Clinical Genomics Laboratory

Phone: (206) 616-4062
Lab Genetic Counselor: (206) 598-8684

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: Congenital heart defect

RESULTS SUMMARY
A pathogenic deletion of chromosome 22q11.21 was detected that causes 22q11.2 microdeletion syndrome. Heterozygous deletions of this region have been found in people with congenital heart defects. *This deletion is likely the cause of the abnormal fetal ultrasound finding*.

Interpretation and Comments
This interstitial deletion is approximately 2.24 Mb in size and contains 45 protein-coding genes, including *TBX1* (OMIM 602054). The deletion coordinates (see ISCN) can be entered into the UCSC Genome Browser [GRCh38] for a complete list. This is the deletion found in the large majority of people with 22q11.2 deletion syndrome.

22q11.2 deletion syndrome is the most common chromosome microdeletion syndrome, with an estimated prevalence of 1 in 4000 live births. The actual occurrence may be higher because of variable expressivity. Grati et al. (2015) found 22q11.21 deletions in 1 in 311 fetuses undergoing prenatal diagnostic testing for a variety of indications. Features common in people with 22q11.2 deletion syndrome include developmental disabilities, learning disabilities, conotruncal heart abnormalities, palatal defects, hypernasal speech, psychiatric illness, immunodeficiency, hypocalcemia, and characteristic facial features. See Fung et al. 2015 and Bassett et al. 2011 for current guidelines in clinical management of people with 22q11.2 deletion syndrome.

Approximately 10% of people with 22q11.2 deletion syndrome have inherited the microdeletion from a parent. Parents may be unaware of their diagnosis because they are unaffected or mildly affected. In these cases, the chance of recurrence in siblings would be 50%. Low-level mosaicism in a parent has also been reported (McDonald-McGinn et al. 2001).

Approximately 90% people with 22q11.2 deletion syndrome have a *de novo* microdeletion. In these cases, the chance of recurrence in siblings is low but still increased over the general population due to the possibility of gonadal mosaicism (McDonald-McGinn and Zackai 2008).

Each child of this individual will have a 50% chance of inheriting the 22q11.2 microdeletion.

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 umbilical cord blood sample.

Results were consistent with two copies of the X chromosome.

Benign and likely benign copy number variants were not reported.

Recommendations:
1. Genetic counseling is recommended.

2. Chromosomal microarray results should be interpreted in the context of clinical and family history. Clinical correlation is recommended.

Ordering Provider: [redacted]

[redacted]

3. Metaphase FISH is available for parents or other family members who want to clarify recurrence risk.

4. If testing of other family members is desired, submit 5cc of peripheral blood collected in green-top sodium heparin 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:

Bassett AS, McDonald-McGinn DM, Devriendt K, et al. Practical Guidelines for Managing Patients with 22q11.2 Deletion Syndrome. J Pediatr 2011;159(2):332-339.

Fung WL, Butcher NJ, Costain G, et al. Practical guidelines for managing adults with 22q11.2 deletion syndrome. Genet Med 2015; 17(8):599-609.

Grati FR, Molina Gomes D, Ferreira JC, et al. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9,500 pregnancies. Prenat Diagn 2015;35(8):801-9. PMID:25962607.

McDonald-McGinn DM, Hain HS, Emanuel BS, et al. 22q11.2 Deletion Syndrome. 1999 Sep 23 [Updated 2020 Feb 27]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1523/

McDonald-McGinn DM, Tonnesen MK, Laufer-Cahana A, et al. Phenotype of the 22q11.2 deletion in individuals identified through an affected relative: Cast a wide FISHing net! 2001 Genet Med;3(1):23-29.

McDonald-McGinn DM and Zackai EH. Genetic counseling for the 22q11.2 deletion. 2008 Dev Disabil Res Rev;14(1):69-74.

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 regions of copy number neutral absence of heterozygosity (cnAOH) 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 cnAOH 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 cnAOH is >5Mb in length or an interstitial region of cnAOH is >10 Mb in length for imprinted chromosomes or >15 Mb in length for non-imprinted chromosomes. Possible identity by descent is reported when regions of cnAOH >3 Mb 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.

Cytogenomic microarray 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, or point mutations that may be responsible for the clinical phenotype. 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, such as DNA sequencing for point mutations, are appropriate. This discussion should be considered in the context of the clinical phenotype.

The performance characteristics of this test have been validated by the Clinical Cytogenomics 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 Nexus Copy Number 10 to identify chromosomal copy number variants and regions of copy number neutral absence or loss of heterozygosity. Genome build GRCh38 was used.

ISCN
arr[GRCh38] 22q11.21(18874235_21109441)x1

Chip ID
[redacted]

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ID:	[redacted]	Test:	SNP Microarray, Constitutional
Type:	Amniotic fluid	Source:	Amniotic fluid
Ordered by:	[redacted]	Authorized by:	[redacted]
Collected:	[redacted]	Last Received:	8/1/2022 12:45 PM
Verified On:	8/12/2022 2:33 PM	Verifying User:	Liu, Yajuan J, PhD

CC List

[redacted]

Resulting Labs

UW CLIN CYTO CLIA: **50D2093534** CAP: **9041681**	UW MEDICINE CLINICAL GENOMICS LABORATORY, 1959 NE Pacific St., Room HSC H-478, Seattle WA 98195-7655	206-616-4062