Inactivation of the Maternal Fragile X Gene Results in Sensitization of GABA<sub>B</sub> Receptor Function in the Offspring

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ABSTRACT

Fragile X syndrome is an X-linked disorder caused by the inactivation of the FMR1 gene, with symptoms ranging from impaired cognitive functions to seizures, anxiety, sensory abnormalities, and hyperactivity. Although fragile X syndrome is a typical Mendelian disorder, we have recently reported that the environment, specifically the fmr1<sup>+/−</sup> or fmr1<sup>−/−</sup> [H or knockout (KO)] maternal environment, elicits on its own a partial fragile X-like phenotype and can contribute to the overall phenotype of KO male offspring. Genetically fmr1<sup>−/−</sup> (WT) males born to H females (H<sub>maternal</sub> > WT<sub>offspring</sub>), similar to KO male offspring born to H and KO mothers (H > KO and KO > KO), exhibit locomotor hyperactivity. These mice also showed reduced D<sub>2</sub> autoreceptor function, indicating a possible diminished feedback inhibition of dopamine (DA) release in the nigrostriatal and mesolimbic systems. The GABAergic system also regulates DA release, in part via presynaptic GABA<sub>B</sub> receptors (Rs) located on midbrain dopaminergic neurons. Here, we show that the locomotor inhibitory effect of the GABA<sub>B</sub>R agonist baclofen [4-amino-3-(4-chlorophenyl)-butanoic acid] is enhanced in all progeny of mutant mothers (H > WT, H > KO, and KO > KO) compared with WT > WT mice, irrespective of their own genotype. However, increased sensitivity to baclofen was selective and limited to the locomotor response because the muscle-relaxant and sedative effects of the drug were not altered by the maternal environment. These data show that GABA<sub>B</sub>R sensitization, traditionally induced pharmacologically, can also be elicited by the fmr1-deficient maternal environment.

Fragile X syndrome (FXS) is an X-linked neuropsychiatric disorder caused, in most cases, by a triplet expansion in the FMR1 gene (Consortium TD-BFX, 1994; Hagerman, 1996). In addition to mental retardation, fragile X individuals display seizures, attention deficit, hyperactivity, anxiety, and symptoms associated with autism. Most fragile X individuals inherit a premutated allele (between 55 and 200 repeats) from their mother that undergoes triplet expansion, resulting in a full mutation (>200 repeats) and the inactivation of the FMR1 gene. In some cases, full mutation is already present in heterozygote carrier mothers who are less affected than males presumably because the mosaic pattern of FMR1 inactivation. Premutation in females does not inactivate the FMR1 gene but nevertheless seems to increase the frequency of mood and anxiety disorders (Roberts et al., 2008).

The mouse model of FXS (Consortium TD-BFX, 1994) reproduces many human symptoms of the disorder including locomotor hyperactivity, social anxiety/avoidance, and sensory hyperreactivity (D’Hooge et al., 1997; Peier et al., 2000; Chen and Toth, 2001; Spencer et al., 2005; Yun et al., 2006). Although FXS is considered to be a purely Mendelian disorder, and it is assumed that all behavioral abnormalities seen in the mouse model are genetic in nature, we have recently reported that the maternal fmr1<sup>+/−</sup> (or fmr1<sup>−/−</sup>) genotype could contribute to the hyperactivity of fmr1<sup>−/−</sup> male H > KO (or KO > KO) offspring, and it is the sole cause of the increased locomotor activity of the genetically normal fmr1<sup>−/−</sup> male (H > WT) offspring. Other behaviors, such as increased seizure sensitivity and changes in startle reactivity and prepulse inhibition followed Mendelian inheritance (H > WT and WT > WT are similar to each other and different from H > KO and KO > KO mice); thus, the maternal influence affects only specific behaviors in the mouse model of FXS. A maternal genotype effect has also been implicated recently in a human study that analyzed maternal-child interactions in dyads affected by FXS (Wheeler et al., 2007), where maternal behavior can profoundly influence the child’s developmental pattern, which, in turn, can influence the affective behavior of the mother.

The striatum is important in the selection, initiation, and expression of movement. It is also involved in emotional and motivational processes that motivate and organize movement. The striatum is a major target of dopaminergic projections from the ventral tegmental area (VTA) and substantia nigra. Dopamine (DA) released in the nigrostriatal and mesolimbic systems can influence a wide range of behaviors, including locomotion, learning, and reward. Changes in DA transmission have been implicated in many psychiatric disorders, including ADHD, attention deficit hyperactivity disorder.
execution of voluntary motor responses (Tucker and Williamson, 1984), and lesions to this area in humans can produce hyperactivity (Solanto, 2002). Motor activity is also regulated by mesolimbic DA neurons originating in the ventral tegmental area (VTA) and projecting to the ventral striatum (Koob and Swerdlow, 1988; Szczypka et al., 2001). It has been hypothesized that low tonic DA activity in the striatum via D2 presynaptic autoreceptors leads to high phasic DA activity and to hyperactivity (Grace, 2001). Consistent with this idea, we found reduced D2 autoreceptor activity in hyperactive offspring born to H and KO mothers (Zupan and Toth, 2008). This indicated that, similar to locomotor activity, D2 receptor function is regulated in part by the nongenetic factor of H or KO maternal environment.

Activity of mesolimbic DA neurons is also modulated by GABA<sub>B</sub>Rs at both somatodendritic and presynaptic locations. Somatodendritic GABA<sub>B</sub>Rs normally inhibit DA release through a K<sup>-</sup>-dependent hyperpolarization mediated by G protein-coupled inwardly rectifying potassium channels that decrease the firing rate and the burst firing activity of DA neurons (Engberg et al., 1993; Yoshida et al., 1994; Madden and Johnson, 1998; Labouebe et al., 2007). Presynaptic GABA<sub>B</sub>Rs in the projection area of DA neurons normally curtail DA release through the inhibition of Ca<sup>2+</sup> influx into terminals (Zoltay and Cooper, 1994; Smolders et al., 1995). Baclofen, a GABA<sub>B</sub>R agonist, has been shown to reduce DA neuron firing pattern and rate in rat midbrain slices (Saitoh et al., 2004; Chen et al., 2005). Reduced firing rates were also observed in the VTA after local microiontophoretic administration of the agonist (Klit enick et al., 1992; Erhardt et al., 2002). Behaviorally, baclofen reduces locomotor activity levels (Cott et al., 1976), and genetic inactivation of the GABA<sub>B</sub>1 subunit results in hyperlocomotion (Schuler et al., 2001). In all, the GABA<sub>B</sub>R, like the DA D2 autoreceptor, plays a role in regulating DA neuron activity and locomotion. In this study, we aimed to determine whether the function of GABA<sub>B</sub>Rs in modulating locomotor activity is altered in WT or fmr1 KO mice reared by mothers with fmr1<sup>+/–</sup> (H > WT or H > KO) or fmr1<sup>+/–</sup> (KO > KO) genotypes. We show here an enhanced GABA<sub>B</sub>R agonist-dependent behavioral response in male H > WT, H > KO, and KO > KO offspring and, furthermore, establish that this response is dependent on the maternal fmr1 genotype.

Materials and Methods

Animals

fmr1-KO mice (Consortium TD-BFX, 1994) on the FVB (FVB/129P<sub>B6-Fmr1<sup>tm1Cre</sup>/J) background and FVB WT mice (FVB/NJ) were purchased from The Jackson Laboratory (Bar Harbor, ME). KO mice were backcrossed at least five times at The Jackson Laboratory and once in our animal facility to the FVB background. Experimental subjects were generated through breeding of fmr1-KO females and males (KO<sub>maternal genotype</sub> > KO<sub>offspring genotype</sub>) or WT females and males (WT > WT) and crossing female homozygotes with male WT mice to generate heterozygote females that were mated with WT males to produce WT and KO littermate offspring (H > WT and H > KO, respectively; Fig. 3A) (Zupan and Toth, 2008).

Experiments were conducted using male WT > WT, H > WT, H > KO, and KO > KO offspring 8 to 12 weeks old. All animals were group housed up to five per cage (in most cases, three to four animals) with 12-h light/dark cycle, with lights on at 6:00 AM. Food and water were available ad libitum. Animal experiments were carried out in accordance with the Weill Cornell Medical College Institutional Animal Care and Use Committee guidelines.

Drugs

(±)-Baclofen was purchased from A.G. Scientific (San Diego, CA). CGP46381 was purchased from Tocris Bioscience (Ellisville, MO). All drugs were dissolved in sterile saline and administered intraperitoneally at 0.1 ml/10 g animal weight.

Behavioral Procedures

Locomotor Activity. Locomotor behavior was recorded using infrared beam-equipped activity chambers (27 × 27 cm; MED Associates, St. Albans, VT). WT > WT and KO > KO animals were allowed to habituate to the behavioral testing room for at least 20 min before the onset of any experiments. Animals were injected with baclofen or vehicle (saline) 30 min before placement into the activity chamber. Once placed inside the chambers, subjects’ locomotor activity was recorded for 30 min, except in 2-h recording sessions, during which activity was measured in 10-min intervals. Cohorts of WT > WT, H > WT, H > KO, and KO > KO animals were used to specify the effect of the maternal environment on locomotor activity. Additional groups of WT > WT, H > WT, H > KO, and KO > KO animals were pretreated with CGP46381 or saline and then injected again 15 min later with baclofen or saline, followed by a 30-min locomotor test 30 min later. Drugs were administered in a crossover design, with the sequence of drug administrations randomly assigned and varied between mouse cages. Tests were performed in 7-day intervals for no more than 3 weeks. Habituation to the locomotor chamber does not occur during this type of repeated testing (Zupan and Toth, 2008).

Rotorod. On the first day, subjects were given four training trials to learn to walk on a rotating beam (Roto-Rod, Series 8; IITC Life Science Inc., Woodland Hills, CA) at increasing rotation speed up from 2 to 10 rpm and maximal time of 300 s. Animals that failed to stay on the Rotorod for at least 250 s by the fourth trial were excluded from the test. On the 2nd and 3rd days, subjects were injected with vehicle or 3, 6, or 10 mg/kg i.p. baclofen using a crossover design, 30 min before being placed onto the accelerating rotating beam (2–10 rpm in 300 s). The order of dosage received was randomly assigned within each group, but once the animals received the 10 mg/kg dose, they were not reused.

Results

Male fmr1 KO Mice Exhibit Increased Baclofen Sensitivity. Administration of baclofen, a selective GABA<sub>B</sub>R agonist, has been shown to reduce locomotor activity in mice (Cott et al., 1976). To probe the functionality of the GABA<sub>B</sub>R in FXS mice, 3, 6, and 10 mg/kg i.p. baclofen was administered 30 min before the onset of locomotor activity assessment. As Fig. 1A shows, baclofen induced a dose-dependent inhibition of locomotor activity in both WT and KO mice equally, only the KO group exhibited a significant locomotor reduction at the 3 mg/kg baclofen dose (two-way treatment × genotype ANOVA; treatment, F<sub>2,148</sub> = 57.68, p < 0.0000001; treatment × genotype, F<sub>2,148</sub> = 7.11, p = 0.00003). The injection procedure alone, presumably because of stress, resulted in a reduction in locomotor activity in the vehicle KO group compared with the no-injection KO group (Fig. 1A, p < 0.01). However, the loss of hyperactivity in the KO group after injection was not consistently observed (see Fig. 1B and unpublished observations) and may be because of variability to stress in the KO group.
To better characterize the baclofen dose that differentiated between the KO and WT mice, we analyzed the locomotor-reducing effect of 3 mg/kg drug over a 120-min observation period (Fig. 1B). Consistent with data displayed in Fig. 1A, two-way repeated measures ANOVA showed a significant treatment × time interaction in the KO (F 11, 154 = 2.61, p = 0.0045) but not in the WT group. In the KO group, the greatest reduction in locomotor activity was observed during the first 30 min of the trial, a time course that is consistent with the relatively short half-life of baclofen (Shellenberger et al., 1999; Schuler et al., 2001; Wiersma et al., 2003).

In view of the fact that baclofen is commonly prescribed for its muscle-relaxant effect, we were interested in assessing whether the increased baclofen sensitivity of KO mice is specific for the locomotor activity or whether it is more generalized and includes the muscle-relaxant/sedative properties of the drug. We tested the effects of 3, 6, and 10 mg/kg i.p. baclofen on performance on the Rotorod, a well established test for measuring muscle strength and coordination in rodents (Fig. 2). A two-way genotype × treatment ANOVA showed a treatment effect (F 3, 73 = 109.35, p = 0.00001) but not genotype effect on Rotorod performance. Although the 3 and 6 mg/kg doses resulted in no significant impairment in either KO or WT mice as measured by the time the animals remained on the rotating beam, 10 mg/kg baclofen produced significant and similar impairments in KO and WT mice (Fig. 2).

Fig. 1. Enhanced sensitivity to baclofen in fmr1 KO compared with WT mice. A, effect of 3, 6, and 10 mg/kg baclofen on locomotor activity measured for 30 min. Both KO and WT male mice show a dose-dependent reduction in locomotor activity after the intraperitoneal administration of baclofen. However, only the KO mice respond to the lowest 3 mg/kg dose (two-way genotype × treatment ANOVA followed by Fisher’s LSD post hoc analysis; N.S., not significant; **, p < 0.01; ***, p < 0.001; no injection, n = 29–32; vehicle and 3 and 6 mg/kg baclofen, n = 14–18; 10 mg/kg baclofen, n = 7–8 per group). B, 2-h time course of the baclofen-induced attenuation of locomotor activity at 3 mg/kg. Baclofen causes no significant behavioral change in WT subjects compared with vehicle controls (n = 7 per group), whereas this dose in KO mice significantly attenuates locomotor activity compared with vehicle control (two-way repeated measures ANOVA; Fisher’s LSD post hoc, *, p < 0.05; **, p < 0.01; ***, p < 0.001; n = 8 per group).

Fig. 2. The locomotor-reducing effect of 3 and 6 mg/kg baclofen is not mediated by the muscle-relaxant or sedative properties of the drug. WT and KO mice respond similarly to baclofen on the Rotorod. Post hoc analysis reveals no significant effects until the administration of 10 mg/kg baclofen (two-way genotype × treatment ANOVA, Fisher’s LSD post hoc, ***, p < 0.001; n = 10–11 per group).
2). These data show that the observed reduction of locomotor activity at 3 and 6 mg/kg baclofen is unlikely to be caused by sedation and muscle relaxation. Furthermore, these data, taken together with the locomotor data described in Fig. 1A, indicate that the increased sensitivity of \textit{fmr1} KO mice to the locomotor-reducing effects of baclofen is specific and is not based on systemic GABA\textsubscript{B}R supersensitivity.

**The Increased Baclofen Sensitivity in the Offspring Is Maternal \textit{fmr1} Genotype-Dependent.** Previous data from our laboratory indicate that the hyperactivity of the \textit{fmr1} KO mice and the D\textsubscript{2} receptor-mediated suppression of this phenotype by an agonist is dependent, at least partly, on the \textit{fmr1} genotype of the mother (Zupan and Toth, 2008). To assess a maternal genotype effect, we took advantage of the possibility that with genetically manipulated mice, WT offspring can be raised in a wild-type or mutant H maternal environment (WT > WT or H > WT offspring, Fig. 3A; see further details on breeding under Materials and Methods). Previous data showed that H > WT mice have increased locomotor activity compared with WT > WT mice (Zupan and Toth, 2008). Any behavioral difference between these groups is because of maternal effect and is not the result of genetic factors because H > WT animals were selected for the WT \textit{fmr1} allele and thus had neither the genetically modified allele nor the associated 129P2/OlaHasd flanking sequences. In addition, at least six backcrosses eliminated the majority of randomly dispersed remnants of the original 129 genome guaranteeing that no locus is uniformly and specifically present in the H > WT mice. The breeding scheme shown in Fig. 3A also results in offspring with both offspring and maternal genotype effects (H > KO and KO > KO), and these mice had even higher levels of locomotor activity than H > WT animals (Zupan and Toth, 2008). Given the increased sensitivity of KO male offspring of KO mothers (KO > KO) to baclofen (Fig. 1), which have both offspring and maternal genotype effects, we asked if mice with only the maternal genotype effect (H > WT) would exhibit the increased drug sensitivity as well. We administered 3 mg/kg i.p. baclofen to WT > WT, H > WT, H > KO, and KO > KO mice and measured locomotor activity for 30 min, starting 30 min after the administration of the drug. As in a previous experiment (Fig. 1A), baclofen suppressed locomotor activity in KO > KO but not in WT > WT mice (Fig. 3B). Importantly, suppression of the locomotor activity also occurred in H > WT and H > KO mice (two-way group \times treatment ANOVA; treatment, \(F_{1,91} = 29.4172, p < 0.00001\) followed by LSD post hoc test), indicating a maternal genotype effect in the locomotor suppressant effect of low-dose baclofen (Fig. 3B). The drug-induced suppression in H > KO animals was not more pronounced than in H > WT animals, suggesting that the offspring KO genotype does not significantly add to the maternal effect under the experimental conditions used here.

**The GABA\textsubscript{B}R Antagonist CGP46381 Reveals a Role for Both Maternal and Offspring \textit{fmr1} Genotypes in the Increased Behavioral Response to Baclofen.** The increased sensitivity of H > WT and H > KO and KO > KO animals to baclofen raised the question of whether GABA\textsubscript{B}Rs are tonically activated in these animals to compensate the hyperactivity of these animals. Therefore, we used the competitive antagonist CGP46381 to block GABA\textsubscript{B}Rs and assessed whether the locomotor activity of H > WT, H > KO, and KO > KO animals is increased above the saline baseline. Surprisingly, CGP46381 at 20 and 40 mg/kg had no apparent effect on locomotor activity of these groups of mice (Fig. 4, B–D). However, there was a small but significant increase in locomotor activity in the WT > WT group at the 20 mg/kg CGP46381 dose (Fig. 4A; one-way ANOVA, CGP treatment, \(F_{2,24} = 4.80, p = 0.017\); LSD post hoc saline versus 20 mg/kg, \(p = 0.007\)), indicating that the tonic activity of GABA\textsubscript{B}Rs may also be under maternal genotype influence.

Next, we tested whether CGP46381 can antagonize the effect of baclofen given at 6 mg/kg, a dose that elicited a behavioral response in all groups (Fig. 4, A–D). Both the 20 and 40 mg/kg CGP46381 doses completely neutralized the baclofen effect in WT > WT mice (one-way ANOVA, treatment, \(F_{5,50} = 11.242, p < 0.00001\)) (Fig. 4A). In contrast, the low 20 mg/kg dose of CGP46381 did not prevent the locomotor suppressant effect of baclofen in H > WT mice and only the larger 40 mg/kg CGP46381 dose was effective in this group (one-way ANOVA, treatment, \(F_{5,54} = 4.641, p = 0.00135\)) (Fig. 1B). These data are indicative of a maternal genotype-dependent increase in baclofen sensitivity in the H > WT animals. In the H > KO (and KO > KO) animals, even the higher 40 mg/kg CGP46381 dose was without effect in reverting baclofen-induced suppressed locomotor activity to baseline levels (Fig. 4, C and D). Taken together, these data reveal an offspring genotype effect, on top of the \textit{fmr1} H
maternal effect seen in the H > WT mice, on sensitivity to baclofen.

Discussion

Our previous finding showing that WT male mice reared by *fmr1* H females (H > WT) exhibit locomotor hyperactivity and reduced DA D2 receptor sensitivity to quinpirole indicated that the maternal Fmrp deficit elicits, on its own, behavioral and neurochemical changes in brain circuits, principally in the nigrostriatal and mesolimbic DA systems of the offspring. Because these maternally determined phenotypes were measured in adult offspring, they are permanent and presumably initiated during the development of the DA system. The DA system is under multiple neurotransmitter controls, and here we asked whether neurotransmitter receptors other than DA are also altered permanently in mice reared by H or KO mothers. GABA<sub>B</sub>Rs are expressed in both DA and GABAergic neurons in the striatum and VTA, and the net effect of receptor activation by the agonist baclofen is a reduction in DA neuronal firing, DA release, and locomotor activity (Cott et al., 1976; Cruz et al., 2004; Saitoh et al., 2004; Chen et al., 2005). Interestingly, 3 mg/kg i.p. baclofen, a behaviorally subthreshold dose in WT mice, elicited a significant, approximately 2-fold, reduction in locomotor activity (Cott et al., 1976; Cruz et al., 2004; Saitoh et al., 2004). In addition, CGP alone increased locomotor activity. B, pretreatment with 40, but not 20 mg/kg, CGP46381 blocks the locomotor-reducing effect of baclofen in the H > WT group (one-way ANOVA, Fisher’s LSD post hoc, n = 8–10 per treatment). CGP alone had no effect on activity. C and D, neither 20 nor 40 mg/kg CGP46381 pretreatment is effective in fully reversing baclofen-induced reduction of locomotor activity in both the H > KO and KO > KO groups (one-way ANOVA Fisher’s LSD post hoc, n = 7–11 per treatment).

Because activation of the GABA<sub>B</sub>R is inhibitory on locomotor activity, it was conceivable that the enhanced drug response of H > WT (and H > KO and KO > KO) mice reflects a compensatory up-regulation of receptor function. Therefore, we expected a further increase in locomotor activity in H > WT, H > KO, and KO > KO mice after the pharmacological blockade of the GABA<sub>B</sub>R. This assumption was also consistent with the increased activity of WT > WT mice after 20 mg/kg CGP46381 (Fig. 3A) that reproduced published data (Colombo et al., 2001) and with the hyperactivity of GABA<sub>B</sub>R1 subunit KO mice (Schuler et al., 2001). However, up-regulation of GABA<sub>B</sub>R function was not compensatory...
because CGP46381 resulted in no detectable effect in locomotor activity in H > WT, H > KO, and KO > KO mice. This suggests that either GABA\(_B\)Rs are not tonically active or the increased receptor functionality is more difficult to block by the antagonist.

We have previously shown that hyperactivity in fmr1 KO male mice reared by fmr1 H females (H > KO) was even higher than the activity of H > WT mice, suggesting that the offspring genotype, on top of the maternal effect, can also lead to or contribute to hyperactivity (Zupan and Toth, 2008). A similar graded response was also observed in GABA\(_B\)R sensitivity. Although the locomotor suppressant effect of 6 mg/kg baclofen was completely reversed by 20 mg/kg CGP46381 in WT > WT mice, only the 40 mg/kg dose was effective in H > WT mice, and even this higher dose was insufficient to neutralize the baclofen effect in H > KO and KO > KO mice. The decreased effectiveness of CGP46381 to block the locomotor-reducing effect of baclofen in mice raised by H or KO mothers is consistent with their increased functional GABA\(_B\)R sensitivity, and it provides further support for the maternal genotype-mediated modulation of GABA\(_B\)R function. Although it is tempting to conclude that the additional increase in locomotor activity and functional GABA\(_B\)R sensitivity in H > KO and KO > KO mice is because of an offspring genotype effect (on top of the maternal effect), the maternal and offspring genotype effects can interact in unpredictable ways. Our breeding strategy does not allow the study of the offspring genotype effect in the absence of the maternal H or KO environment; thus, it is possible that the genetic inactivation of the fmr1 gene in the offspring enhances the maternal effect without having its own effect in that offspring. Alternatively, the offspring genotype can have an effect and may even be dominant by suppressing the maternal effect. Further studies will need to be carried out to elucidate the nature of this particular mother-offspring interaction.

The modulation of GABA\(_B\)R sensitivity in the H > WT offspring by the maternal effect without the actual transmission of a genetic information indicates that this effect is not mediated by a genetic mechanism but rather by an epigenetic mechanism. It has been shown that maternal effects, related to variability in postnatal care, alter the methylation status and chromatin conformation of specific neuronally expressed genes in the offspring and that these epigenetic changes are probably responsible for some of the lifelong behavioral alterations seen in the offspring (Kaffman and Meaney, 2007). Because expression of Fmrp is widespread and includes both neuronal and non-neuronal cells, it is possible that the Fmrp deficiency in H mothers alters their physiology and behavior during the gestational and postnatal periods and that these effects affect the epigenome of the offspring, leading to the lifelong neurochemical abnormalities presented here.

Human studies are consistent with the importance of the mutation status of the mother in FXS. Mothers with FXS have a greater predisposition to anxiety and depression (Mazzocco, 2000; Wheeler et al., 2007), and this could affect the postnatal environment of both healthy and FXS children. Although not demonstrated in FXS directly, studies have shown a negative impact of attention deficit hyperactivity disorder (ADHD) on parenting behaviors (Murray and Johnston, 2006) and improvements in children’s behavior when mothers were treated for ADHD (Daly and Fritsch, 1995). Symptoms of ADHD can often be identified in fragile X individuals (Hagerman et al., 1988). It would be important to specify what manifestations or aspects of FXS and neuropsychiatric disorders in general can be transmitted nongenetically because all progeny, whether genetically affected or not, could be susceptible to these effects.

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References


loss of pre- and postsynaptic GABA(B) responses in mice lacking GABA(B(1)).

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