Implications of the \textit{FMR1} Premutation for Children, Adolescents, Adults, and Their Families

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**BACKGROUND AND OBJECTIVES:** Given the nature of \textit{FMR1} gene expansions, most biological mothers, and often multiple other family members of children with fragile X syndrome (FXS), will have a premutation, which may increase individual and family vulnerabilities. This article summarizes important gaps in knowledge and notes potential implications for pediatric providers with regard to developmental and medical risks for children and adolescents with an \textit{FMR1} premutation, including possible implications into adulthood.

**METHODS:** A structured electronic literature search was conducted on \textit{FMR1} pre- and full mutations, yielding a total of 306 articles examined. Of these, 116 focused primarily on the premutation and are included in this review.

**RESULTS:** Based on the literature review, 5 topic areas are discussed: genetics and epidemiology; phenotypic characteristics of individuals with the premutation; implications for carrier parents of children with FXS; implications for the extended family; and implications for pediatricians.

**CONCLUSIONS:** Although the premutation phenotype is typically less severe in clinical presentation than in FXS, premutation carriers are much more common and are therefore more likely to be seen in a typical pediatric practice. In addition, there is a wide range of medical, cognitive/developmental, and psychiatric associated features that individuals with a premutation are at increased risk for having, which underscores the importance of awareness on the part of pediatricians in identifying and monitoring premutation carriers and recognizing the impact this identification may have on family members.
Once thought to only be affected by an increased risk for having offspring with fragile X syndrome (FXS), individuals with a premutation (PM, “carriers”) are now known to be at increased risk for several health concerns. Most research to date on PM carriers has focused on adults, primarily due to identification of 2 late-onset fragile X–associated disorders (FXADs), fragile X–associated tremor ataxia syndrome (FXTAS) and fragile X–associated primary ovarian insufficiency (FXPOI). After the discovery of the link between these FXADs and the PM, additional research has elucidated several other medical (eg, hypertension and thyroid disease), emotional (eg, anxiety), and cognitive (eg, executive function) challenges, which may occur at a greater frequency among a subset of carriers.1–5 Although interest in the PM phenotype has increased substantially over the last decade as these issues have become more apparent, studies on children remain limited due to a lack of early identification or biased samples who were clinically referred. The goal of this review is to highlight recent findings and gaps in the knowledge base regarding developmental, psychiatric, and medical features of the PM phenotype, as well as the familial impact of FMR1 mutations.

METHODS

The methods for obtaining articles for the literature review, including inclusion and exclusion criteria for articles on both pre- and full mutations, are described in detail in the article by Raspa et al in this supplement (Public Health Literature Review of Fragile X Syndrome). Of the 306 articles retained from the larger review, 51 were excluded because the content focused exclusively on the full mutation of FXS. A total of 116 articles that were specific to the PM are cited in this article (Fig 1).

RESULTS

Genetics and Epidemiology of the FMR1 Premutation

FMR1 mutations refer to an expansion of a trinucleotide repeat (CGG) on the 5′ untranslated region of the FMR1 gene. The normal CGG range of repeats is 6 to 44. Those with 45 to 54 CGG repeats are considered to be intermediate or “gray zone,” and those with 55 to 200 repeats have the premutation, which is unstable and expands when inherited. If the inherited expansion reaches >200 CGG repeats, it is considered a full mutation, also known as FXS. FMR1 mutations are now considered to result in a spectrum of phenotypic involvement, the most severe of which is FXS, but with implications for individuals with a broad range of expanded CGG repeats.

Research on the molecular pathways leading to increased risks for individuals with a PM is still in its infancy, although expanding research using animal models (primarily mice engineered to carry the premutation) has elucidated cognitive, motor, and molecular abnormalities.6,7 In general, the larger the number of CGG repeats, the lower the level of the fragile X mental retardation protein (FMRP), which is essential for
normal brain development. Also, with an increasing number of CGG repeats, there is elevation in FMR1 messenger RNA, which may result in reduced neuronal function and central nervous system dysregulation.10–13 Currently, there is active research on several core mechanisms, such as RNA toxicity, polyglycine-containing FMRP, lowered FMRP, and additive copy number variant (CNV) genetic abnormalities that may be associated with an increased risk for medical or emotional problems.14–17

The PM status of the FMR1 gene is more prevalent than the full mutation status. Several recent population studies (with large sample sizes) have yielded reliable prevalence estimates ranging between 1 in 148 and 1 in 204 for females and between 1 in 290 and 1 in 468 for males.18–22 Thus, although it may not be known unless there is a child with FXS diagnosed in the family, pediatricians have a high likelihood of encountering children and family members with a PM. Increased pediatrician knowledge about potential PM issues could potentially improve identification, as well as promote prevention and early treatment options for symptomatic carriers.

**Phenotypic Characteristics of Individuals With a Premutation**

**Developmental Profile**

Developmental involvement in PM carriers was first reported in 199418 among carrier boys who presented with developmental problems (e.g., autism, intellectual deficits) for which they were clinically referred. In a retrospective case series study of clinically referred children, Renda et al19 found that a high percentage of children with expanded CGG repeats had some type of neurodevelopmental diagnosis. Similarly, Bailey et al20 found a higher rate of developmental disabilities reported by parents of children with the PM compared with noncarrier children. Several case studies23–25 have reported developmental delays in carriers with lower levels of FMRP. However, there is a significant difference in the developmental profile of carriers who were clinically referred, like the cases described above, compared with carriers identified through cascade testing through a family member with FXS. Farzin et al21 found that patients with the PM who presented clinically have more developmental problems than those identified by cascade testing or controls without the PM from the same families. In this study, only those who were clinically referred demonstrated significantly lower IQ scores and increased autism symptoms compared with controls.

In contrast, Myers et al22 found overall intact cognitive and developmental profiles in a study of 14 children with a PM who were not clinically referred. Similarly, for adults with the PM without a diagnosis of FXTAS, overall cognitive abilities are generally unaffected26 whereas for individuals with FXTAS, overall cognition declines with age.27 However, a few studies have documented lower verbal IQ scores among women with a PM compared with female controls28,29 and males with a PM.30 In addition, there may be increased difficulties in specific domains of cognition, especially in executive function (EF),26,31,32 numeric reasoning and spatial-temporal processing,33 language,34,35 working memory,36 and arithmetic.29,37 In one of the few published studies of infants with the PM,38 visual processing deficits were found in 14 babies identified through newborn screening relative to noncarrier controls. The PM infants were as likely as infants with FXS or those with Down syndrome to have visual processing deficits, despite having overall higher developmental scores. These challenges may be very early markers of later EP challenges. These deficits reported in human PM studies parallel findings of locomotor, spatial learning and processing, memory, anxiety, and reaching deficits found in the PM mice.7,39,40

In summary, we do not have a clear picture of developmental outcomes for individuals with a PM. The adult literature would suggest some cognitive challenges beyond what would be expected as a result of normal aging, but the developmental trajectory of FXTAS may confound the generalizability of results suggesting cognitive decline. In children and adolescents, there are several reports suggesting a higher than expected rate of developmental disabilities in PM carriers, but many of these studies are based on clinically referred children, again limiting the generalizability of the findings. More natural history studies of children with a PM are needed to identify relative risks and potential biomarkers associated with those risks.

**Psychiatric Profile**

Comorbid anxiety, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorders (ASD) are the most commonly reported psychiatric conditions for both individuals with PM and those with FXS. In a national parent-report survey, children with a PM were reported to have significantly more attention problems than non-PM children matched on sex, age, and family income, excluding any matches with siblings.20 Similarly, Hunter et al43 found that adult female carriers had significantly more symptoms of inattention and memory than noncarrier controls. In a follow-up study, Hunter et al42 found that the FMR1 CGG repeat accounted for ∼5% of the variance in ADHD symptoms, whereas other genes accounted for ∼50% of the residual variance, suggesting that the PM acts with other genes to influence the severity of ADHD symptoms.
Given that many individuals with FXS are also diagnosed with ASD, several studies have examined the rates and severity of autism in individuals with a PM. One study found an increased rate of ASD in PM siblings of an individual with FXS compared with noncarrier siblings. In a large survey of families, 19% of males and 1% of females with the PM had a diagnosis of ASD. Similarly, in a direct-screening study, 14% of boys and 5% of girls with the PM were found to have ASD. This is an elevated risk relative to the general population, where just over 2% of males and <1% of females have ASD. Even among carriers who do not meet criteria for ASD, elevated autism-like symptoms have been reported. For example, increased rates of social aloofness and a rigid perfectionism have been described among carrier women. Behavioral features of the broad autism phenotype, including pragmatic language problems, have been found in women with a PM, suggesting a possible link between FMR1 and autism-related phenotypes. As with developmental profiles, higher rates of psychiatric problems, such as ASD and ADHD, have been found in children with the PM who were clinically referred compared with those with the PM who were not clinically referred and controls.

Adults with a PM may be at higher risk for mood and anxiety disorders. Recent studies found a relationship between the number of CGG repeats and the prevalence and severity of depressive symptoms. The prevalence of major depressive disorder is high for women with a PM relative to the national average, with a higher than expected rate of first major depressive disorder episodes occurring before the birth of a child with FXS. Other mood disorders (e.g., dysthymia and bipolar disorder) are not higher in carriers compared with controls. Although not studied extensively in children or adolescents with the PM, Bailey et al reported that depression may occur at a higher frequency among younger individuals with a PM compared with a matched sample of noncarriers. Anxiety symptoms, including social avoidance, interpersonal sensitivity, shyness, and eye contact avoidance, are also common in PM carriers, with up to 41% reporting a lifetime diagnosis of an anxiety disorder. Social phobia and panic disorder are the most commonly reported anxiety disorders. Schizotypal personality traits may also be more common among PM carriers. In addition, several case studies have noted the presence of psychotic illnesses. However, given the low rate of psychosis in the general population, it’s challenging to study the relative risk for PM carriers.

Psychiatric issues have been studied more extensively in adults with a PM, although many of these studies are confounded by the high percentage of participants who were also parents of children with FXS and therefore likely impacted by increased caregiver stress. Emerging evidence suggests that there is an increased risk for some psychiatric vulnerabilities, especially anxiety, attention regulation, and autism features in individuals with a PM, which may develop in childhood or adolescence.

Medical Profile

Little is known about relative medical risks, other than seizures, for children or adolescents with a PM. However, several medical problems occur more frequently in adult PM carriers than in noncarriers, and there may be early signs of these issues apparent in adolescence. Brief descriptions of some of these health risks are included below, with typical age of onset reported where known.

Seizures

Seizures have been reported at a higher rate among children with a PM who also display autistic features. Subsequent work on the rat model of early-life seizures has demonstrated that seizures shift FMRP away from the dendritic spine and into the cell body of the neuron. Because seizures can worsen autism features in any genetic or idiopathic cause of autism in patients, it is important to recognize seizures early and treat them appropriately.

FXPOI

FXPOI is associated with premature ovarian failure, cessation of menses before age 40 years, and other indicators of early ovarian aging or dysfunction. Approximately 20% of carriers will be diagnosed with FXPOI. Even among women with the PM that do not have a diagnosis of FXPOI, several hormonal changes have been documented, including decreased levels of anti-Müllerian hormone; increased levels of follicle-stimulating hormone; irregular, shorter, or skipped cycles; subfertility; and hot flashes. PM carriers, on average, reach menopause 5 years earlier than the general population of women. Increased risk for earlier menopause has been associated with mid-range CGG repeats (80–100).

Although girls with PM typically begin menses around the same age as their noncarrier peers, they have an increased risk for irregular periods, especially if they have mid-range CGG lengths. These females are also more likely to have difficulties with fertility and may experience other estrogen-related health concerns, such as lower bone mineral density and osteoporosis. About 3% of adolescents with the PM are expected to have some difficulties with menstruation, and <1% may experience cessation of menses during adolescence. The increased risk for FXPOI and other reproductive challenges have important implications for adolescent and young adult females as they...
make decisions regarding their reproductive future. These potential reproductive challenges, along with their genetic risk for passing on a fully expanded \emph{FMR1} gene, increase the importance of early discussions with girls regarding their PM status. De Caro et al\textsuperscript{76} provide guidelines for genetic counselors and other medical professionals in providing information and support for adolescent PM carriers.

**FXTAS**

Although not a condition thought to affect younger PM carriers, FXTAS is the most well-described FXAD associated with a PM.\textsuperscript{77} The core features of FXTAS are cerebellar gait ataxia and action tremor. Other symptoms include parkinsonism, cognitive decline (especially in EF), peripheral neuropathy, and autonomic dysfunction.\textsuperscript{78} FXTAS occurs in \textasciitilde 40\% of male carriers and 8\% to 16\% of female carriers.\textsuperscript{79,80} Clear signs of FXTAS typically begin at \textasciitilde 60 years of age, although there are rare cases that begin earlier.\textsuperscript{1} Rates of FXTAS increase with age; >75\% of men with PM >80 years of age display signs of FXTAS. Pediatrists should be aware of the risk of FXTAS within families of children with FXS or a PM and note that carrier parents may be at increased risk for stress related to caring for their own aging parent with FXTAS.

**Other Health Risks**

There is a subset of boys with the PM who present with some of the physical characteristics seen in FXS, including large ears, high arched palate, flat feet, and macroorchidism.\textsuperscript{24} Other medical concerns in adults include thyroid problems,\textsuperscript{4,8,12,82–84} fibromyalgia,\textsuperscript{92–94} migraines or similar headaches,\textsuperscript{6,9,85} hypertension,\textsuperscript{81,86} sleep issues,\textsuperscript{97,88} neuropathy,\textsuperscript{6,9,70,79,81,89–91} and vestibular complaints (eg, unbalanced, disequilibrium).\textsuperscript{6,9,70,80,92} These symptoms are seen in carriers with or without FXTAS and often start in young adulthood, particularly hypertension, migraines, or hypothyroidism. Studies that compare symptoms in carrier parents with noncarrier parents caring for children with similar developmental disabilities are needed to sort out the relative contribution of stressful parenting and the genetic risk for these symptoms.\textsuperscript{93}

**Knowledge of Carrier Status**

Not all children will know about or fully understand their PM status, and pediatricians may be called on to assist parents and other caregivers regarding when and how to inform children or adolescents about their carrier status. In an interview study of attitudes about the timing of carrier testing, parents indicated their primary concern was that their children know and understand their carrier status before becoming sexually active.\textsuperscript{94} Parents were also concerned about having the appropriate information and ability to support their child in adjusting to their carrier status. Three papers describe results from a longitudinal study of women at risk for the PM before and after finding out their status.\textsuperscript{95–97} The women who found out they were carriers over the course of this study experienced some initial negative emotions and reported concerns primarily with the impact on their future marriage and motherhood. These women were more likely to endorse early childhood (0–9 years) as the preferred age to be told about carrier status, more so than those who were noncarriers and more so than the age they endorsed before knowing their own status. The primary reason for desiring this information earlier was to provide time to adjust and cope. Ultimately, when parents choose to tell their children about their genetic status, they endorse that this is a family decision; however, pediatricians may play a role in helping children and adolescents with a PM understand and cope with their diagnosis.

**Carrier Parents of Children With FXS**

In addition to being aware of possible risks for their patients with a PM, pediatricians should also be aware that, unless adopted, all of their patients with FXS will have a mother who is herself affected by the PM or FXS (the majority will have a PM). Several studies have examined the impact of raising a child with FXS on maternal health. In general, carrier mothers have elevated rates of stress, depression, anger, and anxiety, with nearly half scoring in the clinically significant range in at least 1 of these areas.\textsuperscript{54} Carrier mothers also have higher lifetime occurrence rates of mood and some anxiety disorders (eg, agoraphobia and panic disorder) compared with national samples of women.\textsuperscript{52,99} Based on a survey of 508 FXS families in 2011, one-third of mothers reported having seen a professional to treat depression, anxiety, or stress in the last year, and one-quarter reported taking prescription medication for these symptoms.\textsuperscript{52,99} Stress is reported to be higher in families of children with FXS than those of children with Down syndrome,\textsuperscript{100,101} which may be a result of increased child behavioral problems in FXS.\textsuperscript{54,102–104}

A more complex picture of stress in mothers with a PM has emerged in recent work. Mothers at higher genetic risk (eg, those with a lower activation ratio of PM versus normal cells) had lower levels of cortisol the day after their child had multiple episodes of behavior problems than mothers at lower levels of genetic risk.\textsuperscript{105} Another study of the same sample found that mothers who had between 90 and 105 CGG repeats and experienced above-average numbers of negative life events (eg, death of a friend or family member and financial or health problems) in the previous year had more depressive symptoms, higher anxiety, and lower
morning cortisol levels compared with those with higher or lower repeat lengths. The opposite pattern was true for mothers with mid-range CGG repeats who experienced below-average numbers of negative life events. These mothers had the lowest levels of depressive symptoms and anxiety and had typical cortisol awakening levels. These studies illustrate how environmental conditions can regulate the stress response in PM carriers.

In contrast to these negative outcomes, mothers of children with FXS have relatively high levels of hope and optimism. Compared with other groups, carrier mothers had levels of positive affect equivalent to mothers of typically developing children but lower levels of well-being compared with mothers of a child with Down syndrome. Hope was also shown to be a strong predictor of quality of life. Higher levels of social support and maintaining a social life may reduce potentially negative child and family factors on quality of life and well-being.

Carrier mothers have elevated rates of adverse physical health symptoms, including a higher proportion of days with headaches, backaches, muscle soreness, fatigue, or hot flashes compared with mothers of children without disabilities.

Implications for the Extended Family

The impact on the extended family is an important consideration for a heritable condition, such as FXS. In a recent pilot study of cascade testing as a result of newborn screening for FXS, Sorensen et al. reported on 27 extended family members who were identified as having an FMR1 mutation resulting from the identification of 14 newborns. This finding highlights the potential challenges for immediate family members regarding communication with extended relatives (ie, ethical implications of providing versus withholding information). Anxiety may be expected to be heightened as a result of receiving any medically relevant news. For inherited conditions, this anxiety may be multiplied as family members consider the impact for multiple loved ones throughout a family system. For example, the parents of a newly diagnosed child may need to consider the possible impact of an FMR1 expansion on not only the child and carrier parent, but also the possibility of a grandparent developing FXTAS, as well as the reproductive impact for siblings, aunts, or cousins. Future reproductive decisions will also be impacted. In qualitative interview studies of reproductive decisions made by carrier mothers, the majority (77%) had decided not to have more biological children because of the 50% risk of passing on the mutation to their child. The impact of an FMR1 mutation can reach many family members, and this “family spillover” of consequences is an important reality for pediatricians to consider in their support of the family system.

Implications for Pediatricians

As primary care physicians, pediatricians are in a unique position to support children, their parents, and extended family members regarding both PM and FXS problems. Boys with the PM are at higher risk than the general population for ADHD, anxiety, and social deficits and these problems usually require an evaluation and often multimodality treatment, such as medication and counseling. Seizures can occur in 8% to 13% of carriers, and other medical problems, such as hypertension, migraines, immune-mediated, and endocrine problems, generally develop in adulthood, but could potentially arise in adolescent carriers. Therefore, pediatricians should be alert to the increased risk for these problems in their patients.

Pediatricians will encounter carrier children because the PM is common in the general population; however, the majority of individuals with the PM will not know they are carriers. For this reason, pediatricians are on the front line when it comes to identifying the spectrum of problems that can arise in PM carriers. Although most of the carriers that they will see will not have overt developmental problems, there are a significant number of children who will have challenges, and there may be an increased risk of susceptibility to stressful situations for all carriers, regardless of their clinical involvement. Even among those without medical or neurocognitive concerns, it will be important to emphasize general guidance regarding staying healthy to decrease risk, as well as encouraging stress reduction and positive coping mechanisms to promote resilience.

Pediatricians may want to review the whole family tree of children with FXS or a PM, because these pedigrees can occur in 8% to 13% of carriers, affecting other affected family members. For instance, pediatricians can provide encouragement for the mother to receive treatment for the anxiety or depression that she may be experiencing, which could have a significant impact on the environment and mental health of her children. Pediatricians can also guide the family in genetic testing of other family members and facilitate or order fragile X DNA testing and assist with managing insurance concerns.
CONCLUSIONS

Several important questions remain unanswered with regards to the \textit{FMR1} PM. These questions form the basis for future research directions.

1. What is the true prevalence and severity of symptoms and comorbid conditions associated with PM status? Although the prevalence of the \textit{FMR1} PM is now better understood, the penetrance and range of severity of associated symptoms is not as well known, nor is the developmental trajectory of associated features. This is especially true outside of the documented conditions of FXPOI and FXTAS. Several medical, psychiatric, and cognitive features have been noted to possibly or likely be related to the PM, but are in need of more empirical documentation. This information is needed to better describe the public health burden of the PM.

2. What mechanistic factors can be used to predict who is at the greatest risk for which outcomes? An important question for researchers is why some individuals with a PM develop cognitive, emotional, and medical conditions whereas others do not. There is some evidence that the higher the number of CGG repeats is within the PM range, the earlier the onset of FXTAS, the greater the level of RNA toxicity and the lower the level of FMRP, which in itself can lead to developmental problems.\textsuperscript{8,9,14} This association requires additional investigation, including possible mediating or protective factors. Identification of preventive measures could enable public health programs to make large strides in improving outcomes for the PM population. Another cause of clinical involvement in PM carriers is the presence of an additional genetic abnormality or a CNV. Because the PM itself can lead to oxidative stress and early cell death in culture,\textsuperscript{113} the addition of a CNV or other genetic lesion may have an additive effect with the PM, whereas by itself it may or may not have a clinical phenotype.\textsuperscript{114} There is clearly a spectrum of affectedness, but it is unclear what mechanisms contribute to this spectrum.

3. To what extent do environmental factors play a role in outcomes? In addition to molecular mechanisms, it also remains unclear as to whether the risks for known conditions (eg, FXPOI and FXTAS) and associated features develop due to cumulative genetic risk, a genetic susceptibility to stress, exposure to stress, or some other genetic or environmental influence. Although some findings regarding the impact of the PM on children can be extrapolated from studies of adults, there is a significant need for more studies focusing on younger individuals. Studies examining the medical, developmental, and emotional trajectories of younger individuals with the PM are currently underway and should shed light on the development of these conditions. The potential differential susceptibility to stress for individuals with a PM\textsuperscript{93} is another important area for future investigation, especially the potential consequences for cumulative stress for children and adolescents with it.

4. What treatments or environmental modifications could prevent or reduce the severity of symptoms? From a molecular viewpoint, there is oxidative stress and mitochondrial dysfunction in the cells of PM carriers both with and without FXTAS.\textsuperscript{10,115,116} Because of these problems, recommendations have been made for the use of antioxidants, healthy eating, and regular exercise to enhance mitochondrial function, increase serotonin levels, and promote neurogenesis.\textsuperscript{112} There is limited research on treatment studies for the learning, emotional, and stress problems seen in some carriers, and the impact of multiple family members with \textit{FMR1} mutations on the family system is not clear. Studies addressing these issues could provide needed information to guide treatment of carriers with clinical problems.

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ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
ASD: autism spectrum disorder
CNV: copy number variant
EF: executive function
FMRP: fragile X mental retardation protein
FXAD: fragile X–associated dystonia
FXPOI: fragile X–associated primary ovarian insufficiency
FXS: fragile X syndrome
FXTAS: fragile X–associated tremor ataxia syndrome
PM: premutation

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