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A Prospective, Longitudinal Study of the Impact of *GJB2/GJB6* Genetic Testing on the Beliefs and Attitudes of Parents of Deaf and Hard-of-Hearing Infants

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Abstract

There are limited data on the impact of incorporating genetic counseling and testing into the newborn hearing screening process. We report on results from a prospective, longitudinal study to determine the impact of genetic counseling and *GJB2/GJB6* genetic testing on parental knowledge, attitudes, and beliefs about genetic testing. One hundred thirty culturally hearing parents of 93 deaf or hard-of-hearing children ages 0 – 3 years primarily identified through newborn hearing screening received pre- and post-test genetic counseling for *GJB2* and *GJB6*. Parents completed questionnaires following pre-test counseling, and 1- and 6-months post-test result disclosure. Results indicate that following pre-test counseling all parents perceived benefits to genetic testing. While parents who received positive results continued to perceive benefits from testing, perceived benefit declined among parents who received inconclusive or negative results. Parents did not perceive genetic testing as harmful following pre-test counseling or receipt of test results. Parents who received positive test results performed better in understanding recurrence and causation of their child's deafness and indicated greater interest in prenatal genetic testing than those who received inconclusive or negative test results. Parents felt that pediatricians and audiologists should inform parents of genetic testing availability; however, there was no consensus on timing of this discussion. Thus culturally hearing parents do not perceive genetic testing of their deaf or hard-of-hearing infants/toddlers as harmful; they feel that primary care providers should discuss genetic testing with them; and positive genetic test results with genetic counseling give rise to better understanding and perceived benefit than negative or inconclusive results.

Keywords

Connexin 26; Cx26; newborn hearing screening; early hearing detection and intervention; EHDI; hearing loss; hearing impairment

INTRODUCTION

Congenital deafness is present in approximately 1–3 per thousand newborn infants [Finitzo et al., 1998; Gorlin et al., 1995; Morton, 1991]. Deafness is an etiologically heterogeneous trait; however, deafness-causing variants in *GJB2* [Denoyelle et al., 1997] the gene that encodes the connexin 26 protein, have been found to provide an explanation for 40–80% of individuals with autosomal recessive nonsyndromic sensorineural deafness [Denoyelle et al., 1997; Gasparini et al., 1997; Kelley et al., 1998; Rabionet et al., 2000], and 10–37% of individuals with deafness of unknown cause [Estivill et al., 1998; Lench et al., 1998; Rabionet et al., 2000]. In addition, the deletion del(GJB6-D13S1830) in *GJB6* [Del Castillo et al., 2002], the gene that encodes the connexin 30 protein, provides additional explanatory power, either through a homozygous state or through a double heterozygous state with a *GJB2* deafness-causing variant [Batissoco et al., 2009; Cama et al., 2009; Del Castillo et al., 2003; Schimmenti et al., 2008]. Because newborn hearing screening is now mandated in the majority of U.S. states and a number of countries [de Swanepoel et al., 2007; Kennedy and McCann, 2004; Morton and Nance, 2006] and because Connexin-related deafness is common, there has been considerable discussion about introducing *GJB2*, and possibly *GJB6*, testing into the newborn hearing screening process [Morton and Nance, 2006; Schimmenti et al., 2004; Tranebjaerg, 2008].

The inclusion of genetic testing for deafness as part of newborn hearing screening raises a series of issues not only because there are different culturally-based perspectives attached to the meaning of ‘being deaf’ [Padden and Humphries, 1988], but also because for many parents this will be their first experience with a deaf individual since 90–95% of deaf and hard-of-hearing babies are born into hearing families [Mitchell and Karchmer, 2004; Schein and Delk Jr., 1974]. For many parents this will also be their first experience with genetic testing; however, a variety of cross-sectional studies of deaf and hearing parents (or potential parents) in sample sizes ranging from 24 to 222 participants suggest that there is interest in testing their deaf or hard-of-hearing children for genes that cause deafness [Brunker et al., 2000; Burton et al., 2006; Dagan et al., 2002; Martinez et al., 2003; Palmer et al., 2008; Steinberg et al., 2007b; Taneja et al., 2004; Withrow et al.]. However, the success of augmenting newborn hearing screening programs with genetic testing will not only depend on *parental interest* but will also depend on the *impact* of genetic testing and information on parents, particularly in light of the scientific and social complexity associated with genetic information and deafness. Prospective, longitudinal studies are needed to define the impact of genetic testing and information on parents when genetic testing is introduced early in the child’s life, e.g., as part of the newborn hearing screening process. Here we report findings from a study that employed a prospective, longitudinal design to evaluate the impact of *GJB2/GJB6* genetic testing and counseling on parental knowledge, attitudes, and beliefs about genetic testing.

There are limited empirical data on the clinical, educational, and psychosocial outcomes of genetic testing for deafness in early-identified deaf and hard-of-hearing infants. Our current understanding of the impact of genetic testing for deafness in pediatric populations comes primarily from cross-sectional studies that have evaluated parental understanding, and beliefs and attitudes toward genetic testing for deafness in contexts ranging from hypothetical genetic testing, pre-genetic testing, or post-genetic testing. The results of this

mixed set of cross-sectional studies suggest that parents are interested in genetic testing to learn why their child is deaf or hard-of-hearing, to learn recurrence information and for future family planning, to help with their child's medical care, and to help their family [Brunger et al., 2000; Burton et al., 2006; Dagan et al., 2002; Palmer et al., 2008; Steinberg et al., 2007b; Withrow et al., 2008]. Studies also suggest that understanding genetic information, particularly information that does not explain why their child is deaf, can be challenging for parents [Brunger et al., 2000; Parker et al., 2000; Steinberg et al., 2007b]. Because these reports are primarily cross-sectional in nature, and used mixed contexts with respect to genetic counseling and testing with little or no explicit inclusion of the genetic counseling and testing process in the study design, they do not provide a clear picture of the short or longer-term impact of genetic counseling and testing on parents of a young deaf or hard-of-hearing child.

More recently, however, there have been two studies that quasi-serially addressed aspects of the referral, genetic counseling, and genetic testing process with respect to parents of a deaf or hard-of-hearing child. The first study reported on qualitative data regarding attitudes toward genetic testing for deafness collected at two time points, one year apart, from parents of 14 deaf or hard-of-hearing children who had been referred for genetics evaluation [Kaimal et al., 2007]. The genetic evaluation and testing process was not included in the study protocol; instead the authors focused on parental accounts of their experiences during this one year period. They concluded that parents' attitudes toward genetic testing for deafness did not change over the one year period. Parents with an overall positive perception of the usefulness of genetic testing remained satisfied with the experience of pursuing genetic testing *regardless* of test result, and parents unconvinced of the usefulness of genetic testing remained that way. This result suggests that specific genetic test results do not engender changes in parents' attitudes and beliefs about genetic testing, and that counseling efforts need not include anticipatory guidance to prepare parents for reactions to specific test results.

The second study compared beliefs and attitudes of two different groups of parents of deaf/hard-of-hearing children: one ascertained before pre-test genetic counseling for deafness (n=77) and the other ascertained after pre-test genetic counseling (n=22) [Li et al., 2007]. Both groups completed the same survey instrument. Group comparisons showed that those assessed after pre-test counseling perceived greater benefits of genetic testing, were less likely to believe that their child's deafness was due to non-genetic causes, and were less inclined to think that they would defer genetic testing compared to the group assessed prior to pre-test counseling. This result differs from the findings of Kaimal et al [2007] because it suggests that pre-test counseling *can* have an impact on parental beliefs about genetic testing. However, consistent with the findings of Kaimal et al [2007], the groups did *not* differ on items of stigma related to genetic information, suggesting that pre-test genetic counseling has no impact on parental perceptions of harms of genetic testing. Overall, this study suggests that some parental attitudes regarding genetic testing for deafness can be fluid and possibly influenced by pre-test genetic counseling and testing, which, if true, is important information for developing counseling efforts that include anticipatory guidance.

The paucity of prospective, longitudinal studies is a potentially significant deficit in our understanding of the impact of genetic testing for deafness, as studies of genetic testing in other realms, e.g, for inherited cancers, Huntington disease, hemochromatosis, and cystic fibrosis, demonstrate that it is important to examine both short and longer term effects of genetic testing [Codori et al., 2004; Croyle et al., 1997; Kinney et al., 2005; Lakeman et al., 2008; Meiser et al., 2005] in order to determine the need for developing anticipatory guidance in the pre- and post-test counseling sessions. Here we report findings from the first prospective, longitudinal study to assess the impact of genetic testing on parents of deaf and

hard of hearing infants and toddlers. In this study we prospectively assessed parental perceptions of benefits and harms of genetic testing, parental understanding of genetic test results (knowledge) and attitudes toward testing. We also assessed parental views on how genetic testing should fit within the newborn hearing screening process. We show that responses to the survey items, particularly perceived benefits of genetic testing, differ based on genetic test results and time post result disclosure, and that parents feel that their primary care providers should discuss the option of genetic testing for deafness.

METHODS

Sample and Procedures

The study sample consists of parents of children between birth and 3 years of age who (i) were referred for additional hearing screening following inpatient hearing screening or (ii) were diagnosed as deaf or hard of hearing and (iii) did not have an obvious syndromic condition associated with their deafness. These eligibility criteria allowed us to focus assessment of parental outcomes of genetic testing in early-identified children who were most likely to have Connexin-related deafness. Participants were recruited through a variety of venues in the Los Angeles area, including the UCLA newborn nursery, genetics, audiology, and otolaryngology clinics, and education intervention programs.

Eligible parents met with a genetic counselor for pre-test counseling, and the option of *GJB2* and *GJB6* genetic testing was discussed in a semi-structured format in the context of etiologic heterogeneity of deafness, Connexin-related deafness, and possible outcomes, benefits and limitations of genetic testing. Genetic counseling sessions were conducted in English, Spanish, or American Sign Language depending on parental preference.

With parental consent, a buccal swab was obtained for genomic DNA isolation followed by *GJB2* genetic testing (sequencing of exons 1 and 2) and *GJB6* deletion testing (del(GJB6-D13S1830) [Schimmenti et al., 2008]. During a second genetic counseling session, genetic test results were disclosed, explained, and put into the context of the family history; clinical implications for the child were discussed; recurrence chance was provided; and questions/concerns were addressed. Parents were given a copy of the test result, the American Academy of Pediatrics Universal Newborn Hearing Screening, Diagnosis and Intervention, Guidelines for Medical Home Providers (http://www.infanthearing.org/medicalhome/aap_gpmhp.pdf), the American College of Medical Genetics guidelines for the evaluation of deaf and hard-of-hearing children [American College of Medical Genetics, 2002], and a written summary of the counseling session with results and recurrence information.

Parents completed three questionnaires in English or Spanish. The first questionnaire (Baseline) was completed ~2 weeks after the pre-test counseling session. The second (1-Month Post-Test) and third (6-Month Post-Test) questionnaires were completed approximately one and six months after the genetic test results disclosure session. These questionnaires assessed reasons for pursuing genetic testing, attitudes and beliefs about genetic testing, knowledge and understanding of genetics and Connexin-related deafness, and psychological constructs such as anxiety and perceived personal control. The research protocol was approved by the relevant institutional review boards. In this paper, we report on data collected longitudinally on parental attitudes, beliefs, and knowledge, and on parental views about which professionals should discuss availability of genetic testing and when this discussion should occur. Figure 1 depicts the study protocol, and additional details of the study are available elsewhere [Palmer et al., 2008; Schimmenti et al., 2008].

A total of one hundred-sixty-four parents from 103 families were enrolled in the study: n=9 were enrolled after their child failed inpatient or outpatient newborn hearing screening and n=155 were enrolled after their child was diagnosed as deaf or hard-of-hearing. Parents in the former group were excluded from these analyses because their perspectives may have additionally been influenced by the fact that their child had only failed newborn hearing screening and follow-up evaluations for nearly all of these infants demonstrated normal hearing thresholds. Twenty-five parents in the latter group were excluded from the analyses for the following reasons: 1) because their child was subsequently determined to hear (n=3 parents); 2) they did not personally return for the genetic test results (although their spouse likely returned) and were no longer eligible to fill out the 1-Month Post-Test and 6-Month Post Test questionnaires (n=13 parents); 3) they enrolled in the study at the time of the result disclosure session and so were not eligible to complete the Baseline questionnaire (n=3 parents); or 4) they did not complete any of the questionnaires (n=6 parents). Of the remaining 130 parents, 129 (98.4%), 115 (87.8%), and 107 (81.7%) completed the Baseline, 1-Month Post-Test, and 6-Month Post-Test questionnaires, with 100 subjects (77%) completing all three questionnaires. Approximately one quarter of the questionnaires were completed in Spanish.

Measures—Demographic information was collected from each respondent. The majority of items assessing attitudes and beliefs about genetic testing were drawn from, or developed on the basis of, a literature review on genetic testing in general or genetic testing for deafness specifically [Brunger et al., 2000; Dagan et al., 2002; Hietala et al., 1995; Lerman et al., 1997; Martinez et al., 2003]. All items on the questionnaire were closed-ended.

Attitudes and beliefs about genetic testing: All three questionnaires contained four statements addressing potential benefits of genetic testing (“The genetic test in this study helped me understand why my child has hearing loss”; “The genetic test results from this study could help me make treatment decisions for my child”; “The genetic test results could help my family”; “The genetic test results from this study could help me with future family planning decisions”) and five statements addressing potential harms of testing (“I am concerned that genetic testing results would somehow harm my child”; “I am concerned that genetic testing will have an effect on our health insurance”; “I am concerned about the effect genetic testing might have on the family”; “I am concerned about emotionally handling genetic information about my child”; “Being offered a genetic test implies that there is something “wrong” with hearing loss”). For each item, respondents were asked to determine how strongly they agreed or disagreed on a 5-point Likert scale with the highest score of 5 given to “strongly agree” and the least score of 1 given to “strongly disagree”.

Importance of Etiology: In all three questionnaires, parents rated how important it was for them to know why their child is deaf on a 3 point Likert scale of ‘not at all important’ (scored as 1) to ‘very important’ (scored as 3).

Knowledge and Understanding: In all three questionnaires, parental understanding of inheritance in general, autosomal recessive inheritance, recurrence chance, and the concept of genetic heterogeneity for deafness were assessed with six true/false items. For each respondent, a knowledge score was constructed from the true/false items as the sum of correct responses (highest score = 6) and used for analysis.

In all three questionnaires, parents were also asked to judge the likelihood that their child has Connexin-related deafness on a 4 point Likert scale ranging from ‘not at all likely’ (1) to ‘definitely’ (4). In the 1- and 6-Month Post-Test questionnaires only, parental understanding of their child’s specific test result was assessed by asking parents to select the cause of their

child's deafness as either being 'genetic', 'not genetic', or 'undetermined'; and by asking parents to identify their recurrence chance from a list of options.

Interest in prenatal diagnosis. In the 1- and 6-Month Post-Test questionnaires only, parents rated their level of interest in *GJB2* testing in a future pregnancy on a 3 point Likert scale ranging from 'not interested (1)' to 'strongly interested (3)'.

Informing parents of testing: In the 1-Month Post-Test questionnaire only, parents were asked to indicate which professionals from a list should inform parents of the option of genetic testing for deafness.

Timing of information on genetic testing: In the Baseline questionnaire only, parents were asked to indicate when they first wanted to learn the cause of their baby's deafness, ranging from 'when the baby did not pass newborn hearing screening in the hospital' to 'when you told your family that your baby has hearing loss'.

Statistical Analyses—Descriptive statistics were generated and reviewed for outliers. For analysis purposes, parents were classified into one of three possible groups (referred to collectively as CxGROUP) based on their child's *GJB2/GJB6* result: CxPOS group for parents of children that had two recessive alleles identified, CxINC group for parents of children who had one recessive allele identified, or CxNEG for parents of children who had no recessive alleles identified. The primary interest of the analyses is to determine the effect of genetic information on parents' attitudes, beliefs, and knowledge over time. To appropriately assess the effect of the interaction between time and genetic test result group (referred to as CxGROUP*TIME) on parental outcomes, we also include the individual main effects of genetic test result group (referred to as CxGROUP) and time (referred to as TIME) in the model, and we include ethnicity/race as a covariate in the model because of its previously reported association with perceived harms and benefits at baseline [Palmer et al., 2008]. In order to statistically account for the 39 instances where there were responses from both members of a couple, we indexed each participant with family "id" index, where both members of a couple who completed a questionnaire have the same family "id" (total of 91 family "ids"). We used a mixed effects linear regression model, with genetic test result group (CxGROUP), ethnicity/race, and time (TIME) as fixed effects, and random intercepts to characterize the 'couple' effect described above. We implemented this mixed effects model using Proc GLIMMIX and Proc MIXED [SAS, 2002] for qualitative or quantitative dependent variables, respectively. Post-hoc pairwise comparisons were performed using Tukey's HSD test to follow up on significant interactions between genetic test result group and time (CxGROUP*TIME) in order to determine the parental groups that differed in their outcome scores. Because the CxINC group had the smallest sample size, analyses were performed with and without these parents. Results were not substantively different, hence we report results from analyses using all three parental groups. Statistical significance was set at $\alpha = 0.05$.

RESULTS

Table I provides summary demographic information on the sample of 130 parents. The sample contains 38 couples and 51 individuals with one early-identified child, and one couple and one individual parent with two early-identified children for a total of 91 families. Twenty-three of the children in the study, approximately a quarter, have a "positive" or bi-allelic *GJB2* or *GJB6* result [Schimmenti et al., 2008]. Six parents (4.6%) in this sample self-reported as deaf or hard of hearing (all communicated orally and were culturally hearing) which is consistent with the statistic that 90–95% of deaf individuals are born to hearing parents [Mitchell and Karchmer, 2004; Schein and Delk Jr., 1974]. The average age

of the respondents' 93 deaf or hard-of-hearing infants at study enrollment was 13.2 months (SD = 10.8 months), demonstrating that our sample is composed of parents with early-identified children. Of the 130 parents in the sample, 34 were classified into the CxPOS group, 15 into the CxINC, and 81 into the CxNEG groups.

Perceived benefits

Figures 2a – 2d plot the least squares mean agreement scores over time for the three genetic test result groups for the four perceived benefit items. Results show that the interaction between genetic test result group and time (CxGROUP*TIME) is significant for all four perceived benefits. Post-hoc tests revealed that there were no group differences at baseline, with all groups reporting high levels of agreement towards these items. However, for three of the items, group differences were apparent one month after learning their test results, while group differences became apparent six months post-test results for the fourth item.

Specifically, for the item assessing “understand why my child is deaf” (Figure 2a), the group differences were immediate and relatively long-lasting. The CxPOS group reported significantly stronger agreement that genetic testing helped them understand why their child is deaf compared to both the CxINC and CxNEG groups at both 1- and 6-months post-test result disclosure. Further inspection of the figure suggests that while the CxPOS group experiences a slight increase in average agreement scores after learning their child's genetic test result, the greatest change occurs in the CxINC and CxNEG groups, where parental responses dropped from strong agreement at baseline to neutral – disagree after learning their child's genetic test results.

For “help my family” (Fig 2b) and “help with treatment decisions” (Fig 2c), the CxPOS group experiences immediate and relatively long-lasting benefit, which is most distinctive 6 months after learning their child's genetic test result. However, the pattern of change over time is more subtle compared to Figure 2a. For ‘help my family’, the CxPOS group experiences a slight increase in average agreement scores after learning their child's genetic test result, and although the other two groups experience a slight decline, their average agreement scores remain in the neutral – agree range, suggesting that their test results provided some benefit in terms of helping their family. For ‘help with treatment decisions’ the CxPOS group experiences a gradual and continued increase in mean agreement scores over time, revealing the importance of examining the impact of genetic testing over time. Analogous to the ‘help my family’ item, the mean scores of the CxINC and CxNEG groups declined slightly after learning their child's genetic test result but remained in the neutral – agree range, suggesting that the test results provided some perceived benefit in terms of treatment decisions.

For ‘future family planning’ (Fig 2d), differences emerged later compared to the other items, with the CxPOS group indicating significantly stronger agreement on this item at 6 months post-test results compared to the CxNEG group. Although there is a decline in mean agreement scores among parents in the CxINC and CxNEG groups, their scores remain in the neutral – agree range. Collectively, these results support the conclusion that parents of children with Connexin-related deafness show significantly greater perceived benefits of genetic testing compared to parents of children without Connexin-related deafness; however, even the latter parents perceive some level of benefit to the genetic counseling and testing process.

Perceived harms

Figures 3a – 3e plot the least squares mean agreement scores over time for the three genetic test result groups for the five perceived harm items. Results show that the interaction

between genetic test result group and time (CxGROUP*TIME) is not significant for any of these items, suggesting that the parental perceptions of potential harms of genetic testing are stable across time and resilient to whether or not genetic testing provides an explanation for why a child is deaf or hard-of-hearing. The main effect of time (TIME) also was non-significant for all five items, providing further evidence for stability of perceptions of harms of genetic testing. On average, parental scores fell into the neutral or disagree range on all of these items, suggesting that there was not a strong concern about potential harms of genetic testing either pre- or post-test results. However somewhat surprisingly, the main effect of genetic test result (CxGROUP) was significant for two of the five items. Specifically, the CxPOS group had the highest mean score for the item “I am concerned that genetic testing will have an effect on our health insurance” (Fig 3a), and the CxNEG group has the highest score for the item “Being offered a genetic test implies that there is something “wrong” with hearing loss” (Fig 3d). Although parental scores fell into the neutral or disagree range, the finding that parents of a child with Connexin-related deafness showed somewhat greater concern regarding health insurance, and that parents of a child who does not have Connexin-related deafness showed somewhat greater concern that genetic testing implied that “something was “wrong” with hearing loss, *even before they knew* their child’s genetic test results suggests that there may be factors confounded with the presence or absence of *GJB2/GJB6* deafness-causing alleles that are operating to influence parents’ perceptions of harms of genetic testing.

Importance of Knowing Cause of Deafness

Figure 4 graphs the least squares mean importance scores over time for the item assessing how important it is to parents to learn why their child is deaf. As shown in the figure, parents responded that it is very important to know why their child is deaf, both before and after genetic testing, and regardless of genetic test result. Consistent with this interpretation, the main effects of genetic test result group (CxGROUP), time (TIME), and their interaction (CxGROUP*TIME) were not significant for this item.

Knowledge and Understanding

Figure 5 illustrates the least squares mean knowledge scores over time for the three genetic test result groups. There was no significant effect of genetic test result group (CxGROUP), time (TIME), or their interaction (CxGROUP*TIME). In general, parental knowledge was quite good as evidenced by the high knowledge scores. In the entire sample, the average knowledge score at baseline (following pre-test genetic counseling) reflected ~85% correct responses, at 1-Month Post-Test results ~89% correct responses, and at 6-Month Post-Test results ~89% correct items.

One month and six months following disclosure of test results, parents were asked whether they thought the cause of their child’s deafness was genetic, not genetic, or not yet determined. There was a significant main effect of genetic test result group (CxGROUP) on parental responses ($p < 0.0001$), whereas time (TIME), and the interaction between genetic test result and time (CxGROUP*TIME), were not significant. Because this item was assessed only *after* receipt of genetic test results, the main effect of genetic test result group (CxGROUP) is a relevant indicator of impact of genetic information. Group differences were observed at 1-month post-test results, where 96.4%, 0%, and 4.41% of CxPOS, CxINC, and CxNEG parents, respectively, indicated that their child’s deafness was genetic in origin; 0%, 0%, and 16.18%, respectively, reported that their child’s deafness was not genetic in origin; and 3.57%, 100%, and 79.41%, respectively, reported that the cause of their child’s deafness was undetermined. These percentages changed very little at 6-months (data not shown), consistent with the non-significant main effect of time (TIME) and its interaction term (CxGROUP*TIME).

Parents' perceptions of how likely it is that their baby has Connexin-related deafness before and after receiving the genetic test results are depicted in Figure 6. There was a significant interaction between genetic test result group and time (CxGROUP*TIME). Post-hoc comparisons revealed a significant difference in perceptions between CxPOS parents and the other two groups at both 1- and 6-months post test result. All three parental groups felt it was 'somewhat likely' that their child had Connexin related deafness at baseline. However, at 1- and 6- months after receiving the genetic test results, parents who received a positive genetic test result indicated that they felt that their child very likely has Connexin-related deafness, while parents who received a negative or inconclusive test result indicated that they felt it was unlikely that their child has Connexin-related deafness. The figure also reveals that the CxINC group had non-significantly higher scores (indicating a 'somewhat likely' response) than the CxNEG group, revealing the complex nature of interpreting the meaning of an inconclusive test result.

In the 1-month and 6-month post-test questionnaires, we asked the parents to indicate their recurrence chance, and their responses to the 1-month questionnaire are depicted in Figure 7. The majority of the CxPOS parents (82%) accurately reported that their recurrence chance is 25%. However, there is considerable variability in what the CxINC and CxNEG parents reported, and this in part reflects natural variability in the recurrence chances provided during the genetic counseling session because family history was also taken into account. However, 86% of the CxNEG parents were provided with a 10–18% recurrence chance in the genetic counseling test result disclosure session, and as shown in Figure 7, only 40% of the parents reported that this is their recurrence chance. Approximately 25–30% of the CxNEG and the CxINC parents reported that their chance of having another deaf or hard-of-hearing child is between 0–5%, (with 6% of the CxNEG parents and 20% of the CxINC parents reporting that their recurrence chance is zero) and only one of these parents was provided with a recurrence chance in this range because the child was adopted into the family. Nearly two thirds of parents reported the same recurrence chance at both the 1-month and 6-month post test assessment time points (data not shown). Discrepancies between the two time points were primarily accounted for by a shift into the “unknown at this time” category at the 6 months assessment (data not shown).

Interest in Prenatal Diagnosis

Parents were assessed as to their interest in prenatal diagnosis in a future pregnancy on the 1- and 6-month Post-Test questionnaires. Figure 8 shows that there was a significant effect of genetic test result group (CxGROUP), with higher level of interest expressed by parents in the CxPOS group, on average, compared to the other parental groups. Because this item was assessed only after receipt of genetic test results, the main effect of genetic test result group (CxGROUP) is a relevant indicator of impact of genetic information. Time (TIME) and the interaction between genetic test result group and time (CxGROUP*TIME) were not significantly associated with parental interest in prenatal diagnosis. However, post-hoc analysis indicated that significant differences among the parental groups occurred at 6-months after receipt of the test results, where the CxPOS group had significantly higher level of interest in prenatal diagnosis compared to the CxNEG group, and non-significantly higher interest compared to the CxINC group ($p=0.08$).

Availability and Timing of Genetic Testing

Figure 9 plots the frequency of parental choices regarding who should tell parents about the option of genetic testing for deafness. As shown in the figure, pediatricians and audiologists were the most frequently selected (>70%), followed by the person doing the inpatient hearing screening, ENTs, and obstetricians (~50%). The least frequently selected was the child's teacher.

There was no consensus on *when* parents feel they should be told about genetic testing, with 25% selecting 'when baby does not pass newborn hearing screening in the hospital', 28% selecting 'when baby does not pass hearing screening in the audiology clinic', and 38% selecting 'when parents are told that the baby has hearing loss'.

DISCUSSION

This is the first prospective, longitudinal study of the impact of *GJB2/GJB6* genetic testing on parents of deaf infants/toddlers, and the first study to examine the impact of receiving inconclusive *GJB2/GJB6* genetic test results on parents. Our results provide insight into the trajectory of parental beliefs, attitudes, knowledge, and understanding of genetic information for the period encompassing pre- test genetic counseling through six months after receipt of genetic test results. Our results suggest that parental perceptions of benefits of genetic testing are high after pre-test counseling, and that parents who receive a positive genetic test result derive considerable benefit from this result compared to parents who receive a negative or inconclusive result. However, even parents who received a negative or inconclusive test result continued to perceive some level of benefit from genetic testing up to six months post-test result disclosure. The parents who received a definitive genetic test result, i.e., bi-allelic deafness-causing variants in *GJB2/GJB6*, felt over time that genetic testing helped them understand why their child is deaf, could help their family, could help with their child's treatment decisions, and could help with future family planning. Generally speaking, these benefits were perceived immediately after receipt of genetic test results and persisted over at least 6 months, with the exception of future family planning which did not emerge as a differential benefit until 6 months after learning their child's genetic test results. In contrast, parents did not perceive genetic testing as particularly harmful when embarking on genetic testing, and being informed of their child's genetic test results did not alter these perceptions.

Our findings suggest that perceived benefits and harms of genetic testing are differentially affected by the genetic counseling and testing process. We found that genetic test results altered perceived benefits of genetic testing, but did not alter perceived harms of genetic testing. Interestingly, Li et al [2007] found that *pre-test* counseling for deafness yielded a similar pattern of results, and together our findings suggest that parental perceptions of benefits of genetic testing for deafness may be dynamic and state-dependent while perceptions of harms of genetic testing may be stable and dependent on an individual's characteristics. Both of these findings are important when considering how to provide anticipatory guidance in the pre- and post-test result counseling sessions.

Previous studies have shown that it is important for parents to know why their child is deaf [Brunker et al., 2000; Burton et al., 2006; Dagan et al., 2002; Palmer et al., 2008; Parker et al., 2000; Steinberg et al., 2007b; Withrow et al., 2008]. The prospective, longitudinal design of our study confirms that parents feel it is important to know why their child is deaf, both before and after genetic testing. Of note, this sense of importance exists for parents who receive an explanation as well as for those who do not receive an explanation, and the magnitude of how important it is to know why their child is deaf does not wane over time. This finding not only likely explains parental interest in genetic testing, but also provides another example of how important it is to many individuals to eliminate or reduce uncertainty [Baty et al., 2006; Wakefield et al., 2008].

Genetic testing for deafness is complex for both scientific and social reasons, and thus introduces complexity into genetic counseling for deafness. The scientific complexity raised by testing stems from the underlying etiological heterogeneity of deafness and the limitations of our current abilities to interpret some genetic test results, i.e., inconclusive

results in which only a single deafness-causing variant is identified or a genetic variant of uncertain significance is detected. Several studies have documented the challenges raised by this scientific complexity in terms of understanding inheritance of deafness, genetic information, and empiric recurrence chances when an etiology for a child's deafness remains unknown [Brunger et al., 2000; Parker et al., 2000; Steinberg et al., 2007b]. In the case of *GJB2/GJB6* testing, a positive result reveals that a child's deafness is genetic in origin, whereas, negative or inconclusive results do not provide definitive information about why a child is deaf. Importantly, negative or inconclusive *GJB2/GJB6* results do not rule out a genetic form of deafness because there are many untested genes that can cause deafness. Although the number of studies evaluating knowledge and understanding of genetic information is small, the most common finding is misinterpretation of the meaning of a lack of explanation for why a child is deaf, either as an outcome of evaluation of clinical and family history information or as a result of a negative genetic test result, where individuals tend to equate a negative result with 'not genetic' and a zero percent recurrence chance [Brunger et al., 2000; Parker et al., 2000; Steinberg et al., 2007b]. These findings are not too surprising and reflect the recognized phenomenon of misinterpretation of "residual risk" [Lakeman et al., 2008; Lewis et al., 2006].

Our results demonstrate that parents can understand concepts of heterogeneity and inheritance in abstract terms after genetic counseling. However, as with previous studies, the way in which parents applied this information to their own circumstances varied depending on their child's genetic test result. Parents who received positive test results understood that their child has Connexin-related deafness, that this is genetic in origin, and that the recurrence chance is 25%, all of which suggests that through genetic counseling one aspect of the meaning of positive test results was successfully conveyed. Although parents who received an inconclusive test result accurately reported that it was still somewhat likely that their child has Connexin-related deafness, and that the etiology of their child's deafness was undetermined, they had less clear understanding of their recurrence chance. Furthermore, although parents who received negative test results accurately reported that it was unlikely that their child has Connexin-related deafness (which is consistent with their low level of interest in prenatal diagnosis), they had less clear understanding of their recurrence chance and that *GJB2/GJB6* testing did not rule out a genetic explanation, substantiating the complexity of conveying negative and inconclusive test results even with genetic counseling. That said, only 5% of parents who received a negative *GJB2/GJB6* result inaccurately estimated their recurrence chance as zero in this study which included pre- and post-test genetic counseling compared to 100% of parents whose child had a negative *GJB2/GJB6* result in Brunger et al [2000] where exposure to pre or post-test genetic counseling was unknown. This comparison provides compelling evidence that the scientific complexity raised by genetic testing for deafness can be ameliorated in part by inclusion of pre and post-test genetic counseling. However, additional research is needed to identify optimal genetic counseling strategies for conveying *GJB2/GJB6* results.

The social complexity of genetic testing for deafness is clear from numerous studies of the attitudes and beliefs of hearing parents, deaf parents, and deaf adults regarding genetic testing for deafness. Although there appear to be some "unanimous" motivations for performing genetic testing on a deaf child, e.g., identifying a cause for the child's deafness, learning an accurate recurrence chance, helping with future family planning [Brunger et al., 2000; Burton et al., 2006; Dagan et al., 2002; Palmer et al., 2008; Steinberg et al., 2007b; Withrow et al., 2008], there is also evidence that cultural, religious, and ethnic heritage factors play a role in determining acceptability of other possible uses of genetic information [Dagan et al., 2002; Palmer et al., 2008; Steinberg et al., 2007b; Withrow et al., 2008]. One frequently cited concern of many culturally Deaf individuals is that genetic information might influence subsequent reproductive decisions through the use of prenatal diagnosis and

termination of fetuses with genotypes associated with deafness [Burton et al., 2006; Dagan et al., 2002; Guillemin and Gillam, 2006; Middleton et al., 1998; Stern et al., 2002]. Several studies, primarily conducted with hearing or non-culturally deaf populations, have documented interest in prenatal genetic testing for deafness for preparing for the language and educational needs of a deaf or hard of hearing child rather than for termination purposes [Brunker et al., 2000; Burton et al., 2006; Dagan et al., 2002; Guillemin and Gillam, 2006; Middleton et al., 2001; Withrow et al., 2008]. The results of our prospective, longitudinal study with actual genetic testing showed that on average, culturally hearing parents who received a positive genetic test result agreed that the results could help them with future family planning decisions, and they expressed some interest in prenatal testing in a future pregnancy. Although we did not explore reasons for prenatal testing, these empirical results are consistent with previously reported interest in more hypothetical situations, and they underscore the importance of considering and addressing the social complexity of genetic testing for deafness in future research.

The newborn hearing screening process is a process that begins with bedside audiometric screening of virtually all newborns prior to discharge and proceeds to outpatient diagnostic audiologic evaluation for a small percentage of infants. During this process, parents are in contact with many health care professionals, including obstetricians, pediatricians, hearing screeners, audiologists, otolaryngologists, and early intervention teachers. Currently there is no formalized protocol for determining who should discuss the availability of genetic counseling and genetic testing to parents nor the timing of this discussion, although the pros and cons of initiating genetic testing at different stages in the process have been described [Schimmenti et al., 2004]. Parents in this study most frequently indicated that pediatricians and audiologists should inform parents of the availability of genetic testing, a result that likely reflects the repeated contact that parents have with these health professionals. These empirical data on parental preferences support current efforts to educate pediatricians and audiologists about genetic evaluation, genetic counseling, and genetic testing for deafness [Harvey et al., 2007; Palmer et al., 2003; Robin et al., 2005; Steinberg et al., 2007a]. There was no consensus on *when* parents felt they should be told about genetic testing, with 25% selecting 'when baby does not pass newborn hearing screening in the hospital', 28% selecting 'when baby does not pass hearing screening in the audiology clinic', and 38% selecting 'when parents are told that the baby has hearing loss'. Although this result differs from a recent study that found that parents preferred that genetic evaluation and testing occur either immediately at or a few months following the audiologic diagnosis of deafness [Withrow et al., 2008], both studies demonstrate that many parents feel that genetic testing and evaluation should be initiated early in their child's life.

This study has several limitations which may limit our ability to generalize the results. First, the data analyzed in this report come only from hearing and hard-of-hearing parents who use oral communication and who culturally affiliate with the hearing community and so results may not generalize to deaf parents who use signed communication and who culturally affiliate with the Deaf community. This is an important area of future research as there is very little data on the impact of pediatric genetic testing on deaf parents or Deaf culture. Second, the study does not solely address inclusion of genetic testing into the newborn hearing screening process because newborn hearing screening was not available to some of the deaf children in the study. Nevertheless, the majority of the children were identified through newborn hearing screening and their mean age at enrollment in the study was 13.2 months, indicating that our study addresses genetic counseling and testing in a very young cohort of early-identified deaf and hard-of-hearing children. Third, our study does not address parents who do not choose genetic testing for their child. Several studies have shown that some parents are not interested in genetic testing for their deaf children [Kaimal et al., 2007; Steinberg et al., 2007b] and further research is needed to understand the factors

that influence parental decisions regarding genetic evaluation and testing for the deaf or hard-of-hearing child. In light of differences in parental preferences for genetic testing for a trait with scientific and social complexities, it would be difficult to justify a mandatory program of genetic testing for deafness or a program without appropriate pre- and post-test genetic counseling.

In summary, this is a prospective, longitudinal study to determine the impact of genetic counseling and testing on parents of early-identified deaf and hard-of-hearing children. Parents do not perceive genetic testing of their deaf or hard-of-hearing infants/toddlers as harmful; they feel that their primary care providers should discuss genetic testing with them; and positive genetic test results with genetic counseling give rise to better understanding and perceived benefit than negative or inconclusive genetic test results. These results may be useful in developing genetic counseling strategies that better facilitate understanding of negative and inconclusive test results and that incorporate anticipatory guidance in pre- and post-test genetic counseling sessions. As a form of anticipatory guidance, parents can be informed during the pre-test genetic counseling session that their reactions to their child's genetic test results will be multi-faceted, and that their feelings may change over time. Specifically, parents can be informed that it is typical to feel that genetic testing can be beneficial to them, but that they will likely experience changes in their perceptions of benefit when their child's test results are disclosed to them. Parents who receive positive results will likely experience increased benefit in several domains, including understanding why their child is deaf, helping their family, helping with treatment decisions, and helping with future family planning. Although those who receive inconclusive or negative results will experience some diminished benefits of testing, on average, even these parents likely will feel some benefit to testing in terms of helping their family, with treatment decisions, and with future family planning. In contrast, parental feelings of perceived harms or stigma of testing are unlikely to change when they learn their child's test result. Since pre-testing concerns about testing are not resolved by the test result, it may be important to explore parental concerns in the pre-test genetic counseling session to identify possible courses of action to ameliorate these concerns that are not dependent upon the test result. Our study also provided compelling evidence that inclusion of pre- and post-test genetic counseling can improve understanding of negative test results. However, because parents who received a conclusive positive test result had better understanding of their results compared to those who received negative or inconclusive results, more research is needed to develop genetic counseling strategies that better facilitate understanding of negative and inconclusive test results.

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Figure 1.
Study protocol flow chart

Figure 2a

Figure 2b

Figure 2c

Figure 2d

Figure 2.

Figure 2a: "The genetic test result in this study could help me (helped me) understand why my child has hearing loss." Results of mixed model analysis: CxGROUP*TIME ($p < 0.0001$), CxGROUP ($p < 0.0001$), TIME ($p < 0.0001$). *Post-hoc tests demonstrate that CxPOS group is significantly different from CxINC and CxNEG groups at 1-Mth and 6-Mth post-test results.

Figure 2b: "The genetic test results from this study could help (helped) my family." Results of mixed model analysis: CxGROUP*TIME ($p = 0.005$), CxGROUP ($p = 0.01$), (TIME) $p = 0.02$. * Post-hoc tests demonstrate that CxPOS group is significantly different from CxNEG group at 1-Mth post-test results; and CxPOS group is significantly different from CxINC and CxNEG groups at 6-Mth post-test results.

Figure 2c: "The genetic test results from this study could help (helped) me make treatment decisions for my child." Results of mixed model analysis: CxGROUP*TIME ($p = 0.002$), CxGROUP ($p = 0.003$), TIME ($p = 0.88$). *Post-hoc tests demonstrate that CxPOS group is significantly different from CxNEG group at 1-Mth post-test results; and CxPOS group is significantly different from CxINC and CxNEG groups at 6-Mth post-test results.

Figure 2d: "The genetic test results from this study could help (helped) me with future family planning decisions." Results of mixed model analysis: CxGROUP*TIME ($p = 0.0007$), CxGROUP ($p = 0.14$), TIME ($p = 0.17$). *Post-hoc tests demonstrate that CxPOS group is significantly different from CxNEG group at 6-Mth post-test results.

Figure 3.

Figure 3a: "I am concerned that genetic testing will have an effect on our health insurance." Results of mixed model analysis: CxGROUP*TIME ($p = 0.26$), CxGROUP ($p = 0.008$), TIME ($p = 0.83$).

Figure 3b: "I am concerned about the effect genetic testing might have on the family." Results of mixed model analysis: CxGROUP*TIME ($p = 0.21$), CxGROUP ($p = 0.63$), TIME ($p = 0.38$).

Figure 3c: "I am concerned about emotionally handling genetic information about my child." Results of mixed model analysis: CxGROUP*TIME ($p = 0.13$), CxGROUP ($p = 0.65$), TIME ($p = 0.70$).

Figure 3d: "Being offered a genetic test implies that there is something "wrong" with hearing loss." Results of mixed model analysis: CxGROUP*TIME ($p = 0.52$), CxGROUP ($p = 0.04$), TIME ($p = 0.86$).

Figure 3e: "I am concerned that the genetic test results from this study would somehow harm my child." Results of mixed model analysis: CxGROUP*TIME ($p = 0.054$), CxGROUP ($p = 0.97$), TIME ($p = 0.78$).

Figure 4. “How important is it to know the cause of your baby’s hearing loss.” Results of mixed model analysis: CxGROUP*TIME ($p = 0.15$), CxGROUP ($p = 0.25$), TIME ($p = 0.25$).

Figure 5. Results of mixed model analysis: CxGROUP*TIME ($p = 0.36$), CxGROUP ($p = 0.41$), TIME ($p = 0.09$).

Figure 6.

“In your opinion, how likely is it that your baby has Connexin 26-related hearing loss?”
 Results of mixed model analysis: CxGROUP*TIME ($p < 0.0001$), CxGROUP ($p < 0.0001$), TIME ($p = 0.37$). *Post-hoc tests demonstrate that CxPOS group is significantly different from CxINC and CxNEG groups at 1-Mth post-test results and at 6-Mth post-test results.

Figure 7.
 “My chance of having another baby with hearing loss is...”

Figure 8.

“How interested are you in having Connexin 26/Connexin 30 genetic testing in a future pregnancy?” Results of mixed model analysis: CxGROUP*TIME ($p = 0.56$), CxGROUP ($p < 0.0001$), TIME ($p = 0.81$). *Post-hoc tests demonstrate that CxPOS group is significantly different from CxNEG group at 6-Mth post-test results.

Figure 9.
“Which of the following persons do you think should inform parents of the option of this genetic test?”

Table 1

Demographic description of sample

	Whole Sample	Mothers	Fathers
N	130	85	45
# families	91	--	--
# couples/# individuals	39/52	--	--
Average age (SD)	32.2y (6.4y)	31.3y (6.2y)	33.9y (6.3y)
Median education	2-year college degree	2-year college degree	2–4 year college degree
Median income	\$35,001 \$50,000	--	--
Ethnic distribution			
Non-Hispanic Caucasian	51 (39.2%)	35 (41.2%)	16 (35.5%)
Hispanic	56 (43.1%)	38 (44.7%)	18 (40.0%)
Asian	18 (13.8%)	9 (10.6%)	9 (20.0%)
African-American	3 (2.3%)	1 (1.2%)	2 (4.4%)
Native Hawaiian/Pacific islander	2 (1.5%)	2 (2.4%)	0
# parents with child with <i>GJB2/GJB6</i> positive results *	34 (26.2%)	22 (25.9%)	12 (26.7%)
# parents with child with <i>GJB2/GJB6</i> inconclusive results	15 (11.5%)	8 (9.4%)	7 (15.6%)
# parents with child with <i>GJB2/GJB6</i> negative results	81 (62.3%)	55 (64.7%)	26 (57.8%)

* Among the 91 families, 23 have child with *GJB2/GJB6* positive result (25.3%), 10 have child with inconclusive result (11%), and 58 have child with negative result (63.7%)