Family as a Context for Child Development: Mothers with the *FMR1* Premutation and Their Children with Fragile X Syndrome

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ABSTRACT

Fragile X syndrome (FXS) is a genetic disorder caused by changes of the *FMR1* gene that is passed along among families. A range of developmental processes may be impacted with wide variation in abilities across individuals with FXS. Mothers of children with FXS are often carriers of a "premutation" expansion on the *FMR1* gene, which is associated with its own clinical phenotype. These maternal features may increase individual and family vulnerabilities, including increased risk for depression and anxiety disorders and difficulties in social and cognitive ability. These characteristics may worsen with age, and potentially interact with a child's challenging behaviors and with family dynamics. Thus, families of children with FXS may experience unique challenges related to genetic risk, manifested across both children and parents, that should be considered in therapeutic planning to optimize outcomes for children and their families. In this article, we review core features of the *FMR1* premutation as expressed in mothers and aspects of the family environment that interface with developmental outcomes of children with FXS. Recommendations for family-centered support services are discussed.

KEYWORDS: fragile X premutation, fragile X syndrome, fragile X carriers, mother–child associations

Learning Outcomes: As a result of this activity, the reader will be able to (1) identify key characteristics of the FMR1 premutation phenotype; (2) describe the significance of potential premature age decline in this population; and (3) explain the relevance of maternal FMR1 premutation characteristics in terms of clinical outcomes in children.

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Neurogenetic Disorders: Exploring the Role of Context and Communication Partners; Guest Editor, Laura J. Mattie, Ph.D.

Semin Speech Lang 2021;42:277–286.
DOI: https://doi.org/10.1055/s-0041-1730988.
ISSN 0734-0478.

Fragile X syndrome (FXS) is an inherited genetic disorder that affects approximately 1 in 7,000 males and 1 in 11,000 females worldwide.[1] The syndrome represents the most common inherited form of intellectual disability and the most common single-gene disorder associated with autism spectrum disorder (ASD). Nearly all males with FXS and about a third of females have intellectual disability,[2] and rates of comorbid ASD are estimated at 55 to 89% in males and 10 to 14% in females.[3–6] Other core features of the FXS phenotype include anxiety, hyperactivity, hyperarousal, and executive dysfunction.[7–10] Speech-language pathologists are often involved in clinical and/or educational services for this population, given that impairments in speech, language, and literacy skills are common in FXS.[11–16] Because FXS is a genetic disorder that is passed through families, family members of individuals with FXS may also experience clinical involvement, including mothers who are genetic carriers of the condition. In this article, we review the core clinical symptoms experienced by mothers of children with FXS in relation to the developmental outcomes of children with FXS and implications for service provision.

FXS is caused by an abnormal expansion of a CGG trinucleotide sequence on the fragile X mental retardation-1 (*FMR1*) gene located on the X chromosome.[17–19] In most individuals in the general population, the *FMR1* CGG sequence repeats between 10 and 54 times. FXS occurs when the CGG sequence exceeds 200 repeats, which causes the gene to "shut down" and disrupts production of fragile X mental retardation protein (FMRP), a protein that is necessary for cognitive development and function.[20–22] A notable feature of FXS that distinguishes it from other common neurogenic syndromes such as Down syndrome is that FXS is a heritable condition where children with FXS inherit the condition from their mothers who are genetic carriers. Mothers of children with FXS, unless they have FXS themselves, are known genetic carriers of a smaller CGG expansion of 55 to 200 repeats, called the *FMR1* "premutation." The *FMR1* premutation is relatively common in the general population; approximately 1:148–291 females and 1:290–855 males worldwide possess the premutation, although many of these individuals are unaware of their genetic status.[1,20,23] While both men and women can carry the *FMR1* premutation, with very few exceptions fathers cannot pass FXS to their children.[1,20,21] When transmitted from fathers, the *FMR1* premutation CGG expansion is stable and does not expand further[20,21,24]; therefore, fathers pass the *FMR1* premutation to all of their daughters and none of their sons (sons will inherit their father's Y chromosome). Mothers, on the other hand, have approximately a 50/50 chance of passing the expanded CGG repeat sequence to all of their children, who may inherit either the *FMR1* premutation or the "full mutation" of FXS if the CGG sequence expands beyond 200 repeats. Given this inheritance pattern, except for very rare exceptions, FXS is always inherited from mothers. Therefore, the clinical problems experienced by mothers who carry the *FMR1* premutation have broader implications, as they can affect outcomes for both the mother and her children with FXS. In this article, we focus on the clinical consequences of the *FMR1* premutation in mothers and implications for children and families.

Historically, mothers with the *FMR1* premutation were thought to be "silent carriers" who were clinically unaffected. Over the last two decades, it has become increasingly clear that mothers with the *FMR1* premutation are at heightened susceptibility for experiencing adverse phenotypes themselves. Two well-documented disorders that are caused by the *FMR1* premutation include fragile X-associated primary ovarian insufficiency (FXPOI) and fragile X-associated tremor/ataxia syndrome (FXTAS). FXPOI is a condition characterized by early menopause and fertility problems, documented in approximately 20% of women with the *FMR1* premutation.[25] FXTAS is a late-onset neurodegenerative disease characterized by movement and cognitive problems that affects approximately 15% of women with the *FMR1* premutation in old age.[7,26] In addition to FXPOI and FXTAS, mothers with the *FMR1* premutation are at an increased risk for a wide range of other medical, cognitive,

and psychiatric symptoms, including mood and anxiety disorders, executive dysfunction, and social-communication differences such as poor eye contact and conversational pragmatic language deficits.[27–30] These maternal features may increase individual and family vulnerabilities and should be considered in therapeutic planning to optimize outcomes for both children with FXS and their families. Below we review core mental health, pragmatic language, and executive function features of the *FMR1* premutation as expressed in mothers, with a focus on the *FMR1* premutation phenotype as an aspect of the family environment that may interface with developmental outcomes of children with FXS.

THE *FMR1* PREMUTATION PHENOTYPE IN MOTHERS

Mental Health Features

Women with the *FMR1* premutation are at increased risk for mental health disorders, including anxiety and depression.[26,31–34] In one study comparing mothers with the *FMR1* premutation ($n = 93$) to a large national database ($n = 2{,}159$), 43% of mothers with the *FMR1* premutation had experienced a major depressive episode in their lifetime, which was significantly elevated compared with the rate of 32% of the women from the comparison sample.[32] This report also detected elevated rates of lifetime panic disorder (9%) and current agoraphobia (3%) in mothers with the *FMR1* premutation.[32] In a related report following a largely overlapping sample longitudinally, Roberts et al[33] found that the rates of depression and anxiety increased significantly in mothers with the *FMR1* premutation across middle age. In a 3-year period, the rates of lifetime major depressive disorder increased from 46 to 54% and the rates of anxiety disorders increased from 28 to 35%. These findings suggest a striking increase in the rates of mental health disorders in mothers with the *FMR1* premutation across middle adulthood and have implications for service delivery, as they suggest that many mothers with the *FMR1* premutation may be struggling to manage their own clinical problems at a time when they are also assuming immense caregiver burden related to parenting a child with FXS.

Both biological and environmental factors are thought to contribute to risk for mental health disorders in mothers with the *FMR1* premutation. For instance, mothers who carry the *FMR1* premutation demonstrate varied repeat lengths of the CGG sequence. In research, premutation CGG repeat expansions are often categorized as low premutation repeats between approximately 55 and 79, midrange expansions of approximately 80 and 110 CGG repeats, and high premutation expansions of approximately 110 and 200 repeats (see Table 1). Several reports have shown that mothers who carry midrange CGG repeat lengths may be more likely to experience depression and anxiety than those with higher or lower premutation repeat numbers.[32,35] Environmental factors, such as child problem behavior and negative life stressors, may also contribute to mental health risk in an additive or interactive manner. For example, having more than one child with FXS or a child who displays increased problem behaviors is associated with increased anxiety and depression risk.[32,33] The relationship between child problem behaviors and maternal mental health risk is likely bidirectional, as studies also suggest that children with FXS demonstrate more challenging behaviors when mothers have increased symptoms of depression or anxiety.[31–33,36,37] Thus, a cyclical pattern may occur where behavioral challenges in children with FXS lead to increased parenting stress and poor

Table 1 *FMR1* CGG Repeat Categories

CGG repeat category	CGG repeat length
No expansion on *FMR1* ("normal")	10–54
Premutation	55–200
Low premutation	~55–79
Midrange premutation	~80–110
High premutation	~110–200
Full mutation	>200

Note: Premutation subcategories reflect potential zones of vulnerability that have been reported in emerging research, and are approximate.[56,59,72] A "full mutation" CGG expansion on *FMR1* is associated with fragile X syndrome.

maternal mental health, which in turn may lead to further increases in challenging behaviors displayed by children. Awareness of the impact of maternal mental health symptoms on the family environment and on child behavior can assist clinicians in prioritizing referrals for psychological counseling and prescribing interventions that are a good match with family characteristics.

Pragmatic Language Features

Pragmatic language difficulties have also been noted in mothers with the *FMR1* premutation. When compared with mothers of children with typical development or ASD, mothers with the *FMR1* premutation show more pragmatic violations during conversation, which include perseverating on topics, talking too much, talking too little, providing too many details, as well as exhibiting difficulties with suprasegmental features of speech, such as use of inappropriate volume and odd intonation.[29,38] Although the pragmatic language difficulties observed in the *FMR1* premutation are typically mild, growing evidence suggests that these features are related to the developmental outcomes of children with FXS. Specifically, maternal pragmatic language difficulties are associated with poorer receptive vocabulary, reduced expressive syntax skills, and increased ASD symptoms in children with FXS.[28,39] This is possibly due to the child being less able to benefit and learn from interactions with their caregivers when they are exposed to ineffective language models, a notion that aligns with a transactional model of developmental theory. Under this model, development is informed by reciprocal exchanges between the child and their social context.[40]

High-quality parental interactions that are emotionally positive and verbally responsive are known to support child engagement, responsiveness, and learning and are associated with enhanced language outcomes in children with FXS.[41–44] For example, Warren et al[44] investigated responsivity in mothers of children with FXS, as characterized by reciprocal maternal behaviors such as comments, gestures, requests, and recasts during interactions with their child. A more responsive maternal interaction style robustly predicted later expressive and receptive language and overall communicative ability in young children with FXS. These findings have been replicated into late childhood and adolescence.[41] Related work suggests that low-quality asynchronous interactions between mothers and their children with FXS are associated with increased maternal pragmatic language difficulties.[45] These findings suggest that maternal pragmatic language skills are a relevant aspect of the child's social learning environment that may influence developmental outcomes of children with FXS via reduced quality of the mother–child interactions.[42–44]

Finally, it is notable that pragmatic language difficulties in mothers with the *FMR1* premutation are also tied to the health and well-being of mothers themselves. Mothers who experience high levels of pragmatic language difficulty are more likely to report loneliness, depression, decreased life satisfaction, and poorer quality of family relationships.[46] Associations between the pragmatic language skills of mothers with the *FMR1* premutation, their own well-being, and their children's outcomes underscore the importance of family-centered practices that recognize the transactional nature of family interactions and relationships and individualize services to the needs of the family as a whole.

Executive Function and Other Cognitive and Linguistic Features

Deficits in cognitive skills such as executive functions (e.g., attention, working memory, inhibition, organization), visuospatial processing, arithmetic, and mathematical reasoning have been documented in a subset of women with the *FMR1* premutation.[47–54] These deficits range in severity and are not universal, which highlights the need to better understand personalized risk factors that can predict which individuals will experience symptoms. Perhaps the most widely documented cognitive difficulty in women with the *FMR1* premutation is in response inhibition, an aspect of executive function that reflects the ability to inhibit prepotent (e.g., automatic) thoughts and behaviors.[30,55–58] Relative to mothers of children with ASD and children with typical development, women with the *FMR1* premutation

show poorer performance on tasks requiring the suppression of prepotent verbal, visual, and oculomotor responses.[28,30,55,57–59] Vulnerability for inhibition deficits in women with the *FMR1* premutation appears to be tied to genetic risk. For example, in a large study of over 100 mothers with the *FMR1* premutation, Klusek et al[56] found that mothers who carried midrange CGG lengths of approximately 80 to 110 repeats showed increased vulnerability for verbal inhibition deficits relative to those with higher or lower premutation CGG expansions. Specifically, latency was longest (indicating poorer inhibition skills) for mothers with midrange CGG repeats relative to those with lower (<80) or higher (~110–120) CGG repeat lengths. Increased latency was also observed among mothers who carried high CGG repeats of greater than 120, suggesting that high CGG repeat lengths may also be associated with increased vulnerability. Older age was also associated with poorer inhibition skills. Fig. 1 depicts the relationship between CGG repeat lengths with response latency (inhibition) across mothers of various ages.[56]

Similar CGG-dependent associations have been detected in the presentation of language disfluencies, which are theoretically tied to deficits in inhibitory control.[60] In language samples, mothers with the *FMR1* premutation tend to produce more disfluencies (i.e., word and phrase repetitions, interjections, filled pauses) relative to mothers of children with other neurodevelopmental disorders such as ASD,[30,59,61] with the highest rate of disfluencies observed among mothers who carried midrange CGG repeat lengths (~80–110).[59] Therefore, there is converging evidence that clinical features of the *FMR1* premutation may have increased severity among those with midrange CGG repeat lengths, suggesting that the length of the premutation CGG expansion may represent a personalized risk factor that may be useful in targeting prevention efforts.[30,55,59,61] With genetic testing becoming increasingly accessible, it is common for mothers with the *FMR1* premutation to know the length of their CGG repeat expansion. As understanding of CGG-associated risk continues to grow, it may soon be possible to apply information about individual CGG repeat numbers to better understand personalized risk and tailor prevention/treatment accordingly.

Older age also appears to be a risk factor for cognitive involvement in mothers with the *FMR1* premutation. A growing number of cross-sectional studies have detected associations between older age and the expression of executive dysfunction symptoms, suggesting that mothers with the *FMR1* premutation may experience premature age-related decline. For example, in a study of 134 mothers with the

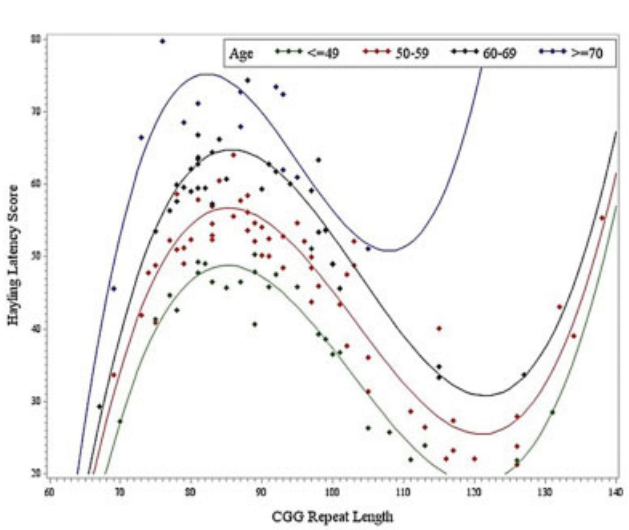

Figure 1 Effect of age and CGG repeat length on response inhibition skills. *Note*: Longer latency on the Hayling reflects poorer inhibition skills. (Reproduced with permission from Klusek et al,[56] Copyright 2020 by Elsevier.)

FMR1 premutation aged 39 to 88 years, Klusek et al[56] documented a significant association between older age and verbal inhibition deficits, with findings suggesting that age-related decline may begin as early as the fourth decade of life and the severity of deficits increase with each passing decade (see Fig. 1 for illustration of age effects).

Other reports have documented similar age effects in the areas of oculomotor inhibition,[55] language fluency,[30] and magnitude comparison and numerical enumeration performance.[49,50] Importantly, in each of these reports, the age effects were not observed in control samples of mothers of children with ASD or typical development and thus are specific to women with the *FMR1* premutation, underscoring that the age-related changes observed in women with the *FMR1* premutation are atypical and diverge from the patterns observed in healthy aging.[30,49,50,55] Longitudinal studies will be important in future work to confirm these early findings based on cross-sectional data and to draw robust longitudinal trajectories. A recent report by Bredin-Oja et al[61] represented one of the few longitudinal investigations of mothers with the *FMR1* premutation conducted to date and provided further support for age-related decline in this group. The researchers followed up 38 mothers with the *FMR1* premutation, aged 36 to 55 years at the last data point, longitudinally over a span of 8 years. As the mothers aged, they made more word retrieval errors and produced fewer words during language samples, providing further support for age-related decline in cognitive–linguistic skills associated with the *FMR1* premutation. Future longitudinal work will further delineate the age-related phenotype of the *FMR1* premutation, particularly as mothers enter old age.

CLINICAL CONSIDERATIONS

Because FXS is a familial disorder, siblings may also inherit FXS or the *FMR1* premutation.[62] Approximately 20% of families have more than one child affected by FXS.[63] Clinicians should be aware of the familial nature of FXS and monitor siblings of children with FXS for early signs of autism, language delay, social impairment, and intellectual disability. Across populations and diagnoses, family and other environmental factors can be sources of risk or resilience for a child's development. Within the context of FXS, variations in the home environment related to genetic risk among family members may be an influencing factor in the selection of therapies that fit the needs of the child and family. For example, the selection of parent-implemented intervention approaches may facilitate the use of parent coaching strategies to help parents build rich communicative interactions into their child's daily routines and provide scaffolding and reinforcement for their children's communicative attempts. These approaches appear promising in FXS[64–66]; for detailed discussion of parent-implemented language interventions, see the study by Bullard and Abbeduto.

Another factor that may influence the expression of *FMR1* phenotype characteristics is age. Notably, emerging research suggests that mothers with the *FMR1* premutation may begin to experience age-related decline as young as their 40s, with symptoms worsening with age.[30,49,50] Evidence of age-related decline in mothers with the *FMR1* premutation is significant because mothers may experience worsening symptoms at a period in their life when parenting responsibilities remain high. Individuals with FXS tend to continue living with and require care from their parents into adulthood. In a survey of 328 adults with FXS aged 22 and older, 70% of men and 50% of women were reported to reside with their parents, and high or very high levels of assistance in everyday life were required by 57% of the men and 19% of the women with FXS.[67] A quarter of the women and over half of the men with FXS were reported to have low or very low levels of independence, as defined by employment, friendships, and engagement in leisure activities, as well as the need for assistance in daily living. Thus, adults with FXS may continue to live with and depend on their aging parents, who themselves may be struggling with increasing health issues as they age. FXS is a lifelong disorder and the need for support services does not end once primary education is complete.

Another critical consideration, and an area of research lacking in the field, is that as children with FXS grow into adolescents and young adults, they may "age out" of speech and language intervention services. This is perhaps because they did not previously demonstrate benefits from therapy, or clinicians mistakenly believe they are past the age of improving speech and language abilities. Neither is appropriate reason for dismissal from speech-language services (see articles by Brady et al[68] and the National Joint Committee for the Communication Needs of Persons With Severe Disabilities,[69] for a review). Provision of services, including speech and language therapy, declines across age in FXS. In a national U.S. survey of over 1,000 families of children with FXS, very few individuals with FXS continued to receive allied health therapies after the age of 20 years.[70] The percentage of children receiving speech and language services dropped sharply as children aged, with approximately 70% of 6- to 10-year-olds with FXS receiving speech-language services, approximately 55% of 10- to 15-year-olds, and approximately 40% of 16- to 20-year-olds, suggesting that many children with FXS are dismissed from speech-language pathologists' caseloads prior to the completion of elementary school.[70] Adolescents and adults with FXS, especially those with more complex phenotypes (e.g., increased mental health symptoms and poorer functioning skills) may benefit from services aimed toward improving functional daily living and social interaction skills.[67] In sum, to maximize individual and family outcomes, clinicians should strongly consider the continuation of services in adolescence and early adulthood to support the family during the transitory phase that follows completion of K-12 education. Families may actually be losing services at a time when families need *more* support, which is compounded by premutation-associated symptoms that may increase with age.[49,71] Implementing appropriate transition plans for postsecondary school or work and ensuring service continuity should be therapeutic priorities. The complex interaction between biology, family environment, parent–child interactions, and developmental outcomes may intensify this populations' need for services across the lifespan.

CONCLUSION

FXS has a known genetic inheritance, and mothers of children with FXS may be vulnerable to adverse phenotypes associated with their genetic status as carriers of the *FMR1* premutation. *FMR1* premutation–associated risks may result in unique challenges for families. Understanding the range of clinical effects experienced by mothers with the *FMR1* premutation is important for identifying family-centered prevention and intervention practices that meet the specific needs of families of children with FXS. Mother's mental health and stressors in the family related to child behaviors are important factors when tailoring a home-based approach. It may be appropriate to make referrals to mental health providers, genetic counseling, and other medical experts in some cases. Clinicians who are knowledgeable about the disorder can ensure families are well-educated about the family of fragile X-associated conditions, can provide appropriate services, and can make recommendations for referral when appropriate.

DISCLOSURES

The authors have no relevant financial or nonfinancial relationships to disclose.

CONFLICT OF INTEREST

None declared.

ACKNOWLEDGMENTS

This research was supported by the National Institutes of Health (1R21DC017804-01, PI: Klusek 1R03HD098291-0, PI Klusek; 2R01HD024356, PI: Abbeduto).

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