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

Physician: Doctor, Example

**Patient: Patient, Example**

| | |
|---|---|
| **DOB** | 12/31/1752 |
| **Sex:** | Male |
| **Patient Identifiers:** | 01234567890ABCD, 012345 |
| **Visit Number (FIN):** | 01234567890ABCD |
| **Collection Date:** | 00/00/0000 00:00 |

## Genome Sequencing

ARUP test code 3019943

WGS PRO Interp **Positive** *

TEST PERFORMED
Genome Sequencing
Specimen tested: Proband

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INDICATION FOR TESTING
Ventricular septal defect, hypotonia, developmental delay, recurrent infections

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RESULT SUMMARY
Primary findings- Related to Phenotype: Heterozygous for a pathogenic deletion in 22q11.21

Secondary Findings: Negative

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PRIMARY FINDINGS- RELATED TO PHENOTYPE

22q11.2 Deletion (DiGeorge/Velocardiofacial syndrome)

Classification: Pathogenic
Zygosity: Heterozygous
Inheritance: Unknown
Size: 2.6 Mb
Gene Count: 91 genes (46 protein-coding genes), including the gene TBX1
Variant: seq[GRCh37] 22q11.21(18875905_21466460)x1

Deletion of this region is associated with the 22q11.2 deletion syndrome, also known as DiGeorge/velocardiofacial syndrome (DGS/VCFS), involving recurrent breakpoints within flanking low-copy repeat regions A and D. The reported size of this deletion may vary across studies due to variability in breakpoints within flanking repeat regions, variability in probe performance and CNV calling, as well as other technical limitations between assays.

This result is consistent with a clinical diagnosis of 22q11.2 deletion syndrome. Features associated with this disorder are variable and may include congenital heart defects (particularly conotruncal and aortic arch malformations), palatal

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

abnormalities, feeding and swallowing difficulties, developmental delay/intellectual disability, immune deficiency due to absent or hypoplastic thymus, hypocalcemia due to parathyroid hypoplasia (which may lead to seizures), hypernasal speech, low platelet counts, hernias, skeletal anomalies, hypotonia, subtle dysmorphic features, and behavioral difficulties. Additional findings may include microcephaly, growth hormone deficiency/short stature, sleep disturbance/apnea, autism, psychiatric disorders, and other anomalies involving various systems.

Up to 10 percent of 22q11.2 deletions are inherited, sometimes from a mildly affected or unaffected parent. Parental testing by FISH or targeted microarray analysis is recommended to evaluate the potential origin of this deletion and for recurrence risk counseling.

Relevant citations: (1-5)

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NEGATIVE RESULTS
The following were not identified in the genome data:
-Clinically relevant sequence variants in the nuclear and mitochondrial genome related to the patient's reported phenotype.
-Homozygous loss of SMN1 exon 7, causative for spinal muscular atrophy.

No secondary findings variants were detected. The American College of Medical Genetics and Genomics (ACMG) recommends analysis of specific, medically actionable secondary findings (SF) genes in all consented individuals undergoing genome sequencing even though these variants may not be related to the indication for testing (6). Although no secondary findings variants involving genes from the ACMG SF v3.3 list (7) were identified in this individual, this result does not exclude the possibility this individual may carry a pathogenic variant involving one of these genes, or another gene that is not included on this list. If there is clinical suspicion or family history of a genetic condition associated with one of the ACMG SF genes, additional targeted testing should be considered as genome sequencing will not identify all pathogenic variants involving these genes. Note that single pathogenic variants in autosomal recessive ACMG SF genes are not generally reported.

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RECOMMENDATIONS
-Genetic counseling.
-Parental testing for the deletion by FISH or targeted microarray analysis may be considered. For FISH testing, please order test code 2002299, Chromosome FISH, Metaphase and request the DiGeorge probe. For targeted microarray, please order test code 3005694, Cytogenomic SNP Microarray, Family-Specific Variant, and include the accession number for this case.

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NOTES
97.1% of bases in the targeted genome were covered by more than 20 sequencing reads. Intergenic variants, deep intronic variants not predicted to alter splicing, and chromosomal rearrangements are not analyzed by this method; therefore, additional variants in the reported genes and regions have not been excluded. Refer to the background information for details of limitations.

Health care providers with questions may contact an ARUP genetic counselor at (800) 242-2787 ext. 2141.

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References
1: Oskarsdottir S, Boot E, Crowley TB et al. Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome. Genet Med 2023. PMID:36729053.
2: Boot E, Oskarsdottir S, Loo JCY et al. Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. Genet Med 2023. PMID:36729052.
3: Burnside RD. 22q11.21 Deletion Syndromes: A Review of Proximal, Central, and Distal Deletions and Their Associated Features. Cytogenet Genome Res 2015. PMID:26278718.
4: The International 22q11.2 Deletion Syndrome Foundation. (www.22q.org)
5: Unique: Understanding Rare Chromosome and Gene Disorders. (www.rarechromo.org)
6: Miller DT, Lee K, Gordon AS, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021. PMID: 34012069.
7: Lee K, Abul-Husn NS, Amendola LM et al. ACMG SF v3.3 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2025. PMID:40568962.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Genome Sequencing

CHARACTERISTICS: The purpose of whole genome sequencing (WGS) is to establish a diagnosis when a genetic condition is suspected but a patients clinical features are not suggestive of a single disorder. WGS utilizes next generation sequencing (NGS) to interrogate more than 92 percent of the genome (excluding telomeric and centromeric regions), including the mitochondrial genome. The inclusion of parental samples is strongly recommended for accurate variant interpretation.

CLINICAL SENSITIVITY: Varies based on clinical symptoms, family history, inheritance pattern, and previous clinical evaluations.

METHODOLOGY: Genomic DNA is extracted from whole blood or saliva, prepared into libraries, then sequenced by NGS. Variant calling is performed using the Illumina DRAGEN Bio-IT Platform incorporated with a custom bioinformatics pipeline. Human genome build 19 (Hg 19) is used for data analysis. The analytical procedure identifies single nucleotide variants (SNVs), small insertions/deletions, and copy number variants (CNVs) known, or suspected to be, disease-causing.

ANALYTICAL SENSITIVITY: The analytical sensitivity of this assay is 99.2 percent for SNVs, 99.2 percent for insertions/duplications/deletions (indels) ranging in size from 1-15 base pairs (bp), and 96.9 percent for indels 16-50 bp in size. For mitochondrial SNVs with heteroplasmy greater than or equal to 3 percent, analytical sensitivity is 98.4 percent. Analytical sensitivity for CNVs is greater than 99.9 percent for variants 10 kb or larger in size, and 84.6 percent for those 1-10 kb in size.

LIMITATIONS OF ANALYSIS: A negative result does not exclude a genetic diagnosis. Due to technical limitations, some regions of the genome cannot be sequenced or interpreted. SNVs in intergenic or deep intronic regions will only be evaluated if an effect on gene expression is predicted based on annotation software. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations related to pseudogenes or repetitive or

homologous regions. This assay is not designed to detect somatic variants, mosaic variants, trinucleotide repeats, uniparental disomy, absence of heterozygosity (AOH), or mitochondrial CNVs. This assay is not designed to detect CNVs greater than 50 bp but less than 1 kb in size. See Additional Technical Information located at http://ltd.aruplab.com/Tests/Pub/3019943 for more information on whole genome sequencing.

REPORTING CONSIDERATIONS: Variant interpretation and reporting is limited to variants known or predicted to have an impact on gene expression. Mitochondrial variant reporting is limited to SNVs with heteroplasmy greater than or equal to 10 percent. Heteroplasmy may vary across tissue types; therefore, reported levels reflect only the tested sample. Variable penetrance and genetic heterogeneity may impact clinical sensitivity. Reported variants are limited to those known or suspected to be causative of the patient's phenotype. Patients may opt in for reporting of secondary pathogenic/likely pathogenic findings, including those involving medically actionable genes on the ACMG Secondary Findings Gene List located at http://ltd.aruplab.com/Tests/Pub/3019943. This gene list is updated periodically and is only accurate for this sample at the time of reporting. Absence of parental data, whether through non-submission, technical failure, or misattributed parentage, will impact interpretation of proband results. Likewise, interpretation of test results may be impacted if any of the tested individuals have undergone allogeneic stem cell transplantation.

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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.

EER WGS PRO — EERUnavailable

VERIFIED/REPORTED DATES

| Procedure | Accession | Collected | Received | Verified/Reported |
|---|---|---|---|---|
| WGS PRO Interp | 25-323-105559 | 00/00/0000 00:00 | 00/00/0000 00:00 | 00/00/0000 00:00 |
| EER WGS PRO | 25-323-105559 | 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