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Patient Report

Patient Age/Gender: 51 years Unknown

Specimen Collected: 10-Mar-21 07:31

Monogenic Diabetes by NGS | **Received: 10-Mar-21 07:31** **Report/Verified: 10-Mar-21 07:33**

Procedure	Result	Units	Reference Interval
Monogenic Diabetes Specimen	Whole Blood		
Monogenic Diabetes Interp	Positive [f1 i1]		

Result Footnote

f1: Monogenic Diabetes Interp

INDICATION FOR TESTING
Symptoms of maturity-onset diabetes of the young

RESULT
One likely pathogenic variant was detected in the HNF1A gene.

LIKELY PATHOGENIC VARIANT
Gene: HNF1A (NM_000545.6)
Nucleic Acid Change: c.1A>G; Heterozygous
Amino Acid Alteration: p.Met1?
Inheritance: Autosomal Dominant

INTERPRETATION
One likely pathogenic variant, c.1A>G; p.Met1?, was detected in the HNF1A gene by massively parallel sequencing and confirmed by Sanger sequencing. Pathogenic HNF1A variants are inherited in an autosomal dominant manner, and are associated with maturity-onset diabetes of the young (MODY) type 3 (MIM: 600496). Therefore, this individual is predicted to have a predisposition for MODY. This individual's offspring have a 50 percent chance of inheriting the likely pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by massively parallel sequencing. Please refer to the background information included in this report for a list of the genes analyzed and limitations of this test.

Evidence for variant classification: The HNF1A c.1A>G; p.Met1? variant (rs193922592), to our knowledge, is not reported in the medical literature but is reported in ClinVar (Variation ID: 36814). This variant is absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant causes a loss of the initiation codon and is expected to result in a truncated protein or mRNA subject to non-sense mediated decay. Based on available information, this variant is considered to be likely pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At risk family members should be offered testing for the identified likely pathogenic HNF1A variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are not included in this report.

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

Test Information

i1: Monogenic Diabetes Interp

BACKGROUND INFORMATION: MODY and Neonatal Diabetes Panel, Sequencing

*=Abnormal, #=Corrected, C=Critical, f=Result Footnote, H-High, i-Test Information, L-Low, t-Interpretive Text, @=Performing lab

Test Information

i1: Monogenic Diabetes Interp

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, BLK, CEL*, EIF2AK3, FOXP3, GATA4, GATA6, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, KLF11, NEUROD1, NEUROG3, PAX4, PDX1, RFX6, SLC19A2, WFS1, ZFP57
* - One or more exons are not covered by sequencing for the indicated gene; see limitations section below.

METHODOLOGY: Targeted 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 confirm reported variants. 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 from 1-10 base pairs in size. Variants greater than 10 base pairs may be detected, but the analytical sensitivity may be reduced.

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 and deep intronic variants will not be identified unless specifically targeted for their clinical

Test Information

i1: Monogenic Diabetes Interp

relevance. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. Diagnostic errors can occur due to rare sequence variations. In some cases, variants may not be identified due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions. This assay may not detect low-level mosaic or somatic variants associated with disease. Interpretation of this test result may be impacted if this patient has had an allogeneic stem cell transplantation. Noncoding transcripts were not analyzed.

The following regions are not sequenced 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.