Ethical Issues in the Prenatal Genetic Diagnosis of Hearing Loss: Management of Expanded Carrier Screening Results

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ABSTRACT

Introduction:
Expanded carrier screening (ECS), a non-invasive prenatal testing method to assess an unborn child's risk of inheriting pathogenic genetic variants, may enable prognostication of hearing loss (HL) progression, early educational intervention, and minimization of unnecessary testing. We sought to study the feasibility, efficacy, and ethical implications of ECS and prenatal genetic consultation for HL.

Methods:
We identified a cohort of parent-infant dyads with positive ECS results for mutations in HL genes, and were seeking prenatal consultation for genetic diagnosis of HL at Boston Children's Hospital. Their medical records were retrospectively reviewed to yield cohesive care narratives including results of ECS, results of genetic diagnostic testing, newborn hearing screening, time to HL diagnosis, and other case specifics.

Results:
15 parental couples with positive ECS results for HL genes were referred for consultation with a pediatric otolaryngologist and genetic counselor, and were offered diagnostic genetic testing. ECS demonstrated pathogenic variants in *GJB2* (14) or *USH2A* (2). 4 couples pursued prenatal genetic diagnosis via amniocentesis and 11 couples deferred genetic testing to post-partum via cord blood sequencing or early auditory brainstem response (ABR) testing. 6 babies were found to have biallelic *GJB2* mutations. Of these, 3 of the six had HL diagnosed by age 4 weeks via ABR; one passed has passed initial ABR and is being monitored for disease progression; one parental couple was lost to follow-up; one baby is expected to be delivered in the coming months.

Conclusion:
Carrier screening and confirmatory prenatal genetic testing provided significant lead time for follow-up auditory testing, hearing aid fitting, and enrollment in speech development and family education programs. However, socioeconomic and geographic disparities in access to integrated tertiary care may limit the feasibility of prenatal genetic screening for HL. The Deaf community has expressed concern that prenatal genetic screening may pathologize deafness. By assessing the management of such prenatal genetic results, we might develop evidence-based approaches to maximize benefits and minimize harms for prospective families seeking carrier screening for HL.

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INTRODUCTION

Congenital hearing loss has an estimated incidence of 1.86 per 1000 newborns in the US[1], with over 50% of these cases attributable to genetic causes.[2,3]

Genetic testing is the standard of care in diagnosing pediatric sensorineural hearing loss (SNHL), currently undertaken after SNHL is verified. However, many commercially available carrier screening panels include common SNHL genes, such as *GJB2, GJB6, USH2A,* and *SLC26A4,*[4,5] introducing the potential for earlier genetic work-up.

Prompt genetic diagnosis of hereditary SNHL may enable earlier otolaryngologic and audiologic intervention, genetic/reproductive counseling, follow-up for extra-auditory features, and potential entry into clinical trials.

METHODS

Parental couples were referred to Boston Children's Hospital (BCH) for positive biparental carrier screening results obtained from a direct-to-consumer (DTC) carrier screening panel ordered by their obstetric care provider. Per parental preference, targeted single-gene Sanger sequencing was performed prenatally on amniotic fluid sample or postnatally on cord blood or salivary sample.

At birth, all babies received standard newborn hearing screening. Auditory brainstem response (ABR) testing was obtained for babies who had been found to have biallelic SNHL gene variants or whose parents had preferred to defer diagnostic genetic sequencing. Babies found to have a hearing loss were managed by audiology and otolaryngology following standard clinical management guidelines.

A retrospective chart review was conducted to collect detailed parental and fetal case narratives, newborn hearing screening time to hearing loss diagnosis, and SNHL genetic testing results.

Table 1. Demographics of a cohort of parental-fetal triads with positive carrier screening results for SNHL genes seen in consultation at BCH.

Total triads	15
Fetal Gestational Age (at consultation) – weeks	
Mean (SD)	19.7 (5.8)
Range	9.7, 34
Gestational Parent Age (at consultation) - years	
Mean (SD)	33.1 (2.6)
Range	28, 38
Gestational Parent Gravidity	
Range	1, 3
Gestational Parent Parity	
Range	0, 1
Gestational Parent Race	
Asian	6 (40.0%)
White	9 (60.0%)
Gestational Parent Education	
High school	1 (6.7%)
College degree	4 (26.7%)
Graduate degree	6 (40.0%)
Declined to identify	4 (26.7%)
Non-Gestational Parent Race	
Asian	6 (40.0%)
White	9 (60.0%)
Non-Gestational Parent Education	
High school	1 (6.7%)
College degree	5 (33.3%)
Graduate degree	5 (33.3%)
Declined to identify	4 (26.7%)
Interpreter Presence	
No interpreter needed (English-speaking)	13 (86.7%)
Interpreter needed	2 (13.3%)

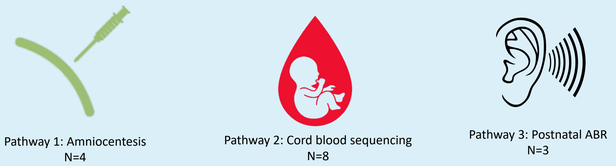
RESULTS

15 parent-infant dyads were referred to BCH on the basis of positive carrier screening results in either *GJB2* (14) or *USH2A* (2) loci. The mean maternal age at the time of consultation was 33.1 (±2.6) years. Gestational age at the time of consultation varied from 9 weeks and 5 days to 34 weeks, with a mean of 19.7 (±5.8) weeks. Parental demographics were 40.0% Asian and 60.0% White, and the majority had attained at least a college education (Table 1).

After discussion with a pediatric otolaryngologist and genetic counselor, parents chose one of three management pathways (Table 2):

1. Prenatal genetic diagnosis via amniocentesis, followed by ABR as needed (n=4)
2. Postnatal genetic diagnosis via cord blood sequencing, followed by ABR (n=8)
3. Postnatal ABR, followed by genetic sequencing per clinical indication (n=3)

6 infants were found to have inherited biallelic variants in *GJB2.* Of these, 4 babies were diagnosed with a HL by 4 weeks and were given standard otolaryngologic and audiologic management. One passed initial ABR and is being monitored for onset of symptoms; one was lost to follow-up; one is anticipated to be delivered.



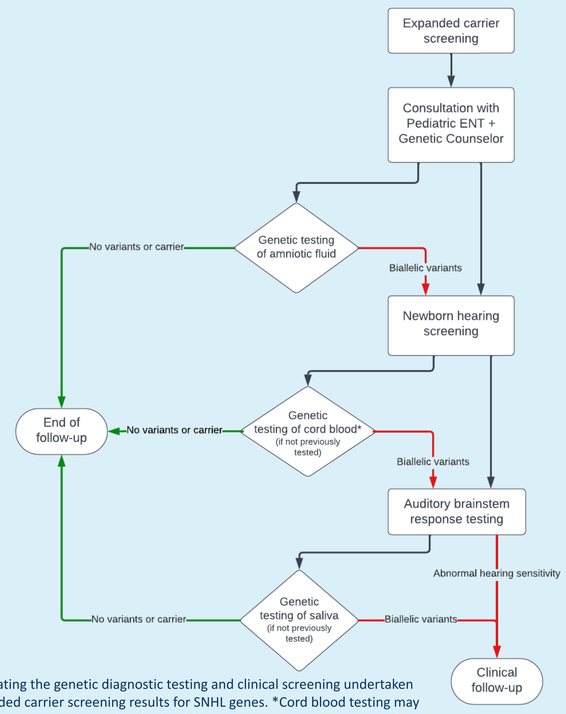


Figure 1. Flowchart illustrating the genetic diagnostic testing and clinical screening undertaken to manage positive expanded carrier screening results for SNHL genes. *Cord blood testing may be repeated to confirm previous genetic results obtained from amniocentesis; repeat genetic testing was obtained per the clinical judgment of the patient's prenatal genetic counselor.

SAMPLE CASE NARRATIVE

Parents M8 and P8 had received results via Myriad Foresight® carrier screening that they each carried the V37I variant in *GJB2*. They chose to undergo cord blood sequencing in their infant at the time of birth.
Baby B8 passed their newborn hearing screen and would not have normally been referred for ABR. However, cord blood sequencing demonstrated B8 was homozygous for the *GJB2* V37I variant. They underwent ABR at 3 weeks, which confirmed bilateral mild high-frequency hearing loss.

DISCUSSION

Ethical Implications of Carrier Screening for SNHL Genes

- Inequitable access to carrier screening among Black and Latino populations despite personal interest[6]
- Exacerbation of health inequities attributed to limited health literacy, insurance status, inadequate access to specialty services, and geographic barriers to care[7,8]
- Direct-to-consumer marketing of carrier screening panels may bypass pretest counseling
- Risk of pathologizing deafness and undermining Deaf cultural identity[9,10]
- Potential additional risk posed by amniocentesis for a non-life-threatening disease
- Potential impact on reproductive decision-making[11] in the context of restricted access to abortion services

All three management pathways enabled early intervention to meet Early Hearing Detection Intervention's national "1-3-6 benchmark" (screening by 1 month, diagnosis by 3 months, intervention by 6 months).[11] Yet, personal motivations, resources needed, and risks incurred differed significantly among pathways.

Early intervention for pediatric SNHL is associated with better linguistic and developmental outcomes.[12,13] Other potential benefits – including reproductive counseling, targeted gene therapies, and family education – remain to be explored in the context of carrier screening for hereditary SNHL.

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