Title
Parent Reactions to Fragile X Premutation Diagnosis in the Newborn Period

Permalink
https://escholarship.org/uc/item/38n6q65b

Author
Sorensen, Page Lundy

Publication Date
2014

Peer reviewed|Thesis/dissertation
UNIVERSITY OF CALIFORNIA

Los Angeles

Parent Reactions to Fragile X
Premutation Diagnosis in the Newborn Period

A thesis submitted in partial satisfaction
of the requirements for the degree Masters of Arts
in Anthropology

by

Page Lundy Sorensen

2014
ABSTRACT OF THE THESIS

Parent Reactions to Fragile X
Premutation Diagnosis in the Newborn Period

by

Page Lundy Sorensen

Master of Arts in Anthropology
University of California, Los Angeles, 2014
Professor Thomas S. Weisner, Chair

This paper explores fragile X newborn screening (FXNBS) from the perspective of parents whose newborns were diagnosed as FX premutation carriers as a result of their participation in a FXNBS pilot project conducted at the University of California, Davis. Interviews conducted with 6 such parents are analyzed and parents grouped into three response categories, negative, mixed, and positive, based on statements about their contentment with participation in the study as communicated in the interviews. Negative aspects of screening, as communicated by parents, include the ambiguous nature of the diagnosis of a low range premutation and heightened anxiety related to the development of the newborn. Positive aspects include feelings of empowerment from the knowledge received about the newborn and confidence that any developmental problems that emerge can be treated by the FX research and treatment team that ran the project.
This paper represents the first report of responses to FXNBS from parents of identified newborns. The analysis presented here leads to three considerations that will minimize harm and maximize benefit if FXNBS is implemented. These include 1) utilizing effective educational materials to inform parents of the risks associated with screening, 2) reporting only FX mutations that likely have clinical relevance, and 3) implementing comprehensive follow-up.
The thesis of Page Lundy Sorensen is approved

Elinor Ochs
Linda C. Garro
Thomas S. Weisner, Committee Chair

University of California, Los Angeles
2014
TABLE OF CONTENTS

Introduction..................................................................................................................................................1
Universal Newborn Screening .........................................................................................................................6
Fragile X Newborn Screening .........................................................................................................................7
Interview Methods ..........................................................................................................................................11
Parent’s Reactions to Newborn Fragile X Premutation Diagnosis .............................................................12
Discussion & Conclusion...............................................................................................................................30
References....................................................................................................................................................34

LIST OF TABLES

Table 1 ..........................................................................................................................................................13
Table 2 ..........................................................................................................................................................15
Table 3 ..........................................................................................................................................................16
Table 4 ..........................................................................................................................................................16
ACKNOWLEDGEMENTS

This work was supported by a National Institute of Health grants R01HD055510, 3P30-HD02274-35S1, HD036071, and 5R01HD040661-11.
Introduction

Discussions of State-mandated newborn screening for fragile X (FX) mutations center on the creation of and adherence to guidelines set forth by the American College of Medical Genetics and subsequent definitions and analyses of the costs and benefits of such screening. It is evident that there exists a myriad of positive aspects of screening newborns for FX, yet there also are some possibly serious drawbacks. Positive aspects may include the reduction of “diagnostic odyssey” resulting in earlier and more effective treatment for individuals with fragile X syndrome (FXS), early communication of reproductive risk to parents who carry premutations, as well as benefits to extended family members who may be at risk. Drawbacks may include parental anxiety related to screening and diagnosis, ethical dilemmas regarding diagnosis of non-symptomatic premutation carriers, and implications of genetic risk in extended family members who never consented to screening.

The concerns discussed above reflect a mostly hypothetical evaluation of FX newborn screening (FXNBS) as, until recently, FXNBS was not implemented. This paper adds to the discussion of FXNBS in the United States by relating the experiences of parents of newborns who were identified as carriers of FX premutations as a result of their participation in a newborn screening pilot program. How do these benefits and potential problems look to parents themselves? What do parents who’ve experienced diagnosis of their newborn as a FX premutation carrier say about these screening experiences? There is very little information available as yet focused on parent experiences. To put this analysis in context, I also review the history of the debate regarding State-mandated newborn screening and FXNBS.

Fragile X mutations are expansions of genetic material that occur at a particular locus on the X chromosome. When these mutations occur, genetic material is repeated more times than
normal, which causes changes in the gene function. These mutations can be passed from a mother to her children or a father to his daughters. Most people have between 5 and 40 repeats and are considered “normal” with respect to this gene. Repeats between 40 and 54 are considered a “grey zone”, denoting a lack of knowledge about the implications of repeats of this size. The expansion is pathologized when more than 54 repeats occur. A locus containing between 55 and 199 repeats is called a premutation and the individual whose cells this mutation occurs in is called a premutation carrier. Within the premutation range, there is a colloquial distinction between “high” and “low”, high being over about 120 repeats and more likely to be associated with clinical pathology (Chonchaiya, Schneider, & Hagerman, 2009).

The most severe form of the mutation occurs when the locus contains 200 repeats or more, and in some cases repeats can be into the thousands. This degree of expansion causes fragile X syndrome (FXS) and is the most common known genetic cause of intellectual disabilities, affecting 1 in 2,500 to 1 in 3,600 males and females (Crawford et al., 2000; Hagerman, 2008). In addition to intellectual disabilities, FXS is associated with a broad range of physical and behavioral features including prominent ears, hyperextensibility, gaze avoidance, hyperactivity, and anxiety. FXS is also associated with high rates of autism spectrum disorders (ASD).

The premutation carrier status, although pathologized in name, is not necessarily associated with clinical symptoms. It is, however, well documented that the “high” premutation status is associated with three significant risk categories; Increased probability of producing an offspring with FXS, Primary Ovarian Insufficiency (FXPOI) (Sullivan, Welt, & Sherman, 2011), and a debilitating late onset neurodegenerative disease called fragile X-associated Tremor/Ataxia syndrome (FXTAS) (S. Jacquemont et al., 2004). Emerging research suggests that carriers may
also be at an increased risk for ASD, attention deficit disorders, autoimmune disorders, and psychiatric disorders, among other things, but these clinical implications may be limited to carriers of “high” range premutations (Chonchaiya et al., 2009).

It is prudent to point out here that the clinical relevance of a FX premutation diagnosis, especially in the “low” range, is contested within the field of FX molecular and behavioral research. Members of the research group conducting the FXNBS referenced in this paper, at UC Davis, from which this data is drawn, are the leading proponents of research investigating premutation involvement. This contestation within the scientific community translates into a necessary ambiguity in the communication of the meaning of this genetic knowledge from clinicians to patients. Each of the newborns discussed in this paper were diagnosed with a premutation in the low range, the newborns’ repeats ranged from a mere 55 to only 76. The sizes of these premutations, even in the most liberal interpretation, are extremely unlikely to produce clinical symptoms. Some instances of FXTAS and FXPOI are reported to occur in the low premutation range (59 repeats is the lowest in both cases), but these cases were identified from high-risk groups, meaning that individuals with movement disorders or with infertility were screened for FX mutations and some of them were found to carry premutations (Rousseau, Labelle, Bussières, & Lindsay, 2011). What this finding means, of course, is that individuals without FX mutations also experience neurodegenerative disorders and infertility, calling into question the relevance of this diagnosis for treatment options. The likelihood that a particular individual with a premutation will ever develop symptoms of ASD, FXTAS, or FXPOI, and what other factors contribute to symptom development, is as yet unknown, particularly for individuals with very low level premutations. Additionally, the risk of this range of premutation expanding to full mutation in one generation is improbable in the newborn screening population.
In families known to have members with FXS, premutations as low as 59 repeats have expanded to full mutations in one generation, but in families with no history of FXS, like all of those in the current study and the majority of newborns who would be screened if FXNBS is implemented, the risk of premutation expansion to full mutation does not increase until around 90 repeats (Geva et al., 2000).

Parents in a voluntary FXNBS pilot program conducted at the University of California, Davis, Medical Center, participated in screening. In this report, I analyze interviews conducted with eight parents of six newborns who screened positive for FX premutations and were a part of this program. These eight parents are in six families, as follows: Four parents comprise two married couples; four parents are mothers who were married but interviewed without their husbands. As mentioned above, the newborns, and subsequently parents, diagnosed as premutation carriers via the FXNBS pilot program at UC Davis all had premutation sizes so small that they were likely not clinically relevant, at least not immediately at the time of diagnosis. This fact led to an ambiguity of meaning of the diagnostic results and this ambiguity is cited by parents in their expressions of uncertainty about participation in an FXNBS study.

What follows is an analysis of parents’ reactions to screening based on the content of their interviews. Evidence includes 1) parent reports of why they chose to participate, 2) answers to forced-choice questions about whether and when FX screening should be done, and 3) parents’ explanations of their answers to the forced-choice questions. Forced-choice questions include whether FXNBS should be conducted on all newborns and when the ideal time to test for FX mutations is. Additionally, parents are organized into three groups based on their perceptions and reactions to FXNBS as expressed in the interviews: negative reactions (parents are unhappy with their participation), mixed reactions (parents vacillate between feeling pleased and unhappy
with participation), and positive reactions (parents are happy about their participation). These reactions reflect a global score given during coding of the interviews, this is elaborated in the methods section.

Many of the parent perceptions and responses discussed here are in line with those reported in three other studies about reactions to NBS that were based on larger samples (Christie et al., 2013; Skinner et al., 2011; Timmermans, 2013). For this reason, both the concerns and benefits described by these eight parents likely reflect what many parents would experience in the event of widespread FXNBS implementation. Therefore, the insights from these interviews can fruitfully be used to improve a (possibly inevitable) FXNBS program in order to minimize potential negative consequences and maximize positive outcomes for most individuals. I end this paper with a discussion of some ways that this goal might be achieved.

Although this is a small sample of interviews, it represents all of the parents of newborns identified at UCDMC throughout the course of the FXNBS project who agreed to longitudinal follow up. It is, therefore, a unique and valuable sample for exploring critical questions related to the implications of FXNBS.

Because of the novelty of perspective contributed by the interview data explored in this paper, this first exploration of parental perspectives of FXNBS necessitates a clear and descriptive analysis as presented here. The parent perspectives, however, beg important questions deserving of interpretation and analysis in subsequent reports. These questions and analysis are beyond the scope of the current paper but include the following: does relaying such low premutation range diagnoses actually create disease where there was none before? How do parents of diagnosed newborns assimilate their own diagnosis into their ideas of themselves, do they worry about their health status in the future? How does diagnosis of FX premutations via FXNBS affect family functioning and spousal relationships? How are extended family members affected by related newborn premutation diagnosis? In the age of “perfect babies”, what does it mean that parents who enroll in newborn screening often do so because they want to know if something is “wrong” with their newborn? What is the history of the definition of FX mutation categories and how have they become defined as they are currently? What are the relevant gender-related issues associated with FXNBS? And possibly many other questions.
Universal Newborn Screening

Universal newborn screening began in most US states by the mid 1970s, ten years after the development of a blood spot screening test for phenylketonuria (PKU) (Bailey, 2004). The inexpensive technology made it possible to screen thousands of newborns and ostensibly save those with this life threatening metabolic condition through early identification and treatment. Subsequently, a gradual addition of screening tests occurred and steps towards systemization were made. A series of reports published from 1968 to 1998 established some guidelines for proceeding with caution in the expansion of NBS. The general consensus from those reports reflects the following points; 1) offering newborn screening using established tests is an appropriate state mandate, 2) testing should address an “important health problem”, 3) testing should only address disorders for which “an accepted treatment is available”, 4) voluntary screening with parental consent is the ideal but consent can be waived in strong cases, 5) screening should be cost-effective while still 6) supporting follow-up care, and 7) “above all, the patient should benefit from screening” (Timmermans, 2013). The second and third points are typically considered to represent the necessary conditions for inclusion of an available screening test on a state panel (Bailey, 2004).

The recommendations listed above represent an ideal in the implementation of universal newborn screening; however, the extent to which they are met is up for debate. The current working definition of “benefit” includes the possible benefits conferred to the families of screened newborns, not just the newborns themselves. This definition has allowed for the consideration of including disorders in NBS that may not have a direct treatment or are not life-threatening on the basis that their identification helps families in other ways (Buchbinder & Timmermans, 2011; Timmermans, 2013).
This is the stage on which the debate surrounding newborn screening for fragile X exists. No state currently screens for FX mutations as part of state mandated expanded newborn screening, though at least three research teams have conducted small-scale voluntary screening in the United States.

**Fragile X Newborn Screening**

*History*

Proponents of newborn screening for fragile X syndrome have argued for the inclusion of fragile X in State screening panels despite their own acknowledgement that the syndrome does not meet all of the “gold standard” criteria. While fragile X syndrome does present a significant public health problem, both because of its prevalence and the severity of symptoms, there is not currently a proven effective medical treatment (Bailey, 2004). It is argued, however, that the potential benefits of identifying newborns with FXS are large enough to counter the lack of effective treatment. The benefits often cited include: 1) reduction of the “diagnostic odyssey” leading to earlier non-medical interventions and early support for families. 2) Communication of reproductive risk to parents enabling them to use this knowledge in subsequent reproductive decision-making. 3) Societal benefits including revealing the true prevalence and lending insights to genotypic and phenotypic profiles (Abrams et al., 2012; Bailey, 2004; Bailey, Skinner, Davis, Whitmarsh, & Powell, 2008). There is precedent in this regard. Bailey et al (2006) report on the expansion of the conception of benefit in newborn screening since the release of the American College of Medical Genetics (ACMG) 2005 report. Benefit is a core aspect of consideration for inclusion on state newborn screening panels and it is not limited to the individual child or dependent upon amelioration of all symptoms of the screened disorder. In
fact, treatments for 51.7% of the ACMG core recommended target conditions prevent only some symptoms (Bailey et al., 2006).

While proponents of FXNBS stress the potential benefits to the newborns and their families, they do not ignore the possible ethical, legal, and social consequences. In a 2008 article on the topic, Bailey et al discuss eight such concerns. Of the eight concerns, four directly affect the families of identified newborns. These include: 1) heightened anxiety and disrupted bonding due to diagnosis of this “untreatable condition”, 2) consent process could overwhelm parents and uptake of screening might be low, 3) revealing FX mutation status could cause stigma or discrimination, and 4) screening for FX mutations would implicate extended family members who never consented to screening. Subsequent papers have echoed the concerns put forth by the Bailey et al paper (Abrams et al., 2012; Sorensen, Gane, Yarborough, Hagerman, & Tassone, 2013).

There is a relative consensus on what are the best approaches to addressing the concerns related to FXNBS. First and foremost, newborn screening for FX mutations should be voluntary. Proponents also recommend heightened and centralized research on FXS, tools for educating families about FX mutations and risks and benefits to screening, and structured support for parents and extended family members of identified newborns. All these will help address the concerns around FXNBS (Abrams et al., 2012; Bailey, 2004; Bailey et al., 2008; Sorensen et al., 2013).

Researchers are taking steps towards addressing concerns about FXNBS. Past and current targeted drug treatment trials show promise for lessening or reversing some symptoms of fragile X syndrome and FXTAS (Berry-Kravis et al., 2009; Berry-Kravis et al., 2012; Hagerman, Lauterborn, Au, & Berry-Kravis, 2012; Hare, Hagerman, & Lozano, 2014; Jacquemont et al.,
In addition, an educational brochure was developed and demonstrated to effectively increase pilot subjects’ understanding of FX mutations as well as inform them of possible positive and harmful consequences of screening their newborn (Bailey et al., 2013). Finally, as will be described below, the UC Davis Newborn Screening for Fragile X and Family Follow up study was designed to address the concerns surrounding FXNBS. Nevertheless, some of the potential concerns were in fact experienced by some parents of newborns identified as premutation carriers, as will be demonstrated below.

Some early reactions to FXNBS indicate high maternal support of screening (Christie et al., 2013; Skinner et al., 2011). In a pilot study similar to the current study but conducted in Australia, 94% of mothers approached to participate in FXNBS in the postnatal period consented to testing and elected to be informed of both premutation and full mutation statuses. The mothers also found the procedure convenient, supported the research endeavor, thought the results would be helpful in planning for future needs of their child and their own future reproductive decisions, and believed it was beneficial to know a diagnosis before signs appeared. Some mothers were anxious about the impending results and some mothers with higher education levels reported that a positive result might change their feelings towards their infant (Christie et al., 2013). A similar study conducted in North Carolina reported similar maternal attitudes, although the participation rate of those mothers was much lower than in the Australian study (63%) (Skinner et al., 2011). In both studies, mothers who declined participation did so due to “drop out”, lack of interest, fatigue/inconvenience, not wanting to know, and lack of partner consent (data only from the Australian study).

Two investigations into medical professionals’ attitudes towards FXNBS report buy-in from medical geneticists, genetic counselors, and developmental and behavioral pediatricians.
74% of developmental and behavioral pediatricians supported universal FXNBS testing for both the pre and full mutations. These professionals reportedly endorse screening for reasons that mirror those put forth by proponent of FXNBS and endorsed by mothers in the two studies discussed above. They also promote the voluntary quality of FXNBS if it is implemented. (Acharya & Ross, 2009; Acharya & Schindler, 2013).

Despite support from parents (Christie et al., 2013; Skinner et al., 2011), some medical professionals (Acharya & Ross, 2009; Acharya & Schindler, 2013), and academic proponents of FXNBS (Abrams et al., 2012; Sorensen et al., 2013), the identification of premutation carriers through FXNBS is problematic because of the uncertainty of clinical implications. FXNBS is likely to reveal mostly premutation carriers with low level repeats. In their study published in (2011), Hanstash et al reported that 75% of premutation carriers identified in the general population (as opposed to from known fragile X families) had premutation alleles with fewer than 70 repeats. As discussed previously, individuals with such low level premutations are likely asymptomatic, will remain that way, and are probably not at an increased risk of producing offspring with FXS. In addition to calling into question the assertion of benefits related to FXNBS, this data suggests that most parents of newborns identified if FXNBS is implemented would receive ambiguous clinical information as a result of a positive screen. As demonstrated in the results presented here, parents respond to the ambiguous nature of the low premutation diagnosis with anxiety and wonder if they were better off not knowing this information.

The Fragile X Newborn Screening and Family Follow up Study

The FXNBS project aimed to investigate the clinical benefits and risks associated with screening newborns for FX mutations. The protocol involved obtaining informed consent from mothers and fathers and a blood spot from newborns within 12-24 hours after birth. Research
assistants approached new parents daily in the recovery rooms of the neonatal unit. The consent process consisted of a researcher knocking, and then entering the room, introducing herself and the project, then asking the parents if they would hear more about the FXNBS project. If the parents allowed a full description of the study, they were asked if they would consent to participation. If the response was positive at this time, the research assistant read through each page of a 15-page consent form with the parents. Parents signed the first and last pages and initialed every other page. The entire process took nearly 30 minutes.

The blood obtained from the bloodspots of newborns whose parents consented to participation was screened for FX mutations and premutation carrier diagnoses were reported initially by phone, followed by genetic counseling. Parents and all available and interested extended family members of identified newborns were subsequently screened. Parents of identified newborns were invited to participate in long-term developmental follow-up with their babies. The semi-structured interviews from which I draw the data for this paper were one component of the long-term follow up. A more detailed description of the pilot project and case study of three families was reported in 2013 (Sorensen et al.).

During the course of the study, 14 newborns screened positive for FX mutations and 44 relatives from 10 families were tested, 27 of those were found to carry FX mutations. Unfortunately, at the time I left the project, few identified families were participating in long-term follow up and only eight parents from six families agreed to interviews.

**Interview Methods**

The semi-structured interview was developed by a collaborating anthropologist at the University of North Carolina at Chapel Hill and was designed to elicit parents’ experiences participating in the FXNBS study.
I conducted interviews with the parents of 6 newborns (3 male, 3 female) identified as FX premutation carriers. 4 parents included in this study were married mothers of identified newborns who were interviewed in the absence of their partners. The other 4 parents comprised 2 husband and wife couples. In both cases, the husband and wife were interviewed together. Interviews were conducted over the phone. In the analysis of narratives I have treated each parents’ narrative separately, even though the husband and wife couples were interviewed together. Although the individual narratives of the husbands and wives are not independent, each parent does contribute his or her own answer to each question and expresses his or her own concerns regarding screening. Given the design of this project, I have no way of knowing how these husbands’ and wives’ narratives may have influenced each other. Likewise I cannot know how previous conversations between the members of these couples or conversations between the 4 other mothers and their husbands may have influenced the current narratives.

The parents were interviewed at one time point when their infant was between 7 and 12 months old, which was 5-10 months after diagnosis. Interviews were transcribed and themes were identified and indexed using a mixed methods data management and analysis tool (Dedoose). Table 1 describes the 6 newborns whose parents were interviewed.

All names in this paper are pseudonyms. Parents are initially referred to by their pseudonym and the ID number of their infant. For example, the mother of newborn 3 is referred to as Julia (03). They are subsequently referred to just by their pseudonym.

Parents’ Reactions to Newborn Fragile X Premutation Diagnosis

Three direct questions posed in the interview gave insight to parents’ reactions to participation and directly address responses reported by Skinner et al (2011) and Christie et al (2013). These questions and answers also set the stage for the categorization of parents into