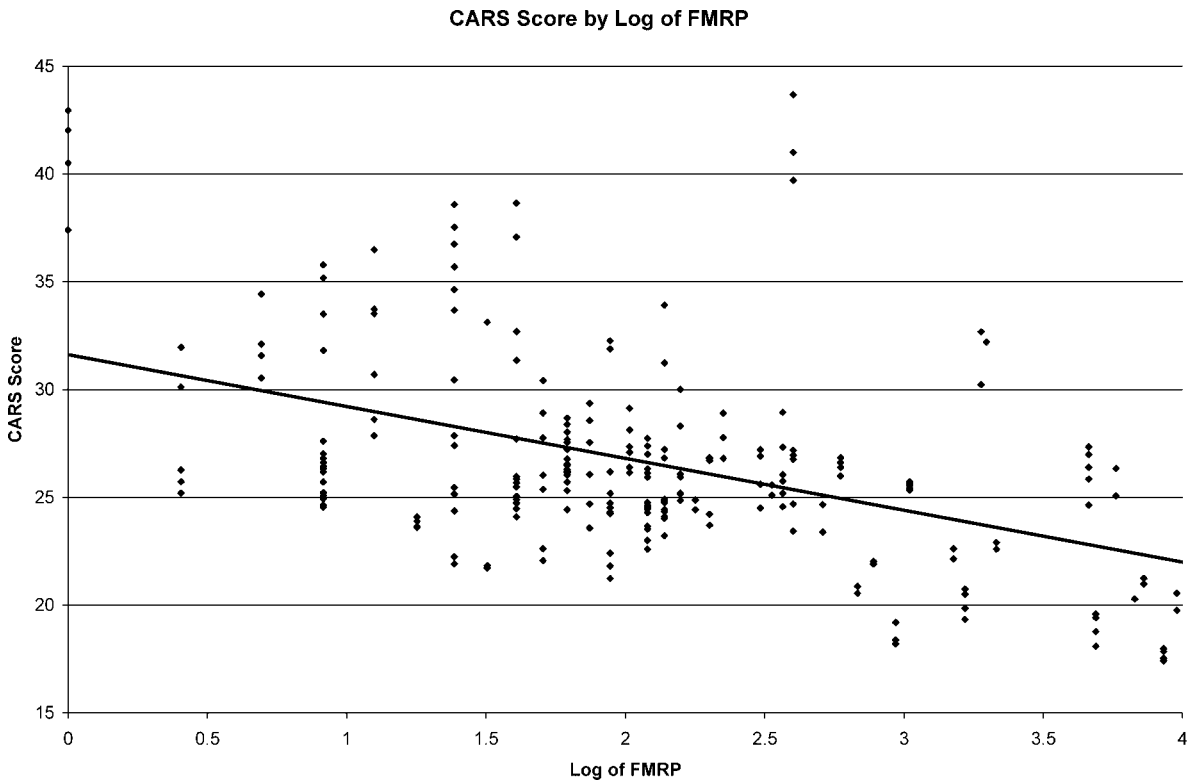

FIG. 2. Relationship between Log 10 of FMRP and CARS scores. X-axis: Log of FMRP. Y-axis: Total CARS scores. Points on graph represent individual CARS scores. FMR, fragile X mental retardation. FMRP, fragile X mental retardation protein. CARS, childhood autism rating scale.

because we collected FMRP at one point in time, and we are not certain about its stability. FMRP should reflect, admittedly to a limited extent because of blood versus brain expression, the impact of the FMR mutation on protein expression and ultimately brain function and behavior. Therefore, this finding is reasonable and is consistent with Mazzocco et al.'s [1997] finding that activation ratio in females is related to repetitive and stereotyped behaviors, with Goodlin-Jones et al.'s [2004] finding that FMRP predicted ASD in individuals with the FXS premutation, and with Hessl et al.'s [2006] findings for girls with FXS.

However, our current results are not consistent with our previous finding that FMRP was not related to autistic behavior in boys [Bailey et al., 2001a] or with Hessl et al.'s findings that FMRP did not predict autistic symptoms in boys with full mutation FXS. The difference in findings compared to our 2001 study is probably due to the current study's larger sample size, more CARS observations, and to the inclusion of girls with more variability in FMRP. Support for those differences is provided by the fact that our results for girls were consistent with Hessl et al., but that our results for boys were not consistent. Also, Hessl et al. co-varied IQ with FMRP, and those two variables are usually highly correlated in males with full mutation FXS. Therefore, it is possible that the impact of IQ obscured that of FMRP.

Lower levels of FMRP expression were associated with higher scores on the CARS, suggesting that lack of FMRP, whether directly related or indirectly related through the regulation of other genes, may contribute to autism in children with FXS, just as it contributes to intellectual disabilities. Mazzocco et al. [1997], Goodlin-Jones et al. [2004], and Hessl et al. [2006] suggest that FMRP probably has a direct impact on autistic behavior, rather than an indirect impact due to lower cognitive abilities. If replicated by other researchers, this finding illustrates a gene to brain to behavior relation in FXS.

Although this study was limited by our reliance on one measure of autistic behavior, the findings contribute in several ways to knowledge of autistic behavior in children with FXS. First, we have documented a prevalence of autistic behavior in approximately 21% of a sample of 179 children (25.9% in boys) that is consistent with numerous reported studies and with studies that are in progress. This study is the first to examine change in autism ratings over time in FXS using a repeated measure design. We found that CARS scores increased slowly, yet significantly, over time and that low levels of FMRP are associated with higher mean levels of autistic behavior but not with changes in autistic behavior over time.

Many children with both FXS and significant autistic behavior would probably qualify for

educational and social services for children with autism. These specialized services may help them achieve their academic potential while also reducing problem behavior that may be related to autistic characteristics. Many communities have extensive social and community supports for individuals with autism that could provide respite and resources for families whose children have more severe autistic behaviors. Therefore, it may be worthwhile for families to consider seeking clinical diagnoses of autism for their children with FXS who also have significant autistic behaviors in order to access more supports and services.

Recognition that autistic behaviors appear to increase slowly over time may also be helpful for families and service providers who may consider earlier and more consistent intervention to address autistic behaviors. Behaviors that may not seem to be that atypical during the preschool years may become much more isolating as children age and expectations for them increase. Literature from the autism field suggests that early and intensive intervention can improve outcomes for children with autism. Perhaps that finding will also apply for children with FXS/autism.

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