

# Idiopathic and Hereditary Pancreatitis

## *TO DETERMINE IF MUTATIONS IN THE CFTR, PRSS1, OR SPINK1 GENES ARE CAUSATIVE/RISK FACTORS FOR PANCREATITIS*

### Disease Overview

- Pancreatitis is an inflammation of the pancreas that causes a release of digestive enzymes that damage tissues surrounding them. Symptoms include sudden pain in the upper abdomen, fever, nausea and vomiting, and a rapid pulse. Acute pancreatitis is associated with an elevation of the pancreatic enzymes amylase and lipase to three times normal levels.
- The exocrine pancreas produces digestive enzymes, such as trypsinogen, which is not normally converted to its active form, trypsin, until it reaches the duodenum.
- Acute pancreatitis is a life-threatening illness of sudden onset that usually resolves after hospitalization for a few days with intravenous fluids, antibiotics, and pain medication. The most common causes of acute pancreatitis are gallstones passing through the common bile duct and chronic heavy alcohol use. Other causes of acute pancreatitis include abdominal trauma, medications, infections, tumors, and genetic abnormalities.
- Chronic pancreatitis is inflammation of the pancreas that does not heal and gets progressively worse over time, leading to permanent tissue damage. It is most commonly caused by many years of heavy alcohol use but may also result from hereditary disorders of the pancreas, cystic fibrosis, hypercalcemia, hyperlipidemia, specific autoimmune conditions, or medications. Symptoms include abdominal pain, nausea, vomiting, weight loss, diarrhea, and oily stools. In advanced stages, pain often decreases, and malabsorption and diabetes may occur. Treatment includes a low-fat diet and enzyme supplements; surgery may be required to remove scar tissue.
- Individuals with chronic pancreatitis may have up to a 40 percent lifetime risk for pancreatic cancer.
- Hereditary pancreatitis is characterized by recurrent episodes of acute pancreatitis usually occurring within the first two decades of life, progressing to chronic pancreatitis. A single mutation in the gene producing cationic trypsinogen (*PRSS1*) may be causative for up to 75 percent of hereditary pancreatitis. *PRSS1* mutations causing pancreatitis are gain-of-function mutations that allow cationic trypsinogen to become activated to trypsin in the pancreas itself, as opposed to in the duodenum.

### Epidemiology

- A prospective study of chronic pancreatitis in Copenhagen found a prevalence of 26.4:100,000 and an incidence of 8.2:100,000 per year.

- Idiopathic cases may account for up to 20 percent of chronic pancreatitis.

### Genetics

- Hereditary pancreatitis is an autosomal dominant disease with variable expression caused by mutations in the *PRSS1* gene.
- The two most common deleterious *PRSS1* gene mutations (R122H and N29I) are reported to have a penetrance of 80 percent for hereditary pancreatitis.
- De novo *PRSS1* mutations are also found in 10 percent of idiopathic chronic pancreatitis patients of all ages and as many as 35 percent of those under age 25.
- Two other genes, *SPINK1* (serine protease inhibitor Kazal type 1) and *CFTR* (cystic fibrosis transmembrane regulator), are risk factors for pancreatitis.
- Mutations in *SPINK1* and *CFTR* may be inherited in an autosomal recessive or multifactorial fashion.
- Approximately 30 percent of individuals with idiopathic pancreatitis have at least one *CFTR* mutation. The presence of two *CFTR* mutations increases the risk for idiopathic pancreatitis by 40 fold.
- 15 percent of individuals with idiopathic pancreatitis have *SPINK1* mutations; approximately 25 percent of children with idiopathic pancreatitis have *SPINK1* mutations.
- The *SPINK1* mutation N34S increases the risk for pancreatitis by 14 fold.
- *SPINK1* mutations do not appear to be increased in individuals with hereditary pancreatitis; furthermore, *SPINK1* mutations do not appear to influence disease severity.

### Indications for Ordering

- For patients with hereditary pancreatitis, order Pancreatitis, Hereditary (*PRSS1*) Sequencing (ARUP test #2002016).
- For patients with chronic idiopathic pancreatitis, order sequencing of all three genes together: Pancreatitis, Idiopathic (*CFTR*, *PRSS1*, *SPINK1*) Sequencing (ARUP test #2002005).

### Contraindications

Prenatal testing.

### Additional Ordering Notes

Please complete the patient history for pancreatitis form and submit with the sample to enable optimal interpretation of test results.

## Interpretation

- Pancreatitis, Hereditary (*PRSSI*) Sequencing
  - The detection of a single gain-of-function *PRSSI* mutation is causative for hereditary pancreatitis.
  - Lack of detection of a mutation in *PRSSI* does not eliminate a genetic etiology for hereditary pancreatitis. Twenty percent of genetic factors causing hereditary pancreatitis are still unknown.
  - Mutations of unknown significance may be detected by sequencing.
- Pancreatitis, Idiopathic (*CFTR*, *PRSSI*, and *SPINK1*) Sequencing
  - The detection of a single gain-of-function *PRSSI* mutation is causative for hereditary pancreatitis.
  - The detection of a single deleterious *CFTR* or *SPINK1* mutation increases the risk for pancreatitis, but is not causative for disease.
  - The detection of both a deleterious *CFTR* and *SPINK1* mutation greatly increases the risk for chronic pancreatitis.
  - If two deleterious *CFTR* or *SPINK1* mutations are detected in an affected individual, they are likely to be causative for pancreatitis.
  - Lack of detection of a mutation in *PRSSI*, *SPINK1*, or *CFTR* does not eliminate a genetic etiology for pancreatitis. There may be undetected mutations (such as large deletions/duplications, promoter, or deep intronic mutations) in the tested genes or mutations in currently unknown genes that are associated with pancreatitis.
  - Mutations of unknown significance may be detected by sequencing.

## Methodology

- Pancreatitis, Hereditary (*PRSSI*) Sequencing
  - PCR followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *PRSSI* gene.
  - Clinical sensitivity for hereditary pancreatitis is 80 percent.
  - Analytic sensitivity and specificity are 99 percent.

- Pancreatitis, Idiopathic (*CFTR*, *PRSSI*, and *SPINK1*) Sequencing
  - PCR followed by bidirectional sequencing of the entire coding region and intron/exon boundaries of the *CFTR*, *PRSSI*, and *SPINK1* genes.
  - Clinical sensitivity for idiopathic pancreatitis is approximately 45 percent.
  - Analytic sensitivity and specificity are 99 percent.

## Limitations

- Regulatory region mutations, deep intronic mutations, and large gene deletion/duplications will not be detected.
- Rare diagnostic errors may occur due to primer-site mutations.

## Related Test

Cystic Fibrosis (*CFTR*) Sequencing (0051110)

## References

1. Audrezet MP, et al. Determination of the relative contribution of three genes; the cystic fibrosis transmembrane conductance regulator gene, the cationic trypsinogen gene, and the pancreatic secretory trypsin inhibitor gene- to the etiology of idiopathic chronic pancreatitis. *Eur J Hum Gen* 2002;10:100–6.
2. Warrell DA, et al. 2005. Oxford textbook of medicine. Oxford, England: Oxford University Press;668.
3. Lowenfels AB. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. *J Natl Cancer Inst* 1997; 89(6):442–6.
4. Keiles S and Kammesheidt A. Identification of *CFTR*, *PRSSI*, and *SPINK1* mutations in 381 patients with pancreatitis. *Pancreas* 2006;33(3)221–7.

## Test Information

<b>2002016</b>	<b>Pancreatitis, Hereditary (<i>PRSSI</i>) Sequencing</b>
<b>2002005</b>	<b>Pancreatitis, Idiopathic (<i>CFTR</i>, <i>PRSSI</i>, <i>SPINK1</i>) Sequencing</b>
<b>2002012</b>	<b>Pancreatitis, Idiopathic (<i>SPINK1</i>) Sequencing</b>

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).