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

Physician: Doctor, Example

Patient: Patient, Example

DOB	6/30/2015
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	01/01/2017 12:34

Guanidinoacetate Methyltransferase (GAMT) Deficiency Sequencing

ARUP test code 2011140

GAMT Sequencing Specimen: Whole Blood

GAMT Sequencing Interpretation: **Positive** *

TEST PERFORMED - 2011140
TEST DESCRIPTION - Guanidinoacetate Methyltransferase (GAMT) Deficiency Sequencing
INDICATION FOR TEST - Confirm Diagnosis

RESULT
One pathogenic and one likely pathogenic variant were detected in the GAMT gene.

DNA VARIANTS
Classification: Pathogenic
Gene: GAMT
Nucleic Acid Change: c.299_311dup Heterozygous
Amino Acid Alteration: p.Arg105fs

Classification: Likely Pathogenic
Gene: GAMT
Nucleic Acid Change: c.503A>C; Heterozygous
Amino Acid Alteration: p.Tyr168Ser

INTERPRETATION
One copy of a pathogenic variant, c.299_311dup; p.Arg105fs, and one copy of a likely pathogenic variant, c.503A>C; p.Tyr168Ser, were detected in the GAMT gene by sequencing. Although the identified variants have not been previously reported to occur on the same chromosome, parental testing could confirm their chromosomal orientation. If these two variants are located on opposite chromosomes, then this molecular result would be consistent with a diagnosis of guanidinoacetate methyltransferase (GAMT) deficiency.

Evidence for variant classifications: The GAMT c.299_311dup; p.Arg105fs variant (rs80338736) has been reported in an individual with GAMT deficiency, who carried an additional GAMT variant on the opposite chromosome (Stockler 1996). The c.299_311dup variant is reported in ClinVar (Variation ID: 8302) and is observed in the general population databases with a low overall allele frequency of 0.005% (11/210322 alleles) in the Genome Aggregation Database. This variant creates a frameshift and is predicted to result in a truncated protein or mRNA that is subject to nonsense mediated decay. Taken together, the c.299_311dup variant is considered pathogenic.

The GAMT c.503A>C; p.Tyr168Ser variant (rs1131691644) has been

reported in the homozygous state in an individual with phenotypic and biochemical evidence of GAMT deficiency (Bodamer 2009), and has been reported as pathogenic in ClinVar (Variation ID: 429874). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. The tyrosine at codon 168 is highly conserved and computational algorithms (SIFT, PolyPhen2, MutationTaster) predict this variant to be damaging to the protein. Based on the currently available information, the p.Tyr168Ser variant is considered likely pathogenic.

RECOMMENDATIONS
Parental testing is recommended to confirm the chromosomal origin of the identified pathogenic variants. At-risk family members should be offered targeted testing for the identified GAMT variants (Familial Mutation, Targeted Sequencing; ARUP test 2001961). Genetic consultation is strongly recommended.

COMMENTS
Reference Sequence: GenBank # NM_000156.5 (GAMT)
Nucleotide numbering begins at the "A" of the ATG initiation codon.

REFERENCES
Bodamer OA et al. Low creatinine: the diagnostic clue for a treatable neurologic disorder. Neurology. 2009 Mar 3;72(9):854-5.

Stockler S et al. Guanidinoacetate methyltransferase deficiency: the first inborn error of creatine metabolism in man. Am J Hum Genet. 1996 May;58(5):914-22.

This result has been reviewed and approved by [redacted]

Background Information for Guanidinoacetate Methyltransferase (GAMT) Deficiency Sequencing:
Characteristics: Intellectual disability and seizure disorder of variable severity. May also include speech / language delays, movement disorder, and behavioral disorders such as autism, hyperactivity, and self-injury.
Incidence: Unknown. More than 50 cases have been described.
Inheritance: Autosomal recessive.
Cause: Pathogenic GAMT gene mutations.
Clinical Sensitivity: Based on limited data, may be as high as 99 percent.
Methodology: Bidirectional sequencing of the entire coding region and intron/exon boundaries of the GAMT gene.
Analytical Sensitivity and Specificity: 99 percent.
Limitations: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations, deep intronic mutations, and large deletions/duplications will not be detected. Mutations in genes other than GAMT are not evaluated.

Counseling and informed consent are recommended for genetic testing. Consent forms are available online at www.aruplab.com.

See Compliance Statement C: www.aruplab.com/CS

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
GAMT Sequencing Specimen	18-199-104750	7/18/2018 10:23:00 AM	7/18/2018 10 29:58 AM	7/18/2018 11:40:00 AM
GAMT Sequencing Interpretation	18-199-104750	7/18/2018 10:23:00 AM	7/18/2018 10 29:58 AM	7/18/2018 11:40:00 AM

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