

# Fragile X Syndrome: Assessment and Treatment Implications

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Fragile X syndrome (FraX) is the most common known cause of inherited mental impairment. *FMR1* gene mutations, the cause of FraX, lead to reduced expression of *FMR1* protein (FMRP) and an increased risk for a particular profile of cognitive, behavioral, and emotional dysfunction. Because of the similarity of these features to important (idiopathic) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses, the study of individuals with FraX provides a unique window of understanding into important disorders such as autism, social phobia, cognitive disability, and depression. The study of FraX also is a portal to the realization of innovative interdisciplinary research that spans multiple clinical and basic scientific domains [1]. Such research provides new insights into understanding how genetic and environmental factors contribute to complex variations in typical and atypical human behavior [1,2].

## Genetics

FraX occurs in approximately 1 in every 4000 live births. The syndrome arises from the disruption in expression of the fragile X mental retardation gene 1 (*FMR1*), most commonly caused by amplification of a CGG repeat in the 5' untranslated region. Physical manifestations associated with the syndrome include macroorchidism, long face, large ears, prominent jaw, and mild features of connective tissue dysplasia, such as joint hyperextensibility, soft skin, and mitral valve prolapse. External physical features are not

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always reliable indicators of the presence of the condition, however, particularly in prepubertal children and women.

In 1991, Verkerk and colleagues [3] reported that a single gene on the X chromosome, *FMRI*, was associated with the symptoms of FraX. Subsequently, it was determined that persons with FraX showed dramatically increased numbers of triplet CGG repeats in the 5' untranslated region of the first exon of *FMRI* on the long arm of the X chromosome (locus Xq27.3). FraX is one of several disorders caused by a dynamic gene mutation resulting in instability and subsequent expansion of trinucleotide repeats through generations. In normal alleles, the CGG repeats vary from 6 to 50, whereas expansions of approximately 50 to 200 repeats are associated with the "premutation" form of the gene seen in carrier women and men. Larger expansions of more than 200 (up to several thousand) CGG repeats are considered "full mutations" and typically are associated with excessive methylation of cytosines in the *FMRI* promoter region. This modification extinguishes transcription of the *FMRI* gene into mRNA, stopping translation of the fragile X mental retardation protein (FMRP) (Fig. 1).

### Cognition and behavior

Studies from our laboratory and others indicate that the most common problem behaviors observed in FraX consist of attentional dysfunction and hyperactivity, hyperarousal, disturbance in language/communication, and social anxiety (see Ref. [1] for a recent review). In boys, problematic behaviors often take the form of social deficits with peers, qualitative abnormalities in communication, unusual responses to sensory stimuli, stereotypic behavior, self-injurious behavior (SIB), aggression, social avoidance, gaze aversion, inattention, impulsivity and hyperactivity. Girls with FraX also seem to exhibit high rates of emotional disturbance and maladaptive behaviors, including problems with depression, social anxiety, and withdrawal and attention deficit [4–10]. Adolescents and women with

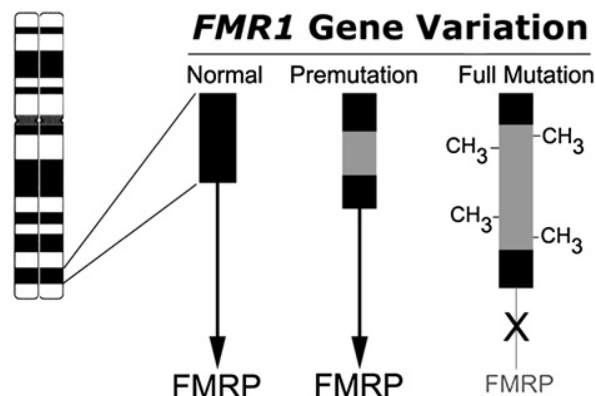


Fig. 1. *FMR1* gene variations in FraX. Methylation of the gene in the full mutation leads to a significant reduction in FMRP levels.

the FraX full mutation are at high risk for major depression as well as anxiety and manifest abnormalities in social interaction and communication [11–16].

Individuals with FraX also are predisposed to manifesting a particular profile of intellectual strengths and weaknesses. This profile is similar in quality for both genders, although girls/women typically function at a much higher overall intellectual level and manifest less severe deficits than do boys/men. The characteristic cognitive profile includes weaknesses in attentional/executive function, visual memory and perception, mental manipulation of visual–spatial relationships among objects, visual–motor coordination, processing of arithmetical stimuli, and theory of mind and relative strengths in verbal-based skills.

Until recently, our understanding of cognitive and behavioral development in individuals with FraX was based primarily on cross-sectional studies [17–19] or a small number of longitudinal investigations that were limited by small sample size, broad age range, widely varying time intervals between assessments, or retrospective design [20–23]. These early studies suggested that, with respect to same aged peers, individuals with FraX showed a slowed developmental trajectory, a phenomenon believed to contribute to the observation of declining standardized IQ and adaptive behavior scores in affected individuals.

More recently, data from large prospective longitudinal investigations of preschool and school-age children with FraX have begun to appear [24–29]. Results from these studies have begun to elucidate the progression of cognitive function, academic skills, and adaptive and autistic behaviors in children with FraX ranging in age from 12 months to 14 years. Overall, results from these studies support the hypothesis that children with FraX are not losing skills over time, but rather have difficulty maintaining a developmental trajectory similar to age-matched peers [29]. These studies also have begun to clarify the effects of FMRP levels and autistic behavior on cognitive, academic, and adaptive behavioral development [27–29]. Overall, the presence of autistic behavior is related to poorer outcome. Developmental strengths in young children with FraX occur in domains related to general knowledge and daily living skills, whereas weaknesses are observed in socialization, communication, and visual–spatial processing.

Although increasing numbers of studies are emerging regarding development in young children with FraX, prospective, longitudinal and even cross-sectional data addressing issues of development in later adolescence and early adulthood are extremely limited. To the best of our knowledge, only two studies incorporating longitudinal design components have included subjects whose age extends into late adolescence or early adulthood. In one study, autistic and psychiatric symptoms were found to be stable over time in 18 boys/men aged 6 to 76 years with FraX; however, this study used nonconventional assessment instruments and retrospective chart review for some aspects of the investigation and did not include measures

of cognitive ability [30]. In a second, multicenter study, the trajectory of adaptive behavior was examined in a broad age range of children, adolescents, and adults with FraX by aggregation of already collected Vineland data across several sites. Strengths in daily living skills were observed in several age groups, whereas weaknesses were observed for the communication domain [31].

Other investigations of FraX examining adolescence and adulthood have been cross-sectional in nature. Two recent studies examining language abilities [32,33] showed that individuals with a diagnosis of FraX and autism have a lower overall nonverbal IQ and do not perform as well on receptive language or theory of mind tasks compared with individuals with FraX without autism. The results of these investigations also suggest that cognitive impairments observed in childhood continue into adolescence and young adulthood [33].

### **Brain structure and function**

Brain imaging studies establish an unambiguous link between FraX and abnormalities of brain morphology. Two recent comprehensive reviews of these findings are available and include a description of linkages among measures of anatomy, cognition, behavior, and FMRP [1,34]. In the context of overall normal brain size in individuals with FraX, disproportionate volume increases are seen in the caudate nucleus, whereas decreases are observed in the superior temporal gyrus, amygdala, and cerebellar vermis. These neuro-anatomic variations in FraX are robust, particularly those observed in the caudate, and can be linked to variation in measures of *FMR1* expression, age, cognition, and behavior. Further, results from diffusion tensor imaging show reduced fractional anisotropy within prefrontal-caudate and parietal pathways in FraX. Abnormalities in white matter connectivity, putatively related to FMRP's function in regulating axonal pathfinding [35], may further disrupt the integrity of critical neurofunctional networks involved in executive function and visual-spatial processing in FraX.

Identifiable associations among measures of FMRP, neuroanatomy, cognition, and behavior in FraX suggest that the morphologic findings described above are clinically meaningful. For example, cerebellar vermis size (reduced in FraX) is positively correlated with measures of IQ and FMRP and negatively correlated with severity of autistic behavior [10,36]. Caudate nucleus volume (increased in FraX) is negatively correlated with measures of IQ and FMRP [37]. Thus, an increasing degree of aberrant brain morphology is associated with lower IQ and FMRP and higher levels of behavioral dysfunction. In contrast, larger caudate size is associated with higher IQ for controls [37]. This suggests that increases in caudate volume in individuals with FraX reflect aberrant neuronal organization.

Despite the high prevalence of FraX as a heritable genetic disorder, detailed postmortem studies of humans are rare. Early studies pointed to

morphologic abnormalities of cortical dendritic processes [38], a finding similar to that reported in the *fMRI* knockout mouse [39,40]. More recent postmortem studies of four human brains revealed inconsistent results, with one study of two brothers with FraX reporting only mild ventricular enlargement [41]. Observations reported in the second study of two unrelated men with FraX included cellular abnormalities of the cerebellum and hippocampus, in addition to dilated lateral ventricles [42]. Quantitative histologic analyses of samples from areas shown to be morphologically abnormal in imaging studies, such as the caudate nucleus, amygdala, and superior temporal gyrus (STG), have not been performed.

Our understanding of the functional neuroanatomy of FraX has increased substantially in the last several years. Consistent with the cognitive and behavioral manifestations associated with FraX, functional MRI studies found aberrant neural patterns associated with tasks that assess visual-spatial and declarative memory [43–45], arithmetic reasoning [46], cognitive interference [47], response inhibition [48–50] (note that Ref. [48] examined response inhibition and set-shifting conditions together), gaze and face processing [51], and emotion processing. A synthesis of these fMRI results strongly support the hypothesis that the following key brain systems are particularly impaired in FraX: the fronto-striatal network underlying executive function and the STG and limbic system underlying gaze and emotion processing, with hyperactivation of the insula reflecting hyperarousal [52].

### Pharmacologic interventions

Few medication trials have been conducted to specifically target cognitive and behavioral problems in FraX. Early case reports indicating that concentration span and attention problems in FraX could be alleviated by administration of high doses of folic acid [53,54] were not proved in double-blind placebo-controlled trials [55–58]. Antidepressant and stimulant medication seem to be the most frequently prescribed classes of drug administered to children and adults with FraX [59]. In the only double-blind placebo-controlled cross-over trial of stimulant medication conducted to date, 15 children with FraX (13 boys, 2 girls), aged 3 to 11 years, received methylphenidate (0.3 mg/kg twice daily) or dextroamphetamine (0.2 mg/kg daily) for 1 week [60]. Ten of the 15 children were judged to be clinical responders on methylphenidate; however, improvements could not be demonstrated for most of the outcome measures, with only teacher ratings indicating improvement in sociability and attention. In a single-case study of a 6-year-old boy with FraX, behavior problems seemed to improve during treatment with the tricyclic antidepressant medication imipramine, but worsened when the child was administered methylphenidate [61]. Large doses of the  $\beta$ -blocker propranolol administered to a 32-year old man with FraX indicated some improvement in aggression and stereotypic behavior [62]. Finally, L-acetylcarnitine, administered at dosages of 50 mg/kg twice daily, also

was reported to be effective in reducing behavior problems in boys with FraX [63]. The low numbers of subjects treated in these studies indicate that larger double-blinded trials should be conducted before these medications can be evaluated judiciously.

More recent pharmacologic interventions have begun to target neurochemical and synaptic deficits specifically generated by the absence of FMRP. An excellent example of this new generation of study is the recent trial of the ampakine (AMPA) compound CX516, a medication that potentiates AMPA receptors in the brain [64]. These receptors play an important role in synaptic transmission; recent studies in the FMR1 knock-out mouse indicated that AMPA receptors are reduced significantly in number and activity. In a randomized, double-blind placebo-controlled trial, 24 adults with FraX (17 men and 7 women, aged 18 to 49 years) received 600 mg daily of CX516 for 1 week, and then the dosage was increased to 900 mg daily for 3 weeks. Side effects were minimal, although three individuals experienced an allergic rash to the compound and one subject did not complete the trial because of a severe rash. Although no clear improvement in cognitive or behavioral measures could be demonstrated, nine individuals who were treated with CX516 in combination with risperidone showed some improvement, suggesting that cotreatment with antipsychotics may be beneficial in some cases.

An open-label pilot study of the antigluocorticoid medication mifepristone (RU-486) was conducted recently in our laboratory. Glucocorticoid type II (GR-II) receptors are reduced significantly in hippocampal neurons in the FMR1 knockout mouse. In addition, boys/men with FraX have elevated levels of cortisol, suggesting that some of the behavioral features observed in FraX (eg, hyperarousal, hyperactivity) may result from dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis [34,65]. At high dosages (600 mg daily), mifepristone actively blocks GR-II receptors in the prefrontal cortex, causing a rapid increase in circulating cortisol by blocking the feedback loop of the HPA axis. We speculated that mifepristone could help to “reset” the normal rhythm of the HPA axis, and, thereby, cause improvements in behavioral functioning associated with HPA axis dysfunction. In an open-label trial, we administered 600 mg daily of mifepristone to eight boys and men with FraX aged 12 to 21 years. Outcome measures included the Aberrant Behavior Checklist, which parents filled out at baseline, day 7, day 14, and 2 weeks following discontinuation of the medication. Four participants developed a mild to moderate skin rash, and, as a precautionary measure, we recommended that they discontinue the medication before the scheduled 14 days (one participant on day 2 and three participants on day 10). Of the seven participants who completed at least 10 days of the trial, behavior problems improved in two participants (as evidenced by decreasing total scores on the Aberrant Behavior Checklist for child 2 and child 4; Fig. 2); however, behavior problems seemed to worsen in one participant (child 5). Therefore, it is unclear at

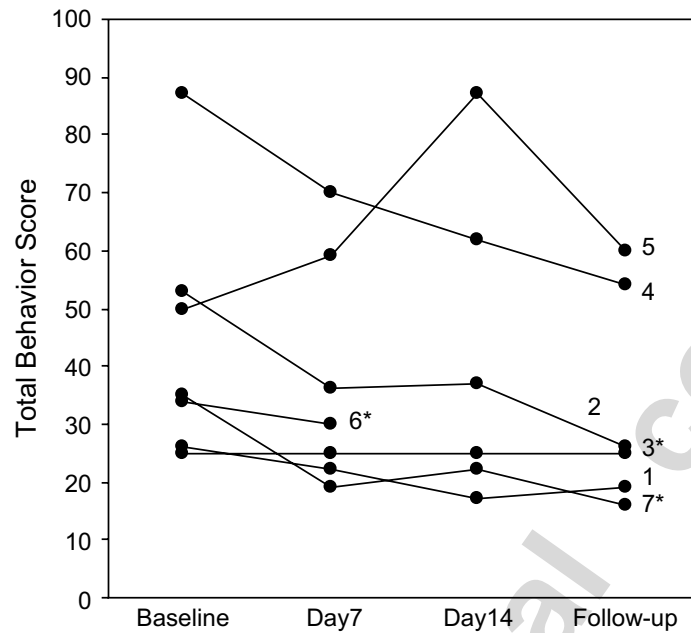


Fig. 2. Scores obtained on the Aberrant Behavior Checklist for seven children (numbered 1–7) at baseline, day 7 of mifepristone, day 14 of mifepristone, and 14 days following discontinuation of mifepristone. Children who discontinued the medication after day 10 are indicated by an asterisk.

this time whether mifepristone may be clinically useful for children with FraX. We plan to titrate the medication in a double-blind trial of mifepristone in a larger group of participants.

In summary, medication trials to specifically target symptoms of FraX are extremely limited. Although mild reduction of symptoms can be obtained in individuals with FraX who are treated with antidepressants or stimulants, there is a pressing need for new, more effective, disease-specific treatments in young children with this condition.

### Behavioral interventions

A large body of literature has emerged documenting the influence of environmental factors on behavior disorders shown by individuals with developmental disabilities [66–69]. These studies showed that many behavior disorders (eg, aggression, self-injury, and stereotypic behaviors) are influenced by antecedent and consequent social-environmental events. These environmental events include antecedent task or social demands, contingent removal of task or social demands, low levels of antecedent attention, contingent presentation of attention, changes in routines, and low levels of sensory stimulation. Manipulation of these environmental events can dramatically reduce the occurrence of these problem behaviors [70–72]. In a large sample of 152 individuals with developmental disabilities who showed self-injurious behavior (SIB), for example, Iwata and colleagues [68] found that in 64% of cases, problem behaviors were maintained by

social-environmental reinforcement contingencies (eg, removal of task demands, delivery of attention); in an additional 25% of cases, SIB was evoked by antecedent nonsocial environmental events (eg, low levels of environmental stimulation). Treatments that were matched to the function of the behavior disorder (eg, ignoring behaviors that were maintained by attention, not allowing the child to escape from social or task demands, or providing alternate forms of sensory stimulation for those behaviors maintained by sensory stimulation) were highly successful.

In a postal survey of 55 boys with FraX, aged 1 to 12 years, parents reported that 58% of the children had shown SIB at some point during their lifetime [73] and that SIB was most likely to occur following changes in routine (87%), the presentation of difficult commands (65%), or difficult tasks (61%) or to gain adult attention (3%). In our laboratory, we systematically manipulated levels of antecedent social and task demands in 114 children with FraX (74 boys and 40 girls) to determine the specific conditions under which problem behaviors in FraX were more likely to occur [74]. By comparing levels of problem behaviors observed during a face-to-face interview, silent reading, oral reading, and a singing task, we showed that problem behaviors were significantly more likely to occur in the interview and singing conditions and were significantly less likely to occur in the silent and oral reading conditions. Therefore, in children with FraX, it seems that behavior problems are maintained predominantly by social escape. Systematic exposure to social interaction (escape extinction) combined with social skills training may be an effective treatment for problem behaviors in FraX [74].

To target eye contact aversion in FraX, we recently piloted a behavioral shaping technique to increase eye contact duration [75]. To aid the shaping process, we used a percentile reinforcement schedule, a method that allows the therapist to carefully track the student's performance and progress. Six boys with FraX, aged 8 to 17 years, underwent the training in two 1-hour sessions. Three of the children required the implementation of an overcorrection procedure (ie, maintaining the child's head in an upright position) to augment the shaping process and eliminate the appearance of problem behaviors. Results showed that even in time-limited, 1-hour sessions, eye contact duration improved significantly in four of the six boys without concomitant increases in hyperarousal or behavioral problems. These data suggest that eye contact aversion, although often believed to be unamenable to change in FraX, can be improved significantly using basic behavioral shaping techniques. We did not set out to resolve this problem in the children permanently, only to show that treatment was possible. Further studies are needed to determine whether these gains can be generalized and maintained.

Thus far, interventions for individuals with FraX have not been targeted to FraX-specific skill deficits, and to date, behavioral interventions have been conducted using heterogeneous strategies, without outcome data to support their efficacy. In the behavior analytic literature, several behavioral

techniques were shown to help children with developmental disabilities improve social and educational skills. These included modeling, coaching, physical guidance, shaping, chaining, fading, matching-to-sample, and errorless learning techniques [76]. Surprisingly, we know of no published studies that have used these techniques to teach children with FraX. In our laboratory, we recently demonstrated the feasibility of teaching basic math and geography concepts to children with FraX using matching-to-sample and errorless learning techniques [77]. Five children (four boys and one girl) were taught to match decimals to fractions and states to capitals using a computerized training program. The children received hundreds of training trials conducted over 1 to 2 days in time-limited sessions on the computer. Results indicated that three of the five children successfully demonstrated knowledge of the geography relations at posttest, and four of the children successfully learned the math relations. These results suggest that some children with FraX may benefit from intensive behavioral training programs similar to those conducted for children with autism [78–80].

### Summary

Many avenues of research on FraX have flourished over the past 25 years. For example, knowledge of the molecular genetic basis of FraX has grown at a rapid pace, and animal models have been created that promise to bring new insight into the effects of FMRP on brain development [81]. Much new information about the neurobehavioral phenotype and developmental trajectory of young children with FraX also has been reported.

Although it is clear that mutations of the *FMR1* gene increase the risk for neuropsychiatric dysfunction, there remains a relative lack of knowledge of how specific neural factors mediate this risk. Information of this nature is vital to understanding the neural basis of brain dysfunction in FraX as well as being required for the judicious design and testing of new disease-specific treatments. Finally, most treatment trials in FraX have been symptom-based or derived from other disorders as opposed to being informed by FraX-specific research data.

Over the past decade, clinical neuroscience research increasingly has begun to interrogate and merge multiple levels of scientific inquiry. A particularly good example is “imaging genomics,” where data derived from assessment of genotype, neural systems, and phenotype are combined to better understand variation in human behavior [82]. Investigators also are increasingly undertaking the study of more homogenous groups in an attempt to map fundamental molecular events to specific changes in brain structure and function, and, ultimately, to cognitive-behavioral outcome. Examples include velo-cardio-facial syndrome [83], Williams syndrome [84], and Turner syndrome [85]. Behavioral neurogenetic research provides a glimpse of the future of neuropsychiatric, and more broadly, clinical neuroscience investigation—where the complex interplay between genetic risk

and environment can be appreciated, described, and elucidated more fully. Thus, although the information gained in this area will have specific benefit to persons with FraX, it also will have broader relevance to understanding how genetic-neurobiologic pathways and environmental factors modify the risk for cognitive, emotional, and behavioral dysfunction.

## References

- [1] Reiss AL, Dant CC. The behavioral neurogenetics of fragile X syndrome: analyzing gene-brain-behavior relationships in child developmental psychopathologies. *Dev Psychopathol* 2003;15(4):927–68.
- [2] Reiss A. Childhood developmental disorders. Presented at the Convergence of Neuroscience, Behavioral Science, Neurology, and Psychiatry. Scottsdale, AZ, January 2005.
- [3] Verkerk AJ, Pieretti M, Sutcliffe JS, et al. 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(5):905–14.
- [4] Freund LS, Reiss AL, Abrams MT. Psychiatric disorders associated with fragile X in the young female. *Pediatrics* 1993;91(2):321–9.
- [5] Hagerman RJ, Jackson C, Amiri K, et al. Girls with fragile X syndrome: physical and neurocognitive status and outcome. *Pediatrics* 1992;89(3):395–400.
- [6] Lachiewicz AM. Abnormal behaviors of young girls with fragile X syndrome. *Am J Med Genet* 1992;43(1–2):72–7.
- [7] Lachiewicz AM, Dawson DV. Behavior problems of young girls with fragile X syndrome: factor scores on the Conners' parent's questionnaire. *Am J Med Genet* 1994;51(4):364–9.
- [8] Lesniak-Karpiak K, Mazzocco MM, Ross JL. Behavioral assessment of social anxiety in females with Turner or fragile X syndrome. *J Autism Dev Disord* 2003;33(1):55–67.
- [9] Mazzocco MM, Baumgardner T, Freund LS, et al. Social functioning among girls with fragile X or Turner syndrome and their sisters. *J Autism Dev Disord* 1998;28(6):509–17.
- [10] Mazzocco MM, Kates WR, Baumgardner TL, et al. Autistic behaviors among girls with fragile X syndrome. *J Autism Dev Disord* 1997;27(4):415–35.
- [11] Freund LS, Reiss AL, Hagerman R, et al. Chromosome fragility and psychopathology in obligate female carriers of the fragile X chromosome. *Arch Gen Psychiatry* 1992;49(1):54–60.
- [12] Hagerman RJ, Sobesky WE. Psychopathology in fragile X syndrome. *Am J Orthopsychiatry* 1989;59(1):142–52.
- [13] Sobesky WE, Hull CE, Hagerman RJ. Symptoms of schizotypal personality disorder in fragile X women. *J Am Acad Child Adolesc Psychiatry* 1994;33(2):247–55.
- [14] Sobesky WE, Taylor AK, Pennington BF, et al. Molecular/clinical correlations in females with fragile X. *Am J Med Genet* 1996;64(2):340–5.
- [15] Thompson NM, Gulley ML, Rogeness GA, et al. Neurobehavioral characteristics of CGG amplification status in fragile X females. *Am J Med Genet* 1994;54(4):378–83.
- [16] Thompson NM, Rogeness GA, McClure E, et al. Influence of depression on cognitive functioning in fragile X females. *Psychiatry Res* 1996;64(2):97–104.
- [17] Dykens E, Leckman J, Paul R, et al. Cognitive, behavioral, and adaptive functioning in fragile X and non-fragile X retarded men. *J Autism Dev Disord* 1988;18(1):41–52.
- [18] Dykens EM, Hodapp RM, Leckman JF. Adaptive and maladaptive functioning of institutionalized and noninstitutionalized fragile X males. *J Am Acad Child Adolesc Psychiatry* 1989;28(3):427–30.
- [19] Wieggers AM, Curfs LM, Vermeer EL, et al. Adaptive behavior in the fragile X syndrome: profile and development. *Am J Med Genet* 1993;47(2):216–20.

- [20] Dykens EM, Hodapp RM, Ort S, et al. The trajectory of cognitive development in males with fragile X syndrome. *J Am Acad Child Adolesc Psychiatry* 1989;28(3):422–6.
- [21] Fisch GS, Carpenter NJ, Holden JJ, et al. Longitudinal assessment of adaptive and maladaptive behaviors in fragile X males: growth, development, and profiles. *Am J Med Genet* 1999;83(4):257–63.
- [22] Fisch GS, Carpenter NJ, Simensen R, et al. Longitudinal changes in cognitive-behavioral levels in three children with FRAXE. *Am J Med Genet* 1999;84(3):291–2.
- [23] Wright-Talamante C, Cheema A, Riddle JE, et al. A controlled study of longitudinal IQ changes in females and males with fragile X syndrome. *Am J Med Genet* 1996;64(2):350–5.
- [24] Bailey DB Jr, Hatton DD, Skinner M, et al. Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome. *J Autism Dev Disord* 2001;31(2):165–74.
- [25] Fisch GS, Simensen RJ, Schroer RJ. Longitudinal changes in cognitive and adaptive behavior scores in children and adolescents with the fragile X mutation or autism. *J Autism Dev Disord* 2002;32(2):107–14.
- [26] Hatton DD, Sideris J, Skinner M, et al. Autistic behavior in children with fragile X syndrome: prevalence, stability, and the impact of FMRP. *Am J Med Genet A* 2006;140:1804–13.
- [27] Hatton DD, Wheeler AC, Skinner ML, et al. Adaptive behavior in children with fragile X syndrome. *Am J Ment Retard* 2003;108(6):373–90.
- [28] Roberts JE, Schaaf JM, Skinner M, et al. Academic skills of boys with fragile X syndrome: profiles and predictors. *Am J Ment Retard* 2005;110(2):107–20.
- [29] Skinner M, Hooper S, Hatton DD, et al. Mapping nonverbal IQ in young boys with fragile X syndrome. *Am J Med Genet A* 2005;132(1):25–32.
- [30] Sabaratnam M, Murthy NV, Wijeratne A, et al. Autistic-like behaviour profile and psychiatric morbidity in fragile X syndrome: a prospective ten-year follow-up study. *Eur Child Adolesc Psychiatry* 2003;12(4):172–7.
- [31] Dykens E, Ort S, Cohen I, et al. Trajectories and profiles of adaptive behavior in males with fragile X syndrome: multicenter studies. *J Autism Dev Disord* 1996;26(3):287–301.
- [32] Abbeduto L, Murphy MM, Cawthon SW, et al. Receptive language skills of adolescents and young adults with Down or fragile X syndrome. *Am J Ment Retard* 2003;108(3):149–60.
- [33] Lewis P, Abbeduto L, Murphy M, et al. Cognitive, language and social-cognitive skills of individuals with fragile X syndrome with and without autism. *J Intellect Disabil Res* 2006;50(Pt 7):532–45.
- [34] Hessler D, Rivera SM, Reiss AL. The neuroanatomy and neuroendocrinology of fragile X syndrome. *Ment Retard Dev Disabil Res Rev* 2004;10(1):17–24.
- [35] Brown V, Jin P, Ceman S, et al. Microarray identification of FMRP-associated brain mRNAs and altered mRNA translational profiles in fragile X syndrome. *Cell* 2001;107(4):477–87.
- [36] Mostofsky SH, Mazzocco MM, Aakalu G, et al. Decreased cerebellar posterior vermis size in fragile X syndrome: correlation with neurocognitive performance. *Neurology* 1998;50(1):121–30.
- [37] Reiss AL, Abrams MT, Greenlaw R, et al. Neurodevelopmental effects of the FMR-1 full mutation in humans. *Nat Med* 1995;1(2):159–67.
- [38] Hinton VJ, Brown WT, Wisniewski K, et al. Analysis of neocortex in three males with the fragile X syndrome. *Am J Med Genet* 1991;41(3):289–94.
- [39] Grossman AW, Elisseou NM, McKinney BC, et al. Hippocampal pyramidal cells in adult Fmr1 knockout mice exhibit an immature-appearing profile of dendritic spines. *Brain Res* 2006;1084(1):158–64.
- [40] Nimchinsky EA, Oberlander AM, Svoboda K. Abnormal development of dendritic spines in FMR1 knock-out mice. *J Neurosci* 2001;21(14):5139–46.
- [41] Reyniers E, Martin JJ, Cras P, et al. Postmortem examination of two fragile X brothers with an FMR1 full mutation. *Am J Med Genet* 1999;84(3):245–9.

- [42] Sabaratnam M. Pathological and neuropathological findings in two males with fragile-X syndrome. *J Intellect Disabil Res* 2000;44(Pt 1):81–5.
- [43] Greicius MD, Boyett-Anderson JM, Menon V, et al. Reduced basal forebrain and hippocampal activation during memory encoding in girls with fragile X syndrome. *Neuroreport* 2004;15(10):1579–83.
- [44] Kwon H, Menon V, Eliez S, et al. Functional neuroanatomy of visuospatial working memory in fragile X syndrome: relation to behavioral and molecular measures. *Am J Psychiatry* 2001;158(7):1040–51.
- [45] Menon V, Kwon H, Eliez S, et al. Functional brain activation during cognition is related to FMR1 gene expression. *Brain Res* 2000;877(2):367–70.
- [46] Rivera SM, Menon V, White CD, et al. Functional brain activation during arithmetic processing in females with fragile X syndrome is related to FMR1 protein expression. *Hum Brain Mapp* 2002;16(4):206–18.
- [47] Tamm L, Menon V, Johnston CK, et al. fMRI study of cognitive interference processing in females with fragile X syndrome. *J Cogn Neurosci* 2002;14(2):160–71.
- [48] Cornish K, Swainson R, Cunnington R, et al. Do women with fragile X syndrome have problems in switching attention: preliminary findings from ERP and fMRI. *Brain Cogn* 2004;54(3):235–9.
- [49] Hoefft F, Hernandez A, Parthasarathy S, et al. Fronto-striatal dysfunction and compensatory mechanisms in male adolescents with fragile X syndrome. *Human Brain Mapping*, in press.
- [50] Menon V, Leroux J, White CD, et al. Frontostriatal deficits in fragile X syndrome: relation to FMR1 gene expression. *Proc Natl Acad Sci USA* 2004;101(10):3615–20.
- [51] Garrett AS, Menon V, MacKenzie K, et al. Here's looking at you, kid: neural systems underlying face and gaze processing in fragile X syndrome. *Arch Gen Psychiatry* 2004;61(3):281–8.
- [52] Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol* 2005;493(1):154–66.
- [53] Brown WT, Jenkins EC, Friedman E, et al. Folic acid therapy in the fragile X syndrome. *Am J Med Genet* 1984;17(1):289–97.
- [54] Gustavson KH, Dahlbom K, Flood A, et al. Effect of folic acid treatment in the fragile X syndrome. *Clin Genet* 1985;27(5):463–7.
- [55] Fisch GS, Cohen IL, Gross AC, et al. Folic acid treatment of fragile X males: a further study. *Am J Med Genet* 1988;30(1–2):393–9.
- [56] Froster-Iskenius U, Bodeker K, Oepen T, et al. Folic acid treatment in males and females with fragile-(X)-syndrome. *Am J Med Genet* 1986;23(1–2):273–89.
- [57] Hagerman RJ, Jackson AW, Levitas A, et al. Oral folic acid versus placebo in the treatment of males with the fragile X syndrome. *Am J Med Genet* 1986;23(1–2):241–62.
- [58] Strom CM, Brusca RM, Pizzi WJ. Double-blind, placebo-controlled crossover study of folinic acid (Leucovorin) for the treatment of fragile X syndrome. *Am J Med Genet* 1992;44(5):676–82.
- [59] Berry-Kravis E, Potanos K. Psychopharmacology in fragile X syndrome—present and future. *Ment Retard Dev Disabil Res Rev* 2004;10(1):42–8.
- [60] Hagerman RJ, Murphy MA, Wittenberger MD. A controlled trial of stimulant medication in children with fragile X syndrome. *Am J Med Genet* 1988;30:377–92.
- [61] Hilton DK, Martin CA, Heffron WM, et al. Imipramine treatment of ADHD in a fragile X child. *J Am Acad Child Adolesc Psychiatry* 1991;30:831–4.
- [62] Cohen IL, Tsiouris JA, Pfadt A. Effects of long-acting propranolol on agonistic and stereotyped behaviors in a man with pervasive developmental disorder and fragile X syndrome: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 1991;11(6):398–9.
- [63] Torrioli MG, Vernacotola S, Mariotti P, et al. Double-blind, placebo-controlled study of L-acetylcarnitine for the treatment of hyperactive behavior in fragile X syndrome. *Am J Med Genet* 1999;87(4):366–8.

- [64] Berry-Kravis E, Krause SE, Block SS, et al. Effect of CX516, an AMPA-modulating compound, on cognition and behavior in fragile X syndrome: a controlled trial. *J Child Adolesc Psychopharmacol* 2006;16(5):525–40.
- [65] Hessel D, Glaser B, Dyer-Friedman J, et al. Cortisol and behavior in fragile X syndrome. *Psychoneuroendocrinology* 2002;27(7):855–72.
- [66] Carr EG, Durand VM. The social-communicative basis of severe behavior problems in children. In: Reiss S, Bootzin R, editors. *Theoretical issues in behavior therapy*. New York: Academic Press; 1985.
- [67] Durand VM, Carr EG. Social influences on “self-stimulatory” behavior: analysis and treatment application. *J Appl Behav Anal* 1987;20:119–32.
- [68] Iwata BA, Pace GM, Dorsey MF, et al. The functions of self-injurious behavior: an experimental epidemiological analysis. *J Appl Behav Anal* 1994;27:215–40.
- [69] Hanley GP, Iwata BA, McCord BE. Functional analysis of problem behavior: a review. *J Appl Behav Anal* 2003;36:147–85.
- [70] Taylor JC, Carr EG. Severe problem behaviors related to social interaction: I. Attention seeking and social avoidance. *Behav Modif* 1992;16:305–35.
- [71] Pelios L, Morren J, Tesch D, et al. The impact of functional analysis methodology on treatment choice for self-injurious and aggressive behavior. *J Appl Behav Anal* 1999;32:185–95.
- [72] Call NA, Wacker DP, Ringdahl JE, et al. An assessment of antecedent events influencing noncompliance in an outpatient clinic. *J Appl Behav Anal* 2004;37:145–58.
- [73] Symons FJ, Clark RD, Hatton DD, et al. Self-injurious behavior in young boys with fragile X syndrome. *Am J Med Genet A* 2003;118(2):115–21.
- [74] Hall S, DeBernardis M, Reiss A. Social escape behaviors in children with fragile X syndrome. *J Autism Dev Disord* 2006;36(7):935–47.
- [75] Hall SS, Maynes NP, Reiss AL. Using percentile schedules to increase eye contact in children with fragile X syndrome. *J Appl Behav Anal*, in press.
- [76] Elliott SN, Gresham FM. *Social skills intervention guide: practical strategies for social skills training*. Circle Pines (MN): American Guidance Service; 1991.
- [77] Hall SS, DeBernardis GM, Reiss AL. The acquisition of stimulus equivalence in individuals with fragile X syndrome. *J Intellect Disabil Res* 2006;50:643–51.
- [78] Cohen H, Amerine-Dickens M, Smith T. Early intensive behavioral treatment: replication of the UCLA model in a community setting. *J Dev Behav Pediatr* 2006;27(2 Suppl):S145–55.
- [79] Lovaas OI. Behavioral treatment and normal educational and intellectual functioning in young autistic children. *J Consult Clin Psychol* 1987;55(1):3–9.
- [80] McEachin JJ, Smith T, Lovaas OI. Long-term outcome for children with autism who received early intensive behavioral treatment. *Am J Ment Retard* 1993;97:359–372.
- [81] Bagni C, Greenough WT. From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome. *Nat Rev Neurosci* 2005;6(5):376–87.
- [82] Hariri AR, Weinberger DR. Imaging genomics. *Br Med Bull* 2003;65:259–70.
- [83] Gothelf D, Eliez S, Thompson T, et al. COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome. *Nat Neurosci* 2005;8(11):1500–2.
- [84] Meyer-Lindenberg A, Mervis CB, Faith Berman K. Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nat Rev Neurosci* 2006;7(5):380–93.
- [85] Hart SJ, Davenport ML, Hooper SR, et al. Visuospatial executive function in Turner syndrome: functional MRI and neurocognitive findings. *Brain* 2006;129(Pt 5):1125–36.