

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

Physician: Doctor, Example

Patient: Patient, Example

DOB: 2/13/1987
Gender: Female
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
Collection Date: 00/00/0000 00:00

Cytogenomic SNP Microarray - Fetal

ARUP test code 2002366

Maternal Contamination Study Fetal Spec

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 [REDACTED]

Maternal Specimen

Yes

Cytogenomic SNP Microarray - Fetal

Abnormal * (Ref Interval: Normal)

Test Performed: Cytogenomic SNP Microarray- Fetal (ARRAY FE)
Specimen Type: Direct (uncultured) villi
Indication for Testing: Patient with 46,XX,t(4;13)(p16.3;q12)
(Quest: EN935475D)

RESULT SUMMARY
Abnormal Microarray Result (Male)

Unbalanced Translocation Involving Chromosomes 4 and 13

Classification: Pathogenic

4p Terminal Deletion (Wolf-Hirschhorn syndrome)
Copy number change: 4p16.3p16.2 loss
Size: 5.1 Mb

13q Proximal Region Deletion
Copy number change: 13q11q12.12 loss
Size: 6.1 Mb

RESULT DESCRIPTION
This analysis showed a terminal deletion (1 copy present) involving chromosome 4 within 4p16.3p16.2 and a proximal interstitial deletion (1 copy present) involving chromosome 13 within 13q11q12.12. This pattern of copy number variants (CNVs), a terminal deletion paired with a proximal region deletion of an acrocentric chromosome, is suggestive of an unbalanced translocation between chromosomes 4 and 13. This type of translocation arises from a 3:1 segregation pattern, resulting in tertiary monosomy (two deletions).

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

The 4p deleted region contains at least 89 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).

The 13q deleted region includes at least 59 genes (also listed below).

NOTE: As the mother of this fetus is reported to carry a balanced translocation between chromosomes 4 and 13, based on the array results, the expected fetal karyotype can be described as 45,XY,der(4)t(4;13)(p16;q12)mat,-13 at the 400 band level of resolution.

INTERPRETATION

4p Terminal Deletion

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 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.

13q Proximal Deletion

Features associated with similar 13q deletions reported in the literature are variable and may include developmental and growth delays, central nervous system anomalies, mild abnormalities of the extremities, and mild craniofacial dysmorphisms.

The clinical presentation of this patient may involve a combination of features associated with these CNVs. Clinical correlation should be performed with careful consideration of this information.

Recommendation:
Genetic counseling

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

References and Resources:

- 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. wolf-Hirschhorn syndrome: A review and update. Am J Med Genet C Semin Med Genet. 2015 Sep;169(3):216-23. PMID: 26239400.
- 3) Pavone et al. wide spectrum of congenital anomalies including choanal atresia, malformed extremities, and brain and spinal malformations in a girl with a de novo 5.6-Mb deletion of 13q12.11-13q12.13. Am J Med Genet A. 2014 Jul;164A(7):1734-43. PMID: 24807585.
- 4) Unique: Understanding Rare Chromosome and Gene Disorders. (www.rarechromo.org)
- 5) The 4p- Support Group. (<http://4p-supportgroup.org>)

Cytogenetic Nomenclature (ISCN):

arr[GRCh37]
4p16.3p16.2(68345_5121450)x1,13q11q12.12(19436286_25491009)x1

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List of genes within the 4p16.3p16.2 deletion:
 ZNF595, ZNF718, ZNF876P, ZNF732, ZNF141, MIR571, ABCA11P,
 ZNF721, PIGG, TMEM271, LOC105374338, PDE6B, ATP5ME, MYL5,
 SLC49A3, PCGF3, LOC100129917, CPLX1, GAK, TMEM175, DGKQ,
 SLC26A1, IDUA, FGFRL1, RNF212, LOC105374344, TMED11P, SPON2,
 LOC100130872, CTBP1-AS, CTBP1, CTBP1-DT, MAEA, UVSSA, CRIPAK,
 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

List of genes within the 13q11q12.12 deletion:
 ANKRD20A9P, LINC00408, LINC00442, LOC107984132, TUBA3C,
 LOC101928697, ANKRD26P3, LINC00421, TPTE2, LINC00350, MPHOSPH8,
 PSPC1, ZMYM5, ZMYM2, LINC01072, GJA3, GJB2, GJB6, CRYL1,
 MIR4499, IFT88, IL17D, EEF1AKMT1, XPO4, LINC00367, LATS2, SAP18,
 SKA3, MRPL57, LINC01046, MIPEPP3, LINC00539, GRK6P1, ZDHHC20,
 MICU2, FGF9, LINC00424, LINC00540, LINC00621, BASP1P1, SGGG,
 SACS, SACS-AS1, LINC00327, TNFRSF19, MIPEP, PCOTH, C1QTNF9B,
 ANKRD20A19P, SPATA13, MIR2276, SPATA13-AS1, C1QTNF9, LINC00566,
 PAPP4, TPTE2P6, ATP12A, RNF17, CENPJ

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

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

- 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, recessive disease risk and recurrent CNVs with established reduced penetrance will be reported
- 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 [REDACTED]

INTERPRETIVE INFORMATION: Cytogenomic SNP Microarray - Fetal

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

EER Cytogenomic SNP Microarray - Fetal

EERUnavailable

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VERIFIED/REPORTED DATES				
Procedure	Accession	Collected	Received	Verified/Reported
Maternal Contamination Study Fetal Spec	20-241-125223	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Maternal Specimen	20-241-125223	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Cytogenomic SNP Microarray - Fetal	20-241-125223	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
EER Cytogenomic SNP Microarray - Fetal	20-241-125223	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

Unless otherwise indicated, testing performed at:

ARUP LABORATORIES | 800-522-2787 | aruplab.com
500 Chipeta Way, Salt Lake City, UT 84108-1221
Tracy I. George, MD, Laboratory Director

Patient: Patient, Example
ARUP Accession: 20-241-125223
Patient Identifiers: 01234567890ABCD, 012345
Visit Number (FIN): 01234567890ABCD
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