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

Physician: Doctor, Example

Patient: Patient, Example

DOB	Unknown
Gender:	Unknown
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Tay-Sachs Disease (HEXA) Sequencing and Deletion/Duplication

ARUP test code 3004486

HEXA Specimen	Whole Blood
HEXA Interp	Positive

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

RESULT
Two apparent copies of a pathogenic variant were detected in the HEXA gene.

PATHOGENIC VARIANT
Gene: HEXA (NM_000520.4)
Nucleic Acid Change: c.1123delG; Homozygous
Amino Acid Alteration: p.Glu375ArgfsTer7
Inheritance: Autosomal Recessive

INTERPRETATION
Two apparent copies of a pathogenic variant, c.1123delG; p.Glu375ArgfsTer7, were detected in the HEXA gene by massively parallel sequencing. Pathogenic variants in HEXA are inherited in an autosomal recessive manner and are associated with Tay-Sachs disease and GM2-gangliosidosis (MIM: 272800). This result is consistent with a diagnosis of Tay-Sachs disease or GM2-gangliosidosis.

Please refer to the background information included in this report for the methodology and limitations of this test.

Evidence for variant classification:
The HEXA c.1123delG; p.Glu375ArgfsTer7 variant (rs766138785) is reported in the literature in multiple individuals affected with Tay-Sachs disease or GM2 gangliosidosis, all of whom also carried a second pathogenic HEXA variant (Jahnova 2019, Jamrozik 2013, Motalvo 2005). This variant is found on only two chromosomes in the Genome Aggregation Database (2/246288 alleles), indicating it is not a common polymorphism. This variant causes a frameshift by deleting a single nucleotide, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. This result should be correlated with clinical findings and hexosaminidase A activity level. Genetic consultation is recommended. Family members should be offered testing for the identified variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants, other than pseudodeficiency variants, are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations:
NONE

REFERENCES
Jahnova H et al. Amyotrophy, cerebellar impairment and psychiatric disease are the main symptoms in a cohort of 14 Czech patients with the late-onset form of Tay-Sachs disease. J Neurol. 2019 Aug;266(8):1953-1959. PMID: 31076878.
Jamrozik Z et al. Late onset GM2 gangliosidosis mimicking spinal muscular atrophy. Gene. 2013 Sep 25;527(2):679-82. PMID: 23820084.
Montalvo AL et al. Molecular analysis of the HEXA gene in Italian patients with infantile and late onset Tay-Sachs disease: detection of fourteen novel alleles. Hum Mutat. 2005 Sep;26(3):282. PMID: 16088929.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Tay-Sachs Disease (HEXA) Sequencing and Deletion/Duplication

CHARACTERISTICS: Hexosaminidase A (HEXA) enzyme deficiency is

characterized by neuronal deterioration resulting in intellectual disability and motor development. Clinical severity is variable. Onset by six months of age with rapid progression occurs with the acute infantile form of Tay-Sachs disease while juvenile- and adult-onset forms manifest a less severe course. HEXA deficiency results in the accumulation and lysosomal storage of GM2 (ganglioside).

INCIDENCE: Varies by ethnicity. 1 in 3,000 for Ashkenazi Jewish and French Canadians; other high-risk populations include Louisiana Cajuns and Old Order Amish. 1 in 300,000 for the general population

INHERITANCE: Autosomal recessive

CAUSE: Two pathogenic variants in the HEXA gene, located on opposite chromosomes

CLINICAL SENSITIVITY: 99 percent

GENE TESTED: HEXA (NM_000520)

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage and to confirm reported variants that do not meet acceptable quality metrics. A proprietary bioinformatic algorithm was used to detect large (single exon-level or larger) deletions or duplications in the indicated genes. Large deletions/duplications were confirmed using an orthogonal exon-level microarray. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY AND SPECIFICITY: The analytical sensitivity is approximately 99 percent for single nucleotide variants (SNVs) and greater than 93 percent for insertions/duplications/deletions (indels) from 1-10 base pairs in size. Indels greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced. Deletions of two exons or larger are detected with sensitivity greater than 97 percent; single exon deletions are detected with 62 percent sensitivity. Duplications of three exons or larger are detected at greater than 83 percent sensitivity. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a diagnosis of Tay-Sachs disease. This test only detects variants within or overlapping the coding regions and intron-exon boundaries of the HEXA gene. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Regulatory region variants and deep intronic variants will not be identified. Precise breakpoints for large deletions or duplications are not determined in this assay and single exon deletions/duplications may not be detected based on the breakpoints of the rearrangement. The actual breakpoints for the deletion or duplication may extend beyond or be within the exon(s) reported. This test is not intended to detect duplications of two or fewer exons in size, though these may be identified. Single exon deletions, such as the 7.6kb deletion common in French-Canadian populations, are reported but at a lower sensitivity. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations caused by the presence of pseudogenes, repetitive, or homologous regions. This test is not intended to detect low-level mosaic or somatic variants, gene conversion events, complex inversions, translocations, mitochondrial DNA (mtDNA) mutations, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts are not analyzed.

This test was developed and its performance characteristics

determined by ARUP Laboratories. It has not been cleared or approved by the U.S. 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
HEXA Specimen	22-301-105028	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
HEXA Interp	22-301-105028	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

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