

Pancreas Diseases Genetic Testing Program

We offer comprehensive analysis of genes associated with pancreatitis and pancreatic insufficiency. Our testing includes two pancreatic panels by next-generation sequencing (NGS), single gene analysis for any gene on the panel, targeted variant analysis, and targeted deletion/duplication analysis.

Pancreas NGS Panels	Genes included
Pancreas Panel	CASR, CEL, CFTR, CLDN2, CPA1, CTRC, PRSS1, SBDS, SPINK1, UBR1 Includes PRSS1 deletion/duplication via MLPA.
Pancreatic Insufficiency Panel	CEL, CFTR, SBDS, UBR1

Description:

Our panels are designed to establish the genetic causes of pancreatitis / pancreatic insufficiency or determine an individual's risk of developing these conditions.

Pancreatitis is characterized by recurrent inflammation of the pancreas which can progress from acute to chronic. Pancreatic insufficiency is the inability of the pancreas to produce sufficient pancreatic digestive enzymes. It is commonly associated with pancreatitis and associated conditions. Chronic pancreatitis presents with mild-severe abdominal pain and exocrine pancreatic insufficiency, leading to digestive issues and endocrine pancreatic insufficiency. These conditions can lead to glucose intolerance / type I diabetes mellitus. Pancreatitis can occur as a part of a syndrome (for example Johanson-Blizzard syndrome or Shwachman-Diamond syndrome) or as an isolated finding. It can be caused by underlying genetic factors, non-genetic environmental factors (e.g. alcohol abuse, infection or trauma), or a combination of both. Pancreatitis is usually categorized as hereditary, familial or idiopathic.

Condition	Gene	Inheritance*
Chronic pancreatitis	CASR	---
Maturity-onset diabetes of the young, type VIII	CEL	AD
Chronic pancreatitis/ Idiopathic pancreatitis	CFTR*	AD/AR
Chronic pancreatitis	CLDN2	---
Chronic pancreatitis, early onset	CPA1	---
Chronic pancreatitis	CTRC*	AD
Hereditary pancreatitis	PRSS1	AD with incomplete penetrance
Shwachman-Diamond syndrome	SBDS	AR
Chronic pancreatitis (tropical calcific pancreatitis)	SPINK1*	AR or AD
Johanson-Blizzard syndrome	UBR1	AR

*The presence of certain specific isolated pathogenic variants in CFTR, CTRC, or SPINK1 can increase the risk for pancreatitis but are insufficient for the diagnosis. Polygenic inheritance is a possibility.

*Key: AD= Autosomal dominant; AR= Autosomal Recessive

Depending on the underlying genetic etiology, it can be inherited in autosomal dominant, autosomal recessive, or polygenic manner.

Indications:

NGS Panels:

- Confirmation of genetic diagnosis in a patient with a chronic pancreatitis / pancreatic insufficiency with unknown etiology.
- Presymptomatic testing for at-risk individuals with a family history of pancreatitis of unknown genetic basis.

Gene Specific Sequencing:

- Confirmation of genetic diagnosis in a patient with pancreatic disease and in whom a specific genetic diagnosis is suspected.

Deletion/Duplication Analysis:

- Completion of the diagnostic evaluation in a patient with a clinical diagnosis of pancreatic disease who has had a negative NGS panel or who is heterozygous for a variant in a gene associated with an autosomal recessive condition

Variant Specific Analysis:

- Carrier testing of parents and other relatives for recurrence risk assessment
- Presymptomatic testing of at-risk family members for medical management
- Prenatal diagnosis of an at-risk fetus, after confirmation of variant(s) in the parent(s) and by prior arrangement only

Specimen:

At least 3 mLs whole blood in a lavender top (EDTA) tube or saliva in an Oragene saliva kit. Please call 513-636-4474 for a free saliva collection kit.

Testing Methodology:

Next Generation Sequencing (NGS) Panels: The Pancreas panel and the Pancreatic Insufficiency panel are both performed by enrichment of the coding exons, flanking intronic and untranslated regions (5' and 3'), as well as known pathogenic variants (HGMD 2018.1) in the promoter and deep intronic regions of the genes specified above using oligonucleotide probe hybridization followed by next-generation sequencing with >50X coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing. Regions with <50X will be filled in by Sanger sequencing. A detailed non-coding variant list is available upon request. For the Pancreas panel, *PRSSI* sequencing is performed by Sanger due to high homologous regions and *PRSSI* deletion/duplication is included and performed by MLPA.

Gene Specific Sequencing: PCR-based sequencing of entire coding region, intron/exon boundaries, as well as known pathogenic variants (HGMD 2018.1) in the promoter and deep intronic regions of the specified gene. *PRSSI* sequencing is included in the Pancreas Panel

and is performed by Sanger sequencing due to high homologous regions.

Deletion/Duplication Analysis: Copy number variant analysis of *CASR*, *CFTR*, *CPAI*, *CTRC*, *SBDS*, *SPINK1* and *UBRI* is performed by comparative genomic hybridization. *PRSSI* deletion/duplication is included on the Pancreas Panel and is performed by multiple ligation-dependent probe amplification (MLPA) analysis.

Variant Specific Analysis: Sanger sequencing following PCR amplification of the targeted variant(s) of the specified gene.

Test Sensitivity:

Clinical Sensitivity: One study identified that 48.2 percent of patients with idiopathic pancreatitis have evidence of a genetic basis for their pancreatitis (Masson et al. 2013). 60-100 percent of families with hereditary pancreatitis have single identifiable heterozygous pathogenic variant in the *PRSSI* gene (LaRusch et al. 2011). Two common *PRSSI* mutations in exon 2 and 3 account for approximately 90 percent of mutations observed in *PRSSI*-related hereditary pancreatitis (Rebours et al. 2009). Additionally, copy number variants involving *PRSSI* have been reported in up to 6% of persons with idiopathic chronic pancreatitis (Masson et al 2008). Isolated pathogenic variants in *CFTR*, *CTRC*, and *SPINK1* have been found to be associated with increased susceptibility to pancreatitis. Pancreatitis and subsequent pancreatic insufficiency are cardinal features in syndromes such as Johanson-Blizzard syndrome, Shwachman-Diamond syndrome and *CEL* maturity-onset diabetes of the young. Variants in *CLDN2*, *CPAI*, and *CTRC* act as risk modifiers for individuals with pancreatitis.

Analytical Sensitivity: The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed.

Limitations: Variants in regulatory regions and non-reported variants in untranslated regions may not be detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and

other complex genetic events will not be identified using NGS methodology. Rare primer site variants may lead to erroneous results.

Note: Single gene sequencing is available for all genes on the panel. Deletion/duplication analysis is available for all genes listed except *CEL* and *CLDN2*.

Turn-Around Time:

- **Pancreas / Pancreatic Insufficiency Panel by NGS:**
28 days
- **Single Gene Sequencing:** 28 days
- **Deletion/duplication Analysis by Targeted CGH:**
28 days

CPT Codes:

- **Pancreas Panel by NGS:** 81223, 81404x2, 81405, 81479x6
- **Pancreatic Insufficiency Panel by NGS:** 81223x1, 81479
- **Single Gene Sequencing, Targeted Variant Analysis, and Deletion/Duplication Analysis:**
call for information

Please call 1-866-450-4198 for current pricing, insurance preauthorization or with any billing questions.

Shipping Instructions:

Please enclose **test requisition** with sample.

All information must be completed before sample can be processed.

Place samples in styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Saturday.

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229*
513-636-4474

*For deliveries arriving on Saturday, please add "Dock 5" under the lab name

Results:

Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for the clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

References:

- Koziel, D., S. Gluszek, et al. (2015) "Genetic Mutations in SPINK1, CFTR, CTSC Genes in Acute Pancreatitis." BMC Gastroenterology 15: 70.*
- LaRusch, J. and D. Whitcomb. (2011) "Genetics of pancreatitis." Curr Opin Gastroenterol 27(5): 467-474.*
- Masson, E., C. Le Marechal, et al. (2008) "Trypsinogen copy number mutations in patients with idiopathic chronic pancreatitis." Clin Gastroenterol Hepatol 6(1): 82-8.*
- Ravi Kanth, V. and R. Nageshwar. (2014) "Genetics of acute and chronic pancreatitis: An update." World J Gastrointest Pathophysio 5(4): 427-37.*
- Whitcomb, D. (2013) "Genetic Risk Factors for Pancreatic Disorders." Gastroenterology 144(6): 1292-1302.*