Specimen Collected: 11-Sep-23 10:27

Cytogenomic SNP Microarray - Fetal	**Received: 12-Sep-23 10:40**	**Report/Verified: 12-Sep-23 10:55**

Procedure	Result	Units	Reference Interval
Maternal Contamination Study Fetal Spec	Unknown Origin [f1]		
Maternal Specimen	No		
Cytogenomic SNP Microarray - Fetal	**Abnormal** * [f2 i1]		[Normal]

Result Footnote

f1: Maternal Contamination Study Fetal Spec
Single genotype. A maternal specimen was not submitted for correlation. The fetal sample was tested using STR markers to rule out maternal cell contamination. Only a single genotype was detected. Testing a maternal sample can confirm that this genotype is from the fetus.

This result has been reviewed and approved [redacted]

f2: Cytogenomic SNP Microarray - Fetal
Test Performed: Cytogenomic SNP Microarray- Fetal (ARRAY FE)
Specimen Type: Direct (uncultured) amniocytes
Indication for Testing: Polyhydramnios and macrosomia

RESULT SUMMARY
Abnormal Microarray Result (Female)

15q11.2 Proximal Deletion (BP1 to BP2 Region)

Classification: Pathogenic, Low Penetrance
Copy number change: 15q11.2 loss
Size: 246 kb

RESULT DESCRIPTION
This analysis showed an interstitial deletion (1 copy present) involving chromosome 15, within 15q11.2. This region contains the following 4 genes: TUBGCP5, CYFIP1, NIPA2, and NIPA1.

This is a deletion of the 15q11.2 proximal region, involving recurrent breakpoints (BPs) within flanking low-copy repeat regions, BP1 and BP2. The reported size of this deletion may vary across studies due to variability in breakpoints within flanking repeat regions.

INTERPRETATION
Deletion of proximal 15q11.2 (BP1-BP2) has been reported in association with highly variable clinical phenotypes. Clinical presentation ranges from apparently unaffected to expression of a variety of relatively nonspecific features. Features observed across affected carriers vary widely and include developmental delay/intellectual disability (particularly in speech), autism, neurological disorders, behavioral difficulties, psychiatric disorders, ataxia, seizures, and/or dysmorphic features. However, this association may represent ascertainment bias as many of these features are common indications for clinical testing. The 15q11.2 proximal deletion is common, occurring at frequencies greater than 1/500 in the general population, and has been observed in both unaffected relatives of probands and individuals from studies of natural genomic variation. It is significantly enriched in patients as compared to control populations.

Studies of the general population have shown lower cognitive function test scores among 15q11.2 (BP1-BP2) deletion carriers as compared to non-carriers. This difference has been reported to be significant, but with a mild effect size (subclinical), consistent with the deletion being a susceptibility locus for

Result Footnote

f2: Cytogenomic SNP Microarray - Fetal
neurodevelopmental phenotypes.

The 15q11.2 proximal deletion shows incomplete penetrance. Expression of any phenotype associated with this deletion is estimated to be between 8-10 percent across multiple studies. This estimate does not define the risk for a specific phenotype but includes all levels of expression that have been observed amongst carriers of the deletion. Thus, it is possible this finding is unrelated to the indication for testing.

One hypothesized explanation for the reduced penetrance and variable expressivity of copy number variants (CNVs) is that expression of clinical phenotypes may require a second hit in genes that affect the same developmental pathways. Although undefined, this second hit may be another CNV, a sequence variant, or involve environmental, epigenetic, or stochastic factors. Thus, in the absence of associated clinical findings, this CNV may represent a predisposing or susceptibility risk factor for expression of associated phenotypes.

Deletions involving proximal 15q11.2 are usually inherited, often from an unaffected or mildly affected parent. Parental testing is unlikely to determine if this CNV is clinically significant, as its presence or absence in a clinically unaffected parent or sibling will neither rule out nor confirm causality; however, it may be considered for recurrence risk counseling.

Recommendations:
1) Genetic counseling
2) Surveillance of the literature for new information concerning this deletion
3) Parental testing for the deletion by genomic microarray analysis may be considered. This test is available, at a charge, through ARUP Laboratories. Please order test code 2003414, Cytogenomic SNP Microarray, and include the accession number for this case (23-181-403009).

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

References:
1) Jønch et al. Estimating the effect size of the 15q11.2 BP1-BP2 deletion and its contribution to neurodevelopmental symptoms: recommendations for practice. J Med Genet. 2019 Oct;56(10):701-710. PMID: 31451536.
2) Kendall et al. Cognitive performance and functional outcomes of carriers of pathogenic copy number variants: analysis of the UK Biobank. Br J Psychiatry. 2019 May;214(5):297-304. PMID: 30767844.
3) van der Meer et al. Association of Copy Number Variation of the 15q11.2 BP1-BP2 Region with Cortical and Subcortical Morphology and Cognition. JAMA Psychiatry. 2019 Oct 30;77(4):1-11. PMID: 31665216.
4) Ulfarsson et al. 15q11.2 CNV affects cognitive, structural and functional correlates of dyslexia and dyscalculia. Transl Psychiatry. 2017 Apr 25;7(4):e1109. PMID: 28440815.
5) Stefansson et al. CNVs conferring risk of autism or schizophrenia affect cognition in controls. Nature. 2014 Jan 16;505(7483):361-6. PMID: 24352232.
6) Hashemi et al. Deletion of 15q11.2 (BP1-BP2) region: Further evidence for lack of phenotypic specificity in a pediatric population. Am J Med Genet A 2015; 167(9):2098-102. PMID: 25946043.
7) Cox and Butler. The 15q11.2 BP1-BP2 Microdeletion Syndrome: A Review. Int J Mol Sci 2015; 16(2):4068-4082. PMID: 25689425.
8) Vanlerberghe et al. 15q11.2 microdeletion (BP1-BP2) and developmental delay, behaviour issues, epilepsy and congenital heart disease: A series of 52 patients. Eur J Med Genet 2015; 58(3):140-7. PMID: 25596525.
9) Coe et al. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat Genet. 2014 Oct;46(10):1063-71. PMID: 25217958.
10) Girirajan et al. Phenotypic heterogeneity of genomic disorders and rare copy-number variants. N Engl J Med. 2012 Oct 4;367(14):1321-31. PMID: 22970919.
11) ClinGen Region Curation for 15q11.2 (BP1-BP2) Region (search.clinicalgenome.org/kb/gene-dosage/region/ISCA-37448)

Result Footnote

f2: Cytogenomic SNP Microarray - Fetal

Cytogenomic Nomenclature (ISCN)
arr[GRCh37] 15q11.2(22836884_23082442)x1

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, 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.

Result Footnote

f2: Cytogenomic SNP Microarray - Fetal

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

A portion of this analysis was performed at the following location(s):

Test Information

i1: Cytogenomic SNP Microarray - Fetal

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.