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Fragile X Screening: Views of Genetic Health Professionals

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Abstract

Objective—Although Genetic health professionals (GHP) are major stakeholders in developing and implementing Fragile X (FrX) testing and screening guidelines, their attitudes about FrX testing and population screening are virtually absent in the literature.

Methods—A survey was conducted of physician geneticists (geneticists) and genetic counselors (GC). The survey addressed GHP's attitudes towards (1) prenatal FrX carrier screening; (2) pre- and full mutation screening of male and female newborns; (3) the single best time for FrX screening over the lifespan; and (4) their willingness to test a normally developing child with a positive family history.

Results—Thirty percent (273/894) of eligible GHP completed surveys. Attitudes of geneticists and GC were mostly indistinguishable. The single most favored screening approaches were (1) preconception screening targeted at women with a positive family history (43%); and (2) universal preconception screening (29%). While only 6% and 11% declared universal prenatal and universal newborn screening (NBS) as the ideal time respectively, 73% and 60% respectively would support such programs. GHP would design a NBS program to test male and female infants and to identify both pre- and full mutations. Over half would agree to order FrX testing on some normally developing children with a positive family history.

Conclusion—In expanding FrX testing and screening to low risk individuals, GHP prefer preconception screening as the single best time. The majority also support prenatal screening and NBS. If NBS were to be introduced, GHP prefer screening to identify boys and girls with both pre- and full mutations.

Keywords

Fragile X; population screening; newborn screening; prenatal screening; professional attitudes

INTRODUCTION

The earliest technology for population-based screening for conditions associated with the Fragile X mental retardation 1 gene (*FMR-1*) was able to identify full mutations and premutations in infant males.[Chow et al, 2003; Dawson et al., 1995; Rife et al, 2002; Rife et al., 2003; Strelnikov et al., 1999] Today, technological advances allow for the population-

wide identification of pre- and full mutations in individuals of both genders.[Strom et al., 2007; Tassone et al., 2008]

Policy decisions however must not only consider technical feasibility, but also social acceptability and the ethical implications of the various testing and screening programs. These decisions are complicated by the wide array of clinical symptoms associated with the spectrum of trinucleotide expansions in the *FMR-1* gene. The *FMR-1* gene has distinct clinical symptoms associated with a full mutation (> 200 repeats) and a premutation (55–200 repeats). In boys, a full mutation presents as Fragile X (FrX) Syndrome, the most common form of inherited intellectual disability (ID). [Sherman et al., 2005] Girls with full mutations, on the other hand, span the spectrum of cognitive functioning: 1/3 with normal cognitive function and 2/3 with mild to moderate ID. [Loesch et al., 2004] It is controversial whether premutation carriers have some developmental delays. [Bailey et al., 2008; Crawford et al., 1999; Hagerman and Hagerman, 2002] Adult men and women with premutations are at risk for Fragile X Tremor Ataxia Syndrome (FXTAS), a neurological disorder with tremor and ataxia, and one of every five women with a premutation is at risk for premature ovarian failure (POF). [Berry-Kravis et al., 2007; Hagerman and Hagerman, 2004a; Hagerman and Hagerman, 2004b; Hagerman et al., 2004; Jacquemont et al., 2007; Sherman, 2000]

The ethical implications of screening depend, then, on three factors: 1) timing (prenatal versus neonatal); 2) the population to be screened (targeted to individuals with a family history of intellectual disability (ID) or autism versus more universal population screening); and 3) the screening methodology (whether to attempt to identify only those who carry the full mutation or both the pre- and full mutation). [Acharya and Ross, 2008] While targeted or universal prenatal screening enhances educated reproductive decision making, the ethical justification of a universal newborn screening (NBS) program depends in part on how one calculates the risks and benefits of: 1) identifying girls with a full mutation when it is not fully prognostic; 2) the identification of individuals with premutations in childhood when symptoms may not develop for decades and reproductive decisions are similarly futuristic; and 3) the introduction of developmental services pre-symptomatically when there are no data to show it is more effective than services begun upon clinical diagnosis. The lack of data to support the introduction of early developmental services pre-symptomatically would suggest that NBS for FrX may not yet fulfill the Wilson and Jungner criteria proposed in 1968 as the basis for an ethically sound and scientifically justifiable population screening program.[Wilson and Jungner, 1968] However, others believe that the time delay from first parental concern to the initiation of developmental services affords sufficient risk to the child, albeit theoretical, to warrant FrX NBS. [Bailey et al., 2000; Bailey et al., 2003]

Despite these ethical concerns, the data that do exist show broad social acceptance of FrX prenatal testing among low-risk women in the US and other countries [Ryynanen et al., 1999; Pessoa et al., 2000; Fanos et al., 2006] and national data to show support for NBS for FrX by lay advocacy groups. [Skinner, 2003] Data about the attitudes of genetic health professionals (GHP) who are the front-line providers of post-screening genetic counseling do not exist. Our study explores the attitudes of physician geneticists (geneticists) and genetic counselors (GC) toward FrX population screening in both prenatal and newborn settings. Given the differences in training between these two professional groups, we also sought to compare and contrast their attitudes and practices.

METHODS

A survey was conducted of 500 geneticists and 500 GC from the 2007 edition of the web-based directories of the American College of Medical Genetics (ACMG) and the National

Society of Genetic Counselors (NSGC) respectively. We excluded GHP when they did not reside in the United States, or did not have an e-mail address listed in the professional directory. Each subject was contacted a maximum of 3 times by email or fax.

The primary measures were a description of GHP's attitudes and a comparison between GC and geneticists in their attitudes towards (1) prenatal FrX carrier screening; (2) pre- and full mutation screening of male and female newborns; (3) the single best time for FrX screening over the lifespan; and (4) whether they would be willing to test a normally developing child with a positive family history of FrX syndrome. The survey also addressed the GHP's familiarity with the clinical syndromes associated with FrX, specifically: ID, POF, and FXTAS. Demographics were also collected.

To ensure current knowledge of the state of affairs regarding prenatal testing and NBS for FrX, GHP were provided with a brief summary (survey available from corresponding author). Specifically, GHP were told that current prenatal recommendations from the American College of Obstetricians and Gynecologists (ACOG) focused on testing women with a family history of ID for FrX, and that ACOG does not currently recommend universal prenatal screening. They were also told that current pediatric recommendations from the American Academy of Pediatrics (AAP) did not support universal NBS programs for FrX, but screening tests for FrX full and/or premutations were being developed that could make FrX NBS feasible.

Following these descriptions, GHP were asked about their support for individual screening approaches. When asked about universal prenatal FrX screening, GHP were given the option of screening all pregnant women or screening all pregnant women with a positive family history. When asked about universal NBS, GHP were given the option of supporting screening with or without informed consent. GHP were also asked to rate the importance of diagnosing FrX full and premutation status in male and female newborns on a 4 point Likert scale [1= not important; 2= minimally important; 3= moderately important and 4= very important]. An additional option (5) was also offered: "It is important to NOT diagnose."

GHP were then asked about the single best time to screen for FrX from the following options: universal screening of all women (preconception), universal screening of all pregnant women, universal NBS, targeted screening of women with a family history of ID (preconception), targeted screening of pregnant women with a family history of ID, targeted screening of fetuses who are "at risk", and only symptomatic testing rather than screening. GHP were also asked if they would agree to order FrX testing on any "normally" developing child with a positive family history of FrX or only on consenting adolescents with a similar history.

Statistical analyses were conducted using SPSS for Windows Version 15.01 (SPSS Inc, Chicago, IL). First, descriptive statistics were generated for each survey measure. For statistical analysis, we excluded responses that were left blank or marked as "not sure". Bivariate analyses were performed to identify demographic differences between GC and geneticists and to identify demographic features that explained differences in attitudes about testing and screening at different stages. Due to small sample size, for bivariate analysis we combined 1) "yes, all pregnant woman," and "yes, all pregnant woman with family history" as supportive of prenatal screening; 2) "yes" and "yes with consent" as supportive of NBS; and 3) "yes, any child" and "yes, only in consenting adolescent" as supportive of testing a typically developing child. For questions with a 4 point Likert, "very important" and "moderately important" responses were combined and "minimally important" and "not important" responses were combined. Option 5 was combined with those who believed that FrX testing was minimally or not important. Multivariate logistic regression analyses were

performed to examine whether bivariate associations persisted after controlling for relevant covariates (genetic profession, gender, and years in practice). Approval from the University of Chicago Institutional Review Board for the project and for waived written consent was obtained before any of the clinicians were contacted.

RESULTS

A total of 1000 surveys were distributed. Thirty-six GHP were excluded because they could not be located and 70 were self-excluded because they did not feel their current practice was relevant to the survey. Of the remaining 894, 273 (30%) GHP completed most or all of the survey, 14 refused (2 %) and 607 (68 %) did not respond.

The demographics of the respondents are listed in Table 1. Fifty-eight percent of respondents were geneticists and 42% were GC. Compared to the geneticists, the GC were more likely to be female ($p<0.001$), and had been practicing for fewer years ($p<0.001$). There were no differences between the groups regarding time spent in direct patient care, practice setting or family history. Most GHP ($n=271$) self-described as being moderately to very familiar with FrX as a cause of ID (100%), and with premutations as a cause of POF (93%) and FXTAS (87%). Familiarity was equivalent across training groups except that geneticists self-described as more familiar with FXTAS than GC (130/139, 94% vs. 82/103, 80%; $p<0.05$). Despite these demographic differences and modest differences in self-described familiarity, geneticists and GC expressed the same attitudes for most issues regarding screening and testing.

Seventy-three percent (170/234) of GHP supported some form of prenatal screening, although there was a slight preference for focusing on women with a positive family history (95/170, 56%). Sixty percent (137/229) of GHP also expressed support for universal FrX NBS. Of those who supported FrX NBS, 79% (108/137) wanted the program to be voluntary whereas 21% (29/137) wanted it to be mandatory. If FrX were to be included in a NBS program, the majority of GHP believed it was at least moderately important for a population-based NBS program to diagnose a FrX full mutation in both male (225/247, 91%) and female (219/247, 89%) infants as illustrated in Figure 1. Fewer found it at least moderately important to diagnose premutation boys (134/245, 55%) and girls (155/245, 63%) in a potential NBS program. GHP practicing more than 15 years were more likely than GHP with less years of practice to respond that it was moderately to very important to identify premutations in male (77/118, 65 % vs. 37/95, 39%; $p<0.001$) and female (85/118, 72% vs. 48/95, 51%; $p<0.005$) infants in a FrX NBS program. Of note, 12% of all GHP felt it was important to NOT diagnose FrX premutation carrier status in a NBS program.

Although the majority of our respondents support both prenatal and neonatal screening, the single most favored approaches to FrX screening were targeted preconception screening of women with a family history of ID (43%) followed by universal preconception screening (29%) as illustrated in Figure 2. Only 11% and 6% respectively preferred universal NBS and universal prenatal screening as the single best time.

GHP were also queried about their attitude towards testing a typically developing child with a positive family history of FrX. Over half of GHP (100/188 or 53%) would agree to order FrX testing of a typically developing child although there was a slight preference (52/100) for testing to occur in adolescence with the teenager's consent. GHP with more than 15 years in practice were more likely to agree to order FrX testing on a typically developing minor than GHP with 15 or fewer years. (70/102, 69% vs. 24/66, 36%, $p<0.001$)

In bivariate analyses, the only findings that distinguished geneticists from GC were 1) geneticists were more likely than GC to believe that NBS should include premutation

detection of both male (79/135 [59%] vs. 42/94 [45%], $p<0.05$) and female (92/135 [68%] vs. 49/94 [52%], $p<0.05$) infants; and 2) geneticists were more likely to agree to test a normally developing child than were GC (70/116 [60%] vs. 22/56 [39%], $p<0.01$).

We performed multivariable logistic regression to assess whether any of the bivariate associations remained significant after controlling for relevant covariates (type of genetics training, gender, and years in practice). Type of genetic training did not remain significant for any survey measure (data not shown). More years in practice independently predicted greater likelihood to support newborn premutation identification of a male infant (2.34, 95% Confidence Interval [CI]: 1.22–4.52); and to agree to order FrX testing on a normally developing child with a positive family history (3.47, 95% CI: 1.60–7.57).

DISCUSSION

The demographics of our respondents are representative of the different demographics between geneticists and GC with respect to gender and years practicing. [Parrott and Del Vecchio, 2006; Cooksey et al., 2005] Despite these demographic differences, GC and geneticists shared virtually the same positions on FrX screening. Both groups of practitioners favored preconception screening over NBS as the single best time for FrX screening. Parents also select preconception screening as the single best time to offer FrX screening. [Skinner et al., 2003] However, our respondents preferred targeted screening to those with a positive family history rather than population based screening, a distinction not offered in the Skinner et al. survey.

Despite judging preconception as the single best time for screening, 73% of our respondents support some form of prenatal screening (targeted > universal). However, routine prenatal screening for FrX rarely occurs. One study measured FrX prenatal testing uptake in women referred for genetic counseling and testing for other medical indications. The women were informed that prenatal testing for FrX was available but not standard of care and that they would have to pay for testing. Only 7.9% of women accepted. [Cronister et al., 2005] Cost was also a barrier in prenatal programs in Israel with uptake of 1.5% in Israeli Muslim women and 24.3% in Israeli Jewish women. [Sher et al. 2003; Sher et al. 2004]

A majority (60%) of our respondents also support NBS programs. This attitude is also true of the general public and parents of a child with FrX Syndrome. In a recent pilot study in the US, 80% of parents consented to NBS for their male infants [Saul et al., 2008]. Within the Fragile X advocacy community, Skinner et al. [2003] have shown that 82% support NBS. However, the traditional NBS program in the US is mandatory which was supported by only 21% of those respondents who were in favor of NBS for FrX. Hiraki et al. [2006] found 20% of GC surveyed supported mandatory universal FrX NBS and 31% of pediatricians surveyed by Acharya et al. [2005] also supported a mandatory NBS program. These two other surveys, however, did not offer an option of voluntary NBS or NBS with informed consent so the data are not strictly comparable.

The attitudes of a significant number of our respondents are in tension with professional societies. Although our respondents were divided in their support for universal prenatal screening versus targeted prenatal screening, universal prenatal screening for FrX is not currently recommended by either ACOG or ACMG. [American College of Obstetricians and Gynecologists Committee on Genetics, 2006; Sherman et al., 2005] Rather, in the prenatal setting, FrX testing is only recommended to women with a family history of ID or autism. [American College of Obstetricians and Gynecologists Committee on Genetics, 2006] Similarly, although a majority of our respondents supported universal NBS for FrX, the AAP, the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns

and Children (ACHDGDNC) and the ACMG do not currently endorse population-wide FrX NBS. [American Academy of Pediatrics Committee on Bioethics, 2001; Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children, 2008; American College of Medical Genetics, 2005; Sherman et al., 2005] Rather, the AAP only recommends FrX testing in childhood as part of the diagnostic evaluation of a child with cognitive impairments and/or autism. [Moeschler et. al, 2006]

Despite broad acceptance that preconception screening is the single best time for FrX screening, most current research initiatives are focused on NBS. [Centers for Disease Control, 2006; Frank Porter Graham Child Development Institute, 2008; UC Davis Health System, 2008; Saul et al, 2008] One reason for this divergence could be that our question did not require consideration of the logistical and economic barriers to implement population-wide preconception screening in contrast with using the existing state-run NBS infrastructure.

Given the research focus on NBS, two decision points must be considered in designing these pilot programs. The first decision point is whether to screen only boys or both boys and girls. The argument in favor of identifying only boys is that they all develop symptoms and will require developmental services. This benefit is muted by the fact that no data exist to support early intervention pre-symptomatically. The objection is that such a program fails to identify girls who also may become symptomatic and need developmental services. The argument in favor of identifying affected infants of both genders is that it would have the advantage of providing access to early developmental services to all infants with a full mutation from birth based on a known diagnosis even before the presence of developmental deficits [Bailey, 2004]. The objection is that up to one-third of the female infants with full mutations may be phenotypically normal and may not need such interventions, yet will be labeled as being “at risk” for intellectual disabilities from birth. This label may inadvertently stigmatize these girls and limit future expectations and achievements. [Finlay and Lyons, 2005]

Despite the potential to over-identify female full mutation carriers, approximately 90% of GHP in our study believed it was at least moderately important for FrX NBS programs to screen infants of both genders and to identify full mutations in all infants. This is consistent with a previous survey of GC in which 94% of those in favor of FrX NBS supported the screening of both genders. [Hiraki et al., 2006] Similarly, in Acharya et al. [2005], 85% of pediatricians who supported FrX NBS preferred screening both boys and girls over screening only male infants.

The second decision point is whether to screen for full mutations or both pre- and full mutations. A slight majority of our respondents supported premutation identification in a NBS program. This may be justified if FrX premutations are associated with some developmental delays that may benefit from early developmental services, but the association of FrX premutation status with developmental delays has not yet been clearly established, and the benefit of pre-symptomatic developmental services for children with FrX pre- or full mutations has not yet been demonstrated. Rather, to the extent that premutation identification is about carrier identification and the risk of adult-onset disorders, identification is inconsistent with published professional guidelines that discourage predictive testing of children for adult-onset conditions and/or for reproductive carrier knowledge. [American Academy of Pediatrics Committee on Bioethics, 2001; American Society of Human Genetics/ American College of Medical Genetics, 1995; Clarke, 1994; Dalby, 1995; Hogben and Boddington, 2005; Sherman et al., 2005]

The identification of infants with premutations also provides the potential benefit of informing parents about their own risk of having an affected child in a future pregnancy. However, whether newborn carrier detection should be undertaken to enhance parental reproductive decision-making is controversial and warrants further ethical discussion. [Ross, 2006]

In our study, over half of GHP would agree to order FrX testing on a typically developing child or adolescent with a positive family history (gender non-specified). Rosen et al. [2002] queried pediatric residents about FrX testing of girls with affected brothers. They found that 56% of pediatric residents would agree to test a cognitively normal 9 year old sister whose brother had FXS, and 68% would agree to provide asymptomatic carrier testing in female adolescent siblings. Although not specific to the FrX scenario, the Genetics Interest Group, an umbrella organization of parental advocacy groups in the United Kingdom, also supports the general right of parents to consent for carrier testing of their children. This willingness and support of testing a normally developing child contradicts current guidelines. [Sherman et al., 2005; American Academy of Pediatrics Committee on Bioethics, 2001; Clarke, 1994; Dalby, 1995; Hogben and Boddington, 2005] New data regarding the psychosocial benefit of testing adolescent girls of affected brothers may support the GHP attitude toward FrX carrier testing, [McConkie-Rosell, 2008] although other data show that some adolescents may have reduced ability to grasp the full meaning of carrier testing. [Boddington and Gregory, 2009] But the focus of these articles and policies is geared to testing adolescents for carrier status for the purpose of reproductive knowledge, and they do not address the impact of discovering incidental full mutation girls who are cognitively intact which may occur in both a NBS or cascade testing program.

One major limitation of our study was the low response rate (30%). As such, our results may reflect a respondent bias and may not be generalizable to GHP as a group. Nevertheless, our study is the first in the literature to document the attitudes of GHP, an important stakeholder group, towards FrX population screening and testing. A second limitation is that genetic understanding of FrX and the health implications of premutation status are evolving. Although most of our respondents stated that they were familiar with the various conditions associated with the different expansions in the *FMR-1* gene, we did not test knowledge. It would be important to know whether greater understanding of premutation health risks would influence their attitude towards designing the ideal population screening program or their attitude towards testing normally developing siblings.

CONCLUSION

Fragile X (FrX) is the most common form of inherited ID. Although current screening programs are targeted to members of at-risk families, population screening may be available in the near future. In expanding screening to low risk individuals, GHP prefer preconception screening (targeted > universal) as the single best screening method. A majority support both prenatal testing and NBS. If NBS were to be introduced, GHP prefer to identify both boys and girls, and both full and premutation carriers. GHP are evenly divided about cascade testing of minor siblings for FrX mutation status. The attitudes of GHP towards testing and screening minors are in tension with professional guidelines and ethical principles which seek to restrict wide-scale screening of children unless there exists an effective treatment that needs to be introduced before clinical diagnosis. Additional empirical research is needed to determine 1) whether pre-symptomatic early intervention is more effective than intervention begun when clinically diagnosed; and 2) whether there is a phenotype in childhood for those who have a premutation that might ethically justify premutation identification in newborns.

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*FM= full mutation; n=247

^PM=premutation; n=245

Figure 1.

In the development of a NBS program, how important is it to diagnose a...

Figure 2.
Single best time to screen (n=246)

Table 1

Demographics

	All GHPs [n (%)] N=273 ^{#^}	Physician-geneticists [n (%)] N=141 [^]	Genetic counselors [n (%)] N=103 [^]
Gender [*]			
Male	70 (28)	67 (48)	3 (3)
Female	176 (72)	72 (52)	100 (97)
Years in Practice [*]			
< or = 15	98 (44)	32 (24)	66 (73)
>16	127 (56)	102 (76)	24 (27)
% of time in direct patient care			
< or = 50%	94 (40)	60 (45)	32 (33)
> 50%	141 (60)	73 (55)	66 (67)
Practice setting			
Urban	171 (71)	94 (69)	76 (75)
Non-urban	70 (29)	42 (31)	26 (25)
Family history of mental retardation	25 (10)	11 (7)	14 (14)
Family history of tremor and/or ataxia	13 (5)	7 (5)	6 (6)

[#] total respondents included 29 GHPs who did not differentiate profession

[^] missing data due to partial non-responders

^{*} p < 0.001 between physician-geneticists and genetic counselors