Clinical Genomics Laboratory

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UW Medicine
LABORATORY MEDICINE & PATHOLOGY

Patient: [redacted]
Sex: female, DOB: [redacted]
MRN: [redacted]
External Patient ID: [redacted]

SNP Microarray, Constitutional (Final result)

Indication for Testing
Abnormal fetal ultrasound: Severe prenatal growth restriction, short long bones, echogenic bowel and kidneys, small thorax and stomach; Recurrent pregnancy loss

RESULTS SUMMARY
No pathogenic or likely pathogenic copy number variants were found by chromosomal SNP microarray analysis of this uncultured amniotic fluid sample. A duplication involving the long arm of chromosome 6 (6q14.2 to q14.3) was detected that is of uncertain significance. This classification could change over time.

Interpretation and Comments
This interstitial duplication is approximately 695 kb in size and includes or overlaps five protein-coding genes. The duplication coordinates (see ISCN) can be entered into the UCSC Genome Browser [GRCh38] for a complete list of genes. None of the genes in this region are known to cause medical problems in humans when an extra copy is present (triplosensitivity), and this is not a known triplosensitive genomic region. However, CMA cannot distinguish tandem duplications from an insertion elsewhere in the genome with potential for pathogenic disruption of genes at the insertion site. The proximal breakpoint of the duplication lies within *SNAP91* (OMIM 607923). It is unknown whether this duplication would disrupt *SNAP91* or affect its expression, and *SNAP91* is currently not a known haploinsufficient gene.

Similar duplications have been reported in public databases and in the medical literature, but not in a prenatal context and not in people with clinical features similar to this fetus. The DECIPHER database contains no patients with a similar duplication, but similar duplications have been submitted to ClinVar sixteen times. One of these reports was of a two-copy gain (triplication). The duplication has been classified in ClinVar variously as Benign (3), Likely Benign (1), and a variant of uncertain significance (12). The reported phenotypes are diverse. Alvarado et al. (2013) detected a similar duplication in a family (5173) in which isolated talipes equinovarus appeared in three out of five generations. The duplication segregated with the phenotype through three generations, though with incomplete penetrance. Manoli et al. (2010) found a similar duplication in a person with severe Chediak-Higashi syndrome (CHS), hypotonia and global developmental delays, but the person also had paternal heterodisomy of chromosome 1. This resulted in homozygosity for a paternal nonsense variant in *LYST*, which causes CHS. A similar duplication (nsv1025798) appears at low frequency in the Database of Genomic Variants but not in gnomAD.

No other pathogenic, likely pathogenic, or copy number variants of uncertain significance, or unusually large or numerous regions of copy number neutral absence of heterozygosity were detected in this uncultured amniotic fluid sample.

Results were consistent with one copy of the X and one copy of the Y chromosome.

Benign and likely benign copy number variants were not reported.

Recommendations:
1. Genetic counseling is recommended.

2. CMA results should be interpreted in the context of the patient's clinical and family history. Clinical correlation is recommended.

Ordering Provider: [redacted]

[redacted]

3. Parental CMA or targeted copy number evaluation using droplet digital PCR (ddPCR) can be done to clarify whether this duplication is *de novo* or inherited. Inherited copy number variants are more likely to be benign, although variable expressivity and incomplete penetrance complicate interpretation.

4. If parental testing is desired, submit 5cc of peripheral blood collected in lavender-top EDTA and include a copy of these results. There is a charge for this testing. Contact the lab genetic counselor at 206-598-8684 if any questions.

References:

Alvarado DM, et al. Copy number analysis of 413 isolated talipes equinovarus patients suggests role for transcriptional regulators of early limb development. Eur J Hum Genet. 2013 Apr;21(4):373-80. PMID: 22892537.

Manoli I, et al. Chediak-Higashi syndrome with early developmental delay resulting from paternal heterodisomy of chromosome 1. Am J Med Genet A. 2010 Jun;152A(6):1474-83. PMID: 20503323.

Riggs ER et al. Genet Med. 2020 Feb;22(2):245-257. PMID: 31690835.
ClinGen: https://www.clinicalgenome.org/
ClinGen Dosage Sensitivity Map: https://dosage.clinicalgenome.org/
ClinVar: https://www.ncbi.nlm.nih.gov/variation/view/
DECIPHER: https://decipher.sanger.ac.uk/
DGV: http://dgv.tcag.ca/dgv/app/home
Ensembl: https://uswest.ensembl.org/index.html
GeneReviews: http://www.ncbi.nlm.nih.gov/books/NBK1116/
gnomAD: https://gnomad.broadinstitute.org/
MANE: https://www.ncbi.nlm.nih.gov/refseq/MANE/
MedGen: http://www.ncbi.nlm.nih.gov/medgen
OMIM: http://omim.org/
UCSC genome browser: http://genome.ucsc.edu/
UniProt: https://www.uniprot.org/

Test Limitations: The Illumina Infinium CytoSNP-850K BeadChip is used in this test for the sole purpose of identifying genomic chromosomal abnormalities. This microarray will detect aneuploidy as well as copy number gains (duplications or amplifications), copy number losses (deletions), and copy-neutral regions of homozygosity (ROH) for the loci represented on the microarray. Analysis in our laboratory is limited to detecting copy number variants (deletions and duplications) that include at least 10 SNPs and regions of ROH that include at least 500 SNPs. Abnormalities below these levels of resolution may not be detected. Uniparental disomy is reported when a telomeric region of ROH is >5 Mb in size or an interstitial region of ROH is >10 Mb in size for imprinted chromosomes or >15 Mb in size for non-imprinted chromosomes. Possible identity by descent is reported when regions of ROH >3 Mb in size comprise ≥1.5% of the autosomal genome. Copy number variants (CNVs) are interpreted according to technical standards established by the American College of Medical Genetics and Genomics (PMID: 31690835). Pathogenic and likely pathogenic CNVs are reported, regardless of size, including deletions conferring probable carrier status for autosomal recessive conditions. CNVs ≥400 kb that are classified as of uncertain significance are reported per provider request; those <400 kb are not reported. Benign and likely benign CNVs are not reported.

Chromosomal SNP microarray analysis will not detect imbalances in the regions not represented on the microarray, low-level mosaicism (<20%), tetraploidy, balanced alterations (e. g. reciprocal translocations, Robertsonian translocations, inversions, balanced insertions), methylation anomalies and other epigenetic events, single nucleotide variations, or small insertions or deletions. The failure to detect an alteration at any locus does not exclude the diagnosis of any of the disorders represented on the microarray. The laboratory can assist the ordering provider in determining whether other types of testing are appropriate. This discussion should be considered in the context of the clinical indication for testing.

The performance characteristics of this test have been validated by the Clinical Genomics Laboratory in the University of Washington School of Medicine as required by CLIA '88 regulations. It has not been cleared or approved for specific uses by the U.S. Food and Drug Administration. Pursuant to the requirements of CLIA '88, this laboratory has established and verified the test's accuracy and precision. The laboratory is regulated under CLIA as qualified to perform high-complexity testing. This test is used for clinical purposes. It should not be regarded as investigational or for research.

Methods Summary: Genomic DNA extracted from the patient sample was amplified, fragmented, and hybridized to the Illumina Infinium CytoSNP-850K BeadChip v1.2. This microarray contains 850,000 probes for SNP markers. The approximate distance between probes covering genes of known relevance in either constitutional or neoplasia settings is 1 kb; the spacing over the remainder of the genomic backbone is about 5 kb (www.illumina.com/content/dam/illumina-

marketing/documents/products/datasheets/datasheet_CytoSNP850K_POP.pdf). After hybridization, the microarray was washed manually, extended and stained by Illumina Automation Tecan 8-tip Robot, and scanned with an Illumina iScan. Allele and intensity ratio data of the fluorescent signals were generated. Microarray data were visualized and analyzed using Illumina BlueFuse Multi 4.5 and NxClinical 6.1 to identify chromosomal copy number variants and copy-neutral regions of homozygosity. Genome build GRCh38 was used

ISCN

arr[GRCh38] 6q14.2q14.3(83639154_84334201)x3
XY sex chromosomes

Chip ID

[redacted]

.

ID:	[redacted]	Test:	SNP Microarray, Constitutional
Type:	Amniotic fluid	Source:	Amniotic fluid
Ordered by:	[redacted]	Authorized by:	[redacted]
Collected:	[redacted]	Last Received:	1/9/2023 12:59 PM
Verified On:	1/20/2023 2:18 PM	Verifying User:	Tsuchiya, Karen D, MD

CC List

[redacted]

Resulting Labs

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