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Climbing the Branches of a Family Tree: Diagnosis of Fragile X Syndrome

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Abstract

Objective—To determine the average number of family members who are diagnosed with a Fragile X Mental Retardation-1 (*FMRI*) mutation after a proband receives the initial diagnosis of Fragile X syndrome (FXS).

Study design—We reviewed pedigrees of families who have been evaluated at the Fragile X Center at Emory University, Atlanta, GA. Through these pedigrees, we determined the number of additional family members diagnosed as *FMRI* premutation carriers or with full mutation FXS, following the initial diagnosis in each proband.

Results—The Fragile X pedigree review identified 176 probands, including 108 males (61%) and 68 females (39%). A total of 785 family members were diagnosed with expanded fragile X alleles, 278 males (35%) and 507 females (65%). These family members included 227 individuals with full mutation FXS (219 males, 8 females) and 558 premutation carriers (59 males, 499 females). After the initial diagnosis of a proband with FXS, there were, on average, at least 5 additional family members who were diagnosed with an *FMRI* mutation.

Conclusions—Our study confirms that taking a detailed family history after diagnosis of a proband with FXS is likely to identify multiple family members with *FMRI* mutations. It is important that the pediatrician or other health care provider making a diagnosis of FXS recognize the value of a detailed family history for timely diagnosis and treatment of additional individuals who may be *FMRI* premutation carriers or have full mutation FXS.

Keywords

Family history; early diagnosis

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Fragile X syndrome (FXS; MIM 300624) is the most common inherited form of intellectual disability and is caused by a CGG trinucleotide expansion in the promoter region of the Fragile X mental retardation-1 (*FMR1*) gene. When this expansion contains over 200 repeats (full mutation), it leads to decreased or absent levels of the fragile X mental retardation protein (FMRP), resulting in FXS. Premutation carriers have unstable alleles with 55 to 200 repeats that can expand to the full mutation during transmission from mother to child.¹ Approximately 1 in 4000 males, and 1 in 8000 females have FXS, and the prevalence of the premutation in the general population is 1 in 130–260 females and 1 in 250–810 males.²

The diagnosis of FXS is critically important not just to the affected child, but also to other siblings, parents, and the immediate and extended family members in each generation. The “fragile X associated disorders” are the clinical outcomes of the expansion mutation which can result in three established medical conditions (FXS, fragile X-associated primary ovarian insufficiency (FXPOI), and fragile X-associated tremor ataxia syndrome (FXTAS)) that can occur throughout the generations in a single family. Female premutation carriers are thought to be at risk for FXPOI, depression, anxiety, and medical issues such as hypothyroidism, fibromyalgia, and neuropathy.^{3–6} Both males and females over age 50 who carry the premutation are at risk for FXTAS, a late onset neurodegenerative disorder.^{7, 8}

Typically, a child with FXS presents with developmental delay, autism, and/or behavioral problems (e.g., hand flapping, decreased eye contact), and may be the first person in the family to be diagnosed with the condition.^{1, 9–11} The pediatrician has an opportunity to take a family history, inform the parents about the inheritance pattern of FXS, and encourage testing and evaluation for all at-risk immediate and extended family members. Our study was designed to determine the average number of family members who are diagnosed as premutation carriers, or with full mutation FXS, after the proband receives the initial diagnosis of FXS.

METHODS

After receiving approval from the Emory University institutional review board, two physicians and genetic counselors at the Fragile X Clinic and Research Center at Emory University, Atlanta, GA, reviewed 176 previously completed pedigrees of families who have been evaluated through our Fragile X Center. Once the proband received the diagnosis of FXS, cascade testing was provided. Cascade testing refers to the identification and the offering of genetic testing to family members of a proband.^{2, 12} For example, the proband's siblings should be offered testing, especially if they have a history of intellectual disability, autism, and social/behavioral, or learning disorders. Female relatives are also recommended to have the *FMR1* DNA testing as they are at risk for infertility and/or premature menopause or to have a child affected with FXS.

Pedigree construction and analysis in our Fragile X Syndrome Center was performed in a standard manner equivalent to the guidelines set by Finucane et al using a cascade method.^{2, 12} Through these pedigrees, the number of additional family members diagnosed with a premutation or full mutation FXS as confirmed by *FMR1* DNA testing was determined, following the initial diagnosis in each proband. An anonymous summary sheet

was developed to standardize the chart review procedures and to track the number of affected probands and family members. The probands and family members were also categorized by sex.

RESULTS

The Fragile X pedigree review identified 176 probands, including 108 males (61%) and 68 females (39%). A total of 785 family members were diagnosed with expanded fragile X alleles, 278 males (35%; 59 premutation, 219 FXS) and 507 females (65%; 499 premutation, 8 FXS). In all, these family members included 227 individuals with full mutation FXS (29%) and 558 premutation carriers (71%). Although males were more commonly diagnosed as the initial proband, more females, particularly premutation carriers, were identified during subsequent analysis of the family history and pedigree. After the initial diagnosis of a proband with FXS, there were, on average, at least 5 additional family members who were diagnosed with FXS or as a premutation carriers.

DISCUSSION

Because FXS has no distinct physical characteristics at birth to prompt the diagnosis, it typically becomes evident after the child presents with developmental delay, behavioral problems, or learning issues. For these reasons, FXS is typically diagnosed at 35–37 months in boys and 41 months in girls. On average, the diagnosis occurs 18 months after the family first identified concerns.^{13, 14} Late diagnosis delays the family's understanding of their reproductive risk, which can be critical for family planning. In a national FXS survey study, 55% of parents already had another child before the first child was diagnosed with FXS.¹⁴

Our results indicate that upon diagnosis of a proband with FXS, subsequent pedigree analysis will reveal additional individuals affected with full mutation FXS. This suggests that taking a detailed family history and recommending genetic testing for individuals within the family who have a history of developmental delays, behavioral problems, and learning deficits, will identify additional family members with FXS.¹⁵ Earlier identification of FXS would allow a child to optimally benefit from early intervention and treatments for developmental and/or emotional disorders, have access to current clinical trials targeting cognitive and behavioral deficits in FXS, and would also alleviate potential parental stress associated with the diagnostic odyssey. Further, studies of the neurobiology and synaptic mechanisms in FXS have led to development of diseasespecific pharmacological treatments, with several drugs currently being tested in Phase 2 and 3 clinical trials in children and adults with FXS, including metabotropic glutamate receptor 5 (mGluR5) blockers, gamma amino-butyric acid (GABA) agonists and minocycline.^{16, 17, 18, 19} These various targeted treatments reveal promising preliminary results that may help with behavior, social functioning, and learning in individuals with FXS.

In our study, identification of a proband with FXS and subsequent pedigree analysis led to diagnosis of over three times as many premutation carriers, predominantly females. These individuals were previously not aware of their carrier status. By knowing their diagnosis, female carriers become aware of medical concerns related to the premutation, such as

FXPOI and FXTAS^{6, 7} but also additional medical and psychiatric problems that can occur in some carriers including: neuropathy, migraines, sleep apnea, hypertension, hypothyroidism, fibromyalgia, anxiety, depression, and obsessive compulsive behavior.^{3, 5, 20, 21, 22} Males carriers over age 50 have an increased likelihood of additional medical problems, such as neuropathy, hypothyroidism, hypertension, arrhythmias, and sleep apnea which may begin prior to the onset of FXTAS.^{3, 20, 23} As such, identification of both male and female premutation carriers can lead to early diagnosis and treatment of these medical and psychiatric issues, potentially improving the individual's quality of life.

Although most children with the premutation do not have neurodevelopmental deficits, recent studies have suggested that as many as 10–20% may experience attention deficit hyperactivity disorder (ADHD), learning problems, shyness, anxiety, or autism.^{24–26} Thus, awareness of the premutation status in immediate and extended family members will help identify related medical, psychosocial, and/or neurodevelopmental problems which can be addressed with appropriate treatments.

The multigenerational mutation process and variable phenotype associated with the *FMRI* mutation have significant implications beyond the immediate concerns of the proband, who is typically a child with FXS. For these reasons, pediatricians should be familiar with the variable clinical manifestations of Fragile X associated disorders including FXS, FXPOI, and FXTAS. Cascade testing is recommended once the child receives the diagnosis of FXS.^{2, 12} For instance, if a male child has FXS, testing for his mother is recommended to determine if she is a premutation carrier or possibly has full mutation FXS herself. If she is a premutation carrier, she is at risk for developing FXPOI and other medical issues, such as hypothyroidism and autoimmune disorders. Importantly, knowing her carrier status will allow her to make an informed decision regarding family planning. Additionally, the cascade testing would indicate subsequent genetic testing for the proband's grandparents, as they could be at risk for developing medical problems associated with the premutation, including FXTAS. The pedigree analysis would document the presentation of any clinical symptoms in the maternal grandmother or maternal grandfather, which may indicate which person should be tested first. Cascade testing will identify other family members who may also be affected with premutation or full mutation FXS, allowing them to seek early and appropriate treatments associated with their fragile X mutation.

The pedigree review from our Fragile X Center at Emory University revealed that, on average, there are at least five family members who are subsequently diagnosed with FXS or as an *FMRI* premutation carrier following the diagnosis of a proband. Because the diagnosis of FXS is typically made by the pediatrician when the child presents with developmental delay and/or behavioral problems, our findings emphasize the need for pediatricians to take a detailed family history for each patient affected by FXS and to encourage testing and evaluation of all at-risk family members. Alternatively, pediatricians may also choose to refer the family for genetic counseling to facilitate cascade testing. Taking a family history to identify at-risk family members is an effective and efficient way to facilitate diagnosis of individuals who may have full mutation FXS or be premutation carriers. This approach also reduces the diagnostic odyssey of symptomatic relatives (eg, FXTAS or FXPOI) who are being evaluated, often without attention to the family history.

One of the study's limitations is the possible refusal of affected family members to be evaluated. Therefore, our finding of 5 affected relatives per family represents a minimum number of individuals expected to be found through a pedigree analysis. All of our participants were clinic and/or research patients at one FXS Center (Emory University). It is possible that their experiences differ from FXS families at other clinics, or from families who do not participate in research. Our sample may be biased in that it represents families who are active in the FXS community and proactive in seeking specialty clinic care for their child. We did not collect parental socioeconomic status, which may contribute to factors involved with communicating the diagnosis and its inheritance pattern to other family members. Participants who were diagnosed as premutation carriers through cascade testing received the *FMR1* testing through our research study; thus, we do not have their clinical information related to symptoms associated with FXPOI or FXTAS. Our results demonstrate that many affected family members exist in a typical FXS family, thus emphasizing the need to take a detailed family history in FXS and similar inherited conditions, and subsequently encourage testing of at-risk family members.

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Abbreviations

FXS	fragile X syndrome
FXPOI	fragile X primary ovarian insufficiency
FXTAS	fragile X-associated tremor ataxia syndrome
ADHD	attention deficit hyperactivity disorder

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