Physician:
Physician NOT IN DATABASE,
BOX 356100

TEST, CASE
CASE #: TS-16-00039

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
1959 NE Pacific St., NW 125, BOX 356100
Seattle, WA 98195-6100
Voice: (206) 598-4488
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Patient Name on Specimen Tested: Test, Case – Baby Girl of

Date Obtained: 11/10/2016 **Age:** 1 day **Sex:** Female **Sample Type:** Molecular

Date Received: 11/10/2016 **Ref Phys:** Smith, MD, Jane M **Source:** Cord Blood

Report Date: 11/16/2016 **Ref Fac:** City Medical Center **Test Type:** SNP Array

Report Status: Final **Other Phys:** Jones, MS, CGC, Carla

Clinical Indication: Hypoplastic heart, Echogenic intracardiac focus

ISCN Diagnosis: arr[GRCh37] 2q36.1(221,819,192-222,401,086)x1

Summary: Female with a 581.9 kb deletion of chromosome 2q36.1 of uncertain clinical significance, no subclassification

Diagnosis and Comments: Constitutional cytogenomic SNP microarray analysis detected a 581.9 kb deletion of chromosome 2q36.1. It is uncertain whether this copy number variant represents an abnormality of clinical significance or a rare variant.

This deletion contains several exons of *EPHA4* (OMIM# 602188). There are no other RefSeq genes in this region. *EPHA4* encodes one of the ephrin receptor protein-tyrosine kinases. Li et al. (2015) hypothesize that *EPHA4* haploinsufficiency causes short stature. *EPHA4* is predicted to be haploinsufficient by both the ExAC algorithm (pLI = 1.00) and the DECIPHER algorithm (HI% = 1.12).

The Database of Genomic Variants (DGV), a database of copy number changes in the general population, contains 3 exonic deletions of *EPHA4* (nsv584512, nsv428407, esv2759115).

Three patients with deletions of 2q36.1 affecting only *EPHA4* are found in DECIPHER, a database of copy number changes seen in individuals undergoing clinical testing. All 3 were de novo: (1) #304170 phenotype of aplasia/hypoplasia of the phalanges of the 2nd finger and aplasia/hypoplasia of the thumb (2) 304166 phenotype of aplasia/hypoplasia of the phalanges of the 2nd finger and aplasia/hypoplasia of the thumb (3) 282314 short digits.

Two patients with small isolated deletions affecting only *EPHA4* are found in the ISCA dataset of copy number changes found in people via clinical testing. Inheritance was unknown in both: (1) nsv931293; classified as likely benign; phenotype was developmental delay and/or other significant developmental or morphological phenotypes; (2) nsv533097 classified as of uncertain clinical significance; phenotype was autism.

No unbalanced genomic variants or regions of copy number neutral absence of heterozygosity known to be pathogenic were detected.

Recommendations:
1. Genetic counseling is recommended.

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

3. Parental studies can be done by either cytogenomic microarray or FISH using a probe that hybridizes within the deleted region to clarify whether this copy number change is de novo or inherited. Inherited copy number changes are more likely to be benign, although variable expressivity and incomplete penetrance complicate interpretation.

4. If parental testing is desired, please submit 5cc of peripheral blood collected in EDTA for microarray or 5cc of peripheral blood collected in sodium heparin for FISH and include the name of the proband. If FISH is used for parental follow-up, a new sample from this individual may be needed as a positive control. There is a charge for these tests. Please contact the lab at 206-598-4488 if any questions.

References:

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/

Li C, Chen R, Fan X, et al. EPHA4 haploinsufficiency is responsible for the short stature of a patient with 2q35-q36.2 deletion and Waardenburg syndrome. BMC Med Genet 2015;16:23.

Abnormality Details:

Copy Number: Copy Loss
Chromosome Band: 2q36.1
Genomic Coordinates: [GRCh37] chr2:221,819,192-222,401,086
Estimated Minimum Size: 581,895 bp
Number of Probes: 184
Average LogR: -0.348

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: 200691440042_R06C01). 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.

Procedures Performed:

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

Lab Director, MD
Cytogeneticist
Electronically signed 09/19/2016

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

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