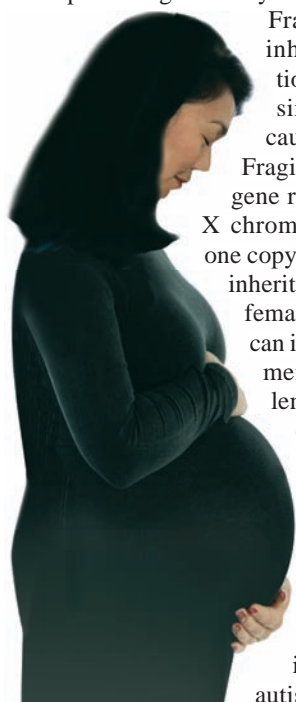


Fragile X syndrome: Is now the time for population screening?

By Feras M. Hantash, MS, PhD

Recently published in *Genetics in Medicine*, the journal of the American College of Medical Genetics (ACMG), were results of a study that validated a new technique for detecting carriers and newborns with Fragile X syndrome — an important step forward in longstanding efforts to develop a better means of detecting genetic carriers of this disorder. The technique, which uses triplet-primed polymerase chain reaction (PCR) with capillary electrophoresis (CE) on specimens of blood, saliva, and dried blood-filter paper spots, can replace the Southern blot technique in 99% of cases without compromising accuracy.



Fragile X syndrome is the leading inherited cause of mental retardation and the most commonly known single-gene cause of autism. It is caused by a genetic mutation of the Fragile X mental-retardation 1 (FMR1) gene residing on the so-called “female” X chromosome. Because men have only one copy of the X chromosome, males who inherit a mutation are twice as likely as females to be affected. The symptoms can include profoundly delayed speech, mental impairment, behavior problems, and distinctive physical traits (e.g., facial features [long faces, prominent ears], connective tissue problems, double-jointedness, and macroorchidism). Although females are less likely to be affected, they, too, can suffer from mental retardation and other effects. Many affected individuals fulfill the criteria for autistic-spectrum disorder.

Despite these challenges, population-screening for Fragile X syndrome, like cystic fibrosis, would confer important benefits.

Because Fragile X is linked to the X chromosome, a woman who is genetic carrier can pass the syndrome to her offspring, regardless of the father’s genetic characteristics. By comparison, two prevalent genetic disorders, cystic fibrosis and Tay-Sachs disease, can occur only when both mother and father are carriers.

Screening demands medical, social, ethical resolutions

Both the ACMG and the American College of Obstetricians and Gynecologists (ACOG) have recommended population-based carrier screening for cystic fibrosis among Caucasians and for Tay-Sachs disease among Ashkenazi Jews. Despite the greater prevalence of Fragile X at-risk couples, guidelines generally recommend that women with a family history of mental retardation be tested for their Fragile X-carrier status. Recommendations do not exist for population or newborn carrier screening.

At the 2010 ACMG meeting, a presentation revealed that the carrier frequency for Fragile X syndrome is one in 236 women in the general U.S. population. This means that a population-based carrier-screening program for the disorder would identify greater than three times more at-risk couples than either cystic fibrosis (1:784) or Tay-Sachs (1:900) diseases.

To a great extent, technical limitations inhibiting high-throughput laboratory testing have prevented population-wide testing for Fragile X syndrome. Now that high-throughput screening is feasible technologically, a number of medical, social, and ethical issues must first be considered by ACMG and ACOG before recommendation for wide screening. These issues — little changed since interest in carrier screening initially emerged with the introduction of the first DNA lab test for Fragile X syndrome in the early 1990s — can broadly be categorized as 1) educating society and healthcare professionals and 2) the potential for social bias.

Education about a complex, multifaceted disorder

One of the challenges in implementing screening revolves around the variable presentation of Fragile X syndrome. Carrier status and the degree of disability depend largely on the number of times a particular pattern of DNA recurs on the FMRI gene.

The frequency of this pattern determines if an individual has a premutation or a full mutation. A woman is a carrier whether she has a full or a premutation. Men with a premutation may escape developmental disorders, yet still be at risk of developing Fragile X-associated tremor/ataxia syndrome (FXTAS), a condition which can mimic Parkinson’s disease later in life. Twenty percent of women with a premutation may experience premature ovarian insufficiency (POI), which prompts early onset of menopause.

Given these complex issues, how can the medical community educate the public about the disorder? And what role can the laboratory play in educating the various types of physicians who may evaluate these patients and seek the laboratory’s interpretative counsel?

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Potential for social bias

Another key challenge relates to the potential for social bias. While there is no cure for Fragile X syndrome, early intervention to help the developing brain may benefit some affected children. Yet, the degree of disability is highly vari-

able. Would newborn screening be beneficial in promoting early intervention, or would it cause children to grow up confronted with damaging prejudices? Would parents be inclined to display confidence-eroding bias toward a child who harbors a premutation, which

may carry little risk of developmental disability?

Despite these challenges, population screening for Fragile X syndrome, like cystic fibrosis, would confer important benefits. Couples who know their risk for the disorder can make more informed decisions. Notably, a recent study found that diagnoses of children with Fragile X often occur after the age of three. By then, unknowing parents may have given birth to other affected siblings.

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Moreover, children who are diagnosed early can receive proper educational and social support. And in the future, medications — including certain pharmaceutical agents now in clinical trials — may be targeted specifically to children with Fragile X syndrome.

Finally, men and women who understand the genetic cause of their FXTAS and POI may be spared the confusion and anxiety that patients often feel when a definitive diagnosis eludes them. Further studies to validate the approach described here are necessary before medical guidelines are likely to change. □

Feras M. Hantash, MS, PhD, principal scientist in charge of molecular-genetics R&D for Quest Diagnostics Nichols Institute — the esoteric R&D testing center of Quest Diagnostics — was instrumental to the development of the company's XSense Fragile X syndrome test. Dr. Hantash was lead investigator on "Qualitative assessment of FMR1 (CGG) in triplet repeat status," a study to validate the technique published in the March 2010 issue of *Genetics in Medicine*.

Editor's note: The abstract of this study mentioned by Dr. Hantash is online at: <http://submissions.miracdc.com/acmg/ContentInfo.aspx?conID=1401>.