



Non-Syndromic Hearing Loss Panel Plus

REFERRING HEALTHCARE PROFESSIONAL

NAME	HOSPITAL
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PATIENT

NAME	DOB	AGE	GENDER	ORDER ID
		3		

PRIMARY SAMPLE TYPE	SAMPLE COLLECTION DATE	CUSTOMER SAMPLE ID
Blood		

SUMMARY OF RESULTS

TEST RESULTS

The patient is hemizygous for *OTOA* c.1882del, p.(Ala628Profs*16), which is likely pathogenic. The patient is heterozygous for a deletion seq[GRCh37] del(16)(p12.12), chr16:g.21689761_21771946del, likely encompassing the whole *OTOA* gene. This alteration is classified as pathogenic.

PRIMARY VARIANT TABLE: SEQUENCE ALTERATIONS

GENE	TRANSCRIPT	NOMENCLATURE	GENOTYPE	CONSEQUENCE	INHERITANCE	CLASSIFICATION
OTOA	NM_144672.3	c.1882del, p.(Ala628Profs*16)	HEM	frameshift_variant	AR	Likely pathogenic
	ID	ASSEMBLY	POS	REF/ALT		
		GRCh37/hg19	16:21737842	AG/A		
	gnomAD AC/AN	POLYPHEN	SIFT	MUTTASTER	PHENOTYPE	
	1/245944	N/A	N/A	N/A	Deafness	

PRIMARY VARIANT TABLE: COPY NUMBER ABERRATIONS

GENE	EVENT	COPY NUMBER	GENOTYPE	IMPACT	LINKS	CLASSIFICATION
OTOA	DELETION	1	HET	Whole gene	UCSC	Pathogenic
	OMIM	PHENOTYPE			COMMENT	
		Deafness			-	

SEQUENCING PERFORMANCE METRICS

PANEL	GENES	EXONS / REGIONS	BASES	BASES > 20X	MEDIAN COVERAGE	PERCENT > 20X
Non-Syndromic Hearing Loss Panel	101	1760	345913	345274	212	99.82
PANEL	GENES	EXONS / REGIONS	BASES	BASES > 1000X	MEDIAN COVERAGE	PERCENT > 1000X
Mitochondrial genome	37	-	15358	15358	21382	100

TARGET REGION AND GENE LIST

The Blueprint Genetics Non-Syndromic Hearing Loss Panel (version 6, Feb 22, 2020) Plus Analysis includes sequence analysis and copy number variation analysis of the following genes: ACTG1*, ADCY1, ATP2B2, BDP1*, BSND, CABP2, CCDC50, CD164, CDC14A, CDH23, CEACAM16, CIB2, CLDN14, CLIC5, COCH, COL11A2, COL4A6, CRYM, DCDC2, DFNA5, DFNB31, DFNB59, DIABLO, DIAPH1, DIAPH3, DMXL2, DSPP, ELMOD3, EPS8, EPS8L2, ESPN*, ESRRB, EYA4, FAM65B, GIPC3, GJB2, GJB3, GJB6, GPSM2, GRHL2, GRXCR1, GRXCR2, HGF, HOMER2, ILDR1, KARS, KCNQ4, LHFPL5, LMX1A, LOXHD1, LRTOMT, MARVELD2, MET, MIR96, MPZL2, MSRB3, MT-ATP6, MT-ATP8, MT-CO1, MT-CO2, MT-CO3, MT-CYB, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-RNR1, MT-RNR2, MT-TA, MT-TC, MT-TD, MT-TE, MT-TF, MT-TG, MT-TH, MT-TI, MT-TK, MT-TL1, MT-TL2, MT-TM, MT-TN, MT-TP, MT-TQ, MT-TR, MT-TS1, MT-TS2, MT-TT, MT-TV, MT-TW, MT-TY, MYH14, MYH9, MYO15A, MYO3A, MYO6, MYO7A, NARS2, OSBPL2, OTOA*,#, OTOF, OTOG, OTOGL, P2RX2, PCDH15, PDE1C, PNPT1*, POU3F4, POU4F3, PRPS1*, RDX*, S1PR2, SERPINB6, SIX1, SLC17A8, SLC22A4, SLC26A4, SLC26A5, SLITRK6, SMPX, STRC*,#, SYNE4, TBC1D24, TECTA, TJP2, TMC1, TMEM132E, TMIE, TMPRSS3, TNC, TPRN#, TRIOBP, TSPEAR, USH1C, WBP2 and WFS1. The following exons are not included in the panel as they are not covered with sufficient high quality sequence reads: OTOA (NM_144672:22-27) and STRC (NM_153700:1-18). This panel targets protein coding exons, exon-intron boundaries (± 20 bps) and selected non-coding, deep intronic variants (listed in Appendix 5). This panel should be used to detect single nucleotide variants and small insertions and deletions (INDELS) and copy number variations defined as single exon or larger deletions and duplications. This panel should not be used for the detection of repeat expansion disorders. The test does not recognize balanced translocations or complex inversions, and it may not detect low-level mosaicism.

*Some, or all, of the gene is duplicated in the genome. Read more: <https://blueprintgenetics.com/pseudogene/>

#The gene has suboptimal coverage when >90% of the gene's target nucleotides are not covered at >20x with mapping quality score (MQ>20) reads.

The sensitivity to detect variants may be limited in genes marked with an asterisk (*) or number sign (#).

STATEMENT

CLINICAL HISTORY

Patient is a 3-year-old child with bilateral sensorineural hearing loss and developmental delay.

CLINICAL REPORT

Sequence analysis using the Blueprint Genetics (BpG) Non-Syndromic Hearing Loss Panel identified a hemizygous 1 bp deletion *OTOA* c.1882del, p.(Ala628Profs*16).

Del/Dup (CNV) analysis using the Blueprint Genetics (BpG) Non-Syndromic Hearing Loss Panel identified a heterozygous deletion seq[GRCh37] del(16)(p12.12), chr16:g.21689761_21771946del, likely encompassing the whole *OTOA* gene (exons 1 to 28).

This gross deletion is estimated to cover the genomic region 16:21689761-21771946 and is approximately 50 kb in size. However, the exact breakpoints of the deletion cannot be determined using the present method, and therefore its exact size and genomic position are unknown. It should be noted that the 3' part of the *OTOA* gene is in segmentally duplicated region, and the short NGS reads cannot be uniquely mapped at the region of exons 22 to 27, and thus, the exons 22 to 27 region is not included in the sequence analysis.

The patient has a seq[GRCh37] del(16)(p12.12), chr16:g.21689761_21771946del deletion encompassing the *OTOA* gene on one parental copy of the gene and *OTOA* c.1882del, p.(Ala628Profs*16) on the other parental copy.

***OTOA* c.1882del, p.(Ala628Profs*16)**

This variant is present in one heterozygous individual in [gnomAD](#), a large reference population database (n>120,000 exomes and >15,000 genomes) which aims to exclude individuals with severe pediatric disease. The variant deletes one base pair in exon 18 (of total 28 exons) and generates a frameshift, leading to a premature stop codon at position 16 in a new reading frame. It is predicted to lead to loss of normal protein function, either through protein truncation or nonsense-mediated mRNA decay. To the best of our knowledge, this variant has not been described in the medical literature or reported in disease-related variation databases such as [ClinVar](#) or [HGMD](#).

***OTOA* whole gene deletion**

There are approximately 150 gross deletions encompassing the whole *OTOA* gene reported in the ExAC control dataset (n>46,000 exomes). In the gnomAD population database of structural variation (>10,000 genomes), a gross deletion of approximately 248 kb in size encompassing the whole *OTOA* gene (and two other genes, *IGSF6* and *METTL9*, which are not OMIM Morbid genes) has been reported as heterozygous in 19 individuals ([gnomAD SVs v2.1](#), ExAC data available in the gnomAD browser). Gross deletions affecting *OTOA* have also been reported in several samples in the Database of Genomic Variants ([DGV](#)). The genomic sequence flanking *OTOA* has multiple clusters of high-identity segmental duplications, which likely give rise to deletions spanning the *OTOA* gene through the nonallelic homologous recombination (PMID [19888295](#)). The identified deletion is located within the known area of the 16p11.2-p12.2 microdeletion syndrome characterized by developmental delay and facial dysmorphism (OMIM #[613604](#), [ORPHA:261211](#), [Decipher](#)). The Decipher database reports more than ten patients with partially overlapping heterozygous deletions affecting *IGSF6*, *METTL9*, and *OTOA* (approximately 140–206 kb in size; Patient IDs: [276978](#), [300202](#), [267149](#), [4073](#), [291432](#), [359830](#), [360957](#), [367414](#), [349809](#), [283539](#), [276011](#)). In addition, there is one patient reported with bilateral conductive hearing impairment who has a homozygous deletion of approximately 140 kb affecting the *IGSF6*, *METTL9*, and *OTOA* genes (Patient ID [350436](#); chr16:21599687-21739885). This deletion is classified in Decipher as pathogenic.

Several gross deletions affecting the *OTOA* gene have been described in association with hearing loss and one in association with autism spectrum disease in the [HGMD](#) Professional database (version 2020.1). *Shahin et al.* identified a homozygous deletion of

the *OTOA* gene in four deaf siblings in a Palestinian family (PMID [19888295](#)). Their parents and another sibling with heterozygous deletion were unaffected. ArrayCGH analysis revealed that the identified deletion was 500 kb in size and it completely deleted the *OTOA* gene. The carrier frequency of the *OTOA* genomic deletion was 1% in unrelated Palestinian controls (PMID [19888295](#)). Bademci *et al.* identified a large homozygous *OTOA* deletion (89–190 kb in size) in three siblings with nonsyndromic hearing loss (PMID [25062256](#)). Tsai *et al.* have reported a patient with hearing loss having a multi-exon deletion of the *OTOA* gene in *trans* with a missense variant c.1249C>T p.(Leu417Phe) (PMID [23897863](#)). Sloan-Heggen *et al.* (PMID [26969326](#)) have reported *OTOA* whole gene deletion as homozygous in three individuals and as heterozygous together with a second *OTOA* variant in four individuals with autosomal recessive nonsyndromic hearing loss. Shearer *et al.* (PMID [24963352](#)) studied the contribution of CNVs to genetic hearing loss and identified 18 CNVs involving *OTOA*, including 15 deletions, 3 conversions and 3 duplications, making CNVs of *OTOA* the second most commonly identified CNVs after *STRC*. In five cases, the CNV was identified as causative for hearing loss: in two patients whole *OTOA* gene deletion was detected as homozygous, and in three patients as heterozygous together with a second variant in the *OTOA* gene (PMID [24963352](#)). Deletion of the whole *OTOA* gene has also been detected in clinical testing, and the Laboratory for Molecular Medicine (LMM) has identified this deletion in 16 individuals with hearing loss including 2 homozygotes; and the deletion has been submitted to ClinVar as pathogenic (chr16:21689836-21771861 on Assembly GRCh37; variation ID [178863](#)). In addition, a deletion of *OTOA* exons 1 to 21 (chr16:21689790-21747769 on Assembly GRCh37; variation ID [505764](#)) and a deletion of exon 21 in *OTOA* (Variation ID [164814](#)) have each been detected in clinical testing in one individual and submitted to ClinVar as pathogenic or likely pathogenic, respectively. A homozygous deletion affecting *IGSF6*, *METTL9*, and *OTOA* has been identified in clinical testing in one individual (ClinVar variation ID [395849](#)). We have previously identified a heterozygous 163 kb deletion encompassing the whole *OTOA* gene (as well as *IGSF6* and *METTL9*) as compound heterozygous with a second disease-causing *OTOA* variant in two patients with sensorineural hearing loss (BpG, unpublished observations).

OTOA

The *OTOA* (OMIM [*607038](#)) gene encodes otoancorin, which belongs to a group of noncollagenous glycoproteins of the acellular gels of the inner ear. Pathogenic variants in *OTOA* cause autosomal recessive nonsyndromic sensorineural hearing loss and deafness (DFNB22; OMIM [#607039](#)). Sensorineural deafness results from damage to the neural receptors of the inner ear, the nerve pathways to the brain, or the area of the brain that receives sound information. Genomic sequencing of *OTOA* in one Palestinian family with moderate-to-severe prelingual sensorineural hearing loss identified a homozygous variant at a splice donor site: c.1320+2T>C (described as IVS12 in the publication; PMID [11972037](#)). A homozygous missense variant, *OTOA* c.1025A>T p.(Asp342Val) (described as 1067A>T D356V in the publication), was identified in six deaf individuals in a Palestinian family (PMID [16460646](#)), and a homozygous deletion of the *OTOA* gene was identified in four deaf siblings in another Palestinian family (PMID [19888295](#)). ArrayCGH analysis revealed that the identified deletion was 500 kb in size and it completely deleted the *OTOA* gene. The carrier frequency of the *OTOA* genomic deletion was 1% in unrelated Palestinian controls (PMID [19888295](#)). Sommen *et al.* analysed 131 patients with presumed autosomal recessive nonsyndromic hearing loss (PMID [27068579](#)). They found two heterozygous *OTOA* frameshift variants in one patient. In addition, a combination of a heterozygous deletion of *OTOA* and a frameshift variant was detected in one patient. Shearer *et al.* identified whole *OTOA* gene deletion as homozygous in two individuals and as heterozygous in six individuals (3/6 individuals had a second variant in the *OTOA* gene) (PMID [24963352](#)).

Deafness is the most frequent form of sensorial deficit with 1:1,000 to 1:700 children being born with profound or severe hearing loss. In developed countries, 60–80% of cases of early-onset hearing loss are of genetic origin. In 85% of cases, the deafness is transmitted as an autosomal recessive trait ([ORPHA 87884](#)). About half of all severe-to-profound autosomal recessive nonsyndromic hearing loss results from pathogenic variants in the *GJB2* gene (also known as connexin 26; OMIM [*121011](#)). Pathogenic variants in *OTOA* are a rare cause of hearing loss. There are currently 30 variants in *OTOA* annotated as disease-causing (DM) in association with hearing loss in the HGMD Professional variant database (version 2020.1), of which 40% are missense variants and 33% are truncating variants (nonsense, frameshift, variants affecting splicing), and 27% are gross deletions. In the ClinVar database, there are 13 pathogenic or likely pathogenic *OTOA* variants that have been identified in clinical testing.

Mutation nomenclature is based on GenBank accession (*OTOA*) and NM_144672.3 (*OTOA*) with nucleotide one being the first nucleotide of the translation initiation codon ATG.

CONCLUSION

We classify the identified gross deletion seq[GRCh37] del(16)(p12.12), chr16:g.21689761_21771946del, likely encompassing the whole *OTOA* gene as pathogenic, considering the current literature and the well-established role of whole *OTOA* gene deletion as a disease-causing variant. *OTOA* c.1882del, p.(Ala628Profs*16) is classified as likely pathogenic, based on the established association between the gene and the patient's phenotype, the variant's rarity in control populations, and variant type: frameshift.

Hearing loss caused by *OTOA* variants is inherited in an autosomal recessive manner. The patient has a deletion of *OTOA* on one parental copy of the gene and *OTOA* c.1882del, p.(Ala628Profs*16) on the other parental copy, which is consistent with autosomal recessive inheritance. If the patient's parents are each found to be heterozygous carriers of one of these variants, then each of the patient's siblings would have a 25% chance of being compound heterozygous for these variants and thus affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being an unaffected non-carrier. Genetic counseling and family member testing are recommended.

STEP	DATE
Order date	
Sample received	
Sample in analysis	
Reported	

On November 1, 2020 the statement has been prepared by our geneticists and physicians, who have together evaluated the sequencing results:



Laura Sarantaus, PhD, CLG
Geneticist



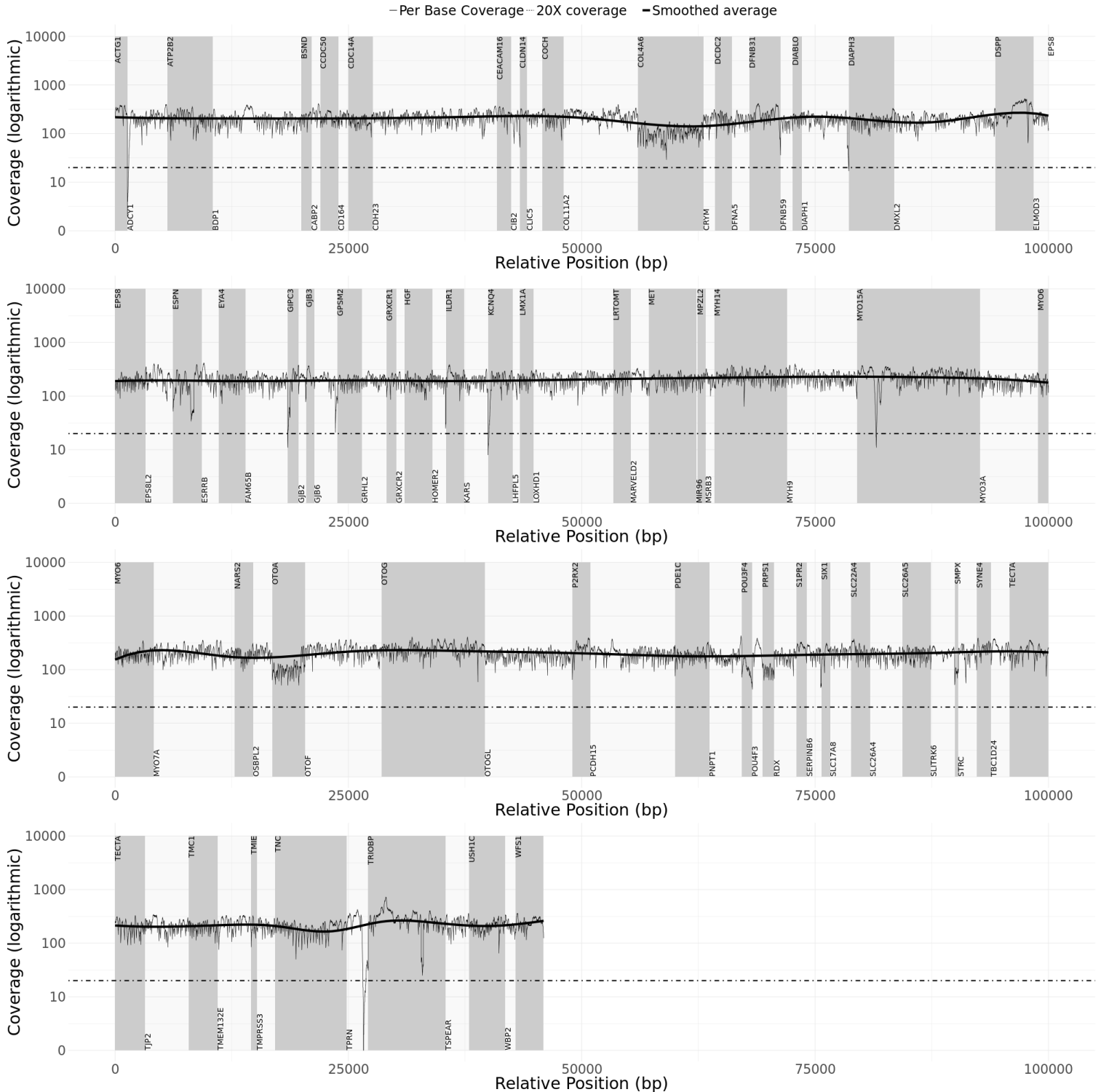
Juha Koskenvuo, MD, PhD
Lab Director, Chief Medical Officer



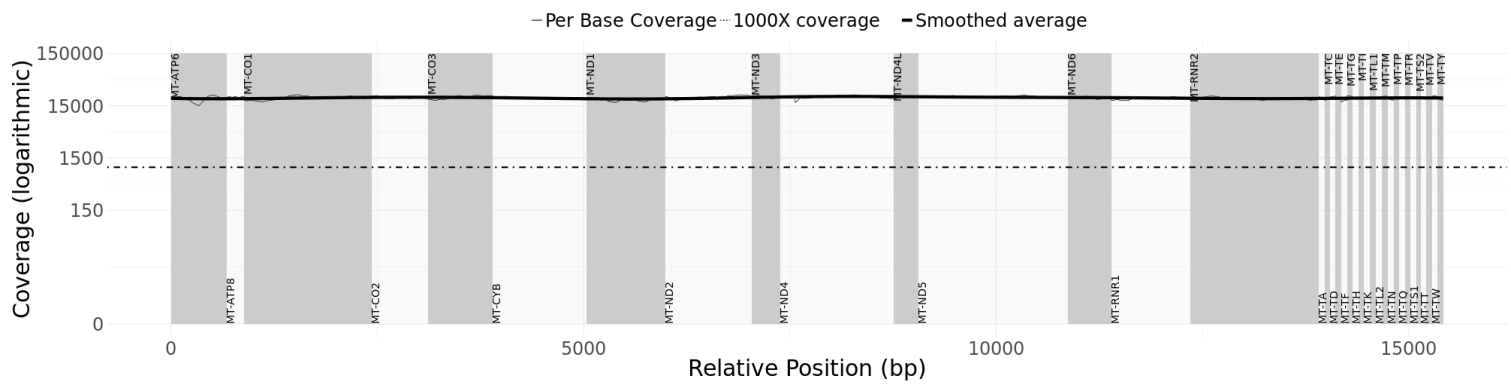
Hatice Duzkale, MD, MPH, Ph.D., FACMG, CGMB

Senior Geneticist

Readability of the coverage plot may be hindered by faxing. A high quality coverage plot can be found with the full report on nucleus.blueprintgenetics.com.



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APPENDIX 5: SUMMARY OF THE TEST

PLUS ANALYSIS

Laboratory process: When required, the total genomic DNA was extracted from the biological sample using bead-based method. DNA quality and quantity were assessed using electrophoretic methods. After assessment of DNA quality, qualified genomic DNA sample was randomly fragmented using non-contact, isothermal sonochemistry processing. Sequencing library was prepared by ligating sequencing adapters to both ends of DNA fragments. Sequencing libraries were size-selected with bead-based method to ensure optimal template size and amplified by polymerase chain reaction (PCR). Regions of interest (exons and intronic targets) were targeted using hybridization-based target capture method. The quality of the completed sequencing library was controlled by ensuring the correct template size and quantity and to eliminate the presence of leftover primers and adapter-adapter dimers. Ready sequencing libraries that passed the quality control were sequenced using the Illumina's sequencing-by-synthesis method using paired-end sequencing (150 by 150 bases). Primary data analysis converting images into base calls and associated quality scores was carried out by the sequencing instrument using Illumina's proprietary software, generating CBCL files as the final output.

Bioinformatics and quality control: Base called raw sequencing data was transformed into FASTQ format using Illumina's software (bcl2fastq). Sequence reads of each sample were mapped to the human reference genome (GRCh37/hg19). Burrows-Wheeler Aligner (BWA-MEM) software was used for read alignment. Duplicate read marking, local realignment around indels, base quality score recalibration and variant calling were performed using GATK algorithms (Sentieon) for nDNA. Variant data for was annotated using a collection of tools (VcfAnno and VEP) with a variety of public variant databases including but not limited to gnomAD, ClinVar and HGMD. The median sequencing depth and coverage across the target regions for the tested sample were calculated based on MQ0 aligned reads. The sequencing run included in-process reference sample(s) for quality control, which passed our thresholds for sensitivity and specificity. The patient's sample was subjected to thorough quality control measures including assessments for contamination and sample mix-up. Copy number variations (CNVs), defined as single exon or larger deletions or duplications (Del/Dups), were detected from the sequence analysis data using a proprietary bioinformatics pipeline. The difference between observed and expected sequencing depth at the targeted genomic regions was calculated and regions were divided into segments with variable DNA copy number. The expected sequencing depth was obtained by using other samples processed in the same sequence analysis as a guiding reference. The sequence data was adjusted to account for the effects of varying guanine and cytosine content.

Interpretation: The clinical interpretation team assessed the pathogenicity of the identified variants by evaluating the information in the patient requisition, reviewing the relevant scientific literature and manually inspecting the sequencing data if needed. All available evidence of the identified variants was compared to classification criteria. Reporting was carried out using HGNC-approved gene nomenclature and mutation nomenclature following the HGVS guidelines. Likely benign and benign variants were not reported.

Variant classification: Our variant classification follows the Blueprint Genetics [Blueprint Genetics Variant Classification Schemes](#) modified from the [ACMG guideline 2015](#). Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report.

Databases: The pathogenicity potential of the identified variants were assessed by considering the predicted consequence of the change, the degree of evolutionary conservation as well as the number of reference population databases and mutation databases such as, but not limited to, the [gnomAD](#), [ClinVar](#), HGMD Professional and Alamut Visual. In addition, the clinical relevance of any identified CNVs was evaluated by reviewing the relevant literature and databases such as [Database of Genomic Variants](#) and [DECIPHER](#). For interpretation of mtDNA variants specific databases including e.g. Mitomap, HmtVar and 1000G were used.

Confirmation of sequence alterations: Sequence variants classified as pathogenic, likely pathogenic and variants of uncertain significance (VUS) were confirmed using bi-directional Sanger sequencing when they did not meet our stringent NGS quality metrics for a true positive call. In addition, prenatal case with diagnostic findings were confirmed.

Confirmation of copy number variants: CNVs (Deletions/Duplications) were confirmed using a digital droplet PCR assay if they covered less than 10 exons (heterozygous), less than 3 exons (homo/hemizygous) or were not confirmed at least three times previously at our laboratory. Furthermore, CNVs of any size were not confirmed when the breakpoints of the call could be

determined.

Analytic validation: The detection performance of this panel is expected to be in the same range as our high-quality, clinical grade NGS sequencing assay used to generate the panel data (nuclear DNA: sensitivity for SNVs 99.89%, indels 1-50 bps 99.2%, one-exon deletion 100% and five exons CNV 98.7%, and specificity >99.9% for most variant types). It does not detect very low-level mosaicism as a variant with minor allele fraction of 14.6% can be detected in 90% of the cases. Detection performance for mtDNA variants (analytic and clinical validation): sensitivity for SNVs and INDELS 100.0% (10-100% heteroplasmy level), 94.7% (5-10% heteroplasmy level), 87.3% (<5% heteroplasmy level) and for gross deletions 100.0%. Specificity is >99.9% for all. **Test**

restrictions: A normal result does not rule out the diagnosis of a genetic disorder since some DNA abnormalities may be undetectable by the applied technology. Test results should always be interpreted in the context of clinical findings, family history, and other relevant data. Inaccurate, or incomplete information may lead to misinterpretation of the results.

Technical limitations: This test does not detect the following: complex inversions, gene conversions, balanced translocations, repeat expansion disorders unless specifically mentioned, non-coding variants deeper than ± 20 base pairs from exon-intron boundary unless otherwise indicated (please see the list of non-coding variants covered by the test). Additionally, this test may not reliably detect the following: low-level mosaicism, stretches of mononucleotide repeats, indels larger than 50bp, single exon deletions or duplications, and variants within pseudogene regions/duplicated segments. The sensitivity of this test may be reduced if DNA is extracted by a laboratory other than Blueprint Genetics. Laboratory error is also possible. Please see the Analytic validation above.

Regulation and accreditations: This test was developed and its performance characteristics determined by Blueprint Genetics (see Analytic validation). It has not been cleared or approved by the US Food and Drug Administration. This analysis has been performed in a CLIA-certified laboratory (#99D2092375), accredited by the College of American Pathologists (CAP #9257331) and by FINAS Finnish Accreditation Service, (laboratory no. T292), accreditation requirement SFS-EN ISO 15189:2013. All the tests are under the scope of the ISO 15189 accreditation (excluding mtDNA testing and digital droplet PCR confirmation).

NON-CODING VARIANTS COVERED BY THE PANEL:

NM_004403.2(DFNA5):c.991-15_991-13delTTC
NM_001042517.1(DIAPH3):c.-172G>A
NM_001042517.1(DIAPH3):c.-173C>T
NM_004100.4(EYA4):c.1282-12T>A
NM_004100.4(EYA4):c.1341-19T>A
NM_004004.5(GJB2):c.-22-2A>C
NM_004004.5(GJB2):c.-23+2T>A
NM_004004.5(GJB2):c.-23+1G>A
NM_004004.5(GJB2):c.-23G>T
NM_004004.5(GJB2):c.-259C>T
NM_004004.5(GJB2):c.-260C>T
NM_024915.3(GRHL2):c.20+133delA
NM_024915.3(GRHL2):c.20+257delT
NM_024915.3(GRHL2):c.20+544G>T
NM_001080476.2(GRXCR1):c.627+19A>T
NM_000601.4(HGF):c.482+1991_482+2000delGATGATGAAA
NM_000601.4(HGF):c.482+1986_482+1988delTGAA
NM_017433.4(MYO3A):c.1777-12G>A
NM_004999.3(MYO6):c.2417-1758T>G
NM_000260.3(MYO7A):c.-48A>G
NM_000260.3(MYO7A):c.3109-21G>A
NM_000260.3(MYO7A):c.5327-14T>G
NM_000260.3(MYO7A):c.5327-11A>G
NM_000260.3(MYO7A):c.5857-27_5857-26insTTGAG
NM_001142763.1(PCDH15):c.-29+1G>C
NM_000441.1(SLC26A4):c.-103T>C

NM_000441.1(SLC26A4):c.-60A>G
NM_000441.1(SLC26A4):c.-4+1G>C
NM_000441.1(SLC26A4):c.-4+5G>A
NM_000441.1(SLC26A4):c.918+45_918+47delCAA
NM_000441.1(SLC26A4):c.1150-35_1150-28delTTTGTAGG
NM_000441.1(SLC26A4):c.1264-12T>A
NM_000441.1(SLC26A4):c.1438-7dupT
NM_000441.1(SLC26A4):c.1708-27_1708-11delTAAGTAACTTGACATTT
NM_000441.1(SLC26A4):c.2090-52_2090-49delCAAA
NM_138691.2(TMC1):c.362+18A>G
NM_006005.3(WFS1):c.-43G>T

GLOSSARY OF USED ABBREVIATIONS:

AD = autosomal dominant

AF = allele fraction (proportion of reads with mutated DNA / all reads)

AR = autosomal recessive

CNV = Copy Number Variation, eg, one exon or multiexon deletion or duplication

gnomAD = genome Aggregation Database (reference population database; >138,600 individuals)

gnomAD AC/AN = allele count/allele number in the genome Aggregation Database (gnomAD)

HEM = hemizygous

HET = heterozygous

HOM = homozygous

ID = rsID in dbSNP

MT = Mitochondria

MutationTaster = *in silico* prediction tools used to evaluate the significance of identified amino acid changes.

Nomenclature = HGVS nomenclature for a variant in the nucleotide and the predicted effect of a variant in the protein level

OMIM = Online Mendelian Inheritance in Man®

PolyPhen = *in silico* prediction tool used to evaluate the significance of amino acid changes.

POS = genomic position of the variant in the format of chromosome:position

SIFT = *in silico* prediction tool used to evaluate the significance of amino acid changes.