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Hereditary Pancreatitis

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Abstract

Hereditary pancreatitis (HP) is a rare autosomal dominant genetic disorder of the pancreas with incomplete penetrance. HP typically presents with acute pancreatitis in early adolescence with a high rate of progression to chronic pancreatitis (CP) by early adulthood. Genetically, HP is generally caused by gain-of-function mutations in the cationic trypsinogen gene (PRSS1), although rare kindreds have been identified with other known or unknown etiologies. While HP is similar to RAP and CP of other etiologies, the onset of HP is dramatically earlier. A lifetime of pancreatic injury and inflammation increases the risk for the most adverse late complication of HP – pancreatic cancer. Furthermore, the natural history of HP cases varies substantially between individuals and families due to gene-gene and gene-environment interactions. Patients with HP should be closely evaluated for pancreatic endocrine and exocrine insufficiency, counseled on lifestyle changes that may reduce severity and progression, and may be evaluated for total pancreatectomy with islet autotransplantation (TP-IAT) when chronic pain does not respond to therapeutic interventions.

1. Introduction

Hereditary pancreatitis (HP) is a rare genetic disorder characterized by recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) that runs in families (16, 23, 24, 41). HP typically presents in childhood with attacks of acute pancreatitis (AP) that become more frequent, leading to the morphologic changes of chronic pancreatitis. Over time, patients may develop the common complications of chronic pancreatitis, including pancreatic fibrosis, pancreatic exocrine insufficiency (PEI), diabetes mellitus (Type 3c; T3cDM (2)), chronic pain syndromes and pancreatic ductal adenocarcinoma (PDAC). However, the age of onset, clinical course and types of complications vary markedly between individuals and families, suggesting that modifier genes and environmental factors play an important role in individual patients (1, 29).

Historically, HP has functioned as a model to understand the progression of acute pancreatitis to RAP and CP. The disease primarily originates from gain-of-function mutations in the cationic trypsinogen gene (protease, serine, 1; PRSS1; OMIM *276000), i.e. *PRSS1* N29I and R122H (21, 56, 77). Specifically, the identification of gain-of-function mutations in the trypsinogen gene brought new insights into the field of pancreatology by indicating that (1) trypsin activity is the proximal cause of AP, (2) CP develops as a result of RAP, and (3) genetic and environmental factors modify the phenotype of RAP and CP.

Following the insights from HP and related advances, the concept of CP has been changed from diagnosing CP by end-stage features, to a new paradigm based on a progression model beginning with asymptomatic risk stage, and proceeding to inflammation (typically AP and RAP) and variable dysfunction of the relevant cell types that contribute to fibrosis, pancreatic exocrine insufficiency, diabetes mellitus and pancreatic cancer. The new mechanistic definition highlights the essence of the disorder (mechanistic pathophysiology), as well as the characteristic features (76).

> **CP Definition (essence):** "Chronic pancreatitis is 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".
>
> **CP Definition (characteristics):** "Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia".

This new approach to defining and identifying CP should facilitate a rational approach to early diagnosis, classification and prognosis for HP and other inflammatory disorders of the pancreas.

2. Diagnosis and Classification

The term "hereditary pancreatitis" is used with both broad and narrow definitions. Online Mendelian Inheritance in Man (OMIM) #167800 defines 'PANCREATITIS, HEREDITARY; PCTT' broadly to include multiple genes associated with RAP and CP including *PRSS1, PRSS2, SPINK1, CFTR* and *CTRC*. Clinical researchers and geneticists generally define HP as autosomal dominant pancreatitis, and use the term "familial pancreatitis" to describe recessive or complex phenotypes in the absence of a recessive syndrome such as cystic fibrosis (CF) or a cystic fibrosis transmembrane conductance regulator gene (*CFTR)*-related disorder (10). In this chapter, we define HP as two or more individuals with RAP or CP in two or more generations of a family (i.e., an autosomal dominant pattern of inheritance) or pancreatitis associated with a known, gain-of-function germline variant in *PRSS1* (64, 80).

Familial Pancreatitis

Familial pancreatitis is a broader term to describe families in which the incidence of pancreatitis is higher than expected according to the frequency of pancreatitis in the general population. Since pancreatitis, especially chronic pancreatitis, is rare, two first- or second-degree relatives with pancreatitis are sufficient for classification as a familial pancreatitis kindred. However, other causes of pancreatitis, including gallstones and trauma, must be excluded. Furthermore, episodic abdominal pain from AP may not be diagnosed in stoic patients, and older members of the family with diabetes mellitus or PDAC may represent late stages of undiagnosed CP. Thus, collecting an accurate family history and identifying familial pancreatitis may be challenging.

The contribution of genetics to familial pancreatitis is often broad and complex. Known genetic contributors to familial pancreatitis include recessive inheritance of mild variable or borderline *CFTR* mutations, pathogenic variants in *SPINK1*, and variants in other genes with small but interacting or additive effects. Whitcomb *et al.* demonstrated the complexity of gene-environment interactions that contribute to familial pancreatitis using a GWAS analysis carried out with next generation sequencing (79). In this HP kindred, two key affected family members were found to have completely different complex combinations of genetic and environmental risk factors (79). The classification of hereditary pancreatitis and familial pancreatitis and examples of genotype-phenotype correlations are given in **Table 1**.

3. Clinical Presentation

The penetrance for *PRSS1* hereditary pancreatitis has been estimated at 80% (1, 26, 59, 65). However, penetrance may vary by the presence of modifying risk factors and type of mutation. For example, one study reported a *PRSS1* R122H kindred in Venezuela with low penetrance, as demonstrated by the presence of only 2 affected individuals in a large family (62).

The complications of HP are similar to those of chronic pancreatitis. Early on it was recognized that some patients had severe acute pancreatitis with portal vein thrombosis (41), but this does not appear to be the most common characteristic. The primary distinguishing features of HP from other forms of pancreatitis are an early age of onset and a family history in the absence of environmental risk factors (e.g. alcohol, tobacco). Furthermore, HP patients who progress to CP have higher cumulative risks for diabetes mellitus and exocrine insufficiency, and a higher overall risk for PDAC. This may be attributed to an early age of onset, resulting in longer lifetime exposure of the pancreas to injury and inflammation. As compared to the general population, lifespan is not reduced in HP patients who do not develop pancreatic cancer (47).

Acute Pancreatitis

Hereditary pancreatitis typically presents in childhood at a median age of 10-12 years **(Figure 1)** (26, 48). However, age at onset can vary dramatically by family, as demonstrated by one kindred where 58% of *PRSS1* R122H family members developed pancreatitis before the age of 5 years (65). A number of studies have shown that the age of onset is earlier in R122H *PRSS1* kindreds compared to N29I *PRSS1* and mutation-negative patients (21, 26, 65). Severity, length, and frequency of attacks can also vary substantially between families. As with other forms of pancreatitis, epigastric abdominal pain is the most common and disabling symptom, affecting at least 83% of HP patients (48). Though attacks are typically 7 or less days in length (26), smoldering pancreatitis and/or persistent pain can occur in some cases (9). Almost 90% of patients report greater than 5 hospitalizations, with a higher reported hospital admission rate for *PRSS1* R122H carriers compared to N29I carriers (0.33 and 0.19 per year, respectively) (26). The same study found no significance difference in the number of attacks by type of mutation, suggesting that the R122H mutation may be associated with more severe attacks but no greater susceptibility (26).

Table 1: Genotype-phenotype correlations of hereditary pancreatitis*

Genotype (variants)	Phenotype (syndromes)	Comment
PRSS1 GOF e.g. p.N29I, p. R122H, p.R122C	Autosomal dominant hereditary pancreatitis	Unregulated trypsin activity with premature activation Genetic counseling recommended for families and predictive testing.
PRSS1 LOF e.g. p.D100H, p.C139F, p.K92N, p.S124F, p.G208A	Sporadic pancreatitis	Unfolded protein stress response. Genetic counseling optional
PRSS1 regulation e.g rs10273639, rs4726576 A	Protection from trypsin-associated pancreatitis	Focus on non-trypsin associated causes of pancreatitis

GOF, gain of function; LOF, loss of function.

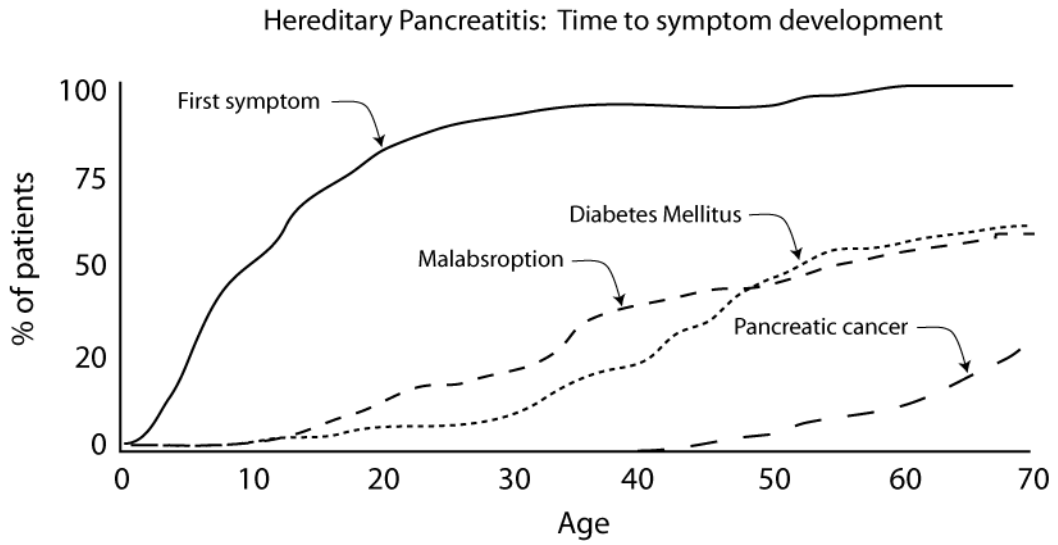

Figure 1. Historic data on the time from birth to detection of first symptoms (e.g. acute pancreatitis), malabsorption (e.g. PEI), Diabetes mellitus (e.g. T3cDM) and pancreatic cancer (i.e. PDAC). Figure based on models by Howes (26).

Chronic Pancreatitis

The majority of HP patients with RAP progress to CP by the 2nd or 3rd decade of life. The degree of fibrosis is influenced by the number of attacks and other modifying factors. Eventually, progressive inflammation and fibrosis lead to pancreatic exocrine insufficiency in a significant amount of patients. The cumulative risk for exocrine failure at 50 years has been estimated at 37.2%, with a median age of 53 years (26). Diabetes arising from destruction of the islets of Langerhans by exocrine pancreatic disease is classified as T3cDM. Destruction of insulin-secreting beta cells also leads to glucose intolerance, followed by pancreatic endocrine insufficiency. Furthermore, loss of glucagon-secreting alpha cells reduces counter-regulatory hormones and places patients at risk for hypoglycemia and "brittle" disease. The cumulative risk for endocrine failure is 47.6% at 50 years, with a median age of diabetes mellitus onset of 53 years (26).

Pancreatic Cancer

Patients with hereditary pancreatitis have a >50-fold increased risk for pancreatic adenocarcinoma (26, 47, 49), with a cumulative risk of 40-<54% at 70 years of age (26, 37, 48). Risk is further increased in the presence of smoking and diabetes mellitus (37, 38). The increased risks for pancreatic cancer appear to result from prolonged pancreatic exposure to chronic inflammation (25, 74, 75, 82), particularly in HP patients who develop pancreatitis in adolescence. However, the risk of PDAC does not tightly correlate with the severity of pancreatic inflammation and fibrosis (49, 50). The presence of shared risk and/or protective factors likely modifies the risk for pancreatic cancer amongst families, as evidenced by extensive variations in pancreatic cancer incidence between HP kindreds.

4. Epidemiology

Hereditary pancreatitis is rare and primarily a disease of Caucasians. The majority of identified families originate from the United States and European countries, including Italy (58, 77), England and Wales (59), Germany (70), France (35, 48), Turkey (69), Denmark (29), Spain (17) and others (26). Reports of HP from Asia are rare, though a few kindreds have been reported from Japan and China (36, 44, 45, 66).

In South America, one Brazilian family (18) and one Venezuelan patient (62), were reported to have HP originating from gain-of-function *PRSS1* mutations. In Mexico, single pancreatitis patients with *PRSS1* V39E or N42S variants were

identified, but no *PRSS1* R122H or N29I variants were observed (46).

No reports of HP families or individuals of African ancestry have been published to date. A *SPINK1* c.36G>C (p.L12F) variant has been observed in some African patients with pancreatitis, but functional analyses showed no detrimental effects from this common polymorphism (33).

One HP family of Aboriginal descent was reported from New Zealand and found to carry the *PRSS1* R122H variant (42). However, a number of this family's ancestors were European, suggesting that the mutation may have been inherited from European ancestors rather than Aboriginals.

The frequency of hereditary pancreatitis seen in clinical practices varies widely by geographic region. In the United States, for example, there are large numbers of HP families throughout Appalachia, including Pennsylvania, Ohio, West Virginia, Kentucky, Tennessee, Georgia, Northern Florida, Oklahoma, Minnesota, and California ((4) and personal observations). The elevated concentration of HP kindreds in these regions is believed to originate from early founders of the disease within large families who tended to remain within the previously described geographic regions. Early estimates of the prevalence of HP in the United States was about 1000 cases (39), although the actual numbers are not known. In a sampling of cases from 30 centers in the United States in the North American Pancreatitis Study (NAPS2) (83) and others used for the first pancreatitis GWAS (79), 19 of 1586 RAP and CP cases (excluding HP families) (1.2%) were found to have *PRSS1* gain-of-function mutations. Overall, among NAPS2 cases the prevalence of *PRSS1* N29I, R122H and R122C was 2.8%, with no gain-of-function mutations in unrelated controls, although referral bias for the cases in this cohort is also possible. The population prevalence in France is estimated to be at least 0.3 per 100,000 according to a national series of HP (48).

5. Pathogenesis and Pathology

Molecular Genetics

PRSS1 Hereditary Pancreatitis

The pathogenesis of hereditary pancreatitis was discovered by Whitcomb *et al.* to be caused by mutations in the cationic trypsinogen gene (*PRSS1*) (78). Trypsinogen is the zymogen precursor to trypsin, a serine protease that hydrolyzes peptide bonds following an arginine or lysine, preferably in the small intestine. Two gain-of-function mutations were identified, the first being R122H and the second, N29I (initially designated R117H and N21I using the chymotrypsin numbering system) (21). These 2 mutations have been identified in the vast majority of hereditary pancreatitis kindreds in the United States and Europe, and comprise 90% of *PRSS1*-positive HP cases. A list of known *PRSS1* variants can be found at http://www.pancreasgenetics.org.

Analysis of trypsinogen's crystal structure reveals insight into the pathogenic mechanisms of gain-of-function mutations. **Figure 2** is an x-ray crystallography figure of cationic trypsinogen illustrating 2 calcium-binding sites and 2 sites of trypsin-catalyzed hydrolysis. The trypsinogen activation peptide (TAP) on the N-terminus maintains the zymogen in an inactive form. First, trypsin can activate other trypsinogen molecules by cleaving the TAP [at residue K12] in the process of autoactivation (81). This process is facilitated by calcium binding to the first calcium binding pocket, which stabilizes the TAP. Once trypsinogen is activated, other trypsin molecules can induce autolysis by hydrolyzing arginine 122 on a flexible side chain (or autolysis loop) that links the 2 globular domains of trypsin (54, 73). The site is flexible, but protected from trypsin by calcium-binding to a second, adjacent pocket.

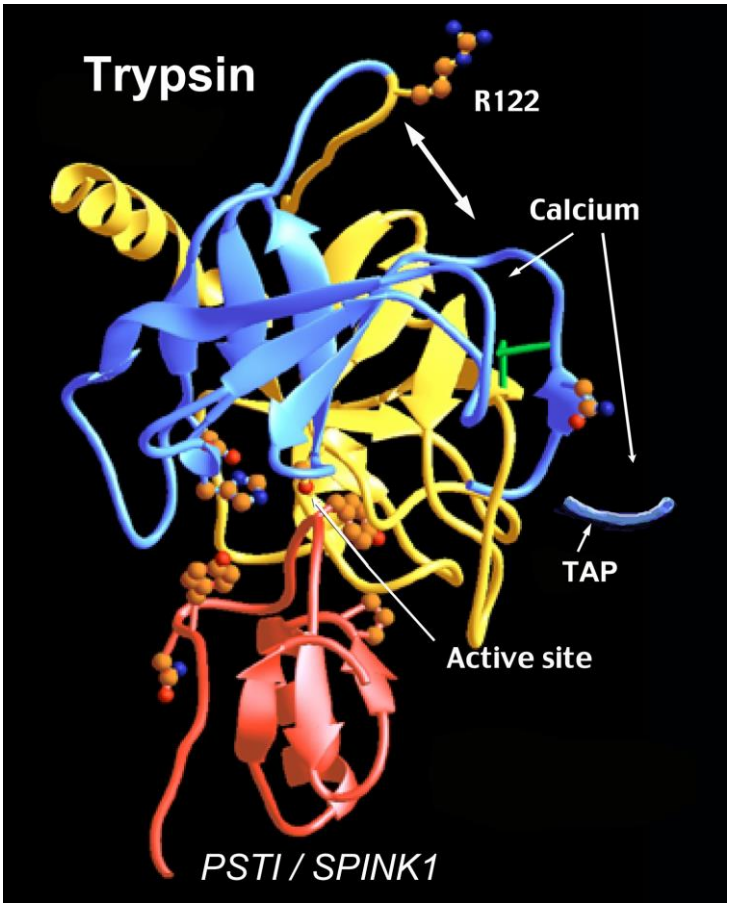

Figure 2. Structural representation of cationic trypsin (PRSS1, blue and yellow) interacting with the suicide inhibitor, pancreatic secretory trypsin inhibitor, SPINK1 (PRSST/SPINK1). The flexible side chain connecting the two globular domains illustrates the location of R122 as an autolysis site, which is the amino acid substituted in the R122H gain-of-function variant. The two calcium binding sites are illustrated by the arrows from calcium, with the activation site of calcium binding being lost by activation and release of trypsinogen activation peptide (TAP).

Table 2

Trypsin AA#	**16**	**29**	**122**
PRSS1	A	N	R
PRSS2	A	I	R
PRSS3	V	T	R
T6	A	N	H

Conversion Mutations between trypsinogen genes and pseudogenes. Comparison of amino acid sequences in PRSS1 with PRSS2, PRSS3 and T6. A alanine; H, Histidine; I, isoleucine; N, asparagine; R, arginine; T, threonine.

Additional inhibitors of trypsin activity include CTRC, which cleaves the calcium binding loop, and SPINK1, which binds to the trypsin active site as a suicide inhibitor. It has been observed that in the presence of elevated calcium concentrations (>1mM Ca^{2+}), the hydrolysis of trypsin by another trypsin or by chymotrypsin C (CTRC) is blocked (68). From a functional standpoint, the trypsinogen or trypsin molecule is susceptible to hydrolysis in low calcium concentrations, as seen

inside the pancreatic acinar cell after synthesis or in the distal intestine, but is resistant to hydrolysis when the calcium levels are high, as seen in the pancreatic duct duodenum and jejunum (15). Thus, in high calcium concentrations, trypsin is more easily activated whereas in lower trypsin concentrations, activation is minimized. The degradation of trypsin is a complex and well-orchestrated process involving both an additional trypsin molecule and CTRC. The interaction of these molecules under various conditions has been defined (see (7) (67))

In the human trypsinogen family, anionic trypsinogen (PRSS2), meso trypsinogen (PRSS3) and three pseudogene paralogs exist that contain variants corresponding to the R122H mutation in *PRSS1* (e.g. T6, **Table 2**). Pseudogenes are noncoding relatives of functional genes that have typically acquired mutations rendering them non-functional. Generally, pseudogenes are harmless, except in cases where sequence homology with its functional paralog leads to recombination and acquisition of a pathogenic variant in the expressed gene. In the first report of a gene conversion event leading to a pathogenic *PRSS1* allele, two patients were identified where recombination events between exon 3 of *PRSS1* and the pseudogene *PRSS3P2* resulted in the accumulation of R122H within *PRSS1* (55). *PRSS3P2* also contains variants corresponding to the known pathogenic A16V and N29T variants, which may also be acquired by *PRSS1* in a gene conversion event.

In one HP family, a novel 9 nucleotide intragenic duplication (c.63_71dup) was identified (30). Functional studies supported this variant as a gain-of-function mutation, as evidenced by a ≥ 10-fold increase in both autoactivation and activation by human cathepsin B (30).

In addition to gain-of function-mutations, trypsin activity can be markedly increased by copy number variations (CNVs). A variety of CNVs have been identified in HP families, and additional copies of *PRSS1* act as gain-of-function mutations by increasing trypsin expression, which predisposes to recurrent pancreatitis and hereditary pancreatitis (12, 40).

Additional mutations have been identified in the trypsin molecule that are associated with chronic pancreatitis, but do not appear to be inherited as highly penetrant autosomal dominant variants. The most common one is the *PRSS1* A16V variant, which appears to act as a secondary or modifier variant to increase risk of pancreatitis (22). Furthermore, not all trypsinogen mutations found in pancreatitis patients are gain-of-function variants. At least a dozen *PRSS1* variants that are rare and scattered throughout the molecule have been identified in case reports, and functional studies suggest that these variants are associated with misfolding of the mutant trypsinogen protein, triggering acinar cell stress through the unfolded protein response (32), (57). Further genotype-phenotype and therapeutic response studies need to be conducted to fully understand the implications of these findings for affected patients.

Other Genes

Additional genes have been associated with recurrent acute and chronic pancreatitis, a number of which regulate trypsin activity. Loss-of-function mutations in chymotrypsinogen C (*CTRC*) and the serine protease inhibitor, Kazal-type 1 (*SPINK1*) reduce the protective functions of these trypsin inhibitors in the pancreas (7, 52, 68, 84). Mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) that impair bicarbonate conductance are associated with RAP, CP and other CFTR-related disorders (34). Next generation sequencing suggests that more complex combinations of genes also play a significant role in the development and progression of CP (61).

Histology

The pathogenicity of the *PRSS1* R122H variant was supported in a transgenic mouse model. Mice expressing the R122H_mPRSS1 transgene

presented with early pancreatic acinar cell injury and inflammation, as well as progressive fibrosis and acinar cell dedifferentiation (6). A later study examined pancreata from 10 *PRSS1*-mutation positive (R122H, N29I, and IVS4-24 C>T) HP patients following a total pancreatectomy. Inspection of pancreatic tissue revealed progressive lipomatous atrophy and fat replacement, with thin and loosely packed fibrosis in comparison to alcoholic and obstructive CP (60).

6. Genetic Testing and Counseling

The goals of genetic testing differ depending on the circumstances surrounding the patient. In general, asymptomatic subjects are not tested, especially if they are not in an HP family. However, testing may be indicated when a mutation has been previously identified in the family and/or for reproductive decision-making. In patients with recurrent acute pancreatitis or early signs of chronic pancreatitis, genetic testing is medically indicated to make a diagnosis, and to develop a management plan. In established CP, genetic testing may be useful for anticipating and managing complications of CP. In end-stage disease, genetic testing is most useful for establishing risk to family members and for research purposes.

Hereditary pancreatitis should be suspected in cases of idiopathic pancreatitis, early onset pancreatitis, and in families with multiple affected individuals. At least a three-generation pedigree should be ascertained and evaluated for pancreatitis, pancreatic cancer, diabetes mellitus, pancreatic exocrine insufficiency, cystic fibrosis, and exposures to smoking and alcohol to establish a HP kindred (63). Risk calculation should always be taken in the context of the family history, particularly genotype (if known), inheritance pattern, environmental exposures, penetrance, ages of onset, and severity.

Following careful evaluation of the patient's personal and family history, targeted genetic testing of members of an established HP family may be considered in cases of unexplained RAP and/or CP, an affected individual with a first or second-degree relative with pancreatitis, unexplained pancreatitis in a child requiring hospitalization and/or when there is a known mutation in the family (19). The patient should be provided with both pre- and post-test counseling to ensure that they understand the benefits, implications, and limitations of testing (5, 20). Insurance discrimination is a major concern for genetic testing in HP patients. Patients in the United States should be informed of the *Genetic Information Nondiscrimination Act of 2008* (GINA, Pub. L, 110–233), which protects against genetic discrimination in health insurance and employment, but affords no protection for life, disability, or long-term care insurance.

Commercial genetic testing is currently available for *PRSS1*[*], *SPINK1*, *CFTR*, and *CTRC*. As noted above, the trypsinogen gene family is complex and both genes and pseudogenes are highly homologous. Therefore, specially designed genetic tests are required – and next generation sequencing approaches such as whole exome sequencing or whole genome sequencing should not be used for *PRSS1* testing because of challenges in sequence alignment.

If a mutation is not identified from sequencing or a targeted mutation analysis, a deletion/duplication analysis can be considered. When a *PRSS1* mutation is identified, patients can be counseled on a 50% or 1 in 2 chance for each child to inherit the deleterious allele from a carrier parent. If the deleterious allele is inherited, the risk to develop hereditary pancreatitis is about 80%. Notably, these calculations should always be provided in the context of family history, as many HP families

[*] Testing for hereditary pancreatitis has been patented (US 6406846 B1) owned by Dr. Whitcomb and licensed initial to Ambry Genetics, but now licensed to Arial Precision Medicine (www.arielmedicine.com).

demonstrate significant differences in penetrance and severity.

Symptomatic Patients

When genetic testing is indicated in a family, testing should always begin in a symptomatic individual. Test results may identify a genetic etiology in a family, thereby accelerating the diagnosis of other affected family members. Results may also have implications for risk to develop other complications, risk to other family members, and family planning. Not all families meeting clinical criteria for hereditary pancreatitis have an identifiable *PRSS1* mutation. Therefore, negative genetic test results in the affected proband of a family does not preclude the diagnosis of hereditary pancreatitis.

Asymptomatic Patients

In families where a deleterious variant has been identified, predictive genetic testing may be considered in close family members. Single-site testing for this mutation can provide information on risk and risk to descendants. Generally, risk to develop pancreatitis in an asymptomatic, mutation-positive adult decreases with age.

A family member who tests negative for the familial mutation has a significantly reduced, but not absent, risk for hereditary pancreatitis. Family members may have other unknown risk factors and are still at risk for pancreatitis of non-genetic etiology.

Genetic testing of asymptomatic family members in a family without an identifiable mutation is uninformative. As always, genetic counseling for risk should be provided in the context of family history.

Children

Genetic testing may be indicated in a child with diagnosed or suspected pancreatitis. Parents or legal guardians are responsible for the decision to pursue genetic testing. However, children 7 years and older should provide assent for the testing. Predictive genetic testing for asymptomatic patients less than 16 years of age is not recommended and does not have clear benefits (19). The lifestyle practices that may be relevant to at risk carriers, such as a healthy low-fat diet and avoidance of alcohol, tobacco, and stress, are recommended for all children (53).

7. Management and Treatment

HP represents a complex syndrome, and studies on management are limited. Acute pancreatitis episodes are managed identically to AP from other etiologies – with attention to intravascular fluid status, oxygenations and pain control (28).

Once the diagnosis is established, the focus is on minimizing recurrence and complications. Generally, patients should be counseled to avoid alcohol and tobacco, and referral to special programs for alcohol and/or smoking cessation in active users is advised. Alcohol lowers the threshold for attacks of acute pancreatitis and contributes to progression to chronic pancreatitis. Smoking further increases the risk for pancreatic cancer by two-fold (38). A low fat diet in the form of multiple small meals a day and good hydration is often recommended but remains unproven. Stress reduction with activities such as running has been reported to be of major benefit in some patients (unpublished communications).

Pain

Pancreatic pain is complex and multifactorial (3). Analgesics are commonly required to help control pain, ranging from acetaminophen and NSAIDs to narcotics. In some patients, antioxidants may also reduce pain by reducing oxidative stress in acinar cells (11, 72). As with other forms of pancreatitis, endoscopic or surgical interventions may also be indicated to alleviate pain. There is growing use of total pancreatectomy with islet autotransplantation (TP-IAT) in the United States, and this appears to be an effective (and radical) treatment in some patients (8, 14) (see below).

Pancreatic Exocrine Insufficiency

About a third to a half of the patients with HP will develop pancreatic exocrine insufficiency (PEI) in their lifetime (27, 48). PEI is a complex condition of insufficient pancreatic enzymes for digestion and absorption of nutrients. The threshold between sufficiency and insufficiency is vague because it depends on the meal, the diet and the capacity of the intestines in addition to the capacity of the pancreas to deliver enzymes (31). If PEI is suspected because of symptoms of maldigestion and/or malnutrition, then function testing or a trial of pancreatic enzyme replacement therapy should be initiated.

Pancreatic Endocrine Insufficiency

Patients with chronic pancreatitis should be monitored for development of T3cDM (51). Diminished insulin secretion resulting from loss of beta islet cells may be further reduced by declines in proximal gut digestion and incretin secretion. Due to loss of glucagon and pancreatic polypeptide secreting alpha and PP cells, patients are at risk to develop “brittle” diabetes, characterized by difficult to control swings in blood glucose levels.

Total pancreatectomy

Total pancreatectomy with islet autotransplantation may be considered in younger patients for unmanageable pain (13, 14). Older patients with longstanding CP may benefit from total pancreatectomy without islet autotransplantation for pain alleviation and to reduce the risk of pancreatic cancer (13, 71).

Clinical Trials

Calcium-channel blockers are being investigated as a therapy to reduce symptoms in individuals with HP. A pilot study demonstrated that amlodipine does not increase risk for an acute attack, cause pain, or significantly reduce quality of life (43). The small trial also demonstrated a trend toward pain alleviation and reduction in quality of life (43).

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