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

Physician: Doctor, Example

Patient: Patient, Example

DOB	3/26/2014
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

Rett Syndrome (MECP2), Sequencing and Deletion/Duplication

ARUP test code 0051614

Rett Syndrome (MECP2) Seq, DelDup Spcm	Whole Blood
Rett Syndrome (MECP2) Seq, DelDup Int	Positive *

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TEST PERFORMED - 0051614
TEST DESCRIPTION - Rett Syndrome (MECP2), Sequencing and
Deletion/Duplication
INDICATION FOR TEST - Not Provided

RESULT
One pathogenic variant was detected in the MECP2 gene.

DNA VARIANT
Classification: Pathogenic
Gene: MECP2
Nucleic Acid Change: c.916C>T; Heterozygous
Amino Acid Alteration: p.Arg306Cys

INTERPRETATION
One copy of the pathogenic variant, c.916C>T; p.Arg306Cys was
detected in the MECP2 gene by sequencing. This result is
consistent with a molecular diagnosis of Rett syndrome.

No large deletions or duplications were detected by
deletion/duplication analysis of the MECP2 gene.

Evidence for variant classification: The MECP2 c.916C>T;
p.Arg306Cys variant (rs28935468) is a recurrent alteration in
individuals diagnosed with Rett syndrome, and often found as a
de novo change (Cheadle 2000, Wan 1999, RettBase). Transgenic
mice expressing the variant protein show developmental and
behavioral phenotypes reminiscent of the clinical symptoms found
in human patients (Brown 2016, Heckman 2014). Functional
characterization of the MECP2 variant protein indicates
disruption in its association with co-repressors, such as HDAC3
and the NCoR complex (Ebert 2013, Heckman 2014, Lyst 2013), and
reduction in in-vivo DNA occupancy (Heckman 2014). This results
in a failure of the MECP2 protein in mediating transcriptional
repression at its targets (Ebert 2013, Lyst 2013). Another
missense variant at this residue, p.Arg306His, has also been
implicated in Rett syndrome (Cheadle 2000, RettBase). The
p.Arg306Cys variant is listed as pathogenic in ClinVar
(Variation ID: 11824), and is not observed in the general
population databases (1000 Genomes Project, Exome Variant
Server, Genome Aggregation Database). Based on the above
information, the p.Arg306Cys variant is classified as pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of
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H=High, L=Low, *=Abnormal, C=Critical

medical screening and management. Testing for the identified variant should be offered to the individual's mother and other relatives who may be at risk for having affected offspring (Familial Mutation, Targeted Sequencing; ARUP test 2001961).

COMMENTS
Reference Sequences: GenBank # NM_001110792.1 (MECP2 exon 1) and NM_004992.3 (MECP2 exon 2-4)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not reported.

REFERENCES
RettBase:
http://mecp2.chw.edu.au/cgi-bin/mecp2/views/basic.cgi?form=basic

Brown K et al. The molecular basis of variable phenotypic severity among common missense mutations causing Rett syndrome. Hum Mol Genet. 2016; 25(3):558-70.

Cheadle J et al. Long-read sequence analysis of the MECP2 gene in Rett syndrome patients: correlation of disease severity with mutation type and location. Hum Mol Genet. 2000; 9(7):1119-29.

Ebert D et al. Activity-dependent phosphorylation of MeCP2 threonine 308 regulates interaction with NCoR. Nature. 2013; 499(7458):341-5.

Heckman L et al. Rett-causing mutations reveal two domains critical for MeCP2 function and for toxicity in MECP2 duplication syndrome mice. Elife. 2014 Jun 26; 3.

Lyst M et al. Rett syndrome mutations abolish the interaction of MeCP2 with the NCoR/SMRT co-repressor. Nat Neurosci. 2013; 16(7):898-902.

Wan M et al. Rett syndrome and beyond: recurrent spontaneous and familial MECP2 mutations at CpG hotspots. Am J Hum Genet. 1999; 65(6):1520-9.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: Rett Syndrome (MECP2), Sequencing and Deletion/Duplication

CHARACTERISTICS: Classic Rett syndrome is a progressive neurodevelopmental disorder characterized by normal development until 6-18 months of age followed by rapid developmental regression, deceleration of head growth, loss of speech and acquired motor skills, and seizures; purposeful use of the hands is replaced by repetitive stereotyped hand movements. MECP2-Related disorders include Rett-like syndrome, severe congenital encephalopathy, or mild to severe mental retardation.
INCIDENCE: 1 in 10,000.
INHERITANCE: X-linked dominant; most cases are sporadic.
CAUSE: Methyl-CpG-Binding Protein 2 (MECP2) gene mutations.
CLINICAL SENSITIVITY: Up to 95 percent.
METHODOLOGY: Bidirectional sequencing of the MECP2 coding regions (exons 1-4) and intron-exon boundaries; Multiplex Ligation-dependent Probe Amplification (MLPA) to detect large deletions/duplications in the MECP2 coding regions (exons 1-4).
ANALYTICAL SENSITIVITY: 99 percent for sequencing and 90 percent for MLPA.
ANALYTICAL SPECIFICITY: 99 percent for sequencing and 98 percent for
MLPA
LIMITATIONS: Breakpoints of large deletions/duplications cannot be determined; deep intronic mutations will not be detected. Diagnostics errors can occur due to rare sequence variations.

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

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

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Rett Syndrome (MECP2) Seq, DelDup Spcm	20-041-400685	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Rett Syndrome (MECP2) Seq, DelDup Int	20-041-400685	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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