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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

Inherited Insulin Resistance Syndromes (INSR) Sequencing

ARUP test code 2006274

INSR Sequencing Specimen	Blood	
INSR Sequencing Interpretation	Positive	*

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

TEST PERFORMED - 2006274
TEST DESCRIPTION - Inherited Insulin Resistance Syndrome (INSR) Sequencing
INDICATION FOR TEST - Not Provided

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

DNA VARIANT
Classification: Likely Pathogenic
Gene: INSR
Nucleic Acid Change: c.3164C>T; Homozygous
Amino Acid Alteration: p.Ala1055Val
Also Known As: Ala1028Val (mature protein)

INTERPRETATION
Two apparent copies of a likely pathogenic variant, c.3164C>T; p.Ala1055Val, were detected in the INSR gene by sequencing. This result is consistent with a diagnosis of an inherited insulin resistance syndrome. Sequence analysis is unable to detect large deletions; therefore, this individual either has two copies of the identified variant or a single copy of the variant and a large deletion on the opposite chromosome. Parental testing could determine which of the above scenarios is correct for the purposes of testing other family members.

Evidence for variant classification: The INSR c.3164C>T; p.Ala1055Val variant, also known in alternative nomenclature as Ala1028Val, is reported in the literature in several individuals affected with type A insulin resistance and Rabson-Mendenhall syndrome (Jiang 2011, Rique 2000). Parental testing of one affected individuals with this variant indicated it occurred de novo (Jiang 2011), while the other affected individual had relatives found to carry this variant who had high serum insulin levels (Rique 2000). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. Functional studies in cultured cells suggest that the p.Ala1055Val protein is poorly processed to its mature form and exhibits decreased signaling activity (Jiang 2011). Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS
Genetic consultation is strongly recommended. At-risk family members should be offered targeted testing for the identified variant (Familial Mutation, Targeted Sequencing; ARUP test code 2001961).

COMMENTS
Reference Sequence: GenBank # NM_000208.2 (INSR)
Nucleotide numbering begins at the "A" of the ATG initiation codon.
Likely benign and benign variants are not included in this report.

REFERENCES
Jiang S et al. Mendenhall syndrome - phenotypic heterogeneity of insulin receptor gene mutations. Endocr J. 2011;58(11):931-40.

Rique S et al. Identification of three novel mutations in the insulin receptor gene in type A insulin resistant patients. Clin Genet. 2000 Jan;57(1):67-9.

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

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BACKGROUND INFORMATION: Insulin Resistance Conditions (INSR) Sequencing:

CHARACTERISTICS: Extreme insulin resistance is characterized by abnormal glucose homeostasis and hyperinsulinemia, leading eventually to ketoacidosis. Donohue syndrome (leprechaunism), Rabson-Mendenhall syndrome, and Type A insulin resistance are all caused by INSR gene mutations, although severity and survival varies greatly among conditions. Symptoms may include intrauterine growth restriction, failure to thrive after birth, characteristic dysmorphic features, lack of subcutaneous fat, acanthosis nigricans, enlargement of genitalia in males and females, cystic ovaries and amenorrhea in females, premature and dysplastic dentition, and pineal hyperplasia.
INCIDENCE: Unknown; rare.
INHERITANCE: Autosomal recessive (Donohue and Rabson-Mendenhall syndromes). Type A insulin resistance can be autosomal recessive or dominant.
CAUSE: Pathogenic INSR gene mutations.
CLINICAL SENSITIVITY: Predicted to be greater than 90 percent in individuals with a clinical diagnosis.
METHODOLOGY: Bidirectional sequencing of the entire coding region and intron/exon boundaries of the INSR 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 INSR are not evaluated.

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
INSR Sequencing Specimen	20-056-112510	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
INSR Sequencing Interpretation	20-056-112510	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