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Original Article

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Predictors of Prenatal Screening for Fragile X Syndrome

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Abstract

Background: We sought to determine the uptake rate and predictors of acceptance of fragile X DNA molecular analysis among pregnant women who are offered this testing.

Methods: We conducted a retrospective cohort study of pregnant patients who met with a genetic counselor in our Prenatal Diagnosis Center. The primary outcome was undergoing fragile X carrier screening. Hypothesized predictors included gestational age, insurance status, family history, the genetic counselor with whom the patient met, duration of the counseling session, and whether the patient underwent amniocentesis or chorionic villi sampling. Multivariate logistic regression was used to analyze the association between acceptance of testing and the aforementioned predictors, controlling for potential confounders.

Results: Nine hundred forty-nine (17.3%) of 5,490 patients underwent fragile X screening. We observed significant variation in uptake by genetic counselor. Additionally, women who had Medical/Medicaid insurance (aOR: 1.99; CI: 1.63 - 2.43), or who had amniocentesis or chorionic villi sampling (aOR: 2.48; CI: 1.99 - 3.08) had increased odds of undergoing fragile X screening.

Conclusions: Numerous factors that are reported in patients' charts are associated with decisions to undergo fragile X DNA molecular diagnosis. Interestingly, modifiable factors including the patient's genetic counselor and insurance status appear to have a significant impact on acceptance of fragile X screening.

Keywords: Genetic screening; Fragile X; Prenatal; Uptake; Counselors

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Introduction

Fragile X syndrome is the most common cause of inherited intellectual disability, passed to offspring via nontraditional X-linked transmission. Carrier frequency for a premutation or full mutation ranges from 1 in 86 for females with a family history of mental retardation [1] to 1 in 209 in those with no known risk factors [2], resulting in a clinical phenotype in 1 in 4,000 males [3] and 1 in 8,000 females [4]. The maternal frequency of an intermediate allele is 1 in 35 [5]. Fragile X carrier screening and prenatal diagnosis is performed with polymerase chain reaction to assess the number of cytosine-guanine-guanine (CGG) [6] repeats and Southern blot to determine full mutation and methylation status of the *FMR1* gene [7]. Knowledge of carrier status can provide prospective parents with options including planning for the birth of an affected infant, terminating a pregnancy, and/or preparing for future pregnancies with pre-implantation genetic diagnosis egg donation (with donor screened to rule out fragile X) and polar body analysis. Patients may also consider the option of adoption. Fragile X carrier screening has been shown to be cost effective by providing early intervention, decreasing societal costs and preventing excess medical evaluations with unnecessary testing [8, 9].

The American College of Medical Genetics (ACMG) and American College of Obstetrics and Gynecology (ACOG) recommend fragile X carrier screening for women with a family history of fragile X-related disorders, unexplained mental retardation, developmental delay, or autism [10, 11]. The major difference between the ACMG and ACOG guidelines is that ACOG also recommends that fragile X testing should be made available to pregnant patients who request it, regardless of family history. Finally, the National Society of Genetic Counselors (NSGC) acknowledges the efficacy of fragile X screening and recommends that both pre-test and post-test counseling be available in centers where population screening is offered [12]. In 2009, the University of California, San Francisco (UCSF), adopted a policy of offering fragile X carrier screening to all pregnant patients who meet with a genetic counselor at the Prenatal Diagnosis Center.

Language, insurance status, and counseling time are known to affect patients' decisions to obtain first trimester screening for Down syndrome [13]. We sought to determine the rate at which patients undergo fragile X screening, and to examine whether these factors are also associated with deci-

Table 1. Fragile X Results by Family History

	Family history of fragile X (N = 222)		No history of fragile X (N = 5,268)	
	n	%	N	%
Not tested	149	67.1	4,392	83.4
Normal	72	32.4	852	16.2
Intermediate	0	0	20	0.4
Premutation	1	0.5	4	0.08
Full mutation	0	0	0	0

sions to undergo fragile X screening among pregnant patients receiving genetic counseling.

Materials and Methods

We conducted a retrospective cohort study of all pregnant patients who met with a genetic counselor at the UCSF Prenatal Diagnosis Center between January 1, 2010, and January 1, 2012. Patients seen for pre-conception counseling or referred from physicians who did not authorize fragile X counseling were excluded. Approval was obtained from our Committee on Human Research and informed consent was waived.

Procedures

At our center, after each consultation, the genetic counselor is required to create a letter pre-populated with a fragile X carrier screening statement, indicating whether the patient accepted or declined screening. Patients who had fragile X molecular testing were categorized as accepting screening; if they did not undergo testing they were categorized as declining screening. Fragile X carrier screening results included normal (< 45 repeats), intermediate (45 - 54 repeats), premutation (55 - 200) or affected (> 200 repeats).

Analysis

Our hypothesized predictors included the fetus' gestational age; the patient's insurance status and family history; the genetic counselor the patient met with and the duration of the entire counseling session; and whether the patient underwent amniocentesis or chorionic villi sampling. Covariates included the patient's age, ethnicity/ancestry, primary language, and indication for visit.

The median gestational age of presentation was calculated to be 16 weeks and the patients were then dichotomized as greater or less than 16 weeks gestation at presentation. Insurance status was categorized as government (Medical/Medicaid) or private. The family history documented in each patient's chart was reviewed by a board certified geneticist and categorized as family history of fragile X per ACOG criteria (family history of fragile X-related disorders, unexplained mental retardation, developmental delay, or autism), other inheritable condition (including maternal carrier status or family history), multifactorial condition or other (maternal disease or family history), or non-contributory. Counseling time was grouped into four categories: 1) 5 min or less, 2) greater than 5 but less than 30 min, 3) 30 to 60 min, and 4) greater than 60 min. Counseling staff included eight different counselors who were assigned numbers 1 through 8. Counselor number 8, whose patients were least likely to have fragile X testing, was used as the reference category. Patients also were dichotomized according to whether or not they had undergone invasive diagnostic testing (chorionic villi sampling and/or amniocentesis).

Patient age was dichotomized by greater than or equal to 35 years or less than 35 years. Options for ethnicity/ancestry included Ashkenazi Jewish, Hispanic, Asian, Caucasian, African American, Asian Indian and other. Language categories included English, Spanish or other. Patients were grouped into one of five indication categories: 1) patients less than 35 years of age who presented for first (PAPP-A, hCG and/or nuchal translucency) or second trimester screening (AFP, estriol, hCG, inhibin-A and/or anatomy ultrasound), 2) patients greater than or equal to 35 years who presented for screening (advanced maternal age), 3) patients who presented with a positive first or second trimester screen (screen positive), 4) patients who had a fetal chromosome or congenital anomaly, and 5) patients with another indication (other).

Multivariate logistic regression was used to analyze the association between acceptance of testing and the aforementioned predictors, controlling for potential confounders. All analyses were implemented using SAS Version 9.3 (SAS Institute, Cary, NC).

Results

This cohort included 5,490 patients who were candidates for fragile X screening over the 2-year period. The majority of these patients (82.2%) presented at less than 16 weeks gestation and had private insurance (73.3%), a non-contributory family history (80.5%), did not undergo an invasive procedure (88.2%), were < 35 years old (63.9%), and spoke English (87.7%). The number of patients seen by each of eight counselors ranged from 1,382 (25.6% of the cohort) to 107 (2.0% of the cohort). Nearly half of the sample (46.0%) was white, and the most common indication for their visit was routine screening (43.4%).

Nine hundred forty-nine (17.3%) of the patients who were

Table 2. Unadjusted and Adjusted Predictors of Fragile X Carrier Screening

	Not tested (N = 4,541) (%)	Tested (N = 949) (%)	Unadjusted OR (95% CI)	P-value	Adjusted aOR* (95% CI)	P-value
Gestational age at visit						
< 16 weeks	3,715 (81.8)	799 (84.2)	1.18 (0.98 - 1.43)	0.08	1.53 (1.21 - 1.95)	< 0.001
≥ 16 weeks	826 (18.2)	150 (15.8)	Reference		Reference	
Insurance type						
Medical/Medicaid	1,145 (25.3)	317 (33.5)	1.49 (1.28 - 1.73)	< 0.001	1.96 (1.61 - 2.39)	< 0.001
Private	3,382 (74.7)	630 (66.5)	Reference		Reference	
Family history						
Fragile X	149 (3.3)	73 (7.7)	2.90 (2.17 - 3.89)	< 0.001	2.06 (1.48 - 2.86)	< 0.001
Inheritable	231 (5.1)	79 (8.3)	2.03 (1.55 - 2.65)	< 0.001	1.44 (1.06 - 1.96)	0.02
Multifactorial	381 (8.4)	159 (16.8)	2.47 (2.02 - 3.03)	< 0.001	1.88 (1.47 - 2.40)	< 0.001
Non-contributory	3,780 (83.2)	638 (67.2)	Reference		Reference	
Counselor						
1	409 (9.2)	210 (22.2)	14.04 (9.60 - 20.54)	< 0.001	12.63 (8.54 - 18.67)	< 0.001
2	1,064 (23.8)	323 (34.1)	8.30 (5.77 - 11.95)	< 0.001	7.88 (5.42 - 11.47)	< 0.001
3	403 (9.0)	98 (10.3)	6.65 (4.43 - 9.99)	< 0.001	5.62 (3.69 - 8.56)	< 0.001
4	349 (7.8)	76 (8.0)	5.96 (3.90 - 9.09)	< 0.001	5.48 (3.55 - 8.48)	< 0.001
5	404 (9.1)	73 (7.7)	4.94 (3.24 - 7.55)	< 0.001	4.55 (2.94 - 7.05)	< 0.001
6	808 (18.1)	120 (12.7)	4.06 (2.74 - 6.01)	< 0.001	3.48 (2.32 - 5.22)	< 0.001
7	95 (2.1)	13 (1.4)	3.74 (1.91 - 7.34)	< 0.001	3.46 (1.72 - 6.97)	< 0.001
8	930 (20.8)	34 (3.6)	Reference		Reference	
Counseling time						
≥ 60 min	1,071 (23.6)	325 (34.2)	2.24 (1.89 - 2.66)	< 0.001	2.87 (2.04 - 4.02)	< 0.001
> 30 - 60 min	781 (17.2)	251 (26.4)	2.37 (1.97 - 2.85)	< 0.001	2.55 (1.80 - 3.61)	< 0.001
> 5 - 30 min	363 (8.0)	58 (6.1)	1.18 (0.87 - 1.59)	0.28	1.66 (1.10 - 2.52)	0.02
≤ 5 min	2,326 (51.2)	315 (33.2)	Reference		Reference	
Invasive procedure						
Yes	431 (9.5)	218 (23.0)	2.84 (2.37 - 3.41)	< 0.001	2.46 (1.98 - 3.06)	< 0.001
No	4,110 (90.5)	731 (77.0)	Reference		Reference	
Maternal age						
≥ 35 years	1,542 (34.0)	441 (46.5)	1.69 (1.47 - 1.95)	< 0.001	0.97 (0.75 - 1.25)	0.83
< 35 years	2,999 (66.0)	508 (53.5)	Reference		Reference	
Ethnicity/ancestry						
Ashkenazi Jewish	137 (3.0)	59 (6.2)	2.23 (1.62 - 3.08)	< 0.001	1.38 (0.96 - 1.97)	0.08
African American	297 (6.5)	57 (6.0)	0.99 (0.73 - 1.35)	0.97	0.95 (0.68 - 1.32)	0.75
Asian	762 (16.8)	160 (16.9)	1.09 (0.89 - 1.33)	0.41	1.07 (0.86 - 1.34)	0.53
Asian Indian	128 (2.8)	33 (3.5)	1.34 (0.90 - 1.99)	0.15	1.48 (0.96 - 2.28)	0.08
Hispanic	1,022 (22.5)	219 (23.1)	1.11 (0.93 - 1.33)	0.26	0.89 (0.68 - 1.15)	0.37
White	2,119 (46.7)	409 (43.1)	Reference		Reference	
Other	76 (1.7)	12 (1.3)	0.82 (0.44 - 1.52)	0.52	0.86 (0.44 - 1.67)	0.66
Language						
Spanish	444 (9.8)	121 (12.8)	1.36 (1.09 - 1.68)	0.006	1.31 (0.95 - 1.80)	0.10
English	4,008 (88.3)	806 (84.9)	Reference		Reference	

Table 2. Unadjusted and Adjusted Predictors of Fragile X Carrier Screening - *(Continued)*

	Not tested (N = 4,541) (%)	Tested (N = 949) (%)	Unadjusted OR (95% CI)	P-value	Adjusted aOR* (95% CI)	P-value
Other	89 (2.0)	22 (2.3)	1.23 (0.77 - 1.97)	0.39	1.21 (0.71 - 2.07)	0.48
Indication						
Screening	2,060 (45.4)	322 (33.9)	1.12 (0.85 - 1.47)	0.43	3.66 (2.42 - 5.54)	< 0.001
Maternal age	1,190 (26.2)	364 (38.4)	2.19 (1.66 - 2.89)	< 0.001	2.46 (1.73 - 3.50)	< 0.001
Screen positive	398 (8.8)	76 (8.0)	1.37 (0.96 - 1.94)	0.08	1.83 (1.24 - 2.72)	0.002
Fetal anomaly	501 (11.0)	70 (7.4)	Reference		Reference	
Other	392 (8.6)	117 (12.3)	2.14 (1.54 - 2.95)	< 0.001	2.10 (1.47 - 3.00)	< 0.001

*Controlled for all predictors and covariates.

counseled had fragile X carrier screening. Among these women, 924 (97.4%) received normal results, 20 (2.1%) received results that were classified as intermediate, and five (0.5%) were found to have premutations (Table 1). None of the patients were found to have a full mutation.

Results of our multivariable logistic regression analysis identified several independent predictors of undergoing fragile X carrier screening. We observed a substantial amount of variation in the fragile X screening acceptance rate by genetic counselor; patients who were seen by the counselor with the highest uptake rate (22.1%) had over 12 times the odds of being tested than those who were seen by the counselor with the lowest uptake rate, 1.4% (aOR: 12.6; CI: 8.5 - 18.7). Other predictors of uptake included presentation to the PDC at less than 16 weeks gestation age (aOR: 1.5; CI: 1.2 - 2.0), Medical/Medicaid insurance (aOR: 2.0; CI: 1.6 - 2.4), a family history of fragile X (ACOG criteria) (aOR: 2.1; CI: 1.5 - 2.9) versus a non-contributory family history, having a counseling session that lasted > 60 min (aOR: 2.9; CI: 2.0 - 4.0) verses a less than or equal to 5-min session, and having undergone an invasive procedure (aOR: 2.5; CI: 2.0 - 3.1; Table 2). Finally, patients who were carrying a fetus with a fetal chromosomal or congenital abnormality were least likely to obtain fragile X testing. In addition, we found that the uptake of fragile X screening increased during the studied period (aOR: 1.26; CI: 1.1 - 1.5 per year).

Discussion

Advances in genetic testing are creating increasingly affordable options for the diagnoses of a much wider range of conditions than were available in the past. ACMG and ACOG policies do not always agree on the optimal management strategy for implementing new testing programs. While physicians and genetic counselors often work together to determine the appropriate tests to offer patients and the indications for which these tests should be offered, factors unrelated to patients' indications for testing can affect whether or not patients undergo testing.

The percentage of patients who accepted fragile X testing in our study was 17.3%. This is high when compared to the uptake rate of 7.9% in a prior US study [1], but similar to the 20% uptake rate in Israel [14] and low compared to a study performed in Finland that had an impressive uptake rate of 85%. Fragile X testing has been offered prenatally in Israel for a number of years. The uptake of studies varies significantly likely due in part to the way that testing is presented and whether the program is an "opt in" or "opt out" program in addition to the out-of-pocket costs to testing.

Although predictors of fragile X uptake have not been well studies, this prenatal genetic screening can be compared to the differences in uptake for prenatal screening for Down syndrome, which have been found to be associated with language, insurance status and counseling time [13]. In our study, language was not associated with uptake after controlling for confounders; however, insurance status and counseling time were predictors of uptake.

It is possible that insurance coverage is a predictor of uptake simply due to differences in out of pocket costs to the patients. In the US study that had a 7.9% uptake rate, patients were told that the cost of testing "could be as high as $350" and that third party payers may not cover the cost of fragile X DNA analysis. In Finland, on the other hand, fragile X testing is free; this may explain the very high uptake rate reported in the Finnish study. In Israel, where cystic fibrosis screening is free, the observed uptake rate of that test was 85%, while fragile X testing, which is not fully covered, yielded an uptake of rate 20%. In our study there was a higher rate of uptake in patients with Medical/Medicaid, which is likely due to the fact that fragile X testing was performed for patients with Medical/Medicaid with no out-of-pocket expenses, while other insurances vary in their coverage. The cost to a patient is discussed during genetic counseling and may explain why patients with Medical/Medicaid were more likely to undergo screening.

However, differences in insurance coverage and out-of-pocket costs do not completely explain differences in uptake; if they did we would have expected 85% uptake of fragile X testing among patients with Medical/Medicaid in our study. But only 28% of our patients with Medical/Medicaid accepted testing, suggesting other factors are at play. We also found that counseling time was an important contributor. Women who had longer counseling sessions were more likely to have testing than women who had short sessions. This could mean that when counselors have the time to more fully explain the benefits of fragile X testing and to help the patient explore and

connect with her values, the patients become more interested in accepting the offer. Alternatively, longer appointments may simply reflect a greater underlying interest in fragile X carrier testing on the part of the patient or counselor.

As expected, patients who had a family history of fragile X-related disorders, unexplained mental retardation, developmental delay, or autism (meeting ACMG criteria for fragile X testing) were the most likely to accept testing and to be found to have a premutation. Nonetheless in our cohort only five patients had premutations and no patients had full mutations. An additional 20 patients had intermediate mutations. The expected mutation (premutation and full mutation) carrier rate of our population is about 1/200 [2], therefore we would have expected 27mutations. Only 2 - 3 of these mutations were predicted to be in found in the 222 patients meeting ACMG criteria for fragile X testing and may have been captured if all patients meeting ACMG criteria had undergone carrier screening; the rest would have been missed by using ACMG criteria for screening. None of the patients with intermediate mutations would have been identified by ACMG criteria. Our policy only captured four premutation carriers that would not have been diagnosed using ACMG's criteria. Our study findings support use of the ACOG guidelines, which are broader, rather than following the more limited screening recommendations made by the ACMG.

We also found that patients seen at an early gestational age were more likely to have fragile X testing than others. This may be because early in gestation the patient perceives she has more time to proceed with diagnostic testing if she is found to be a premutation carrier and also that she has more time to make a decision about pregnancy termination if the fetus is found to be affected.

Similar to other studies, we found that patients who underwent an invasive procedure were more likely to accept fragile X carrier screening. This may be because patients who have a lower tolerance for a child with cognitive disability are more willing to undergo an invasive procedure and are also more likely to desire a blood test for a serious disorder. These patients may be more inclined to desire information and may be more likely to take action if the testing yields an abnormal result.

An important limitation of this study was that uptake was measured by whether or not a test was performed rather than whether or not it was documented as offered and performed. Differences in uptake between counselors may have been due to counseling style or may have simply been due to the lack of some counselor's adherence to the policy of offering fragile X testing. Similarly, patients who had shorter counseling sessions may have been less likely to be offered testing than those with longer session. The slight increase in uptake over time may also be a reflection of policy adherence rather than a change in counseling style. In summary, policy adherence may affect many of the studied predictors. We believe that the study findings are important despite this limitation, as they address the predictors of uptake in the setting of an organizational policy. It is also possible, but unlikely, that some patients who were referred to the PDC had fragile X testing at their institution and were not candidates for testing.

This study was also limited by its retrospective nature. The methods of the study also involved grouping patients by indication and family history. A specific indication or family history, such a maternal carrier of genetic disease, may actually be a stronger predictor of screening than demonstrated by our method. Importantly, we did not address patients' desires for obtaining testing as we only used data available in the patient's chart.

We found that the likelihood of having fragile X screening was significantly affected by the genetic counselor with whom the patient met. This was true even after controlling for other predictors and covariates. This is concordant with other studies that demonstrate variability between information provided by counselor [15]. The uptake for fragile X also increased with time irrespective of which counselor the patients saw. The reasons for this variation cannot be explained with the data we collected for this study. The finding that the counselor with the highest percentage uptake actually saw less patients (8%) with a family history of fragile X than the other counselors (14-33%) suggests that there is something inherently different about the way these counselors describe the condition or the test or both. The increase over time may also be due to the way the counseling changed as the counseling became more familiar and routine.

Based on the differences in uptake rates between the US study and the Finnish study, it is very possible that there were differences in the way that the counselors described the cost of the test, which then affected uptake. Another possibility is that the counselors with the highest uptake rate in our study may have been more willing to obtain insurance pre-authorization for patients than the counselor with the lowest uptake. Counselors may also have varied in how encouraging of testing they are for patients who have an indication for testing. Regardless of the reason for this variation, our data underscore the need to establish consistent, evidence-based counseling practices, as the variation in uptake of this and other types of prenatal tests should be attributable to variations in patient circumstances and preferences, and not to provider beliefs or biases.

The information gained from this study suggests that a policy implemented with a goal of identifying all prenatal carriers of a condition is limited by other factors. It is possible that standardized counseling protocols, duration of appointments, and insurance coverage could improve the effectiveness of universally offering testing. Surveys performed on caregivers who were offered newborn screening has provided invaluable information about the importance of offering testing multiple times [16]. Future studies in prenatal carrier testing that include patient interviews, such as those underway in Australia [17], are needed to gain a more nuanced understanding of the factors that underlie patients' decisions regarding fragile X screening. In addition, observational studies of changes in uptake rates that may follow changes in insurance coverage and out of pocket payments due to implementation of the Affordable Healthcare Act, will also shed light on the extent to which cost considerations underlie the current relatively low uptake rate of fragile X testing in this country.

Conflict of Interest

There are no conflicts of interest.

Author Note

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