Genetic Counselors are Critical in Providing Comprehensive and Tailored Care for Individuals with Hearing Loss and Their Families

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Introduction

- The allelic and locus heterogeneity of hearing loss (HL) requires the expertise of a multidisciplinary team to provide an accurate diagnosis if these genetic findings are to be correctly applied in clinical care.
- The knowledge and expertise of genetic counselors in molecular genetics, medical genetics, and counseling make them vital players in incorporating genetic knowledge into comprehensive and tailored clinical care for the deaf and hard of hearing community.

Who are genetic counselors?

- Genetic counselors (GCs) are healthcare professionals who work in a variety of settings including laboratories, hospitals and public health clinics.
- GCs help patients and families understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease through tasks such as:

Interpreting Medical and Family Histories	Educating about Health and Genetics	Identifying Appropriate Genetic Testing Options
Explaining Genetic Test Results to Patients and Families	Providing Emotional Support and Counseling	

Our data highlight cases in which the specialized training and knowledge of genetic counselors was essential in the comprehensive and tailored care for individuals who are deaf or hard of hearing and their families.

Methods

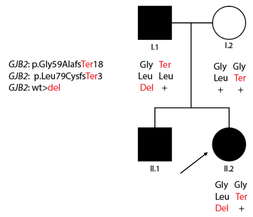
- A targeted-gene panel called OtoSCOPE® was used to screen 152 hearing loss-associated genes and multiple common syndromic forms of HL.
  - Sequencing: Agilent SureSelect Design, Illumina HiSeq or NextSeq sequencing and a custom bioinformatics pipeline.
  - Single nucleotide variant (SNV) filtering: QD≥5; Qvar≥50; MAF<2%; non-synonymous, indels and splice-site variants.
  - Copy number variations (CNVs): identified by normalizing read-depth data by sample batch and comparing average read-depth followed by manual curation.
  - Segregation analysis: performed using Sanger sequencing.
- Genetic results were discussed at a multidisciplinary meeting with physicians, geneticists, bioinformaticians, and genetic counselors in the context of the patient's clinical data and history.

Cases

Case 1

Clinical Information:

- 2 year old Asian female
- Congenital bilateral sensorineural HL (SNHL)
- Family history: brother and father with HL



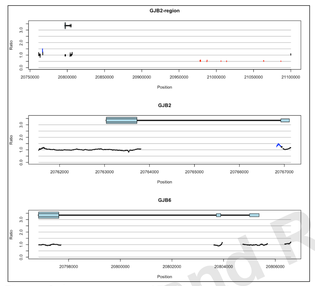


Figure 1: heterozygous 179 kb deletion upstream of DFNB1 identified in II.2 and I.1.

Table 1: Causative SNV identified

Gene	Nuc. Change	AA Change	Zygosity	MAF (%) Max GnomAD	MAF (%) Max Pop	GERP	PhyloP	PP2	SIFT	Mut	LRT	CADD	DVD
GJB2	c.235delC	p.Leu79CysfsTer3	het	0.65%	EA	ND	ND	ND	ND	ND	ND	32	Path
GJB2	c.176_191del	p.Gly59AlafsTer18	het	0.016%	EA	ND	ND	ND	ND	ND	ND	35	Path

ACMG Criteria: Variant 1 - Pathogenic (PVS1, PM3, PS3, BS1); Variant 2 –Pathogenic (PVS1, PM2, PM3) NM_004004.5

Abbreviations: AA: amino acid, MAF: minor allele frequency, EA: East Asian, het: heterozygous, hemi: hemizygous, GERP: GERP++ RS, PP2: Polyphen2 HDIV, Mut: Mutation Taster, DVD: Deafness Variation Database, ND: no data, C: conserved, D: damaging, Path: pathogenic

Diagnosis:
DFNB1 non-syndromic HL due to a CNV and two pathogenic variants

GC impacts care:

- Counseling on unanticipated pseudodominant inheritance
- Calculation of tailored recurrence risk

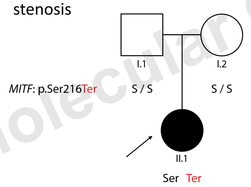
	Ind. I.1	Ind. I.2	Reproductive risk: child with DFNB1	Ind. II.2	Ind II.2 Partner	Reproductive risk: child with DFNB1
Chance carrier of pathogenic *GJB2* variant	100%	100%	50% or 1/2	100%	1/40*	1.25% or 1/80
Chance of passing on pathogenic *GJB2* variant	100%	50%		100%	50%	

*General population carrier frequency for pathogenic variant in *GJB2*. Risk can be further refined with ancestry information for the partner.

Case 3

Clinical Information:

- 3 year old Caucasian female
- Congenital profound SNHL
- Family history: neg
- Bilateral external auditory canal stenosis



Diagnosis:
Waardenburg syndrome type 2A due to *de novo* heterozygous pathogenic variant in *MITF*

GC impacts care:

- Tailored reproductive counseling
  - Risk of second child carrying the variant is not 0% given the possibility of germline mosaicism, estimated at 1-5%
  - Identification of *de novo* variant for this couple reduces reproductive risk related to this pathogenic variant from 50% to <5%

Table 3: Causative SNV identified

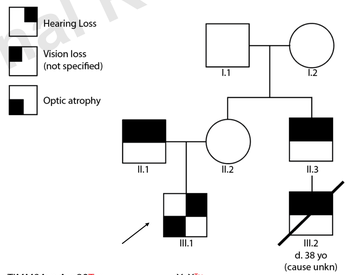
Gene	Nuc. Change	AA Change	Zygosity	MAF (%) Max GnomAD	MAF (%) Max Pop	GERP	PhyloP	PP2	SIFT	Mutation Taster	LRT	CADD	DVD
MITF	c.647C>G	p.Ser216Ter	het	ND	ND	C	NC	ND	ND	D	D	37	ND

ACMG Criteria: Variant 1 - Pathogenic (PVS1, PS2, PM2, PP3) NM_198159.2

Case 2

Clinical Information:

- 38 year old French male
- Profound SNHL diagnosed at 18 months
- Medical history: glaucoma, optic atrophy
- Family history: father and maternal relatives *reported* to have Usher syndrome



GC impacts care pre-genetic testing:

- Interprets medical and family history
  - Optic atrophy is *not* characteristic of Usher syndrome
  - Pedigree suggestive of multiple genetic causes of HL
- Builds differential diagnosis and selects appropriate genetic testing
  - Optic Atrophy 1
  - Deafness-Dystonia-Optic Neuronopathy syndrome (DDON)
  - Charcot-Marie-Tooth Type 5
- Provides anticipatory emotional support (DDON causes early onset dementia, psychiatric disease, and dystonia)

Diagnosis:
X-linked Deafness-Dystonia-Optic Neuronopathy syndrome (DDON; Mohr-Tranebjaerg syndrome) due to pathogenic variant in *TIMM8A*

Table 3: Causative SNV identified

Gene	Nuc. Change	AA Change	Zygosity	MAF (%) Max GnomAD	MAF (%) Max Pop	GERP	PhyloP	PP2	SIFT	Mut.	LRT	CADD	DVD
TIMM8A	c.238C>T	p.Arg80Ter	hemi	ND	ND	C	C	ND	ND	D	D	39	Path

ACMG Criteria: Pathogenic (PVS1, PM2, PP3) NM_004085.3

GC impacts care post-genetic testing:

- Provides psychosocial counseling and identifies support groups
- Arranges follow-up care with psychiatry and neurology

Case 4

Clinical Information:

- 12 year old Palestinian male
- Moderately-severe upsloping to moderate mixed HL diagnosed at 2 years old
- Family history: distant cousins w/ HL
- Bilateral incomplete partition II of the cochlea

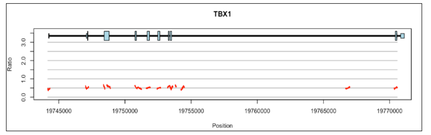


Figure 3: Heterozygous deletion of *TBX1*

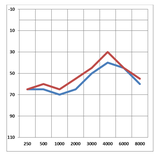
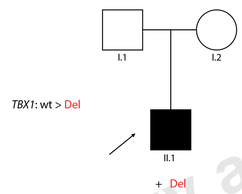


Figure 2: Audiogram of proband.

Diagnosis:
22q11.2 deletion syndrome due to a heterozygous deletion of *TBX1*



GC impacts care:

- Educates on clinical features and variability of phenotype
- Arranges referrals to cardiology, otolaryngology, endocrinology, and nephrology based on guidelines (Bassett et al, 2011)
- Provides reproductive counseling: more than 90% of cases of 22q11.2 are *de novo*
- Coordinates parental testing

Conclusions

Genetic counselors are critical members of the healthcare team in providing comprehensive and tailored care for individuals with hearing loss and their families by:

- Performing accurate interpretation of medical and family history
- Identifying syndromic presentation of HL and selecting appropriate genetic test
- Providing psychosocial counseling and identifying support groups
- Counseling on complicated inheritance patterns including: pseudodominance and *de novo* variants
- Calculating tailored reproductive risk assessments
- Coordinating appropriate follow-up care and referrals for syndromic diagnoses

Genetic counselors are at the *crossroads* of Precision Medicine.

GCs have unique training and knowledge crucial to the interpretation, translation, and implementation of genetic results and follow-up care for deaf and hard-of-hearing persons.

To learn more about genetic counselors and how they can benefit your research or clinical practices, please visit:

www.nsgc.org
www.aboutgeneticcounselors.org

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Acknowledgements

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