ARUP LABORATORIES
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Jonathan R. Genzen, MD, PhD, Chief Medical Officer

Client: Example Client ABC123
123 Test Drive
Salt Lake City, UT 84108
UNITED STATES

Physician: Doctor, Example

Patient: Patient, Example

DOB	4/1/1997
Gender:	Male
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Cytogenomic SNP Microarray Buccal Swab

ARUP test code 2006267

Cytogenomic SNP Microarray Buccal Swab

Abnormal * **(Ref Interval: Normal)**

Test Performed: Cytogenomic SNP Microarray-Buccal Swab (CMA BUCCAL)
Specimen Type: Buccal
Indication for Testing: Suspect Smith-Magenis syndrome; bilateral kidney tumors

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RESULT SUMMARY
Abnormal Microarray Result (Male)

17p11.2 Deletion (Smith-Magenis syndrome)

Classification: Pathogenic
Copy number change: 17p11.2 loss
Size: 3.4 Mb

RESULT DESCRIPTION
This analysis showed an interstitial deletion (1 copy present) involving chromosome 17, within 17p11.2. This region contains at least 80 genes (listed below), including RAI1 and FLCN.

INTERPRETATION
This result is consistent with a clinical diagnosis of Smith-Magenis syndrome (SMS). Features commonly associated with this disorder include infantile hypotonia with feeding difficulties and failure to thrive, developmental delay/ intellectual disability, a subtly distinctive facial appearance that becomes more evident with age, obesity, sleep disturbance, and a distinct neurobehavioral phenotype that includes maladaptive, stereotypic, and self-injurious behaviors. Additional features may include short stature, scoliosis, brachydactyly, otolaryngologic and ocular abnormalities, hearing loss, peripheral neuropathy with insensitivity to pain, heart defects, and recurrent infections. Some individuals with SMS due to deletion of 17p11.2 also show features of Birt-Hogg-Dub (BHD) syndrome related to haploinsufficiency of the gene FLCN. BHD is an adult-onset hereditary cancer syndrome characterized by cutaneous fibrofolliculomas, pulmonary cysts, spontaneous pneumothorax, and renal tumors.

The majority of 17p11.2 deletions are de novo occurrences. In the absence of clinical findings in the parents of this patient, parental testing may not be warranted.

Recommendation:
Genetic counseling

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

H=High, L=Low, *=Abnormal, C=Critical

References:
1) Smith et al. Smith-Magenis Syndrome. GeneReviews. 2022. (www.ncbi.nlm.nih.gov/books/NBK1310/). PMID: 20301487.
2) Rinaldi et al. Smith-Magenis Syndrome-Clinical Review, Biological Background and Related Disorders. Genes (Basel). 2022 Feb 11;13(2):335. PMID: 35205380.
3) Vocke et al. A diagnosis of Birt-Hogg-Dub syndrome in individuals with Smith-Magenis syndrome: Recommendation for cancer screening. Am J Med Genet A. 2023 Feb;191(2):490-497. PMID: 36513625.
4) Girirajan et al. Genotype-phenotype correlation in Smith-Magenis syndrome: Evidence that multiple genes in 17p11.2 contribute to the clinical spectrum. Genet Med. 2006 Jul;8(7):417-27. PMID: 16845274.
5) Elsea and Girirajan. Smith-Magenis syndrome. Eur J Hum Genet. 2008 Apr;16(4):412-21. PMID: 18231123.
6) Parents and Researchers Interested in Smith-Magenis Syndrome (PRISMS). (www.prisms.org)

Cytogenomic Nomenclature (ISCN):
arr[GRCh37] 17p11.2(16816656_20213006)x1

Genes within the 17p11.2 deleted region:
TBC1D27P, TNFRSF13B, LOC284191, LINC02090, MPRIP, PLD6, FLCN, COPS3, NT5M, MED9, RASD1, PEMT, SMCR2, RAI1, RAI1-AS1, SMCR5, SREBF1, MIR6777, MIR33B, TOM1L2, DRC3, ATPAF2, GID4, DRG2, LOC105371566, MYO15A, ALKBH5, LLGL1, FLII, MIEF2, TOP3A, SMCR8, SHMT1, MIR6778, EVPLL, LINC02076, KRT17P5, KRT17P2, KRT16P1, LGALS9C, USP32P2, FAM106A, CCDC144B, TBC1D28, ZNF286B, FOXO3B, TRIM16L, FBXW10, TVP23B, LOC101929141, PRPSAP2, SLC5A10, FAM83G, GRAP, SNORD3B-1, SNORD3B-2, LOC102724624, LOC388436, LOC79999, SNORD3D, GRAPL, SNORD3A, SNORD3C, EPN2, EPN2-IT1, EPN2-AS1, B9D1, MIR1180, MAPK7, MFAP4, RNF112, SLC47A1, SNORA59A, SNORA59B, ALDH3A2, SLC47A2, ALDH3A1, ULK2, AKAP10, SPECC1

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
- Variants that do not fall within these 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

H=High, L=Low, *=Abnormal, C=Critical

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.

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Cytogenomic SNP Microarray Buccal Swab	23-048-151666	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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