ARUP LABORATORIES | aruplab.com
500 Chipeta Way, Salt Lake City, Utah 84108-1221
phone: 801-583-2787, toll free: 800-522-2787
Tracy I. George, MD, Chief Medical Officer

Patient Report

Patient Age/Sex: Male

Specimen Collected: 20-Dec-21 09:54

Cytogenomic SNP Microarray Buccal Sponge | **Received: 21-Dec-21 10:47** | **Report/Verified: 21-Dec-21 10:49**

Procedure	Result	Units	Reference Interval
Cytogenomic SNP Microarray Buccal Swab	**Abnormal** * f1 i1		Normal

Result Footnote

f1: Cytogenomic SNP Microarray Buccal Swab
Test Performed: Cytogenomic SNP Microarray-Buccal Swab (CMA BUCCAL)
Specimen Type: Buccal Swab
Indication for Testing: Hyperphagia, gross motor delay, learning disability, hypotonia, bone fragility
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RESULT SUMMARY
Abnormal Microarray Result (Male)

16p11.2 Distal Deletion (BP2 to BP3 Region)

Classification: Pathogenic, Reduced Penetrance
Copy number change: 16p11.2 loss
Size: 219 kb

RESULT DESCRIPTION
This analysis showed an interstitial deletion (1 copy present) involving chromosome 16, within 16p11.2. This region contains at least 12 genes (listed below), including the gene SH2B1.

This is a deletion of the 16p11.2 distal (SH2B1) region, involving recurrent breakpoints (BPs) within flanking low-copy repeat regions, BP2 and BP3. The reported size of this deletion may vary across studies due to variability in breakpoints within flanking repeat regions. Please note this region is distinct from the recurrent 16p11.2 proximal (TBX6) region, which involves breakpoints BP4-BP5.

INTERPRETATION
Deletion of the 16p11.2 (SH2B1) distal region has been reported in association with a variable clinical phenotype that may include obesity, developmental delay/intellectual disability, behavioral difficulties, autism, ADHD, schizophrenia, and craniofacial dysmorphism.

The 16p11.2 distal deletion shows incomplete penetrance. Expression of any phenotype associated with this deletion has been estimated to be 62.4 percent (26.8–94.4, 95 percent confidence interval) (Rosenfeld et al. 2013). 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. It is significantly enriched in patients as compared to control populations.

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 susceptibility factor for expression of associated phenotypes.

This deletion may be de novo or inherited from a carrier parent. If warranted, parental testing by microarray analysis may be considered to evaluate the potential origin of this deletion and for recurrence risk counseling.

Recommendations:
1) Genetic counseling
2) Parental testing for the deletion by genomic microarray analysis may be considered. This test is

Result Footnote

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available, at a charge, through ARUP Laboratories. Please order test code 2003414, Cytogenomic SNP Microarray, and include the accession number for this case.

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

References:
1) Loviglio et al. Chromosomal contacts connect loci associated with autism, BMI and head circumference phenotypes. Mol Psychiatry. 2017 Jun;22(6):836-849. PMID: 27240531.
2) Bachmann-Gagescu et al. Recurrent 200-kb deletions of 16p11.2 that include the SH2B1 gene are associated with developmental delay and obesity. Genet Med. 2010 Oct;12(10):641-7. PMID: 20808231.
3) Barge-Schaapveld et al. The atypical 16p11.2 deletion: a not so atypical microdeletion syndrome? Am J Med Genet A. 2011 May;155A(5):1066-72. PMID: 21465664.
4) Bochukova et al. Large, rare chromosomal deletions associated with severe early-onset obesity. Nature. 2010 Feb 4;463(7281):666-70. PMID: 19966786.
5) Guha et al. Implication of a rare deletion at distal 16p11.2 in schizophrenia. JAMA Psychiatry. 2013 Mar;70(3):253-60. PMID: 23325106.
6) Rosenfeld et al. Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med. 2013 Jun;15(6):478-81. PMID: 23258348.

Cytogenetic Nomenclature (ISCN):
arr[GRCh37] 16p11.2(28824491_29043972)x1

Genes in the 16p11.2 deleted region:
ATXN2L, TUFM, MIR4721, SH2B1, ATP2A1, ATP2A1-AS1, RABEP2, CD19, NFATC2IP, MIR4517, SPNS1, LAT

Technical Information
- This assay was performed using the CytoScan(TM) 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) as well as copy-neutral alterations (regions of homozygosity; ROH) that indicate an absence- or loss-of-heterozygosity (AOH or LOH)
- AOH may be present due to 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, likely pathogenic, or variant of uncertain significance are generally reported, based on information available at the time of review
- Known or expected pathogenic CNVs affecting genes with known clinical significance but which are unrelated to the indication for testing will generally be reported

Result Footnote

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- 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 50 kb and gains greater than 400 kb are generally reported, dependent on genomic content
- ROH are generally reported when a single terminal ROH is greater than 3 Mb and a single interstitial ROH is greater than 10-15 Mb (dependent upon chromosomal location and likelihood of imprinting disorder) or when total autosomal homozygosity is greater than 3 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. 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)

Data Sharing
In cooperation with the National Institutes of Health's effort to improve understanding of specific genetic variants, ARUP submits HIPAA-compliant, de-identified (cannot be traced back to the patient) genetic test results and health information to public databases. The confidentiality of each sample is maintained. If you prefer that your test result not be shared, call ARUP Laboratories at (800) 242-2787 ext. 3301. Your de-identified information will not be disclosed to public databases after your request is received, but a separate request is required for each genetic test. Additionally, patients have the opportunity to participate in patient registries and research. To learn more, visit ARUP's Genetics website at www.aruplab.com/genetics.

This result has been reviewed and approved by Julie Leana Cox, PhD, FACMG

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

Test Information

i1: Cytogenomic SNP Microarray Buccal Swab

INTERPRETIVE INFORMATION: Cytogenomic SNP Microarray Buccal Swab

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.

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

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Counseling and informed consent are recommended for genetic testing. Consent forms are available online.

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