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PROFESSIONAL ISSUES

Genetic Counseling and Testing for *FMR1* Gene Mutations: Practice Guidelines of the National Society of Genetic Counselors

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Abstract Fragile X syndrome (FXS) is one of several clinical disorders associated with mutations in the X-linked Fragile X Mental Retardation-1 (*FMR1*) gene. With evolving knowledge about the phenotypic consequences of *FMR1* transcription and translation, sharp clinical distinctions between pre- and full mutations have become more fluid. The complexity of the issues surrounding genetic testing and management of *FMR1*-associated disorders has increased; and several aspects of genetic counseling for *FMR1* mutations remain challenging, including risk assessment for intermediate alleles and the widely variable clinical prognosis for females with full mutations. *FMR1* mutation testing is increasingly being offered to women without known risk factors, and newborn screening for FXS is underway in research-based pilot studies. Each diagnosis of an *FMR1* mutation has far-reaching clinical and reproductive implications for the extended family. The interest in large-scale population screening is likely to increase due to patient demand and awareness, and as targeted pharmaceutical treatments for FXS become available over the next decade. Given these developments and the likelihood of more widespread screening, genetic counselors across a variety of healthcare settings will increasingly be called upon to address complex diagnostic, psychosocial, and management issues related to *FMR1* gene mutations. The following guidelines are intended to assist genetic counselors in providing accurate risk assessment and appropriate educational and supportive counseling for individuals with positive test results and families affected by *FMR1*-associated disorders.

Keywords Fragile X · *FMR1* · FXTAS · FXPOI · Genetic counseling

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Introduction

The *FMR1* gene is characterized by a repetitive trinucleotide sequence that includes 6 to 44 CGG repeats in the normal allele. *Premutation* alleles result from an unstable trinucleotide expansion in the range of 55 to 200 CGG repeats and are unmethylated. During oogenesis in females and during post-zygotic mitosis in males

or females, premutations may undergo further size expansions to become methylated *full mutations* with more than 200 CGG repeats; hypermethylation leads to transcriptional silencing of Fragile X Mental Retardation Protein (FMRP). Mosaicism occurs related to both repeat number (size mosaics) and less commonly, degree of hypermethylation (methylation mosaics) (Rousseau et al. 1994)). The chance of *FMR1* expansion in females is correlated with repeat size (Table 1) and may be increased in women with a family history of FXS as compared to those without (Nolin et al. 2011). Expansion is influenced by the absence of normally interspersed AGG triplets and the length of total and uninterrupted CGG repeats at the 3′ end of the repeated CGG region (Yrigollen, et al. 2012). Recently developed PCR assays (Chen et al. 2010) should provide definitive data on which of these factors more accurately estimates the risk for instability as compared to repeat size alone. Research is also needed to determine the impact, if any, of routinely incorporating AGG testing results into genetic counseling practice for *FMR1* mutations.

Intermediate or gray zone alleles overlap the junction between the normal and premutation ranges and are defined by the American College of Medical Genetics (ACMG) as having between 45 and 54 CGG repeats (Sherman et al. 2005). These intermediate size alleles may or may not be unstable. An unstable intermediate allele can expand to a premutation in offspring and to a full mutation in subsequent generations. It should be noted that expansions and contractions of CGG repeat number can occur in alleles of any size, even those within the normal range. The vast majority of intermediate alleles are stable (Levesque et al. 2009), and most often an expansion or contraction is minimal (from 1 to 5 CGG repeats). There have been a few reports of alleles in the 50 to 54 repeat range with expansions or contractions of >10 CGG repeats (Nolin et al. 2003). Expansion to a full mutation in one generation from a maternal allele with fewer than 56 repeats has not been reported.

Table 1 Transmission of the premutation in females

Maternal Repeat Size	Risk of Expansion to Full Mutation
55–59	3.70 %
60–69	5.30 %
70–79	31.10 %
80–89	57.80 %
90–99	80.10 %
>100	94–100 %

*Nolin et al. Am J Hum Genet 2003; 72: 454–464

Prevalence

Population studies suggest a prevalence of FXS in 1 in 4,000 males and 1 in 8,000 females (Crawford et al. 2001). Mutation prevalence studies vary in terms of repeat cutoffs and sample sizes, and there is some evidence for ethnic and racial variability. Premutation frequencies in females range from 1/151 - 1/259 (North America) to 1/113 (Israel) (Rousseau et al. 1995; Toledano-Alhadef et al. 2001; Seltzer et al. 2012), while the rate in males ranges from 1/468 to 1/813 (Dombrowski et al. 2002; Seltzer et al. 2012). Intermediate alleles are observed in approximately 1/35 to 1/57 females (Cronister et al. 2008; Seltzer et al. 2012) and are often coincidentally identified on general population prenatal screening, during the diagnostic work-up of a child with developmental delay or autism, or as part of an infertility evaluation. Population-based screening studies will provide valuable data which will more accurately define the prevalence of all *FMR1* alleles.

Laboratory Testing

The *FMR1* gene can be analyzed using a combination of polymerase chain reaction (PCR) and Southern blot analysis. Testing is 99 % sensitive, missing only rare individuals who have FXS due to point mutations or deletions located outside the CGG repeat region. ACMG's *Standards and Guidelines for Clinical Genetics Laboratories* (Spector and Kronquist 2006) details testing methodology and defines the normal and mutation categories and corresponding CGG repeat ranges. Alternative methods for determining the length of uninterrupted CGGs (Chen et al. 2010; Nolin et al. 2011), and assessing full mutation (Filipovic-Sadic et al. 2010; Chen et al. 2010) and methylation status (Chen et al. 2011) without performing Southern blot are under development and available through select laboratories, as are other novel PCR methodologies (Lyon et al. 2010). Although FMR1 analysis is highly accurate, laboratories typically state that the reported allele size may vary by ±1 to 4 CGG repeats for alleles less than ~120 CGG repeats. For larger alleles, the accuracy is ±10 %. This generally has no implications for the patient, although occasionally, additional family studies may aid interpretation. As always, when counseling patients, the session should be based on the specific results reported and include a discussion of the risk for expansion based on the laboratory's interpretation of those results.

Clinical Presentation

A wide range of clinical effects is associated with expanded *FMR1* alleles. Hypermethylated full mutations fail to

produce FMRP, resulting in clinical symptoms of FXS. FMRP is one of a family of interactive proteins that regulate the metabotropic glutamate receptor (mGluR) pathway. The absence of FMRP results in dysregulation of mGluR-mediated protein synthesis, leading to abnormal synaptic signaling and dendritic development (Bear et al. 2004). By contrast, *FMR1* premutations produce relatively normal levels of FMRP but are associated with elevated mRNA. Premutation disorders such as Fragile X-associated tremor ataxia syndrome (FXTAS) and Fragile X-associated primary ovarian insufficiency (FXPOI) are thought to be related to mRNA toxicity which results in sequestration of proteins and mitochondrial dysfunction (Garcia-Arocena and Hagerman 2010). Overlap exists among the FMRP levels, mRNA levels, and clinical phenotypes associated with premutation and full mutation expansion ranges, and these should be viewed as a continuum rather than distinct allele types (Hagerman and Hagerman 2004) (Table 2).

Full Mutations

In males and females, full mutations are associated with FXS, a spectrum of clinical effects that includes physical, cognitive, and behavioral aspects (Table 3). Variability in the clinical phenotype is related to methylation status, mosaicism, and X-inactivation. Most males with FXS function within the mild to severe range of intellectual disability and exhibit a variety of maladaptive behaviors which significantly overlap behavioral criteria for autism spectrum disorders (Hagerman 2002).

Females with full mutations show greater clinical variability than males (De Vries et al. 1996). Half manifest symptoms of FXS, although intellectual impairment is often milder. Emotional and psychiatric problems are common (Keysor and Mazzocco 2002), even among intellectually normal females with full mutations. Some females appear to be completely unaffected by the full mutation, and others exhibit subtle neurobehavioral features, such as difficulty with math or excessive shyness, without other major phenotypic effects (Cronister et al. 1991).

Premutations

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

Characterized by progressive neurological, cognitive, and psychiatric features, FXTAS is a neurodegenerative condition associated with *FMR1* premutations (Hagerman et al. 2001), with typical onset after age 50. Neurologically, the disorder is associated with intention tremor, cerebellar ataxia, peripheral neuropathy, atypical parkinsonism, and dementia. Cognitive features include declines in intellect, short-term memory, and executive functioning. Psychiatric symptoms may be present, such as personality or mood changes, increased irritability, and impulsive behavior. The diagnosis of FXTAS is based on clinical findings in older adults confirmed to have *FMR1* alleles in the premutation range. Hyperintensities of the middle cerebellar peduncles are often seen on brain MRI in patients with FXTAS and may be a useful diagnostic sign (Hagerman et al. 2001). Approximately 46 % of males and as many as 17 % of females with premutations develop neurodegenerative symptoms of FXTAS after age 50 (Rodriguez-Revenga et al. 2009); some individuals may experience neurological symptoms that do not meet full clinical criteria for the diagnosis of FXTAS (Table 4).

Table 2 *FMR1* alleles and associated phenotypes

Allele Type	Repeat Range	Associated Features	Clinical Variations
Normal	5–44		
Intermediate	45–54	Small risk for expansion to PM	Research needed to determine association, if any, with clinical symptoms
Premutation (PM)	55–200 (unmethylated)	FXTAS, FXPOI	Rare association with developmental/ behavioral disorders
		Variable risk of expansion to FM when PM passed from mother to offspring	Mental health issues
		PM size generally remains stable when paternally transmitted	Autoimmune disorders
			Potential for FXS characteristics in males and females with PM's >150 repeats
Full Mutation (FM)	>200 (methylated)	FXS in males and some females	Clinical phenotype often milder in females and in those with size or methylation mosaicism
		50 % risk of transmission of FM from mother to offspring	No reports of FXTAS or FXPOI associated with FM
			Sperm in males with FM contain only PM alleles

Table 3 Clinical presentation of individuals with *FMR1* full mutations

Physical	Distinctive facial characteristics, including large and/or protruding ears, a long face, prominent forehead, mandibular prognathism, strabismus, and high arched palate with occasional cleft palate
	Connective tissue findings such as hyperflexible joints, soft velvety skin, flat feet, and mitral valve prolapse
	Macroorchidism (testicles of more than 25 ml in size)
	Macrocephaly
	Seizures
Cognitive	Mild to severe intellectual disability in males
	Normal development, learning disabilities, or variable intellectual disability (mild>severe) in females
Behavioral	Attention deficits, usually with hyperactivity
	Speech and language impairments, perseverative speech, echolalia
	Anxiety
	Stereotypic movements such as hand flapping
	Hand biting
	Tactile defensiveness, sensory hyperarousal
	Gaze aversion
	Autism spectrum disorders

Clinical features are highly variable and tend to be more pronounced in males than females; macroorchidism and distinctive facial characteristics may not become apparent until after puberty

Fragile X-Associated Primary Ovarian Insufficiency (FXPOI)

Cronister et al. (1991) first reported an increased incidence of premature ovarian failure (POF) in women with *FMR1* premutations. At the time, the full extent of FXPOI was not yet appreciated. Features of FXPOI include diminished ovarian reserve leading to irregular menses, elevated FSH levels, reduced fertility, and POF (cessation of menses prior to age 40). Overall, FXPOI affects 15 to 20 % of women with *FMR1* premutations (Sherman 2000) and is correlated in a non-linear association with CGG repeat number. The risk for FXPOI increases with CGG repeat numbers from 55 to about 95, plateaus at about 100, and then drops off as premutations approach 200 repeats (Allen et al. 2007). The prevalence of *FMR1* premutations is approximately 2 to 7 % in women who have sporadic ovarian insufficiency and 10 to 15 % in those with a family history of ovarian insufficiency (Wittenberger et al. 2007). The risk of developing FXPOI is not increased for women with *FMR1* full mutations, nor is there convincing evidence for a significant increase in FXPOI among women who have intermediate *FMR1* alleles (Bennett et al. 2010).

Table 4 Criteria for definite, probable, and possible FXTAS in individuals with *FMR1* premutations

Molecular	55–200 CGG repeats
Clinical	*Major:* intention tremor, cerebellar gait ataxia
	Minor: Parkinsonism, moderate to severe short term memory deficit, executive function deficit
Radiological	*Major:* MRI white matter lesions involving middle cerebellar peduncles
	Minor: MRI lesions involving cerebral white matter, moderate to severe generalized brain atrophy
Diagnostic categories	
	Definite: one major clinical and one major radiological, or presence of FXTAS inclusions
	Probable: two major clinical, or one minor clinical and one minor radiological
	Possible: one major clinical and one minor radiological

Adapted from Jacquemont et al. 2003 and Hagerman and Hagerman 2004

Other Premutation-Associated Issues

Research has shown the vast majority of males and females with *FMR1* premutations to have normal intellectual functioning. There have been a handful of case reports of children with premutations who have learning and/or behavioral disabilities (Aziz et al. 2003), in some cases with documented decreases in FMRP, illustrating the overlap in clinical features between repeat ranges (Loesch et al. 2009a). An increased incidence of hypertension, thyroid disorders, fibromyalgia, tremor, and neuropathy has been reported among adult women with premutation alleles (Coffey et al. 2008). Additionally there is a higher than expected prevalence of mental health issues in these women which appear to be independent of (although likely exacerbated by) the stress of raising a child with FXS (Hagerman and Hagerman 2004; Lachiewicz et al. 2010). Hunter et al. (2010) found that women with FXPOI reported higher rates of thyroid problems, depression, and anxiety, suggesting a possible link to ovarian dysfunction. There is also evidence that anxiety may be among the clinical symptoms related to mRNA toxicity in FXTAS or FXPOI. Hessl et al. (2005) reported elevated levels of mRNA in individuals with premutations who had psychiatric symptoms; and MRI changes were found to correlate with anxiety in women with *FMR1* premutations, even in those without a clinical diagnosis of FXTAS (Adams et al. 2010).

Intermediate Alleles

FXS, FXTAS, or FXPOI have not been reported in males or females with intermediate alleles. Some research findings have suggested associations between intermediate alleles and Parkinson's disease (Loesch et al. 2009b), primary ovarian insufficiency (Bodega et al. 2006), and autism and cognitive disabilities (Aziz et al. 2003; Loesch et al. 2009a). However, these findings have not consistently been supported

by other studies (Ennis et al. 2006; Bennett et al. 2010) and can be difficult to interpret due to inconsistencies in the way researchers have defined the intermediate range. Additional research is needed to clarify the clinical relevance of intermediate alleles.

Population Screening

The ACMG's Policy Statement on FXS (Sherman et al. 2005) describes individuals for whom *FMR1* mutation testing should be considered. Likewise, the American College of Obstetrics and Gynecology (ACOG) has published a committee opinion on premutation screening for FXS (ACOG 2010) (Table 5). Although currently not endorsed by ACMG, *FMR1* mutation testing is increasingly being offered to women without known risk factors for FXS. ACOG is cautious about widespread population-based screening but recommends offering testing, along with genetic counseling, to women who request it, regardless of family history. General population studies of *FMR1* testing in women have demonstrated its efficacy and cost effectiveness (Musci and Caughey 2005). Voluntary screening for *FMR1* mutations appears to be acceptable to women in the general population and to the parents of affected children (Bailey et al. 2003; Hill et al. 2010). Genetic counseling and education are essential, and research on the psychological impact of positive fragile X results is needed before population-based screening is endorsed more broadly. Newborn screening for FXS is also under consideration, but further research is needed to determine its acceptability and efficacy (Hill et al. 2010).

Table 5 *FMR1* testing guidelines (Sherman et al. 2005; ACOG 2010)

FMR1 mutation testing is recommended for:
Individuals of either sex with intellectual disability[a], developmental delay or autism
Individuals with FXS who were diagnosed through cytogenetic testing, or their relatives, in order to provide accurate genetic risk assessment
Individuals seen for reproductive counseling who have a family history of FXS or undiagnosed intellectual disability. The more recent ACOG Committee Opinion also recommends testing for women with a family history of *FMR1*-related disorders, including FXPOI, and for those who request testing, regardless of family history
Women with reproductive or fertility problems associated with elevated levels of follicle stimulating hormone (FSH)
Individuals with late onset tremor or cerebellar ataxia of unknown origin

[a] originally described as "mental retardation"

Prenatal and Pre-implantation Genetic Diagnosis

Prenatal detection of *FMR1* mutations by amniocentesis and chorionic villus sampling (CVS) is accurate and reliable (Nolin et al. 2011). Although *FMR1* methylation is incomplete in placental tissue at 10 to 12 weeks gestation, methylation patterns can usually be interpreted and used to distinguish between pre- and full mutations. On rare occasions, follow-up amniocentesis may be needed to confirm the presence or absence of an unmethylated full mutation. A variety of other pre- and post-conception options, including pre-implantation genetic diagnosis (PGD), adoption, and gamete donation, is available to couples at risk for having children with *FMR1* gene mutations. PGD for FXS using PCR and linked polymorphic markers can be hampered by difficulties with oocyte retrieval, amplification of the CGG repeat, and the ability to distinguish *FMR1* alleles (Tsafrir et al. 2010).

Management of FXS

Children with FXS benefit from a comprehensive developmental and educational evaluation to identify appropriate interventions. A team approach which includes parental concerns and integrates occupational, physical, and speech therapies within a special education program is recommended (Braden 1996). A combination of environmental supports and psychotropic medications can be used to treat FXS behavioral symptoms (Hagerman et al. 2009). Research suggests that epigenetic polymorphisms related to drug metabolism may help predict responses to specific medications in people with FXS (Hagerman et al. 2009).

Because its physiological mechanism is well-elucidated and has been replicated in animal models, FXS shows particular promise for the development of targeted pharmaceuticals aimed at addressing the underlying biochemical basis for the disorder (Hagerman et al. 2009). Targeted treatment approaches focus on regulation of the mGluR pathway through drugs that mimic the effect of FMRP. Studies of mGluR antagonists in FXS knockout mice have shown a positive effect on seizures, behavior, and cognition (Ogren and Lombroso 2008). Some of these medications are currently in human clinical trials and expected to enter the drug market within the next few years. The development of pharmaceuticals that target dysregulation of the mGluR pathway offers hope to families affected by FXS; these drugs may also prove effective for the broader treatment of autism unrelated to FXS (Hagerman et al. 2009).

Recommendations

Genetic counselors play a pivotal role in providing pre-test information to individuals at significantly increased risk for *FMR1* gene mutations (Table 6); preparing them for possible outcomes; reporting results and educating them about *FMR1*-associated disorders; and facilitating communication among family members. Counseling families with *FMR1* mutations requires a solid understanding of X-linked inheritance in the context of trinucleotide repeat instability and a changing clinical landscape. In addition to the known challenges of addressing informational and psychosocial aspects of a genetic condition, counseling for *FMR1* mutations poses additional specific issues in a number of areas.

Counseling Considerations

- Centers offering population screening should ensure that they have the resources available to provide pre- and post-test genetic counseling that supports the psychosocial and clinical needs of the patient and family. In light of widespread *FMR1* testing among women without known risk factors, genetic counselors should anticipate seeing patients who did not receive any pre-test information, have no prior knowledge of *FMR1*-associated disorders, and are unprepared to learn that they have an *FMR1* mutation.
- Although many genetic counselors are familiar with FXS, fewer have experience with FXTAS and FXPOI. As such, they may underestimate the scope of clinical inquiry needed for risk assessment in families with *FMR1* mutations. Taking a pedigree in these families requires attention to a diverse constellation of developmental, neurodegenerative, and reproductive symptoms that vary widely in age of onset and severity across multiple generations. Specific family history queries designed to identify individuals with the full spectrum of *FMR1* gene mutations are listed in Table 7. Given the subjective nature of behavioral and cognitive symptoms, psychiatric and educational records should be obtained whenever possible to confirm a reported history of developmental issues.
- The diagnosis of *FMR1*-associated disorders can have far-reaching genetic and emotional implications for extended family members. When an *FMR1* mutation is identified in a family, genetic counselors should assist patients in developing strategies to inform relatives.
- Parents should be encouraged to explore open and meaningful discussion with their children about *FMR1*-associated disorders and genetic risk. Genetic counselors should work toward helping parents develop a positive, resilient communication style which may aid in the long-term adaptation of children to *FMR1*-related risk.
- Psychiatric issues, as well as cognitive decline, are common among patients with FXTAS. They may experience confusion and emotional reactions to learning the genetic nature of their condition and its implications for their children and other relatives. With the patient's consent, it may be important to involve other family members and caregivers in these discussions so that genetic and management information is accurately communicated.

Table 6 Pre-test genetic counseling for *FMR1* mutations

General	Assess awareness and knowledge about *FMR1*-related disorders
	Regardless of family history or clinical presentation, discuss possibility and implications of detecting alleles in the premutation, full mutation, and intermediate ranges
	Review anticipated follow-up options in case a mutation or intermediate allele is found
	Discuss anticipated emotional reactions to test results, including implications specific to the patient's current stage of life
Known family history of *FMR1* mutations	Elicit patient's experience with *FMR1* mutations in family, including attitudes toward disability
	Assess self-perception of genetic risk
	Use family history to illustrate inheritance patterns
	Where appropriate, include at-risk minor children in the counseling discussion
	Assist parents to carefully weigh medical and emotional benefits of *FMR1* testing against potential harms in pre-symptomatic children and teens
Adults with cognitive/behavioral impairment	Identify FXS or FXTAS-related neurological symptoms that may impact patient's understanding and decision-making
	Ascertain guardianship status of adult prior to testing when appropriate
	Include family member or caretaker in the discussion with the patient's permission
	Access legal and social work resources for questions involving competency and informed consent for genetic testing
Prenatal testing	Alert patient that follow-up amniocentesis may be needed to further clarify CVS results

Table 7 Suggested targeted family history inquiries for *FMR1*-associated disorders

Note for appropriate relatives any history and the age of onset of:
Cognitive effects: intellectual disability, developmental delay, language delay, learning disabilities, specifically, problems with mathematics
Speech delay or unusual speech pattern
Autism spectrum disorders or autistic-like behaviors (gaze avoidance, repetitive behaviors, hand-flapping, hand biting, touch avoidance, etc.)
Attention deficit disorder (ADD) or attention deficit hyperactivity disorder (ADHD)
Dysmorphic features: macrocephaly, large ears, long face, broad forehead, prominent jaw, strabismus
Connective tissue features: hyperextensible joints (especially fingers), flat feet, hypotonia, mitral valve prolapse, large testicles, hernias, recurrent ear infections
Neurological symptoms: seizures, adult-onset progressive tremor, ataxia, difficulty walking, balance problems, short-term memory loss, loss of sensation in limbs
Mental illness/personality disorders: depression, schizophrenia, bipolar disorder, obsessive-compulsive disorder, schizoaffective disorder, schizoid personality, etc.
Behavioral problems: impulsivity, anger outbursts, violent behavior, solitary behavior, counseling or medication for behavioral difficulties.
Shyness, social anxiety, excessive worrying, counseling or medication for emotional difficulties
Reproductive and fertility problems, including primary ovarian insufficiency, early menopause

- Patients who have normal laboratory results should be counseled that *FMR1* testing does not rule out other genetic conditions or determine the cause of undiagnosed developmental disabilities, infertility, or neurodegenerative disorders in other family members.

Intermediate Alleles

- Conflicting research on the phenotypic and reproductive implications of intermediate alleles makes it difficult for genetic counselors to provide clear cut guidance to these patients. Counseling in these situations should include a discussion of known reproductive and clinical implications of intermediate alleles. In the absence of further data to the contrary, the focus should be on the low rate of instability and limited evidence to indicate increased risk for developing *FMR1*-associated disorders.
- Patients with intermediate alleles who present with clinical signs suggestive of *FMR1*-associated disorders should be counseled about the likely possibility of an unrelated etiology for their symptoms and referred, as indicated, for additional diagnostic work-up.
- Intermediate alleles are common and often detected coincidentally as part of an infertility work-up, through general population screening in women without a family history of *FMR1* mutation disorders, or in children undergoing evaluation of developmental delay or autism. Genetic counselors should anticipate a heightened level of anxiety and reactions in these patients, particularly since many have had little or no pre-test counseling to prepare them for the result.

Reproductive Issues

- Prenatal diagnosis should be offered to women with pre- or full mutations. Males with premutation alleles should receive genetic counseling about potential phenotypic risks to their daughters, all of whom will inherit premutations.
- Genetic counselors should be alert to female family members who could be pursuing fertility treatments while unaware that they have an underlying *FMR1* premutation and a risk for having children with FXS.
- Since a main determinant of successful PGD is ovarian function, women with *FMR1* premutations should be evaluated for subfertility prior to consideration of PGD.
- At this time, there are no reports of intermediate alleles expanding to full mutations in a single generation, and invasive prenatal diagnosis is not medically indicated. Despite this, some patients with intermediate alleles, especially if they are already pursuing prenatal diagnosis for another indication, request fragile X prenatal testing to confirm that the fetus does not have a full mutation. Less frequently, patients may ask for prenatal testing to determine if an intermediate allele is unstable and has expanded into a premutation, based on concerns about potential phenotypic features, most of which would manifest in adulthood, if at all. In these circumstances, genetic counseling is crucial given the issues surrounding prenatal testing for adult onset disorders and the inability to predict the premutation phenotype.

Treatment and Resources

- In light of the rapid pace of drug development for FXS, genetic counselors need to be informed about current research on targeted pharmaceuticals. While these are still in the research phase, genetic counselors can facilitate the informational process and help families consider both positive and negative aspects of enrolling in a clinical research study.
- The National Fragile X Foundation (www.fragileX.org) provides extensive educational resources and support for families and professionals. The Foundation maintains a

Facebook social networking site for families affected by fragile X-associated disorders, as well as a separate informational site for individuals with FXTAS (www.fxtas.org).

- FRAXA Research Foundation (www.fraxa.org) raises funds to accelerate research progress toward effective treatments, and it also supports families and raises awareness about FXS.
- The Fragile X Clinical and Research Consortium (www.fxcrc.org) fosters the international development of fragile X specialty clinics and provides a structure for collaborative research efforts, including drug trials. Families should be encouraged to contact the consortium to locate their nearest FXCRC center about clinical management of FXS and other *FMR1*-related disorders.

Conclusion

When FXS was originally described as a rare, X-linked pediatric disorder (Lubs 1969), genetics professionals could not have anticipated the layers of molecular and phenotypic complexity that would eventually be revealed about *FMR1* and its associated disorders. Research into *FMR1*-related genetic and clinical phenotypes is actively being pursued on many fronts, including: molecular features that influence gene instability; epigenetic factors that contribute to clinical variability; targeted pharmaceuticals; and the emotional and societal impact of population screening. As our understanding of these issues evolves, genetic counselors will need to regularly update their knowledge of *FMR1*-associated disorders and adjust their counseling approaches to address the far-reaching impact of these conditions on patients and families.

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