SNP Array

PATIENT
Name: **Patient, Sample**
Accession #: 00-000000
DOB: 00/00/0000
Gender: N/A
MRN: N/A
Indication: Diagnostic
Ethnicity: N/A

TEST INFORMATION
Portal Order #: 000000
Family #: 000000
Specimen #: N/A
Specimen type: Blood EDTA (Purple top)
Collection date: N/A
Received date: N/A
Final Report:

PHYSICIAN
Physician, Sample

ADDITIONAL RECIPIENTS
Sample Client
Phone: (000) 000-0000
Fax: (000) 000-0000

FACILITY
Ambry Genetics

, CA

NOTE: THIS IS A SAMPLE REPORT AND MAY NOT REFLECT ACTUAL PATIENT DATA. FORMAT AND/OR CONTENT MAY BE UPDATED PERIODICALLY.

POSITIVE: Pathogenic CNV Detected

Results

Change	Chromosome Region	Classification	Genomic Coordinates	Min Size	Max Size
GAIN	**22q11.21**	**Pathogenic**	**18916828 - 21804911**	**2.888 Mb**	**3.266 Mb**

SNP Array Result: arr[GRCh37] 22q11.21(18916828_21804911)x3

Interpretation

COPY NUMBER VARIATIONS

The results of this test indicate an interstitial **copy number GAIN** at **22q11.21**, which is a minimum of 2.888 Mb in size and involves 83 genes (see RefSeq genes below), including *TBX1*. This copy number gain is the reciprocal duplication of the ~3 Mb region deleted in patients with DiGeorge/velocardiofacial syndrome and is mediated by LCRA and LCRD (also known as LCR22-2 and LCR22-4) (Ou, 2008; Portnoi, 2009). Similar copy gains have been reported in the literature in individuals with variable features including mild to moderate intellectual disability, developmental delays, speech delay, behavioral concerns, autism spectrum disorder, minor dysmorphic facial features, and hypotonia. Other reported features include failure to thrive, congenital heart defects, cleft palate, velopharyngeal insufficiency, hearing loss, and urogenital abnormalities (Ou, 2008; Portnoi, 2009; Wenger, 2016; Wentzel, 2008). The 22q11.2 microduplications are characterized by both reduced penetrance and variable expressivity, and thus may be inherited from an individual who is unaffected or mildly affected (Ou, 2008; Portnoi, 2009; Wentzel, 2008). Please note, this assay cannot assess if this copy gain is in tandem or inserted elsewhere in the genome (Mazzarella and Schlessinger, 1998). Based on gene content and supporting literature, this copy gain is considered to be pathogenic. Clinical correlation is recommended.

Genetic testing for pathogenic alterations in family members can be helpful in identifying at-risk individuals.

REGIONS OF HOMOZYGOSITY

No regions of homozygosity were detected.

Genetic counseling is a recommended option for all patients undergoing genetic testing.

Electronically Signed By **Sample Director, on 00/00/0000 at 0:00:00 PM**

All content hereafter is supplemental information to the preceding report.

References

- Mazzarella R and Schlessinger D (1998) Genome Res 8(10):1007-1021. **PMID:** 9799789
- Ou Z, et al. (2008) Genet Med 10(4):267-277. **PMID:** 18414210
- Portnoi M. (2009) Eur J Med Genet 52(2-3):88-93. **PMID:** 19254783
- Wenger TL, et al. (2016) Mol Autism 7:27. **PMID:** 27158440
- Wentzel C, et al. (2008) Eur J Med Genet 51(6):501-510. **PMID:** 18707033

RefSeq Genes

The **22q11.21** region contains 83 genes: *PRODH, DGCR5, DGCR9, DGCR10, DGCR11, DGCR2, TSSK2, ESS2, GSC2, LINC01311, SLC25A1, CLTCL1, HIRA, MRPL40, C22orf39, UFD1, CDC45, CLDN5, LINC00895, SEPT5, SEPT5-GP1BB, GP1BB, TBX1, GNB1L, RTL10, TXNRD2, COMT, MIR4761, ARVCF, MIR185, TANGO2, MIR3618, MIR1306, DGCR8, TRMT2A, MIR6816, RANBP1, SNORA77B, ZDHHC8, CCDC188, LOC284865, LINC00896, MIR1286, RTN4R, DGCR6L, FAM230A, GGTLC3, TMEM191B, PI4KAP1, RIMBP3, LOC101927859, LINC01660, ZNF74, SCARF2, KLHL22, MED15, POM121L4P, TMEM191A, SERPIND1, PI4KA, SNAP29, CRKL, LINC01637, AIFM3, LZTR1, THAP7, THAP7-AS1, TUBA3FP, P2RX6, SLC7A4, MIR649, P2RX6P, LRRC74B, BCRP2, LOC102724728, FAM230B, GGT2, LOC102724728, POM121L8P, LOC100996335, RIMBP3C, RIMBP3B, HIC2*

SNP Array Assay Information

General Information: Genomic imbalances are an underlying cause of congenital anomalies, developmental delay, intellectual disability, autism, dysmorphism and numerous genetic syndromes. Routine karyotype analysis can detect some common chromosomal imbalances such as aneuploidies but cannot detect smaller DNA rearrangements. Chromosomal Microarray Analysis (CMA) is a technique that allows for high resolution genome-wide detection of unbalanced structural and numerical chromosomal abnormalities. In addition, SNP probes are used to detect copy-neutral chromosomal changes, such as regions of homozygosity (ROH), including patterns consistent with uniparental disomy (UPD), consanguinity, and/or identity by descent. Importantly, not all copy-neutral chromosomal changes will be detectable by the methodology due to the underlying genetic mechanism. The level of resolution of SNP Array depends primarily on the number and spacing of the oligonucleotide probes on the array.

Methodology: Genomic deoxyribonucleic acid (gDNA) is isolated from the patient's specimen using a standardized kit, quantified, labeled and hybridized to an oligonucleotide array with more than 1.9 million copy number probes and nearly 750,000 SNP probes used for genotyping and copy number analysis. This array allows for detection of loss of copy number (deletion), gain of copy number (duplication), and regions of homozygosity.

Analytical Range: The Ambry CMA: SNP Microarray (Affymetrix® CytoScan™ HD Array, Santa Clara, CA) backbone probe spacing is set at an average of 1.1 kb throughout the entire human genome and an average of 880 basepairs in intragenic regions throughout the genome. A copy loss of size greater than 100kb and copy gain of size greater than 300kb is reported, unless the copy number variant (CNV) is classified as benign or likely benign based on a multifactorial classification scheme or does not include any coding sequence. Smaller copy number change may be reported when it includes a gene(s) with potential clinical relevance. The array detects currently known microdeletion/duplication syndromes, UPD due to isodisomy and most disorders detected by chromosomal analysis and FISH tests, excluding balanced rearrangements and polyploidy. Genomic regions with lower complexity or significant sequence homology may have decreased probe density and/or analytic sensitivity. Copy number alterations restricted to the pseudoautosomal regions of the sex chromosomes are not routinely reported. Copy number neutral ROHs greater than 10 Mb in size are reported. ROH totaling 2.5% or greater of the covered genome will be reported.

Expected (Normal) Value: Diagnostic: No significant copy number changes or regions of homozygosity were detected. Family History or Carrier Screen: No significant copy number changes or regions of homozygosity were detected.

Result Reports: The CNV location is reported by region and location on the chromosome, and includes the min/max size (Mb) of the span of loss or gain. Minimum size (Min size Mb/kb) represents the distance between the first deviated proximal and last deviated distal probes of the CNV. Maximum size (Max size Mb/kb) represents the distance between the first non-deviated proximal and distal probes flanking the CNV, and genomic coordinates are reported based on the combination of the deviated copy number and SNP probes at the CNV boundaries. Array nomenclature is based on the ISCN (International System for Human Cytogenetic Nomenclature) 2016 guidelines. Analysis is based on genome assembly GRCh 37/hg19. CNVs in the following classifications are always reported and are based on the following definitions:

- **Pathogenic:** CNV with sufficient evidence to classify as pathogenic.
- **Likely Pathogenic:** CNV with strong evidence in favor of pathogenicity.
- **Uncertain Clinical Significance:** CNV with limited and/or conflicting evidence regarding pathogenicity.

Reclassification Reports: The SNP array analysis and CNV(s) classification and interpretation are performed based on the information and literature available as of the date the proband SNP array report was issued. Over time, as new information evolves and becomes available, the CNV(s) classification and interpretation may change. Clients should recontact the laboratory with any pertinent changes in clinical phenotype and periodically to determine if a reported alteration has been reclassified. An unsolicited reclassification report may also be issued if the laboratory identifies new information that impacts the overall classification and interpretation of the reported SNP array results.

Resources:
The following references are used in copy number variation classification when applicable for observed alterations.
1. HGMD® [Internet]: Stenson PD et al. *Genome Med.* 2009;1(1):13 World Wide Web URL: www.hgmd.cf.ac.uk.
2. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), Copyright® 1966-2017. World Wide Web URL: http://omim.org
3. DECIPHER database [Internet]: Bragin E, et al. *Nucleic Acids Res* 2014:42(Database issue):D993-D1000 World Wide Web URL: http://decipher.sanger.ac.uk
4. Database of Genomic Variants: MacDonald JR, et al. *Nucleic Acids Res* 2014 Jan;42(Database issue):D986-92. World Wide Web URL: http://dgv.tcag.ca/dgv/app/home
5. UCSC Genome Browser: Kent WJ, et al. *Genome Res* 2002 Jun;12(6):996-1006. World Wide Web URL: https://genome.ucsc.edu/
6. ClinGen. Rehm H.L, et al. *N Engl J Med* 2015 372(23):2235-42. World Wide Web URL: https://www.clinicalgenome.org/

Disclaimer: This test was developed, and its performance characteristics were determined by Ambry Genetics Corporation. It has not been cleared or approved by the US Food and Drug Administration. The FDA does not require this test to go through premarket FDA review. It should not be regarded as investigational or for research. This test should be interpreted in context with other clinical findings. The Ambry Test: SNP Array will only detect net gain or loss of genomic material and regions of homozygosity (ROH) meeting reporting criteria and therefore is not intended to analyze the following types of chromosomal aberrations: balanced translocations, Robertsonian translocations, balanced insertions, inversions, point mutations, low level mosaicism, epigenetic abnormalities, heterodisomic or mosaic UPD or any microdeletions and duplications that are under the resolution of the array or not represented on the array. A negative result from the analysis cannot rule out the possibility that a tested individual carries an aberration in the undetectable group. Although molecular tests are highly accurate, rare diagnostic errors may occur. Possible diagnostic errors include sample mix-up, technical errors, and clerical errors. This report does not represent medical advice. Any questions, suggestions, or concerns regarding interpretation of results should be forwarded to a genetic counselor, medical geneticist, or physician skilled in interpretation of the relevant medical literature. This laboratory is certified under the Clinical Laboratory Improvement Amendments (CLIA) as qualified to perform high complexity clinical laboratory testing.