Genetic Aspects of Pancreatitis

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Key Words

acute pancreatitis, chronic pancreatitis, cystic fibrosis, hyperlipidemia, hypertriglyceridemia

Abstract

Acute pancreatitis and chronic pancreatitis are complex inflammatory disorders of the pancreas with unpredictable severity, complications, and clinical courses. Growing evidence for genetic risk and modifying factors, plus strong evidence that only a minority of patients with these disorders are heavy alcohol drinkers, has revolutionized our concept of these diseases. Once considered a self-inflicted injury, pancreatitis is now recognized as a complex inflammatory condition like inflammatory bowel disease. Genetic linkage and candidate gene studies have identified six pancreas-targeting factors that are associated with changes in susceptibility to acute and/or chronic pancreatitis, including cationic trypsinogen (*PRSS1*), anionic trypsinogen (*PRSS2*), serine protease inhibitor Kazal 1 (*SPINK1*), cystic fibrosis transmembrane conductance regulator (CFTR), chymotrypsinogen C (CTRC) and calcium-sensing receptor (CASR). Patients with mutations in these genes are at increased risk of pancreatitis caused by a variety of stresses including hyperlipidemia and hypercalcemia. Multiple studies are reporting new polymorphisms, as well as complex gene × gene and gene × environmental interactions.

INTRODUCTION

AP: acute pancreatitis

CP: chronic pancreatitis

RAP: recurrent acute pancreatitis

There is growing recognition that genetic variants underlie susceptibility to, and severity of, acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer. The discovery that gain-of-function mutations in trypsinogen lead to hereditary pancreatitis became the "Rosetta Stone" of pancreatic disease. The vast majority of factors that cause AP, recurrent acute pancreatitis (RAP), and/or CP are linked to either premature activation of trypsinogen to trypsin or the failure to eliminate active trypsin within the pancreas (**Figure 1**). However, pancreatitis may be the result of other mechanisms, as evidenced by entities such as autoimmune pancreatitis. Additionally, the role of environmental factors (e.g., ethanol consumption and tobacco smoking) is important, and continued research on their impact is needed. This review focuses first on susceptibility and severity factors influencing AP and thereafter on these issues for CP.

ACUTE PANCREATITIS

AP is a syndrome of acute inflammation of the pancreatic gland that is clinically recognized by a patient's sudden onset of upper abdominal pain, elevated serum levels of digestive enzymes (e.g., pancreatic amylase; pancreatic lipase >3x upper limit of normal), and/or characteristic findings on abdominal imaging studies (e.g., edema, peripancreatic fat stranding, fluid collections). AP is a process initiated by an acute injury, which is followed by an acute inflammatory response that is often out of proportion to the degree of tissue injury. This exaggerated response is believed to be the result of premature activation of pancreatic digestive enzymes that

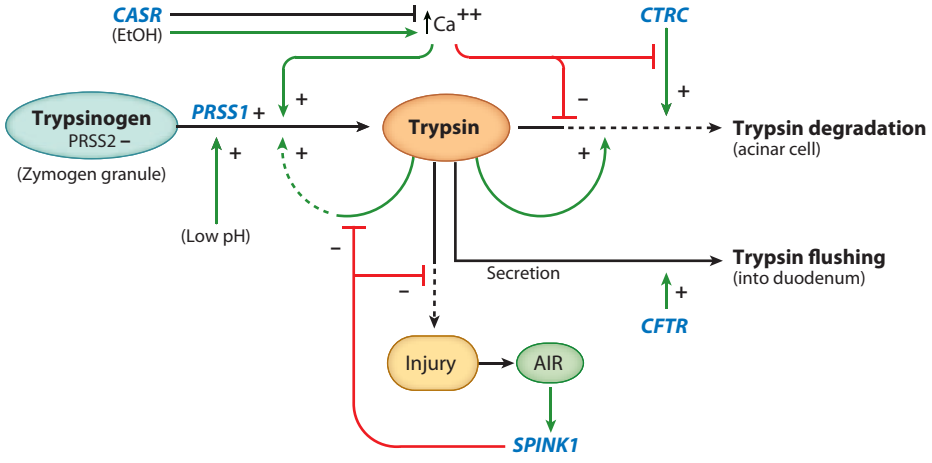

Figure 1

Genetic factors influencing trypsinogen activation and trypsin inactivation. Early activation of trypsinogen to trypsin within the pancreas is crucial in the development of pancreatitis. Trypsinogen activation is promoted by cationic trypsinogen mutations (*PRSS1+*), active trypsin, high calcium (Ca^{2+}), and low pH. Calcium levels are regulated in part by calcium-sensing receptor (*CASR*) and dysregulated by ethanol (EtOH). Active trypsin degradation is facilitated by *CTRC* and by other active trypsin molecules, but blocked by high calcium. Active trypsin within the pancreas leads to pancreatic injury, which leads to an acute inflammatory response (AIR). AIR upregulates expression of serine protease inhibitor Kazal 1 (*SPINK1*), which blocks active trypsin and therefore prevents further activation of trypsinogen and limits further tissue injury. Cystic fibrosis transmembrane conductance regulator (*CFTR*) represents an extra–acinar cell mechanism to eliminate trypsin by flushing it out of the pancreatic duct and into the duodenum. Mutations in *CFTR* reduce fluid secretion and trypsinogen/trypsin wash-out. Gene symbols in blue italic type indicate that genetic variants are associated with pancreatitis. (Figure by D. Whitcomb, all rights reserved; adapted for publication by Annual Reviews.)

digest pancreatic tissue and release digestion products that consequently activate the inflammatory cascade. Activated pancreatic digestive enzymes may also directly cross-activate the immune system.

The primary etiologic risk factors associated with AP are listed in **Table 1**. Of note, major genetic factors that increase susceptibility to CP, i.e., cationic trypsinogen (*PRSS1*) variants, are thought to do so by facilitating RAP (1). The focus of AP research is on gene-environment interactions that either increase risk or modify the severity of the AP syndrome.

Hypertriglyceridemia as a Risk Factor for Acute Pancreatitis

Individuals recognized as having familial hyperlipidemias, and especially individuals with type I hyperlipoproteinemia from lipoprotein lipase (LPL) mutations or apolipoprotein C-II deficiency, are known to be at increased risk for developing AP (2–4). However, only a small subset of patients with hypertriglyceridemia develop AP. Growing evidence suggests that episodes of AP during times of hypertriglyceridemia require some type of pancreatic injury to initiate injury and the release of pancreatic lipase, and that the more severe injury that triggers an acute inflammatory response is caused by free fatty acids. Wang et al. (5) used LPL-deficient mice to study the role of pancreatic injury and pancreatic lipase in the context of hypertriglyceridemia. None of the hypertriglyceridemic mice in their study spontaneously developed AP. Injury required hyperstimulation of the pancreas by cerulein, a cholecystokinin receptor agonist that causes AP via the activation of digestive enzymes from pancreatic acinar cells. Once pancreatitis was initiated, the injury was more severe in LPL-deficient mice than in wild-type mice, primarily because they suffered greater degrees of hemorrhage and necrosis. In vitro studies have demonstrated that, in the presence of pancreatic lipase, chylomicrons release more free fatty acids than triglycerides, and it is the free fatty acids that cause injury, as previously demonstrated by Saharia et al. (6).

Table 1 Risk factors for acute pancreatitis

Susceptibility factors
Duct obstruction
gallstones
parasites
tumors
anatomical abnormalities
endoscopic retrograde cholangio-pancreatography
Metabolic factors
hyperlipidemia
hypercalcemia
acidosis (e.g., diabetic ketoacidosis)
Toxins
ethyl alcohol (high doses)
ooganophosphorus insecticides (acetylcholinesterase inhibitors)
scorpion toxin (Caribbean and South American varieties)
Medications[a]—partial list
acetaminophen
azathioprine
erythromycin
estrogen
exenatide (Byetta)
furosemide
6-mercaptopurine
metronidazole
NSAIDs
pentamidine
stavudine
sulindac
tetracycline
valproic acid
Genetic susceptibility factors
cystic fibrosis gene (*CFTR*)
trypsinogen gene (*PRSS1*)
pancreatic secretory trypsin inhibitor gene (*SPINK1*, recurrent acute pancreatitis only)
alcohol-associated injury
Infections
viruses
bacteria
Trauma
blunt or penetrating
surgical
Ischemia
idiopathic
Modifying factors
alcoholism (e.g., >2–5 drinks per day)
obesity (e.g. BMI > 30)
genetic factors (see text)

[a]Multiple mechanisms; usually idiosyncratic reactions or linked to hypertriglycerdia (57).

Genetic variants associated with AP in patients with hypertriglyceridemia. In support of this concept of hyperlipidemia plus pancreatic injury to cause AP was a genetic epidemiology study from Taiwan, which included 126 patients with hypertrigliceridemia: 46 with a previous diagnosis of AP, and 80 without an AP diagnosis (7). All subjects were screened for mutations in the cationic trypsinogen gene (*PRSS1*), the serine protease inhibitor Kazal type 1 gene (*SPINK1*), the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), and the gene for tumor necrosis factor (TNF) superfamily member 2 (*TNF2*). There were significant differences in patient characteristics ($p < 0.05$) in mean serum triglyceride levels (4.26 mmol/L without AP versus 14.07 mmol/L with AP), as well as in the rates of diabetes, and fasting serum glucose and HbA1c levels. No *PRSS1* or *SPINK1* mutations were detected. However, the *CFTR* I556V $CF^{mild-variant}$ mutation was observed in 12 of 46 (26.1%) patients with AP, and only in 1 of 80 (1.3%) hypertriglyceridemic patients without AP ($p < 0.0001$). This mutation was seen in ~1% of the control population. Furthermore, five *CFTR* variants (125G > C, 1001 + 11 > CT, M470V, 2694T > G and 4521G > A) were identified, with the 125G > C and M470V variants being more common in subjects with AP.

Chang et al. (7) thereafter performed a haplotype analysis with the five single nucleotide polymorphisms (SNPs) and identified seven common haplotypes, of which GCMTG was the most common (72.7%) and was not associated with pancreatitis ($p = 0.001$) whereas the GCVTG (20.6%) and CCVTG (3.7%) haplotypes were associated with AP ($p = 0.014$, OR 2.7 and $p = 0.004$, OR 21.94, respectively). The *TNFα* promoter variant −863A, but not −1031C, −857T, −308A, or −238A, was also associated with heightened risk of AP (71.7% versus 31.3%, $p = 0.001$). A multivariate analysis of the hyperlipidemic patients indicated that triglycerides, *CFTR* 470Val, and *TNFα* promoter 863A were independent risk markers for AP.

These findings are remarkable, first, in that the investigators were able to recruit and evaluate a relatively large cohort of hyperlipidemic patients, with and without pancreatitis, for detailed analysis. Second, the finding of a high-risk *CFTR* haplotype that encompasses the M470V variant is interesting, since it was previously associated with pancreatitis in both Korea (8) and Switzerland (9). Steiner et al. (9) previously reported a haplotype that included the M470V variant and conferred a high risk for developing AP. Steiner et al. (9) provided some functional evidence that their high-risk *CFTR* haplotype may have affected pre-mRNA splicing, which was detected in nasal epithelial cells of all individuals evaluated, by changing regulatory sequence motifs of exonic splice enhancers, leading to lower amounts of normal transcripts.

In summary, the data by Wang et al. (5) suggest that pancreatitis is triggered after pancreatic injury and/or release of lipase from pancreatic acinar cells. The study by Chang et al. (7) suggests that CFTR and/or TNFα variants whose effects are not severe enough to cause pancreatitis alone can be part of a high-risk complex that produces clinically evident AP in the presence of hyperlipidemia.

Cytokines and modifying factors. Genetic polymorphisms that are hypothesized to alter the immunological response to pancreatic injury and increase the risk of specific pathologic outcomes continue to be investigated. DeMadaria et al. (10) reported the results of a study of 84 patients with AP who were screened for known polymorphisms in *TNFα*, interleukin 1 (*IL-1*), IL-1 receptor antagonist (*IL1RN*), *IL-6*, and *IL-10* for etiology-associated susceptibility and severity. The primary finding of their study was that the *TNFα* −238 AG genotype, but not *TNFα* −308 SNP, was associated with organ failure (shock and/or respiratory failure) during AP (the *TNFα* –1031 –863, and –857 SNPs were not studied).

TNFα is a major early proinflammatory cytokine that, along with IL-1, mediates the systemic inflammatory response syndrome (SIRS)

(11–13). About half of patients with SIRS go on to develop multi-organ failure, primarily involving the lungs (acute lung injury), cardiovascular system dysfunction (shock), and acute renal failure. The *TNFα* –238 and –308 SNPs, have been investigated by other researchers; Tukiainen et al. (14) reported no association between *TNFα* –308 and the severity of pancreatitis in 397 patients from Finland, although they did not investigate the –238 SNP. These results were similar to the case-control studies by Powell et al. (15) on 190 AP patients and 102 controls and by Sargen et al. (16) on 135 AP patients and 107 controls. These studies, both from the United Kingdom, found no association between the *TNFα* –308 SNP and AP susceptibility, etiology (16), or severity. Of note, the *TNFα* –308 SNP did not appear to be a risk factor in the study by Chang et al. (7), reviewed above.

However, the TNFα –308 A allele was reported to be associated with severe AP in Balog et al.'s (17) study of 77 (29 mild, 48 severe) Hungarian patients. A case-control study by Zhang et al. (18) in 208 AP cases and 116 ethnically matched controls showed that the TNFα –308 A allele was associated with shock in patients with severe AP (53.1% versus 20%, $p = 0.001$).

The *TNFα* –308A allele was previously shown to be associated with adverse outcome in several infections and inflammatory diseases (19). There is a strong association of this allele with susceptibility to septic shock (20). Thus, there is some evidence that genetic variants in *TNFα* affect the response to sepsis and AP—possibly through driving SIRS—but no conclusions can currently be drawn about the role of *TNFα* variants and AP. Future studies should include all functional SNPs rather than just *TNFα* –308, stratification according to other risk factors (e.g., obesity and alcohol consumption), and a focus on SIRS and downstream effects of TNFα activity (e.g., IL-6 or C-reactive protein levels). Furthermore, future studies must be adequately powered, and replicated in a comparable population.

CHRONIC PANCREATITIS

The genetics of CP is becoming clearer. The risk factors and etiologies of RAP and CP (**Table 2**), though diverse, generally rely on the same mechanism: trypsinogen activation. All of the major known susceptibility factors for CP can be categorized as members of the intrapancreatic trypsin regulatory mechanism (**Figure 1**). These findings strengthen the

Table 2 TIGAR-O (Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent acute or severe acute pancreatitis, or Obstruction) classification of risk factors for recurrent acute and chronic pancreatitis (58, 59)

Toxic-metabolic
alcohol
tobacco smoking
hypercalcemia
hyperlipidemia
chronic renal failure
medications
toxins
Idiopathic
early onset
late onset
tropical
Genetic
cationic trypsinogen mutation
CFTR mutations
SPINK1 mutations
alpha-1 antitrypsin deficiency
other
Autoimmune
isolated autoimmine chronic pancreatitis
syndromic autoimmune chronic pancreatitis
Sjogren's syndrome–associated chronic pancreatitis
inflammatory bowel disease–associated chronic pancreatitis
primary biliary cirrhosis–associated chronic pancreatitis
other
Recurrent and severe acute pancreatitis–associated chronic pancreatitis
postnecrotic (severe acute pancreatitis)
vascular disease/ischemic
post-irradiation
Obstructive
pancreas divisum
sphincter of Oddi disorders
duct obstruction (e.g., tumor)
preampullary duodenal wall cysts
post-traumatic pancreatic duct scars

argument that trypsin activation and/or diminished inactivation is the primary interface point between the influences of environment and recurrent pancreatic injury. Tempering this conclusion is the fact that, with the exception of *PRSS1*, all susceptibility factors have been found using a candidate-gene approach based on the trypsin-activity model. Thus, because no genome-wide association study (GWAS) has yet been performed, the approach to date has been biased. However, the argument in favor of the trypsin-activity model is further strengthened by the recognition that, in the vast majority of hereditary pancreatitis kindreds (autosomal dominant-appearing risk) and familial pancreatitis families (higher than expected clustering of cases of unclear inheritance pattern), the susceptibility factor is proven to be linked to trypsin.

The genetic factors linked to altered trypsin activity in the pancreas are also summarized in **Figure 1**. The most significant new findings are related to replicating the association between CP and SNPs in the chymotrypsinogen C gene (*CTRC*), the calcium-sensing receptor gene (*CASR*), and the anonic trypsinogen gene (*PRSS2*). Additional sequence variants in *PRSS1*, *SPINK1*, and *CFTR* have also been reported in new and established populations.

Chymotrypsin C

Chymotrypsin C is a digestive enzyme encoded by the chymotrypsinogen C gene (*CTRC*) and produced by pancreatic acinar cells; it is packaged in zymogen granules and secreted with other digestive enzymes from the pancreas. Compared to other forms of chymotrypsin, chymotrypsin C is produced in trace amounts, and it appears to be identical to the elusive trypsinogen degrader that was named enzyme Y by Rinderknecht et al. in 1988 (21, 22). As seen in **Figure 1**, *CTRC* is a crucial candidate gene because it destroys prematurely activated trypsin by attacking the molecule within the calcium-binding loop in the absence of calcium (21).

Rosendahl et al. (23) screened 901 individuals with the diagnosis of idiopathic or hereditary CP and 2804 healthy control subjects from Germany and identified *CTRC* variants in 4.8% of pancreatitis patients (especially a missense mutation R254W and an in-frame deletion of eight amino acids K247_R254del) compared to 0.7% of healthy controls. These mutations increase the risk of CP about fivefold. The findings from Germany were replicated in a French cohort study of 216 idiopathic CP patients and 350 controls (24). An important observation in the French study was that, in addition to the two most common German variants, 18 rare variants were identified, with a minor allele frequency of 0%–0.3% in the control population. Each of these rare variants was always observed to occur more frequently in the CP patients than in the controls, and their combined frequency in the CP patients was 12.0% compared to 1.1% in controls ($p < 0/00001$, OR 11.8; 95% CI 3.9–40.6). This latter finding not only replicates the German finding but also highlights the importance of rare mutations in complex genetic disorders.

Calcium-Sensing Receptor

The trypsinogen molecule activates to trypsin and is also degraded by other trypsin molecules—a process called auto-activation and autolysis. Trypsinogen has two specific cleavage sites for potential attack by other trypsin molecules. The first vulnerable site is lysine 23, and cleavage causes trypsinogen activation to trypsin with the release of the eight-amino-acid trypsinogen activation peptide (TAP). The second vulnerable site is arginine 122 (R122), and cleavage causes trypsin inactivation. The susceptibility of each of the two sites to attack is regulated by the ambient concentration of calcium and concentration-dependent occupation of the calcium binding sites (25). Low calcium concentrations, such as those present in normal acinar cells, limit trypsinogen activation and promote trypsin inactivation by exposing R122; high calcium concentrations, as in acinar cells during

hyperstimulation or calcium dysregulation, favor trypsinogen activation and prevent trypsin inactivation (1). Thus, regulation of intra–acinar cell calcium is critical for the prevention of trypsinogen activation and pancreatic injury (**Figure 1**).

The calcium-sensing receptor (CASR) is a membrane-bound G-protein-coupled receptor (26). CASR plays an important role in overall calcium homeostasis through its effects on the parathyroid gland and renal tubules. Multiple genetic variants of CASR have been associated with a variety of hypercalcemia-associated syndromes (27). CASR gene expression has been identified in both human pancreatic acinar and ductal cells, as well as in various nonexocrine tissues (28). In 2003, Felderbauer et al. (29) described a familial pancreatitis family in which only patients with both *SPINK1* mutations and a novel *CASR* c.518T > C SNP (where c. refers to the dDNA sequence) had developed CP. This original observation was recently extended. Felderbauer et al. (30) reported their findings from the review of 826 cases of primary hyperparathyroidism (pHPT) in which they identified 38 pHPT patients with pancreatitis (4.6%). Of the entire cohort of pHPT patients, 25 with pancreatitis and 50 without pancreatitis were screened for mutations in *SPINK1*, *PRSS1*, and *CFTR*. *SPINK1* mutations were identified in 16% of pHPT subjects with pancreatitis and 0% of subjects who did not have pancreatitis ($p < 0.05$), while cystic fibrosis-associated *CFTR* mutations were identified in 8% of pHPT patients with pancreatitis and 2% without pancreatitis (a single 5T allele). These data demonstrate the importance of pancreas-targeting trypsin-related variants as part of a complex gene-gene risk for pancreatitis.

A potential association between additional *CASR* variants in sporadic CP, with or without *SPINK1* mutations, has now been described in a small study of 35 patients with pancreatitis and 35 controls from India (31), and in a U.S. study of 306 controls and 238 patients with idiopathic and alcoholic CP who were selected based on known *SPINK1* genotypes (32). Muddana et al. (32) screened the exons previously demonstrated to harbor hypercalcemia-associated mutations (i.e., 2–5 and 7). *CASR* exon 7 R990G was significantly associated with CP ($p = 0.015$, OR 2.01, 95% CI 1.12–3.59). Additionally, the association between *CASR* R990G and CP was stronger in subjects who reported moderate or heavy alcohol consumption ($p = 0.018$, OR 3.12, 95% CI 1.14–9.13). In contrast to earlier studies, there was no association noted between the various *CASR* genotypes and *SPINK1* N34S high-risk haplotype in subjects with pancreatitis. Together, these association studies support a model of dysregulated calcium and recurrent trypsin activation/failed inhibition (**Figure 1**), in which CP risk increases in parallel with alcohol use, which may also lead to intracellular calcium dysregulation (33).

Trypsinogen Genes

The pancreas is known to express three trypsinogen genes, approximately two thirds as cationic trypsinogen (*PRSS1*), one third as anionic trypsinogen (*PRSS2*), and <5% as mesotrypsinogen (*PRSS3*). Gain-of-function mutations in the *PRSS1* gene (e.g., A16V, N29I, R122H) are responsible for the vast majority of hereditary pancreatitis cases in Caucasians (34–36). The impact of hereditary pancreatitis was highlighted in a study performed in France (37), where *PRSS1* mutations were found in two thirds of subjects with hereditary pancreatitis. Phenotypic evaluation of representative families demonstrated 93% penetrance. Furthermore, the mutation type identified was not correlated with clinical/morphological expression, and pancreatic adenocarcinoma was the cause of nearly half of the deaths that were observed in these patients (37).

An interesting study from China found that the *PRSS1* D162D variant (c.488 C > T) was associated with an increased risk of CP. Liu et al. (38) reported that 25 of 54 Chinese (Han) subjects with CP had the C/T genotype, whereas only 6 of 120 controls carried this genotype ($p < 0.001$, OR 16.4, CI 5.6–53.4). A D162D variant was originally reported by Gorry et al.

(35) in a family with the *PRSS1* R29I mutation, and again by Teich et al. (39), although the mutation occurred through a different SNP (c.486 G > T). This strong effect may reflect a high-risk haplotype, since the D162D variant would not change the amino acid sequence of the protein. In addition, Liu et al. identified a novel *PRSS1* A121T variant in two patients [which was independently reported in Germany (40)], and no R122H, N29I, or A16V mutations, which are the most common variants among Caucasians. In Korea, Oh et al. (41) reported that 2 of 37 subjects with idiopathic CP and 4 of 10 subjects with hereditary pancreatitis carried the *PRSS1* R122H mutation, and no other variant was found with sequencing of all exons.

More complex genetic variants of *PRSS1* are also associated with pancreatitis. One interesting observation has been that the *PRSS1* R122H mutation appears to be a gene-conversion mutation from other trypsinogen-like genes (42), including the N29I variant form *PRSS2* (43). In addition, trypsinogen copy number variants—duplications and triplications—now appear to be associated with idiopathic CP in some populations (44). Masson et al. (45) reported on a study of hereditary pancreatitis patients from France with a newly identified hybrid gene, in which exons 1 and 2 are derived from *PRSS2* and exons 3–5 from *PRSS1*. This variant is hypothesized to increase risk of developing pancreatitis through a copy-number variant plus a conversion event, resulting in the equivalent of an N29I mutation. Copy-number variants in *PRSS3* are not associated with CP (46).

To date, no gain-of-function mutations have been observed in *PRSS2*. However, a loss-of-function *PRSS2* G191R mutation was previously identified that creates a trypsin-sensitive cleavage site on the surface of the mutated molecule, resulting in rapid elimination of this form of trypsin (47). This year, that finding was confirmed by Santhosh et al. (48) in a study of 140 CP patients and 350 healthy controls from Hungary. The frequency of this variant was 5.4% of the control population but only 0.9% of the pancreatitis patients ($p = 0.0096$, OR 0.13, 95% CI 0.017, 0.945), which is consistent with the hypothesis that a loss-of-function mutation is protective against developing pancreatitis. Taken together, these data suggest that drugs specifically decreasing the expression or intrapancreatic activity of one or more trypsinogens may be of benefit to people at high risk for RAP or CP.

SPINK1/PSTI

SPINK1/PSTI [serine protease inhibitor, Kazal type 1 (SPINK1)/pancreatic secretory trypsin inhibitor (PSTI)] is an acute phase protein and specific trypsin inhibitor that is markedly upregulated in the pancreas in the context of active inflammation (49). SPINK1 is expressed in the acinar cell and follows the secretory pathway of trypsinogen, ensuring that it colocalizes with trypsin in pathological states. SPINK1 appears to be important in limiting ongoing trypsin activity after the onset of an acute inflammatory reaction and in opposing recurrence (**Figure 1**). The *SPINK1* pN34S high-risk haplotype is common in the general population (1%–4%) and is associated with CP through a wide variety of etiologies in scores of small studies (reviewed in Reference 50). Despite nearly a decade of work, the functional SNP in the *SPINK1* pN34S high-risk haplotype remains elusive (51).

Cystic Fibrosis Transmembrane Conductance Regulator Gene

Although *CFTR* variants are strongly correlated with pancreatitis, the pathological impact of this gene continues to be debated. The major problems complicating *CFTR* research include the large size of the gene (27 exons), the large number of known variants (>1600), uncertainty whether single heterozygous variants confer risk, and a dearth of functional data for the rare mutations. A substantial number of unusual variants that do not cause typical cystic fibrosis have also been identified in pancreatitis, leading to the hypothesis that some variants

specifically alter bicarbonate conductance and therefore target the pancreas (which secretes juice with a very high bicarbonate concentration) but not sweat glands, the respiratory system, or other organs using CFTR as a chloride channel. This hypothesis is known as the Whitcomb-Ermentrout model (52). An alternative hypothesis is that the CFTR dysfunction exceeds the critical threshold in the pancreas before it does so in other more resilient organs. Furthermore, *CFTR* variants that are not disease causing alone may be important in complex gene × gene interactions.

Probably the most important new contribution to our growing knowledge about *CFTR* variants in CP is a complete genetic screening of *CFTR* in 136 CP patients from France. Audrezed et al. (53) identified 28 mutations and 22 polymorphisms in these subjects, including 15 not seen in controls (see Table 3 of Reference 49). Of note, 33 carried a single *CFTR* mutation, and 8 were compound heterozygous. Other recent case reports and small studies have associated pancreatitis with the following *CFTR* mutations: D1152H/D1152H (54), W1282X/5T, D1152H/5T, W1282X/– (55), and in Hispanics, S531P/S531P (56). In addition, *CFTR* appears to influence susceptibility to pancreatitis in patients with hypertriglyceridemia (7), as discussed above. It is clear that *CFTR* variants are associated with CP, but dedicated functional and quantatitive phenotyping studies are required to identify the mechanism of risk.

DISCLOSURE STATEMENT

Dr. Whitcomb holds U.S. patent 6406846, entitled "Method for determining whether a human patient is susceptible to hereditary pancreatitis, and primers therefore," which has been licensed and provides royalty income.

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Errata

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