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Testing for Fragile X Gene Mutations Throughout the Life Span

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Mutations of a single gene, fragile x mental retardation 1 (*FMRI*), give rise to a family of disorders occurring throughout the entire life span, including the most common heritable form of intellectual disability, fragile X syndrome, and premature menopause (primary ovarian insufficiency). Moreover, mutations of *FMRI* are the cause of one of the most common single-gene, late-onset neurodegenerative disorders, fragile X–associated tremor/ataxia syndrome (FXTAS). Some clinicians might assume they will rarely if ever encounter one of these disorders; that assumption would be both false and unwise.

Because of the risks associated with these disorders, newborn screening is being considered. The recent development of an accurate and inexpensive blood spot screening test capable of identifying both premutation and full mutation alleles¹ is facilitating at least 2 large-scale newborn screening studies to move forward in the United States. New-born screening for expanded alleles of the *FMRI* gene will lead to earlier intervention for individuals with developmental delays in both full mutation and premutation categories; genetic counseling before the birth of a second child with fragile X syndrome; elimination of the prolonged diagnostic odyssey families experience prior to the correct diagnosis; and identification of a range of fragile X–associated disorders among adults and across the extended family, thus permitting earlier treatments for many individuals.²

FMRI belongs to a growing family of genes that lead to disease through trinucleotide repeat expansions; *DMPK* (myotonic dystrophy) and *HD* (Huntington disease) are 2 examples. For individuals with *FMRI* (CGG repeat) expansions in the full mutation range (>200 CGG repeats), the gene is generally silenced, resulting in the absence of a protein (FMRP) important for synaptic function. More recently, it has become clear that clinical involvement also can occur in carriers of smaller, premutation alleles (55–200 CGG repeats), in which disease pathogenesis occurs by a completely different mechanism involving increased expression and RNA toxicity (Figure).

Individuals who carry a full mutation form of the gene experience a broad range of intellectual and developmental disability, and clinical involvement can include psychiatric or emotional difficulties even in those with a normal or borderline IQ. Autistic behavior is seen in the majority of boys with fragile X syndrome and approximately 30% fulfill all *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) diagnostic criteria for autism.³ Autisticlike behavior also is common in girls with the full mutation; however, shyness and social anxiety are even more prevalent in girls. Although the majority of children with the premutation have normal cognitive abilities, evidence is emerging that they also may have

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developmental problems, particularly deficits in attention and social communication in boys.⁴

Premutation alleles are relatively common in the general population, occurring in approximately 1 in 130 to 250 women and 1 in 250 to 810 men.⁵ Premutation expansions give rise to enhanced production (≤ 8 -fold) of the expanded CGG-repeat messenger RNA, resulting in a messenger RNA-dependent dysregulation of numerous proteins (eg, nuclear lamin A/C) and cellular stress response proteins (eg, α B-crystallin, Hsp27).⁶

An important clinical consequence of premutation-associated messenger RNA toxicity is the development of progressive neurological dysfunction in older adults, which includes peripheral neuropathy, cognitive decline or dementia, psychiatric problems, parkinsonism, tremor, and gait ataxia. Indeed, it was the clinical association between the neurodegenerative features in grandfathers of children with fragile X syndrome and excess gene activity that led to the messenger RNA toxicity hypothesis for FXTAS, which occurs in 40% of male carriers and a smaller portion of female carriers who have been ascertained through families with fragile X syndrome.⁷

For carriers who have not developed the core features of FXTAS, a variety of neurological and psychiatric problems may occur, including hypertension, orthostatic hypotension, neuropathy, migraines, anxiety, shyness or social deficits, and depression.^{8,9} These symptoms reflect the molecular and cellular changes that occur in neural cells in the central nervous system as well as in autonomic ganglia and nonneural cells outside the central nervous system.¹⁰ Because carriers of premutation alleles are common in the general population, clinical involvement associated with the premutation will likely contribute to clinical populations with other initial diagnoses,¹¹ and will be comorbid with Alzheimer disease, Parkinson disease with Lewy bodies, and multiple sclerosis. Among younger adults, nearly one-fifth of female premutation carriers will experience primary ovarian insufficiency. Moreover, the premutation is the leading genetic cause of primary ovarian insufficiency, present in 7% to 12% of familial cases and in 2% to 7% of sporadic cases.¹² In addition, female carriers with FXTAS are at higher risk for hypothyroidism (50% of cases) and fibromyalgia (42% of cases) compared with the general population.⁸

It is time to seriously consider routine testing for fragile X in some patient groups, particularly in children with intellectual and developmental disabilities, developmental delays or autistic behaviors, adult women with features of early menopause, or older adults with gait ataxia, intention tremor, or both. It also is important to test those individuals with cognitive deficits or dementia, peripheral neuropathy, parkinsonism, atypical multiple sclerosis, and anxiety disorders, particularly if there is a family history of intellectual and developmental disability, autistic behavior, or both. Testing is important to diagnose both premutation and full-mutation disorders because knowledge of genetic status is critical for early intervention across the spectrum of disorders. Such interventions include genetic counseling for the entire family, direct behavioral and medical intervention for the developmentally disabled child, improved reproductive options for women who are at risk of developing primary ovarian insufficiency, treatment for adults with the premutation who are starting to show signs of FXTAS, and early treatment of anxiety or depression.^{13,14} Newborn screening will facilitate the early intervention process for the children and the genetic counseling, early identification, and treatment for many other family members.

One of the most exciting advances in the treatment of fragile X syndrome was the discovery that the absence of FMRP leads to enhanced long-term depression of synaptic function of glutamatergic neurons, and that inhibition of the metabotropic (mGluR5) glutamate receptor at least partially normalizes long-term depression.¹⁵ This discovery has led to the study of a

number of mGluR5 antagonists that have demonstrated significant benefit in animal models of fragile X syndrome, leading in turn to the development of newer mGluR5 antagonists that are currently undergoing clinical trials in patients with fragile X syndrome. These trials, if successful, make the case of newborn screening more compelling and raise the prospect of future intervention during the developmental period to prevent long-term disability.

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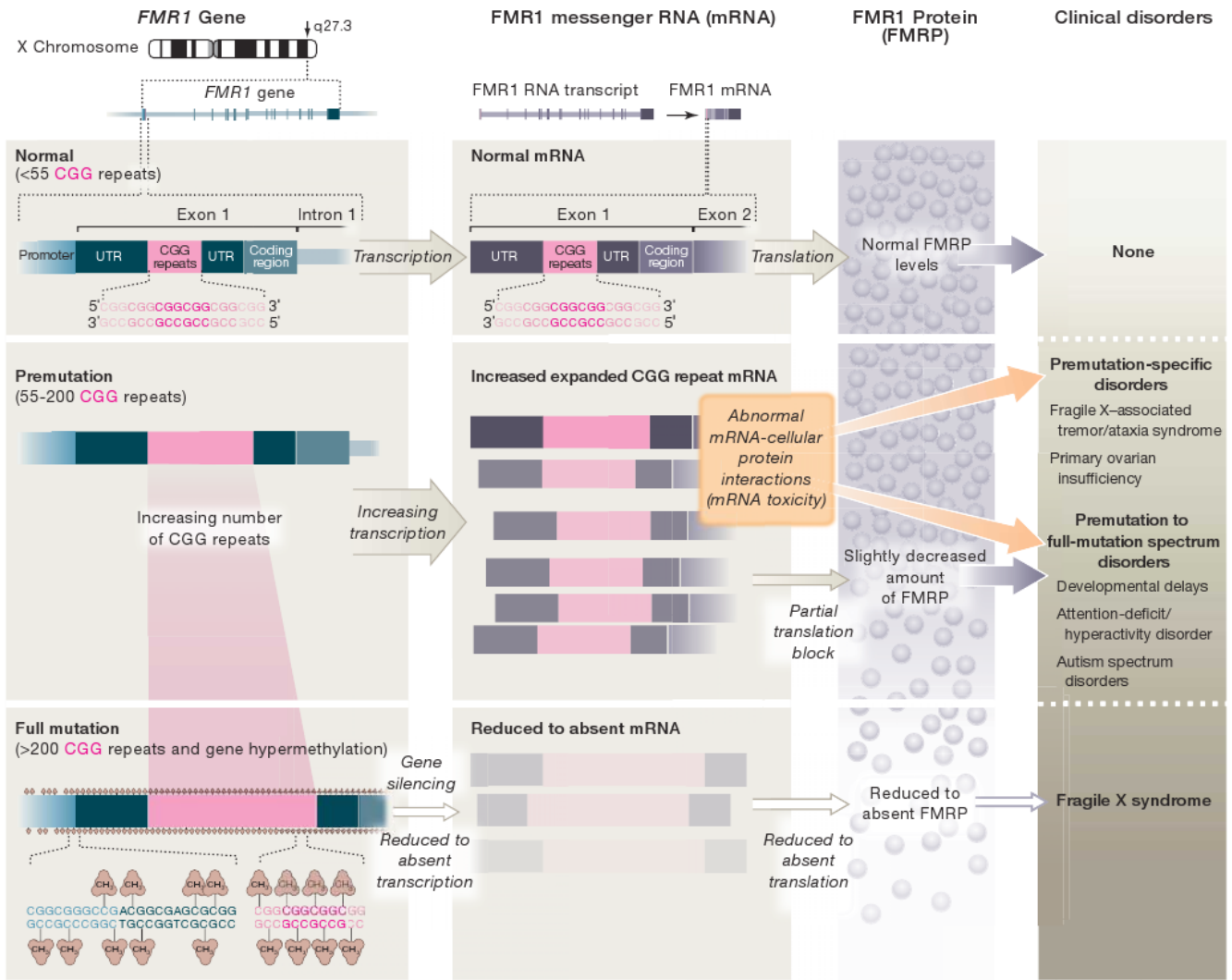


Figure. Expression of the *FMR1* Gene and Associated Clinical Disorders
 Expression of the fragile X mental retardation 1 (*FMR1*) gene depends on the length of the CGG repeat. Premutation alleles result in elevated mRNA levels (increased RNA synthesis). Within this CGG repeat range, the expanded CGG repeat in *FMR1* mRNA partially blocks translation to an extent that depends on the size of the repeat. Full mutation alleles are generally hypermethylated and silenced, thus producing little or no mRNA or protein. The excess premutation mRNA is now believed to give rise to the premutation-specific disorders, fragile X-associated tremor/ataxia syndrome and primary ovarian insufficiency, and may also contribute to developmental delays, attention-deficit/hyperactivity disorder, or autism spectrum disorders in some children with the premutation. By contrast, fragile X syndrome is caused by the absence of the *FMR1* mRNA and protein (FMRP). In the upper portion of the premutation CGG repeat range, mRNA toxicity and reduced FMRP levels may both contribute to clinical involvement. UTR indicates 5' untranslated region.