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:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Cytogenomic SNP Microarray - Fetal

ARUP test code 2002366

Maternal Contamination Study Fetal Spec: Fetal Cells

Fetal Cells
Single fetal genotype present; no maternal cells present. Fetal and maternal samples were tested using STR markers to rule out maternal cell contamination.
This result has been reviewed and approved by

Maternal Specimen: Yes

Cytogenomic SNP Microarray - Fetal: **Abnormal** * (Ref Interval: Normal)

Test Performed: Cytogenomic SNP Microarray- Fetal (ARRAY FE)
Specimen Type: Direct (uncultured) amniocytes
Indication for Testing: Oligohydramnios, VSD, absent nasal bone, renal agenesis

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RESULT SUMMARY
Abnormal Microarray Result (Female)

4p Deletion (4p-/Wolf-Hirschhorn syndrome)

Classification: Pathogenic
Copy number change: 4p16.3p14 loss
Size: 38.6 Mb

RESULT DESCRIPTION
This analysis showed a terminal deletion (1 copy present) involving chromosome 4 from 4p16.3 to 4p14. This region contains at least 262 genes (listed below), including the genes NSD2 (WHSC1), NELFA (WHSC2), LETM1, TACC3, and FGFR3. Deletion of this region is associated with Wolf-Hirschhorn syndrome (WHS).

INTERPRETATION
This result is consistent with a clinical diagnosis of 4p-/Wolf-Hirschhorn syndrome. Features associated with this disorder are variable, but in the prenatal period typically include increased nuchal translucency, severe and early onset intrauterine growth restriction, renal dysplasia and oligohydramnios. Postnatal features include growth deficiency, hypotonia with muscle underdevelopment, developmental delay/intellectual disability, and seizures. The typical craniofacial gestalt may include broad, flat nasal bridge, high forehead with prominent glabella, cranial asymmetry,

microcephaly, widely spaced eyes and poorly formed ears with pits/tags. Additional clinical findings may include skeletal anomalies, congenital heart defects, hearing loss (mostly conductive), urinary tract malformations, and structural brain abnormalities. Clinical correlation should be performed with careful consideration, as the size of the deletions reported in the literature may vary from the deletion reported here.

Note that certain genes within this patient's deleted interval also confer autosomal recessive disease risk. Correlation of the patient's phenotype with the clinical features of these recessive conditions, if possible, may be considered. Online tools available to assist in the identification of candidate recessive genes within this deletion: www.sivotecbioinformatics.com/ and https://genescout.omim.org/. If indicated, additional molecular testing may be warranted, as microarray technology cannot identify all types of pathogenic variants.

This deletion may represent an isolated event or an unbalanced rearrangement from a balanced translocation involving sequences outside of probe coverage on the array. Therefore, parental chromosome analysis is recommended to evaluate the potential origin of this deletion and for recurrence risk counseling.

Recommendations:
1) Genetic counseling
2) Parental testing by chromosome analysis. This test is available, at a charge, through ARUP Laboratories. Please order test code 2002289, Chromosome Analysis, Constitutional Peripheral Blood, and include the accession number for this case.

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

References:
1) Zollino et al. On the nosology and pathogenesis of Wolf-Hirschhorn syndrome: genotype-phenotype correlation analysis of 80 patients and literature review. Am J Med Genet C Semin Med Genet. 2008 Nov 15;148C:257-69. PMID: 18932124.
2) Battaglia et al. WolfHirschhorn syndrome: A review and update. Am J Med Genet C Semin Med Genet. 2015 Sep;169(3):216-23. PMID: 26239400.
3) Unique: Understanding Rare Chromosome and Gene Disorders. (www.rarechromo.org)
4) The 4p- Support Group. (http://4p-supportgroup.org)

Cytogenomic Nomenclature (ISCN):
arr[GRCh37] 4p16.3p14(68346_38678107)x1

Genes within the 4p16.3 deleted region:
ZNF595, ZNF718, ZNF876P, ZNF732, ZNF141, MIR571, ABCA11P, ZNF721, PIGG, TMEM271, LOC105374338, PDE6B, ATP5ME, MYL5, SLC49A3, PCGF3, PCGF3-AS1, CPLX1, GAK, TMEM175, DGKQ, SLC26A1, IDUA, FGFRL1, RNF212, LOC105374344, TMED11P, SPON2, LOC100130872, CTBP1-AS, CTBP1, CTBP1-DT, MAEA, UVSSA, NKX1-1, FAM53A, SLBP, TMEM129, TACC3, FGFR3, LETM1, NSD2, SCARNA22, NELFA, MIR943, C4orf48, NAT8L, POLN, HAUS3, MXD4, MIR4800, ZFYVE28, CFAP99, RNF4, FAM193A, TNIP2, SH3BP2, ADD1, MFSD10, NOP14-AS1, NOP14, GRK4, HTT-AS, HTT, MSANTD1, RGS12, HGFAC, DOK7, LRPAP1, LINC00955, LINC02171, ADRA2C, FAM86EP, OTOP1, TMEM128, LYAR, ZBTB49, NSG1, STX18, STX18-IT1, STX18-AS1, SNORD162, LOC101928279, LINC01396, MSX1, LOC101928306, CYTL1, STK32B, LINC01587, EVC2, EVC, CRMP1, MIR378D1, C4orf50, JAKMIP1, JAKMIP1-DT, WFS1, PPP2R2C, MAN2B2, MRFAP1, LINC02482, LOC93622, LINC02481, S100P, MRFAP1L1, BLOC1S4, KIAA0232, TBC1D14, LOC100129931, CCDC96, TADA2B, GRPEL1, LINC02447, SORCS2, MIR4798, PSAPL1, MIR4274, AFAP1-AS1, AFAP1, LOC389199, ABLIM2, MIR95, SH3TC1, HTRA3, LINC02517, ACOX3, TRMT44, GPR78, CPZ, HMX1, FAM90A26, USP17L10, USP17L11, USP17L12, USP17L13,

USP17L15, USP17L17, USP17L18, USP17L19, USP17L20, USP17L21, USP17L22, USP17L24, USP17L25, USP17L26, USP17L5, USP17L27, USP17L28, USP17L29, USP17L9P, USP17L30, USP17L6P, DEFB131A, MIR548I2, DRD5, SLC2A9, WDR1, MIR3138, ZNF518B, CLNK, MIR572, HS3ST1, LINC02360, MIR12113, LINC02270, RAB28, LINC01097, NKX3-2, LINC01096, BOD1L1, MIR5091, LINC01182, LINC01085, LINC00504, CPEB2-DT, CPEB2, C1QTNF7-AS1, C1QTNF7, CC2D2A, FBXL5, FAM200B, BST1, CD38, FGFBP1, FGFBP2, PROM1, TAPT1, TAPT1-AS1, LDB2, LINC02493, SNORA75B, QDPR, CLRN2, LAP3, MED28, FAM184B, DCAF16, NCAPG, LCORL, SLIT2, SLIT2-IT1, MIR218-1, PACRGL, KCNIP4, MIR7978, LOC105374516, KCNIP4-IT1, LOC100505912, ADGRA3, MIR12115, GBA3, PPARGC1A, MIR573, DHX15, SOD3, CCDC149, LGI2, SEPSECS, SEPSECS-AS1, PI4K2B, ZCCHC4, ANAPC4, LOC101929161, SLC34A2, SEL1L3, SMIM20, RBPJ, CCKAR, TBC1D19, STIM2-AS1, STIM2, LINC02261, MIR4275, LINC02364, LINC02472, PCDH7, LINC02497, LINC02501, LINC02506, LOC105377651, LINC02353, LOC101928622, LINC02484, ARAP2, LOC439933, DTHD1, MIR1255B1, LINC02505, LINC02616, MIR4801, NWD2, C4orf19, RELL1, PGM2, TBC1D1, PTTG2, LINC02513, LINC01258, LINC01259, LINC02278, KLF3-AS1, KLF3

Technical Information
- This assay was performed using the CytoScan HD Suite (Thermo Fisher Scientific) according to validated protocols within the Genomic Microarray Laboratory at ARUP Laboratories
- This assay is designed to detect alterations to DNA copy number state (gains and losses), copy-neutral alterations (regions of homozygosity; ROH) that indicate an absence- or loss-of-heterozygosity (AOH or LOH), and certain alterations to ploidy state due to errors at fertilization or early embryonic cell division (i.e. triploidy, molar pregnancy)
- AOH may be present due to molar pregnancy, parental relatedness (consanguinity) or uniparental disomy (UPD)
- LOH may be present due to acquired UPD (segmental or whole chromosome)
- The detection sensitivity (resolution) for any particular genomic region may vary dependent upon the number of probes (markers), probe spacing, and thresholds for copy number and ROH determination
- The CytoScan HD array contains 2.67 million markers across the genome with average probe spacing of 1.15 kb, including 750,000 SNP probes and 1.9 million non-polymorphic probes
- In general, the genome-wide resolution is approximately 25-50 kb for copy number changes and approximately 3 Mb for ROH (See reporting criteria)
- The limit of detection for mosaicism varies dependent upon the size and type of genomic imbalance. In general, genotype mixture due to mosaicism (distinct cell lines from the same individual) or chimerism (cell lines from different individuals) will be detected when present at greater than 20-30 percent in the sample
- Genomic coordinates correspond to the Genome Reference Consortium human genome build 37/human genome issue 19 (GRCh37/hg19)

Variant Classification and Reporting Criteria
- Copy number variant (CNV) analysis is performed in accordance with recommendations by the American College of Medical Genetics and Genomics (ACMG), using standard 5-tier CNV classification terminology: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign
- CNVs classified as pathogenic or likely pathogenic are generally reported based on information available at the time of review
- CNVs classified as VUS are generally reported when found to have suspected clinical relevance based on information available at the time of review, or when meeting size criteria
- Known or expected pathogenic CNVs affecting genes with known clinical significance but which are unrelated to the indication for testing will generally be reported
- Variants that do not fall within the standard 5-tier CNV classification categories may be reported with descriptive

language specific to that variant
- In general, recurrent CNVs with established reduced penetrance will be reported
- In general, recessive disease risk will not be reported unless consistent with submitted clinical information
- For a list of databases used in CNV classification, please refer to ARUP Constitutional CNV Assertion Criteria, which can be found on ARUP's Genetics website at www.aruplab.com/genetics
- CNVs classified as likely benign or benign that are devoid of relevant gene content or reported as common findings in the general population, are generally not reported
- CNV reporting (size) criteria: losses greater than 1 Mb and gains greater than 2 Mb are generally reported, dependent on genomic content
- Regions of homozygosity (ROH) are generally reported when a single terminal ROH is greater than 3 Mb and a single interstitial ROH is greater than 10-20 Mb (dependent upon chromosomal location and likelihood of imprinting disorder) or when total autosomal homozygosity is greater than 5 percent (only autosomal ROH greater than 3 Mb are considered for this estimate)

Limitations
This analysis cannot provide structural (positional) information associated with genomic imbalance. Therefore, additional cytogenetic testing by chromosome analysis or fluorescence in situ hybridization (FISH) may be recommended.

Certain genomic alterations may not or cannot be detected by this technology. These alterations may include, but are not limited to:
- CNVs below the limit of resolution of this platform
- Sequence-level variants (mutations) including point mutations and indels
- Low-level mosaicism (generally, less than 20-30 percent)
- Balanced chromosomal rearrangements (translocations, inversions and insertions)
- Genomic imbalance in repetitive DNA regions (centromeres, telomeres, segmental duplications, and acrocentric chromosome short arms)
- Most cases of tetraploidy

This result has been reviewed and approved by

INTERPRETIVE INFORMATION: Cytogenomic SNP Microarray - Fetal

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
Maternal Contamination Study Fetal Spec	25-098-118476	4/8/2025 2:20:00 PM	4/8/2025 2:21:32 PM	4/8/2025 2:28:00 PM
Maternal Specimen	25-098-118476	4/8/2025 2:20:00 PM	4/8/2025 2:21:32 PM	4/8/2025 2:28:00 PM
Cytogenomic SNP Microarray - Fetal	25-098-118476	4/8/2025 2:20:00 PM	4/8/2025 2:21:32 PM	4/8/2025 2:28:00 PM

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

END OF CHART

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