Journal of Genetic Counseling, Vol. 14, No. 4, August 2005 (© 2005)
DOI: 10.1007/s10897-005-1159-6

Original Research

Women's Attitudes Toward Testing for Fragile X Carrier Status: A Qualitative Analysis

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Fragile X syndrome (FXS) is primarily due to a repeat expansion mutation found in the *FMR1* X-linked gene. We have conducted a qualitative analysis of responses from women concerning their attitudes toward testing for carrier status of the fragile X mutation among reproductive-age women. We obtained responses from focus groups including women with and without FXS in their families. We found the following themes: (1) mothers of children with FXS have difficulty formulating their opinions on population screening because of their unique experiences surrounding their own carrier diagnosis and their relationship with their children with FXS, (2) the motivation for carrier testing and need for information differ by family history of FXS and parental status, and (3) the timing of carrier testing with respect to a woman's life stage dictates whether carrier information will be viewed as beneficial or detrimental. There was evidence that non-carrier women from the general population would be wholly unprepared for positive carrier results. These findings have significant implications for genetic counseling as well as for population screening.

KEY WORDS: population screening; fragile X carriers; focus group; carrier testing.

INTRODUCTION

The fragile X syndrome (FXS), a type of inherited X-linked mental retardation, is primarily due to a unique mutation that leads to the silencing of the *FMR1* X-linked gene. Population screening for FXS has been a topic of consideration since the *FMR1* gene was identified in 1991 and an accurate test developed to identify the hyperexpanded CGG repeat sequence, the mutation occurring in the vast majority of individuals with FXS. Such discussions have taken place prior to the identification of unique and significant clinical consequences of other allelic forms of the expanded repeats, primarily the premutation form. In this report, we will consider an important target population for population screening that has been discussed minimally in the literature, namely women of reproductive age. There are many issues that need to be considered prior to instituting a population-based screening program including the significance of the condition, the clinical and analytical validity of screening tests, feasibility of implementing the screening program, and access to results and resources needed to implement the program. As part of the investigation of the feasibility of implementing a screening program, we have initiated studies to understand the attitudes of women with respect to carrier testing for the fragile X mutation and the effects of obtaining this genetic information.

The mutation leading to almost all of the cases of FXS is due to an expansion of an unstable CGG repeat sequence located in the 5′ untranslated region (UTR) of the *FMR1* gene (Fu *et al.*, 1991; Verkerk

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et al., 1991). This "full" mutation form of the *FMR1* gene consists of over 200 repeats and is abnormally hypermethylated. Consequently, no mRNA is produced and the lack of the gene product, FMRP, an RNA-binding protein, is responsible for mental retardation (Ashley *et al.*, 1993). Approximately 1/4000 males have FXS and by inference, about 1/8000 females have FXS (for review, see Crawford *et al.*, 2001). There are essentially three other allelic forms of the gene characterized by their CGG repeat size and stability during transmission from parent to child: stable common alleles, intermediate alleles, and unstable premutation alleles. Premutation alleles are defined as long, unmethylated repeat tracks that are unstably transmitted from parent to child. Approximately 1/350 females and 1/1000 males carry premutation alleles of the range 61–200 repeats. This repeat range definition is probably too narrow a description for premutation alleles as unstable alleles with 50–60 repeats are sometimes identified in the older generations of families with FXS and clearly are "premutation" alleles. But when such alleles are identified in the general population through a population survey, transmission instability may not occur (Sullivan *et al.*, 2002; Nolin *et al.*, 2003). Sometimes such alleles are put into the "intermediate" category, as they are only predisposed to instability.

A clinical consequence of the expanded CGG repeat in the *FMR1* gene was thought to be restricted to those with the full mutation (hence the term "full"), namely overt mental retardation. However, the unmethylated, long CGG repeat track found in premutation carriers has been associated with specific phenotypes unrelated to FXS and unrelated to full mutation carriers. The significant consequence for women who carry the premutation is an increased risk for premature ovarian failure (POF) (for review, see Sherman, 2000). In 1% of the general population, cessation of menses occurs before the age of 40 and is clinically defined as POF. In contrast, approximately 21% of premutation carriers have POF compared with only 1% in the general population, or a relative risk of 21. The cause of the ovarian failure and the risk factors associated with the *FMR1* gene are under investigation.

More recently, a significant increase in the risk for a late onset tremor/ataxia syndrome (FXTAS) has been identified in men who carry the premutation, and in a smaller proportion of women. Hagerman *et al.* (2001) were the first to report five older premutation carrier males who developed an intention and resting tremor in their 50s or 60s and subsequently developed ataxia with a wide-based gait and frequent falling. In a more recent review of 26 patients, they outline the primary clinical features, neuroimaging and molecular correlates (Jacquemont *et al.*, 2003). Cognitive deficits including short-term memory loss, executive function deficits and cognitive decline were present. Other symptoms included parkinsonism, peripheral neuropathy, lower limb proximal muscle weakness and autonomic dysfunction. Initial studies indicate that about 20–30% of men with the premutation are at risk for FXTAS (Smits *et al.*, 2002; Rogers *et al.*, 2003; Jacquemont *et al.*, 2004). To date, all reported work is based on limited sample sizes; thus, more work is needed to understand the natural history of FXTAS and the associated risk factors. Importantly, further investigation is needed to establish genetic counseling recommendations.

The unique inheritance pattern of this X-linked mutation and the variable phenotype of the different allelic forms lead to complicated issues related to an individual's knowledge of their own carrier status and that of other family members. In most settings, the fragile X mutation segregating in a family is identified through a child with FXS, the full mutation, due to their developmental delay or mental retardation. In general, the fragile X mutation follows the basic rules of X-linked inheritance: 50% of offspring from carrier mothers will receive the mutation and all the daughters and none of the sons of carrier fathers receive the mutation. However, the risk of expansion of the CGG repeats in a premutation allele to a full mutation overlays the transmission pattern. Expansion from a premutation to the full mutation in a transmission from a carrier woman depends on the size of the woman's repeat (Nolin *et al.*, 2003). The risk of expansion to the full mutation from carrier men to their daughters is almost zero. That is, premutation males pass on the premutation to all of their daughters, usually with only small expansions or contractions.

In some situations, carrier status is revealed simply by taking a family history of the individual with FXS. Thus, diagnosis of FXS uncovers premutation carrier status of all relatives linked to those affected with FXS, thereby revealing an individual's risk for a late age disorder, POF and/or FXTAS. The choice of "knowing/not knowing" carrier status is removed. This significantly complicates genetic counseling.

Population screening for FXS at a public health level has been considered for several target populations prior to the identification

of premutation-associated clinical phenotypes. The target populations include: pregnant women (prenatal screening), newborns, children with developmental delay, and women of reproductive age (for review, see Meadows and Sherman, 1996). In addition, women's attitudes related to carrier testing for FXS in a clinical diagnostic setting have been examined by McConkie-Rosell and her colleagues from several different levels: attitudes and opinions of obligate carrier females (McConkie-Rosell *et al.*, 1997), parental attitudes regarding carrier testing in children at risk for FXS (McConkie-Rosell *et al.*, 1999) and effect of carrier testing on a woman's self-concept (McConkie-Rosell *et al.*, 2000). Their work re-enforces the importance to assess the feasibility of population screening of women of reproductive age.

Understanding the attitudes related to clinical and population testing has been restricted to individuals who are in families with FXS. Previous studies to identify attitudes on carrier testing for FXS have been based on women at risk for carrying the fragile X mutation identified from families with FXS. Information was obtained using questionnaires and follow-up interviews (e.g., McConkie-Rosell *et al.*, 1997, 1999, 2000). No assessment of attitudes has been performed on individuals at low risk for carrying the fragile X mutation, i.e., the general population. Furthermore, no studies have been conducted concerning the effect of learning ambiguous results related to risk of having affected offspring (i.e., women who carry alleles with 50–60 repeats).

In this initial report, we used a qualitative approach to determine issues related to carrier testing and population screening for premutation carrier women. We conducted focus groups among women from families with FXS and those from the general population to obtain opinions on the benefits/risks of population carrier screening among reproductive-age women. We also explored many topics addressed by McConkie-Rosell and her colleagues, such as motivation for testing, perceptions about the carrier testing process, reactions to knowing their carrier status, self-concept, and concerns for family planning.

STUDY POPULATION AND METHOD

Study Population

Focus groups were conducted in the fall of 2002. Women participating in the focus groups were drawn from two larger studies: (1) Emory Study of Adult Learning (ESAL) and (2) Emory Fragile X Family Study (EFXS). The goals of these studies were (1) to characterize the neuropsychological and reproductive profile of individuals who carried high repeat alleles, a research question, and (2) to offer carrier screening for fragile X syndrome, a community service. A brief description of fragile X syndrome and the inheritance was described in the materials provided to each participant. Risks associated with identifying carrier status were outlined including emotional risks and potential insurance discrimination. At the initiation of these studies, ovarian failure was the only phenotype well established among premutation carriers. The tremor/ataxia syndrome had not been identified. Thus, in recruitment/study materials, only the reproductive phenotype was described. Human subjects and ethical issues for all three studies were each reviewed by the Internal Review Board (IRB) at Emory University School of Medicine and approved.

Source Sample

All participants in ESAL and EFXS were between the ages of 18–50 years, lived in the metropolitan Atlanta area and had English as their primary language (requirement for neuropsychological testing). For ESAL, a study brochure and a video, depending on the venue, were provided to potential participants to describe the goals of the study. The study team was on site to describe the study further on an individual basis and to answer questions. All individuals provided a buccal sample for CGG repeat analysis once a consent form was signed. If a participant for ESAL had more than 40 repeats, they were invited to participate in a follow-up study that included psychometric testing and administration of a reproductive, medical history and demographic questionnaire. For every participant enrolled in ESAL, an individual was recruited who had fewer than 41 repeats and matched by gender, age, ascertainment site and ethnic/racial group for the same follow-up protocol. Individuals were told their results if they requested them. A similar protocol was followed for EFXS. All family members of an individual diagnosed with FXS were surveyed for the premutation carrier status. If a carrier of the premutation was identified, they and their non-carrier siblings were recruited into the follow-up study.

Focus Group Sample

At the time of focus group formation, 2620 women had provided buccal samples through the ESAL and EFXS protocols of which 181 participated in the associated follow-up study (psychometric testing and questionnaires). We sent out a survey to these 181 enrolled women to collect information on demographics and attitudes toward population screening. Forty-six percent returned the survey and of those we invited 62 women to participate in one of the six focus groups as described below. Approximately 10 women per focus group were invited. We chose women to increase ethnic/racial and economic diversity. No selection was made based on attitudes toward screening obtained through the survey. Of those, 65% agreed to participate ($n = 40$, Table I). Participants ranged in age from 21 to 50. They came from two ethnic/racial backgrounds in the Atlanta area, non-Hispanic white and non-Hispanic black. Since English as a primary language was part of eligibility for the overall ESAL/EFXS studies, other racial groups were not available. Overall, 23% of the participants were non-Hispanic black, close to the proportion found in the metropolitan Atlanta area.

Focus groups were planned as follows: three groups included women from the general population whose test results were in the normal range (general population) and three consisted of women with a known family history of FXS whose test results were in the premutation range (carriers). Both types of groups were further divided by status of children: within the general population groups, groups were subdivided into those who had children and those who did not have children. Within the carrier groups, groups were subdivided into those who had children with FXS and those who did not have children with FXS. Upon reaching saturation quickly in the general population group, the third focus group was cancelled, resulting in a total of five focus groups for analysis (Table I).

One subset of the population was excluded from the focus groups: women in the general population whose results were in the premutation range. We assumed that their concerns would be too sensitive to explore in a group setting. Thus, these women are being recruited into a follow-up study using in-depth interviews. Also included in the follow-up study are women with a family history of FXS with no children since they may have opinions similar to the general population women identified as carriers. These in-depth interviews are ongoing and results will be presented in a later report.

Procedure

Each focus group session lasted approximately one hour and was led by a moderator. The moderator of the group followed the same guide for all groups with minor changes related to ascertainment group (i.e., general population [ESAL] or family with FXS [EFXS]). Questions were asked to initiate discussion and are listed in Table II. For women who had been identified as carriers through the diagnosis of their child with FXS, it was necessary to remind them that the questions posed in the discussion were to elicit information about themselves—that the point was to talk about them, not their child's diagnosis of FXS. This is discussed further in Results.

All focus groups were audio and video recorded. Tapes were transcribed and the participants' grammar has not been corrected in order to preserve the flavor of the sessions.

Analysis

Transcripts of the focus groups were copied and master copies stored for reference. Transcripts were grouped according to sample (e.g. general population without children) for analysis. Primary patterns in the data were noted and classified into potential themes, with particular emphasis on similarities and differences within and between study groups (e.g., inter-participant and category analysis). Data were analyzed independently by the study team members who then collaborated throughout the process to compare and discuss classification and the development of themes. Once complete and prioritized, salient supporting passages were identified and checked against original recordings for accuracy as needed. Themes were then compared to existing literature to determine consistency or novel findings.

Throughout the Results section, we included supporting passages which are followed by a notation indicating in which group the respondent participated. The notations are as follows.

GP-0: general population, non-carrier, no children;
GP-ch: general population, non-carrier, with children;
Pre-0: premutation carriers from FXS families, no children or no children with FXS;
Pre-FXS: premutation carriers from FXS families, with children with FXS.

Table I. Description of Participants in the Six Focus Groups (F1–F6)

General population (ESAL): (i.e., non-carriers from the general population); original ($n = 22$) and final ($n = 13$)	F1 ($n = 6$): White 4 and Af. Amer 2[a] F2 ($n = 7$): White 5 and Af. Amer 2[b] F3 ($n = 9$): White 7, Af. Amer 1 and other 1 (group cancelled)[b]
Carriers (EFXS): (i.e., premutation carriers identified through families with FXS); ($n = 18$)	F4 ($n = 6$): White 4 and Af. Amer 2[c] F5 ($n = 6$): White 6 and Af. Amer 0[c] F6 ($n = 6$): White 5 and Af. Amer 1[d]

[a]Women with children.
[b]Women without children.
[c]Women with FXS children.
[d]Women without children or with children without FXS.

RESULTS

Difficulty Separating Issues Regarding Carrier Testing From Child's Diagnosis of FXS

There was a significant difference in attempting to obtain information about attitudes towards screening reproductive-age women from carrier women with children with FXS compared with the other groups. Women in the carrier groups were tested in a clinical situation, almost always as a result of efforts to diagnose their children. Perhaps the most salient finding is that, throughout their discussions, issues for carriers were closely, and sometimes inextricably, tied to issues of their children. When opening these groups, it was necessary to remind the women that the questions posed in the discussion were to elicit information about themselves. In just the opening minutes of one

Table II. Moderator's Guide for Each Focus Group

Questions for women from FXS families	Specific probes
Genetic testing is a sensitive issue. One could imagine that some people would hesitate to get genetic testing. Did you have any hesitations? Can you describe to me what they were?	
Given your hesitations (if applicable), what motivated you to participate in the study?	
When you started this process—getting tested for fragile X (*the screening*)—what do you wish you had known in the beginning?	What information was missing? What did you have to find on your own?
How did your family play a role in your decision to be tested? (*Let's talk about your family. How did you discuss the testing with them? What was their reaction?*)	(*What was your understanding of how the results might affect them?*)
Let's talk about when you received your results. How would you describe your first reaction to getting your result?	Which emotion did you feel? Indifference? Relief? Shock? Anxiety? Guilt? Anger? Depression? Shame?
Did your test result cause you to take any action or make any decisions about your life plans?	Did you make any changes to your plans to have children, go to school, work, relationship? Were the changes primarily positive or negative?
Let's talk more about your emotional response. Did your result make you feel anything new about yourself? Did it change your perception of yourself in any way? As a mother? As a wife or partner? As a member of your family? Did the result affect your relationship with them?	What, if anything, does the result validate, what fears were allayed or magnified, were you reassured or made more anxious—how are you responding to those feelings?
Knowing what you know now, if you could go back, would you still be tested?	
Over all of the things we have talked about—some of your hesitations—the changes you have made and felt. . . if you were going to give advice to other women considering testing, how would you help them think about balancing the benefits of knowing versus the possible challenges?	What factors need to be present to prevent the negative effect from over-riding the benefit?

Note. Changes in wording for women selected from the general population are in italics and parentheses.

session, a woman responded to this point with a seemingly almost offhand remark:

> I don't think there is myself anymore. (Pre-FXS)

Uptake of Carrier Screening—Lack of Hesitation to Test, But Different Motivations

Across all groups, there was little hesitation to be tested for carrier status, although the reasons differed significantly between the general population non-carriers and premutation carrier women. Among non-carrier women in the general population, most reported an "*interest*" in science that is "*fascinating*" (GP-ch) as their motivation for being tested. Some stated that they were "*caught*" (GP-0) by researchers seeking participants in a cheek swab test:

> They were giving a piece of candy away. (GP-0)

> . . . oh we just did it with a friend and forgot about it. (GP-ch)

For most, they participated in the test and gave it very little further thought:

> And it's kind of nice to know that I don't have it and that I'm not a carrier or anything that I know of. And I it just kind of made me feel that's one less thing that I have to worry about. (GP-0)

> I'm a little older than everybody so you know it was nice to know but I knew I wasn't going to have any children so it really didn't. . . it was really just more a matter of curiosity. (GP-0)

General population women differed in their responses according to their parental status. For example, women without children considered that being tested for carrier status was similar to having your "*cholesterol*" tested. Those with children showed a greater interest in the effects of their carrier status on their children and grandchildren. Some were interested in understanding family planning issues for their children.

Premutation carrier women from FXS families shared the general population's lack of hesitation, although for most of these women, the strongest motivators for obtaining FXS testing were to help their child or to reassure themselves:

> I needed confirmation that I was right. These kids are different. I just needed confirmation that the things that I said about them were right. The things that I had to battle my way through the school system about were right. . .. And the whole time I'm thinking this is like a breakdown, this isn't something they're choosing to do. And just have that confirmed. . .. That your instincts were right. (Pre-FXS)

The women who discovered their own carrier status through the process of diagnosis of a child were significantly more expressive about their motivation being related to family planning. For many of the women who already knew that they were likely to be carriers, the motivation to test for certainty was related to their families, either to provide information to their own children or to an extended relative for family planning. Yet this did not always happen without reluctance:

> You know we told family because like I said I had a sister going through it and others that were having babies, but I didn't get tested until after some of them did because it just didn't matter to me. (Pre-FXS)

> And we left thinking well you know if he thinks it's fragile X we're fine by that we don't have to know officially. And we're not having any more kids and probably at this point, so why does it even matter. So we really, we were good on theory. And we really weren't that anxious to know. . . then I had a cousin. . . who wanted to have, to start having children. . .. And she probably thought if this was genetic she needed to know. And then sure enough it was she who kind of forced our hands. . . even when we were going to the doctors it was like oh, I can't believe I'm doing this. But I guess I need to. (Pre-FXS)

Carrier Screening Provides Important Information for Most

The importance of information was seen in all of the groups. However, the reasons for wanting the information were significantly different for carrier women than the non-carrier women in the general population. For some non-carrier women in the general population, information was important for the sake of information—they suggested the belief that if their results had been different, they would have wanted a lot of information ("*information*," "*. . . lots and lots of information*," and "*. . . a whole bunch of information.*" [*GP-0*]). They stated that obtaining that information would be their major advice to women who were found to be carriers—either for their own choices or for the choices of their children. For other women, they did not think that information on carrier status was important:

> If really there is just a family history, then you may as well but for the average like woman there is no reason, there's no point in worrying about it or thinking about it. (GP-0)

> There are so many different chromosomes that okay it's not that one it's something else. (GP-ch)

There was a desire among carrier women from FXS families to know their status in order that other family members could make more informed choices. An awareness of the importance of information for the purposes of family planning was voiced by all carrier women, but particularly salient among carriers without children with FXS:

> Absolutely. That's the main reason, the only reason. It makes a big difference. (Pre-0)

> We were getting ready to start a family and when this came it was like we're putting this on hold until we find out whether or not I am. (Pre-0)

Immediate Reactions to Testing

Nearly all carriers from FXS families reported some sort of guilt experience. One woman referred to sharing her diagnosis as being begged to "*come out of the closet*" (Pre-FXS)—a phrase often associated with stigma and shame. It is important to note that guilt was not always the most salient immediate reaction, such as with one carrier whose child had FXS, and only indirectly realized she had experienced any level of guilt:

> This is a round about way to realize that I felt something about it toward my husband is that when an old boyfriend came by I thought well you're very lucky. [inaudible] and when I thought about that I thought I guess it's really bothering me that my husband could have had a wife that didn't carry Fragile X and look what he got, kind of like the booby prize. But it took, it actually took, I wasn't thinking about it on a conscience level until this boyfriend came and I, oh aren't you lucky. . .. I thought he would just probably go 'whew'. But my husband has actually been fabulous about it. . . and you know he feels like that's the luck of the draw. And he's also a very spiritual person and feels like life puts you in the place that you're supposed to be. But he's never, ever made me feel anything except that he's the luckiest man alive to have these children. So I have to thank him because it wasn't guilt with me but later I guess I realized I actually had carried a little bit of it. (Pre-FXS)

Some of the women in the carrier groups said they experienced a "*grieving period*" (Pre-FXS) or "*mourning like there had been a death in the family*" (Pre-FXS).

Reactions of relief were expressed equally as strongly as were reactions of guilt, as nearly all discovered their carrier status as a result of finding a diagnosis for their child. One woman said that she was "*thrilled*" (Pre-FXS) to get the news. Thus, new knowledge of being a carrier was sublimated to the relief of finally having an answer to their children's problems:

> I don't know if that will come later because my diagnosis is so new and everything but I really don't feel any of the guilt. I just, I wish that I had known earlier so that I didn't have to go through all of the you know the testing that you know gives you a diagnosis but you know they'd say will you come back in a year because that could change? But you know with the genetic testing you know it's just, this is the answer, you know there is not another test. You go back to the doctor and you don't have to be re-evaluated in a year. This is the answer, this is what it is. (Pre-FXS)

Long-Term Reactions to Testing

All groups expressed that positive carrier results (would have) led to their reconsidering life plans especially their decision to have children. The effect of knowing carrier status on the decision to have more children was especially complex among carrier women from FXS families; the differences in women's perspectives were magnified depending on whether or not they already had children at all. Those without affected children expressed a strong desire "*to figure out a way to end it with me*" (Pre-0) or said that they "*chose to end it here*" (Pre-0) even if that meant severe changes in plans.

Carrier women with children with FXS thought that the knowledge of carrier status could, in fact, have a significant effect on a woman's plans. Many ended plans for more children. Some were not convinced that such changes would be for the best in the long run:

> I would have had another one after the diagnosis, but I didn't. I already had a second child. . .. We were planning on four. In fact it came right at the wrong time because it came at the time we were planning. And so then we curtailed the plans and then we just never got around to it because for us to go to genetic counseling at that point was just more than I wanted to deal with when I was dealing with what we had. (Pre-FXS)

Other Family Members' Reaction to Testing Process/Results—Carrier Guilt Reported Among Grandmothers in All Groups

The most salient findings with regard to family members were related to the grandmother—the

participant's mother. For several carriers whose children did not have FXS, grandmothers were reported to have felt that they "*caused it all*." (Pre-0) One woman remarked in reference to her daughter's potential for having a child: "*it wouldn't be wise*". (Pre-0) The very concept being expressed by the participants about their mothers—concern for the effects on the grandchild, either with FXS or as a carrier—were reflected by participants who were themselves grandmothers:

> I mean it's a little late for me as having children. But it's kind of scary to know what might be down the road with my grandchildren, it's really scary for me. (Pre-0)

However, the women expressed that the issues for their mothers were not the same as the issues they, themselves, were facing:

> My mother was extremely guilty. I was not, I didn't have any guilt feelings, I mean it wasn't something that I chose for my child or chose for myself. My mother was however very guilty and she said, I feel so bad I gave this to you. And I was like but you know it wasn't something that you chose, I mean it just came through the family you know. (Pre-FXS)

Women May Not Want to Know Their Carrier Status

The idea that one might not want to know in advance surfaced in the non-carrier general population women when considering how they might have reacted to a different test result:

> I get a lot of pressure from my family that I need to have kids one day and I would like to have kids one day. And I don't want to know that there is a 25% chance that my kid's going to be a carrier and a 25% chance that my kid's going to have this problem. And what's the extent of the problem? It's just too many variables. It's not like say well you're definitely going to have a kid like this or you're definitely not going to have a kid like this. And you're exactly right and that's exactly what went through my head. Do I want to have to worry about it? It's one thing to have something like that thrust upon you, it's another thing to go into it willingly. And things like adopting is you know you can do those kind of things, it's not a problem. But I didn't want to know that there was a chance because I know that would deter me when it was time for family planning and discussing kids, I would have this in the back of head. And you shouldn't go into it automatically thinking the negative. (GP-0)

For those with children with FXS, there was a desire among the carrier women to know their status for the benefit of other family members. However, they showed difficulty considering the possibility of having had carrier information before they had children:

> I think with my choice it's just, it's really hard to know. I could never imagine my life without my son. And he really is an extraordinary person and we find him extremely interesting. And he has so much going for him, but knowing myself and my years when I was, you know, able to have children and would choose to have children, I'm sure that if I had the knowledge I probably would have just chosen—I know me, I would have said I'll just adopt children. (Pre-FXS)

Another carrier woman voiced concern for knowing one's carrier status well before having children:

> I feel sorry for a kid knowing very young that they're a Fragile X carrier because I think that growing up they would take things that happened differently. Every girl, little girl, with the baby dolls and stuff like that and talking to friends about having kids someday and all. I think that if you knew that ahead of time, it would be very hard to deal with. I mean I know right now if someone told me in 30 years you're going to have Alzheimer's, I mean, it would devastate me and then you'd start to see—to live it. (Pre-FXS)

Furthermore, this idea was approached by another carrier woman with mixed feelings:

> Yeah you know as I said I didn't test to find out what was going on for me I test to find out what was going on with the children. And we were devastated by the testing. So we were right in the middle of having our family. We had intended to have four children. And we just knocked off so I had my tubes tied. And I regret doing that, I wished that I had not known. I would have had more children. (Pre-FXS)

Carrier Testing Can Provide Choices—Those Choices Depend on the Reproductive Life History of the Woman

Almost across the board, carrier women from FXS families supported providing the information to others to make informed choices. Women seemed to differ about possible choices depending on whether or not they already had children. For example, some women expressed the concern that they could not make the choice to abort now that they were mothers:

> I think it's really hard to say what you would have done because it's easy to say one thing but if it actually had happened I don't know that I would have done the same thing. I mean I would have said off the bat if I had known I never would have had kids, I would have an abortion or whatever. But you know

> now after having them I don't know. I don't know if you can go back and give you an honest answer. (Pre-FXS)

> . . . when I was a teenager I had a girlfriend who I took to have an abortion. . . it could have been me. . . but once you are actually a mother it really just wasn't an option. I thought that's just the most feeble alternative you could ever offer me is in six weeks we'll do this test and we'll take care of it. (Pre-FXS)

Feelings about abortion overshadowed feelings about carrier screening. For some non-carrier general population women and carrier women from FXS families, they did not view abortion as an option:

> What are you going to do about it. (GP-0)

> Because what am I going to do, have an abortion? (Pre-FXS)

> Well spiritually speaking it's up to the most high whether I have a child or not. So I can't really stop the process of anything but I must admit I kind of didn't want to take any part of the process, if you understand what I mean, because of the fear. (Pre-0)

However, even if abortion was not an option, testing would still provide information:

> Choices about pregnancies whether you want to keep the pregnancy or not keep the pregnancy. So it's a pregnant choice. I didn't have that choice. So the truth of the matter is I believe that it's not a bad idea to be able to make a choice whether to carry a child full term or not to carry a child. You have a choice and that's what I would think the information would be good for. (Pre-FXS)

If abortion was an option, carrier women from FXS families stated carrier testing would provide choices:

> I did know that this is a real thing that I might be a carrier I might not and I really do at this point in this country have a choice. And so that I was able to say okay now there's a real diagnosis, this is you know definitively what is and what is not and then I could make an educated decision on what I did when I got pregnant. (Pre-0)

Timing

Carrier women from FXS families with children tend not to question whether the information should be given to their children before family planning:

> And I think I could be more relaxed about it without knowing. . .. I am not saying it bettered [my son] by me not knowing but I think personally for me it did. Now on the other hand my daughter's a carrier and she knows and so she's just going. And my nieces, I've got three nieces that are all of childbearing years you know, they're not married though. There's a big difference. But anyway I think they're going into it differently. They're going into it knowing that they've got to deal with this as an issue. (Pre-FXS)

Advice to Others

Carrier women expressed advice to others regarding testing based on their own experiences. For example, one woman related her own comfort with not having known before making her own family planning decisions. However, she wanted others to have that information for their choices:

> I think if I had found out I was a carrier back in the '80s, when there really wasn't anything to do except hit or miss pregnancy, I probably would have rather not known. Because I wouldn't have had children and that experience and so forth. That would have been my choice. . . but I think my daughter for example I'm glad that she knows. And I would want her to use that information to either decide I'm going to have my own healthy children and I'm going to choose not to have my Fragile X children. Or I'm going to let God take the choice. So they have a whole different kind of prospect than we did when we were that age. (Pre-FXS)

Another carrier woman's advice was from a different perspective—consider raising a disabled child:

> Now see this would be my advice. If you were to say to me what should I do? I am going to say well the only question is would you abort a pregnancy if your child was disabled. And if your answer is no then you ask yourself would I raise a disabled child? And if your answer is no, then you better find out. But if you're the kind of person that says if I get pregnant I'm going to have a child if he's disabled and I will be happy with it, then why find out? Why not just assume everything is wonderful and then deal with whatever you get? (Pre-FXS)

The idea that testing provides choices was voiced even by one who has regret:

> I want the children to have the knowledge and I certainly want her to have that choice. But then you got to really kind of think about, I mean I had the choice so I made the choice and it seemed like a perfect choice or the only choice really. It wasn't the perfect choice. We cried a lot about it. And now I regret that choice. If I had not known I might have had more children, and they might have had Fragile X and they might not have. (Pre-FXS)

Another participant recognized that women may handle information from carrier testing differently:

> So on a theoretical level I really do believe informed choices are better. It doesn't hurt to know that you have a heart condition because you'll take care of yourself in a certain way, so that's good. And if you're informed before you have children, have marriage or whatever if you're informed then if you decide to have the child you'll know to get educational treatment immediately and all that. So actually that's my stance. But however the variable that I hadn't thought as seriously about is that some individuals (a) can't handle it and (b) it's going to be more detrimental to who they are and to how they welcome this child into the world then if they didn't know it as individuals. And I was actually just to me.... I like information, give me the information and let me make my informed decision and I will live with it... so I actually I don't know how you do this personality test for them when they're getting married to say well this information is good for you and I don't know how you break down that component. So I have to say I'm baffled. (Pre-FXS)

DISCUSSION AND IMPLICATIONS

We confirmed many of the findings of McConkie-Rosell and her colleagues on attitudes toward carrier testing identified among women from FXS families (McConkie-Rosell *et al.*, 1997, 1999). In addition, we identified the following primary themes: (1) mothers of children with FXS have difficulty formulating their opinions on screening of others because of their unique experiences surrounding their own diagnosis of FXS and their relationship with their children with FXS, (2) the motivation for carrier testing and the intensity level for the need of information differ by family history of FXS and parental status, and (3) the timing of the carrier testing with respect to a woman's life stage dictates whether the information on carrier status will be seen as beneficial or detrimental. These findings have significant implications for genetic counseling of women who carry the fragile X mutation as well as for population screening women of reproductive age.

The most important implication of this study is that attitudes of women in families with FXS toward screening and use of the information cannot be easily transferred to the general population. Women who do not have experience with FXS and are diagnosed through population screening will be wholly unprepared and will need significantly more information. Clearly, education programs outlining the implications of carrier testing for FXS or any genetic disorder are necessary before population screening programs should be initiated.

Carrier women (whose carrier status was usually identified secondarily to their child's diagnosis of FXS) who have lived with and reared children with FXS have a difficult time formulating their own opinions and feelings about carrier testing. They desired to know their status in order that other family members could make more informed choices. However, they showed difficulty considering the possibility of having had carrier information before they had children. It appears that they are living lives that make it difficult to extrapolate or to abstract whether or not they would have wanted to know of their carrier status in advance. This would, by default, raise issues of whether or not they were content with the life they now lead. Thus, results from previous studies based on experiences of carrier women from FXS families would be difficult to interpret as it applies to the general population. The more applicable studies would evaluate experiences from carriers identified in the general population without a history of FXS in the family.

Similar to carrier screening for other genetic disorders such as cystic fibrosis (CF) (Bekker *et al.*, 1994; Brock, 1996), our study revealed there was a general lack of hesitation for the uptake of testing in the general population. Although those from the general population suggested the lack of importance for screening individuals who did not have a family history of FXS or mental retardation, they had a "why not" attitude. This attitude could be seen as a positive factor on the uptake of testing when made available. However, the lack of understanding and/or processing of the implications of a genetic carrier test is troublesome. They would be unprepared for the consequences of a positive result. Interestingly, the willingness to be screened may be based on method of sample collection. In a population-based CF carrier screening assessment study, obtaining a buccal sample verses a finger stick was cited as a preferred method that would have increased interest in testing (Clayton *et al.*, 1996). Perhaps screening studies should not be tailored for ease of sample collection in order to ensure that participants weigh the importance of obtaining carrier status information.

While carrier women whose children had FXS sometimes may have wished to have delayed the knowledge for themselves, they almost demanded that the knowledge be passed to others so their children or other women would have the choices that sometimes they did not. This conflict within them

is apparent, often even to them. This view supports that population screening should be made available, however, the uptake of the testing may be difficult to predict.

This need for information varied based on the individual's experience with FXS and their parental status. In the general population, carrier screening was seen more as an opportunity for aiding research. For those with children and/or a family history of FXS, carrier testing was seen as an opportunity to obtain information for family planning. In addition to revealing women's readiness for carrier testing, our study identified other themes related to motivation. Although the results obtained from focus groups cannot be generalized, we found similar themes among women who carry the premutation as other studies using different methods. First, as shown by McConkie-Rosell *et al.* (1997), the overall motivating factor for women with a child with FXS was the need for more information on FXS as it applied primarily to their children and to other family members. Premutation carriers who did not have children wanted to know their carrier status for family planning. Interestingly, the topic of a limited reproductive life span due to premature ovarian failure was rarely discussed, although the increased risk was described in the study materials.

As seen in related FXS literature, the emotional reactions of carriers with and without children with FXS to learning their carrier status were relief and guilt (McConkie-Rosell *et al.*, 2000, 2001). Also observed in our study and in similar CF carrier screening studies, the women report their anxiety regarding screening dissipated either immediately or over a few months (Bekker *et al.*, 1993). This observation was also true in the study for McConkie-Rosell *et al.* (2001).

Unique to our study, the emotional reaction of "grandmother guilt" is not well understood and may be related to dominantly or X-linked inherited disorders. James *et al.* (2003) noted that mothers of X-linked disorders were more likely to blame themselves and feel guilty for their child's condition as compared with carrier mothers of autosomal recessive disorders. Further, fathers in families with an X-linked disorder were more likely than carrier fathers of autosomal recessive disorder to admit to blaming the other parent. Thus, the mode of inheritance could have a psychosocial influence on families. Our study supports their findings for mothers, with the extension to grandmothers; however, there was no indication from the focus groups that partners blamed the women for their carrier status.

Knowledge was important to all carriers for the sake of making informed choices. The most substantive differences within the carrier groups were not related to the issue of whether their child had FXS, but rather to whether they had children at all. Carrier women, believe that the information should be given to their children before family planning. This is consistent with the literature, where many parents want to ensure that their children have this information before the possibility of reproduction (McConkie-Rosell *et al.*, 1999). This was true even though they had mixed feelings about the timing of the testing.

The women in our focus groups were at different stages in their family planning when they learned of their carrier status. For some, the idea of carrier testing was seen as granting options by providing them with a choice—to have children with FXS or not. For others, learning their carrier status limited their options by taking away their confidence in their ability to have "normal" children. These differing attitudes were heavily influenced by their attitude on abortion, which in turn was affected by their parental status. It seems that carrier testing should be done prior to having children for a woman to view this information as providing the most options.

Study Limitations

The study limitations are associated with the focus group study sample: it was not representative of the general population. First, the participant had to be enrolled in either ESAL or EFXS to be eligible for the focus group sample. Second, they had to respond to the survey and, if they did, had to chose to participate in the focus group. However, the intention of a focus group study is to provide qualitative data for insight and direction based on the perceptions and opinions of a small number of people. Although we recognize that the results cannot be generalized to the population, we made every effort to represent the widest range of opinions possible. This report is meant to summarize the major patterns and themes in the data and does not give adequate weight to the subtleties of non-verbal communication and group dynamics.

CONCLUSIONS

The findings of this study provide insight into the important differences in attitudes related to the stage of life in which carrier screening is performed. That is, the timing of carrier screening influences whether the knowledge of carrier status is viewed as beneficial

or detrimental. To further explore these findings, we have begun a follow-up study of in-depth interviews with women from the general population who were identified as premutation carriers. In these studies, we hope to gain insight into each woman's motivation, understanding, and use of their knowledge of their carrier status and to achieve an understanding of what information is needed to prepare those in the general population who elect carrier screening. Future studies should re-evaluate attitudes for population carrier testing with the added information on the risk of the premutation associated, late-onset tremor/ataxia syndrome (FXTAS). Some may consider that such studies should be done once more information is obtained on FXTAS with respect to the natural history among men and women and associated risk factors. However, the potential for population screening is being evaluated now. Thus, studies should move forward quickly. Lastly, additional studies need to be conducted among other cultural/ethnic groups that make up a large proportion of the US population. Attitudes may differ significantly and will point to different education needs.

ACKNOWLEDGMENTS

We would like to thank the research team of the ESAL and EFXS studies for their recruitment efforts and genetic testing. We would also like to thank Dr Allyn McConkie-Rosell and Ms Tiffany Woyboy for their helpful discussions. Lastly, we would like to thank all the women who participated in these focus groups for their lively and open discussions. This work was supported by NIH R01 HD29909 and P01 HD35576.

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