Genetic and Environmental Influences on the Cognitive Outcomes of Children With Fragile X Syndrome

JENNIFER DYER-FRIEDMAN, PH.D., BRONWYN GLASER, B.A., DAVID HESSL, PH.D., CINDY JOHNSTON, B.A., LYNNE C. HUFFMAN, M.D., ANNETTE TAYLOR, PH.D., JACOB WISBECK, M.S., AND ALLAN L. REISS, M.D.

ABSTRACT

Objective: To measure the genetic and environmental factors influencing the cognitive outcomes in children with fragile X, a common genetic disorder causing cognitive impairments. **Method:** In-home evaluations were conducted on 120 children (80 boys and 40 girls) with the fragile X full mutation and their unaffected siblings. **Results:** Multiple regression analyses show that the cognitive outcomes for girls with fragile X are most strongly predicted by the mean IQ of their parents, with a small proportion of the variance accounted for by the quality of their home environment. FMR1 protein (FMRP) was associated with girls' levels of distractibility. Mean parental IQ was associated only with boys' Performance IQs, while FMRP was associated with boys' Full Scale IQs. The quality of boys' home environments accounted for more of the variance in their cognitive outcomes than it did for affected girls. **Conclusions:** Both biological/genetic factors and environmental factors are significant predictors of IQ in children with fragile X syndrome; however, the influence of specific factors differs between girls and boys. These findings lay the foundation for further investigation into biological and environmental interventions. *J. Am. Acad. Child Adolesc. Psychiatry*, 2002, 41(3):237–244. **Key Words:** fragile X syndrome, cognitive phenotype, home environment, special education, neurobehavioral disorders.

Fragile X syndrome is the most common known cause of inherited developmental disability; it occurs in 1 out of every 2,000 to 5,000 live births. It is caused by mutations in a single gene on the long arm of the X chromosome, which lead to diminished production of the FMR1 protein (FMRP) and aberrant brain development. The fragile X phenotype includes cognitive impairments ranging from learning disabilities to severe mental retardation (Rousseau et al., 1994); behavioral dysfunction such as hyperarousal, social anxiety, withdrawal, and attention problems (Baumgardner et al., 1995; Boccia and Roberts, 2000; Cohen, 1995; Freund et al., 1993); and subtle physical abnormalities including a long, narrow face, prominent ears, prominent forehead and jaw, and in males, macroorchidism.

In females with fragile X, production of FMRP is maintained to varying degrees by the presence of the second, unaffected X chromosome. Affected females have a much broader range of deficits and generally function at a higher cognitive level than do males with the full mutation. Nearly 100% of males with the full mutation have IQ levels ranging from severe to mild mental retardation (Rousseau et al., 1994). In comparison, females with the full mutation have IQ levels ranging from severe mental retardation to normal (Hagerman et al., 1992; Rousseau et al., 1994), with approximately one third of this group having cognitive function in the mental retardation spectrum (Freund and Reiss, 1996; Mazzocco et al., 1992).

While the cognitive phenotype of fragile X has been well established, there is considerably less information pertaining to influential factors associated with variations in the phenotype. Studies that have addressed this issue have

Accepted October 16, 2001.

Drs. Dyer-Friedman and Hessl and Ms. Johnston, Ms. Glaser, and Mr. Wisbeck are with the Department of Psychiatry, Stanford University, Stanford, CA. Dr. Huffman is with the Department of Pediatrics, Stanford University, and the Children's Health Council, Palo Alto, CA. Dr. Taylor is with Kimball Genetics, Inc., Denver. Professor Reiss is Director, Division of Child and Adolescent Psychiatry, Department of Psychiatry, Stanford University.

This work was supported by NIH grants MHO1142 and MH50047. Further support was received from the Packard Foundation and the Lynda and Scott Canel Fund for Fragile X Research. The authors thank Christine Blasey for statistical consultation.

Correspondence to Dr. Dyer-Friedman, Department of Psychiatry, Child Division, 401 Quarry Road, Stanford University School of Medicine, Stanford, CA 94305-5719; e-mail: jennydf@stanford.edu.

been limited to examining the association between measures of FMRP and outcome (Kaufmann et al., 1999; Reiss et al., 1995; Tassone et al., 1999). The goal of this study was to determine the relative contributions of biological/genetic factors as well as environmental factors to the cognitive outcomes of boys and girls with fragile X syndrome, particularly in comparison with their unaffected siblings. Thus this study incorporated molecular analysis of FMRP, cognitive evaluations of parents and children, direct observation of the home environment, and a measure of the effectiveness of the children's educational and therapeutic services.

The hypotheses underlying this study focus on two general areas: (1) the cognitive phenotype of girls and boys with fragile X and (2) the influential factors significantly associated with the cognitive phenotype. First, we expected to replicate previous findings pertaining to the fragile X phenotype: girls would have, on average, a higher level of general cognitive ability than boys and would have greater strengths in the verbal domain than in the performance domain. Boys' relative strengths and weaknesses would be minimal and, perhaps, only observable at the subtest level. Second, we expected to find that biological/genetic *and* environmental factors would be significantly associated with the cognitive outcomes of both girls and boys with fragile X. More specifically, we predicted that the pattern of factors associated with the girls' outcomes would be more similar to that of their unaffected siblings than to that of the boys.

METHOD

Subjects

Families were recruited from an existing fragile X registry, through advertisements in fragile X association newsletters and web sites, and through referrals from clinicians and families. To determine eligibility, families completed a telephone-screening interview covering basic demographic information, family history of fragile X, and their children's developmental histories. Subjects were excluded because of other known medical problems or signs of current illness. Confirmatory DNA testing for the FMR1 mutation was carried out on all affected children and on previously untested family members.

For this study, 120 families with one child with fragile X and one unaffected sibling were assessed. In all families, the fathers and mothers were the biological parents of both children and the mothers had a fragile X premutation (i.e., 50–200 CGG repeats with normal methylation patterns). For all affected children, unaffected siblings, and mothers, the presence or absence of the fragile X mutation was confirmed by Southern blot DNA analysis. Of the 120 children with fragile X, 40 were females and 80 were males. Of the 120 unaffected siblings, 62 were females and 58 were males. All mothers and 85% (n = 102) of fathers participated in the study. Children were between 6 and 17 years of age (mean age of children with fragile X = 10.76 years ± 2.83; mean age of unaffected siblings = 11.20 years ± 3.10). The ethnic distribution of the study sample of children was 91.7% white, 2.5% Hispanic, 2.5% African American, 1.7% Asian, 0.8% Pacific Islander, and 0.8% multiethnic. Families in 36 U.S. states and Canada, across urban, suburban, and rural areas, were represented in the sample. The highest level of education attained by either parent, representing the educational level of the households in this sample, was as follows: 0.8% partial high school, 10.8% high school diploma, 34.2% partial college, 54.1% college degree or more.

Procedures

This study was part of a larger research project for which two researchers, a licensed psychologist and trained research associate, conducted an 8-hour, home-based evaluation of each participating family. Blood samples were required from all children with fragile X in order to calculate their FMRP percentages. Blood testing kits were mailed to families in advance of the home visit, allowing the blood draw(s) to be conducted in their own physician's office or at a community clinic. Blood samples were sent directly from the blood draw site to the genetics testing facility by overnight mail.

Measures

Cognitive Assessment (Child). The WISC-III (Wechsler, 1991), a standardized aptitude test for children aged 6 through 16 years, was administered to each child. Three scale scores and four index scores are generated from this test.

Cognitive Assessment (Parent). The WAIS-III (Wechsler, 1997), a standardized aptitude test for adults aged 16 through 89 years, was administered to each parent. Similar to the WISC-III, it generates three scale scores and four index scores. As IQ is known to be largely heritable (Plomin et al., 1997), the mean of the parents' Full Scale IQ (FSIQ) scores (MPIQ) was used to account for the cognitive abilities transmitted to each child independent of the genetic mutation. (When paternal FSIQ was not available, the mother's FSIQ score was used instead of MPIQ.)

Assessment of Home and Family Environment. The home environment was assessed with the Home Observation for Measurement of the Environment (HOME) (Bradley, 1993; Caldwell and Bradley, 1984). The HOME is a semistructured interview done in the family home that assesses parental support for learning and enrichment of the home environment. The HOME is completed in reference to a specific child, so two children within the same family may have discrepant scores based on the enrichment and opportunities offered to the individual child. To determine interrater reliability, two examiners independently rated the observation items of the HOME during their visits to 22 families. The second examiner then contacted these families within 2 weeks after their visit and readministered the interview items of the HOME. Interrater reliability was high (intraclass correlation for total HOME score = 0.84).

Family Economic Status. Parents reported gross annual household income on a demographics questionnaire. To better estimate a family's discretionary income available for services and enrichment for their children, gross household income was adjusted for regional differences in housing and cost of living and expressed as a percentage by way of the following calculation: adjusted household income = gross household income/median household income for family's zip code area. The zip code median income was determined by Decisionmark Corporation and based on the 1990 U.S. Census data for 1990, estimates for 1998, and projections for 2003. These data were obtained from the World Wide Web via *www.Homes.com*.

Assessment of Educational Services. The Special Curriculum Opportunity Rating Scale (SCORS) (Dyer-Friedman et al., 2001), a new measure,

assesses the effectiveness of education services. The SCORS includes two 15-item Q-sorts ranked by the parent to describe the following constructs: (1) the cognitive and behavioral skills that a child needs to develop, and (2) the cognitive and behavioral skills that have recently improved. The correlation of the two Q-sorts is considered an index of the effectiveness of a child's educational and therapeutic services in meeting his or her current developmental needs (i.e., Effectiveness of Educational Services Index, EESI). Initial studies of the test-retest reliability of the SCORS Q-sorts yield reliability scores for the two scales of 0.70 and 0.67. Initial validation studies demonstrate that the SCORS has good convergent and discriminant validity within this fragile X sample and strong concurrent validity in comparison with IQ and Child Behavior Checklist scores (Dyer-Friedman et al., 2001).

Fragile X Diagnosis and FMRP Analysis. Southern blot analyses were performed according to (Taylor et al., 1994) by Kimball Genetics, Inc. (Denver). FMRP immunostaining, an indirect alkaline phosphatase technique, was used (Willemsen et al., 1995, 1997). For each slide, 200 lymphocytes were scored and the percentage of lymphocytes expressing FMRP was determined. Scoring was performed in a blind fashion with respect to DNA results.

Statistical Analyses

To examine the differences in IQ scales between gender and diagnostic groups, we conducted multivariate analyses of variance on FSIQ, Verbal IQ (VIQ), and Performance IQ (PIQ). Follow-up analyses (Tukey honestly significant difference) were conducted to specify the between-group differences. A probability of <.05, two-tailed, was required as evidence for statistical significance.

To examine the variance in IQ accounted for by biological and environmental factors, we conducted hierarchical multiple regression analyses separately for three groups: unaffected siblings (males and females were combined; see "Results"), females with fragile X, and males with fragile X. The hierarchical approach, as opposed to simultaneous, allowed us to determine the relative contributions of biological/genetic factors (accounted for first) and environmental factors (accounted for second) to child IQ and to test a priori hypotheses in a more specific fashion.

The dependent variables used in seven discrete multiple regressions were the children's three IQ scale scores and four index scores: FSIQ, VIQ, PIQ, Verbal Comprehension (VCI), Perceptual Organization (POI), Freedom From Distractibility (FDI), and Processing Speed (PSI). The independent variables included in the first step were age, gender, MPIQ, and percent FMRP. (Gender was included in the regression models for the unaffected sibling group only.) The independent variables included in the second step were adjusted family income, total HOME score, and the EESI. It should be noted that FMRP and EESI were not relevant to the analysis of unaffected siblings and were not included in regression models pertaining to that group.

RESULTS

There were no significant differences between unaffected female siblings and unaffected male siblings on any of the IQ scales. Therefore, the unaffected male and female siblings were combined into one comparison group. A multivariate analysis of variance revealed an overall group effect for the three IQ scales: FSIQ (F_3 = 324.35, p < .000), PIQ (F_3 = 293.26, p < .000), and VIQ (F_3 = 254.52, p < .000). Follow-up Tukey honestly significant difference pairwise tests revealed significant group differences between males with fragile X and the two other subject groups (p < .000) and females with fragile X and the two other subject groups (p < .000).

Descriptive Statistics

Descriptive statistics for each independent variable are presented by group in Table 1. Males with fragile X had lower FMRP levels than affected females. The other biological/genetic factors were similar across the three groups. The MPIQ scores were within the average range and consistent with the normative sample of the WAIS-III (Wechsler, 1997). From among the environmental factors, the mean HOME scores for all groups were comparable with those of the normative sample (Bradley, 1993). The effectiveness of educational services (EESI) as rated by mothers ranged from –0.88 to 0.93. Females with fragile X had a higher mean EESI score than the males with fragile X. Finally, adjusted family income was similar across all

TABLE 1
Descriptive Statistics of Independent Variables in Multiple Regression

Independent Variables	Control Siblings (n = 120)			Males With Fragile X (n = 80)			Females With Fragile X (n = 40)		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Age	11.20	3.10	5.97–18.01	10.94	2.69	6.00–16.95	10.42	3.10	5.99–16.60
MPIQ	107.38	12.31	69–140	106.23	11.59	69–139	109.67	13.52	87–140
FMRP %	NA	NA	NA	12.09	11.57	1.50–74.00	51.03	18.57	14.00–77.70
HOME	48.72	7.05	23–58	45.29	7.05	26–57	48.40	6.60	24–57
EESI	NA	NA	NA	0.25	0.40	–0.88–0.90	0.41	0.33	–0.52–0.93
Income ratio	1.16	0.71	0.13–4.33	1.09	0.58	0.13–2.78	1.30	0.91	0.15–4.33

Note: MPIQ is the mean Full Scale IQ of the two biological parents of each family. The Home Observation for Measurement of the Environment (HOME) scores are derived from separate interviews about each child and may differ between children with fragile X and their siblings. Income ratio is total household income divided by the median household income in the zip code area of the family's home. FMRP = FMR1 protein; EESI = Effectiveness of Educational Services Index; NA = not applicable.

TABLE 2
Descriptive Statistics of Dependent Variables in Multiple Regression

	Control Siblings (n = 120)			Males With Fragile X (n = 80)			Females With Fragile X (n = 40)		
Scales/Indices	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD
FSIQ	120	107.55	12.22	80	46.35	9.46	40	75.48	22.30
PIQ	120	107.31	12.90	80	50.65	8.40	40	76.85	20.62
VIQ	120	106.80	12.92	80	50.92	9.79	40	78.05	22.30
VCI	118	106.45	12.11	80	55.03	9.94	40	81.95	22.44
POI	118	106.91	12.60	80	53.66	7.65	40	76.70	19.92
FDI	109	103.15	12.84	72	50.74	2.03	37	70.22	18.05
PSI	109	108.48	13.65	72	53.53	7.34	37	80.84	19.79

Note: FSIQ = Full Scale IQ; PIQ = Performance IQ; VIQ = Verbal IQ; VCI = Verbal Comprehension Index; POI = Perceptual Organization Index; FDI = Freedom From Distractibility Index; PSI = Processing Speed Index.

groups and was distributed in a normal curve ranging from 13% to 433%.

Descriptive statistics for the dependent variables (three IQ scale scores and four IQ index scores) are listed by group in Table 2. The comparison group of unaffected siblings had IQ scale and index scores within the average range of the WISC-III with no significant strengths or weaknesses. The females with fragile X syndrome had mean IQ scale scores in the "borderline intellectual functioning" range. Their mean index scores ranged from "low average" to "borderline." Their relative strengths, in terms of IQ indices, were in the domains of Verbal Comprehension and Processing Speed, and their relative weakness was in the domain of Freedom From Distractibility. In contrast, the males with fragile X syndrome had mean IQ scale and index scores all within the "intellectually deficient" range. As a group they demonstrated no areas of relative strength or weakness.

Multiple Regression Analyses

Standardized regression coefficients and p values for all dependent variables on the IQ scales are shown by group in Table 3, and on the IQ indices by group in Table 4. In the following sections all reported associations are positive unless otherwise noted.

Comparison Siblings

From among the biological/genetic factors, only MPIQ was associated with the unaffected subjects' IQ scale scores, accounting for a significant amount of the variance in

TABLE 3
β Weights From a Hierarchical Multiple Regression Analysis Predicting IQ Scale Scores

	Control Siblings			Males With Fragile X			Females With Fragile X		
	FSIQ	PIQ	VIQ	FSIQ	PIQ	VIQ	FSIQ	PIQ	VIQ
Step 1 (bio/genetic)									
Age	.010	–.043	.043	–.250*	–.130	–.340**	–.089	–.103	–.070
Gender	–.099	–.084	–.068	NA	NA	NA	NA	NA	NA
MPIQ	.523***	.474***	.471***	.172	.246*	.145	.470***	.413**	.473**
FMRP%	NA	NA	NA	.223*	.146	.197	.257	.253	.259
R^2 (step 1)	.279***	.232***	.226***	.146**	.104*	.180**	.264*	.219*	.264*
Step 2 (environmental)									
HOME	.083	–.075	.207*	.269*	.148	.384**	.310*	.263	.327*
EESI	NA	NA	NA	.019	.051	.036	.168	.114	.200
Income	.050	.075	.010	–.176	–.100	–.215	.141	.108	.171
R^2 (step 2)	.010	.007	.038	.057	.020	.111*	.122	.081	.147*
Total R^2	.290***	.239***	.264***	.202*	.124	.291***	.386**	.300*	.411**
No.	120	120	120	80	80	80	40	40	40

Note: FSIQ = Full Scale IQ; PIQ = Performance IQ; VIQ = Verbal IQ; MPIQ = Mean Full Scale IQ of the two biological parents of each family; FMRP = FMR1 protein; HOME = Home Observation for Measurement of the Environment; ESSI = Effectiveness of Educational Services Index; NA = not applicable.

Significance of the variable at each step of the model: * $p < .05$; ** $p < .01$; *** $p < .001$.

TABLE 4
β Weights From a Hierarchical Multiple Regression Analysis Predicting IQ Index Scores

	Control Siblings				Males With Fragile X				Females With Fragile X			
	VCI	POI	FDI	PSI	VCI	POI	FDI	PSI	VCI	POI	FDI	PSI
Step 1 (bio/genetic)												
Age	–.121	–.041	.005	–.088	–.345**	–.158	–.231	.064	–.088	–.112	–.048	–.021
Gender	.031	–.010	.034	–.233	NA	NA	NA	NA	NA	NA	NA	NA
MPIQ	.426***	.429***	.416***	.301**	.168	.253*	.163	.264*	.483**	.405**	.380*	.316
FMRP %	NA	NA	NA	NA	.197	.169	.213	.166	.250	.247	.389*	.314
R^2	.196***	.187***	.174***	.142**	.193**	.123*	.131*	.088	.271**	.212*	.233*	.156
Step 2 (environmental)												
HOME	.239**	–.163	.140	.167	.386**	.098	.387**	.254	.323*	.237	.327*	.314
EESI	NA	NA	NA	NA	.036	.133	.020	–.093	.166	.149	.253	.148
Income	.006	.068	–.061	.021	–.222	–.102	–.172	–.169	.150	.173	.157	–.036
R^2	.051*	.022	.017	.027	.113*	.030	.107*	.055	.132	.090	.119	.100
Total R^2	.246***	.209***	.191***	.168**	.306***	.153	.238**	.143	.403**	.302	.312	.255
No.	118	118	109	109	79	79	72	72	40	40	37	37

Note: VCI = Verbal Comprehension Index; POI = Perceptual Organization Index; FDI = Freedom From Distractibility Index; PSI = Processing Speed Index; MPIQ = Mean Full Scale IQ of the two biological parents of each family; FMRP = FMR1 protein; HOME = Home Observation for Measurement of the Environment; ESSI = Effectiveness of Educational Services Index; NA = not applicable.

Significance of the variable at each step of the model: * $p < .05$; ** $p < .01$; *** $p < .001$.

FSIQ, VIQ, and PIQ. Environmental factors had little effect on the IQ scale scores of unaffected subjects, though the quality of the home environment (as measured by the HOME) was associated with VIQ.

As with the scaled scores, MPIQ was the only biological factor associated with the IQ index scores, accounting for a significant proportion of the variance in VCI, POI, FDI, and PSI. Home environment accounted for a significant proportion of the variance in VCI only.

Females With Fragile X

For females with fragile X, MPIQ was the only biological factor accounting for the variance in IQ scale scores: FSIQ, PIQ, and VIQ. From among the environmental factors, the quality of the home environment was associated with females' FSIQ and VIQ scores.

MPIQ also was associated with three of the four IQ index scores of the females with fragile X: VCI, POI, and FDI. FMRP accounted for an additional significant proportion of the variance in FDI for the females. Combined, biological factors accounted for 27% of the variance in VCI, 21% of the variance in POI, and 23% of the variance in FDI. From the environmental factors, the quality of the home environment accounted for a significant proportion of the variance in females' VCI and FDI scores.

Males With Fragile X

Among the biological factors, age was associated with the FSIQ and VIQ scale scores of the males with fragile X. This association was in a negative direction, reflecting the putative decline in males' acquisition of cognitive skills as they age. MPIQ was associated with the males' PIQ scores, and FMRP was associated with males' FSIQ scores. In combination, biological factors accounted for 15% of the variance in FSIQ, 10% in PIQ, and 18% in VIQ. From among the environmental factors, the quality of the home environment was associated with FSIQ and VIQ. As a group, environmental factors accounted for an additional 5% and 11% of the variance in FSIQ and VIQ, respectively.

For males with fragile X, age and MPIQ were the biological factors associated with IQ index scores. Age contributed to the variance in VCI scores and MPIQ contributed to the variance in POI and PSI scores. The quality of the home environment was associated with males' VCI and FDI scores.

DISCUSSION

This study aimed to describe the cognitive profiles of girls and boys with fragile X and to investigate the potential contributions of both biological/genetic and environmental factors to the cognitive outcomes of these children. As predicted, girls with fragile X had somewhat higher cognitive abilities than did boys with fragile X and had relative strengths in verbal domains. Importantly, we also observed that both biological/genetic factors and the qual-

ity of the home environment contribute to the intellectual aptitude of female and male children with fragile X.

The primary determinant of the IQ scores of comparison siblings was MPIQ. To a small extent, the quality of the home environment additionally influenced their verbal development. These findings serve as a template with which to compare their siblings with fragile X and are consistent with findings from behavioral genetics. Based on studies of monozygotic twins reared together and apart, estimates of the heritability of general cognitive ability range from 0.52 to 0.78 (Plomin et al., 1997). In complementary fashion, adoption studies suggest that the environment accounts for nearly 20% of the variance in general cognitive ability. While we used indirect measures of genetic and environmental influences (e.g., IQ tests and HOME observations) which may be limited by their psychometric properties, our data reveal a similar pattern: parental cognitive ability is the substantial determinant of a child's cognitive outcome, and the home environment plays a lesser but significant role as well.

Our study revealed that biological/genetic factors made a significant contribution to the variance in cognitive outcomes of girls with fragile X. MPIQ, which in part marks genetic contributions to a child's cognitive capacity, accounted for nearly one quarter of the variance in IQ scale scores. The predictive role of FMRP also was significant but limited in scope, contributing only to the FDI score. Nonetheless, given the import of inattention and distractibility in the behavioral profile of girls with fragile X, the specificity of the relation between level of FMRP and "freedom from distractibility" deserves further investigation. Moreover, one may speculate that in comparison with the other IQ scales, FDI most closely measures a child's facility for organized processing of sensory information, which may underlie several of the cognitive deficits caused by fragile X. Notably, after biological/genetic factors were considered, aspects of the home environment were found to make unique contributions to the overall cognitive outcome, and in particular to verbal and attention skills in girls with fragile X.

In several ways, influences on the cognitive outcomes of the males with fragile X were disparate from those on both comparison siblings and females with fragile X. Only in males did we find that age was a significant predictor of cognitive outcome. This finding is consistent with findings from other longitudinal and cross-sectional studies, in which a plateauing of cognitive development in males with fragile X (as distinct from skill loss) has been described (Bennetto and Pennington, 1996; Dykens et al., 1996; Fisch et al., 1996). As well, FMRP contributed to the overall cognitive outcomes of males but only the attention skills of females with fragile X.

Furthermore, although parental IQ contributed to the cognitive outcomes in all groups, specific effects differed between groups. Parental IQ was associated with all the outcome scores in the sibling group and all but processing speed in the female group. In the male group, however, MPIQ was associated with only the performance and processing scale scores (PIQ, POI, PSI), which are widely regarded to measure fluid intelligence (as distinct from crystallized intelligence). In contrast, aspects of the home environment were associated only with the verbal skills of the siblings, while they were associated with overall cognitive development, verbal skills, and attention skills in both the males and females with fragile X. These findings are provocative in comparison with behavioral genetics studies of specific cognitive abilities in typically developing, European-American children. In comparison with processing speed and visual memory, verbal skills and visual-spatial skills have been shown to have the highest heritability rates (DeFries et al., 1979). It appears that for males with fragile X, the influence of parental intelligence is greatly diminished in the verbal domain. Moreover, qualities of the home environment make a more significant contribution to the development of verbal skills, attention skills, and overall cognitive aptitude in both males and females with fragile X in comparison with their siblings.

One surprising finding of this study was that FMRP was not more strongly correlated with cognitive outcomes of either boys or girls with fragile X. While the mean levels of FMRP within this sample are consistent with previous literature, the correlations between FMRP and their cognitive outcomes appear inconsistent with previous reports. FMRP and activation ratio (which highly correlates with FMRP) have been found to account for 24% to 33% of the variance in females' IQ scale scores and 38% in mosaic males' IQ scores (Reiss et al., 1995). The apparent discrepancy between the FMRP results presented here and in previous studies is likely to be related to sampling issues. First, the males evaluated in this study, unlike smaller samples enriched for methylation or mutation mosaicism (Tassone et al., 1999), had a relatively restricted range of FMRP values. Thus studies using smaller, highly selected samples and more narrowly focused on the impact of FMRP will likely generate significantly different estimates of the influence of FMRP on cognitive outcome. When studied in a large, heterogeneous sample and con-

sidered as one among many biological factors influencing children's outcomes, the statistical impact of this molecular variable may indeed be more limited in scope. Second, while our findings indicate that the impact of FMRP on general cognitive ability (i.e., FSIQ) among females with fragile X is less significant than among boys, interpretations of this finding must be qualified by the discrepancy between the sample sizes of males and females in this study. (Indeed, the β weight for FMRP in association with FSIQ for females was higher than that for males but the sample size was smaller, decreasing its statistical significance.)

Another notable finding was that the effectiveness of special education and therapies, as rated by the child's parent, was not significantly associated with cognitive outcomes in any of the three groups. As reported elsewhere, we found that EESI was associated with the behavioral outcomes of boys with fragile X (Hessl et al., 2001). We speculate that the lack of association with these cognitive outcomes may be due to the widely varying services offered to these children in addition to selected outcome measures that are relatively insensitive to recent cognitive gains (i.e., we measured aptitude rather than achievement).

Clinical Implications

Our findings are of particular importance for the design of future biological, clinical, and educational interventions. Noting the role of FMRP in both males (related to overall cognitive functioning) and females (related to executive functioning), we are able to specify target variables for measuring change due to biological interventions, ranging from gene therapy to the functional enhancement of specific neural pathways affected by FMRP. Our finding that qualities of the home environment predict the cognitive outcomes of males and females with fragile X indicates that greater attention and innovation should be given to developing home-based interventions. These interventions should enrich the environment of affected children in developmentally appropriate and syndrome-specific ways as well as reducing distractions and anxiety-provoking stimuli in order to augment the development of adaptive attention skills. These findings also support the development of studies using prospective, longitudinal designs and clinical trials focused on manipulating salient environmental variables in an attempt to improve functional outcome in affected children.

Limitations

This study has limitations affecting the interpretation of the findings. First, using IQ, or cognitive aptitude data, as the sole measure of cognitive outcomes may have limited our findings concerning the influences of environmental factors. In comparison with achievement, cognitive aptitude is known to be relatively invariant. Future studies that include measures of both aptitude and achievement may yield clearer impressions of the influences of the home environment as well as educational and therapeutic services. Second, the cross-sectional design of the study does not make it possible to infer causal relationships between variables. Longitudinal studies will be needed to examine causal links between home environment, family characteristics, and children's cognitive development. Finally, the relatively high level of education attained by the parents in these families and the lack of ethnic diversity in our sample limit the generalizability of the results. Forty-four percent of all the mothers and fathers included in this study had attained a bachelor's degree or more, compared with 25% of all adults in the nation (according to the U.S. census report, 2000). No firm data are available on the prevalence of fragile X in different ethnic groups, but there are several possible systemic reasons for the lack of minority representation in this type of research. These include lower detection and referral rates for genetic testing among ethnic minorities, a reluctance to participate in genetic research due to feelings of distrust and shame, and limitations in recruitment approaches. Given our concerted effort to recruit an ethnically diverse sample, however, more planning and financial resources must be allocated in advance to overcome the barriers to including ethnic minorities in genetic research.

Conclusion

In summary, the findings of this study elucidate a complex picture of the factors influencing the cognitive outcomes of children with fragile X. For girls, who have the compensatory effect of a second, unaffected *FMR1* gene, their general genetic background (as measured by MPIQ) has as much influence on their cognitive outcomes as it does for their unaffected siblings. The quality of their home environment and, to a limited degree, FMRP significantly influence the degree of their deficits. For males, the effects of fragile X are of greater severity and scope and, by virtue of the genetics of X-linked disorders, more homogeneous. Nonetheless, the enrichment, structure, and support for maturation and learning within their home environment plays a significant role in the optimization of their cognitive abilities. These findings lay the foundation for further investigation into biological and environmental interventions.

REFERENCES

Baumgardner TL, Reiss AL, Freund LS, Abrams MT (1995), Specification of the neurobehavioral phenotype in males with fragile X syndrome. *Pediatrics* 95:744–752

Bennetto L, Pennington BF (1996), The neuropsychology of fragile X syndrome. In: *Fragile X Syndrome: Diagnosis, Treatment, and Research,* Hagerman RJ, ed. Baltimore: Johns Hopkins University Press, pp 210–248

Boccia ML, Roberts JE (2000), Behavior and autonomic nervous system function assessed via heart period measures: the case of hyperarousal in boys with fragile X syndrome. *Behav Res Methods Instrum Comput* 32:5–10

Bradley RH (1993), Children's home environments, health, behavior, and intervention efforts: a review using the HOME inventory as a marker measure. *Genet Soc Gen Psychol Monogr* 119:437–490

Caldwell BM, Bradley RH (1984), *Home Observation for Measurement of the Environment,* Revised Edition. Little Rock: University of Arkansas (*www.ualr.edu/~crtldept/home4.htm; http://156.98.150.12/divs/fh/mch/homeinv.html*)

Cohen IL (1995), A theoretical analysis of the role of hyperarousal in the learning and behavior of fragile X males. *Mental Retardation Dev Disabilities Res Rev* 1:286–291

DeFries JC, Johnson RC, Kuse AR et al. (1979), Familial resemblance for specific cognitive abilities. *Behav Genet* 9:23–43

Dyer-Friedman J, Hessl D, Glaser B, Kosaraju A, Reiss AL (2001), The Special Curriculum Opportunity Rating Scale (SCORS): a measure of educational and therapeutic effectiveness. Presented at the 14th Annual Research Conference, A System of Care for Children's Mental Health: Expanding the Research Base, Tampa, FL

Dykens E, Ort S, Cohen I, Finucane B et al. (1996), Trajectories and profiles of adaptive behavior in males with fragile X syndrome: multicenter studies. *J Autism Dev Disord* 26:287–301

Fisch GS, Simensen R, Tarleton J et al. (1996), Longitudinal study of cognitive abilities and adaptive behavior levels in fragile X males: a prospective multicenter analysis. *Am J Med Genet* 64:356–361

Freund LS, Reiss AL (1996), A neurocognitive phenotype of young males and females with fragile X. *Neuropsychiatry Genet* 28:223–238

Freund LS, Reiss AL, Abrams MT (1993), Psychiatric disorders associated with fragile X in the young female. *Pediatrics* 91:321–329

Hagerman RJ, Jackson C, Amiri K, Silverman AC, O'Connor R, Sobesky W (1992), Girls with fragile X syndrome: physical and neurocognitive status and outcome. *Pediatrics* 89:395–400

Hessl D, Dyer-Friedman J, Glaser B et al. (2001), The influence of environmental and genetic factors on behavior problems and autistic symptoms in boys and girls with fragile X syndrome. *Pediatrics* 108:88

Kaufmann WE, Abrams MT, Chen W, Reiss AL (1999), Genotype, molecular phenotype, and cognitive phenotype: correlations in fragile X syndrome. *Am J Med Genet* 83:286–295

Mazzocco MM, Hagerman RJ, Pennington BF (1992), Problem solving limitations among cytogenetically expressing fragile X women. *Am J Med Genet* 43:78–86

Plomin R, DeFries J, McClearn G, Rutter M (1997), *Behavioral Genetics,* 3rd ed. New York: WH Freeman

Reiss AL, Freund LS, Baumgardner TL, Abrams MT, Denckla MB (1995), Contribution of the FMR1 gene mutation to human intellectual dysfunction. *Nat Genet* 11:331–334

Rousseau F, Heitz D, Tarleton J et al. (1994), A multicenter study on genotype-phenotype correlations in the fragile X syndrome, using direct diagnosis with probe StB12.3: the first 2,253 cases. *Am J Hum Genet* 55:225–237

Tassone F, Hagerman RJ, Ikle DN et al. (1999), FMRP expression as a potential prognostic indicator in fragile X syndrome. *Am J Med Genet* 84:250–261

Taylor AK, Safanda JF, Fall MZ et al. (1994), Molecular predictors of cognitive involvement in female carriers of fragile X syndrome (see comments). *JAMA* 271:507–514

Wechsler D (1991), *Wechsler Intelligence Scale for Children, Third Edition: Manual.* San Antonio, TX: Psychological Corporation

Wechsler D (1997), *Wechsler Adult Intelligence Scale, Third Edition: Manual.* San Antonio, TX: Psychological Corporation

Willemsen R, Los F, Mohkamsing S et al. (1997), Rapid antibody test for prenatal diagnosis of fragile X syndrome on amniotic fluid cells: a new appraisal. *J Med Genet* 34:250–251

Willemsen R, Mohkamsing S, de Vries B et al. (1995), Rapid antibody test for fragile X syndrome. *Lancet* 345:1147–1148