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Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	7/17/2005
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	

Hearing Loss, Nonsyndromic Panel (GJB2) Sequencing, (GJB6) 2 Deletions and Mitochondrial DNA 2 Mutations

ARUP test code 2001992

HL Panel Specimen	Whole Blood
GJB2 Sequencing	2 mutations *
Mitochondrial DNA, 2 Mutations	0 mutations
Connexin 30 GJB6 Deletions	0 mutations
Hearing Loss Panel Interpretation	Positive *

TEST PERFORMED - 2001992
TEST DESCRIPTION - Hearing Loss, Nonsyndromic Panel (GJB2) Sequencing, (GJB6) 2 Deletions and Mitochondrial DNA 2 Mutations
INDICATION FOR TEST - Predictive Testing

RESULT
Two apparent copies of a pathogenic variant were detected in the GJB2 gene.

DNA VARIANT(S)
Classification: Pathogenic
Gene: GJB2
Nucleic Acid Change: c.35delG; Homozygous
Amino Acid Alteration: p.Gly12fs

INTERPRETATION
Two apparent copies of a pathogenic variant, c.35delG; p.Gly12fs, were identified in the GJB2 gene by sequencing. This individual is predicted to have autosomal recessive nonsyndromic hearing loss.

Neither of the targeted GJB6 (Connexin 30) deletions, nor the two targeted pathogenic mitochondrial DNA variants, were detected.

Evidence for variant classification: The GJB2 c.35delG; p.Gly12fs variant (rs80338939) is the most common pathogenic GJB2 variant found among individuals with European ancestry (Estivill 1998, Gasparini 2000). It has been described in the homozygous and compound heterozygous state in individuals

H=High, L=Low, *=Abnormal, C=Critical

affected with autosomal recessive nonsyndromic hearing loss with severity ranging from mild to profound (Estivill 1998, Gasparini 2000, Putcha 2007). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 17004) and is observed in the general population at an overall frequency of 0.6% (1721/275002 alleles, 10 homozygotes) in the Genome Aggregation Database. This variant causes a frameshift by deleting a single nucleotide, and in vitro functional studies demonstrate a loss of connexin 26 function (DAndrea 2002). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Family members should be offered targeted testing for the identified pathogenic GJB2 variant (Familial Mutation, Targeted Sequencing; ARUP test code 2001961). This individual's reproductive partner should be offered GJB2 and GBJ6 screening.

COMMENTS
Reference Sequences: GenBank # NM_004004.5 (GJB2), NC_012920 (MT-RNR1 and MT-TS1)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Benign variants are not included in this report but are available upon request.

REFERENCES
DAndrea P et al. Hearing loss: frequency and functional studies of the most common connexin26 alleles. Biochem Biophys Res Commun. 2002 Aug 23;296(3):685-91.

Estivill X et al. Connexin-26 mutations in sporadic and inherited sensorineural deafness. Lancet. 1998 Feb 7;351(9100):394-8.

Gasparini P et al. High carrier frequency of the 35delG deafness mutation in European populations. Genetic Analysis Consortium of GJB2 35delG. Eur J Hum Genet. 2000 Jan;8(1):19-23.

Putcha G et al. A multicenter study of the frequency and distribution of GJB2 and GJB6 mutations in a large North American cohort. Genet Med. 2007 Jul;9(7):413-26.

This result has been reviewed and approved by Elaine Lyon, Ph.D.

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BACKGROUND INFORMATION: Hearing Loss, Nonsyndromic Panel (GJB2) Sequencing, (GJB6) 2 Deletions and Mitochondrial DNA 2 Mutations

CHARACTERISTICS: Nonsyndromic hearing loss (NSHL).
INCIDENCE: Approximately 1 in 2600 for NSHL; 50 percent due to GJB2 mutations, 2-4 percent associated with GJB6 deletions, and 1-2 percent related to mitochondrial mutations.
INHERITANCE: Dependent on gene. GJB2: Autosomal recessive; rarely dominant. GJB6: Autosomal recessive; resulting from either two GJB6 deletions or one GJB6 deletion and one GJB2 mutation on the opposite chromosome. Mitochondrial DNA: Dominant maternal inheritance.
PENETRANCE: Complete for GJB6; variable for GJB2 and mitochondrial DNA.
CAUSE: Deleterious GJB2, GJB6, and mitochondrial DNA mutations.
MUTATIONS TESTED: GJB2: Coding region, intron-exon boundary and 5'-UTR mutations. GJB6: 309kb del(GJB6-D13S1830), previously reported as 342kb, and 232kb del(GJB6-D13S1854). Mitochondrial: m.1555A>G and m.7445A>G.
CLINICAL SENSITIVITY: 50-55 percent for Caucasians with NSHL; unknown in other ethnicities.
METHODOLOGY FOR GJB2 SEQUENCING: Bidirectional sequencing of the entire coding region, intron-exon boundaries, and 5'-UTR of the GJB2 gene.
METHODOLOGY FOR GJB6 2 DELETIONS: Multiplex PCR using deletion-specific primers followed by capillary gel electrophoresis.
METHODOLOGY FOR MITOCHONDRIAL DNA 2 MUTATIONS: Targeted bidirectional sequencing of mitochondrial mt-RNR1 m.1555A>G and mt-TS1 m.7445A>G.
ANALYTICAL SENSITIVITY AND SPECIFICITY: Greater than 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. GJB2 regulatory region mutations, deep intronic mutations and large deletions or duplications will not be detected. GJB6 and mitochondrial DNA mutations, aside from those targeted will not be detected. The etiology of hearing loss due to other genetic or environmental causes will not be determined.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
HL Panel Specimen	18-199-112357	7/18/2018 1:40:00 PM	7/18/2018 1:40:54 PM	7/18/2018 3:02:00 PM
GJB2 Sequencing	18-199-112357	7/18/2018 1:40:00 PM	7/18/2018 1:40:54 PM	7/18/2018 3:02:00 PM
Mitochondrial DNA, 2 Mutations	18-199-112357	7/18/2018 1:40:00 PM	7/18/2018 1:40:54 PM	7/18/2018 3:02:00 PM
Connexin 30 GJB6 Deletions	18-199-112357	7/18/2018 1:40:00 PM	7/18/2018 1:40:54 PM	7/18/2018 3:02:00 PM
Hearing Loss Panel Interpretation	18-199-112357	7/18/2018 1:40:00 PM	7/18/2018 1:40:54 PM	7/18/2018 3:02:00 PM

END OF CHART

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