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Patient Report

Patient Age/Sex: Male

Specimen Collected: 08-Mar-22 07:45

Pancreatitis Panel by NGS | **Received: 08-Mar-22 07:45** **Report/Verified: 08-Mar-22 08:33**

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

Result Footnote

f1: PANC Interp

RESULT
One pathogenic variant was detected in the PRSS1 gene. No pathogenic variants were detected in the CFTR, SPINK1, or CTRC genes.

PATHOGENIC VARIANT
Gene: PRSS1 (NM_002769.5)
Nucleic Acid Change: c.365G>A; heterozygous
Amino Acid Alteration: p.Arg122His
Inheritance: Autosomal dominant

INTERPRETATION
One copy of a pathogenic variant, c.365G>A; p.Arg122His, was detected in the PRSS1 gene by massively parallel sequencing and confirmed by Sanger sequencing. PRSS1 gene variants are primarily dominant gain-of-function variants that cause pancreatitis by promoting premature trypsinogen activation in the pancreas. Thus, this individual is at risk for autosomal dominant hereditary pancreatitis. Clinical manifestations of hereditary pancreatitis are variable and age dependent. Offspring of this individual have a 50 percent chance of inheriting the pathogenic variant.

No additional pathogenic variants were identified in the targeted genes by sequencing. Please refer to the background information included in this report for the clinical sensitivity and limitations of this test.

Evidence for variant classification: The PRSS1 c.365G>A; p.Arg122His variant (rs111033565) is reported in the literature as the most common pathogenic variant associated with hereditary pancreatitis (Nemeth, 2014). This variant is reported as pathogenic by multiple laboratories in ClinVar (Variation ID: 11876). This variant increases the autoactivation and stability of trypsin, even in the presence of inhibitory factors such as chymotrypsin C (Sahin-Toth, 2000; Szabo, 2012; Whitcomb, 1996) and leads to chronic pancreatic inflammation and acinar cell necrosis in a mouse model (Archer, 2006). Based on available information, this variant is considered pathogenic for the development of pancreatitis.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. At-risk family members should be offered testing for the identified pathogenic PRSS1 variant (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Likely benign and benign variants are reported.

REFERENCES
Archer H, et al. A mouse model of hereditary pancreatitis generated by transgenic expression of R122H trypsinogen. Gastroenterology. 2006;131(6):1844-55. PMID: 17087933.

Nemeth BC, et al. Human cationic trypsinogen (PRSS1) variants and chronic pancreatitis. Am J Physiol Gastrointest Liver Physiol. 2014;306(6):G466-73. PMID: 24458023.

Sahin-Toth M, et al. Gain-of-function mutations associated with hereditary pancreatitis enhance autoactivation of human cationic trypsinogen. Biochem Biophys Res Commun. 2000;278(2):286-9. PMID:

Result Footnote

f1: PANC Interp
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Szabo A, et al. Increased activation of hereditary pancreatitis-associated human cationic trypsinogen mutants in presence of chymotrypsin C. J Biol Chem. 2012;287(24):20701-10. PMID: 22539344.

Whitcomb D, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet. 1996;14(2):141-5. PMID: 8841182.

Test Information

i1: PANC Interp
BACKGROUND INFORMATION: Pancreatitis Panel (CFTR, CTRC, PRSS1, SPINK1), Sequencing

CHARACTERISTICS: Pancreatitis is a relatively common disorder with multiple etiologies that causes inflammation in the pancreas. Acute pancreatitis (AP) is a result of sudden inflammation, and patients may present with increased pancreatic enzyme concentrations. Chronic pancreatitis (CP) is a syndrome of progressive inflammation that may lead to permanent damage to pancreatic structure and function. Genetic testing can be utilized to determine a genetic cause of idiopathic or hereditary AP or CP and/or to assess risk of disease in family members.

EPIDEMIOLOGY: CP affects approximately 4-12 per 100,000 individuals per year.

CAUSE: Pathogenic germline variants in genes associated with idiopathic pancreatitis.

INHERITANCE: Autosomal dominant for PRSS1; autosomal recessive/digenic for CFTR, CTRC, and SPINK1.

CLINICAL SENSITIVITY: Approximately 48 percent of idiopathic pancreatitis.

GENES TESTED: CFTR (NM_000492), CTRC (NM_007272), PRSS1 (NM_002769), SPINK1 (NM_003122)
Deletion/duplication analysis is not available for these genes.

METHODOLOGY: Probe hybridization-based capture of all coding exons and exon-intron junctions of the targeted genes, including intronic variants 5T (IVS8), c.1680-886A>G (c.1679+1.6kbA>G), and c.3718-2477C>T of the CFTR gene, followed by massively parallel sequencing. Sanger sequencing was performed as necessary to fill in regions of low coverage or known low quality, and to confirm reported variants that do not meet acceptable quality metrics.

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

Test Information

i1: PANC Interp

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 pancreatitis. This test only detects variants within the coding regions and intron-exon boundaries of the targeted genes. Deletions/duplications/insertions of any size may not be detected by massively parallel sequencing. 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) mutations, 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.

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