Physician:
Physician NOT IN DATABASE,
BOX 356100

TEST, CASE
CASE #: TS-16-00038

Sex: F, DOB: 1/1/1980
Collected Date: 11/10/2016
Received Date: 11/10/2016
ASN/CSN:

Cytogenetics & Genomics Laboratory
University of Washington Medical Center
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Seattle, WA 98195-6100
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Patient Name on Specimen Tested: Test, Case - Fetus of

Date Obtained: 11/10/2016	**Maternal Age:** 36	**Sample Type:** Molecular
Date Received: 11/10/2016	**Ref Phys:** Smith, MD, Jane M	**Source:** Amniotic fluid
Report Date: 11/14/2016	**Ref Fac:** City Medical Center	**Test Type:** SNP Array
Report Status: Final		**Other Phys:** Jones, MS, CGC, Carla

Clinical Indication: Abnormal fetal ultrasound: Abnormal cardiac axis, great toe position, possible Dandy-Walker variant

ISCN Diagnosis: arr[GRCh37] 16p13.3(3,814,227_3,929,941)x1

Summary: ABNORMAL male with a 116 kb deletion of chromosome 16p13.3 that encompasses multiple exons of the *CREBBP* gene. Loss-of function mutations in *CREBBP* cause Rubenstein-Taybi syndrome.

Diagnosis and Comments: Constitutional cytogenomic SNP microarray analysis detected a 116 kb deletion of chromosome 16p13.3 that encompasses exons 1 to 16 of *CREBBP* (NM_004380; OMIM# 600140). Enter the deletion coordinates (see Abnormality Details below) into the UCSC Genome Browser (http://genome.ucsc.edu/) to see a graphic representation of the deletion.

Loss-of function mutations in *CREBBP* cause Rubenstein-Taybi syndrome (RSTS - OMIM# 180849). A recent series of people with RSTS showed that 20 of 86 (23%) with pathogenic *CREBBP* mutations had deletions ranging in size from 0.9 kb to 1.35 Mb (Rusconi et al. 2015). RSTS is characterized by short stature, cardiac abnormalities, agenesis of the corpus callosum, broad and often angulated great toes and thumbs, distinctive facial features, and moderate to severe intellectual disability (GeneReviews).

RSTS typically occurs as the result of a de novo genetic abnormality, though there are reports of mildly affected parents with somatic mosaicism (Chiang et al 2009, Bartsch et al. 2010). Germline mosaicism has also been reported in parents of individuals with RSTS (Chiang et al. 2009, Tajir et al. 2013).

Each child of this individual has a 50% chance of inheriting the deletion and, thus, of also having RSTS.

No other clinically significant unbalanced genomic variants or regions of copy number neutral absence of heterozygosity were detected in this cultured amniocyte sample.

Recommendations:
1. Genetic counseling is recommended.

2. Cytogenomic microarray results should be interpreted in the context of the patient's clinical and family history. Clinical correlation and evaluation of both parents for subtle manifestations of RSTS are recommended.

Report copies to:
Physician NOT IN DATABASE

References:
GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1526/
PrenatalArray.org: https://prenatal.patientcrossroads.org/
UCSC genome browser: http://genome.ucsc.edu/
CCS SNP Array Evaluation Tool: http://firefly.ccs.miami.edu/cgi-bin/ROH/ROH_analysis_tool.cgi
DGV: http://dgv.tcag.ca/dgv/app/home
DECIPHER: https://decipher.sanger.ac.uk/
OMIM: http://omim.org/
dbVar: http://www.ncbi.nlm.nih.gov/dbvar/browse/
ClinGen: http://www.ncbi.nlm.nih.gov/projects/dbvar/clingen/
ExAC: http://exac.broadinstitute.org/

Rusconi D, Negri G, Colapietro P, et al. Characterization of 14 novel deletions underlying Rubinstein-Taybi syndrome: an update of the CREBBP deletion repertoire. Hum Genet 2015;134(6):613-626.

Chiang PW, Lee NC, Chien N, et al. Somatic and germ-line mosaicism in Rubinstein-Taybi syndrome. Am J Med Genet A 2009;149A(7):1463-1467.

Bartsch O, Kress W, Kempf O, et al. Inheritance and variable expression in Rubinstein-Taybi syndrome. Am J Med Genet A 2010;152A(9):2254-2261.

Tajir M, Fergelot P, Lancelot G, et al. Germline mosaicism in Rubinstein-Taybi syndrome. Gene 2013;518(2):476-478.

Abnormality Details:
Copy Number: Copy Loss
Chromosome Band: 16p13.3
Genomic Coordinates: [GRCh37] chr16:3,814,227-3,929,941
Estimated Minimum Size: 115,715 bp
Number of Probes: 239
Average LogR: -0.376

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 or loss of heterozygosity (cnAOH or cnLOH) for the loci represented on the microarray. Analysis in our laboratory is limited to detecting copy number changes (deletions and duplications) that include at least 10 probes and regions of cnAOH that include at least 500 probes. We cannot exclude abnormalities below these levels of resolution. UPD is reported when telomeric regions of cnAOH are >5Mb in length and interstitial regions of cnAOH are >15 Mb in length. Possible identity by descent is reported when regions of cnAOH > 3 Mb comprise ≥1.5% of the autosomal genome. Deletions and duplications of ≥400 kb are reported, even if clinical significance is unclear, as per provider request. Smaller deletions or duplications in regions of known microdeletion/microduplication syndromes or in clinically relevant genes will also be reported. Benign genomic variants are not reported. For neoplasia arrays, likely constitutional variants of unclear clinical significance 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 University of Washington Medicine Cytogenetics and Genomics Laboratory 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 v1.1 (Chip ID: 123456789123_R01C01). This microarray contains 850,000 probes for SNP markers. Additional details of this microarray can be found at: http://www.illumina.com/content/dam/illumina-marketing/documents/products/datasheets/datasheet_CytoSNP850K_POP.pdf

After hybridization, the microarray was washed, labeled, stained, 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 4.3 to identify chromosomal copy number variants and regions of copy number neutral absence or loss of heterozygosity.

Prelim. Called By: Lab GC Date: 11-14-2016 To: Carla Jones, MS, CGC

Procedures Performed:

81229 ZB149 Array CGH, Constitutional
G0452 Cytogenetics, Molecular, Complex Interpretation by an MD

Lab Director, MD
Cytogeneticist
Electronically signed 11/14/2016

In compliance with CMS regulations, the pathologist's signature on this report indicates that the case has been personally reviewed, and the diagnosis made or confirmed by, the Attending Pathologist. Microscopic examination was used to arrive at the diagnosis unless indicated otherwise.

Kathleen Leppig MD
Pathologist
Electronically signed 11/10/2016

In compliance with CMS regulations, the pathologist's signature on this report indicates that the case has been personally reviewed, and the diagnosis made or confirmed by, the Attending Pathologist. Microscopic examination was used to arrive at the diagnosis unless indicated otherwise.