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Client: ARUP Example Report Only
500 Chipeta Way
Salt Lake City, UT 84108
UNITED STATES

Physician: TEST, DR

Patient: Test, GBA3

DOB	
Gender:	Female
Patient Identifiers:	18263
Visit Number (FIN):	18484
Collection Date:	8/22/2019 08:55

Gaucher Disease (GBA) Sequencing

ARUP test code 3001648

GBA FGS- Specimen	Whole Blood
GBA FGS Interpretation	**Positive** *

TEST PERFORMED - 3001648
TEST DESCRIPTION - Gaucher Disease (GBA) Sequencing
INDICATION FOR TEST - Not Provided

RESULT
Two pathogenic variants were detected in the GBA gene.

DNA VARIANTS
Classification: Pathogenic
Gene: GBA
Nucleic Acid Change: c.259C>T; Heterozygous
Amino Acid Alteration: p.Arg87Trp

Classification: Pathogenic
Gene: GBA
Nucleic Acid Change: c.475C>T; Heterozygous
Amino Acid Alteration: p.Arg159Trp

INTERPRETATION
Two pathogenic variants, c.259C>T; p.Arg87Trp and c.475C>T; p.Arg159Trp, were detected in the GBA gene by sequencing. This individual is predicted to be affected with Gaucher disease if the two identified variants are on opposite chromosomes. Symptoms and age of onset are highly variable. Parental testing could confirm whether the variants are in cis or trans.

Evidence for variant classification:
The GBA c.259C>T; p.Arg87Trp variant (rs1141814), also known as p.Arg48Trp, is reported in the homozygous and compound heterozygous state in several individuals affected with Gaucher disease (Beutler 1995, Lei 2018, Kim 2017). The variant is listed in the ClinVar database (Variation ID: 4321) and is reported in the general population with an overall allele frequency of 0.002% (7/251272 alleles) in the Genome Aggregation Database. The arginine at this position is highly conserved and computational algorithms (PolyPhen-2, SIFT) predict this variant is deleterious. Considering available information, this variant is classified as pathogenic.

The GBA c.475C>T; p.Arg159Trp variant (rs439898), also known as p.Arg120Trp, is reported in several individuals affected with Gaucher disease, Parkinsons disease, and dementia with Lewy bodies (Li 2014, Momosaki 2018, Nalls 2013, Potnis 2018). The variant is listed in the ClinVar database (Variation ID: 65570) and is reported in the general population with an overall allele

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

frequency of 0.002% (6/282498 alleles) in the Genome Aggregation Database. The arginine at this position is highly conserved and computational algorithms (PolyPhen-2, SIFT) predict this variant is deleterious. Considering available information, this variant is classified as pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Parental testing should be considered to confirm the chromosomal origin of the identified pathogenic variants (Familial Mutation, Targeted Sequencing, ARUP test code 2001961). Family members should be offered testing for the variant identified in their family lineage. Carrier screening for Gaucher disease should be offered to this individual's reproductive partner.

COMMENTS
Reference Sequence: GenBank # NM_001005741.2 (GBA)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not included in this report.

REFERENCES
Beutler E et al. Five new Gaucher disease mutations. Blood Cells Mol Dis. 1995;21(1):20-4.

Kim YM et al. Case report of unexpected gastrointestinal involvement in type 1 Gaucher disease: comparison of eliglustat tartrate treatment and enzyme replacement therapy. BMC Med Genet. 2017 May 15;18(1):55.

Lei K et al. A pilot screening of high-risk Gaucher disease children using dried blood spot methods in Shandong province of China. Orphanet J Rare Dis. 2018 Apr 6;13(1):48.

Li Y et al. Clinicogenetic study of GBA mutations in patients with familial Parkinson's disease. Neurobiol Aging. 2014 Apr;35(4):935.e3-8.

Momosaki K et al. High-risk screening for Gaucher disease in patients with neurological symptoms. J Hum Genet. 2018 Jun;63(6):717-721.

Nalls MA et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 2013 Jun;70(6):727-35.

Potnis KC et al. Corticobasal syndrome in a man with Gaucher disease type 1: Expansion of the understanding of the neurological spectrum. Mol Genet Metab Rep. 2018 Oct 18;17:69-72.

This result has been reviewed and approved by Rong Mao, M.D.

BACKGROUND INFORMATION: Gaucher Disease (GBA) Sequencing

CHARACTERISTICS: Gaucher disease (GD) is a lysosomal storage disorder with phenotypes ranging from perinatal lethality to lack of symptoms. There are three GD subtypes. Type 1 GD manifests with bone disease, hepatosplenomegaly, anemia, thrombocytopenia, and lung disease but no central nervous system (CNS) involvement. Type 2 GD exhibits CNS symptoms before age 2 and rapidly progresses resulting in death by age 4. Type 3 GD presents as early as age 2 with CNS symptoms that slowly progress resulting in death during the third or fourth decade.
INCIDENCE: 1 in 900 Ashkenazi Jewish individuals; approximately 1 in 57,000 to 1 in 75,000 in general population.
INHERITENCE: Autosomal recessive.
CAUSE: Two pathogenic GBA variants on opposite chromosomes.
CLINICAL SENSITIVITY: 99 percent.
METHODOLOGY: Long range PCR followed by bidirectional sequencing of all coding regions and intron-exon boundaries of the GBA gene.
ANALYTICAL SENSITIVITY AND SPECIFICITY: approximately 99 percent.
LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region variants, deep intronic variants, large deletions/duplications/insertions, gene conversion and complex gene events may not be detected.

Test developed and characteristics determined by ARUP Laboratories. See Compliance Statement C: aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
GBA FGS- Specimen	19-234-102576	8/22/2019 8:55:00 AM	8/22/2019 10:47:53 AM	8/22/2019 1:56:00 PM
GBA FGS Interpretation	19-234-102576	8/22/2019 8:55:00 AM	8/22/2019 10:47:53 AM	8/22/2019 1:56:00 PM

END OF CHART

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