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Maternal Consequences of the Detection of Fragile X Carriers in Newborn Screening

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abstract

OBJECTIVES: The possibility of newborn screening for fragile X syndrome is complicated by the potential for identifying premutation carriers. Although knowing the child's carrier status has potential benefits, the possibility of late-onset disorders in carrier children and their parents raises concerns about whether such information would be distressing to parents and potentially more harmful than helpful. This study sought to answer this question by offering voluntary fragile X screening to new parents and returning results for both the full mutation and premutation *FMR1* gene expansions. We tested the assumption that such information could lead to adverse mental health outcomes or decision regret. We also wanted to know if child age and spousal support were associated with the outcomes of interest.

METHODS: Eighteen mothers of screen-positive infants with the premutation and 15 comparison mothers completed a battery of assessments of maternal anxiety, postpartum depression, stress, family quality of life, decision regret, and spousal support. The study was longitudinal, with an average of 3 assessments per mother.

RESULTS: The premutation group was not statistically different from the comparison group on measures of anxiety, depression, stress, or quality of life. A subset of mothers experienced clinically significant anxiety and decision regret, but factors associated with these outcomes could not be identified. Greater spousal support was generally associated with more positive outcomes.

CONCLUSIONS: Although we did not find evidence of significant adverse events, disclosure of newborn carrier status remains an important consideration in newborn screening policy.



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Dr Bailey conceptualized and designed the study, wrote the first draft of the manuscript, integrated edits from all coauthors, and prepared the final manuscript for submission; Dr Wheeler conducted follow-up assessments at the North Carolina site, wrote part of the Results section, and reviewed and revised the manuscript; Dr Berry-Kravis conceptualized and designed the study, directed all research at the Illinois site, and reviewed and revised the manuscript; Dr Hagerman conceptualized and designed the study, directed the clinical research at the California site, and reviewed and revised the manuscript; Dr Tassone conceptualized and designed the study, developed the screening test, directed the laboratory analyses at the California site, and reviewed and revised the manuscript; Dr Powell directed the clinical follow-up at the North Carolina site and reviewed and revised the manuscript; Ms Roche provided genetic counseling at the North Carolina site and reviewed and revised the manuscript; Ms Gane provided counseling services at the California site and reviewed and revised the manuscript; Dr Sideris conducted all statistical analyses and wrote part of the Results section; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Parents generally adapt well to newborn screening results, but reactions to carrier status for X-linked conditions are unknown.

WHAT THIS STUDY ADDS: Results suggest that detection and disclosure of *FMR1* newborn carrier status may not result in significant adverse events for mothers.

Fragile X syndrome (FXS) is the most common inherited form of intellectual disability. Because physical features are not evident at birth, FXS must be detected through abnormalities in development or behavior during childhood. Parents typically experience an extended “odyssey” before FXS is diagnosed.^{1,2} The average age of diagnosis is 36 months for boys and later for girls, because females are usually more mildly affected.³ As a result, many children with FXS have delayed opportunities to participate in early-intervention programs.⁴ In addition, as many as 25% to 30% of families have a second child with FXS before the diagnosis of the first child.³

Newborn screening is the only way all children with FXS could be identified early. However, FXS does not currently meet criteria for inclusion in the Recommended Uniform Screening Panel by the Secretary’s Discretionary Committee on Heritable Disorders in Newborns and Children⁵ for 2 primary reasons: (1) it is not considered “medically actionable” and no studies have shown that early intervention significantly impacts development and behavior and (2) no studies have determined the costs or feasibility of conducting high-through-put screening in a state health laboratory.

Among the issues evoked by screening for FXS in newborns, one of the most concerning is the incidental detection of carriers.⁶ The normal *FMR1* gene typically contains <45 repetitions of the nucleotides cytosine and guanine in CGG triplets, a number that typically remains stable across generations. Individuals with expansions of 55 to 200 repeats are premutation carriers. This repeat length is unstable and can further expand in future generations, causing female carriers to be at risk of having children of either gender with the full mutation (>200 CGG repeats), associated with *FMR1* methylation and transcriptional silencing, resulting in FXS.

A DNA-based screening test for FXS would also identify carrier infants. This information could be useful to parents, informing them of their reproductive risk of having a child with FXS and alerting them to possible future health problems. Although the American Academy of Pediatrics and the American College of Medical Genetics and Genomics^{7,8} do not recommend routine carrier testing for minors, both acknowledge that if carriers are detected in newborn screening, it should be disclosed to parents. Parents of children with FXS strongly support carrier disclosure,^{9,10} and a majority of parents in the general population accepted the possibility of carrier detection in 2 pilot studies.^{11,12} But disclosure of *FMR1* carriers is controversial because carrier status is associated with risk of health, cognitive, and emotional problems.¹³ Female carriers are at risk of primary ovarian insufficiency,¹⁴ and both genders are at risk of fragile X-associated tremor ataxia syndrome.^{15,16} Some carriers are also at risk of learning problems and brain function abnormalities,^{17,18} autism spectrum features,¹⁹ and depression or anxiety disorders.^{20–22} Thus, if newborn screening for FXS were to identify carrier children, it would imply that they and the carrier parent may be at increased risk of developmental, behavioral, and medical concerns.

Learning about carrier status could increase the risk of anxiety, depression, or stress, especially for mothers. Postpartum depression and anxiety are relatively common in the general population.^{23–25} Females are generally more likely to experience depression than males,²⁶ and mothers with the premutation are at risk of elevated depression and anxiety, risks that could be exacerbated by disclosure of their infant’s carrier status.^{20–22} Research on the impact of parents’ learning that their healthy-appearing newborn has a disorder provides mixed

evidence of increased depressive symptoms or anxiety (eg, refs 27–31). This finding may be due to evidence that other factors such as lower income, minority status, and lack of social support are also strongly associated with adverse mental health outcomes.³²

Although much has been written about public attitudes toward the return of genomic research findings, most data come from hypothetical studies.³³ We recently completed a multisite fragile X newborn screening pilot study on the basis of the assumption that research studying the experiences of offering testing and communicating results is needed to fully understand benefits and harms. We previously reported acceptance rates and reasons for accepting or declining screening,¹² prevalence of *FMR1* premutation expansions,³⁴ fathers’ participation in the consent process,³⁵ examples of how the identification of a target child can lead to identifying other family members,³⁶ and the development and evaluation of a brochure to support informed decision-making about study participation.^{37,38}

Here we report findings from an assessment of maternal reactions to the disclosure of their child’s *FMR1* carrier status after newborn screening. Our primary goal was to determine whether these mothers experienced adverse mental health outcomes (stress, anxiety, depressive symptoms, low quality of life), whether they regretted the decision to participate, and how adaptation over time varied as a function of the child’s age or the availability of spousal support.

METHODS

Setting and Procedures

The study was conducted in 3 university-based hospitals in North Carolina, California, and Illinois. Study recruitment procedures¹² and laboratory methods³⁴ are detailed in previous reports and briefly

summarized here. Recruitment processes varied slightly at each hospital; but in general, shortly after birth, families were approached by a trained recruiter who asked if they would be willing to hear about a research project, to which most families agreed. Families were given brief written information and a short verbal overview of the study. Those who expressed interest were given much more detailed information by the recruiter, including the comprehensive consent form.

Approximately halfway through the project a new brochure was developed to support informed decision-making^{37,38} and was used at all 3 sites. The brochure included a section on what it means to be a “fragile X carrier,” addressed the implications of carrier status for both newborns and parents, and made it clear that carrier detection was a much more likely outcome than the detection of children with FXS.

Across the 3 sites, ~20 374 families were approached, and of those, 19 951 (97.9%) agreed to hear about the study. Of those, 63.7% (12 709) agreed to have their infant screened. One infant screened positive for a full mutation (not included in this article) and 45 screened positive for a premutation allele, including 2 sets of twins.

Families of screen-positive children were called by a genetic counselor, pediatrician, or medical geneticist on the research team, notified of results, and offered a genetic counseling appointment and confirmatory testing. During this visit, families were counseled about the potential adult-onset health implications of carrier status. Thirty infants had the confirmatory testing. Of these, 2 were found not to be carriers. Sixteen families did not have confirmatory testing for the following reasons: declined genetic counseling ($n = 3$), failed to show for the appointment ($n = 2$), declined repeat testing of the infant ($n = 3$), or were unable to be reached via phone or mail ($n = 8$).

All families whose positive screening result was confirmed ($n = 28$) were invited to join the longitudinal component of the study. Three declined participation or were unable to be reached to schedule a visit. Twenty-three families (26 infants) participated in at least 1 longitudinal assessment, but 5 mothers did not participate in the family assessments, leaving a total of 18 mothers of premutation infants reported here. Fifteen mothers whose infants screened negative who were matched with the screen-positive group on ethnicity, language, education, and income were recruited as a comparison group.

Because a substantial number of parents did not participate in the follow-up study, we compared screen-positive participants and nonparticipants on 5 variables (maternal age, marital status, race/ethnicity, maternal education, and CGG repeat length of the identified child) using t tests for continuous variables (maternal age, CGG repeat range) and χ^2 test for categorical variables (marital status, race/ethnicity, maternal education). The results are shown in Table 1. No significant differences were detected between the groups on any of these variables.

The following 5 well-validated measures were used to determine whether mothers experienced adverse outcomes and if they were satisfied with their decision to participate: (1) the 36-item short form of the Parenting Stress Index³⁹; (2) the Spielberger State-Trait Anxiety Inventory⁴⁰; (3) the Edinburgh Postnatal Depression Scale⁴¹; (4) the Quality of Life Inventory (QOLI)⁴²; and (5) the Decision Regret Scale.⁴³ The Emotional Intimacy Subscale of the Personal Assessment of Intimate Relationships Inventory⁴⁴ was used to assess spousal support.

Data Analysis

Data were collected at 1 to 7 occasions. The primary reason for this

variation was length of time in the study, which lasted ~4 years. The family with 7 assessments was one of the first identified, whereas families with only 1 assessment mostly were those identified toward the end of the funding period. The mean number of assessments was 3.1 for the screen-positive group and 3.0 for the comparison group. The 3 primary research questions were as follows: (1) whether mothers of screen-positive children reported elevated stress, anxiety, depression, or low quality of life compared with mothers in the comparison group; (2) whether these mothers experienced significant regret about their decision to participate in the study; and (3) the extent to which spousal support and age of the child were related to the outcomes measured. We first tested 3-way interactions of category (premutation versus those who screened negative) $\times$ spousal support $\times$ child age. Finding no evidence for higher order effects, we retained only the 2-way interactions. The initial models also included tests of nonlinear (quadratic) change over time, but there was no evidence that such trends existed, so all models were simplified to include only linear terms. We treated the models as 2-level, random-intercept hierarchical linear models with time nested within family. Random effects are commonly used to estimate and control nonindependence in a model that arises from clustering of data⁴⁵; in this case, data were clustered within participants, resulting from repeated measurements over time. Given our relatively small sample size, we used the Kenward-Roger⁴⁶ adjustment to the degrees of freedom to test model parameters.

RESULTS

Models were conducted testing group differences and interaction effects of child's age and spousal support on stress, depression, anxiety, quality of life, and decision regret. Parameter estimates are presented in Table 2.

TABLE 1 Comparison of Participants and Nonparticipants in the Longitudinal Study on Selected Demographic Variables

Variable	Participants	Nonparticipants	<i>P</i>
Mothers			
<i>n</i>	20	24	.23
Mean age (SD; range), y	30.6 (5.8; 18–44)	28.6 (4.99; 21–37)	
Marital status, %			.44
Married	52	48	
Divorced/separated	17	36	
Never married	22	12	
Unknown	9	4	
Race/ethnicity, %			.97
White	46	59	
African American	26	24	
Hispanic	9	6	
Other	13	12	
Maternal education, %			.61
High school or less	9	16	
Some college	39	40	
College degree	26	28	
Advanced degree	26	12	
Unknown	0	7	
Child			
<i>n</i>	23	16	.93
Mean CGG repeat range (SD; range)	68.1 (17.8; 55–129)	67.6 (19.4; 55–129)	

Parenting Stress

Across all assessments, the mean total Parenting Stress Index score was 61.8 for mothers of children with the premutation and 63.1 for mothers of comparison children. A score ≥ 91 is considered clinically significant and scores of 86 to 91 are considered above normal, so both groups were well within the typical range. Stress scores did not differ significantly by group (premutation versus comparison) or child age. Spousal support was strongly associated with total stress; mothers reporting high levels of spousal support reported lower stress. No interaction effects were detected, indicating that spousal support and child age were not differentially associated with stress in premutation versus comparison mothers. Across all assessments, 6% of mothers of children with the premutation and 7% of mothers of comparison children had at least 1 stress assessment in the clinically significant range.

Maternal Depression

Across all assessments, the mean Edinburgh Postnatal Depression Scale

score was 4.1 for mothers of children with the premutation and 5.3 for mothers of comparison children. A score ≥ 10 is considered clinically significant, so both groups were well within the typical range. Depression scores did not differ significantly by group (premutation versus comparison) or child age. Spousal support was strongly associated with depression; mothers who perceived greater support reported fewer depressive symptoms. A significant interaction effect was detected; spousal support was differentially associated with stress in premutation versus comparison mothers. Across all assessments 12% of mothers of children with the premutation and 15% of mothers of comparison children had at least 1 depression score in the clinically significant range.

Maternal Anxiety

Across all assessments, the mean State-Trait Anxiety Inventory score was 34.3 for mothers of children with the premutation and 31.7 for mothers of comparison children. A score ≥ 45 is considered clinically significant, so the

mean scores of both groups were well within the typical range. Maternal anxiety did not differ significantly by group (premutation versus comparison) or child age. Spousal support was not directly associated with anxiety, nor was a significant group $\times$ support interaction detected. However, across all assessments, 29% of mothers of children with the premutation and 7% of mothers of comparison children had at least 1 anxiety assessment in the clinically significant range.

Quality of Life

Across all assessments, the mean QOLI score was 46 for mothers of children with the premutation and 47.8 for mothers of comparison children. A score < 40 is considered significantly low, so both groups were within the typical range. QOLI ratings did not differ significantly by group (premutation versus comparison). Child age was significantly associated with QOLI scores; mothers of younger children reported lower QOLI ratings than mothers of older children, but no group $\times$ age interaction was found. We did not find a main effect for spousal support but did find a significant group $\times$ support interaction. Spousal support was more important in predicting quality of life for mothers of children with the premutation than for comparison mothers. Across all assessments, 42% of mothers of children with the premutation and 38% of mothers of comparison children had at least 1 assessment with a low quality-of-life rating.

Decision Regret

The Decision Regret Scale is a 5-item measure designed to assess “remorse or distress over a decision”⁴³ (p 281). Here the decision for mothers was whether to have their child screened for the *FMR1* expansion. Each item (eg, “It was the right

TABLE 2 Parameter Estimates (SEs) for Total Stress (Parenting Stress Index), Depression (Edinburg Postnatal Depression Scale), Anxiety (Spielberger State-Trait Anxiety Scale), Quality of Life (QOL), and Decision Regret (Decision Regret Scale)

Effect	Total Stress	Depression	Anxiety	Quality of Life	Decision Regret
Intercept	62.7 (2.8)	4.4 (0.9)	35.5 (1.8)	47.3 (2.2)	2.2 (0.3)
Group	−0.8 (4.2)	0.4 (1.3)	−4.4 (2.7)	1.9 (3.3)	−0.9 (0.4)*
Age	0.3 (0.2)	−0.2 (0.1)	0.03 (0.2)	−0.3 (0.1)*	−0.01 (0.01)
Spousal support	−14.4 (3.9)***	−3.7 (1.2)**	−7.1 (2.9)	10.0 (2.8)	−0.2 (0.3)
Group × age	−0.2 (0.3)	0.1 (0.2)	0.1 (0.3)	0.1 (0.3)	0.01 (0.02)
Group × support	7.6 (6.2)	5.2 (2.3)*	6.9 (4.4)	−11.0 (4.7)*	0.02 (0.5)
Age × support	0.2 (0.2)	−0.3 (0.2)	−0.2 (0.2)	0.3 (0.1)	0.00 (0.01)

* $P < .05$, ** $P < .01$, *** $P < .001$.

decision”) is rated on a scale from 1 (strongly agree) to 5 (strongly disagree). Because some items are stated positively (eg, “It was the right decision”) and some negatively (eg, “I regret the choice that was made”), we reverse-scored the positive items so that a higher score indicated greater regret. The authors suggest converting scores to a 0 (no regret) to 100 (high regret) scale by subtracting 1 from each item, multiplying by 25, and summing the items. Across all assessments, the mean converted score was 32.3 (range: 0–100) for mothers of children with the premutation and 5.7 (range: 0–25) for mothers of comparison children. Regret scores were significantly higher for mothers of children with the premutation. The group differences were almost entirely accounted for by 2 mothers, one who reported high (90–100) regret at each assessment occasion and a second who was in the 75–80 range each time. Decision regret was not associated with child age or spousal support, and no interaction effects were found.

DISCUSSION

The detection of *FMR1* carriers by FXS screening in newborns and its potential for harm and benefits have been discussed extensively, but until now concerns have been speculative. Here we report findings from the first study to offer FXS newborn screening, return carrier results to parents, and follow mothers of

infants to determine adaptation and reactions over time. Our primary goal was not to provide evidence that screening was beneficial but rather to attempt to detect significant potential harms.

We found no group differences in the domains assessed: depression, anxiety, stress, or quality of life. Mothers of screen-positive infants as a group were no different from a comparison group of mothers of screen-negative infants on any measure, both groups were well within the range of typical scores, and, with the exception of maternal anxiety, there were no differences in the number of mothers with clinically significant scores. Six (29%) mothers of children with the premutation had at least 1 anxiety assessment in the clinically significant range, compared with only 2 comparison mothers. An analysis of interviews and other scores with these 6 mothers reveals a complex picture, not easily leading to a generalized explanation. Three of the mothers had consistently low regret scores, 2 had high regret. Four of the 6 mothers had children with the premutation who were showing developmental or behavioral problems, and 3 of the 6 had 2 children with the premutation (2 sets of twins and 1 mother had a second child with the premutation during the study). Three mothers were premutation carriers and thus potentially at risk of elevated anxiety. These observations suggest that

maternal anxiety is a complex and multifaceted construct, likely influenced by child and parent characteristics, genetic factors, family context, and spousal support.

Consistent with previous literature, we found that mothers who reported higher levels of spousal support had lower stress and lower depression scores than mothers who reported lower levels of support. We did find significant interaction effects, showing that high spousal support was more strongly associated with lower depression and higher quality of life in mothers of carrier infants than in mothers of comparison children.

We found significant group differences in decision regret. Mothers of infants with the premutation expressed greater regret about study participation than did mothers of comparison children. Comparison-group mothers had nothing to regret, and thus most of their scores were near zero. Most mothers of identified children were less likely to strongly agree with the positively worded items, but their average responses remained in the positive range; a group mean of 50 would indicate an average neutral score, and the premutation group average was 32.3. But mothers of identified children were generally more ambivalent about the study and perhaps still uncertain as to their ultimate assessment of benefit or harm. Two mothers clearly wished that they had not participated in the study. Although the written materials, including the consent form, and conversations with the recruiter clearly specified the possibility of carrier detection, the setting and timing of recruitment (a few hours after birth) may not have allowed sufficient time for these mothers to give full consideration to the study. As such, it is possible that these and other mothers had some residual regret or at least uncertainty as to whether study participation is

something they would agree to if they had the opportunity to reconsider their decision.

Our findings should be interpreted with some caution for several reasons. The first and most important limitation is potential bias in the study sample due to lack of participation in follow-up by a number of screen-positive families. To partially address this concern, we compared participants and nonparticipants on several variables (maternal age, marital status, race/ethnicity, maternal education, and CGG repeat length of the identified newborn) and found no group differences. These findings increase confidence in our conclusions, but we acknowledge that we still do not know why some families did not participate. Some may have been unconcerned about carrier status and chose not to participate because it did not seem immediately important or relevant. Others may not have participated because of adverse events or decision regret. A second limitation is the possibility that the study was not sufficiently powered to detect significant group differences. Although possible, the

absolute differences between the groups were quite small, so it is unlikely that a larger sample would have affected the findings. However, the small sample size meant that we were not able to assess factors other than child age or spousal support associated with variability in the outcomes measured.

Despite these limitations, we found little evidence that the disclosure of carrier status in newborn screening for FXS, when conducted under a voluntary consent protocol with consent obtained from both parents when possible, significantly elevates the risk of stress, anxiety, depression, or low quality of life. Some mothers regretted participating in the study, suggesting that the newborn setting may hinder full understanding of the implications of consent. In addition, some mothers experienced elevated anxiety, although we cannot unequivocally demonstrate that learning their child's carrier status was the cause.

Several features of FXS currently make it unsuitable for inclusion on mandatory newborn screening

panels, a situation that will remain until data show that earlier identification results in measurable benefits for children. Until then, this study suggests that the disclosure of newborn carrier status, although an important consequence to consider when making policy decisions about screening, consent, and follow-up services, may not have a significantly negative impact on mothers of identified children, especially in families where spousal support is adequate.

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ABBREVIATIONS

FXS: fragile X syndrome
QOLI: Quality of Life Inventory

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