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

Physician: Doctor, Example

Patient: Patient, Example

DOB	8/11/2016
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Expanded Hearing Loss Panel, Sequencing and Deletion/Duplication

ARUP test code 2008803

Expanded Hearing Loss Panel Specimen	Whole Blood

Expanded Hearing Loss Panel Interp

Positive

INDICATION FOR TESTING
Patient with a diagnosis of macrocytic thrombocytopenia.

RESULT
One likely pathogenic variant was detected in the MYH9 gene. Three variants of uncertain significance were detected, one each in the DIAPH1, TRIOBP, and CDH23 genes.

LIKELY PATHOGENIC VARIANT
Gene: MYH9 (NM_002473.5)
Nucleic Acid Change: c.5765+2T>C Heterozygous
Inheritance: Autosomal dominant

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: DIAPH1 (NM_005219.4)
Nucleic Acid Change: c.1269C>G; Heterozygous
Amino Acid Alteration: p.Asp423Glu
Inheritance: Autosomal dominant / Autosomal recessive

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: TRIOBP (NM_001039141.2)
Nucleic Acid Change: c.2434C>G; Heterozygous
Amino Acid Alteration: p.Gln812Glu
Inheritance: Autosomal recessive

VARIANT OF UNCERTAIN SIGNIFICANCE
Gene: CDH23 (NM_022124.5)
Nucleic Acid Change: c.6809G>A; Heterozygous
Amino Acid Alteration: p.Arg2270His
Inheritance: Autosomal recessive / Digenic recessive

INTERPRETATION
One copy of a likely pathogenic variant, c.5765+2T>C was detected in the MYH9 gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic variants in MYH9 are associated with autosomal dominant deafness 17 (MIM: 603622) and autosomal dominant macrothrombocytopenia/granulocyte inclusions with or without nephritis or sensorineural hearing loss (MIM: 155100). This result is consistent with a diagnosis of deafness or macrothrombocytopenia/granulocyte inclusions with or without nephritis or sensorineural hearing loss. Clinical correlation is indicated.

In additional, several variants of uncertain clinical significance were identified. (1) One copy of a variant of

uncertain clinical significance, c.1269C>G; p.Asp423Glu, was detected in the DIAPH1 gene by massively parallel sequencing. Pathogenic variants in DIAPH1 are associated with autosomal dominant deafness 1 (MIM: 124900) and autosomal recessive seizures, cortical blindness, microcephaly syndrome (MIM: 616632). (2) One copy of a variant of uncertain clinical significance, c.2434C>G; p.Gln812Glu, was detected in the TRIOBP gene by massively parallel sequencing. Pathogenic variants in TRIOBP are associated with autosomal recessive deafness-28 (MIM: 609823). (3) One copy of a variant of uncertain clinical significance, c.6809G>A; p.Arg2270His, was detected in the CDH23 gene by massively parallel sequencing. Pathogenic variants in CDH23 are associated with autosomal recessive deafness-12 (MIM: 601386) and autosomal recessive and digenic (CDH23/PCDH15) recessive Usher syndrome type ID/F (MIM: 601067).

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing or deletion/duplication analysis. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification:
The MYH9 c.5765+2T>C variant (rs878924546), to our knowledge, is not reported in the medical literature or gene specific databases. This variant is also absent from the Genome Aggregation Database, indicating it is not a common polymorphism. This variant disrupts the canonical splice donor site of intron 40, which is likely to negatively impact gene function. Another variant at this position has been reported in an individual with macrothrombocytopenia and deafness and results in usage of a cryptic splice site and a frameshift in the final exon (Saposnik 2014). Other truncating variants in the final exon have been described in individuals with MYH9-related disorders and are considered pathogenic (Pecci 2008, Saposnik 2014). Based on available information, this variant is considered to be likely pathogenic.

The DIAPH1 c.1269C>G, p.Asp423Glu variant (rs367981585), to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 475696). This variant is found in the African/African-American population with an allele frequency of 0.05% (12/24,196 alleles) in the Genome Aggregation Database. The aspartic acid at codon 423 is moderately conserved, and computational analyses are uncertain whether this variant is neutral or deleterious (REVEL: 0.669). Due to limited information, the clinical significance of the p.Asp423Glu variant is uncertain at this time.

The TRIOBP c.2434C>G; p.Gln812Glu variant (rs760563869), to our knowledge, is not reported in the medical literature or gene specific databases. This variant is found in the Latino/Admixed American population with an allele frequency of 0.028% (10/35,374 alleles) in the Genome Aggregation Database. The glutamine at codon 812 is weakly conserved, but computational analyses predict that this variant is neutral (REVEL: 0.011). Due to limited information, the clinical significance of the p.Gln812Glu variant is uncertain at this time.

The CDH23 c.6809G>A p.Arg2270His variant (rs139409005), to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 178310). This variant is found in the general population with an allele frequency of 0.04% (112/278,652 alleles) in the Genome Aggregation Database. The arginine at codon 2270 is moderately conserved, but multiple mammalian species have a histidine at this position and computational analyses predict that this variant is neutral (REVEL: 0.028). However, given the lack of clinical and functional data, the significance of the p.Arg2270His variant is uncertain at this time.

RECOMMENDATIONS

Genetic consultation is recommended, including a discussion of medical screening and management. At-risk family members, beginning with both parents, should be offered testing for the identified likely pathogenic MYH9 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Surveillance of the literature for new information concerning the uncertain variants is recommended.

COMMENTS
Unless otherwise specified, confirmation by Sanger sequencing was not performed for variants with acceptable quality metrics. Likely benign and benign variants are not reported.
Variants in the following region could not be detected with sufficient confidence in this sample due to technical limitations:
TPRN (NM_001128228.2) exon 1 - chr9:140094633-140094713

REFERENCES
Pecci et al. Position of nonmuscle myosin heavy chain IIA (NMMHC-IIA) mutations predicts the natural history of MYH9-related disease. Hum Mutat. 2008 Mar;29(3):409-17. PMID: 18059020

Saposnik et al. Mutation spectrum and genotype-phenotype correlations in a large French cohort of MYH9-Related Disorders. Mol Genet Genomic Med. 2014 Jul;2(4):297-312. PMID: 25077172

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Expanded Hearing Loss Panel, Sequencing and Deletion/Duplication

CHARACTERISTICS: Hereditary hearing loss can be nonsyndromic (hearing loss with no other associated findings) or syndromic (hearing loss with external ear malformations or abnormalities in other organ systems). Categorized as conductive, sensorineural, or mixed, depending on the etiology of the hearing loss. Onset of symptoms may be prelingual or postlingual, and hearing loss may be progressive or stable. Clinical presentation may vary depending on the genetic and environmental cause(s) of the hearing loss.

EPIDEMIOLOGY: 1 in 500 infants are born with hearing loss; 50 percent are due to a genetic cause.

CAUSE: Pathogenic germline variants in genes associated with hereditary hearing loss.

INHERITANCE: Variable; dependent on the gene(s) involved. May be autosomal recessive, autosomal dominant, or X-linked.

GENES TESTED: ACTG1, ADGRV1, CCDC50, CDH23, CEACAM16, CLDN14, CLRN1, COCH*, COL11A2, CRYM, DIAPH1, DNMT1*, DSPP, ESPN**, ESRRB, EYA4, GIPC3**, GJB2, GJB3, GJB6, GPSM2, GRHL2, GSDME, HARS2, HSD17B4, ILDR1**, KCNQ4, LHFPL5, LOXHD1**, LRTOMT**, MARVELD2, MASP1, MT-RNR1***, MYH14, MYH9, MYO15A, MYO3A, MYO6, MYO7A, OTOA***, OTOF, PCDH15, PDZD7**, PJVK, POU3F4, POU4F3, RDX, SIX1**, SLC26A4, SLC26A5, SMPX, TECTA, TMC1, TMIE, TMPRSS3, TPRN, TRIOBP, USH1C, USH1G, USH2A, WFS1, WHRN

* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.
** - Deletion/duplication detection is not available for this gene.
*** - One or more exons are not covered by sequencing, and deletion/duplication detection is not available for this gene; see limitations section below.

METHODOLOGY: Targeted capture of all coding exons and exon-intron junctions of the targeted genes, followed by

massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and confirm reported variants. A custom tiled comparative genomic hybridization array (aCGH) was used to detect large deletions or duplications in the indicated subset of genes. Human genome build 19 (Hg 19) was used for data analysis. Targeted Sanger sequencing was performed to detect the MT-RNR1 m.1555A>G variant.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this test is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

LIMITATIONS: A negative result does not exclude a heritable form of hearing loss. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants and deep intronic variants will not be identified and breakpoints of large deletions/duplications will not be determined. Single exon deletions/duplications or deletions/duplications less than 1kb may not be detected. Deletions/duplications/insertions of any size may not be detected by massive parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Heteroplasmy present at less than 25 percent may not be detected for the MT-RNR1 m.1555A>G variant. Non-coding transcripts were not analyzed.

The following regions are not sequenced due to technical limitations of the assay:
COCH (NM_001347720) exon(s) 2
DNMT1(NM_001130823) exon(s) 5
OTOA(NM_144672) exon(s) 20,21,22,23,24,25,26,27,28
MT-RNR1: targeted sequencing is performed for m.1555A>G only. Other variants in this gene will not be detected.

Single exon deletions/duplications will not be called for the following exons:
CCDC50(NM_178335) 1,12; CDH23(NM_022124) 28,63; CLRN1(NM_001195794) 3; CLRN1(NM_001256819) 2; CLRN1(NM_052995) 1,4; COL11A2(NM_080680) 62; DIAPH1(NM_001314007) 29; DIAPH1(NM_005219) 18,28; DNMT1(NM_001130823) 1,5,41;HARS2(NM_012208) 1; HSD17B4(NM_000414) 24; HSD17B4(NM_001199291) 1; KCNQ4(NM_004700) 9; MASP1(NM_139125) 1; MYH14(NM_024729) 3,13,17,24,25,30,34;MYH9(NM_002473) 13,23,29,30,39;MYO15A(NM_016239) 25,26,33,49,62;MYO7A(NM_000260) 17,26,29; OTOF(NM_194248) 26; PCDH15(NM_001142769) 13; RDX(NM_001260495) 3; RDX(NM_001260496) 5; RDX(NM_002906) 6,10; SLC26A4(NM_000441) 21; SLC26A5(NM_001321787) 19;SLC26A5(NM_206884) 15; TMC1(NM_138691) 6,24; TMIE(NM_147196) 1; TMPRSS3(NM_024022) 4; TRIOBP(NM_001039141) 14,21;TRIOBP(NM_138632) 8; USH1C(NM_005709) 1; USH1C(NM_153676) 26

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US Food and Drug Administration. This test was performed in a CLIA certified laboratory and is intended for clinical purposes.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Expanded Hearing Loss Panel Specimen	21-061-402284	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Expanded Hearing Loss Panel Interp	21-061-402284	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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