Idiopathic and Hereditary Pancreatitis

Indications for Ordering

Confirm diagnosis and/or genetic cause for pancreatitis in symptomatic individuals

Test Description

Polymerase chain reaction followed by bidirectional sequencing of coding regions and intron/exon borders

Tests to Consider

Primary tests

Pancreatitis, Panel (*CFTR, CTRC, PRSS1, SPINK1*) Sequencing 2010876
- Preferred test for individuals with history of idiopathic pancreatitis

Pancreatitis (*CTRC*) Sequencing 2010703
- For adults with idiopathic pancreatitis if other components of panel (*CFTR, PRSS1, SPINK1*) have been sequenced without providing a complete explanation for the pancreatitis

Pancreatitis (*PRSS1*) Sequencing 2002016
- Preferred test for individuals with idiopathic pancreatitis who
  - Are <20 years of age **OR**
  - Have 2 affected first-degree relatives

Pancreatitis (*SPINK1*) Sequencing 2002012
- For adults with idiopathic pancreatitis if other components of panel (*CFTR, CTRC, PRSS1*) have been sequenced without providing a complete explanation for the pancreatitis

Related tests

Cystic Fibrosis (*CFTR*) Sequencing 0051110
- May be used to test for variants causative for mild cystic fibrosis for individuals with idiopathic pancreatitis

Familial Mutation, Targeted Sequencing 2001961
- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

Incidence/prevalence
- Chronic pancreatitis
  - Incidence – 5-12/100,000 per year (Yadav, 2013)
  - Prevalence – ~50/100,000 (Yadav, 2013)
- Idiopathic chronic pancreatitis
  - ~20% of all cases of pancreatitis (Masson, 2013)

Symptoms
- Acute pancreatitis
  - Can be life-threatening
  - Symptoms
    - Sudden onset of pain in the upper abdomen, fever, nausea and vomiting, rapid pulse
    - Pancreatic enzymes (amylase, lipase) – increased levels
  - Etiologies
    - Common – gallstone passage or obstruction; chronic, heavy alcohol use
    - Other – abdominal trauma, medications, infections, tumors, genetic abnormalities
- Chronic pancreatitis
  - Chronic inflammation and progressive disease
  - May lead to permanent tissue damage
  - Up to a 40% lifetime risk for pancreatic cancer
  - Symptoms
    - Abdominal pain, nausea, vomiting, weight loss, diarrhea, oily stools
    - Advanced stages – pain often decreases, malabsorption and diabetes may occur
  - Etiologies
    - Chronic, heavy alcohol use (70% of cases)
    - Other factors (10% of cases)
      - Autoimmune
      - Hereditary disorders of the pancreas
        - Cystic fibrosis
      - Hypercalcemia
      - Hyperlipidemia
      - Hyperparathyroidism
      - Medications
    - Idiopathic (20% of cases)

Genetics

Genes – *CFTR, CTRC, PRSS1, SPINK1*

Inheritance

- *PRSS1* – autosomal dominant with gain-of-function variants
- *CFTR, CTRC, SPINK1* – autosomal recessive/digenic

Penetrance – 80% for PRSS1 variants R122H and N29I (Sossenheimer, 1997)

Test Interpretation

Sensitivity/specificity in idiopathic pancreatitis

- Clinical sensitivity for contributory or causative variants
  - Pancreatitis panel (*CFTR, CTRC, PRSS1, SPINK1*) sequencing – ~48% (Masson, 2013)
  - Pancreatitis (*CFTR*) sequencing – ~28%
  - Pancreatitis (*SPINK1*) sequencing – ~16%
  - Pancreatitis (*PRSS1*) sequencing – ~ 9%
  - Pancreatitis (*CTRC*) sequencing – ~4%
- Analytical sensitivity/specificity – 99%

Results

- Positive
  - Single gain-of-function *PRSS1* gene variant detected, **OR**
  - Two pathogenic *CFTR*, *SPINK1,* or *CTRC* gene variants detected, **OR** one pathogenic variant detected in two different genes (digenic inheritance)
    - Causative for pancreatitis
  - Single pathogenic *CFTR, SPINK1,* or *CTRC* gene variant detected
    - Increased risk for pancreatitis, but not causative
- Negative
  - No pathogenic variants detected in *CFTR, CTRC, PRSS1,* or *SPINK1* genes
    - No genetic etiology for pancreatitis determined
      - Does not exclude genetic etiology
- Inconclusive
  - Gene variant detected, but whether variant is pathogenic or benign is unknown

Limitations

- Not detected
  - Regulatory region and deep intronic mutations
  - Large deletions/duplications
- Diagnostic errors can occur due to rare sequence variations
- Variants in currently unknown genes may be associated with pancreatitis

References

- LaRusch J, Witcomb DC. Genetics of pancreatitis. Curr Opin Gastroenterol. 2011;27(5):467-474
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- Sossenheimer MJ, Aston CE, et al. Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype. The Midwest Multicenter Pancreatic Study Group (MMPSG). Am J Gastroenterol. 1997;92:1113-1116
- Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144: 1252–1261