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 Age/Sex: 1 day Female

Specimen Collected: 23-Nov-21 14:56

Tay-Sachs Disease (HEXA) by NGS, DelDup **|Received: 24-Nov-21 12:19** **Report/Verified: 24-Nov-21 12:25**

Procedure	Result	Units	Reference Interval
HEXA Specimen	Whole Blood		
HEXA Interp	See Note [i1]		

Test Information

i1: HEXA Interp

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

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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.