Fragile X syndrome: causes, diagnosis, mechanisms, and therapeutics

Claudia Bagni,1,2,3 Flora Tassone,4,5 Giovanni Neri,6 and Randi Hagerman5,7

1Katholieke Universiteit Leuven, Center for Human Genetics, Leuven, Belgium. 2VIB Center for the Biology of Disease, Leuven, Belgium. 3Department of Biomedicine and Prevention, University of Rome “Tor Vergata,” Rome, Italy. 4Department of Biochemistry and Molecular Medicine, UCD, School of Medicine, Davis, California, USA. 5UC Davis MIND Institute, UCD, Medical Center, Sacramento, California, USA. 6Institute of Medical Genetics, Catholic University, Rome, Italy. 7Department of Pediatrics, UCD, Davis Medical Center, Sacramento, California, USA.

Fragile X syndrome (FXS) is the most frequent form of inherited intellectual disability and is also linked to other neurologic and psychiatric disorders. FXS is caused by a triplet expansion that inhibits expression of the FMR1 gene; the gene product, FMRP, regulates mRNA metabolism in the brain and thus controls the expression of key molecules involved in receptor signaling and spine morphology. While there is no definitive cure for FXS, the understanding of FMRP function has paved the way for rational treatment designs that could potentially reverse many of the neurobiological changes observed in FXS. Additionally, behavioral, pharmacological, and cognitive interventions can raise the quality of life for both patients and their families.

Genetics of fragile X

Fragile X syndrome (FXS), an X-linked condition first described by Martin and Bell (1), is the leading cause of inherited intellectual disability (ID). Estimates report that FXS affects approximately 1 in 2,500 to 5,000 men and 1 in 4,000 to 6,000 women (2, 3). FXS is caused by mutations in the FMR1 gene, which is located on the X chromosome and whose locus at Xq27.3 coincides with the folate-sensitive fragile site (4, 5). Cytogenetic methods (6) used in the past to diagnose FXS have been replaced by molecular diagnostic of FMR1 DNA using Southern blot analysis and, more recently, PCR.

Affected men display varying degrees of symptoms ranging from mild to severe. Due to compensation by the unaffected X chromosome, only one-third of female carriers with a full mutation (FM) have ID; the majority have normal IQ, although learning difficulties and emotional problems are common (7).

Identified in 1991 by positional cloning (8), the FMR1 gene is characterized by the presence of a polymorphic CGG triplet sequence in the 5’ UTR (8, 9). Expansion in this triplet sequence gives rise to FXS, which is the prototype of unstable triplet expansion disorders. The triplet variability defines four types of alleles (Figure 1). Normal alleles have a number of CGG repeats, ranging from 5 to 54, with a mode of 30. Premutation (PM) alleles have a number of CGG repeats, ranging from 55 to 200. Premutation (PM) alleles are unstable and have a strong tendency to expand to FM alleles upon maternal transmission. Expansion from a maternal PM to FM in the offspring.

FMR1 silencing is the consequence of rather complex epigenetic modifications (13). In FXS, cytosines located approximately up to 1-kb upstream of the CGG repeat sequences, including the FMR1 promoter, are methylated (14, 15). Normal alleles are also methylated in the FMR1 promoter region but not in close proximity to the CGG repeat, which seems to be a “boundary” in the normal allele that prevents methylation from spreading. This boundary is missing in FM alleles, and the cytosines upstream of the CGG repeat become methylated around the thirteenth week of embryonic development (16). As a consequence, gene transcription is inhibited, leading to the absence of its protein product FMRP (17).

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Clinical diagnosis of fragile X in young and adult patients

Early diagnosis. A diagnosis of FXS is often made in young children of approximately 3 years of age (23), who show delayed or absent speech. Among the recurrent problems that may occur in children before 2 years of age are hypotonia, delayed motor milestones, hand flapping,
poor eye contact, frequent emesis and/or otitis media, and irritability. The behavior of boys with FXS typically includes attention deficit hyperactivity disorder (ADHD), with significant impulsivity and anxiety, as well as behaviors that include repetitive language, hand biting, hand stereotypies, rocking, and sometimes head banging (24, 25). These behaviors, combined with social and language deficits, often lead to a diagnosis of autism spectrum disorder (ASD) before the diagnosis of FXS is made. Approximately 30% of boys with FXS meet the diagnostic criteria for autism, and these children have the lowest developmental and adaptive behavior scores of those with FXS. A child with FXS is often described as hyperaroused; an imbalance of the excitatory and inhibitory synaptic pathways described in the “From RNA metabolism to synaptic receptor dysfunction” section may contribute to such a clinical phenotype. Studies on postmortem brains from patients with FM and lacking FMRP revealed a neuronal spine dysmorphogenesis (26).

After the proband is diagnosed with FXS, a subsequent cascade testing of family members will identify relatives with either the PM or FM. Since FXS is complex, consulting a genetic counselor to ensure correct interpretation of all positive fragile X test results is advisable, allowing the provision of appropriate clinical advice for those with PM or FM (27). Relatives may also be at risk of having children with ID and therefore should also be offered genetic counseling.

Other clinical observations in the family may reveal the FXS phenotype. Sometimes a family history of ID, ASD, neurological problems (such as tremor, ataxia, or dementia in one of the grandparents), or early menopause (before 40 years of age) will lead the clinician to diagnose FXS in the family. The neurological problems described above are associated with a recently identified neurodegenerative disorder seen in PM carriers, the fragile X–associated tremor ataxia syndrome (FXTAS) (28). FXTAS (Figure 1) has been reported to affect approximately 46% of male and 17% of female adult carriers (28).

Over the last few years, insight into the spectrum of phenotypes in both the PM and the FM alleles has substantially increased. In PM carriers, shyness, anxiety, social deficits, and ADHD are some of the most common features observed, particularly in boys (29–31). In addition, fragile X–associated primary ovarian insufficiency (FXPOI), defined by the cessation of menses prior to the age of 40, occurs in approximately 20% of women with PM (32).

Late diagnosis. A late diagnosis may occur for older patients who may have undergone genetic testing prior to the 1991 discovery of the FMR1 gene (8) or for patients that carry a mild form of the disease, showing atypical symptoms as often occurs for the UFM alleles. Occasionally, individuals with FXS were institutionalized in adolescence or adulthood, without a subsequent diagnostic study to find the cause of their ID. In addition, the majority of women with FM often do not have ID, and they are frequently diagnosed with FM following the diagnosis of FXS in their children.

Screening for FXS alleles: early diagnosis
The results of a pilot newborn screening (NBS) study for FXS in the United States, based on the screening of 11,217 newborns, indicated that the observed prevalence of a PM allele is 1:188 in females and 1:480 in males, while the prevalence of gray-zone alleles (45–54 CGG repeats) is 1:70 in females and 1:107 in males (33). PM prevalence was found to be different in various ethnic groups; it was higher in people of mixed European descent compared with that in African American and Hispanic people (for both males and females) and shows a higher incidence for PM compared with that in previous studies (34, 35). NBS for FMR1 mutations is not currently included in the NBS program, mainly because it may also identify FMR1 mutations that may not develop a severe FXS due to partial inactivation (UFM) as well as carriers that may develop FXTAS later in life. NBS has recently captured attention with the introduction of targeted treatments with encouraging results (36, 37) and the use of new PCR-based population screening approaches (34, 38–43). Of note, in a recent European study of 213 FXS prenatal diagnoses, 17.6% of those with a family history of unknown ID were found to be FXS carriers (44).

Clinical crosstalk between fragile X and autism
The fragile X mutation is the most common single genetic cause of autism, occurring in 1% to 6% of boys with ASD (7). Individuals with ASD and FXS have a lower IQ and lower receptive and

Figure 1
The four alleles of the human FMR1 gene. According to the degree of CGG triplet expansion and the level of FMR1 mRNA transcription and translation changes, four alleles are generated: normal, PM, UFM, and FM.
expressive language abilities compared with individuals having FXS alone (45). Most individuals with FXS and ASD have, in addition to the described hand mannerisms and speech problems, significant deficits in social interaction and communication persistently over time (46). Children with FXS and seizures (47) as well as additional medical problems that affect the CNS, such as birth asphyxia or additional gene mutations, are at greater risk of having autism in addition to FXS (48). Very recent studies on patients with FXS and FXS plus ASD supported the endophenotype of social withdrawal via decrease of cortico-cortical connectivity and organization (49). Thus initiating established behavioral interventions for patients with FXS and ASD is important, including Applied Behavioral Analysis and the Early Start Denver Model (50, 51), alongside the “symptomatic” pharmacological approaches discussed below.

Recent evidence indicates that dysregulation and or mutations of FMRP-interacting proteins, such as the cytoplasmic FMRP-interacting protein 1 (CYFIP1) (52–55), eukaryotic initiation factor 4 (eIF4E) (56, 57), and a subset of FMRP mRNA targets (58), may contribute to the FXS dysmorphic spine as well.

**From RNA metabolism to synaptic receptor dysfunction**

FMRP is an RNA-binding protein, and, despite its clear shuttling from the nucleus to the cytoplasm (59, 60), only the cytoplasmic function of FMRP has been well characterized. FMRP forms large cytoplasmic ribonucleoparticles containing several other proteins (61) and RNAs (62, 63). FMRP has been detected in P bodies and stress granules as well, where it forms translationally silent preinitiation complexes (64) (Figure 2). FMRP regulates stability, subcellular transport, and translation of neuronal mRNAs encoding for proteins involved in synaptic structure and function (58, 65–67). The best-characterized function of FMRP, based on studies of the Fmr1 KO mouse model (68),

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**Figure 2**

Effects of receptor signaling pathways on FMRP-mediated regulation at synapses. A complex cascade of molecules downstream of glutamate (NMDA, AMPA, mGluR5) and BDNF receptors modulates FMRP activity at synapses. FMRP is affected by mTOR and Mnk1 signaling pathways (89) that regulate phosphorylation of general eIF4E-binding proteins and consequently protein synthesis. FMRP can be phosphorylated by S6 kinase (S6K) (72) or dephosphorylated by protein phosphatase 2A (PP2A) (137). The phosphorylation status affects its RNA-binding properties as well as its translational regulation. Mechanistically, FMRP has been shown to interact with the initiation factor eIF4E and regulate translational through the specific eIF4E-binding protein CYFIP1 (52). Further studies are required to verify whether FMRP also binds general eIF4E-BPs and whether these signaling pathways affect the FMRP-CYFIP1 complex as well. FMRP may also affect translational elongation (58). In absence of FMRP, the upstream kinase phosphatidylinositol 3-kinase 3-kinase (PI3K) is upregulated, leading to the increased mTOR phosphorylation and activity observed in patients with FXS as well as in the Fmr1 KO mouse (87, 89), culminating in an increased protein synthesis. Similar and possibly convergent effects are due to an upregulation of ERK (72, 87–89) and TrkB (85) signaling. In absence of FMRP, there is an increase of a subset of locally synthesized proteins (Arc, Map1B, αCAMKII, postsynaptic density-95 [PSD-95], MMP9, GSK-3β, among others). The increased Arc level contributes to an increased AMPA internalization and reduced AMPA in the membrane. At the same time, Arc, Map1B, PSD-95, and other dysregulated proteins involved in cytoskeleton scaffolding and remodeling may contribute to the FXS dysmorphic spine as well.

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is as a translational repressor (Figure 2), and the absence of FMRP thus leads to increased protein synthesis (52, 69–74). High-throughput screenings supported by accompanying small scale studies have revealed that a wide array of neuronal mRNAs, with a large proportion encoding for presynaptic and postsynaptic proteins, is deregulated in the absence of FMRP, suggesting that concerted alteration of many proteins contributes to the FXS phenotype (62).

Spine dysmorphogenesis represents the quantitative measure widely adopted in the mouse model for FXS to understand cellular and network changes in the absence of FMRP (61). Furthermore, extensive electrophysiological studies in the Fmr1 KO mouse model indicated an excitation/inhibition (glutamate/GABA; see below) imbalance (75–77). Because the mouse model recapitulates morphological changes and behavioral deficits seen in human patients, these molecular insights have led clinicians to design targeted treatments (see below).

Over the last five years, there have been major advances in our understanding of the signaling pathways acting on FMRP as well as regulated by FMRP (Figure 2). FMRP activity is regulated in response to metabotropic glutamate receptors (mGluRs) (78), 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) receptors (79), γ-aminobutyric acid (GABA) receptors (76, 80, 81), N-methyl-d-aspartate (NMDA) receptors (82–84), and the tyrosine kinase or BDNF/NT-3 growth factor (TrkB) receptors (85). Upon receptor activation, the FMRP-mediated translational block is released, possibly due to changes (86) in its phosphorylation status, and protein synthesis can ensue. In the absence of FMRP, there is an increase in the synthesis of several proteins involved in cytoskeleton remodeling and receptor internalization (i.e., Arc) (Figure 2) as well as reduction of other proteins due to a reduced stability of their mRNAs (i.e., GABA-R subunits). Elevation of the glutamate receptors mGluR1 and mGluR5 and the reduced insertion of AMPA receptors into the postsynaptic membrane are two of the central mechanics of impaired synaptic plasticity in FXS: such a dysregulated signaling is the basis of mGluR theory (75). This receptor unbalance results in enhanced mGluR–long-term depression (mGluR-LTD), the most commonly studied forms of hippocampal synaptic plasticity.

The molecular signaling pathways orchestrating protein synthesis, spine shape, and synaptic plasticity, such as mTOR and ERK (Figure 2), are also impaired in FXS (72, 87–89), possibly because some FMRP target mRNAs encode members of second messenger cascades converging on ERK (88, 89).

Amelioration of the phenotype in the mouse model: a genetic approach

Several laboratories have successfully attempted to genetically rescue the FXS phenotype, with varying degrees of efficacy. mGluRs (mGluR1 and mGluR5) are members of the G protein-coupled receptor family that influence synaptic plasticity-regulating processes, such as learning, memory, and anxiety as well as perception of pain. Activation of mGluRs leads to LTD of the post-synapses that is local protein synthesis dependent. Absence of FMRP leads to an increase of local protein synthesis (Figures 2 and 3), initially shown for the activity-regulated cytoskeleton protein (Arc), microtubule-associated protein 1B (Map1B), and alpha Ca2+/calmodulin-dependent kinase II (αCaMKII) proteins (69).
As mentioned, mGluR-LTD is enhanced in mice lacking FMRP (78). These findings suggest that downregulation of mGluRs may be a potential target for FXS therapeutic interventions. Elevated LTD causes loss of AMPA and NMDA receptors from the surface of postsynaptic structures, possibly affecting the elongation of dendritic spines (75, 79). The mGluR theory was initially tested by crossing mice heterozygous for the mGluR5 encoding gene (Gmrk5') with Fmr1 KO mice. The resulting 50% reduction in mGluR5 protein levels in the offspring led to the correction of typical FXS phenotypic features, including spine dysmorphogenesis and audiogenic seizures, and restored mGluR-LTD (90).

Interestingly, the amyloid β-protein precursor (AβPP) is upregulated in the FXS mouse model (52, 73). Genetic reduction of AβPP in Fmr1 KO mice rescues characteristic FXS phenotypes, such as audiogenic seizures, the ratio of mature versus immature dendritic spines, and mGluR-LTD (91). Future studies are required to identify the mechanism of AβPP action at FXS synapses.

In another study, mice heterozygous for the tuberous sclerosis complex 2 (Tsc2') mice, a GTPase-activating protein known to inhibit the kinase mTOR (Figure 2), were crossed with the Fmr1 KO mice. Also in this case, the FXS phenotype was rescued with normalization of neuronal protein synthesis and electrophysiological responses (92). Because both mouse models have upregulated mTOR pathway activity, the authors propose that normal synaptic plasticity and cognition occur within an optimal range of mGluR-mediated protein synthesis, such that deviations in either direction can lead to shared behavioral impairments.

FMRP has been shown to interact with the p21-activated kinase (PAK), an enzyme known to play a critical role in actin polymerization and dendritic spine morphogenesis. Expression of a dominant-negative mutant of PAK in the forebrain of Fmr1 KO mice led to an improvement of several behavioral abnormalities, such as impaired locomotor activity, stereotypical anxiety, and trace fear conditioning, suggesting that the PAK signaling pathway could also represent a bona fide site for therapeutic intervention (93).

Recently, the striatal enriched protein tyrosine phosphatase (STEP) has been shown to be upregulated in FXS, and genetic reduction of STEP diminished seizures and restored selected social and nonsocial anxiety-related behaviors in the Fmr1 KO mice (94). Because STEP acts on at least three molecules (ERK1/2, NMDA, and AMPA) affected in FXS, strategies to inhibit STEP activity may be considered for treating patients with FXS.

Therapeutic approaches to FXS

During the past decade, intense effort has been focused on the development of specific FXS treatments that might lead to eventual cure. Two possible approaches are presently being considered for a substantial treatment of FXS: (a) reactivation of the affected gene and (b) compensating for the lack of FMRP.

Epigenetic modulators. The strategy of restoring FMR1 gene activity, which is based on the presence of the intact FMR1 coding sequence, targets potentially reversible epigenetic changes, primarily DNA methylation. The first compound tested on cells derived from patients with FXS was the drug 5-aza-deoxycytidine (5-azadC, a methyltransferase inhibitor; Figure 3A), which restored transcription and translation of the FMR1 gene (95). Furthermore, treatment with histone deacetylase inhibitors (TSA, butyrate, and 4-phenylbutyrate) potentiated the effect of 5-azadC (96). Reactivation was accompanied not only by DNA demethylation but also by changes in the epigenetic code of histones H3 and H4 (97). As result of these changes, the inactive, methylated FM allele became similar to the active UFM allele. Even though the cause of this reduction in methylation is unknown, converting a carrier of a methylated FM allele into a carrier of an UFM allele, by pharmacological intervention, appears to be a logical approach. While the action of 5-azadC appears to be specific in the context of the FMR1 gene, as shown by its lack of effect on the methylated sequence upstream of the FMR1 boundary (G. Neri, unpublished observations), effects on other methylated genes cannot be excluded. Furthermore, 5-azadC cannot be readily used in vivo because of safety issues (induction of apoptosis). Moreover, it is presumed to be effective only on dividing cells, which excludes postmitotic neurons. Acetyl-l-carnitine (Nicetile, a natural compound improving cell metabolism), shown to inhibit cytogentic expression of the fragile X site in patient-derived cultured lymphocytes (98), was administered to boys with FXS (99). A significant amelioration of the hyperactivity and adaptive behavior of drug-treated boys (compared with those treated with placebo) was observed; however, the methylation state of FMR1 did not change, and the expression of the gene did not increase (100). The third tested compound is valproic acid (101), which is already known as a reactivator of silenced genes (102) that appeared to be a weak reactivator of FM (103). On a small, open-label trial of 10 boys with FXS, essentially meant to be a safety trial, treatment with valproic acid resulted in a general improvement in hyperactivity and attention deficit (104).

Glutamatergic system. Several receptor-signaling pathways (Figure 2) are impaired in FXS. The reduced functional AMPA receptor in the FXS mouse model has led clinicians to use, in an open trial with FXS patients, a positive allosteric modulator of AMPA receptors (CX516; Figure 3B). No significant improvement in the primary outcome measure or in secondary measures of language, attention/executive function, or behavior was observed when compared with placebo, possibly due to the potency or dosage of CX516 used (105).

Treatment of Fmr1 KO mice with the mGluR antagonist 2-methyl-6-(phenylethynyl)-pyridine (MEP) (Figure 3B) resulted in suppression of the audiogenic seizure phenotype (106) and rescue of dendritic spine morphology in the Fmr1 KO mouse (107). Long term use of a similar mGluR5 antagonist, CTEC, in adult animals corrected elevated hippocampal LTD, protein synthesis, spine dysmorphogenesis, overactive ERK and mTOR signaling, and partially corrected macroorchidism (108). These studies paved the way for treatments in humans. Fenobam, used in the past for anxiety treatment (109), was recently tested in adults with FXS (37). Beneficial effects such as reduced anxiety and hyperarousal, improved prepulse inhibition of startle, and better accuracy on a continuous performance task were also reported. Additional trials focused on AFQ056, another mGluR5 antagonist. Intriguingly, in this small trial, improvements in inappropriate speech, stereotypic behavior, and hyperactivity and efficacy have been reported in adults with FXS who have a fully methylated FM allele but not in those with mosaicism (36). Currently, two large multicenter controlled clinical trials with mGluR antagonists (AFQ056, Novartis; RO4917523, Hoffmann-La Roche) are taking place both in adolescents and adults with FXS, followed by an open-label continuation for up to 2 years. Results from these studies are pending (110, 111). Another compound, STX107 (Sea-Side Therapeutics), acts similarly and will possibly be used in the future for additional clinical trials (112).
GABAergic system. The GABA receptor system has also been reported as downregulated in FXS, partially due to destabilization of the mRNAs encoding the GABA receptor subunits (76, 80, 113). Consequently, impaired GABAergic transmission in different brain regions, such as the amygdala, striatum, and cerebral cortex, is believed to contribute to FXS behavioral abnormalities. Pharmacological approaches targeting the GABAergic system have been successfully exploited to correct amygdala-based symptoms in FXS (114). Acamprosate, a molecule used to maintain abstinence from alcohol, is able to block NMDA-R as well as activate GABA_A receptors and was recently tested in three young adult patients with FXS, who showed global benefit (as rated by the CGI-I scale) and marked communication improvement (115). If efficacy is shown, treatment studies will likely combine ganaxolone with an mGluR5 antagonist to assess synergistic efficacy. Baclofen, a GABA_B-R agonist, reduced withdrawal balance appear to be the effects of the disease, further studies are necessary to fully address this question. In addition, FMRP is also required for neural stem and progenitor cell proliferation, differentiation, and survival, suggesting additional mechanisms that could explain certain features of the disease (136). Intensive educational interventions in FXS, in addition to these targeted treatments, are important to both strengthen synaptic connections and improve the quality of life for patients. The continued development of new, targeted treatments for FXS, together with existing induced pluripotent stem cell models for FXS (63), give hope that reversing the behavioral and cognitive deficits seen in individuals with this disorder may someday be possible.

Conclusions and perspectives

While the molecular roles of FMRP are still being delineated, FMRP is largely established to function in regulating mRNA metabolism in brain. The plethora of putative mRNA targets and several FMRP-interacting proteins with overlapping function could explain the wide and variable physical phenotypes observed in FXS. While observed alterations in excitation/inhibition balance appear to be the effects of the disease, further studies are necessary to fully address this question. In addition, FMRP is also required for neural stem and progenitor cell proliferation, differentiation, and survival, suggesting additional mechanisms that could explain certain features of the disease (136). Intensive educational interventions in FXS, in addition to these targeted treatments, are important to both strengthen synaptic connections and improve the quality of life for patients. The continued development of new, targeted treatments for FXS, together with existing induced pluripotent stem cell models for FXS (63), give hope that reversing the behavioral and cognitive deficits seen in individuals with this disorder may someday be possible.

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Address correspondence to: Claudia Bagni, Faculty of Medicine, VIB Center for the Biology of Disease Catholic University of Leuven, O&N I Herestraat 49 - bus 602, 3000 Leuven, Belgium. Phone: 32.16330944; Fax: 39.16330939; E-mail: claudia.bagni@med.kuleuven.be; or: Claudia Bagni, Faculty of Medicine, Department of Biomedicine and Prevention, University of Rome “Tor Vergata”, Via Montpellier, I. 00133 Rome, Italy. Phone: 39.06.72596063; Fax: 39.06.72596058; E-mail: claudia.bagni@uniroma2.it.
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