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PRSS1-Related Hereditary Pancreatitis

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Summary

Clinical characteristics

PRSS1-related hereditary pancreatitis (HP) is characterized by episodes of acute pancreatitis (AP) and recurrent acute pancreatitis (RAP: >1 episode of AP), with frequent progression to chronic pancreatitis (CP). Manifestations of acute pancreatitis can range from vague abdominal pain lasting one to three days to severe abdominal pain lasting days to weeks and requiring hospitalization.

Diagnosis/testing

The diagnosis of *PRSS1*-related hereditary pancreatitis is established in a proband with episodes of AP, RAP, and/or CP and a heterozygous pathogenic gain-of-function variant in *PRSS1* identified by molecular genetic testing. Note that, because of incomplete penetrance, identification of a disease-associated *PRSS1* variant in an asymptomatic individual is not sufficient for a clinical diagnosis.

High-penetrance *PRSS1* pathogenic variants include p.Asn29Ile and p.Arg122His, and lower-penetrance pathogenic variants include p.Arg16Val and p.Arg122Cys. Other pathogenic *PRSS1* variants are recognized; these latter variants typically require additional risk factors to cause disease and do not cause autosomal dominant hereditary pancreatitis.

Management

Treatment of manifestations: AP episodes are treated with rapid assessment of severity and fluid resuscitation as needed. Individuals with HP should be counseled not to delay in being assessed for AP since hypovolemia and shock leads to serious organ dysfunction and failure. For chronic pancreatitis, continue strategies to prevent RAP attacks. Antioxidants may have some benefit. Pancreatic enzyme replacement therapy to improve digestion in those with pancreatic insufficiency and bloating, steatorrhea, diarrhea, unexplained weight loss, and/or micronutrient deficiencies (e.g., vitamins A, D, B_{12}); treatment of glucose intolerance with a regimen typically

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including metformin. Management of pain can be challenging but should begin with medical therapy, with endoscopic therapies for obstructions and surgery for more severe pain – including total pancreatectomy with islet autotransplantation in selected individuals.

Prevention of primary manifestations: Avoid smoking, alcohol abuse. Recommended: a healthy diet that is low in red meat, multiple small meals if it improves symptoms, good hydration (especially during exercise), vitamins, and antioxidants. Some individuals report that moderate exercise helps control episodes of pain and reduce pain severity.

Surveillance: Referral to a surveillance program.

Agents/circumstances to avoid: Alcohol and tobacco use; dehydration; physical and emotional stress.

Evaluation of relatives at risk: Molecular genetic testing for the family-specific germline *PRSS1* pathogenic variant to allow early diagnosis and prevention and/or management of symptoms.

Genetic counseling

HP caused by gain-of-function *PRSS1* pathogenic variants is inherited in an autosomal dominant manner. The proportion of *PRSS1*-related HP caused by a *de novo* pathogenic variant is unknown. Each child of an individual with autosomal dominant *PRSS1*-related HP has a 50% chance of inheriting the variant. Prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant of an affected family member has been identified. A number of other variants in the coding and noncoding regions of the *PRSS1* locus are associated with risk for pancreatitis, but they typically do not cause autosomal dominant hereditary pancreatitis.

Diagnosis

The clinical features of *PRSS1*-related hereditary pancreatitis (HP) are clinically indistinguishable from other forms of acute and chronic pancreatitis.

Suggestive Findings

PRSS1-related HP **should be suspected** in individuals with the following:

- Acute pancreatitis occurring in childhood
- Recurrent acute attacks of pancreatitis of unknown cause
- Chronic pancreatitis of unknown cause, particularly with onset before age 25 years
- A family history of recurrent acute pancreatitis, chronic pancreatitis, and/or childhood pancreatitis consistent with autosomal dominant inheritance
- A family history of pancreatitis, diabetes mellitus, or pancreatic cancer

Acute pancreatitis (AP) is characterized by sudden onset of typical epigastric abdominal pain that may radiate to the back, serum pancreatic digestive enzymes (e.g., amylase, lipase) that are more than threefold the upper limits of normal, and/or characteristic findings of pancreatic inflammation on abdominal imaging [Banks et al 2013].

Recurrent acute pancreatitis (RAP) is defined as a syndrome of multiple distinct acute inflammatory responses originating within the pancreas in individuals with genetic, environmental, traumatic, morphologic, metabolic, biologic, and/or other risk factors who experienced two or more episodes of documented acute pancreatitis, separated by at least three months [Guda et al 2018].

Chronic pancreatitis (CP) is defined as a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress [Whitcomb et al 2016]. The features of established and advanced chronic

pancreatitis include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, and calcifications; pancreatic exocrine dysfunction; and pancreatic endocrine dysfunction and dysplasia [Whitcomb et al 2016].

Establishing the Diagnosis

The diagnosis of *PRSS1*-related HP **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *PRSS1* by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *PRSS1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *PRSS1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *PRSS1* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in *PRSS1*-Related Hereditary Pancreatitis

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PRSS1	Sequence analysis [3]	≥94% [4]
	Gene-targeted deletion/duplication analysis [5]	≤6% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. One of two pathogenic variants (p.Asn29Ile or p.Arg122His) is identified in 90% of affected individuals [Rebours et al 2009].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Masson et al [2008a]. Among copy number variants identified: duplication and triplication of a 605-kb segment containing *PRSS1* and *PRSS2* [Le Maréchal et al 2006, Masson et al 2008b].

Clinical Characteristics

Clinical Description

In *PRSS1*-related hereditary pancreatitis (HP) the range of symptoms and disease course vary from person to person. On average, acute pancreatitis occurs by age ten years, chronic pancreatitis by age 20 years, and the incidence of pancreatic cancer rises at age 50 years.

Acute pancreatitis (sudden onset; duration <6 months) can be mild, moderate, or severe, depending on the local and systemic complications [Banks et al 2013]. Findings can range from vague abdominal pain lasting three to four days to sudden onset of severe upper abdominal pain radiating to the back with nausea, vomiting, orthostatic hypotension, confusion, and shortness of breath. Mild cases typically require one to two days of hospitalization. Severe cases may require intensive care management, result in prolonged hospitalization, and/or require six months or more to recover.

Persons with a *PRSS1*-related HP may also have other risk factors for pancreatitis, such as gallstones, alcohol consumption, smoking, and/or pathogenic variants in other pancreatitis-associated genes. Of note, persons with hereditary pancreatitis report that even small amounts of alcohol may sometimes trigger episodes of pain or acute pancreatitis.

Chronic pancreatitis. Approximately half of individuals with *PRSS1*-related HP progress to chronic inflammation and/or irreversible morphologic changes classified as chronic pancreatitis (CP). The characteristics of CP include variable features of pancreatic atrophy, fibrosis, pain, duct distortion and strictures, and calcifications; pancreatic exocrine dysfunction; and pancreatic endocrine dysfunction and dysplasia [Whitcomb et al 2016].

Long-standing inflammation results in complications that can include the following:

- Episodic or continuous mild-to-severe abdominal pain. Pain is usually sharp and stabbing in initial attacks, becoming deep and burning as the syndrome progresses. The most psychologically distressing pain is constant chronic pain, regardless of intensity [Machicado et al 2017].
- Exocrine pancreatic insufficiency leading to maldigestion with symptoms of gas and bloating and the appearance of diarrhea, oil in the stool (steatorrhea), and/or floating stools. Other signs of maldigestion

include weight loss, fat-soluble-vitamin deficiency, and protein deficiency with low albumin, prealbumin, or retinol-binding protein detected on blood testing.

- Pancreatic endocrine insufficiency manifesting initially as inappropriately elevated levels of blood glucose (glucose intolerance). Up to 48% of persons with *PRSS1*-related HP develop diabetes mellitus [Howes et al 2004, Rebours et al 2009], which is similar to the rates in other types of chronic pancreatitis [Bellin et al 2017]. Type 3c diabetes mellitus (pancreatogenic diabetes mellitus) is caused by loss of pancreatic tissue as a result of surgery or chronic pancreatitis; type 3c is associated with loss of both the insulin-producing beta cells and the glucagon-producing alpha cells, which results in loss of counter-regulatory hormones and risk of hypoglycemia. It is not clear what percentage of individuals with pancreatitis and diabetes have complete loss of islet cells versus beta cell dysfunction and/or peripheral insulin resistance as in typical type 2 diabetes mellitus.

Pancreatic cancer. Chronic inflammation of the pancreas is associated with an increased risk for pancreatic cancer. Persons with HP are at increased risk for pancreatic cancer because the onset of chronic pancreatitis is 20-30 years earlier than in the general population [Rebours et al 2008]. The risk of developing pancreatic cancer by age 70 years was reported to be 18.8%-40%, but a more recent study suggested that the cumulative risk of pancreatic cancer in individuals with *PRSS1*-related HP by age 70 years is 7.2% [Zhan et al 2018].

Genotype-Phenotype Correlations

Four gain-of-function *PRSS1* variants have been associated with autosomal dominant hereditary pancreatitis. These include high-penetrance *PRSS1* pathogenic variants p.Asn29Ile and p.Arg122His and lower-penetrance pathogenic variants p.Ala16Val and p.Arg122Cys. Other *PRSS1* variants have been associated with disease, but typically require additional risk factors to cause disease and do not segregate as autosomal dominant hereditary pancreatitis.

Penetrance

The reported penetrance of *PRSS1*-related HP varies:

- 40% in Spain for p.Arg122Cys [de las Heras-Castaño et al 2009]
- 43% in Europe for p.Ala16Val [Grocock et al 2010]
- 80% in the US for p.Asn29Ile and p.Arg122His [Sossenheimer et al 1997]
- 93% in France for p.Asn29Ile and p.Arg122His [Rebours et al 2009]
- 80% [Sibert 1978] to 96% in England [Howes et al 2004] for p.Asn29Ile and p.Arg122His

The median age for diagnosis of pancreatitis in a large multifamily US cohort was seven years (IQR 3-16; range <1-73) [Shelton et al 2018].

Nomenclature

In some instances, *PRSS1*-related hereditary pancreatitis has been described as chronic calcific pancreatitis, familial pancreatitis, or recurrent or relapsing acute or chronic pancreatitis; however, these are clinical diagnoses and do not describe the molecular basis of the disorder.

Prevalence

A report from France estimated a population prevalence of 0.3:100,000 persons with *PRSS1*-related hereditary pancreatitis [Rebours et al 2009].

PRSS1-related HP is found at highly variable rates in different populations of individuals with chronic pancreatitis.

In Germany 5.0% of individuals with chronic pancreatitis had *PRSS1* pathogenic variants p.Asn29Ile or p.Arg122His; additional reported variants included p.Ala16Val (2.1%), p.Arg122Cys (0.8%), and other rare variants [Rosendahl et al 2013].

In Denmark, of 12.4% of persons initially classified as having idiopathic acute and chronic pancreatitis, 9% were found to have a *PRSS1* pathogenic variant (1% of all individuals with pancreatitis) [Joergensen et al 2010].

In Spain, 7.7% of individuals with chronic pancreatitis had *PRSS1* pathogenic variant p.Asn29Ile [Mora et al 2009].

In the North American Pancreatitis Study II about 5% of individuals had *PRSS1* variants [Phillips et al 2018].

Among children with pancreatitis, the incidence of *PRSS1* pathogenic variants varies: Poland 9.6% [Sobczyńska-Tomaszewska et al 2006], Mexico 1.1% [Sánchez-Ramírez et al 2012], China 9.3% [Wang et al 2013], and Korea 9.6% [Cho et al 2016]. In India, *PRSS1* variants are rare [Chandak et al 2004, Poddar et al 2017].

In the INSPPIRE cohort of 301 children primarily from the United States, 17% of individuals with recurrent acute pancreatitis and 46% of children with chronic pancreatitis had a *PRSS1* pathogenic variant [Kumar et al 2016]. Furthermore, the children with a *PRSS1* pathogenic variant had a younger age of onset than children with CP of other etiologies [Giefer et al 2017].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PRSS1*.

Differential Diagnosis

The morphologic features and laboratory findings of *PRSS1*-related hereditary pancreatitis are the same as those of other causes of hereditary (Table 2) and non-hereditary pancreatitis.

Table 2. Other Causes of Hereditary Pancreatitis: Genes and Distinguishing Clinical Features

Gene [1]	MOI	Distinguishing Clinical Features	References / Selected OMIM Links
CASR	AD [2]	• Hypercalcemia • RAP/CP	OMIM 601199; see Pancreatitis Overview.
CEL	AD	• Diabetes mellitus • Pancreatic lipomatosis • Pancreatic exocrine insufficiency • Chronic pancreatitis w/out severe malnutrition • RAP/CP	Fjeld et al [2015]
CFTR	AR [2]	• Features of cystic fibrosis • RAP/CP	See Cystic Fibrosis.
CLDN2	XL	Alcoholic pancreatitis	Whitcomb et al [2012], Derikx et al [2015], Giri et al [2016]
CPA1	AD	Early-onset, nonalcoholic chronic pancreatitis	OMIM 114850
CTRC	AD [2]	• RAP/CP • History of smoking	See Pancreatitis Overview.

Table 2. continued from previous page.

Gene [1]	MOI	Distinguishing Clinical Features	References / Selected OMIM Links
SPINK1	AR [2]	• ↑ risk for chronic pancreatitis following acute pancreatitis • Also AR early-onset, aggressive pancreatitis	See Pancreatitis Overview.

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; RAP/CP = recurrent acute pancreatitis and/or chronic pancreatitis

1. Genes are listed in alphabetic order.

2. Predisposition to hereditary pancreatitis caused by pathogenic variants in this gene may be polygenic and/or multifactorial.

Non-hereditary causes of acute, recurrent acute, and chronic pancreatitis to consider. Most acute pancreatitis is caused by gallstones (biliary), alcohol, or hypertriglyceridemia, or is idiopathic.

Non-hereditary recurrent acute pancreatitis and chronic pancreatitis can be simple or complex disorders and typically are associated with one or more factors on the TIGAR-O list [adapted from Etemad & Whitcomb 2001].

- **Toxic-metabolic**
  - Alcohol
  - Smoking
  - Hypercalcemia
  - Hypertriglyceridemia
  - Medications (e.g., azothioprine)
  - Toxins (e.g., as a result of chronic renal failure)
- **Idiopathic**
  - Early onset (age <35 years)
  - Late onset (age ≥35 years)
- **Autoimmune**
  - Type 1 (IgG4-related disease)
  - Type 2
- **Recurrent or severe acute pancreatitis.** Postnecrotic (severe acute pancreatitis)
- **Obstructive**
  - Pancreatic divisum
  - Ampullary stenosis
  - Duct obstruction (e.g., tumor)
  - Post-traumatic pancreatic duct scars

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PRSS1*-related hereditary pancreatitis (HP), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Referral to a gastroenterologist for evaluation of pancreatic exocrine function using invasive or noninvasive testing
  - Fecal elastase-1 analysis. It can be falsely positive with diarrhea but can be used while an individual is taking pancreatic enzyme replacement therapy. The test is insensitive for mild pancreatic exocrine insufficiency.

    - Secretin-stimulated pancreatic bicarbonate secretion testing, which requires intubation of the duodenum and careful measure of pancreatic bicarbonate secretion over about an hour (depending on the method). It is considered very sensitive, but only assesses duct function.
    - Cholecystokinin (CCK) and its analogs (e.g., CCK-8) or receptor agonists (e.g., cerulean); have also been used to assess acinar cell function.
    - Serum trypsinogen levels to measure pancreatic acinar cell mass [Couper et al 1995]. Levels are useful if the individual is *not* experiencing pain and/or an acute pancreatitis flair, as levels will be increased along with amylase and lipase [Pezzilli et al 2000].
- Diffusion-weighted MRI. Various "functional" tests have been advocated using abdominal imaging techniques, including secretin-stimulated MRI. Although diffusion-weighted MRI is probably better at detecting the structural changes of chronic pancreatitis than standard MRI [Akisik et al 2009], it does not measure function, and fluid volume cannot measure bicarbonate output.
- Referral to an endocrinologist for evaluation of pancreatic endocrine function (i.e., assessment of glucose tolerance)
- Referral to a pancreatic cancer surveillance program in persons with chronic pancreatitis and/or risk factors for pancreatic cancer (e.g., age >40 years, family history of pancreatic cancer, history of smoking)
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Medical treatment and management for *PRSS1*-related HP are similar to those for non-hereditary pancreatitis.

Acute Pancreatitis

Treatment of acute pancreatitis usually focuses on acute fluid and pain management. Discontinuation of smoking and alcohol use reduces the frequency of recurrent attacks, slows the rate of progression, and decreases the likelihood of complications, including diabetes mellitus and pancreatic cancer.

Pancreatic pain can result from pancreatic duct obstruction, parenchyma hypertension, pancreatic ischemia, inflammation, neuropathy, and central pain.

- Analgesics are offered when pancreatic enzyme replacement therapy is not sufficient to control pain.
- Antioxidants have been reported to improve pain control in a few individuals with hereditary pancreatitis. In India, antioxidant treatment was associated with better pain control and outcomes [Shalimar et al 2017].
- Endoscopic or surgical interventions may be useful for treating obstructive pain [Clarke et al 2012], pseudocysts, bile duct or duodenal obstruction, infected pancreatic necrosis, and malignancy.
- Total pancreatectomy with islet autotransplantation may be considered in individuals with severe pain and/or inflammation that cannot be controlled by other approaches. Efficacy increases when this is done approximately two years before chronic pain develops [Anderson et al 2016, Drewes et al 2017]. It is recommended that persons in whom pancreatectomy is being considered be referred to expert centers. In persons with adequate endocrine pancreatic function, islet cell isolation and autotransplantation may be considered at the time of total pancreatectomy [Bellin et al 2008, Bellin et al 2018]. Consideration of individuals for total pancreatectomy with islet transplantation should include age and disease duration, both of which adversely affect postsurgical outcomes [Bellin et al 2018]. Note: Islet autotransplantation should not be offered to older adults with long-standing chronic pancreatitis and diabetes mellitus because the implanted cells may be malignant.

In addition to severe pain, endoscopic and surgical interventions are reserved for complications such as pseudocysts, bile duct or duodenal obstruction, infected pancreatic necrosis, and malignancy.

Obstructions or calcifications in the pancreatic ducts may be relieved by procedures such as endoscopic retrograde cholangiopancreatography (ERCP), in which endoscopic cannulation of the common bile duct and pancreatic duct is followed by injection of radiographic dye. Decompressing/clearing of blockage decreases pain as well as the number of hospitalizations and recurrent attacks in many persons with HP [Dever et al 2010]. Note: Because of the risk of acute pancreatitis following ERCP, it is only recommended for obtaining brushings (for evaluation of strictures) and for therapeutic intervention, not diagnosis.

Although a variety of surgical approaches are used for noncancerous pancreatic disorders that cause pain or obstruction from multiple strictures, pancreatic drainage surgeries in those with hereditary pancreatitis are unlikely to stop the underlying inflammatory process. Furthermore, pancreatic surgery often reduces the number of islet cells, which are essential in pancreatic endocrine function [Sutton et al 2010, Kobayashi et al 2011]. Because total pancreatectomy with islet cell auto-transplantation is an option for some persons with HP, retaining as many islet cells as possible is an important consideration before proceeding with any pancreatic surgery [Bellin et al 2014].

Chronic Pancreatitis

Treatment of chronic pancreatitis focuses on improving quality of life by managing pancreatic pain, maldigestion, and diabetes mellitus.

Pain is a variable complication of recurrent and chronic inflammation and ranges from minimal to severe and disabling. Pain can result from inflammation, ischemia, obstructed ducts, pseudocysts, and/or maldigestion [Fasanella et al 2007].

- One small study from Italy suggested that vitamins and antioxidants reduced pain in *PRSS1*-related hereditary pancreatitis [Uomo et al 2001].
- Pain from maldigestion is improved with pancreatic digestive enzymes [Burton et al 2011].
- If the main pancreatic duct is obstructed, a trial of endoscopic treatment is often used for diagnostic, therapeutic, and prognostic reasons in determining longer-term therapy.
- Surgery has been reported to be helpful by many individuals; however, surgical approaches should be postponed if islet autotransplantation is being considered.
- Several expert groups (e.g., University of Minnesota, University of Pittsburgh) are offering pancreatic islet autotransplantation in an effort to both control severe pain and delay the development of diabetes mellitus [Sutton et al 2010, Kobayashi et al 2011]. It is recommended that physicians and affected individuals work closely with expert centers since the process is irreversible.

Maldigestion as a result of pancreatic exocrine insufficiency:

- Pancreatic enzyme replacement therapy improves digestion in those with pancreatic insufficiency who have pain with eating, steatorrhea (fat in the stool), and/or diarrhea [Burton et al 2011].
- The amount of pancreatic enzyme replacement necessary depends on the diet and on the amount of residual pancreatic function (which diminishes over time). The normal amount of lipase secreted is about 750,000-1,000,000 units (USP) per meal. (Note that earlier papers used IU, and 1 IU = 3 USP units) [Pongprasobchai & DiMagno 2005]. Since a minimum of 10% of normal pancreatic enzyme output is needed to digest a meal, about 70,000-80,000 USP units of lipase are required for an average-sized adult (70 kg) with total pancreatic insufficiency. The amount can be reduced for smaller persons and those with residual pancreatic exocrine function – while monitoring symptoms and nutritional parameters.

Pancreatic endocrine insufficiency occurs in individuals with chronic pancreatitis and is associated with a gradual loss of function resulting in diabetes mellitus.

- Monitor for glucose intolerance.

- Optimize nutrient digestion with pancreatic enzyme replacement therapy to stimulate foregut hormone release and minimize hindgut hormone release. Metformin is recommended as an oral antidiabetic agent [Decensi et al 2010].
- Synchronize the digestion and absorption of nutrients with insulin therapy delivery, with special attention to hypoglycemia resulting from loss of glucagon cells.

Prevention of Primary Manifestations

The ability to prevent the primary manifestations of *PRSS1*-related HP is limited. The following recommendations are for individuals with (or at risk for) *PRSS1*-related HP. Following these recommendations from early childhood may help prevent attacks of acute pancreatitis:

- **Low-fat diet.** No formal guidelines for amount of dietary fat exist; however, some physicians recommend a low-fat diet to minimize pancreatic stimulation. If a low-fat diet is chosen, extra attention to providing fat-soluble vitamins (A, D, E, K) is needed.
- **Multiple small meals.** No evidence-based guidelines exist; however, small meals may minimize pancreatic exocrine stimulation.
- **Good hydration.** Maintaining good hydration may be helpful in minimizing attacks, especially since nausea, vomiting, and loss of appetite limit oral intake during an attack. Recognition of acute pancreatitis and prompt medical treatment with adequate intravenous hydration can be beneficial in decreasing the severity of the attack [de-Madaria et al 2018].
- **Antioxidants.** One small study suggested that antioxidants may be useful in reducing the likelihood of acute pancreatitis in persons at risk for hereditary pancreatitis [Uomo et al 2001].
- **Exercise, yoga, and other relaxation techniques** may increase quality of life in persons with pancreatitis [Sareen et al 2007]. Some individuals report that regular exercise, such as running, helps reduce the frequency of episodes of pancreatitis [Authors, unpublished].

Surveillance

Surveillance for pancreatic cancer may benefit individuals with *PRSS1*-related HP age 40 years and older who have long-standing chronic pancreatitis and a strong family history of pancreatic cancer [Chang et al 2014]. Because long-standing chronic pancreatitis results in pancreatic scarring and fibrosis that make assessment of abnormalities difficult [Ulrich 2001, Brand et al 2007], it is recommended that concerned individuals be referred to a surveillance program that includes biomarker research and other new techniques.

Agents/Circumstances to Avoid

Alcohol and tobacco. Smoking doubles the risk for all forms of pancreatitis, including hereditary pancreatitis [Maisonneuve et al 2005, Yadav et al 2009]. In combination, smoking and alcohol use increases the risk of developing pancreatitis eightfold [Yadav et al 2009]. Tobacco use also doubles the risk of pancreatic cancer and is associated with earlier-onset pancreatic cancer [Lowenfels et al 2001].

Dehydration worsens episodes of acute pancreatitis, and in severe cases can contribute to complications such as acute kidney injury and cardiovascular shock.

Physical and emotional stresses aggravate pancreatitis [Applebaum et al 2000]. Avoiding these stressors in individuals with *PRSS1*-related HP may prevent or delay worsening of symptoms and progression of disease.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing for the *PRSS1* pathogenic variant in the family in order to

identify as early as possible those who would benefit from screening for pancreatic exocrine and endocrine dysfunction.

Note: Predictive testing of children is appropriate in families with early-onset symptoms (i.e., onset age <25 years). In families with onset at or later than age 25 years, predictive genetic testing of asymptomatic children younger than age 16 years is not thought to be of medical benefit [Ellis et al 2001].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

A recognition of the need for new treatments and the challenges in developing classic pharmaceutical trials for rare diseases led to an NIH workshop during PancreasFest 2018 [Abbruzzese et al 2018, Abu-El-Haija et al 2018, Forsmark et al 2018, Lowe et al 2018, Uc et al 2018].

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Hereditary pancreatitis (HP) caused by gain-of-function *PRSS1* pathogenic variants is inherited in an autosomal dominant manner (see Genotype-Phenotype Correlations).

Note: A number of other variants in the coding and noncoding regions of the *PRSS1* locus are associated with a risk of pancreatitis, but they typically do not cause autosomal dominant hereditary pancreatitis.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with *PRSS1*-related HP have an affected parent.
- A proband with *PRSS1*-related HP may have the disorder as the result of a *de novo* pathogenic variant. Because simplex cases (i.e., a single occurrence in a family) have not been evaluated sufficiently to determine if the variant was *de novo*, the proportion of *PRSS1*-related hereditary pancreatitis caused by *de novo* pathogenic variants is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing for the *PRSS1* variant identified in the proband. Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of a milder phenotypic presentation.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.
- Although most individuals diagnosed with *PRSS1*-related HP have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. If the parent is

the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected or has a *PRSS1* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. However, sibs who inherit a *PRSS1* pathogenic variant may not develop pancreatitis because of reduced penetrance (penetrance of *PRSS1* varies; see Penetrance).
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *PRSS1* pathogenic variant but are clinically unaffected, sibs of a proband are still at increased risk for *PRSS1*-related hereditary pancreatitis because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *PRSS1*-related hereditary pancreatitis has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *PRSS1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for *PRSS1*-related hereditary pancreatitis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Pancreas Foundation (NPF)**
  101 Federal Street
  Suite 1900
  Boston MA 02210
  Phone: 866-726-2737 (toll-free); 617-342-7019
  Fax: 617-342-7080
  Email: info@pancreasfoundation.org
  www.pancreasfoundation.org

- **Pancreatica.org**
  149 Bonifacio Place
  Monterey CA 93940
  Phone: 831-658-0600
  Email: webmaster@pancreatica.org
  www.pancreatica.org

- **Pancreatic Cancer Action Network**
  2221 Rosecrans Avenue
  Suite 7000
  El Segundo CA 90245
  Phone: 877-272-6226 (toll-free); 310-725-0025
  Fax: 310-725-0029
  Email: info@pancan.org
  www.pancan.org

- **European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer**
  NIHR Pancreas Biomedical Research Unit, Royal Liverpool University Hospital
  5th Floor UCD Building
  Daulby Street
  Liverpool L69 3GA
  United Kingdom
  Phone: +44 (0) 151 706 4168
  Fax: +44 (0) 151 706 5826
  Email: europac@liverpool.ac.uk
  European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. PRSS1-Related Hereditary Pancreatitis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PRSS1	7q34	Serine protease 1	PRSS1 database	PRSS1	PRSS1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for PRSS1-Related Hereditary Pancreatitis (View All in OMIM)

167800	PANCREATITIS, HEREDITARY; PCTT

Table B. continued from previous page.

276000	PROTEASE, SERINE, 1; PRSS1

Molecular Pathogenesis

Introduction. Three trypsinogens are synthesized by the pancreas as digestive enzymes [Whitcomb & Lowe 2007]:

- Cationic trypsinogen (2/3s of trypsinogens) encoded by *PRSS1*
- Anionic trypsinogen (1/3 of trypsinogens) encoded by *PRSS2*
- Mesotrypsinogen (<5% of trypsinogens) encoded by *PRSS3*

Trypsinogens are expressed as a pre-propeptide that is processed to trypsinogen by cleavage of a signal peptide. Trypsinogen is activated to trypsin by cleavage of an eight-amino acid trypsinogen activation peptide (TAP), which is typically initiated in the intestine by the action of enterokinase. The TAP can also be cleaved by trypsin in the presence of calcium and association with a binding site formed in the activation region. Trypsin is an endopeptidase that cleaves peptide chains following an arginine or lysine residue that also serves as the master activator of pancreatic zymogens by cleaving the activation peptide of most major digestive enzymes made by the pancreas.

Trypsinogen has a second calcium-binding site that persists in trypsin which, when occupied by calcium, prevents trypsin autolysis at p.Arg122 and degradation by chymotrypsin C (CTRC) binding at p.Leu81 [Szmola & Sahin-Toth 2007].

Gain-of-function variants increase conversion of trypsinogen to active trypsin, or reduce the degradation of active trypsin; thus, the amount of active, intrapancreatic trypsin is increased. Active intrapancreatic trypsin may activate other zymogens (preactivated digestive enzymes), cross-activate the immune system, and/or cause direct injury [Whitcomb 2004].

The effect of premature trypsin activation may be accentuated by loss of function in modifier genes including the genes encoding the following proteins [Chen & Ferec 2009, Whitcomb 2010]:

- Pancreatic secretory trypsin inhibitor (encoded by *SPINK1*)
- Chymotrypsin C (*CTRC*)
- Calcium-sensing receptor (*CASR*)
- Cystic fibrosis transmembrane conductance regulator (*CFTR*)

This suggestion is based on the observation that the non-*PRSS1* variants are seen as part of a complex genotype more often than would be expected by chance alone.

Mechanism of disease causation. *PRSS1* variants associated with disease are gain-of-function variants. Gain-of-function variants have altered regulation leading to enhanced activation or delayed/impaired inactivation. Four gain-of-function variants (see Table 3) have been associated with Mendelian inheritance.

***PRSS1*-specific laboratory considerations.** Other disease-associated *PRSS1* variants cause protein misfolding, leading to endoplasmic reticulum stress [Schnúr et al 2014]. However, the damaging effects do not appear to be sufficient to cause recurrent acute pancreatitis and chronic pancreatitis in most individuals, suggesting that additional risk factors are necessary. A common *PRSS1-PRSS2* haplotype appears to affect PRSS1 expression and modify risk of pancreatitis from other factors, including alcohol [Whitcomb et al 2012, Avanthi et al 2015, Derikx et al 2015].

Copy number variants, including duplication of *PRSS1* and gene conversion between *PRSS1* and *PRSS2*, have been reported in affected individuals [Masson et al 2008a].

Table 3. Notable *PRSS1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_002769.4 NP_002760.1	c.47C>T	p.Ala16Val	Low-penetrance pathogenic variant
	c.86A>T	p.Asn29Ile	Together these variants account for ~90% of individuals w/molecularly confirmed *PRSS1*-related hereditary pancreatitis [Rebours et al 2009].
	c.365G>A	p.Arg122His	
	c.364C>T	p.Arg122Cys	Low-penetrance pathogenic variant

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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- 25 April 2019 (sw) Comprehensive update posted live
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