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ORIGINAL ARTICLE

Cognitive and Visual Processing Skills and Their Relationship to Mutation Size in Full and Premutation Female Fragile X Carriers

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ABSTRACT: *Background:* The fragile X gene contains an unstable trinucleotide (CGG) repeat that expands as it is passed from female carriers to the affected offspring. Obligate female carriers may have a premutation or full mutation genotype. *Methods:* In this study, fragile X premutation and full mutation female carriers were compared on three tasks of visual processing and cognitive skills. *Results:* In each case, there were significant differences between premutation and full mutation carriers on a number of the subtests or the full test scores. Specifically, full mutation female carriers performed more poorly in visual-motor processing and analysis-synthesis on the Woodcock-Johnson Psycho-Educational Battery–Revised, The Developmental Test of Visual Motor Integration, and on five of the seven subtests of the Test of Visual-Perceptual Skills. Regression analyses revealed significant negative correlations between mutation size and cognitive ability. *Conclusions:* These findings have implications in educational planning decisions for full mutation carriers who may present with specific cognitive deficits. (Optom Vis Sci 2000;77:592–599)

Key Words: fragile X syndrome, intelligence, visual processing, fragile X females

Fragile X syndrome is one of the most frequently encountered inherited forms of mental retardation. Other characteristics of fragile X syndrome include behavioral difficulties, facial dysmorphism, speech/language deficits, macroorchidism, and connective tissue abnormalities such as hyperextensible joints and mitral valve prolapse (Table 1 has a more complete list of characteristics associated with fragile X).[1] The prevalence of fragile X syndrome was initially estimated at 1/1200 males and 1/2500 females.[2] However, early prevalence estimates were based on karyotype analysis, which is not as accurate as current DNA-based testing. More recent population-based estimates give a prevalence of fragile X syndrome at 1/4000 to 1/5000 for males.[3] The estimated prevalence of female carriers with no clinical features is at least 1/500 and recently as high as 1/259 in general populations.[4]

The fragile X syndrome was first reported in 1943 by Martin and Bell,[5] who described a family in which this form of mental retardation appeared to be an X-linked trait. Later, the syndrome was found to be associated with a folate sensitive fragile site (constriction) on the X chromosome at band q27.3, leading to the use of the term fragile X syndrome to describe the syndrome.[6] Initially, the diagnosis of fragile X syndrome was made on the basis of clinical features along with the observation of the fragile site on the X chromosome seen in cultured cells.

In 1991, the fragile X gene (FMR-1, fragile X mental retardation-1) was isolated and found to contain a trinucleotide (CGG) repeat in the promoter region that is mutated in fragile X affected individuals.[7] New molecular analysis techniques resulted in improved diagnosis and revealed a unique genetic mechanism for transmission of the syndrome. Normal individuals carry approximately 6 to 52 repeat units, and CGG repeat number remains constant over generations. Individuals with a fragile X chromosome have a greater number of CGG repeats, and the CGG repeat number is unstable and tends to increase as the gene is passed from generation to generation.[8–10] These expanded forms of the FMR-1 gene present on the fragile X chromosome can be divided into two groups based on the phenotypic effects: the premutation (about 50 to 200 CGG repeats) and the full mutation (>200 CGG repeats).[4] The premutation generally has little affect on FMR-1 gene expression,[11] and because the CGG repeat is transcribed but not translated, individuals with the premutation do not clinically manifest

TABLE 1.
Characteristics associated with fragile X syndrome

Physical features		
Large prominent ears	Long narrow face	Prominent jaw
Large head in relation to body	High arched palate	Velvetlike skin
Flat feet	Heart murmur or click	Mitral valve prolapse
Narrow palpebral fissures	Strabismus	Puffiness around eyes
Epicanthal folds	Macroorchidism	Pectus excavatum
Double-jointed thumb	Single palmar crease	Hand calluses
Hyperextensible finger joints	Seizures	Hypotonia
Premature ovarian failure	Nystagmus	Refractive error
Behavioral features		
Emotional difficulties	Attentional problems	Hyperactivity
Perseveration: speech and behavior	Mental handicaps	Tantrums
Autism or autistic-like features (poor eye contact, hand flapping, hand biting, and tactile defensiveness)		

the fragile X syndrome. The full mutation results in silencing of the FMR-1 gene and full phenotypic expression of the syndrome in males.[11] Female premutation carriers can pass a full mutation to their offspring, whereas males with the premutation only pass the premutation to their daughters.[8]

The FMR-1 gene is thought to produce a protein (FMRP) that is necessary for normal brain development and function. Recent evidence suggests that FMRP is an RNA binding protein that may act as a translation factor, possibly regulating dendritic protein synthesis in response to synaptic stimuli.[12] FMRP is present in normal amounts in the premutation carriers but is absent in individuals with the full mutation because of silencing of the FMR-1 gene by the large expansion mutation.[13]

Because fragile X syndrome is X-linked, males are more severely affected than females, who make FMRP from their FMR-1 gene in the fraction of cells with active normal X chromosome. In males, moderate mental retardation is frequently encountered with a smaller percentage functioning at upper and lower cognitive levels. The prevalence of mental retardation in female full mutation carriers has been estimated at 55%.[14] Among female full mutation carriers of normal intelligence, reported deficits are similar to those seen in persons with learning disabilities, particularly visual-spatial processing problems.[15, 16]

The ability to diagnose fragile X syndrome at the molecular level has led investigators to wonder whether there is a relationship between the size of the expanded gene and deficits in visual information processing and cognitive skills. These relationships may be studied more effectively in females who are easily identified through their affected male children and present with a range of CGG repeats. In the studies conducted before fragile X DNA testing, the issue of prediction of cognitive function was addressed largely by studying female groups categorized as "expressing" or "nonexpressing" based on the percentage of cells showing the fragile site and/or by studying female groups divided on the basis of intelligence scores.[15, 17, 18] There are methodological difficulties with these studies, however, because cytogenetic identification yields a high false-negative rate, and in some studies, female carriers may have been misclassified if they did not appear affected. The advent of DNA testing allows for specific genetic findings to be linked to learning and behavioral characteristics. The ability to predict the cognitive and visual processing levels of individuals based on genotype has important implications for prevention, education, and vocational programming.

Although a small body of research exists concerning the cognitive, social, and emotional characteristics of females with fragile X syndrome, only a few studies have examined the relationship between these characteristics and the size of the expanded gene. Fewer studies have addressed differences between females with premutations vs. those with full mutations. Lower IQ's in females with full mutations compared with females with premutations have been reported in a number of studies.[19–24] An inverse relationship between IQ and the number of CGG repeats has been reported for the female population overall, but not within groups divided by full and premutation status.[19–22, 24, 25] Findings have been inconsistent in studies investigating specific cognitive processes and social/emotional functioning. There is evidence to suggest that executive functions (functions thought to be monitored by the frontal lobes) and nonverbal functions are impaired in females with full mutations but not in females with premutations.[21, 22, 26] No relationship has been found between the number of CGG repeats, measures of adaptive behavior,[25] and measures of perspective taking.[18]

The purpose of the present study was to compare the cognitive and visual processing abilities of females with premutations and full mutations and to examine the relationship between these abilities and the number of CGG repeats in the FMR-1 gene. The first objective was to describe differences in cognitive processing using the Woodcock-Johnson Psycho-Educational Battery–Revised, a measure often used in educational settings to detect learning disabilities. It has been suggested that learning disabilities are relatively common among females with fragile X syndrome, but the identification of specific areas of deficit, including nonverbal abilities and short-term memory, has not been consistent.[27–31] The second objective was to describe differences in motor and nonmotor visual information processing skills. Ocular anomalies and difficulties in visual-spatial abilities have been noted in the literature as affecting both males and females (e.g., Amin and Maino,[32] Maes et al.,[33] Maino et al.,[34] and Cornish et al.[35]). Little, however, is known about the range of visual processing abilities in higher functioning adult females with fragile X. Third, we explored the relationship between FMR-1 mutation size (number of CGG repeats) and levels of cognitive functioning and visual processing skills.

TABLE 2.
Subtests of the Woodcock-Johnson Psycho-Educational Battery–Revised

Memory for Names	Evaluates long-term retrieval of information as measured by the ability to verbally recall the nonsense labels given to visual images (space creatures)
Memory for Sentences	Evaluates short-term memory as measured by the ability to verbally recall sentences of increasing length and complexity
Visual Matching	Evaluates processing speed as measured by the ability to visually match and then circle identical numbers in a timed task
Incomplete Words	Evaluates auditory processing as measured by the ability to verbally identify words in which sounds are omitted
Visual Closure	Evaluates visual processing as measured by the ability to verbally identify pictures of objects in which parts of the objects are obscured
Picture Vocabulary	Evaluates comprehension-knowledge as measured by the ability to verbally identify pictures of people, places, and objects
Analysis-Synthesis	Evaluates fluid reasoning as measured by the ability to solve problems involving color codes

METHODS

Subjects

Subjects for this study were recruited through The Fragile X Clinical/Research Group[a] at Rush-Presbyterian St. Lukes Medical Center in Chicago, Illinois. The medical center sponsors a monthly clinic that includes medical, optometric, educational, speech/language, and advocacy services. The majority of clients are referred to the clinic by the Fragile X Association of America, a parent support and information group operating in Illinois. At the initiation of the study, the clinic had an active list of approximately 35 families. Approval for this study was obtained from the Rush-Presbyterian St. Lukes Medical Center Institutional Review Board. Of this group, 25 biological mothers aged 24 to 46 years agreed to participate in the study, and informed consent was obtained. These mothers came from middle-class urban, suburban, and rural settings. The group consisted of 22 Caucasians, 2 African Americans, and 1 Asian American.

Direct mutation analysis of the fragile X gene carried out on DNA isolated from blood samples revealed that 10 mothers carried the full mutation, whereas 15 mothers carried the premutation. Full mutations were sized via comparison to molecular weight standards on Southern blots, and the number of CGG repeats in premutations were determined by polymerase chain reaction[36] with comparisons of product sizes to those of standards with known CGG repeat numbers. DNA from all but two study participants (both with full mutations) was analyzed by the Rush Molecular Diagnostics Laboratory. The two individuals tested elsewhere had DNA analysis via essentially the same method used at Rush. Because significant oculo-visual problems have been associated with Fragile X syndrome[37, 38] each subject received a complete eye and vision evaluation before participating in this study to rule out any detrimental effects caused by the presence of significant refractive error, strabismus, amblyopia, or other similar anomaly. No subject was excluded because of ocular problems.

Instruments

The three standardized assessment instruments used in this study were Woodcock-Johnson Psycho-Educational Battery–Revised (WJ-R),[39] test of Visual-Perceptual Skills (TVPS),[40] and The Developmental Test of Visual Motor Integration-(3R) (VMI).[41]

WJ-R. The WJ-R is a measure of cognitive and academic ability. The standard cognitive battery, which was the only part of the WJ-R used in this study, consists of seven subtests designed to measure a variety of processing abilities (Table 2). An overall measure of cognitive ability is derived from the subtest scores.

TVPS. The TVPS is a nonmotor test of visual information processing skills that was designed for children aged 4 though 12 years. Although an adult version of the test was available, the children's version was used because clinical experience suggested that the upper level battery would be too difficult for many of the mothers to complete. In addition, Gardner has stated that nonmotor visual processing performance levels off in early adolescence, and the test is appropriate for adults if norms for the oldest age group are used.[41] The TVPS consists of seven subtests designed to investigate different aspects of visual processing (Table 3).

VMI. The VMI evaluates an individual's ability to integrate visually presented information with the motor skills involved in copying. The instrument consists of a developmental sequence of 24 geometric forms to be reproduced with paper and pencil.

Procedure

The majority of mothers were tested in small examination rooms at the medical center. For those unable to travel to the hospital setting, examiners made home visits to conduct the testing. Every effort was made to administer all three instruments to each mother; however, this was not possible in all cases. The WJ-R was administered to 19 of the 25 mothers, whereas the TVPS and the VMI were administered to 24 of the 25 mothers. All examiners were experienced test administrators. Assessments of cognitive and visual processing were typically conducted on separate days to avoid subject fatigue. Each session lasted approximately 1 h. The examiners were blinded to the results of the subjects' DNA testing and whether the subjects fell into the premutation or the full mutation group.

Statistical Analysis

Comparisons between the premutation and full mutation groups used the Student's t-test for independent groups, except in those group comparisons with unequal variance, in which case the

[a] The Fragile X Clinical/Research Group is composed of individuals from area universities and colleges; these institutions include Northeastern Illinois University, Illinois College of Optometry, and Rush Medical College.

TABLE 3.
Descriptions of the subtests of the Test of Visual-Perceptual Skills (non-motor)

Visual Discrimination	Evaluates the ability to match or determine the characteristics of a form from among similar forms
Visual Memory	Evaluates the ability to remember for immediate recall the characteristics of a given form
Visual Sequential Memory	Evaluates the ability to remember for immediate recall a series of forms from among a group of similar forms
Visual Spatial Relations	Evaluates the ability to determine from among forms of identical configuration, the one single form that is arranged in the same direction as the stimulus
Visual Form Constancy	Evaluates the ability to find an individual form when it is presented in such a way that it is smaller, larger, rotated, reversed, or hidden among other forms
Visual Figure-Ground	Evaluates the ability to discriminate the figure to be attended to relative to the background information and to be aware of the relationship between the stimulus figure and the background
Visual Closure	Evaluates the ability to be aware of clues in the visual figure that help to determine what the figure would be if all details were present

nonparametric Mann-Whitney U test was used. All regression analyses used a linear model. Premutation and full mutation carriers were included in regression analysis because recent data indicates that premutation carriers with >100 repeats may show mild clinical affectedness[42] caused by diminished translation efficiency for FMRP when long CGG repeat sequences are present in the FMR-1 mRNA.[42] Also, our study group contained a number of patients with large premutation alleles or small full mutation alleles that might potentially produce phenotypic effects intermediate between those seen in premutation (no significant cognitive effects expected) and full mutation groups. Thus, although our carriers of smaller premutations were expected to form a grouping showing essentially normal performance, patients with larger alleles might theoretically form a continuum, at least at repeat sizes <300. Statistical calculations were performed using the GB Statistical software package (Dynamic Microsystems, Inc., Silverspring, MD). An alpha level of $p < 0.05$ (two-tailed) was the significance level set for rejection of the null hypothesis.

RESULTS

Cognitive Processing: WJ-R

Significant differences in performance were observed on two of the seven subtests on the WJ-R in mothers with full mutations compared with mothers with premutations (Table 4). Mothers with full mutations had lower scores in processing speed (Visual Matching, $p < 0.03$) and in abstract problem solving (Analysis-Synthesis, $p < 0.05$). On the overall measure of cognitive ability, differences between mothers with full mutations and premutations approached significance at $p < 0.06$ with lower scores in mothers with full mutations. Regression analysis revealed significant negative correlations between the number of CGG repeats and scores on processing speed (visual matching, $r = -0.56$, $p < 0.02$) and abstract problem solving (analysis-synthesis, $r = -0.51$, $p < 0.03$) and the overall cognitive level (broad cognitive ability, $r = -0.60$, $p < 0.007$) of the WJ-R (Fig. 1). No significant differences between groups were found in long-term retrieval (Memory for Names), short-term memory (Memory for Sentences), and comprehension knowledge (Picture Vocabulary). There were also no significant differences found between groups in auditory or visual closure skills (Incomplete Words and Visual Closure, respectively).

TABLE 4.
Results of Cognitive Processing Tests: mean and SD for each subtest

Subtest	Premutation (N = 11)	Full Mutation (N = 8)	p Value
Memory for Names	93.5 ± 18.9	87.9 ± 26.6	NS
Memory for Sentences	100.8 ± 19.0	97.4 ± 14.6	NS
Visual Matching	109.9 ± 12.0	95.0 ± 14.2	0.03
Incomplete Words	95.3 ± 8.5	94.9 ± 7.5	NS
Visual Closure	108.5 ± 13.9	101.5 ± 9.0	NS
Picture Vocabulary	92.9 ± 11.6	90.6 ± 7.7	NS
Analysis-Synthesis	101.8 ± 13.8	89.9 ± 8.4	0.05
Broad Cognitive Ability	98.5 ± 10.4	88.8 ± 10.8	NS

Visual Processing: TVPS and VMI

Significant performance differences in visual processing were found in mothers with premutations compared with mothers with full mutations. Mothers with full mutations had lower scores on five of the seven subtests of the TVPS: visual discrimination, visual memory, visual form constancy, visual figure ground, and visual closure (see Table 5 for means and p values). Mothers with full mutations also had lower scores on the VMI ($p < 0.007$). Regression analysis revealed significant negative correlations between the number of CGG repeats and scores on each of the individual TVPS subtests (Fig. 2) as well as the VMI (Fig. 3 and see Table 6 for r and p values). No significant differences in performance between groups were found on the visual spatial relations or visual sequential memory subtests of the TVPS.

DISCUSSION

Four major findings were described in this study. First, the female full mutation group performed significantly below the female premutation group in two of the seven areas of cognitive processing measured by the WJ-R. These areas involved visual-motor processing speed and analysis-synthesis skills. In addition, the difference between groups on broad cognitive ability approached significance ($p < 0.06$). No subjects fell below a score of 70, which is a historic indicator of mental retardation. Second, the full mutation group performed significantly below the premuta-

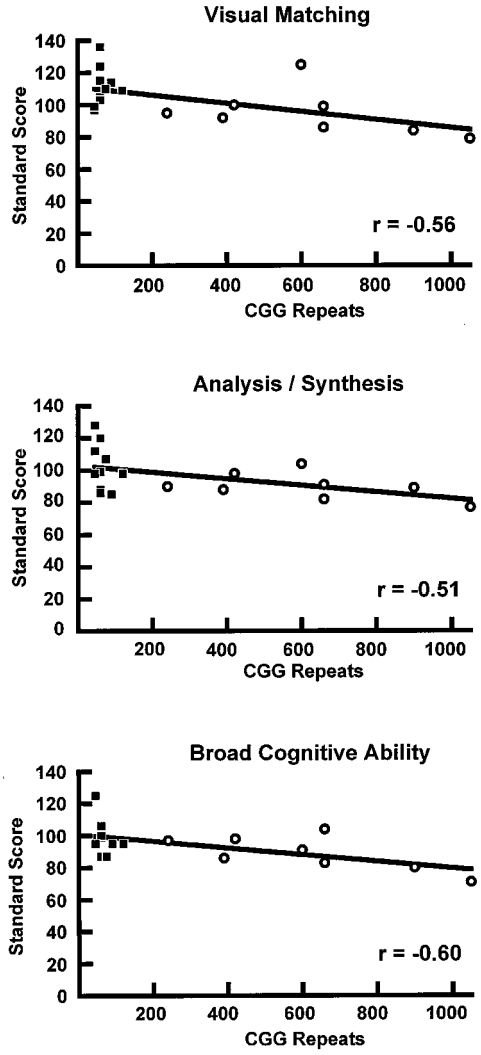

FIGURE 1.

Regression plots showing the relationship between standard scores on the WJ-R and the size of the expanded gene (kb) for two subtests and overall cognitive ability.

TABLE 5.

Results of Visual Information Processing Tests: mean and SD for each subtest

Subtest	Premutation (N = 15)	Full Mutation (N = 9)	p Value
Visual Discrimination	15.3 ± 0.8	13.6 ± 1.7	0.005
Visual Memory	13.3 ± 1.8	10.7 ± 1.7	0.002
Visual-Spatial Relationships	14.9 ± 1.5	13.7 ± 1.5	NS
Visual Form Constancy	13.1 ± 1.8	11.4 ± 1.7	0.04
Visual Sequential Memory	14.7 ± 1.3	11.6 ± 4.3	NS
Visual-Figure Ground	14.7 ± 1.8	10.0 ± 4.7	0.02
Visual Closure	14.9 ± 1.7	11.2 ± 3.1	0.002
Raw Score	36.7 ± 8.2	25.8 ± 9.6	0.007

tion group on tests of visual processing motor skills as measured by the VMI and on nonmotor visual processing areas measured by the TVPS with the exception of sequential memory and spatial relations. Third, regression analysis revealed significant negative correlations between the number of CGG repeats and broad cognitive ability for the combined full and premutation groups. Fourth, regression analysis showed significant negative correlations between the number of CGG repeats and each of the visual processing abilities measured for the combined full and premutation groups. These findings have two primary implications. First, they suggest that females with full mutations are at risk of having visual information processing deficits similar to those found in learning disabilities. Second, our findings indicate that knowledge of mutation size may be useful in predicting the extent to which the fragile X syndrome affects specific processing abilities and overall functioning on an individual basis.

Data from this study provide evidence that patterns of performance of premutation and full mutation women differ most in the area of nonmotor visual information processing and visual-motor integration. If the Visual Matching and Visual Closure subtests of the WJ-R are combined with the TVPS and the VMI, a total of 10 measures of visual processing ability were evaluated. Performance of the full mutation group was significantly below that of the premutation group on 7 of the 10 measures. In contrast, previous studies that did not use DNA analysis in the identification of fragile X syndrome reported conflicting findings with regard to various visual processing abilities in female carriers, indicating the importance of reexamining prior conclusions about visual abilities using more advanced DNA-based identification techniques.[30, 31, 43]

Data from this study also indicate that larger mutation size predicts more severe deficits in visual processing and cognitive functioning. Similar correlations have been noted in other studies that analyzed data from mixed premutation and full mutation groups.[19, 20, 25] When premutation and full mutation groups were analyzed alone, such correlations have not been noted,[20, 25] although one of these studies reported a correlation approaching significance ($p = 0.05$) between mutation size and cognitive functioning in a full mutation group.[25] Variability in the strength of correlation between repeat size and cognitive function is likely somewhat dependent on the portion of individuals analyzed with large premutations or small full mutations, which are variably methlyated and produce an intermediate phenotypic effect[44] and result in a continuum of phenotypes rather than an "all or none" effect. Recent molecular data demonstrates that even fully unmethylated large premutations are inefficiently translated[42] despite cellular upregulation of FMR-1 mRNA levels,[45] providing an additional molecular mechanism through which large premutations may produce a mild continuum of clinical phenotypes. Our patient set included four patients with CGG repeat numbers between 100 and 300, likely contributing to the observed correlations in the regression analysis. As is typical for large premutation and small full mutation alleles, several of these patients showed a partial methylation of their expanded allele. Indeed, future studies would benefit from measurement of activation ratios that are more sensitive and directly measure the proportion of active FMR-1 genes in a DNA sample and, conversely, indicate the amount of normally active FMR-1 genes that have been inactivated by a mutation in individual subjects. Previous research has indicated that the proportion of active normal X (inactive fragile X) chromosomes correlates with overall cognitive performance[46] and that activation ratios in DNA correlate with cognitive abilities,[25, 47] particularly

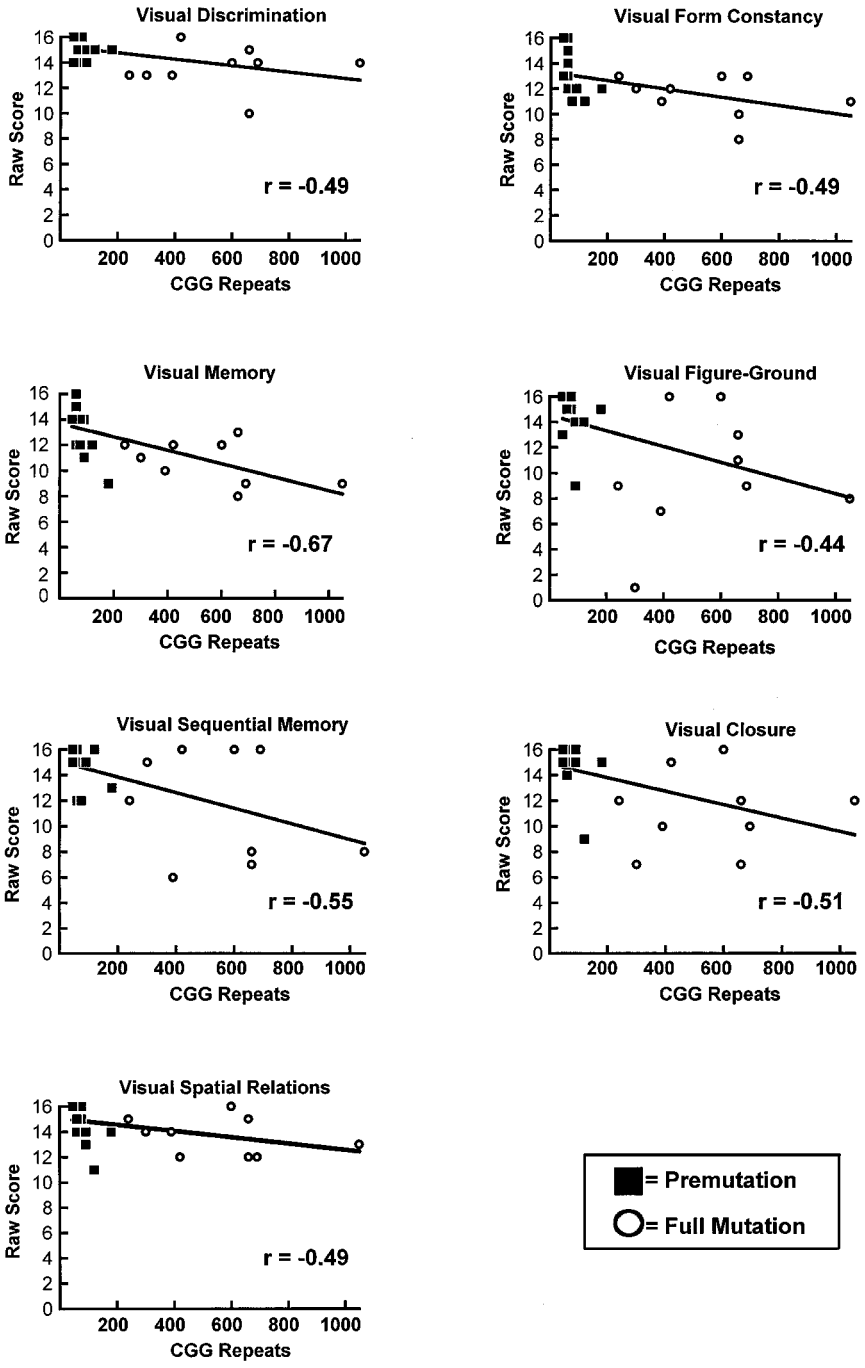

FIGURE 2.

Regression plots showing the relationship between raw scores on the individual subtests of the TVPS and the size of the expanded gene (kb).

with nonverbal intelligence measures including visual spatial information processing[21, 24, 48] and with executive functions.[22] This link has not been demonstrated in all cases.[20] Unfortunately, activation ratios were not available for all of the full mutation carriers participating in this study. Ongoing studies with larger sample sizes will be needed to further explore the relationship of activation ratios, actual FMRP levels, and mutation size to visual information processing and cognitive functioning.

The conclusion that premutation status does not seem to adversely affect overall cognitive ability, specific cognitive, or visual processes is supported by data in this study and by previous research in which subjects were also categorized by mutation status.[19, 20, 26] The failure to identify specific processing deficits or patterns in nonexpressing female carriers in studies that used older diagnostic methods can be interpreted as further support of this conclusion.[15, 18, 49] Overall, a preponderance of the evidence suggests no difference on cognitive measures between most female fragile X carriers who have premutations in at least small or moderate size range and noncarrier peers.

Previous studies that did not use DNA analysis in the identification of fragile X have reported conflicting findings with regard to various visual processing abilities in females.[30, 31, 42] The clear dif-

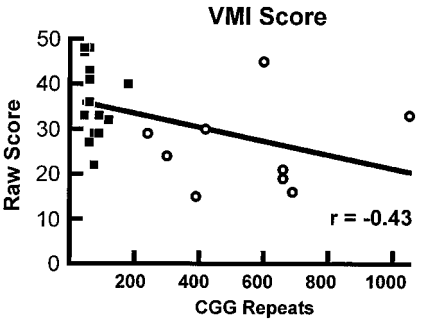

FIGURE 3.

Regression plots showing the relationship between raw scores on the VMI and the size of the expanded gene (kb).

TABLE 6.
Regression analysis for cognitive and visual information processing subtests

Subtest	r Value	p Value
WJ-R		
Memory for Names	NS	NS
Memory for Sentences	NS	NS
Visual Matching	−0.56	0.02
Incomplete Words	NS	NS
Visual Closure	NS	NS
Picture Vocabulary	NS	NS
Analysis-Synthesis	−0.51	0.03
Broad Cognitive Ability	NS	NS
TVPS		
Visual Discrimination	−0.49	0.02
Visual Memory	−0.68	0.0004
Visual-spatial Relationships	−0.45	0.03
Visual Form Constancy	−0.49	0.02
Visual Sequential Memory	−0.55	0.006
Visual Figure-Ground	−0.44	0.03
Visual Closure	−0.51	0.01
VMI	−0.43	0.04

ferences between full and premutation groups reported in this study, however, should help to identify future areas of study.

This study has clear implications for educators in providing appropriate programs for fragile X females with the full mutations who function in the average range of intelligence. We have demonstrated that these females have visual information processing deficits, which, if they remain unaddressed, may interfere with their ability to learn.[50] Indeed, children who have been diagnosed with specific learning difficulties according to criteria in the Individuals with Disabilities Education Act[51] often demonstrate deficits in recognizing, recalling, and manipulating visual information as well as difficulties integrating visual information with motor output.[52, 53]

These deficits may present as educational difficulties, including problems in spelling, mathematics, handwriting, and reading performance. Individuals at risk for visually related learning problems should be referred for a comprehensive vision evaluation that would include an assessment of basic visual and visual information processing skills.[54, 55] The study described in this paper suggests that female carriers of the fragile X full mutation are an identifiable group at risk for visual information processing problems and should be evaluated for such problems.

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REFERENCES

1. Hagerman RJ. Physical and behavioral phenotype. In: Hagerman RJ, Cronister A, eds. Fragile X Syndrome: Diagnosis, Treatment and Research. Baltimore: Johns Hopkins University Press, 1996:3–87.
2. Stern HJ, Stanley WS. The fragile X syndrome. J Int Fed Clin Chem 1994;6:38–41.
3. Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. Am J Med Genet 1996;64:196–7.
4. Hagerman RJ. Fragile X syndrome: molecular and clinical insights and treatment issues. West J Med 1997;166:129–37.
5. Martin JP, Bell J. A pedigree of mental defect showing sex-linkage. J Neurol Psychiatry 1943;6:154–57.
6. Lubs HA. A marker X chromosome. Am J Hum Genet 1969;21: 231–44.
7. Verkerk AJ, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DP, Pizzuti A, Reiner O, Richards S, Victoria MF, Zhang F, Eussen BE, van Ommen GJ, Blonden LA, Riggins GJ, Chastain JL, Kunst CB, Galjaard H, Caskey CT, Nelson DL, Oostra BA, Warren ST. Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 1991;65:905–14.
8. Fu YH, Kuhl DP, Pizzuti A, Pieretti M, Sutcliffe JS, Richards S, Verkerk AJ, Holden JJ, Fenwick RG Jr, Warren ST, Oostra BA, Nelson DL, Caskey CT. Variation of the CGG repeat at the fragile X site results in genetic instability: resolution of the Sherman paradox. Cell 1991;67:1047–58.
9. Reiss AL, Kazazian HH Jr, Krebs CM, McAughan A, Boehm CD, Abrams MT, Nelson DL. Frequency and stability of the fragile X premutation. Hum Mol Genet 1994;3:393–8.
10. 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. Familial transmission of the FMR1 CGG repeat. Am J Hum Genet 1996;59:1252–61.
11. Pieretti M, Zhang FP, Fu YH, Warren ST, Oostra BA, Caskey CT, Nelson DL. Absence of expression of the FMR-1 gene in fragile X syndrome. Cell 1991;66:817–22.
12. Weiler IJ, Irwin SA, Klintsova AY, Spencer CM, Brazelton AD, Miyashiro K, Comery TA, Patel B, Eberwine J, Greenough WT. Fragile X mental retardation protein is translated near synapses in response to neurotransmitter activation. Proc Natl Acad Sci USA 1997;94: 5395–400.
13. Devys D, Lutz Y, Rouyer N, Bellocq JP, Mandel JL. The FMR-1 protein is cytoplasmic, most abundant in neurons and appears normal in carriers of a fragile X premutation. Nat Genet 1993;4:335–40.
14. Cronister A, Hagerman RJ, Wittenberger M, Amiri K. Mental impairment in cytogenetically positive fragile X females. Am J Med Genet 1991;38:503–4.
15. Brainard SS, Schreiner RA, Hagerman RJ. Cognitive profiles of the carrier fragile X woman. Am J Med Genet 1991;38:505–8.

16. Wolff PH, Gardner J, Lappen J, Paccia J, Meryash D. Variable expression of the fragile X syndrome in heterozygous females of normal intelligence. Am J Med Genet 1988;30:213–25.
17. Freund LS, Reiss AL, Hagerman R, Vinogradov S. Chromosome fragility and psychopathology in obligate female carriers of the fragile X chromosome. Arch Gen Psychiatry 1992;49:54–60.
18. Mazzocco MM, Pennington BF, Hagerman RJ. The neurocognitive phenotype of female carriers of fragile X: additional evidence for specificity. J Dev Behav Pediatr 1993;14:328–35.
19. Sobesky WE, Pennington BF, Porter D, Hull CE, Hagerman RJ. Emotional and neurocognitive deficits in fragile X. Am J Med Genet 1994;51:378–85.
20. Taylor AK, Safanda JF, Fall MZ, Quince C, Lang KA, Hull CE, Carpenter I, Staley LW, Hagerman RJ. Molecular predictors of cognitive involvement in female carriers of fragile X syndrome. JAMA 1994;271:507–14.
21. de Vries BB, Wiegers AM, Smits AP, Mohkamsing S, Duivenvoorden HJ, Fryns JP, Curfs LM, Halley DJ, Oostra BA, van den Ouweland AM, Niermeijer MF. Mental status of females with an FMR1 gene full mutation. Am J Hum Genet 1996;58:1025–32.
22. Sobesky WE, Taylor AK, Pennington BF, Bennetto L, Porter D, Riddle J, Hagerman RJ. Molecular/clinical correlations in females with fragile X. Am J Med Genet 1996;64:340–5.
23. Franke P, Maier W, Hautzinger M, Weiffenbach O, Gansicke M, Iwers B, Poustka F, Schwab SG, Froster U. Fragile-X carrier females: evidence for a distinct psychopathological phenotype? Am J Med Genet 1996;64:334–9.
24. Riddle JE, Cheema A, Sobesky WE, Gardner SC, Taylor AK, Pennington BF, Hagerman RJ. Phenotypic involvement in females with the FMR1 gene mutation. Am J Ment Retard 1998;102:590–601.
25. Abrams MT, Reiss AL, Freund LS, Baumgardner TL, Chase GA, Denckla MB. Molecular-neurobehavioral associations in females with the fragile X full mutation. Am J Med Genet 1994;51:317–27.
26. Sobesky WE, Hull CE, Hagerman RJ. Symptoms of schizotypal personality disorder in fragile X women. J Am Acad Child Adolesc Psychiatry 1994;33:247–55.
27. Grigsby JP, Kemper MB, Hagerman RJ. Developmental Gerstmann syndrome without aphasia in fragile X syndrome. Neuropsychologia 1987;25:881–91.
28. Chudley AE, Shepel L, McGahey E, Knoll J, Gerrard JW. Behavioral phenotype. In: Opitz JM, Sutherland, GR, eds. Conference Report: International Workshop on the Fragile X and X-linked Mental Retardation. Am J Med Genet 1984;17:45–9.
29. Miezejeski CM, Jenkins EC, Hill AL, Wisniewski K, French JH, Brown WT. A profile of cognitive deficit in females from fragile X families. Neuropsychologia 1986;24:405–9.
30. de von Flindt R, Bybel B, Chudley AE, Lopes F. Short-term memory and cognitive variability in adult fragile X females. Am J Med Genet 1991;38:488–92.
31. Freund LS, Reiss AL. Cognitive profiles associated with the fra(X) syndrome in males and females. Am J Med Genet 1991;38:542–7.
32. Amin VR, Maino DM. The fragile X female: a case report of the visual, visual perceptual, and ocular health findings. J Am Optom Assoc 1995;66:290–5.
33. Maes B, Fryns JP, Van Walleghem M, Van den Berghe H. Cognitive functioning and information processing of adult mentally retarded men with fragile-X syndrome. Am J Med Genet 1994;50:190–200.
34. Maino DM, Schlange D, Maino JH, Caden B. Ocular anomalies in fragile X syndrome. J Am Optom Assoc 1990;61:316–23.
35. Cornish KM, Munir F, Cross G. Spatial cognition in males with fragile-X syndrome: evidence for a neuropsychological phenotype. Cortex 1999;35:263–71.
36. Berry-Kravis E, Hicar M, Ciurlionis R. Reduced cyclic AMP production in fragile X syndrome: cytogenetic and molecular correlations. Pediatr Res 1995;38:638–43.
37. Maino DM, Wesson M, Schlange D, Cibis G, Maino JH. Optometric findings in the fragile X syndrome. Optom Vis Sci 1991;68: 634–40.
38. Hatton DD, Buckley E, Lachiewicz A, Roberts J. Ocular status of boys with fragile X syndrome: a prospective study. J AAPOS 1998;2: 298–302.
39. Woodcock, RW, Johnson, MB, Mather N. Woodcock-Johnson Psycho-Educational Battery—Revised. Allen, TX: DLM Teaching Resources, 1989.
40. Gardner MF. Test of Visual-Perceptual Skills (Non-Motor) Manual. San Francisco: Health Publishing Company, 1988.
41. Beery KE. The Developmental Test of Visual-Motor. 3rd rev. Cleveland: Modern Curriculum Press, 1989.
42. Tassone F, Hagerman RJ, Taylor AK, Mills JB, Harris SW, Gane LW, Hagerman PJ. Clinical involvement and protein expression in individuals with the FMR1 premutation. Am J Med Genet 2000;91: 144–52.
43. Steyaert J, Borghgraef M, Fryns JP. Apparently enhanced visual information processing in female fragile X carriers: preliminary findings. Am J Med Genet 1994;51:374–7.
44. Taylor AK, Tassone F, Dyer PN, Hersch SM, Harris JB, Greenough WT, Hagerman RJ. Tissue heterogeneity of the FMR1 mutation in a high-functioning male with fragile X syndrome. Am J Med Genet 1999;84:233–9.
45. Tassone F, Hagerman RJ, Taylor AK, Gane LW, Godfrey TE, Hagerman PJ. Elevated levels of FMR1 mRNA in carrier males: a new mechanism of involvement in the fragile-X syndrome. Am J Hum Genet 2000;66:6–15.
46. Tuckerman E, Webb T. The inactivation of the fragile X chromosome in female carriers of the Martin Bell syndrome as studied by two different methods. Clin Genet 1989;36:25–30.
47. Kolehmainen K, Karant Y. Modeling methylation and IQ scores in fragile X females and mosaic males. Am J Med Genet 1994;51:328–38.
48. Reiss AL, Freund LS, Baumgardner TL, Abrams MT, Denckla MB. Contribution of the FMR1 gene mutation to human intellectual dysfunction. Nat Genet 1995;11:331–4.
49. Mazzocco MM, Hagerman RJ, Cronister-Silverman A, Pennington BF. Specific frontal lobe deficits among women with the fragile X gene. J Am Acad Child Adolesc Psychiatry 1992;31:1141–8.
50. Flax N, Solan HA, Suchoff IB. Optometry and dyslexia. J Am Optom Assoc 1983;54:593–4.
51. Individuals with Disabilities Education Act. Washington, DC: U.S. Government Printing Office, 1997.
52. Borsting E. Visual perception and reading. In: Garzia RP, ed. Vision and Reading. St. Louis: Mosby, 1996:149–75.
53. Lerner JW. Learning Disabilities: Theories, Diagnosis, and Teaching Strategies. 8th ed. Boston: Houghton-Muffin, 2000.
54. American Academy of Optometry, American Optometric Association. Vision, learning, and dyslexia. A joint organizational policy statement. American Academy of Optometry. American Optometric Association. Optom Vis Sci 1997;74:868–70.
55. Evans BJ. The underachieving child. Ophthalmic Physiol Opt 1998; 18:153–9.

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