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

Physician: Doctor, Example

Patient: Patient, Example

DOB	11/17/1999
Gender:	Female
Patient Identifiers:	01234567890ABCD, 012345
Visit Number (FIN):	01234567890ABCD
Collection Date:	00/00/0000 00:00

MODY and Neonatal Diabetes Panel, Sequencing

ARUP test code 3001593

Monogenic Diabetes Specimen	Whole Blood

Monogenic Diabetes Interp

Positive

RESULT
One pathogenic variant was detected in the HNF1A gene.

PATHOGENIC VARIANT
Gene: HNF1A (NM_000545.8)
Nucleic Acid Change: c.608G>A; Heterozygous
Amino Acid Alteration: p.Arg203His
Inheritance: Autosomal Dominant

INTERPRETATION
One pathogenic variant, c.608G>A; p.Arg203His, was detected in the HNF1A gene by massively parallel sequencing. Pathogenic HNF1A variants are inherited in an autosomal dominant manner, and are associated with maturity-onset diabetes of the young (MODY) type III (MIM: 600496; OMIM(R)). Therefore, this individual is predicted to have a predisposition for maturity-onset diabetes of the young (MODY). This individual's offspring have a 50 percent chance of inheriting the pathogenic variant.

Please refer to the background information included in this report for a list of the genes analyzed, methodology, and limitations of this test.

Evidence for variant classification:
The HNF1A c.608G>A; p.Arg203His variant (rs587780357, ClinVar Variation ID 129235) is reported in the literature in multiple individuals affected with monogenic diabetes (Ivanoshchuk 2023, Mirshahi 2022, Svalastoga 2023, Tsoi 2024, Wang 2022). This variant is only observed on two alleles in the Genome Aggregation Database (v2.1.1), indicating it is not a common polymorphism. Additionally, other amino acid substitutions at this codon (Arg203Cys, Arg203Gly, and Arg203Ser) have also been reported in individuals with monogenic diabetes (Lopez 2011, Mirshahi 2022, Santos Monteiro 2023). Functional analyses of the variant protein show reduced DNA binding and decreased transactivation by Arg203His variant (Althari 2020). Computational analyses predict that this variant is deleterious (REVEL: 0.958). Based on available information, this variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic and endocrinology consultations are indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic

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

HNF1A variant (Familial Targeted Sequencing, ARUP test code 3005867).

COMMENTS
Likely benign and benign variants are not reported.
Variants in the following region(s) may not be detected by NGS with sufficient confidence in this sample due to technical limitations: None

REFERENCES

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Lopez AP et al. HNF1 alpha gene coding regions mutations screening, in a Caucasian population clinically characterized as MODY from Argentina. Diabetes Res Clin Pract. 2011 Feb. PMID: 21168233.
Mirshahi UL et al. Reduced penetrance of MODY-associated HNF1A/HNF4A variants but not GCK variants in clinically unselected cohorts. Am J Hum Genet. 2022 Nov 3. PMID: 36257325.
Santos Monteiro S et al. Maturity-onset diabetes of the young in a large Portuguese cohort. Acta Diabetol. 2023 Jan. PMID: 36208343.
Svalastoga P et al. Characterisation of HNF1A variants in paediatric diabetes in Norway using functional and clinical investigations to unmask phenotype and monogenic diabetes. Diabetologia. 2023 Dec. PMID: 37798422.
Tsoi STF et al. Monogenic diabetes in a Chinese population with young-onset diabetes: A 17-year prospective follow-up study in Hong Kong. Diabetes Metab Res Rev. 2024 Jul. PMID: 38821874.
Wang DW et al. Early-onset diabetes involving three consecutive generations had different clinical features from age-matched type 2 diabetes without a family history in China. Endocrine. 2022 Oct. PMID: 35921062.

This result has been reviewed and approved by [redacted]

BACKGROUND INFORMATION: MODY and Neonatal Diabetes Panel, Sequencing
CHARACTERISTICS: Maturity-onset diabetes of the young (MODY) is a group of inherited disorders that cause nonautoimmune diabetes mellitus with a typical onset before age 35. Most affected individuals have features that are atypical for type 1 and type 2 diabetes, including a lack of pancreatic islet autoantibodies, normal weight, triglycerides, and HDL, no acanthosis nigricans, low insulin requirements, and no ketoacidosis when insulin is omitted from treatment. Individuals with neonatal diabetes (ND) mellitus have complete or partial insulin deficiency and develop hyperglycemia by 6 months of age. Affected individuals often have intrauterine growth restriction, glucosuria, osmotic polyuria, severe dehydration, and failure to thrive.

EPIDEMIOLOGY: MODY accounts for 1-3 percent of all cases of diabetes with no ethnic predilection; prevalence of ND is 1 in 160,000 in Austria and 1 in 215,000 in Slovakia.

CAUSE: Pathogenic germline variants in numerous genes.

INHERITANCE: Autosomal dominant or autosomal recessive, depending on the causative gene.

CLINICAL SENSITIVITY: Greater than 70 percent for MODY and greater than 73 percent for ND.

GENES TESTED: ABCC8*; APPL1; CEL*; EIF2AK3; FOXP3; GATA4; GATA6;

GCK; HNF1A; HNF1B; HNF4A; INS; KCNJ11; NEUROD1; NEUROG3; PDX1; RFX6; SLC19A2; WFS1; ZFP57
*One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

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. Human genome build 19 (Hg 19) was used for data analysis.

ANALYTICAL SENSITIVITY/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. Specificity is greater than 99.9 percent for all variant classes.

LIMITATIONS: A negative result does not exclude a heritable form of MODY or ND mellitus. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Regulatory region variants, deep intronic variants, and large deletions/duplications will not be identified. 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) variants, or repeat expansions. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.
SNVs and indels will not be called in the following regions due to technical limitations of the assay:
CEL (NM_001807) exons 1, 8, 9, 11
ABCC8 (NM_001351295) partial exon 14 (Chr11:17449973-17450018)

This test was developed and its performance characteristics determined by ARUP Laboratories. It has not been cleared or approved by the US 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.

VERIFIED/REPORTED DATES

Procedure	Accession	Collected	Received	Verified/Reported
Monogenic Diabetes Specimen	24-296-127388	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00
Monogenic Diabetes Interp	24-296-127388	00/00/0000 00:00	00/00/0000 00:00	00/00/0000 00:00

END OF CHART

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