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Descriptive analysis of seizures and comorbidities associated with fragile X syndrome

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Abstract

Background: Fragile X syndrome is characterized by a myriad of physical features, behavioral features, and medical problems. Commonly found behavioral features are hyperactivity, anxiety, socialization difficulties, and ASD. There is also a higher incidence than in the general population of strabismus, otitis media, and mitral valve prolapse. In addition, one of the most common medical problems associated with FXS is an increased risk of seizures. A subset of individuals carrying the full mutation of the FMR1 gene and diagnosed with fragile X syndrome (FXS) are reported to experience seizures, mostly during the first 10 years of their life span.

Methods: As part of a larger project to identify genetic variants that modify the risk of seizures, we collected clinical information from 49 carriers with FXS who experienced seizures and 46 without seizures. We compared seizure type and comorbid conditions based on the source of data as well as family history of seizures.

Results: We found that the concordance of seizure types observed by parents and medical specialists varied by type of seizure. The most common comorbid condition among those with seizures was autism spectrum disorder (47% per medical

records vs. 33% per parent report compared with 19% among those without seizures per parent report); the frequency of other comorbid conditions did not differ among groups. We found a slightly higher frequency of family members who experienced seizures among the seizure group compared with the nonseizure group. **Conclusion:** This study confirms previously reported features of seizures in FXS, supports additional genetic factors, and highlights the importance of information sources, altogether contributing to a better understanding of seizures in FXS.

KEYWORDS

ADHD, autism spectrum disorder, epilepsy, fragile X syndrome, seizures

1 | INTRODUCTION

Fragile X syndrome (FXS) is caused by an expansion of an unstable trinucleotide repeat (CGG) in the 5′UTR of the *FMR1* gene, to greater than 200 repeats. This large expansion, referred to as the "full" mutation, leads to the silencing of the *FMR1* gene and the loss of its product, FMRP, which in turn underlies the clinical manifestations of FXS. The *FMR1* gene is located at q27.3 on the X chromosome and, due to its location on the X chromosome, the prevalence of males affected with FXS of ~1/7000 is higher than that of affected females, ~1/11,000 (Hunter et al., 2014). These frequencies make FXS the most common inherited cause of intellectual disability and the most common monogenic cause of autism spectrum disorder (ASD).

Fragile X syndrome is characterized by a myriad of physical features, behavioral features, and medical problems (Lozano et al., 2016). Among the physical features, it is common to find large ears, an elongated face, macrocephaly, and macroorchidism. Additionally, commonly found behavioral features are hyperactivity, anxiety, socialization difficulties, and ASD. Although the majority of those affected with FXS do not suffer from fragile X-associated medical conditions, there is a higher incidence than in the general population of strabismus, otitis media, and mitral valve prolapse (Berry-Kravis, 2002; Hagerman et al., 2009). In addition, one of the most common medical problems associated with FXS is an increased risk of seizures (Hagerman & Stafstrom, 2009). Previous studies have estimated that between 10% and 40% of males carrying the full mutation of the *FMR1* gene experience seizures (Bailey et al., 2008; Berry-Kravis, 2002; Musumeci et al., 1999; Sabaratnam et al., 2001). In the majority of cases, seizures in those with FXS are easy to control with medications and they tend to resolve during childhood (Berry-Kravis, 2002). Several studies have described the presence of focal or localized seizures, generalized seizures, or both in patients with FXS, with focal or localized seizures being the most common type (Berry-Kravis et al., 2010).

FMRP protein is an RNA-binding protein that plays key roles in several processes, with a direct influence on dendritic formation and maturation (Comery et al., 1997; Weiler et al., 2004) and synaptic plasticity (Sidorov et al., 2013). Several studies have shown that lack or reduced levels of FMRP lead to an increase of immature dendritic spines in the brain (Bagni & Greenough, 2005). Similarly, studies in mice have shown synaptic abnormalities due to deficits in long-term potentiation (LTP) in the cortical and hippocampal regions and increased long-term depression (LTD) in the hippocampal region (Huber et al., 2002; Lauterborn et al., 2007; Li et al., 2002). These synaptic abnormalities are responsible for the audiogenic seizures observed in the *Fmr1* knock-out mice (Chuang et al., 2005) and in patients with FXS (Hagerman & Stafstrom, 2009).

Because the literature is limited with respect to the seizure phenotype in FXS, the goal of our study was to describe a series of individuals affected by FXS who had seizures and compare them with individuals with FXS who did not have evidence of seizures. This cohort is part of a larger study to identify modifying factors that might explain the presence of seizures (i.e., the incomplete penetrance) in this genetically susceptible group. Here, we detail the demographic information, general medical information, and clinical information regarding the presence and description of seizures including time of diagnosis, duration of first seizure, medications taken for seizures, age at last seizure, and number and type of seizures. Data were obtained from both medical records and parent reports, allowing us the opportunity to study the differences that arise in the interpretation of the seizure classification between medical professionals and parents.

2 | METHODS

2.1 | Participants and recruitment

This descriptive study is part of a larger parent study that has the goal to identify modifying genetic variants for

the increased susceptibility of seizures on a full mutation background. Eligible participants included those with documented FXS due to an *FMR1* full mutation. Cases were defined as those with at least one seizure, including both males and females and all ethnic groups. Controls were defined as males with FXS who did not experience a seizure by age 17 years. The reason for not including females with FXS in the control group was that the penetrance of seizures is much lower due to the masking of the normal *FMR1* allele. In contrast, they were included in the case group, as a female having seizures suggests that they may have increased genetic load of seizure susceptibility variants.

Participants and samples were identified through a wide net of resources, all coordinated through the National Fragile X Center at Emory University. Thus, both cases and controls were considered a convenience sample. Recruitment sources included the fragile X specialty or general genetics clinics, the Fragile X Clinic and Research Consortium (FXCRC), the Fragile X Research Participant Registry of the Carolina Institute for Developmental Disabilities, fragile X family conferences, fragile X listservs, parent support groups and collaborators directing FXS research programs. At the Emory Fragile X Center, once contact was made with a family diagnosed with fragile X-associated disorder, all family members were screened for eligibility. The Emory team conducted screening, consenting, and data collection. The caregiver (usually the mother) completed a semi-structured interview that determined seizure status. Medical records were collected for those with a seizure, once caregiver permission was obtained. Parent-reported data included general demographics of the proband (e.g., date of birth, age at last evaluation, sex, race/ethnicity, documentation of FXS), general medical information (family history of seizures, cooccurring medical conditions, current and past medications), and for those with a seizure, seizure-specific information (diagnosis, duration of first seizure, medications taken for seizures, age at last seizure, number and type of seizures, etc.). The caregiver was also asked to complete the Social Communication Questionnaire-Lifetime (SCQ; Berument et al., 1999, Rutter et al., 2003) for the proband. Table 1 provides the demographics of the study sample.

Protocols and consent forms were approved by Emory University Institutional Review Board, and informed consent was obtained from legal guardians for the proband. Assent was also obtained if the proband was able. Collaborators at other recruitment sites that provided clinical information obtained an institutional review for their data collection. Only deidentified information was provided to the study sample.

2.2 | Statistical analyses

A 2×2 χ^2 test of independence with one degree of freedom was performed to test for differences in the presence of comorbid conditions between cases and controls. A Student's t test was used to compare groups on continuous measures (i.e., SCQ scores).

3 | RESULTS

3.1 | Study population

In our study, 49 individuals were enrolled (44 males and 5 females) carrying the full mutation of the *FMR1* gene who had a history of seizures. Additionally, our study included 46 males older than age 17 carrying the full mutation who had no history of seizures. Our sample study contained individuals with a wide age distribution from 6 to 50 years old.

The distribution of self-identified ethnicity among all participants stratified by case/control status is shown in Table 1. The vast majority of participants self-identified as White/Caucasian, with about 12% reporting as other ethnicities. The percentage of participants who did not state their information or were stated as unknown among cases was 6.1%.

TABLE 1 Demographics of the study population

	FXS with seizures (cases = 49)	FXS without seizures (controls = 46)
Age at evaluation (mean ± SD)	19.9 ± 10.8	26.1 ± 7.9
Sex: % male	89.8	100
Ethnicity (%)		
White	40 (81.6)	39 (84.8)
Black	3 (6.1)	2 (4.3)
Asian	0 (0)	1 (2.2)
Hispanic	3 (6.1)	4 (8.7)
Unknown/declined to answer	3 (6.1)	0 (0)

3.2 | Seizure description and response to medication

The majority of individuals enrolled in our study suffered their first seizure before the age of 10, both in males (40/44, 90.1%) and in females (4/5, 80%), with the vast majority having their last seizure more than 6 months prior to the time of interview. We performed our analysis both with and without these five cases (ages 11–28), and we did not observe any statistically significant difference in our results. Thus, we have included all cases for the following descriptions. In males, these seizures were described as focal or localized in 31.8% (14/44), generalized in 11.4% (5/44), and both types in 27.3% (12/44). Additionally, one male was reported as having febrile seizures, and in 12 cases, the seizures were not described. Among the five females, one reported having focal or localized seizures, two reported generalized seizures, one reported both type of seizures, and one was classified as unknown. Most of the patients who suffered seizures reported taking one medication to control them (24/49, 48.9%) with fewer reporting two or more drugs (14/49, 28.6%); and even fewer (5/49, 10.2%) reporting no medications for seizure control. Six cases did not provide this information. Additionally, at the time of the interview, 48.9% (24/49) of the patients were still taking medications to control the seizures.

The study of seizures and other conditions associated with FXS is a complex process that many times requires information from caretakers as well as medical professionals. This is especially true for seizures, as the event itself typically does not occur in the presence of the medical professional. Here we compare the seizure diagnosis from each source of information among our case seizure group. Table 2 shows the type of seizures and the number of cases reported in medical reports compared with the seizure category reported by parents, along with the percentage of concordance when applicable.

We note that there is lower concordance between medical and parent reports for the focal or "both" seizure type categories (33.3% and 30.8%, respectively) compared with the generalized category (71.4%).

3.3 | Study of the family history of seizures

We also studied the family history of seizures in individuals with FXS who did and did not experience seizures. We hypothesized that case probands would have an increased risk of harbor seizure-related susceptibility variants that may increase the risk of seizures in their relatives compared with relatives of our control probands. We obtained parent reports on the family history of seizures on 42 case probands and 46 control probands. Among case probands, 12 (28.6%) had members in their family who suffered seizures at some point during their lifetime; in five of the 12 families (41.7%), the family member was a first-degree relative to the case proband. Among control probands, six of 46 (13%) had a family history of seizures, and two (33.3%) were first-degree relatives who had suffered seizures. Because we did not have full pedigrees and, thus, did not know the total number of relatives on whom the parents of probands were reporting, we did not perform a statistical comparison. Irrespective, the data are consistent with our hypothesis.

3.4 | Analyses of seizures and cooccurring conditions

We evaluated cooccurring medical conditions among those with and without seizures. We collected medical records from all the cases included in this study. No medical records were obtained from controls; however, parent report of cooccurring medical conditions was collected on both cases and controls. Table 3 lists the conditions that occurred in more than five of the 49 cases and their corresponding frequency in control individuals. Using the medical records to document-diagnosed conditions, we found that ASD (46.9%), attention deficit hyperactivity disorder (ADHD, 28.6%), anxiety (24.5%), sleep disorders (16.3%), otitis or ear problems (14.3%), behavioral disorders or aggressive behavior (12.2%), and gastroesophageal reflux disease (GERD) (12.2%) were the most common

TABLE 2 Type of seizures by information sources ("unknown" includes both checking unknown seizure type and not providing an answer)

Medical report	No. of cases	Parent report	% concordance
Febrile	1	Febrile = 1	100%
Focal	15	Focal = 5, Generalized = 2, 1 Both = 1, Unknown = 7	33.3%
Generalized	7	Generalized = 5 Both = 1, Unknown = 1	71.4%
Both (focal and generalized)	13	Both = 4, Focal = 4, Generalized = 4, Unknown = 1	30.8%
Unknown	13	Both = 2, Focal = 2, Generalized = 6, Unknown = 3	n/a

TABLE 3 Cooccurring conditions in individuals with FXS with and without seizures (conditions listed occurred in >5 patients in the case group using medical records)

Comorbid condition	Cases (with seizures, $n = 49$) Medical records	Cases (with seizures, $n = 42$) Parent report	Controls (without seizures, $n = 46$) Parent report	p value comparing parent-reported case/control frequencies
ASD	23 (46.9%)	14 (33.3%)	9 (19.5%)	0.14
ADHD	14 (28.6%)	12 (28.6%)	11 (23.9%)	0.62
Anxiety	12 (24.5%)	6 (14.3%)	8 (17.4%)	0.69
Sleep disorders	8 (16.3%)	4 (9.5%)	2 (4.3%)	0.34
Otitis/ear problems	7 (14.3%)	3 (7.1%)	1 (2.1%)	0.26
GERD	6 (12.2%)	4 (9.5%)	5 (10.8%)	0.84
Behavioral disorder/ aggression	6 (12.2%)	3 (7.1%)	3 (6.5%)	0.91

Abbreviations: ASD, autism spectrum disorder; ADHD, attention deficit hyperactivity disorder; GERD, gastroesophageal reflux disease.

conditions associated with the presence of seizures in patients with FXS.

To compare the frequency of these co-occurring conditions in our control group without seizures, we were only able to use parent reports; medical records were not collected. Parent report information was obtained through a detailed questionnaire answered by the families of both groups in our study. Noting that limitation, we had information from 46 controls, a similar number to our case study group for which we were able to collect medical reports. In general, the percentage of patients with FXS who had a cooccurring condition was lower in the control vs. case group for the most common cooccurring conditions; however, no difference was statistically significant when comparing diagnoses in both groups (Table 3). Nonetheless, recognizing the limitations of comparing frequencies based on different sources of information, we did find that the presence of ASD was statistically higher among cases based on medical records compared with controls based on parent reports (p value adjusted by the number of comparisons = 0.035).

3.5 | Study of the ASD risk using the social communication questionnaire-lifetime (SCQ)

The SCQ is a widely used screener for symptoms of ASD. We compared the SCQ total score and the percent of probands who had a total score of ≥15, a cutoff that suggests the proband is at high risk for ASD. The SCQ was completed for 42 cases and 39 controls. Although the mean total score (±SD) for cases (18.7 ± 6.9) was slightly elevated compared with that of controls (17.6 ± 7.8), this difference was not statistically significant (t test; $p = 0.52$). Comparing the percent of probands with a total score ≥15, the case group showed an elevated percentage of high-risk scores compared with controls (54.2% vs. 45.7%); however, this difference was not statistically significant (chi-square test; $p = 0.48$).

4 | DISCUSSION

We present a descriptive study of seizures that have been reported to occur in 10%–40% of males carrying the full mutation of the *FMR1* gene and diagnosed with FXS (Bailey et al., 2008; Berry-Kravis, 2002; García-Nonell et al., 2008; Musumeci et al., 1999; Sabaratnam et al., 2001). In 2010, Berry-Kravis et al. published a study on the characteristics and treatment of seizures in individuals carrying the *FMR1* full mutation. This study was part of a larger survey (Bailey et al., 2010) focused on identifying the needs of families with a member who had FXS or carried a full mutation. More specifically, questionnaires were generated by researchers and clinicians with the help of parents of children with FXS and were sent to families to complete and return. The authors collected demographic information, seizure characteristics, and treatment from a total of 173 individuals (154 males and 19 females). Additionally, the results from this survey were compared with physician-generated data from the Rush University Medical Center Fragile X Clinic. Clinical information from a total of 46 individuals from this clinic (39 males and 7 females) was used in this comparison. This step allowed researchres to corroborate from a clinical perspective, the results obtained from the parent report surveys.

For our study, we were able to collect information describing the seizures in detail, such as time of diagnosis, duration of first seizure, age at last seizure, the number and type of seizures, as well as demographic information to help us better understand the presence of this symptom

in patients with FXS. We were also able to obtain parent reports and medical reports from the same individuals who suffered seizures. This is especially important, as it allows a direct comparison between both sources of information regarding seizures. This comparison also serves as proof of validation to parent reports, as this is usually the main source of information to establish the presence and type of seizures in patients.

As in the study of Berry-Kravis et al. in 2010, our study confirms that the majority of patients suffered their first seizure before the age of 10, both in males (90.1% in our study vs 92% Berry-Kravis et al.) and in females (80% vs 80%, respectively). Additionally, it is worth noting that, with the exception of the one case of febrile seizures where the physician's and parent's reports coincide, there was a low concordance between medical reports and parent reports, with parents reporting generalized seizures more often than any other type of seizure (Table 2). One possible interpretation is that seizures may appear to be "generalized" to the untrained eye of the parents compared with a medical professional. This highlights the importance of gathering information from both sources to assess the prevalence of the different types of seizures that are associated with FXS.

With respect to cooccurring conditions, we found that most conditions were reported at a higher frequency in medical records than in parent reports among case probands (comparison was not possible for controls). For the comparison of cases vs. controls using parent reports, no condition was found to statistically significantly differ between groups.

However, there was a suggestion that ASD was more common among cases than among controls: 33% or 47% of cases were diagnosed with ASD based on parent reports or medical records, respectively, compared with 19% among controls based on parent reports. Also, 54% of cases vs. 46% of controls had a high risk for ASD as measured by the SCQ. Again, the different frequencies based on the source of information highlight the complexity and the importance of using medical reports and parent reports for the same individuals in order to better understand the symptoms associated with FXS. These results are consistent with previous studies that observed an association between FXS and the presence of ASD and seizures (reviewed in Manman et al., 2017). For example, in a study by Kaufmann et al. (2017), the authors compared patients with FXS with and without a diagnosis of ASD. Their results showed a higher prevalence of seizures among those who had a diagnosis of ASD and also a higher occurrence of comorbidities, such as behavioral problems or sleep disorders. ADHD, the second most common condition we found among those with and without seizures (28.6% and 23.9%, respectively), was previously found associated with a specific type of electroencephalography (EEG) (Cowley et al., 2016). This study, based on 11 children diagnosed with FXS, found that a specific "epileptiform" endophenotype was associated with the diagnosis of attention problems. We speculate that using seizure endophenotypes instead of clinical/parent observation may better identify possible associated conditions. Indeed, Cowley et al. (2016) suggest that children diagnosed with FXS might benefit from more personalized treatments that take into consideration comorbid disease symptoms. Other comorbid conditions of FXS reported in our study are consistent with many studies, some being associated with other major findings. For example, Budimirovic et al. (2022) focused on cooccurring conditions associated with the presence of sleep problems in patients with FXS. They found that sleep difficulties were associated with behavioral problems such as irritability or aggression, anxiety, and hyperactivity; all conditions reported in our data set.

Finally, our hypothesis that case probands have an increased risk of harbor seizure-related susceptibility variants with respect to relatives and control probands were supported by family histories, although these data were limited.

In summary, our study confirmed previously reported features of seizures in FXS including their relatively benign evolution and association with ASD. It also supported additional genetic factors among those with FXS and seizures. However, our findings also highlighted the importance of information sources for studies of seizures in FXS. Altogether, these data contribute to a better understanding of seizures and other common co-occurring conditions in FXS. Similar to others (e.g., Erickson et al., 2017), we emphasize the importance of understanding the etiology of serious comorbidities, such as seizure disorders, in individuals with FXS to help target therapeutics that aim to ameliorate the clinical impact of the fragile X mutation.

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CONFLICT OF INTEREST

RH has received funding from Zynerba and the Azrieli Foundation for treatment studies in FXS. WEK is currently the Chief Medical Officer of Anavex Life Sciences Corp. The other authors have no conflict of interest to declare. All coauthors have seen and agree with the contents of the manuscript and there is no financial interest to report.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated, or the article describes entirely theoretical research.

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REFERENCES

Bagni, C., & Greenough, W. T. (2005). From mRNP trafficking to spine dysmorphogenesis: The roots of fragile X syndrome. *Nature Reviews. Neuroscience*, *6*(5), 376–387. https://doi.org/10.1038/nrn1667

Bailey, D. B., Raspa, M., & Olmsted, M. G. (2010). Using a parent survey to advance knowledge about the nature and consequences of fragile X syndrome. *American Journal on Intellectual and Developmental Disabilities*, *115*(6), 447–460. https://doi.org/10.1352/1944-7558-115.6.447

Bailey, D. B., Jr., Raspa, M., Olmsted, M., & Holiday, D. B. (2008). Co-occurring conditions associated with FMR1 gene variations: Findings from a national parent survey. *American Journal of Medical Genetics. Part A*, *146A*(16), 2060–2069. https://doi.org/10.1002/ajmg.a.32439

Berry-Kravis, E. (2002). Epilepsy in fragile X syndrome. *Developmental Medicine and Child Neurology*, *44*(11), 724–728. https://doi.org/10.1017/s0012162201002833

Berry-Kravis, E., Raspa, M., Loggin-Hester, L., Bishop, E., Holiday, D., & Bailey, D. B. (2010). Seizures in fragile X syndrome: Characteristics and comorbid diagnoses. *American Journal on Intellectual and Developmental Disabilities*, *115*(6), 461–472. https://doi.org/10.1352/1944-7558-115.6.461

Berument, S. K., Rutter, M., Lord, C., Pickles, A., & Bailey, A. (1999). Autism screening questionnaire: Diagnostic validity. *The British Journal of Psychiatry*, *175*, 444–451. https://doi.org/10.1192/bjp.175.5.444

Budimirovic, D. B., Protic, D. D., Delahunty, C. M., Andrews, H. F., Choo, T. H., Xu, Q., Berry-Kravis, E., Kaufmann, W. E., & FORWARD Consortium. (2022). Sleep problems in fragile X syndrome: Cross-sectional analysis of a large clinic-based cohort. *American Journal of Medical Genetics. Part A*, *188*(4), 1029–1039. https://doi.org/10.1002/ajmg.a.62601

Chuang, S. C., Zhao, W., Bauchwitz, R., Yan, Q., Bianchi, R., & Wong, R. K. (2005). Prolonged epileptiform discharges induced by altered group I metabotropic glutamate receptor-mediated synaptic responses in hippocampal slices of a fragile X mouse model. *The Journal of Neuroscience*, *25*(35), 8048–8055. https://doi.org/10.1523/JNEUROSCI.1777-05.2005

Comery, T. A., Harris, J. B., Willems, P. J., Oostra, B. A., Irwin, S. A., Weiler, I. J., & Greenough, W. T. (1997). Abnormal dendritic spines in fragile X knockout mice: Maturation and pruning deficits. *Proceedings of the National Academy of Sciences of the United States of America*, *94*(10), 5401–5404. https://doi.org/10.1073/pnas.94.10.5401

Cowley, B., Kirjanen, S., Partanen, J., & Castren, M. L. (2016). Epileptic electroencephalography profile associates with attention problems in children with fragile X síndrome: Review and case series. *Frontiers in Human Neuroscience*, *10*, 353. https://doi.org/10.3389/fnhum.2016.00353

Erickson, C. A., Davenport, M. H., Schaefer, T. L., Wink, L. K., Pedapati, E. V., Sweeney, J. A., Fitzpatrick, S. E., Brown, W. T., Budimirovic, D., Hagerman, R. J., Hessl, D., Kaufmann, W. E., & Berry-Kravis, E. (2017). Fragile X targeted pharmacotherapy: Lessons learned and future directions. *Journal of Neurodevelopmental Disorders*, *9*, 1–14. https://doi.org/10.1186/s11689-017-9186-9

García-Nonell, C., Ratera, E. R., Harris, S., Hessl, D., Ono, M. Y., Tartaglia, N., Marvin, E., Tassone, F., & Hagerman, R. J. (2008). Secondary medical diagnosis in fragile X syndrome with and without autism spectrum disorder. *American Journal of Medical Genetics. Part A*, *146A*(15), 1911–1916. https://doi.org/10.1002/ajmg.a.32290

Hagerman, P. J., & Stafstrom, C. E. (2009). Origins of epilepsy in fragile X syndrome. *Epilepsy Currents*, *9*(4), 108–112. https://doi.org/10.1111/j.1535-7511.2009.01309.x

Hagerman, R. J., Berry-Kravis, E., Kaufmann, W. E., Ono, M. Y., Tartaglia, N., Lachiewicz, A., Kronk, R., Delahunty, C., Hessl, D., Visootsak, J., Picker, J., Gane, L., & Tranfaglia, M. (2009). Advances in the treatment of fragile X syndrome. *Pediatrics*, *123*(1), 378–390. https://doi.org/10.1542/peds.2008-0317

Huber, K. M., Gallagher, S. M., Warren, S. T., & Bear, M. F. (2002). Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(11), 7746–7750. https://doi.org/10.1073/pnas.122205699

Hunter, J., Rivero-Arias, O., Angelov, A., Kim, E., Fotheringham, I., & Leal, J. (2014). Epidemiology of fragile X syndrome: A systematic review and meta-analysis. *American Journal of Medical Genetics Part A*, *164A*(7), 1648–1658.

Kaufmann, W. E., Kidd, S. A., Andrews, H. F., Budimirovic, D. B., Esler, A., Haas-Givler, B., Stackhouse, T., Riley, C., Peacock, G., Sherman, S. L., Brown, W. T., & Berry-Kravis, E. (2017). Autism Spectrum disorder in fragile X syndrome: Cooccurring conditions and current treatment. *Pediatrics*, *139*(Supplement_3), S194–S206. https://doi.org/10.1542/peds.2016-1159F

Lauterborn, J. C., Rex, C. S., Kramár, E., Chen, L. Y., Pandyarajan, V., Lynch, G., & Gall, C. M. (2007). Brain-derived neurotrophic factor rescues synaptic plasticity in a mouse model of fragile X syndrome. *The Journal of Neuroscience*, *27*(40), 10685–10694. https://doi.org/10.1523/JNEUROSCI.2624-07.2007

Li, J., Pelletier, M. R., Perez Velazquez, J. L., & Carlen, P. L. (2002). Reduced cortical synaptic plasticity and GluR1 expression

associated with fragile X mental retardation protein deficiency. *Molecular and Cellular Neurosciences*, *19*(2), 138–151. https://doi.org/10.1006/mcne.2001.1085

Lozano, R., Azarang, A., Wilaisakditipakorn, T., & Hagerman, R. J. (2016). Fragile X syndrome: A review of clinical management. *Intractable & Rare Diseases Research*, *5*(3), 145–157. https://doi.org/10.5582/irdr.2016.01048

Manman, N., Ying, H., Dy, A. B. C., Du, J., Jin, H., Qin, J., Zhang, J., Li, Q., & Hagerman, R. J. (2017). Autism symptoms in fragile X syndrome. *Journal of Child Neurology*, *32*(10), 903–909. https://doi.org/10.1177/0883073817712875

Musumeci, S. A., Hagerman, R. J., Ferri, R., Bosco, P., Dalla Bernardina, B., Tassinari, C. A., De Sarro, G. B., & Elia, M. (1999). Epilepsy and EEG findings in males with fragile X syndrome. *Epilepsia*, *40*(8), 1092–1099. https://doi.org/10.1111/j.1528-1157.1999.tb00824.x

Rutter, M., Bailey, A., & Lord, C. (2003). *Social communication questionnaire*. Western Psychological Services.

Sabaratnam, M., Vroegop, P. G., & Gangadharan, S. K. (2001). Epilepsy and EEG findings in 18 males with fragile X syndrome. *Seizure*, *10*(1), 60–63. https://doi.org/10.1053/seiz.2000.0492

Sidorov, M. S., Auerbach, B. D., & Bear, M. F. (2013). Fragile X mental retardation protein and synaptic plasticity. *Molecular Brain*, *8*(6), 15. https://doi.org/10.1186/1756-6606-6-15

Weiler, I. J., Spangler, C. C., Klintsova, A. Y., Grossman, A. W., Kim, S. H., Bertaina-Anglade, V., Khaliq, H., de Vries, F. E., Lambers, F. A., Hatia, F., Base, C. K., & Greenough, W. T. (2004). Fragile X mental retardation protein is necessary for neurotransmitter-activated protein translation at synapses. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(50), 17504–17509. https://doi.org/10.1073/pnas.0407533101

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