

# 3 Fragile X Syndrome: The Journey from Genes to Behavior

Kimberly M. Cornish, Andrew Levitas, and Vicki Sudhalter

**Case 3.1: Harold** Harold is a 6-year-old boy recently evaluated by his pediatrician for developmental delay and autistic-like features. Harold's mother reported early problems with speech production, hyperactivity, and aggressive outbursts. More recently the behavioral problems have intensified, and Harold has begun to hand bite. On physical examination, the pediatrician notes that Harold has a slightly longer face, larger ears, and more prominent jaw than would be expected for a boy his age but nothing too unusual. A family history reveals that Harold's sister and maternal cousin, both females, have mild learning difficulties including attention problems, chronic shyness, and social anxiety. Molecular analysis revealed fragile X syndrome.

Fragile X syndrome is the most prevalent known inherited cause of developmental delay in humans, affecting 1 in 4,000 males and 1 in 8,000 females (de Vries, Halley, Oostra, & Niermeijer, 1998; Kooy, Willesden, & Oostra, 2000; Turner, Webb, Wake, & Robinson, 1996). Elongated face, large prominent ears and forehead, and macroorchidism (postpuberty) can characterize some children with the condition (Lachiewicz, Dawson, & Spiridigliozzi, 2000), alongside more subtle features that include narrow intereye distance, a highly arched palate of the mouth, and hyperextensible metacarpophalangeal joints. However, the wide variability in expression, in both males and females, makes diagnosis on physical features alone almost impossible. See figure 3.1, which illustrates the facial features of two siblings, both with the full mutation, ranging in age from 4–9 years. The most defining feature of fragile X syndrome, especially in boys with the condition, is mental retardation and the resulting behavioral phenotype. It is precisely because of their quite normal appearance that many affected children are not recognized until relatively later in development as having fragile X, which is why a close examination of the phenotypic signature and its developmental timeline is crucial in helping clinicians toward an early diagnosis. See table 3.1 for a summary of the clinical and medical problems associated with fragile X syndrome.



sister and brother (L-R) aged 4 & 2 years



brother and sister (L-R)  
aged 7 and 9 years



sister – 4 years



brother – 6 years

**Figure 3.1**  
Siblings with fragile X syndrome. Abbreviations: L, left; R, right.

**Table 3.1**

Prevalence of characteristic physical, cognitive, and behavioral symptoms in children with fragile X syndrome and prevalence of fragile X syndrome among persons with clinical presentation of these symptoms

Characteristic/Symptom	% of Cases in All Individuals with Fragile X Syndrome	% of Fragile X Cases Among Persons with Symptom	
		Males	Females
Epilepsy	13–20 <sup>8</sup> 23 <sup>14</sup> 0 <sup>13</sup>	No studies found	
Cardiac abnormalities	1 <sup>8</sup>	No studies found	
Macroorchidism	68 <sup>5</sup>	39 <sup>12</sup>	
Mental retardation	70 <sup>8</sup> 50–70 (full mutation females) <sup>6</sup> 100 <sup>7</sup>	0.9–8.9 <sup>1</sup> 2–3 <sup>11</sup>	0.3–1 <sup>1</sup>
Elongated face	50 <sup>7</sup>	No studies found	
Large ears	100 <sup>7</sup>	No studies found	
Language delay	75 <sup>8</sup>	0.56 <sup>9</sup>	
Speech problems	70 <sup>8</sup>	No studies found	
Attention and concentration difficulties	100 <sup>8</sup>	No studies found	
Autism	24–33 <sup>2</sup> 15–33 <sup>3</sup>	2–16 <sup>2</sup>	
Autistic-like features	90 <sup>8</sup> 58 <sup>7</sup>	7.5 <sup>10</sup>	
Attention deficit/hyperactivity disorder	80 <sup>4</sup> 67 <sup>7</sup>	1 <sup>4</sup>	
Social anxiety and hyperarousal	100 <sup>8</sup>	No studies found	
	% of Cases in All Individuals with Fragile X Syndrome	% of Non-Fragile X Syndrome Cases with Fragile X Symptom	
Mental retardation and:			
Elongated face	51 <sup>5</sup>	7 <sup>5</sup>	
Large ears	27 <sup>5</sup>	11 <sup>5</sup>	
Hyperextensible finger joints	41 <sup>5</sup>	23 <sup>5</sup>	
Soft/smooth skin	22 <sup>5</sup>	4 <sup>5</sup>	
Macroorchidism	68 <sup>5</sup>	16 <sup>5</sup> 27 <sup>11</sup>	
Characteristic personality	63 <sup>5</sup>	4 <sup>5</sup>	

1. Pooled data, numerous worldwide studies 1983–2005.

2. Pooled data, reviewed in the following: Demark, J. L., Feldman, M. A., & Holden, J. J. A. (2003). Behavioral relationship between autism and fragile X syndrome. *American Journal on Mental Retardation*, 108, 314–326.

3. Pooled data, reviewed in this chapter.

4. Bastain, T. M., Lewczyk, C. M., Sharp, W. S., James, R. S., Long, R. T., Eagen, P. B., et al. (2002). Cytogenetic abnormalities in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41, 806–810.

5. de Vries, B. B. A., Mohkamsing, S., van den Ouweland, A. M. W., Mol, E., Gelsema, K., van Rijn, M., et al. (1999). Screening for the fragile X syndrome among the mentally retarded: A clinical study. *Journal of Medical Genetics*, 36, 467–470.

**Table 3.1**  
(continued)

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6. de Vries, B. B. A., Wiegers, A. M., Smits, A. P. T., Mohkamsing, A., Duivenvoorden, H. J., Fryns, J.-P., et al. (1996). Mental status of females with an FMR1 gene full mutation. *American Journal of Human Genetics*, *58*, 1025–1032.
  7. Giangreco, C. A., Steele, M. W., Aston, C. E., Cummins, J. H., & Wenger, S. L. (1996). A simplified six-item checklist for screening for fragile X syndrome in the pediatric population. *Journal of Pediatrics*, *129*, 611–614.
  8. Hagerman, R. J., & Cronister, A. (Eds.). (1996). *Fragile X syndrome: Diagnosis, treatment and research* (2nd ed.). Baltimore: Johns Hopkins University Press.
  9. Mazzocco, M. M., Myers, G. F., Hamner, J. L., Panoscha, R., Shapiro, B. K., & Reiss, A. L. (1998). The prevalence of the FMR1 and FMR2 mutations among preschool children with language delay. *Journal of Pediatrics*, *132*, 795–801.
  10. Sherman, S. (1996). Epidemiology. In R. J. Hagerman & A. Cronister (Eds.), *Fragile X syndrome: Diagnosis, treatment and research* (2nd ed., pp. 165–192). Baltimore: Johns Hopkins University Press.
  11. Slaney, S. F., Wilkie, A. O. M., Hirst, M. C., Charlton, R., McKinley, M., Pointon, J., et al. (1995). DNA testing for fragile X syndrome in schools for learning difficulties. *Archives of Disease in Childhood*, *72*, 33–37.
  12. Vatta, S., Cigui, I., Demori, E., Morgutti, M., Pecile, V., Benussi, D. G., et al. (1998). Fragile X syndrome, mental retardation and macroorchidism [Letter to the Editor]. *Clinical Genetics*, *54*, 366–367.
  13. Vieregge, P., & Froster-Iskenius, U. (1989). Clinico-neurological investigations in the fra(X) form of mental retardation. *Journal of Neurology*, *236*, 85–92.
  14. Wisniewski, K. E., Segan, S. M., Miezjeski, C. M., Sersen, E. A., & Rudelli, R. D. (1991). The Fra(X) syndrome: Neurological, electrophysiological, and neuropathological abnormalities. *American Journal of Medical Genetics*, *38*, 476–480.

Fragile X syndrome's single-gene etiology affords us the unique opportunity to begin to understand the relationships among genes, brain, and behavior. To that end, we provide a description of the recent advances that define the syndrome at the genetic and brain level, a description of the defining clinical features, and profile of cognitive strengths and weaknesses. We conclude with some ideas for medical and educational interventions.

### **Fragile X Syndrome—Genetic and Brain-Level Considerations**

By virtue of its single-gene etiology, fragile X syndrome represents an important model for understanding the impact of the fragile X mental retardation gene—1 (FMR1) expression on the development and normal functioning of the central nervous system. While it is becoming commonplace to investigate the phenotypic effects resulting from the loss of a single gene product in animal models, few naturally occurring genetic anomalies exist in humans that allow us to examine the specific contribution of a single gene to behavior, although that contribution might be by way of modification of the action of many other genes. The syndrome is caused by the silencing of a single gene on the X chromosome, FMR1 (Verkerk et al., 1991). The FMR1 gene carries a CGG trinucleotide repeat in the 5' untranslated region. The American College of Medical Genetics guidelines define unaffected individuals

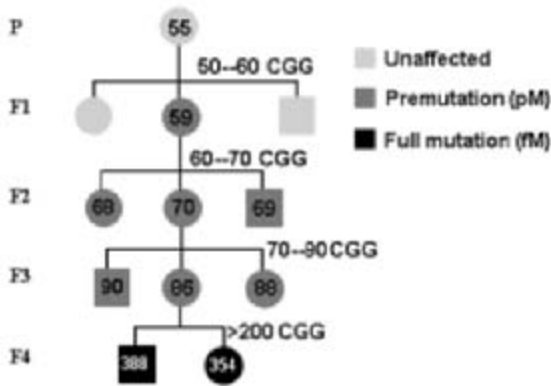
as having between 7 and 55 repeats, with 30 repeats the most common allele and a “gray zone” of ~45–54 CGG repeats with lesser size instability on transmission (Hagerman & Hagerman, 2004). In fully clinically affected individuals the CGG region expands to over 200 repeats, resulting in the silencing of the gene and loss of the encoded protein, fragile X mental retardation protein (FMRP). Due to X linkage, almost all affected males present with mental retardation compared to approximately one half of affected females. In nearly all cases, the disorder is caused by an expansion of the CGG repeat at the beginning of the FMR1 gene on the X chromosome, leading to methylation of the promoter sequence and loss of the FMRP in individuals with 200 or more repeats (Turner et al., 1996; Verkerk et al., 1991).

Alleles with between 55~200 repeats are called “premutations” and typically are associated with normal or slightly reduced levels of protein production, generating some protein. However, these premutations can be unstable through successive generations, giving rise to the fragile X syndrome phenotype upon full expansion (Kooy, 2003; O’Donnell & Warren, 2002). When 200 or more CGG repeats are present, usually (unless there is a failure of methylation) there is hypermethylation and a subsequent silencing of the FMR1 gene. This is commonly referred to as the FMR1 *full mutation*. Although both males and females can be carriers of fragile X syndrome, inheritance of the full mutation can only be from a female who carries either a full mutation or a premutation that is *unstable* on female transmission. In contrast, male carriers can only transmit their premutation to their daughters. Figure 3.2 illustrates the pattern of inheritance and its expansion over generations.

The abnormal CGG repeat sequences can be detected and quantified using restriction endonuclease digestion and Southern blot technology. Cleavage of the FMR1 gene by EcoR1 yields a 5.2-kb fragment; this is further cleaved by Eag1 into 2.4- and 2.8-kb fragments if unmethylated. Abnormal-sized DNA fragments caused by increases in numbers of CGG repeats in the 5′ untranslated region are detected and quantified by migration on Southern blot (see figures 3.3, 3.4, and 3.5).

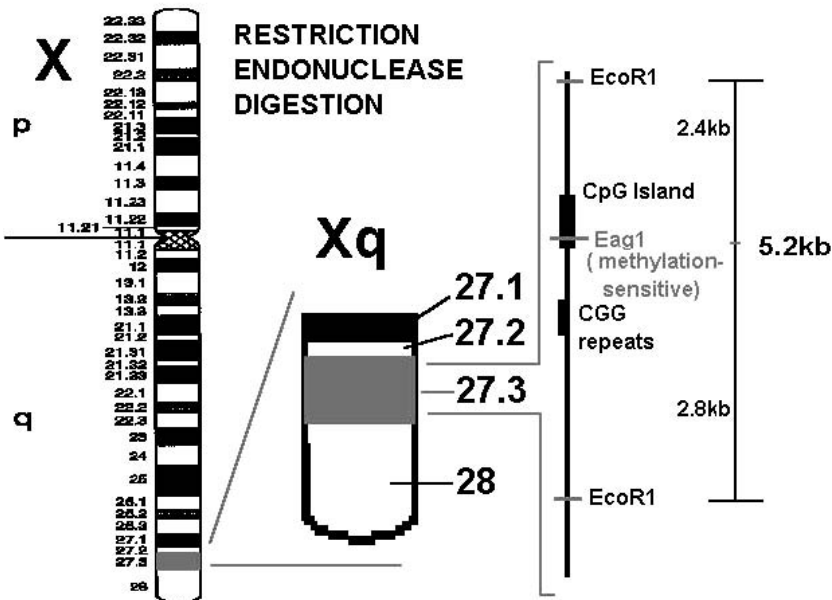
It is now established that the FMR1 gene is the major contributor to the pathogenesis of fragile X syndrome and that the key issues relate to a lack of messenger RNA (mRNA) and a lack or absence of the protein product of the FMR1 gene—FMRP—resulting in the fM. (See figure 3.6.) In contrast, premutation males and females possess unmethylated versions of the FMR1 gene and therefore have normal or near-normal levels of FMRP and the expanded (premutation) CGG repeat element results in both elevated FMR1 mRNA levels and slight to moderate reductions in FMRP.

The extent to which these discoveries explain some of the phenotypic outcomes of fragile X syndrome are beginning to be unraveled with converging evidence indicating a possible role in early neuronal development. First, FMRP is especially critical in the early embryonic stages of development including the neonatal stage (Bakker et al., 2000). And second, FMRP is an important regulator of synaptic activity and



**Figure 3.2**

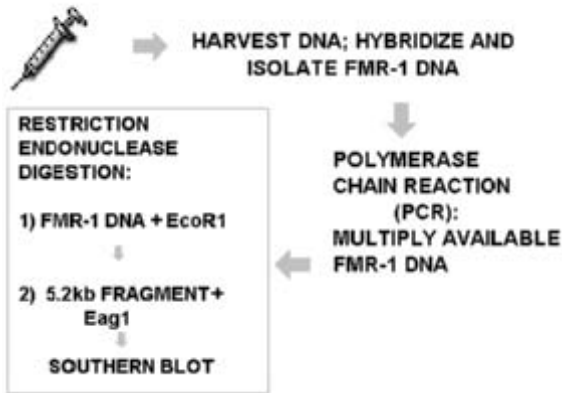
Hypothetical genogram of 5 generations of a family with fragile X syndrome. P: carrier female (premutation; pM) with 55 CGG repeats; unaffected. F1: A male and female inherit mother's normal X chromosome; a female pM with 59 CGG repeats. F2: a childless female pM with 68 CGG repeats, mild neuropsychological deficits, and hyperactivity; a childless male pM with 69 CGG repeats and attention deficit/hyperactivity disorder; a female pM with 70 CGG repeats, moderate neuropsychological deficits. F3: childless male pM with 90 CGG repeats, hyperactivity, borderline intellectual functioning; childless female pM with 88 CGG repeats, borderline intellectual functioning, and schizotypal disorder; a female pM with 86 CGG repeats, moderate neuropsychological deficits, generalized anxiety disorder, major depressive disorder. F4: male fM (full mutation) and female fM both with more than 200 CGG repeats, mental retardation and autistic disorder.



**Figure 3.3**

Endonuclease digestion of FMR1 yields a 2.8-kb DNA fragment if unmethylated.

**FXS DNA DIAGNOSIS PROCEDURE**



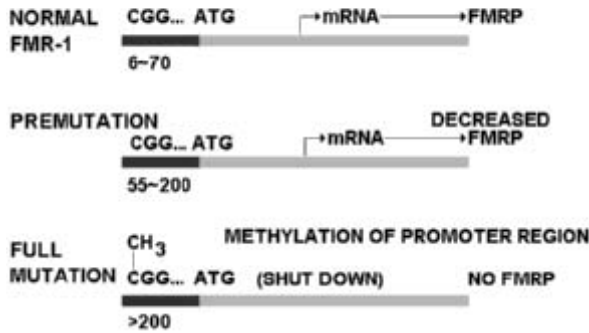
**Figure 3.4**  
Procedure for fragile X syndrome (FXS) DNA laboratory analysis.

**FXS DNA DIAGNOSIS PROCEDURE  
SOUTHERN BLOT**

1		Normal male
2		Normal female (methylated inactive X)
3		Transmitting male (>2.8 kb)
4		Premutation female (>2.8, >5.2)
	2.8kb      5.2kb	
5		Full mutation male (>>5.2 kb)
6		Full mutation female (>> 5.2kb)
7		Mosaic male (5.2+ >5.2kb smear)
8		Mosaic female (2.8 + >2.8; 5.2+ +)

**Figure 3.5**  
DNA fragments in eight possible Southern Blot outcomes. Note the single FMR1 fragment seen in males (one X chromosome), the two in females (two X chromosomes, one normal X chromosome; the normal or the fragile X chromosome may be inactivated by methylation). Abbreviation: FXS, fragile X syndrome.

## FXS MOLECULAR PATHOLOGY

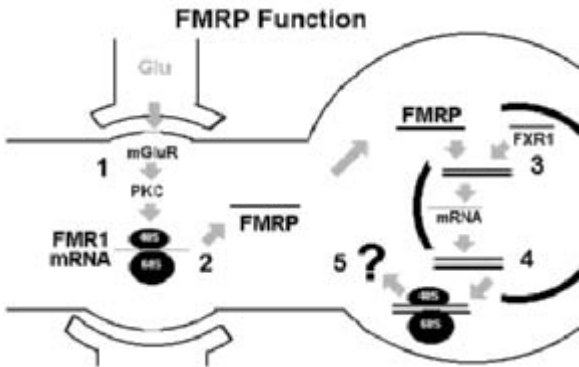


**Figure 3.6**  
Fragile X syndrome (FXS) molecular pathology.

organization because of its role in the transportation of selective mRNAs molecules to dendrites in response to neural stimulation (Bardoni, Mandel, & Fisch, 2000; Irwin et al., 2001; see figure 3.7). Indeed, systematic studies of FMR1 knock-out mice and autopsied human brains of individuals with fragile X have indicated that the absence of the FMRP affects postsynaptic changes in dendrite spine morphology that include an abundance of long, thin, and tortuous spines; more spines with an immature-appearing structure; and a greater density of spines overall (e.g., Galvez & Greenough, 2005; Irwin et al., 2002). One current theory, the mGluR theory, proposed by Bear, Huber, and Warren (2004), suggests that an early disruption to the molecular pathways involved in synaptic development and regulation may have a differential impact on early brain development to produce the phenotypic outcomes we associate with the syndrome. However, *development itself* will also play a critical role in defining the fragile X syndrome phenotype (Cornish, Scerif, & Karmiloff-Smith, in press; Karmiloff-Smith, 1998).

At the brain level, studies have revealed decreased size of the posterior vermis of the cerebellum in males and females (Mostofsky et al., 1998; Reiss, Alyward, Freund, Joshi, & Bryan, 1991). Other structures affected by FMR1 status include the caudate nucleus (Eliez, Blasey, Freund, Hastie, & Reiss, 2001) and the hippocampus (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997; Reiss, Lee, & Freund, 1994). In addition, several studies reported a correlation between neuroanatomical abnormalities and the degree of functional impairment in the full mutation. For example, posterior vermis volumes are positively correlated with performance on specific measures of intelligence, visual-spatial ability, and executive function, suggesting a putative functional role for this structure (Mostofsky et al., 1998). Taken





**Figure 3.7**

Normal fragile X mental retardation protein (FMRP) function. Activated metabotropic mGlu receptor (1) activates protein kinase C, which stimulates translation of prepositioned FMR1 messenger RNA (mRNA) ribonucleoprotein complexes at the synapse, producing FMRP (2). FMRP is imported into the nucleus, where, with FXR1 or FXR2 (3), it links to mRNA of other genes (4), transporting it to ribosomes where the mRNA is translated into as yet unknown proteins (5).

together, the purely structural and combined structural/functional studies implicate the cerebellum, caudate nucleus, and hippocampus as potential sites for phenotypic effects from abnormal FMR1 gene expression. However, it is important to stress that abnormal structures form part of widely distributed networks and that deficits may be observed across a broad range of activities.

In the following section we briefly describe the recent advances that have helped to define the fragile X syndrome phenotype at the behavioral and cognitive levels. We especially focus on the variations within the condition itself, most notably between affected males and females.

### **Fragile X Syndrome—Cognitive and Behavioral Considerations**

*Mental retardation* is seen as the most defining clinical feature of boys with fragile X syndrome with almost all affected males presenting with IQs within the moderate–severe range of impairment with profiles emerging as young as 3 years of age (Skinner et al., 2005). In females, the phenotypic variation is such that some girls only show subclinical learning disabilities (Bennetto & Pennington, 2002), while approximately 50% display more moderate–severe mental retardation similar in profile to boys with fragile X syndrome. The X-inactivation status of females with fragile X is seen as the major contributor to the heterogeneity of intellectual disability and neuropsychological deficits. In some males, the presence of mosaicism may produce a higher level of cognitive functioning, but these cases are relatively rare, although well documented (Hagerman, Hull et al., 1994; Merenstein et al., 1996).

## Behavioral Concerns

Severity of behavioral difficulties in boys and girls with fragile X syndrome will vary across and within gender. In addition, there is the added complication of comorbidities that have implications for early diagnosis and treatment. Here we target three areas of behavioral difficulties that have been frequently documented in boys and girls with fragile X.

**Social Anxiety and Hyperarousal** Hypersensitivity and hyperarousal are recognized as early prominent behavioral features of children with fragile X syndrome, with and without autism (Belser & Sudhalter, 1995; Hagerman, 1996; Miller et al., 1999). Key-sor, Mazzocco, McLeod, and Hoehn-Saric (2002) demonstrated higher arousal levels at baseline for girls with fragile X relative to girls with Turner syndrome or typical developing children, with a small rise on anxiety-provoking cognitive tasks compared to that seen in girls with Turner syndrome, resulting in eventual comparable anxiety in both groups on these tasks. Despite an evident desire for social contact (Simon & Finucane, 1996; Turk & Cornish, 1998), children with fragile X syndrome (with and without autism) show social anxiety, with delay in initiating interaction, gaze avoidance, and failure to understand gaze direction (Garrett, Menon, MacKenzie, & Reiss, 2004; Kau, Reider, Payne, Meyer, & Freund, 2000; Turk, 1998; Wolff, Gardner, Paccia, & Lappen, 1989) associated with their greater difficulty (Lachiewicz, 1992; Lachiewicz & Dawson, 1994).

Lesniak-Karpiak, Mazzocco, and Ross (2003) demonstrated different manifestations of social anxiety/social deficit in girls with fragile X versus girls with Turner syndrome. In a pilot study using psychophysiological and behavioral measures, Belser and Sudhalter (1995) demonstrated that males with fragile X syndrome were more aroused by eye contact than their matched cohorts with either mental retardation or attention deficit/hyperactivity disorder (ADHD). It was additionally demonstrated that the arousal disrupted the language of the males with fragile X syndrome.

Miller et al. (1999) investigated the relationship between hyperarousal as measured by electrodermal responses and reaction to sensory stimuli in individuals with fragile X syndrome. The research demonstrated that reactions in one modality predicted reactions in another; there was a negative relationship between FMRP expression and electrodermal responses, and the pattern of electrodermal responses did differentiate males with fragile X from normal controls. Taken together, these data suggested that males with fragile X syndrome may have a multimodal sensory defensiveness that may underlie or at least influence hyperarousal. The authors also suggest that the sympathetic nervous system may be affected in individual with fragile X based on the pattern of results from the research.

Roberts, Boccia, Bailey, Hatton, and Skinner (2001) present research comparing heart rate variability in boys with fragile X syndrome and typically developing boys

matched for chronological age. They predicted that boys with fragile X would display higher levels of heart activity and different patterns of modulation, as measured by shorter interbeat intervals (IBIs) than chronologically matched controls. In addition, they hypothesized that the heart activity of boys with fragile X would reflect lower vagal tone estimates and different patterns of modulation than chronologically matched controls. The participants completed a 30-min procedure consisting of alternating passive (i.e., watching a video) and active (i.e., completing cognitive tasks) phases. Heart rate activity was collected while the participants were engaged in these activities. Post hoc tests confirmed hypotheses. Boys with fragile X displayed shorter IBIs and higher sympathetic tone estimates during the passive tasks than the control group and displayed lower vagal tone estimates across all phases of the task and showed no modulation of vagal tone, while the typically developing boys showed higher level of vagal tone and suppression during phrases of increased demand. Finally, the typically developing boys displayed coordinated responses between the vagal and sympathetic systems, while the boys with fragile X did not. The authors suggest that these results demonstrate that boys with fragile X do not discriminate between phases of a task and modulate their heart rate activity through increased sympathetic tone rather than suppression of vagal tone, which is the demonstrated pattern of typically developing boys. This pattern of increased sympathetic input is in accordance with the findings of other studies (Belser & Sudhalter, 1995; Miller et al., 1999). The authors also suggest that the inefficient self-regulation mechanisms demonstrated by individuals with fragile X syndrome may help explain the behavioral arousal problems evidenced in the population.

The bases for hyperarousal, anxiety, and social anxiety/deficit may differ markedly among genetic syndromes, but hypersensitivity in all sensory modalities, low threshold for anxious or catastrophic reaction, and social anxiety may make separation from parents, experiences in crowds or noisy, echoing spaces, new clothing, all but a few foods (in some children), and some odors, especially when unexpected, very problematic to the point of severe “tantrum” behavior. Children with fragile X syndrome may be overwhelmed by the demands created by social involvement, novel or unexpected situations, and changes, even by the common transitions of daily life. Generalized anxiety and/or panic disorder may occur (Hagerman, Hull et al., 1994). Recently, Turk, Robbins, and Woodhead (2005) described two cases of post-traumatic stress disorder (PTSD) in persons with fragile X syndrome, one a 13-year-old boy.

**Autism** There are currently very few single-gene studies for which there is a certainty of the involvement of autism; fragile X is one of those disorders. Although still controversial, a plethora of recent studies using a variety of standardized measures (e.g., Autism Diagnostic Observation Schedule-Generic [ADOS-G], Autism Diagnostic Interview-revised [ADI], Childhood Autism Rating Scale [CARS]) indicate a

range of between 15%~33% of individuals with fragile X syndrome will fulfill a clinical diagnosis of autism (Bailey et al., 1998; Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; Bailey, Hatton, Skinner, & Mesibov, 2001; Baumgardner, Reiss, Freund, & Abrams, 1995; Reiss & Freund, 1992; Rogers, Hepburn, Stackhouse, & Wehner, 2003). One argument is that the prevalence of autism in fragile X syndrome may simply be an artifact of general cognitive delay that is inherent in many disorders of mental retardation. However, closer examination of studies that have compared performance of children with fragile X syndrome and autism (fragile X syndrome + autism), children with fragile X without autism (fragile X alone), and children with autism without fragile X (autism alone) indicate quite different developmental profiles. For example, Hatton et al. (2003) observed lower adaptive scores as measured by the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984) in children with fragile X syndrome + autism compared to children with fragile X alone. In terms of social functioning, Kau et al. (2004) found children with fragile X syndrome + autism to display a distinct social profile that differentiated them from children with idiopathic autism and fragile X without autism. However, commonalities between fragile X syndrome + autism and idiopathic autism were striking on other domains, notably problem/aberrant behavior and adaptive behaviors. These domains were not as impaired in children with fragile X syndrome without autism. In the domain of language, Philofsky, Hepburn, Hayes, Hagerman, and Rogers (2004) report a relative strength in receptive language compared to expressive language for children with fragile X without autism. This pattern was not replicated in children with fragile X syndrome + autism, whose performance was much lower than children with fragile X alone but similar to that of children with idiopathic autism. They speculate that low receptive language may be a marker for autism symptoms in young children with fragile X syndrome.

**Autistic-like Features** Although not all children with fragile X syndrome present with a clinical diagnosis of autism, almost all will display a range of “autistic-like” features, which include language delay, echolalia, and perseverative speech (see Cornish, Sudhalter, & Turk, 2004, for a review) alongside poor eye contact and stereotypic movements. However, the cause of these autistic-like behaviours in individuals with fragile X (without autistic disorder) may differ from the cause in individuals with autistic disorder who also have fragile X syndrome. It is well recognized that individuals with autistic disorder have a deficit in understanding social relationships, semantics, and pragmatics and in establishing interpersonal attachments. These deficits in turn interfere with the acquisition of social behaviors such as language, play, and empathy. On the other hand, males and females with fragile X syndrome are frequently described as friendly, loving, and extremely empathetic; however, they experience hyperarousal and social anxiety (as described above), which interferes with the

expression of these emotions (Hagerman, 1996; Cohen, 1995; Cohen et al., 1991). Hyperarousal and social anxiety will cause the individuals to avert their eyes (so as to minimize social interactions or to avoid the sensory stimulation of eye contact), avoid parties and interactions, and produce atypical language (see below). Thus, males and females with fragile X syndrome will exhibit autistic-like behaviors, which are symptomatic of their hyperarousal and social anxiety rather than an inherent lack of understanding of the social situation.

**Attention Deficit and Hyperactivity Disorder** Among the most distinctive and pervasive behavioral features of young boys with fragile X syndrome are attentional and hyperactivity problems (e.g., Baumgardner et al., 1995; Cornish, Munir, & Wilding, 2001; Hatton et al., 2002; Turk, 1998), the severity of which often leads to a clinical diagnosis of ADHD. Using the Child Behavior Checklist (CBCL; Achenbach, 1991), Hatton et al. (2002) report that approximately 57% of young boys with fragile X syndrome (4–12 years old) scored in the borderline or clinical range on the attention subscale of the CBCL. In a comparison study of 25 older boys with fragile X syndrome (ages 8–15 years) and 25 boys with Down syndrome (ages 7–15 years), Cornish, Munir, and Cross (2001) found greater attention problems (as measured by the CBCL attention subscale) and hyperactivity (as measured by the ADHD Comprehensive Teacher Rating [ACTeRs] scale; Ullman, Sleator, & Sprague, 1984) in boys with fragile X syndrome compared to boys with Down syndrome. In one of the most comprehensive studies to date, Turk (1998) compared the ADHD profiles of 49 boys with fragile X (ages 4–16 years) to that of 45 boys with Down syndrome (ages 4–16 years), and 42 boys with mental retardation of an unknown cause (ages 4–16 years). Although both groups of boys showed similar levels of motor activity, the boys with fragile X syndrome showed significantly more inattentiveness, restlessness, fidgetiness, distractibility, and impulsive tendencies as measured by the CBCL and the Parental Account of Childhood Symptoms questionnaire (Taylor, Schachar, & Hepstinall, 1993) than the group with unknown etiology. Furthermore, these features did not appear to improve spontaneously over time and are present early in development. Together, these findings highlight a distinctive ADHD profile in boys with fragile X that is not simply the artifact of mental retardation. In girls with fragile X, the profile is less well documented with more variability. Unlike affected boys, only about one third of girls appear to meet the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) diagnostic criteria for ADHD (Freund, Reiss, & Abrams, 1993), although many will present with some ADHD symptomology, notably inattentiveness rather than hyperactivity (Hagerman et al., 1992; Mazzocco, Baumgardner, Freund, & Reiss, 1998). Other studies, however, using parental rating scales have reported significant problems with hyperactivity ranging from 38%–47% of affected girls.

## Cognitive Profile

Although early reports indicated a slight verbal versus nonverbal discrepancy with better Verbal IQ scores than Performance IQ scores in males and females with fragile X syndrome (Theobald, Hay, & Judge, 1987; Veenema, Veenema, & Geraedts, 1987), it is now not regarded as a hallmark of the syndrome. Instead, and as will be described in detail below, the fragile X syndrome profile is characterized by uneven abilities within and across cognitive domains (Cornish et al., 2004). In essence, the cognitive dysfunction can be described as more “skill specific” rather than “global” in nature.

## Cognitive Strengths and Difficulties

It is now well established that boys and girls with fragile X syndrome present with distinct cognitive profiles that differentiate them from children with other developmental disorders. Although mental retardation is a core clinical feature of fragile X, especially in boys, recent evidence clearly points to an uneven profile of cognitive strengths and difficulties that represents a developmental pathway that is atypical rather than simply delayed. Here we highlight recent findings from five cognitive domains known to be impaired in children with fragile X syndrome: speech and language, memory, motor, number, and attention. See table 3.2 for a summary of the fragile X syndrome cognitive phenotype. Note that strengths as well as deficits characterize this syndrome.

**Speech and Language** It is well established that children with fragile X syndrome have delayed language acquisition (Fisch et al., 1999; Roberts, Mirrett, & Burchinal, 2001). There are at least four consequences of having fragile X syndrome that contribute to this delay. Individuals with fragile X syndrome are prone to recurrent ear infections (Hagerman, Altshul-Stark, & McBogg, 1987), low tone or hypotonia (Hagerman, Smith, & Mariner, 1983; Wisniewski, Segan, Mizejeski, Sersen, & Rudelli, 1991) sensory integration problems, and mental retardation. These consequences contribute to the late onset of language abilities. Once the individual with

**Table 3.2**  
The fragile X syndrome cognitive phenotype

Strengths	Difficulties
Vocabulary acquisition	Speech (perseverative)
Memory for meaningful information	Memory for abstract information
Visuoperceptual processing	Visuomotor processing
Selective attention	Attentional control/inhibition
	Number processing

fragile X syndrome begins to speak, language is characterized by both delayed and atypical language/speech forms. An example of delayed language is the relatively spared semantic, morphological, and syntactic knowledge (Abbeduto et al., 2003; Sudhalter, Scarborough, & Cohen, 1991) of males with fragile X syndrome. Examples of the atypical language produced by males with fragile X are found within their social or conversational interactions. These interactions contain tangential language (Sudhalter & Belser, 2001), perseverative language (Ferrier, Bashir, Meryash, Johnston, & Wolff, 1991; Sudhalter, Cohen, Silverman, & Wolf-Schein, 1990), and repetitive speech (Hanson, Jackson, & Hagerman, 1986; Belser & Sudhalter, 2001). Each of these atypical language types is described below.

**Tangential and Perseverative Language** Tangential language refers to off-topic questions, responses, or comments that do not logically follow the preceding conversational thread. Perseverative language refers to the reintroduction of favorite topics over and over, even in the presence of conflicting conversational demands. Studies comparing males with fragile X syndrome to verbal and chronologically matched individuals with mental retardation and individuals with autistic disorder demonstrated that males with fragile X syndrome produced significantly more tangential (Sudhalter & Belser, 2001) and perseverative language (Sudhalter et al., 1990; Ferrier et al., 1991) than either of the other cohorts. This suggests that these forms of atypical language production are not the consequence of being delayed or of undiagnosed autistic disorder.

**Repetitive Speech** Repetitive speech refers to the repetition of sounds, words, or phrases within an utterance or conversational turn. In addition to the atypical types of language described above, another common linguistic characteristic of males with fragile X syndrome is repetitive speech (Belser & Sudhalter, 2001; Borghgraef, Frons, Dielkens, Pyck, & Van Den Berghe, 1987; Hanson et al., 1986). In studies comparing males with fragile X syndrome to chronologically and cognitively matched cohorts with either mental retardation or autistic disorder, it was demonstrated that males with fragile X produced significantly more repetitive speech than either of their matched cohorts.

We have suggested that one of the causes for these atypical language forms is the hyperarousal that social interactions cause in the males with fragile X. In a very small pilot study (described above) Belser and Sudhalter (1995) demonstrated that the language of males with fragile X syndrome was disturbed during periods of eye contact. When the males were not asked to maintain eye contact, their language contained significantly fewer examples of atypical language/speech. In subsequent papers, the authors suggested that the effects of hyperarousal induced the production of repetitive speech by causing the male to speak more quickly, thus interfering with

productive abilities (Belser & Sudhalter, 2001), and additionally that hyperarousal interferes with the normal workings of the mental lexicon (a neural network of word meanings) thus promoting tangential language (Sudhalter & Belser, 2001).

The language of females with fragile X has not been described in the detail that the language of males has been. Lesniak-Karpiak et al. (2003) demonstrated that females with fragile X syndrome required significantly more time to initiate interactions than females with Turner syndrome, suggesting that females as well as males with fragile X are affected by social anxiety and that this anxiety may interfere with verbal production within social situations.

**Memory** Not all components of memory are equally affected by fragile X syndrome. In boys, evidence clearly points to *relative* strengths in long-term and short-term recall for meaningful information including memory for faces (Turk & Cornish, 1998) and story recall (Munir, Cornish, & Wilding, 2000) with performance at a level equivalent to typical children matched on *developmental* level (but not chronological age level). No equivalent published studies have been conducted in girls with fragile X syndrome. In terms of *working memory* (the ability to retain and manipulate information “online” over short periods, which is crucial in guiding attention and behavior during the course of an activity), accumulating evidence points to a relative weakness in visuospatial working memory compared to verbal working memory (Cornish, Munir, & Cross, 1999; Munir et al., 2000). For example, Munir et al. (2000) examined working memory performance in 25 boys with fragile X syndrome, ages 8–15 years, 25 boys with Down syndrome (trisomy 21) ages 7–15 years, and two groups (25 in each) of typically developing children matched to the syndrome groups on developmental level (mental age) and on chronological age. At first glance the findings indicated general weaknesses across both verbal and visual memory skills that were not syndrome specific but suggestive of developmental delay. However, closer inspection revealed that the impairment of the group with fragile X syndrome relative to that of the Down syndrome group was significantly larger on tasks that tapped visuospatial memory skills than for tasks that tapped verbal memory skills. In comparison to boys with fragile, few studies have addressed working memory in affected girls and those that have focused almost exclusively on adult women. However, two recent studies by Mazzocco and colleagues highlight difficulties in working memory thresholds that also include a specific deficit in visual memory (Mazzocco, Bhatia, & Lesniak-Karpiak, 2006; Kirk, Mazzocco, & Kover, 2005). Less than 53% of affected girls (compared to 96% of typically developing females) were able to recreate the gestalt of a design by memory even though they could correctly identify the object. This finding lends some support to a tentative hypothesis that visuospatial impairment may be a defining feature of the phenotype in both boys and girls irrespective of degree of intellectual impairment. However, one must



show some caution here in giving the impression that visual memory is a global person with weakness in fragile X syndrome. Variability, especially in the female phenotype, is inevitable, and studies of adult women have reported visual memory skills that are within the normal range (Mazzocco, Pennington, & Hagerman, 1993).

**Visual–Motor Coordination** Another striking aspect of fragile X syndrome is the observed visuomotor deficits. In affected boys, there have been several reports of sensorimotor integration difficulties and visual–motor impairments (Busca Safont Tria, 2001; Cornish et al., 1999; Freund & Reiss, 1991). At a finer level of analysis, a number of recent neuropsychological studies have revealed lacunae in performance for tasks requiring the integration of visual information for effective motor control. For example, Cornish et al. (1999) recently demonstrated impairments in boys with fragile X syndrome (ages between 7 and 12 years) as compared to typical developing boys matched on developmental level for abstract visuoconstructive tasks, such as the Block Design subtest of the Wechsler Intelligence Scale for Children—Revised, and on a task of drawing (Draw-a-Person task). In contrast, these same boys did not show impairments in their performance on neuropsychological tasks that measure visuo perceptual abilities. A similar pattern of performance has been reported in girls with fragile X (Cornish et al., 1998). In contrast, relative strengths have been reported on visuo perceptual tasks and face recognition tasks (Hodapp et al., 1992; Cornish et al., 1999; Turk & Cornish, 1998). One possible explanation for this dissociation has come from a series of recent neurobiological studies by Kogan and colleagues (e.g., Kogan, Boutet et al., 2004; Kogan, Bertone et al., 2004) that speculate that fragile X syndrome is associated with selective deficits in magnocellular/dorsal stream visual functioning that result in an underlying impairment in regions of the brain devoted to processing visual information for the purpose of control of action. In contrast, the parvocellular/ventral stream is a transformer of visual input necessary for the conscious perception of visual information (e.g., color and recognition). Because fragile X syndrome is caused by a single gene, Kogan, Boutet et al. (2004) proposed that the protein normally expressed by the FMR1 gene and lacking in protein (FMRP) might be more important to normal magnocellular (M) neuron function or structure than parvocellular (P) function. Indeed, postmortem analyses did reveal FMRP to be expressed in greater abundance in the M pathway of monkey and human brains, suggesting that this pathway is more reliant on the protein for normal functioning. In contrast, postmortem analyses of an adult with fragile X syndrome revealed abnormal neuromorphology of LGN neurons such that they appear more like P neurons than M neurons. Kogan et al. concluded that abnormal visual–motor behavior in fragile X syndrome can be partially attributed to an M pathway deficiency in FMRP. These findings highlight the need for medical and pedagogical treatment to focus on improving early visual–motor coordination.

**Number Processing** Both boys and girls with fragile X syndrome experience considerable difficulty in acquiring math skills irrespective of academic attainment. Early work by Dykens and colleagues (e.g., Dykens, Hodapp, & Leckman, 1987; Hodapp, Dykens, Ort, Zelinsky, & Leckman, 1991) using the Kaufman Assessment Battery for Children (Kaufman & Kaufman, 1983) identified a specific deficit in arithmetic in boys with fragile X syndrome compared to the performance of boys with Down syndrome and typically developing children. Similar findings were also reported by Kemper, Hagerman, and Altshul-Stark (1988). Together, these findings suggest that poor arithmetic skills in boys with fragile X syndrome may not solely be attributed to general developmental delay but may be syndrome specific. More recent work has begun to define the math profile at a finer grained level. Roberts et al. (2005), for example, did not find a relative deficit in math skills in boys ages 3–14 years when the math problem was put into a meaningful context rather than requiring an abstract calculation. This finding is the first to suggest that context may place a crucial role in math development in boys with fragile. In girls with fragile X syndrome, math achievement is also an area of considerable difficulty, and problems have been reported as early as 5 years of age (Mazzocco, 2001). When present, the math difficulties are almost always persistent and thus do not diminish over time (Murphy, Mazzocco, Gerner, & Henry, 2006). Recent studies, however, highlight the variability in math performance among girls with fragile X by suggesting that not all math skills are comparably impaired. In the most recent study to date, Mazzocco et al. (2006) examined math performance in 15 girls with fragile X syndrome, 15 girls with Turner syndrome (a disorder that is caused by the partial or total loss of an X chromosome), and 15 IQ-matched comparison children (7–9 years of age). Although they found that girls with fragile X syndrome had a specific weakness on measures that tapped both formal, learned math (such as the procedures used in addition algorithms) and informal, intuitive math (recognizing which of two sets of items has more items), the impairment of the group with fragile X relative to that of the comparison group for tasks that required basic counting or calculating skills did not reach significance. When Mazzocco and colleagues (Murphy et al., 2006) examined counting skills more closely, they found that girls with fragile X had difficulty understanding counting rules and applications of counting knowledge, whereas rote counting skills were comparable to skills observed in an age- and grade-matched comparison group. Thus, while mathematics difficulties in girls with fragile X may not pertain to all aspects of mathematics, the persistence and nature of these difficulties suggest that mathematics achievement is likely to pose lifelong challenges and should thus be monitored periodically to determine appropriate educational support.

**Attention** Impairments in attentional focus alongside excessive distractibility and poor inhibitory control are well documented characteristics of both boys and girls

with fragile X (see Cornish et al., 2004, for a review). Although the majority of research has focused on late childhood, recent evidence suggests that attention difficulties emerge early in development: Hooper, Hatton, Baranek, Roberts, and Bailey (2000) showed that children with fragile X from 4 years of age display striking difficulties in attention and memory subscales of the Leiter International Performance Scale Revised (Leiter-R; Roid & Miller, 1997), a nonverbal assessment tool. In a series of recent studies, Scerif, Cornish, and Karmiloff-Smith have demonstrated even earlier difficulties in the control of attention in children with fragile X as young as 12 months of age (Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004; Scerif et al., 2005; Cornish et al., in press). These studies aimed at tracing developmental trajectories of attentional control in children with fragile and in typically developing groups. While typically developing toddlers displayed gradual improvements in the accuracy with which they searched their visual environment, toddlers with fragile X tended to perseverate and were unable to shift attention away from previously correct responses, regardless of their overall developmental level. These findings replicate the pattern of difficulties seen in older boys (ages 7–12 years; Wilding, Cornish, & Munir, 2002) and in young adult men (ages 18–30 years; Cornish, Munir, & Cross, 2001). Similar difficulties in attention switching in girls with fragile X (ages 8–16 years) have also been reported (Kovar, 1993). Thus, difficulties in perseveration and in shifting attentional focus are core deficits in fragile X syndrome and appear to remain constant with age. In contrast, the ability to select relevant from irrelevant information (selective attention) is a relative strength at least in males with fragile X and this continues to develop linearly with increasing chronological age (Cornish et al., in press). Comparable developmental studies in females are needed to understand the range of attention dysfunction and its relation with age and IQ. To date, however, the current findings underscore the importance of recognizing and treating early attention deficits that left untreated will impact significantly across development and learning.

### **The Importance of Recognizing Comorbidities in Fragile X Syndrome and Their Impact on Early Identification**

The child with fragile X syndrome and ADHD, alone or as part of an autism spectrum disorder, may display motor overactivity (sometimes seen as aimless activity or exploration), inability to concentrate or focus, distractibility, and inability to inhibit impulses (see section above). To some extent, these behaviors overlap with those seen in children with anxiety disorders, making it difficult to distinguish between them. The child with an anxiety disorder may have any or all of these symptoms, plus difficulty sleeping, obvious fright in some situations, signs of autonomic arousal not seen in ADHD (flushing, pallor, tachypnea [rapid breathing], tachycardia [rapid

pulse], diaphoresis [sweating]), or frank panic episodes (sudden panicky running, aggression, or self-injury accompanied by signs of autonomic arousal). Both ADHD and anxiety disorders are part of the behavioral phenotype of fragile X syndrome, and it is possible for a child to have both ADHD and an anxiety disorder, evolving separately or together, making complete treatment a matter of a combined approach. Likewise, autistic-like features or a diagnosis of an autism spectrum disorder may precede an initial diagnosis of fragile X syndrome. DNA testing for fragile X is therefore an important part of the evaluation of any child with an autism spectrum disorder, and any child with ADHD, panic disorder, generalized anxiety disorder, and a maternal family history of developmental, learning, or anxiety disorders.

## **Interventions**

### **Nonmedical Interventions**

As with any disability, whether physical or cognitive, the sooner the child enters into early intervention the better. Some of the early symptoms of fragile X syndrome such as hypotonia, physical delays, oral motor difficulties, and speech delay can be addressed through speech and language therapy, oral motor therapy and occupational therapy. For instance, through oral motor therapy, boys or girls will learn how to eat more efficiently and produce language sounds. If the child has difficulty attaining motor milestones, physical and occupational therapy may assist in the acquisition of important daily living skills. Speech therapy will help the child to learn social interactive skills and to acquire vocabulary and syntax while the speech apparatus matures to the point that language sounds can be produced. It has been the experience of the fragile X community that combining therapies often produces beneficial results—that is, having the speech and language therapist use sensory motor techniques to calm the child while teaching language; similarly, the occupational therapist should encourage as much verbalization and communication as possible while teaching sensory techniques.

Many young boys and girls children with fragile X syndrome have difficulty with transitions, sensory stimulation, and hyperarousal (see above). These difficulties can manifest as behavior problems such as noncompliance, aggression, or tantrumming. Very often, a careful analysis of the environment within which the child is interacting can give clues as to both the reasons for the child's actions and appropriate remedies for the child's behavior. For instance if confronted with a visually and auditorily stimulating environment, the child may become uncomfortable. The easiest solution is to reduce the stimulation and place the child in a less stimulating place. Of course, preschools and elementary schools can be loud and youngsters cannot be asked to be quiet all the time. At those times when the environment does become loud, it will be

important that the child have a quiet place to go or something he can do (e.g., put on earmuffs or sun glasses if tolerated) to help reduce the sensory stimulation. As the child gets older, when the teachers or parents know that the environment is going to become too overwhelming, the child should be allowed to go someplace safe and quiet (i.e., bedroom or library) to avoid the environment that may cause difficulties. Additionally, it will be important to give the child an awareness of what will and will not cause discomfort and support teaching the child effective strategies to cope with the environment. In this regard sensory integration techniques may be beneficial throughout the child's tenure in school. Transitions can be especially troublesome individuals with fragile X syndrome. Visual aids, sensory motor integrative techniques, and preparation for the transition can all be helpful tools to assist the child as he transitions through the day.

Individuals with fragile X syndrome are often misunderstood. The influence of the environment on their behavior is often overlooked. In addition, anticipatory anxiety, which is the awareness that some activity is looming, often influences behavior in individuals with fragile X (by causing either perseverative language or noncompliance) and is usually not appreciated. Often, all it takes to understand what is bothering the individual is to listen to the individual, who may tell you through perseverative language what is anticipated. Often times behavioral techniques can be very beneficial. However, it will be important that the behaviorist who is evaluating the child and interpreting behavior of a child with fragile X syndrome is familiar with the syndrome and understands the hyperarousal and anxiety associated with social situations for children affected by fragile X.

### **Psychopharmacological Interventions**

Fragile X syndrome presents several potentially medication-responsive symptoms and comorbid psychiatric disorders. There are no drugs uniquely effective or uniquely ineffective for children with fragile X, nor are there drugs to treat the core symptoms of the syndrome itself. The targets of our available agents are common secondary disorders such as ADHD, or comorbid disorders such as anxiety disorders, or problems such as mood instability that may or may not be characteristic of fragile X but are exacerbated by it. Surveys of drug use at fragile X clinics (Amaria, Billeisen, & Hagerman, 2001; Tsiouris & Brown, 2004) show use of the wide variety of agents typical of any child psychiatric clinic or clinic for children with intellectual disabilities.

From the standpoint of the clinician, studies of these drugs, taken together, demonstrate only their safety and efficacy. A few studies have established the effectiveness of some classes of drugs in persons with fragile X syndrome (Hagerman, Murphy, & Wittenberger, 1988; Hagerman, Fulton et al., 1994; Hagerman et al., 1995). There are no studies of comparative efficacy (with a single exception: Riley,

Ikle, & Hagerman, 2000), and studies comparing one drug approach to another for a particular symptom or disorder are rare and almost never include persons with intellectual disabilities. The clinician is left to choose treatment from a catalog of agents, based upon psychiatric diagnosis and individual patient variables. Within classes of drugs (mood stabilizers, SSRIs) there is little to help the clinician choose among available agents. Even in the rare instances of comparative efficacy studies, only one has included patients with fragile X syndrome (Riley et al., 2000). The best guide to effective treatment is accurate diagnosis of the psychiatric symptom or comorbid disorder. Drug responsive components of the behavioral phenotype of fragile X syndrome—ADHD, obsessive–compulsive features of autism spectrum disorders, generalized anxiety disorder, panic disorder, PTSD, major depressive disorder, and bipolar disorder—can all be recognized from their effects on behavior, autonomic arousal, level of activity, and sleep and appetite (Levitas, Hurley, & Pary, 2001; Levitas & Silka, 2001). Family history of psychiatric disorder can be a guide to diagnosis, even within the behavioral phenotype of fragile X syndrome.

As important as diagnosing psychiatric disorder is ruling it out; isolated problem behaviors might proceed from environmental variables (inappropriate school setting or other demand, overstimulation or particular noxious events for a person with hyperarousal problems—e.g., fire drills—unfortunate family events, abuse, and other trauma) or may simply be based on hyperarousal. Many endocrine and neurological disorders have behavioral manifestations, and these must be ruled out as well. Such isolated behaviors are very unlikely to respond to medication or to medication alone. Family history of drug response may be a guide to choice of pharmacologic agent, but two family members might have completely different responses to the same drug. In the end, these may be guides to no more than a first choice of medication for trial, with many trials being necessary to establish the optimal treatment, or, more usually, a treatment that is “good enough” to allow the child and family to proceed with development.

**Case 3.2: Ian** Ian is a 9-year-old boy with fragile X syndrome, referred for evaluation for possible ADHD. Until fourth grade he had been in a special class setting; he was now in a self-contained classroom with mainstreaming for some subjects, but was severely language impaired. Ian required repeated redirection to focus on classroom work, even with minimal demand and distraction. Motor overactivity was not severe. He showed some perseverative speech, was easily distracted, and demonstrated extreme social anxiety when meeting new people and in novel situations. Ian’s maternal family history of fragile X was well-documented. His birth weight was 8 lbs. 2 oz. As an infant, Ian cuddled and breast-fed poorly, and he showed gaze-avoidance from a very early age. Speech and language were also delayed. He continued receiving speech and occupational therapies, and in second and third grade Ian attended a school for children with communication-based learning problems. Poor attention span and distractibility were noted. He could self-calm, and he denied anxieties. At interview Ian displayed mild gaze avoidance but was personable and outgoing. He acknowledged difficulty concentrating and ignoring distractions and was willing to consider a trial of medication for this. Diagnosis was ADHD.

**Intervention** As stated above, ADHD is frequently documented in children with fragile X and can impact across many domains of learning and behavior both at home and school. In Ian's case, this child had already acquired some very important skills, such as self calming—which is very important in children with fragile X. It would be important to make Ian aware of those environmental and social variables that cause him to be uncomfortable. If, for instance, Ian has a school peer who makes a lot of noise (causing him to lose focus), he should learn how to ask for quiet. To that end, role play would be a very useful tool. Ian could practice routines that he would need in his everyday life. Once these verbal routines were practiced, he would then be able to access them when needed.

Role play may also help Ian with his language difficulties, as it would supply him with practiced routines which he could use when needed. The task of having to create language when anxious or upset usually results in repetitive or dysfluent language in individuals with fragile X. Ian would also benefit greatly from social skills training. To that end, Carol Gray stories are a very helpful component in that social skills training, as they are designed to build social awareness and help children learn social routines. Carol Gray first defined social stories in 1991. In her way of thinking, social stories address the needs of individuals with difficulties in understanding the social milieu within which they find themselves. There are four types of sentences found within social stories, each designed to help the reader understand the story, how the protagonist may feel, and how to act when confronted with a similar situation. For example, the social story is written with descriptive sentences that are truthful, opinion- and assumption-free statements of fact; perspective sentences refer to or describe a person's internal states; directive sentences help the reader find ways of responding or acting; and affirmative sentences enhance the meaning of the story by expressing the value structure of a given culture (Gray, 2000). These stories can not only be enjoyable but also help the child with social skills deficits begin to understand how to act in socially acceptable ways.

Ian may also benefit from continued occupational therapy until he has attained age-appropriate daily living skills and handwriting ability. Also the sensory motor techniques that he learns may be used when Ian begins to feel overwhelmed and overloaded in his classroom.

Ian's teachers should provide him with visual aids whenever possible. These visual aids will assist with concentration and take some of the burden of school tasks off his auditory memory. A visual chart can also be created for the child so he can know what is expected of him at any given time. Once a task is completed, Ian can have the pleasure of taking the visual symbol of that task and placing it in a completed pile. He would also know what to go on to next. Visual aids can also be used to prompt the child through tasks. Children with ADHD have difficulty organizing their time; thus, these visual aids will be the external organizer the child needs in order to complete his work.

From a *medical perspective*, a stimulant should be tried; methylphenidate/Ritalin first; Dexedrine mixed salts/Adderall or Dexedrine could be tried if Ritalin proves ineffective, or an  $\alpha$ -adrenergic if stimulants are poorly tolerated. Standard preparations should be tried first, in divided doses; these can be converted to long-acting preparations (Concerta, Adderall-XR) if desired.

**Case 3.3: Jeremy** Jeremy was a 5-year-old boy referred for evaluation of aggressive episodes. He was described as “always going a hundred miles an hour,” with distractibility and impulsivity. Episodes were precipitated by unwanted limits or interactions with siblings, transitions, or even pleasurable excitement, and consisted of screaming, crying, and various forms of self-injury or assault, usually on brother. Jeremy slept poorly, waking at least twice every night, and at 5 a.m. for the day. DNA testing revealed  $CGG > 200$  at 36 months. Jeremy’s mother’s pregnancy was medically unremarkable, with labor induced at 40 weeks’ gestation. His birth weight was 6 lbs., 15 oz., with Apgars 8/9. He was gaze avoidant and did not cuddle. Jeremy walked at 14 months, with toe walking, hand flapping, and other stereotypy. He ignored toys except to line them up or throw them, ignored peers, and exhibited hyperacusis. He began speech therapy at 19 months, finally speaking at 36 months; speech was a mix of communication and echolalia. Short attention span was noted in school and home. Jeremy’s speech therapist noted that he greeted her with a mix of approach and anxious withdrawal, displaying “cluttering” in his speech. He rapidly explored her office, playing briefly and indiscriminately with both toys and office equipment. The diagnosis was autistic disorder, with comorbid ADHD.

**Intervention** Many children with fragile X syndrome exhibit autistic-like behaviors similar to those described above. Many of the techniques that work with children with autism without fragile X will also be successful with Jeremy. These techniques include speech and language therapy, Applied Behavioral Analytic therapy and occupational therapy. However, it will be important for those individuals who work with this child to appreciate the differences between a child with autistic disorder and fragile X and a child with autistic disorder without fragile X. For instance, the child with only autistic disorder will not have the same response to the stimulation in his environment as the child with fragile X. The sensory stimulation may cause the child with autism but without fragile X to be distracted or not pay attention, whereas the sensory stimulation may cause the child with a dual diagnosis of autism and fragile X syndrome to become hyperaroused and therefore engage in maladaptive behaviors. It is likely that using only behavioral techniques to stop these maladaptive behaviors without “fixing” the environmental problems would not be effective in changing Jeremy’s behavior.

Additionally, it is traditional to teach children with autism to maintain eye contact so that the child can focus and learn language. One would not want to encourage a child with fragile X syndrome to maintain eye contact. The maintenance of eye contact is aversive for the child as has been described above. The forcing of eye contact could also induce maladaptive behavior in the child with fragile X.



From a *medical perspective*, treatment must begin with consideration of which set of symptoms appears most in need of remediation and which medications type is most likely to be tolerated by the patient. Stimulants and a-adrenergics used for ADHD are better tolerated by younger children than are the SSRIs used to treat anxiety disorders; a-adrenergics may decrease anxiety by decreasing hyperarousal. Often a good strategy when both problems are present is to start by treating hyperactivity and adding an SSRI if necessary, bearing in mind the necessity to monitor cardiac side effects when a-adrenergics and SSRIs are used together.

## Conclusion

Infants and children with fragile X syndrome represent a unique constellation of strengths and difficulties that impact across developmental time, affecting both cognitive and behavioral functioning. The last decade has seen tremendous advances in our understanding of this syndrome and its variability across many different levels—the genetic level, the brain level, and the cognitive and behavioral levels. Most recently, the role of environmental influences in helping define the “fragile X syndrome signature” has been explored (Hessl et al., 2001; Kuo, Reiss, Freund, & Huffman, 2002). Together, these advances highlight the importance of recognizing the distinct phenotypic outcomes that characterize a child with fragile X syndrome. They provide a multidisciplinary approach to investigating the developmental, cognitive, and behavioral symptoms of fragile X and to a recognition that the syndrome may co-occur with more common disorders such as ADHD and autism. Early diagnosis is crucial if educational and clinical interventions are to have maximum impact in enabling children with fragile X syndrome to develop to their maximum potential.

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## References

- Abbeduto, L., Murphy, M. M., Cawthorn, S. W., Richmond, E. K., Weissman, M. D., Karadottir, S., et al. (2003). Receptive language skills of adolescents and young adults with Down or fragile X syndrome. *American Journal on Mental Retardation*, *108*, 149–160.
- Achenbach, T. M. (1991). *Manual for the Child Behaviour Checklist/4-18*. Burlington: University of Vermont, Department of Psychiatry.

- Amaria, R. N., Billeisen, L. L., & Hagerman, R. J. (2001). Medication use in fragile X syndrome. *Mental Health Aspects of Developmental Disabilities, 4*, 143–147.
- Bailey, D. B., Jr., Hatton, D. D., Mesibov, G., Ament, N., & Skinner, M. (2000). Early development, temperament, and functional impairment in autism and fragile X syndrome. *Journal of Autism and Developmental Disorders, 30*, 49–59.
- Bailey, D. B., Jr., Hatton, D. D., Skinner, M., & Mesibov, G. B. (2001). Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome. *Journal of Autism and Developmental Disorders, 31*, 65–174.
- Bailey, D. B., Jr., Mesibov, G. B., Hatton, D. D., Clark, R. D., Roberts, J. E., & Mayhew, L. (1998). Autistic behavior in young boys with fragile X syndrome. *Journal of Autism and Developmental Disorders, 28*, 499–508.
- Bakker, C. E., Otero, Y. D., Bonteko, C., Raghoe, P., Luteijn, T., Hoogeveen, A. T., et al. (2000). Immunocytochemical and biochemical characterization of FMRP, FXR1P, and FXR2P in the mouse. *Experimental Cell Research, 258*, 162–170.
- Bardoni, B., Mandel, J. L., & Fisch, G. S. (2000). FMR1 gene and fragile X syndrome. *American Journal of Medical Genetics, 97*, 153–163.
- Baumgardner, T. L., Reiss, A. L., Freund, L. S., & Abrams, M. T. (1995). Specification of the neurobehavioral phenotype in males with fragile X syndrome. *Pediatrics, 95*, 744–752.
- Bear, M. F., Huber, K. M., & Warren, S. T. (2004). The mGluR theory of fragile X mental retardation. *Trends in Neuroscience, 27*, 370–377.
- Belser, R. C., & Sudhalter, V. (1995). Arousal difficulties in males with fragile X syndrome: A preliminary report. *Developmental Brain Dysfunction, 8*, 252–269.
- Belser, R. C., & Sudhalter, V. (2001). Conversational Characteristics of Children with Fragile X Syndrome: Repetitive Speech. *American Journal on Mental Retardation, 106*, 28–38.
- Bennetto, L., & Pennington, B. F. (2002). Neuropsychology. In R. J. Hagerman, & P. J. Hagerman (Eds.), *Fragile X syndrome: Diagnosis, treatment, and research* (pp. 206–248). Baltimore: Johns Hopkins University Press.
- Borghgraef, M., Frons, J. P., Dielkens, A., Pyck, K., & Van Den Berghe, H. (1987). Fragile X syndrome: A study of the psychological profile in 23 prepubertal patients. *Clinical Genetics, 32*, 179–186.
- Busca Safont-Tria, N. (2002). Psychomotricity and fragile X syndrome. *Revista de Neurologia, 33* (Suppl. 1), S77–S81.
- Cohen, I. L. (1995). Behavioral profiles of autistic and nonautistic fragile X males. *Developmental Brain Dysfunction, 8*, 252–269.
- Cohen, I. L., Sudhalter, V., Pfadt, A., Jenkins, E. C., Brown, W. T., & Vietze, P. M. (1991). Why are autism and the fragile X syndrome associated? Conceptual and methodological issues. *American Journal of Human Genetics, 48*, 195–202.
- Cornish, K. M., Munir, F., & Cross, G. (1998). The nature of the spatial deficit in young females with fragile-X syndrome: A neuropsychological and molecular perspective. *Neuropsychologia, 11*, 1239–1246.
- Cornish, K. M., Munir, F., & Cross, G. (1999). Spatial cognition in males with fragile X syndrome: Evidence for a neuropsychological phenotype. *Cortex, 35*, 263–271.
- Cornish, K. M., Munir, F., & Cross, G. (2001). Differential impact of the FMR-1 full mutation on memory and attention functioning: A neuropsychological perspective. *Journal of Cognitive Neuroscience, 13*, 1–7.
- Cornish, K., Munir, F., & Wilding, J. (2001). A neuropsychological and behavioural profile of attention deficits in fragile X syndrome. *Revista de Neurologia, 33* (Suppl. 1), S24–S9.
- Cornish, K., Scerif, G., & Karmiloff-Smith, A. (2007). Tracing syndrome-specific trajectories of attention across the lifespan. *Cortex*.
- Cornish, K., Sudhalter, V., & Turk, J. (2004). Attention and language in fragile X. *Mental Retardation and Developmental Disabilities Research Reviews, 10*, 11–16.

- de Vries, B. B., Halley, D. J., Oostra, B. A., & Niermeijer, M. F. (1998). Fragile X syndrome. *Journal of Medical Genetics*, 7, 579–589.
- Dykens, E. M., Hodapp, R. M., & Leckman, J. F. (1987). Strengths and weaknesses in the intellectual functioning of males with fragile X syndrome. *American Journal of Mental Deficiency*, 92, 234–236.
- Eliez, S., Blasey, C. M., Freund, L. S., Hastie, T., & Reiss, A. L. (2001). Brain anatomy, gender and IQ in children and adolescents with fragile X syndrome. *Brain*, 24, 1610–1618.
- Ferrier, L. J., Bashir, A. S., Meryash, D. L., Johnston, J., & Wolff, P. (1991). Conversational skills of individuals with fragile-X syndrome: A comparison with autism and Down syndrome. *Developmental Medicine and Child Neurology*, 33, 776–788.
- Fisch, G. S., Holden, J. J., Carpenter, N. J., Howard-Peebles, P. N., Maddalena, A., Pandya, A., et al. (1999). Age-related language characteristics of children and adolescents with fragile X syndrome. *American Journal of Medical Genetic*, 83, 253–256.
- Freund, L. S., & Reiss, A. L. (1991). Cognitive profiles associated with the fra(X) syndrome in males and females. *American Journal of Medical Genetics*, 38, 542–547.
- Freund, L. S., Reiss, A. L., & Abrams, M. T. (1993). Psychiatric disorders associated with fragile X in the young female. *Pediatrics*, 91, 321–329.
- Galvez, R., & Greenough, W. T. (2005). Sequence of abnormal dendritic spine development in primary somatosensory cortex of a mouse model of the fragile X mental retardation syndrome. *American Journal of Medical Genetics*, 135, 155–160.
- Garrett, A. S., Menon, V., MacKenzie, K., & Reiss, A. L. (2004). Here's looking at you, kid: Neural systems underlying face and gaze processing in fragile X syndrome. *Archives of General Psychiatry*, 61, 281–288.
- Gray, C. (2000). *The new social story book*. Arlington, VA: Future Horizon.
- Hagerman, R. J. (1996). Physical and behavioral phenotype. In R. J. Hagerman & A. C. Cronister (Eds.), *Fragile X syndrome: Diagnosis, treatment and research* (pp. 3–87). Baltimore: Johns Hopkins University Press.
- Hagerman, R. J., Altshul-Stark, D., & McBogg, P. (1987). Recurrent otitis media in boys with fragile X syndrome. *American Journal of Disease of Children*, 141, 184–187.
- Hagerman, R. J., Fulton, M. J., Leaman, A., Riddle, J., Hagerman, K., & Sobesky, W. (1994a). A survey of fluoxetine therapy in fragile X syndrome. *Developmental Brain Dysfunction*, 7, 155–164.
- Hagerman, P. J., & Hagerman, R. J. (2004). The fragile X premutation: A maturing perspective. *American Journal of Human Genetics*, 74, 805–816.
- Hagerman, R. J., Hull, C. E., Safanda, J. F., Carpenter, I., Staley, L. W., O'Connor, R. A., et al. (1994b). High functioning fragile X males: Demonstration of an unmethylated fully expanded FMR-1 mutation associated with protein expression. *American Journal of Medical Genetics*, 51, 298–308.
- Hagerman, R. J., Jackson, C., Amiri, K., Silverman, A. C., O'Connor, R., & Sobesky, W. (1992). Girls with fragile X syndrome: Physical and neurocognitive status and outcome. *Pediatrics*, 89, 395–400.
- Hagerman, R. J., Murphy, M. A., & Wittenberger, M. D. (1988). A controlled trial of stimulant medication in children with the fragile X syndrome. *American Journal of Medical Genetics*, 30, 377–392.
- Hagerman, R. J., Riddle, J. E., Roberts, L. S., Brease, K., & Fulton, M. (1995). A survey of the efficacy of clonidine in fragile X syndrome. *Developmental Brain Dysfunction*, 8, 336–344.
- Hagerman, R. J., Smith, A., & Mariner, R. (1983). Clinical features of the fragile X syndrome. In R. J. Hagerman, & P. McBogg (Eds.), *The fragile X syndrome: Diagnosis, biochemistry and intervention* (pp. 17–53). Dillon, CO: Spectra Publishing.
- Hanson, D. M., Jackson, A. W., & Hagerman, R. J. (1986). Speech disturbances (cluttering) in mildly impaired males with Martin-Bell/fragile X syndrome. *American Journal of Medical Genetics*, 23, 195–206.
- Hatton, D. D., Hooper, S. R., Bailey, D. B., Skinner, M. L., Sullivan, K. M., & Wheeler, A. (2002). Problem behavior in boys with fragile X syndrome. *American Journal of Medical Genetics*, 108, 105–116.

- Hatton, D. D., Wheeler, A. C., Skinner, M. L., Bailey, D. B., Sullivan, K. M., Roberts, J. E., et al. (2003). Adaptive behavior in children with fragile X syndrome. *American Journal on Mental Retardation*, *108*, 373–390.
- Hessl, D., Dyer-Friedman, J., Glaser, B., Wisbeck, J., Barajas, R. G., Taylor, A., 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.
- Hodapp, R. M., Dykens, E. M., Ort, S. I., Zelinsky, D. G., & Leckman, J. F. (1991). Changing patterns of intellectual strengths and weaknesses in males with fragile X syndrome. *Journal of Autism and Developmental Disorders*, *21*, 503–516.
- Hodapp, R. M., Leckman, J. F., Dykens, E. M., Sparrow, S. S., Zelinsky, D. G., & Ort, S. I. (1992). K-ABC profiles in children with fragile X syndrome, Down syndrome, and nonspecific mental retardation. *American Journal on Mental Retardation*, *97*, 39–46.
- Hooper, S. R., Hatton, D. D., Baranek, G. T., Roberts, J., & Bailey, D. B. (2000). Nonverbal assessment of cognitive abilities in children with fragile X syndrome: The utility of the Leiter International Performance Scale—Revised. *Journal of Psychoeducational Assessment*, *18*, 255–267.
- Irwin, S. A., Idupulapati, M., Gilbert, M. E., Harris, J. B., Chakravarti, A. B., Rogers, E. J., et al. (2002). Dendritic spine and dendritic field characteristics of layer V pyramidal neurons in the visual cortex of fragile-X knockout mice. *American Journal of Medical Genetics*, *111*, 140–146.
- Irwin, S. A., Patel, B., Idupulapati, M., Harris, J. B., Crisostomo, R. A., Larsen, B. P., et al. (2001). Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: A quantitative examination. *American Journal of Medical Genetics*, *98*, 161–167.
- Karmiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences*, *2*, 389–399.
- Kates, W. R., Abrams, M. T., Kaufmann, W. E., Breiter, S. N., & Reiss, A. L. (1997). Reliability and validity of MRI measurement of the amygdala and hippocampus in children with fragile X syndrome. *Psychiatry Research*, *75*, 31–48.
- Kau, A. S. M., Reider, E. E., Payne, L., Meyer, W. A., & Freund, L. (2000). Early behavior signs of psychiatric phenotypes in fragile X syndrome. *American Journal on Mental Retardation*, *105*, 286–299.
- Kau, A. S. M., Tierney, E., Bukelis, I., Stump, M., Kates, W. R., Trescher, W. H., et al. (2004). Social behavior profile in young males with fragile X syndrome: Characteristics and specificity. *American Journal of Medical Genetics*, *126*, 9–17.
- Kaufman, A. S., & Kaufman, N. L. (1983). *Kaufman Assessment Battery for Children (K-ABC)*. Circle Pines, MN: American Guidance Service.
- Kemper, M. B., Hagerman, R. J., & Altschul-Stark, D. (1988). Cognitive profiles of boys with the fragile X syndrome. *American Journal of Medical Genetics*, *30*, 191–200.
- Keysor, C. S., Mazzocco, M. M. M., McLeod, D. R., & Hoehn-Saric, R. (2002). Physiological arousal in females with fragile X or Turner syndrome. *Developmental Psychobiology*, *41*, 133–146.
- Kirk, J. W., Mazzocco, M. M. M., & Kover, S. T. (2005). Assessing executive dysfunction in girls with fragile X or Turner syndrome using the Contingency Naming Test (CNT). *Developmental Neuropsychology*, *28*, 755–777.
- Kogan, C. S., Bertone, A., Cornish, K., Boutet, I., Der Kaloustian, V. M., Andermann, E., et al. (2004). Integrative cortical dysfunction and pervasive motion perception deficit in fragile X syndrome. *Neurology*, *63*, 1634–1639.
- Kogan, C. S., Boutet, I., Cornish, K., Zangenehpour, S., Mullen, K. T., Holden, J. J., et al. (2004). Differential impact of the FMR1 gene on visual processing in fragile X syndrome. *Brain*, *127*, 591–601.
- Kooy, R. F. (2003). Of mice and the fragile X syndrome. *Trends in Genetics*, *19*, 148–154.
- Kooy, R. F., Willesden, R., & Oostra, B. A. (2000). Fragile X syndrome at the turn of the century. *Molecular Medicine Today*, *6*, 193–198.
- Kovar, C. (1993). *The neurocognitive phenotype of fragile X girls*. Unpublished master's thesis, University of Denver, Denver, CO.

- Kuo, A. Y., Reiss, A. L., Freund, L. S., & Huffman, L. C. (2002). Family environment and cognitive abilities in girls with fragile-X syndrome. *Journal of Intellectual Disability Research, 46*, 328–339.
- Lachiewicz, A. M. (1992). Abnormal behavior in young girls with fragile X syndrome. *American Journal of Medical Genetics, 43*, 72–77.
- Lachiewicz, A. M., & Dawson, D. V. (1994). Behavior problems of young girls with fragile X: Scores on the Conners' Parents' Questionnaire. *American Journal of Medical Genetics, 51*, 364–369.
- Lachiewicz, A. M., Dawson, D. V., & Spiridigliozzi, G. A. (2000). Physical characteristics of young boys with fragile X syndrome: Reasons for difficulties in making a diagnosis in young males. *American Journal of Medical Genetics, 5*, 229–236.
- Lesniak-Karpiak, K., Mazzocco, M. M. M., & Ross, J. L. (2003). Behavioral assessment of social anxiety in females with Turner or fragile X syndrome. *Journal of Autism and Developmental Disorders, 33*, 55–67.
- Levitas, A., Hurley, A., & Pary, R. (2001). The mental status examination in patients with mental retardation and developmental disabilities. *Mental Health Aspects of Developmental Disabilities, 4*, 2–16.
- Levitas, A., & Silka, V. R. (2001). Mental health clinical assessment of persons with mental retardation and developmental disabilities. *Mental Health Aspects of Developmental Disabilities, 4*, 31–42.
- Mazzocco, M. M. M. (2001). Math learning disability and math LD subtypes: Evidence from studies of Turner syndrome, fragile X syndrome, and neurofibromatosis type 1. *Journal of Learning Disabilities, 34*, 520–533.
- Mazzocco, M. M. M., Baumgardner, T., Freund, L. S., & Reiss, A. L. (1998). Social functioning among girls with fragile X or Turner syndrome and their sisters. *Journal of Autism and Developmental Disorders, 28*, 509–517.
- Mazzocco, M. M. M., Bhatia, N. S., & Lesniak-Karpiak, K. (2006). Visuo-spatial deficits in fragile X or Turner's syndrome. *Child Neuropsychology, 12*, 87–110.
- Mazzocco, M. M. M., Pennington, B. F., & Hagerman, R. J. (1993). The neurocognitive phenotype of female carriers of fragile X: Additional evidence for specificity. *Journal of Developmental and Behavioral Pediatrics, 14*, 328–335.
- Merenstein, S. A., Sobesky, W. E., Taylor, A. K., Riddle, J. E., Tran, H. X., & Hagerman, R. J. (1996). Molecular-clinical correlations in males with an expanded FMR1 mutation. *American Journal of Medical Genetics, 64*, 388–394.
- Miller, L. J., McIntosh, D. N., McGrath, J., Shyu, V., Lampe, M., Taylor, A. K., et al. (1999). Electrodermal responses to sensory stimuli in individuals with fragile X syndrome: A preliminary report. *American Journal of Medical Genetics, 83*, 268–279.
- Mostofsky, S. H., Mazzocco, M. M. M., Aakalu, G., Warsofsky, I. S., Denckla, M. B., & Reiss, A. L. (1998). Decreased cerebellar posterior vermis size in fragile X syndrome: Correlation with neurocognitive performance. *Neurology, 50*, 121–130.
- Munir, F., Cornish, K. M., & Wilding, J. (2000). Nature of the working memory deficit in fragile-X syndrome. *Brain and Cognition, 44*, 387–401.
- Murphy, M. M., Mazzocco, M. M. M., Gerner, G., & Henry, A. E. (2006). Mathematics learning disability in girls with Turner syndrome or fragile X syndrome. *Brain and Cognition, 61*, 195–210.
- O'Donnell, W. T., & Warren, S. T. (2002). A decade of molecular studies of fragile X syndrome. *Annual Review of Neuroscience, 25*, 315–338.
- Philofsky, A., Hepburn, S. L., Hayes, A., Hagerman, R., & Rogers, S. J. (2004). Linguistic and cognitive functioning and autism symptoms in young children with fragile X syndrome. *American Journal on Mental Retardation, 109*, 208–218.
- Reiss, A., Alyward, E., Freund, L., Joshi, P. K., & Bryan, R. N. (1991). Neuroanatomy of fragile X syndrome: The posterior fossa. *Annals of Neurology, 29*, 26–32.
- Reiss, A. L., & Freund, L. (1992). Behavioral phenotype of fragile X syndrome: *DSM-III-R* autistic behavior in male children. *American Journal of Medical Genetics, 43*, 35–46.
- Reiss, A. L., Lee, J., & Freund, L. (1994). Neuroanatomy of fragile X syndrome: The temporal lobe. *Neurology, 44*, 1317–1324.

- Riley, K., Ikle, L. O., & Hagerman, R. J. (2000). *A randomized, double-blind comparative trial of Adderall in the treatment of attention deficit disorder in children with fragile X*. Paper presented at the Seventh International Fragile X Conference, Los Angeles, CA.
- Roberts, J. E., Boccia, M. L., Bailey, D. B., Jr., Hatton, D. D., & Skinner, M. (2001). Cardiovascular indices of physiological arousal in boys with fragile X syndrome. *Developmental Psychobiology*, *39*, 107–123.
- Roberts, J. E., Mirrett, P., & Burchinal, M. (2001). Receptive and expressive communication development of young males with fragile X syndrome. *American Journal on Mental Retardation*, *106*, 216–240.
- Roberts, J. E., Schaaf, J. M., Skinner, M., Wheeler, A., Hooper, S., Hatton, D. D., et al. (2005). Academic skills of boys with fragile X syndrome: Profiles and predictors. *American Journal Mental on Retardation*, *110*, 107–120.
- Rogers, S. J., Hepburn, S. L., Stackhouse, T., & Wehner, E. (2003). Imitation performance in toddlers with autism and those with other developmental disorders. *Journal of Child Psychology and Psychiatry*, *44*, 763–781.
- Roid, G. H., & Miller, L. J. (1997). *Leiter International Performance Scale—Revised*. Wood Dale, IL: Stoelting.
- Scerif, G., Cornish, K., Wilding, J., Driver, J., & Karmiloff-Smith, A. (2004). Visual search in typically developing toddlers and toddlers with fragile X or Williams syndrome. *Developmental Science*, *7*, 116–130.
- Scerif, G., Karmiloff-Smith, A., Campos, R., Elsabbagh, M., Driver, J., & Cornish, K. (2005). To look or not to look? Typical and atypical development of oculomotor control. *Journal of Cognitive Neuroscience*, *17*, 591–604.
- Simon, E. W., & Finucane, B. M. (1996). Facial emotion identification in males with fragile X syndrome. *American Journal of Medical Genetics*, *67*, 77–80.
- Skinner, M., Hooper, S., Hatton, D. D., Robert, J., Mirrett, P., Schaaf, J., et al. (2005). Mapping nonverbal IQ in young boys with fragile X syndrome. *American Journal of Medical Genetics*, *132A*, 25–32.
- Sparrow, S., Balla, D., & Cicchetti, D. (1984). *Vineland Adaptive Behavior Scales*. Circle Pines, MN: American Guidance Service.
- Sudhalter, V., & Belser, R. (2001). Conversational characteristics of children with fragile X syndrome: Tangential language. *American Journal on Mental Retardation*, *106*, 389–400.
- Sudhalter, V., Cohen, I. L., Silverman, W., & Wolf-Schein, E. G. (1990). Conversational analyses of males with fragile X, Down syndrome and autism: A comparison of the emergence of deviant language. *American Journal on Mental Retardation*, *94*, 431–442.
- Sudhalter, V., Scarborough, H., & Cohen, I. L. (1991). The syntactic delay and pragmatic deviance of the language of fragile X males. *American Journal of Medical Genetics*, *38*, 493–497.
- Taylor, E., Schachar, R., & Hepstinall, E. (1993). *Manual for Parental Account of Childhood Symptoms Interview*. London: Maudsley Hospital.
- Theobald, T. M., Hay, D. A., & Judge, C. (1987). Individual variation and specific cognitive deficits in the fragile X syndrome. *American Journal of Medical Genetics*, *28*, 1–11.
- Tsiouris, J. A., & Brown, T. (2004). Neuropsychiatric symptoms of fragile X syndrome: Pathophysiology and pharmacotherapy. *CNS Drugs*, *18*, 687–703.
- Turk, J. (1998). Fragile X syndrome and attentional deficits. *Journal of Applied Research in Intellectual Disabilities*, *11*, 175–191.
- Turk, J., & Cornish, K. (1998). Face recognition and emotional perception in boys with fragile X syndrome. *Journal of Intellectual Disability Research*, *42*, 490–499.
- Turk, J., Robbins, I., & Woodhead, M. (2005). Post-traumatic stress disorder in young people with intellectual disability. *Journal of Intellectual Disability Research*, *49*, 872–875.
- Turner, G., Webb, T., Wake, S., & Robinson, H. (1996). Prevalence of fragile X syndrome. *American Journal of Medical Genetics*, *64*, 196–197.
- Ullman, R. K., Sleator, E. K., & Sprague, R. L. (1984). A new rating scale for diagnosis and monitoring of ADD children. *Psychopharmacology Bulletin*, *20*, 160–164.

Veenema, H., Veenema, T., & Geraedts, J. P. M. (1987). The fragile X syndrome in a large family: Two psychological investigations. *Journal of Medical Genetics, 24*, 32–38.

Verkerk, A., Pieretti, M., Sutcliffe, J. S., Fu, Y. H., Kuhl, D. P., Pizzuti, A., et al. (1991). Identification of a gene (FMR-1) containing a CGG repeat coincident with a break-point cluster region exhibiting length variation in fragile X syndrome. *Cell, 65*, 905–914.

Wilding, J., Cornish, K., & Munir, F. (2002). Further delineation of the executive deficit in males with fragile X syndrome. *Neuropsychologia, 40*, 1343–1349.

Wisniewski, K. E., Segan, S. M., Mizejeski, C. M., Sersen, E. A., & Rudelli, R. D. (1991). The fra(X) syndrome: Neurological, electrophysiological and neuropathological abnormalities. *American Journal of Medical Genetics, 38*, 476–480.

Wolff, P. H., Gardner, J., Paccia, J., & Lappen, J. (1989). The greeting behavior in fragile X males. *American Journal on Mental Retardation, 93*, 406–411.