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: Female
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 00/00/0000 00:00

Genome Sequencing, Familial Comparator

ARUP test code 3019951

WGS FM Interp

Positive *

TEST PERFORMED
Genome Sequencing, Familial Comparator

RESULT
One pathogenic deletion was detected involving the VHL gene.
PATHOGENIC DELETION
Gene (Transcript): VHL (NM_000551.4)
OMIM(R) disease: von Hippel-Lindau syndrome (MIM: 193300; (1))
Mode of Inheritance: Autosomal Dominant
Zygosity: Heterozygous
Size: 141 kb
Gene Count: 5 genes, including 3 protein-coding genes
Variant: seq[GRCh37] 3p25.3(10185529_10325991)x1

INTERPRETATION
One pathogenic interstitial deletion involving chromosome 3 within 3p25.3 was detected by massively parallel sequencing. This region contains 5 genes, including the haploinsufficient gene VHL. Heterozygous pathogenic variants involving VHL are associated with von Hippel-Lindau syndrome (vHL), a hereditary multi-organ tumor predisposition syndrome. Features of this disorder may include hemangioblastomas of the CNS and retina, renal cystsf, renal cell carcinoma, pheochromocytoma, paragangliomas, pancreatic cysts and neuroendocrine tumors, endolymphatic sac tumors, as well as epididymal and broad ligament cystadenomas. This result is consistent with a diagnosis of vHL type 1. The vHL type 1 phenotype is associated with a low risk for pheochromocytoma. Clinical manifestations of VHL are variable and age dependent. Individuals with this variant have a 50 percent chance of transmitting it to offspring.

The American College of Medical Genetics and Genomics (ACMG) recommends analysis of specific medically actionable secondary findings (SF) genes, including VHL, in all consented individuals undergoing genome sequencing even though these genes may not be related to the indication for testing (2).

Evidence for variant classification: The deletion of VHL exons 2-3 has been previously described in the medical literature in individuals and families affected with vHL type 1 (3-6). Similar deletions are also reported in ClinVar (Variation IDs: 456563, 659603). Based on available information, this variant is classified as pathogenic.

No additional secondary findings variants involving the ACMG SF

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

v3.3 gene list (7) were detected. This result does not exclude the possibility this individual may carry another 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 in these genes. Note that single pathogenic variants in autosomal recessive ACMG SF genes are not reported. Please refer to the background information below for the methodology and limitations of this test.

RECOMMENDATIONS
- Genetic consultation is indicated, including a discussion of medical screening and management.
- At-risk family members should be offered targeted testing for the 3p25.3 deletion. Please order ARUP test code 3005694, Cytogenomic SNP Microarray, Family-Specific Variant, and include the accession number for this case.

References
1: OMIM(R): Copyright (C) 1996 - Present year, Johns Hopkins University All rights reserved.
2: 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.
3: van Leeuwaarde RS, Ahmad S, van Nesselrooij B et al. Von Hippel-Lindau Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. GeneReviews. University of Washington, Seattle. Updated May 2025. PMID: 20301636.
4: Binderup M, Smerdel M, Borgwadt L et al. von Hippel-Lindau disease: Updated guideline for diagnosis and surveillance. Eur J Med Genet 2022. PMID:35709961.
5: Hes FJ, van der Luijt RB, Janssen AL et al. Frequency of Von Hippel-Lindau germline mutations in classic and non-classic Von Hippel-Lindau disease identified by DNA sequencing, Southern blot analysis and multiplex ligation-dependent probe amplification. Clin Genet 2007. PMID:17661816.
6: McNeill A, Rattenberry E, Barber R et al. Genotype-phenotype correlations in VHL exon deletions. Am J Med Genet A 2009. PMID:19764026.
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,
Familial Comparator
CHARACTERISTICS: Whole genome sequencing (WGS) of familial comparator(s) is used to help determine the cause(s) of a disorder in a family proband. 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 American College of Medical Genetics and Genomics (ACMG) recommends analysis of certain genes for secondary findings in all individuals undergoing genome sequencing. Please refer to ACMG Secondary Findings Gene List (http://ltd.aruplab.com/Tests/Pub/3019951) for a list of genes analyzed. Note that this gene list is updated periodically and is only accurate for this sample at the time of reporting.

INHERITANCE: Varies by gene and/or variant.

CLINICAL SENSITIVITY: Varies by gene.

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.

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/3019951 for more information on whole genome sequencing.

REPORTING CONSIDERATIONS: Secondary findings, including disease-associated variants identified in genes on the ACMG-recommended list, or other medically actionable variants at ARUP's discretion, are reported when elected. 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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
WGS FM Interp	25-310-116292	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART