Genetic Evaluation of Pancreatitis

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KEYWORDS

• Pancreatitis • Genetics • Hereditary pancreatitis • Familial pancreatitis • *PRSS1* • *SPINK1* • *CFTR*

KEY POINTS

- Genetic testing is important in evaluating patients with a family history of hereditary pancreatitis (HP), as well as a personal history of unexplained recurrent acute pancreatitis or chronic pancreatitis (CP).
- Certain lifestyle changes are critical for disease modulations, such as tobacco and alcohol cessation. All patients should be counseled, but particularly for carriers of *PRSS1*, *CTRC*, and *CLDN2* mutations.
- Patients with familial pancreatitis should be screened for endocrine and exocrine insufficiency, as well as pancreatic cancer. A multidisciplinary approach including pain management and psychosocial counseling is beneficial.

INTRODUCTION

The initial description of multiple cases of autosomal dominant inherited chronic pancreatitis (CP) in a single family there have been many advances in the understanding of the genetic susceptibility to pancreatitis.[1] Following Since a report on the significant role of serine protease 1 (*PRSS1*) gene in hereditary pancreatitis (HP) in the late 1990s, the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) was also associated with recurrent acute pancreatitis (RAP) and CP.[2–4] In 2000, the serine protease inhibitor gene (*SPINK1*) was also linked to CP.[5] In the next 2 decades, other genes including calcium-sensing receptor (*CASR*),[6–9] chymotrypsin C (*CTRC*),[10] claudin-2 (*CLDN2*),[11] carboxypeptidase A1 (*CPA1*),[12] carboxyl ester lipase (*CEL*),[13] chymotrypsin B1 and B2 (*CTRB1*/*CTRB2*),[14] and transient receptor cation channel subfamily V member 6 gene (*TRPV6*)[15] have also been associated with RAP and/or CP.

Some patients who present with RAP or CP have a genetic predisposition and the disease may be better characterized as HP or familial pancreatitis.[16] HP has been

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traditionally defined as the presence of ≥2 blood relatives with pancreatitis across ≥2 generations with apparent autosomal dominant inheritance, or pancreatitis in the setting of a pathogenic germline variant in *PRSS1*.[17,18] In comparison, FP is used to describe a broader category of families with higher incidence of pancreatitis than the general population. FP requires ≥2 blood relatives with idiopathic pancreatitis not clearly caused by obstruction or environmental (eg, alcohol) causes, typically in the absence of an identifiable genetic defect.

Patients with genetic predispositions have often been diagnosed initially with RAP and CP, and developed irreversible pancreatic fibrosis, endocrine and exocrine disorders by the time they were diagnosed with HP.[19] Therefore, it is imperative for clinicians to have early suspicion to initiate appropriate management and disease modification. In this review, we summarize the current data on the genetic abnormalities in pancreatitis and discuss the evaluation and clinical management.

OVERALL EPIDEMIOLOGY

The epidemiology of CP and HP is incompletely understood, in part due to challenges with long-term follow-up, variability of disease phenotype, and lack of consistent disease definitions. The estimated prevalence of HP ranges from 0.3 to 0.57 per 100,000, with worldwide variability.[20–22] Most of the data on HP are derived from European cohorts and associated with specific germline variants, as discussed in the following.

GERMLINE VARIANTS

PRSS1

Pathogenic *PRSS1* variants, with penetrance ranging between 40% and 90% in HP families, lead to autosomal dominant expression of pancreatitis.[17] Although more than 40 variants in *PRSS1* have been associated with HP, the most prevalent variants are R122H, N29I, and A16V.[23,24]

Prevalence

As the most recognized genetic variant in HP, the prevalence of *PRSS1* variants has been explored in multiple studies in Europe, Asia, and North America and found in up to 80% of HP worldwide.[23] In 418 individuals from the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC), pathogenic germline variants in *PRSS1* were detected in 327 (78%); 19 (5%) of patients did not pursue testing. Among the pathogenic variants, 58 (52%) of 112 families (222 (53%) of 418 patients) were found to harbor R122H, 24 (21%) families (94 (22%) patients) N29I, and 5 (4%) families (11 (3%) patients) A16V.[18] In a nationwide survey from Japan, 30 (41.1%) of families who underwent genetic testing harbored a *PRSS1* variant: 22 (30.1%) with R122H and 6 (8.2%) N29I. In a study of more than 200 *PRSS1* carriers in the United States, the most common variants were R122H (83.9%) and N29I (11.5).[25] Interestingly, one study found *PRSS1* A16V variants to be present in 0.66% of the general population (4.32% in the African population compared with 0.47% in the European population), suggesting that this variant may have a variable phenotype.[23]

Mechanism of action

The *PRSS1* gene encodes cationic trypsinogen, a zymogen precursor to trypsin. After being secreted by the pancreas into the small intestine, trypsin activates other zymogens in the small intestine. Pancreatic acinar and ductal cells regulate trypsin and prevent premature or excessive trypsin activation, which may lead to an immune response.[2] (**Fig. 1**) Most of the *PRSS1* variants result in single amino acid changes

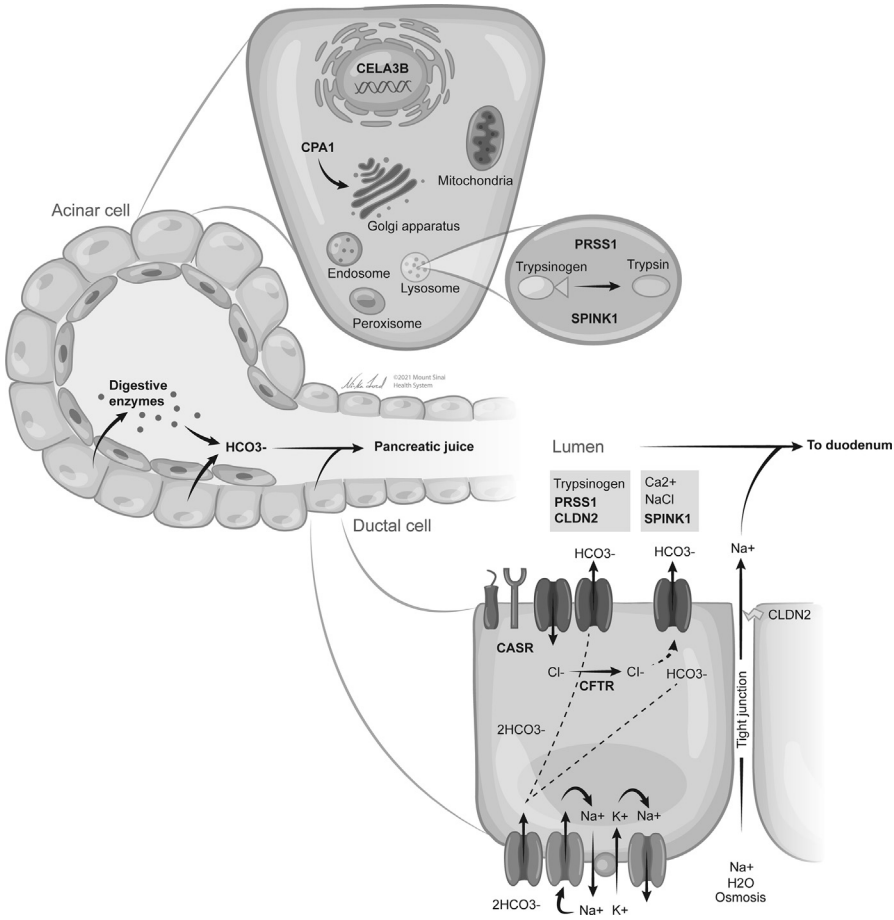

Fig. 1. Genetic variants in chronic pancreatitis. Left panel: several genes affect trypsin activation (*SPINK1*, *PRSS1*, *CELA3B*), secretion (*PRSS1*, *UBR1*, *CEL*), and degradation (*PRSS1*, *CTRC*, *PHLIP*). *CPA1* causes protein misfolding and stress in the endoplasmic reticulum. Right panel: *CFTR* affects duct cell secretion. *CASR* is involved in both calcium regulation and duct cell secretion. *CLDN2* regulates water and sodium transport in the pancreatic duct. (Printed with permission from © Mount Sinai Health System.)

in cationic trypsinogen and some result in an enzyme product that prematurely converts cationic trypsinogen to trypsin within the pancreas, whereas others prevent the degradation of trypsin (**Table 1**). There are 56 known *PRSS1* variants in patients with hereditary, familial, or idiopathic CP, all of which are categorized into copy number variants, gene conversion, and point variants.[23,24] R122H inhibits trypsin autolysis, whereas A16V mutation increases auto-activation and N29I affects both trypsinogen degradation and activation.[26,27] *PRSS1* variants that cause a gain of function of the trypsin TRY-1 proteins have the deleterious effect of promoting increased autoactivation and higher intrapancreatic trypsin activity.[28–30] In addition, less prevalent variants such as R116C, S124F, D100H, C139F, K29N, G208A have been associated with moderate to severe reduction in trypsinogen secretion, which can lead to protein misfolding and endoplasmic reticulum (ER) stress, causing pancreatic injury.[27,31,32]

Table 1
Common pathogenic variants associated with chronic pancreatitis

Gene and Variant	Mode of Inheritance	Functional Consequence	References
PRSS1 (R122H)	Autosomal dominant	Inhibits trypsin autolysis	Whitcomb,[2] Nemoda,[26]
PRSS1 (N29I)	Autosomal dominant	Inhibits trypsin degradation and increases activation	Szabo[27]
PRSS1 (A16V)	Autosomal dominant, low-penetrance pathogenic variant	Increases auto-activation	
PRSS1 (R116C, S124F, D100H, C139F, K29N, G208A)	Autosomal dominant	Causes moderate to severe reduction in trypsinogen secretion	Szabo,[27] Sahin-Toth,[31] Schnur[32]
SPINK1 (N34S)	Autosomal recessive or polygenic	Causes premature trypsinogen activation	Witt[5], Whitcomb,[28] Muller[38]
CFTR (F508del)	Autosomal recessive or polygenic	Impairs water secretion which causes protein plugs	Rowntree,[41] Cohn,[42] Weiss[43]
CTRC (A73T)	Autosomal dominant	Causes severe reduction in CTRC secretion and decrease in trypsin degradation	Rosendahl,[39] LaRusch[56]
CTRC (R254W)	Autosomal dominant	Promotes CTRC degradation	
CTRC (V235I)	Autosomal dominant	Decreases CTRC activity	
CTRC (K247_R254del)	Autosomal dominant	Produces inactive CTRC	
CPA1 (K374E, N256K)	Autosomal dominant	Causes protein misfolding-induced ER stress	Witt,[12] Nemeth[58]
CASR	Autosomal dominant	Causes hypercalcemia which leads to premature activation of trypsinogen inducing autodigestion	Racz[61]
CLDN2	X chromosome linked	Impairs water and sodium transport in the proximal pancreatic duct	Amasheh,[62] Whitcomb[11]
CEL	Autosomal dominant	Impairs secretion, leading to intracellular accumulation and ER stress	Raeder,[3] Fjeld[13]
CELA3B (R90C)	Autosomal dominant	Enhances the rate of translation, therefore, increasing the total amount of active enzyme	Uhlen,[66] Moore[67]
PHLIP (F300L)	Autosomal recessive	Increases degradation by trypsin and chymotrypsin	Behar[68] Szabo[69]
UBR1	Autosomal recessive	Diminishes response to secretion signals, causing acinar cell stress	Zenker[71]

The pathogenic gene variants with known mechanisms and described in families with chronic and hereditary pancreatitis are summarized later in this article.

Clinical manifestations

Individuals carrying a pathologic *PRSS1* variant can develop symptoms as early as 7 to 13 years, which is significantly earlier than non-*PRSS1* carriers.[18,21,22,25,29] Similar to other forms of pancreatitis, patients present with acute abdominal pain and elevated amylase and lipase. The onset of *PRSS1*-associated pancreatitis is typically before age 20. Howes and colleagues[18] studied 527 individuals from 112 families with HP in 14 countries, demonstrating a median age of pancreatitis onset of 12. In a French study of 200 patients with HP, the onset of pancreatitis was before the age of 10, and morphologic changes such as pancreatic calcification began at 20 to 25 years old.[22] Similar data have been reported from Japan, whereby the mean age of symptom onset was 17.8 years.[21] In the EUROPAC study, patients with R122H had a younger age of onset than other variants and this was not observed in the Japanese study.[18,21]

Signs of CP, such as calcification, may present by the mid-20s.[22] A Japanese study reported exocrine pancreatic insufficiency (EPI) at a median age of 42 years, significantly earlier than HP patients without *PRSS1* or *SPINK1* pathogenic variants.[21] In the European population, the median age to develop EPI in the setting of a pathogenic *PRSS1* variant was 53 years but no differences in age of onset of EPI were noted for those with R122H, N29I, or a different *PRSS1* variant.[18] Additionally, Japanese patients with pathogenic *PRSS1* variants developed diabetes at a median age of 42. Later onset of diabetes was noted in the EUROPAC cohort, with a median age of 58 for R122H carriers and 46 for N29I carriers. Neither study showed a difference in the time to diabetes onset in patients with HP with versus without *PRSS1* variants.[18,21]

SPINK1

The association between *SPINK1* variants and pancreatitis was established in 2000 and more than 30 *SPINK1* variants have been reported.[5]

Prevalence

There is a 2% prevalence of *SPINK1* pathogenic variants (N34S and P55S) among the healthy general population, yet less than 1% of *SPINK1* carriers develop pancreatitis.[33] However, among patients with idiopathic CP, *SPINK1* variants may be seen in up to 23% of cases.[5,34–36] The N34S variant is the most prevalent pathogenic haplotype in the US, Europe, and Japan, and IVS3+2T>C is commonly found in Japan and China.[21,37,38] In a European study, 21.3% and 9.1% of patients with CP exhibited a comutation involving *CFTR* and *CTRC*, respectively, which was higher than 4% in the general population.[38]

Mechanism of action

Located on chromosome 5q32, *SPINK1* encodes a pancreatic secretory trypsin inhibitor. During acute inflammation, this inhibitor is expressed in the pancreatic acinar cells and binds to activated trypsin, and can inhibit 20% of trypsin activity.[5,28] Pathogenic *SPINK1* variants do not lead to pancreatitis in the absence of early or excessive activation of trypsin and inflammation. *SPINK1* may cause CP in the setting of autosomal recessive inheritance; however, most patients with pancreatitis in the setting of *SPINK1* pathogenic variants are heterozygotes with more complex inheritance patterns of pancreatitis including modification by environmental factors. By lowering the threshold for the development of pancreatitis, *SPINK1* variants likely function as a disease modifier because they may not cause pancreatitis in the absence of other supporting factors.[39]

Clinical manifestations

In a histopathologic examination of 28 cases of *SPINK1*-associated CP, there was an increased loss of both acinar cell epithelium and intralobular ducts as the duration of pancreatic symptoms lengthened, as well as intralobular, interlobular, and perilobular fibrosis. Lipomatous atrophy, commonly associated with *PRSS1* and *CFTR* pancreatitis, was not present.[40] Variants in *SPINK1* are associated with a 12-fold increase in pancreatitis; however, controversy exists on whether *SPINK1* is the causative of disease or functions as a disease modifier. For example, in a Japanese study, patients harboring *SPINK1* variants did not develop pancreatitis earlier than controls.[21] In contrast, a large Chinese study of more than 1000 patients with CP and a European study of 209 patients with *SPINK1* mutations did demonstrate a significant difference (27 years and 21 years earlier, respectively) in the age of pancreatitis onset.[37,38] A similar proportion of patients developed diabetes and EPI in the European study, but the *SPINK1* group developed both diabetes and EPI approximately 15 years earlier.[38] Compound heterozygotes, such as those with both *SPINK1* and *CFTR* or *CTR,* exhibit a younger age of disease onset than those with *SPINK1* alone. Additionally, the presence of homozygous N34S did not confer an earlier age of pancreatitis symptom onset, diabetes, or EPI compared with heterozygotes.[38] These observations suggest that compound heterozygosity of *SPINK1*, or other unidentified environmental or genetic factors, rather than *SPINK1* mutation alone enhance the risk for pancreatitis.

Cystic fibrosis transmembrane conductance regulator gene

CFTR variants are associated with pancreatitis, even in the absence of other symptoms of cystic fibrosis (CF). The severity of pancreatitis is related to the specific variant and consequent defects in the CFTR protein, as well as zygosity.[41]

Prevalence

Approximately 1% to 4% of patients with CF will experience an episode of pancreatitis; conversely, approximately 15% of adults with CP carry a *CFTR* variant.[17,42] Incidence of CF varies worldwide and the highest incidence (1/2500) is in Northern Europeans. The most common variant, F508del, can be seen in approximately 70% of those with CF and 40% of those with HP who are found to have a variant in *CFTR*. There are more than 2000 *CFTR* gene variants and they are classified by the primary molecular defect in the protein with Class I–III variants of severe disruptions and Class IV–V of milder dysfunction.[41]

CFTR variants have complex inheritance patterns and heterozygous carriers have a 2-to 5-fold increased risk of pancreatitis.[42,43] In case–control studies from Europe and US, individuals with CP are at least twice more likely to have an aberrant *CFTR* gene than healthy controls.[43–45] In a study of 984 cases from the North America Pancreatitis Study 2 (NAPS2) population of 1000 subjects (460 RAP, 540 CP) and 695 controls, 43 *CFTR* variants were identified and 9 of them were reported in recurrent and CP but not CF. These variants were more prevalent in the pancreatitis cases than controls (14.2% vs 9.8%).[46] In a study of individuals with CP in China, 16 rare *CFTR* variants (allele frequency <1% of the control population) were identified from nearly 1900 individuals, and the aggregated *CFTR* variants confer an odds ratio (OR) of 3.71 for CP.[37]

Mechanism of action

CFTR, an epithelial cell anion channel, regulates chloride and bicarbonate secretion in the ductal cells of the lungs, pancreas, and other organs, thereby affecting the

production of sweat, mucus, and digestive fluids.[41] It is theorized that the mutated *CFTR* gene leads to inadequate alkalization of the pancreatic acinar cells and the retained zymogens in the duct digest the surrounding pancreatic tissue, leading to pancreatitis. In fact, electrophysiology studies of the cloned *CFTR* with the 43 variants from the NAPS2 study confirmed diminished bicarbonate conductance.[46] However, some animal model studies suggested that the pathogenesis is more likely linked to the impaired water secretion which causes protein plugs in the pancreatic duct, as well as overexpression of proinflammatory cytokine genes in CFTR knockout and F508del mice.[47,48]

Clinical manifestations

CFTR-associated pancreatitis varies in its manifestations based on the pathogenic variants and other environmental modifiers. The disease patterns and relationship to *CFTR* mutations generally fall into one of the several categories.

Patients with classic CF and abnormal sweat chloride measurement (≥60 mmol/L) have 2 pathogenic *CFTR* alleles (homozygous or compound heterozygous). Pancreatic damage has typically been so severe early in life that their pancreatic acinar reserve is too low to elicit pancreatitis. Freeman and Ooi suggested that a "critical mass" of acinar tissue in the setting of ductal obstruction is required for symptomatic pancreatitis.[49,50] Instead, up to 95% of patients with CF present with severe EPI.[4] In comparison, the risk of developing pancreatitis was 71% higher in patients with a mild genotype than in the moderate–severe group.[50]

Another manifestation of *CFTR* variants is called the *CFTR*-related pancreas-sinus-vas deferens syndrome. There are 9 variants (R117H, R74Q, R75Q, R170H, L967S, L997F, D1152H, S1235R, and D1270N) associated with the development of CP, chronic sinusitis, and male infertility but with minimal lung involvement. Individuals with *CFTR*-related pancreas-sinus-vas deferens syndrome usually have normal or mildly abnormal sweat chloride values, as the variants cause a select deficiency in bicarbonate conductance.[46] Interestingly, patients with less than 2 severe *CFTR* mutations have likely normal sweat chloride values (30–59 mmol/L) and do not meet the criteria for the diagnosis of CF, but still suffer symptoms of CP.[51] For example, one of these variants, R75Q, has deleterious effects on the pancreas but not on the lungs.[52] These patients have *CFTR*-related disorder, typically described as exhibiting one clinical manifestation (eg, pancreatitis or absence of vas deferens) associated with *CFTR* dysfunction.

Patients with *CFTR*-related pancreatitis are typically *CFTR* heterozygotes and have sweat chloride levels less than 30 mmol/L.[42,43,51] This group is generally healthy, but does exhibit a 3- to 4-fold risk of developing CP compared to the general population, especially when there is coexisting *SPINK1*, *CTRC,* or other genotypes.[39,52] Any factors that result in diminished pancreatic juice flow or increased duct resistance can precipitate pancreatitis. Therefore, tobacco use or pancreas divisum in the presence of *CFTR* variants may increase the risk of CP.[53–55]

Chymotrypsin C

CTRC is an enzyme that degrades trypsin in the setting of lower calcium concentrations. Its role in controlling prematurely activated trypsin has sparked interest in its association with pancreatitis.

Prevalence

In a German study, *CTRC* variants were found in 2.9% of patients with CP than 0.7% of controls. *CTRC* variants were also found in 14.1% of Indian patients with tropical

pancreatitis than 1.2% of controls.[10] In a North American population, the *CTRC* R254W variant was found to be equally present in CP, RAP, and controls, whereas the G60G variant, which causes decreased CTRC mRNA, was detected in 16.8% of CP, 11.9% of RAP, and 10.8% of controls. Specifically, there is a high association of G60G variant with CP in people who had a history of smoking than nonsmokers or drinking-only.[56] The evidence is less clear in other populations. In a Chinese study, when all *CTRC* variants were combined, an OR of 3.58 was found for CP. However, no increased odds of CP were found when individual variants were examined, possibly due to the small sample size of each individual variant.[37] These findings suggest that rather than independently causing CP, *CTRC* variants may be disease modifiers that exacerbate subclinical pancreatitis in the setting of other inciting factors.[57]

Mechanism of action

The *CTRC* gene is located on chromosome 19p13 and encodes CTRC. It cleaves trypsin at specific binding sites and its trypsin-regulatory function is affected by calcium concentration. *CTRC* variants include A73T, which causes a severe reduction in CTRC secretion, R254W which promotes CTRC degradation, V235I which decreases CTRC activity, and K247_R254del which produces inactive CTRC.[39,56]

ADDITIONAL GENES ASSOCIATED WITH PANCREATITIS

Several genes have been implicated in recent studies for the development of CP or HP, including *CPA1*, CASR, *CLDN2*, *CEL*, and others. These genes are considered disease modifying and increase the risk of pancreatitis progression.

Carboxypeptidase A1

The *CPA1* gene is located on chromosome 7q32 and encodes CPA1, a pancreatic enzyme that cleaves dietary proteins and involves in zymogen inhibition.[12] Mutations in *CPA1*, such as K374E and N256K, can cause protein misfolding-induced ER stress, thus increasing risks of pancreatitis.[12,58] N256K is the most frequently described variant. In a large German study, N256K was observed in 0.7% (7/944) of patients with nonalcoholic CP and 0% (0/3938) of controls.[12] Pathogenic variants including V251M, N256K, S282P have also been reported in the US, Poland, and Japan.[21,59,60] *CPA1* variants are associated with early-onset pancreatitis, as the risk increasing by 38-fold in patients younger than 20 years and 84-fold in those younger than 10 years.[12]

Calcium-sensing receptor gene CASR

A member of the G protein-coupled receptor family, is expressed in pancreatic acinar and ductal cells. It increases pancreatic ductal fluid secretion in response to high calcium concentrations in the pancreatic juice, thus preventing stone formation and pancreatitis.[61] The initial study that associated *CASR* with CP included a family of 5 individuals heterozygous for the *SPINK1* N34S and only 2 of these individuals developed CP and both were found to have variants in *CASR*. Several additional studies have further analyzed the relationship between *CASR* variants and pancreatitis in the setting of *SPINK1* mutations and alcohol.[6,8] *CASR* R990G is associated with the development of CP (OR: 2) and even more in the setting of heavy alcohol consumption (OR: 3.12). In some families, individuals with CP were found to have either *CASR* variants alone or in combination with *SPINK1* mutations, whereas healthy adults and children had *SPINK1* alone, suggesting that *CASR* variants may also function as disease modifiers in the development of CP, particularly in conjunction with pathogenic

variants in other genes.[6,8] In a subsequent study of 253 young French idiopathic patients with CP and nearly 500 healthy controls, 10 rare *CASR* coding variants were identified, but only A986 homozygosity was associated with CP. Of note, 3 of the 9 patients with CP with rare *CASR* variants were found to also have variants in *SPINK1* or *CFTR*.[9] Further work is required to better understand the mechanism of *CASR*-associated pancreatitis.

Claudin-2 gene

CLDN2 is expressed along the tight junctions and forms cation-ion and water channels between endothelial cells. It regulates sodium and water movement into the ductal lumen.[62] Interestingly, *CLDN2* has no association with acute pancreatitis. Rather, *CLDN2* variants accelerate the progression from acute pancreatitis to CP. *CLDN2* is located on the X chromosome; therefore, risk CP seems dominant in men and recessive in women. The T allele (rs128688220) is seen in 25.8% of male controls and 6.9% of female controls. However, it has been described in 47.6% men with alcohol-associated CP than 4% of male controls with heavy alcohol use, suggesting an association of the T allele with alcohol-induced CP in male carriers.[11] In subsequent studies in Japan and India, the T allele was associated with significantly increased risk for both alcohol-associated CP and idiopathic CP in male patients.[29,63–65]

Carboxyl ester lipase

CEL is a pancreatic enzyme encoded by the *CEL* gene. Mutations in *CEL* are associated with maturity-onset diabetes of the young type 8 (MODY8) and pancreatic exocrine insufficiency, suggesting the destruction of the islet cells.[3] Another hybrid *CEL* mutation with its adjacent pseudogene, *CELP*, causes a hybrid protein with impaired secretion and intracellular accumulation leading to ER stress. This pathogenic allele was detected in 3.7% (42/1122) of nonalcoholic patients with CP versus 0.7% (30/4152) controls.[13]

Others

Chymotrypsin-like elastase 3B (CELA3B) is a member of 6 elastases, 4 of which are exclusively produced in and secreted by pancreatic acinar cells. CELA3B is cleaved by trypsin on secretion and converted to an active protease.[66] A *CELA3B* R90C variant was recently discovered in a patient with personal and family history of CP.[67] The variant enhances the rate of CELA3B translation, thereby increasing the total amount of active enzyme and risk of pancreatic injury. Subsequent in vitro and murine studies with CRISPR genome editing demonstrated that homozygous *CELA3B* mutant mice only developed pancreatitis after a second insult. Taken together, this illustrates a different pathway from the typical disruption of trypsin regulation or increased ER stress.[67]

The *PNLIP* gene is located on chromosome 10q25. Protease-sensitive pancreatic lipase (PNLIP) is critical for the digestion of dietary triglycerides and is expressed only in the exocrine pancreas.[68,69] In a study of 2 European cohorts of 1052 nonalcoholic CP and 1557 control subjects, missense variants were enriched in 1.7% (18/1061) of patients with CP compared to 0.6% (10/1557) of controls. The most frequent variant was F300L (8/1061), unique to the CP group. Five variants, including F300L, P245A, I265R, S304F, and F314L, showed increased degradation by trypsin and chymotrypsin. These protease-sensitive *PNLIP* variants were found in 1.1% mild RAP pediatric or young adult patients and 0.1% controls (OR: 11.3). These missense variants were subsequently detected in both Japanese patients with CP and controls, but no variants were found in CP cohorts from India and US.[70] Although this study showcased a novel F300L variant associated with potentially early-onset CP, further evidence is needed to characterize its impact on a wider population.

The *UBR1* gene encodes ubiquitin-protein ligase E3, which is expressed in the pancreatic acinar cells and regulates protein degradation. UBR1 deficiency leads to acinar cell destruction that resembles pancreatitis. Homozygous or compound heterozygous mutations in *UBR1* cause Johanson–Blizzard syndrome, characterized by severe EPI and hypoplasia of the nasal alae.[71] In a study of 389 Japanese patients with idiopathic, alcoholic, or hereditary CP, 17 variants were identified in the exons of *UBR1*, albeit in similar frequencies in both cases and controls.[72] In a US study of 100 patients with AP, RAP, or CP, 121 genetic variants in *PRSS1, CFTR, SPINK1, CTRC* as well as *UBR1* were identified by RNA-sequencing. Co-expression analysis revealed the co-occurrence of genes involved in stress response, such as *UBR1* or gamma-glutamyl transferase 1 (*GGT1*), together with at least 1 acinar- or duct-associated gene, such as *CFTR*. Some of the *UBR1* variants were in the noncoding region.[73] This suggested that the generic risk of *UBR1* mutations may not fit a Mendelian model and *UBR1* variants alone may not confer any deleterious effect.

TRPV6 is an active calcium selective ion channel and regulates apical calcium entry in absorptive and secretory tissues. TRPV6 is expressed approximately 6 times higher in pancreatic ductal cells than in acinar cells.[74] In a recent study by Masamune and colleagues,[15] functionally defective *TRPV6* variants caused impaired calcium uptake, and was enriched in both Japanese (4.3%, 13/300) and European patients (2.0%, 18/880) with nonalcoholic CP compared with controls (Japanese: 0.1%, OR: 48.4; European: 0%). It was also correlated with the onset of disease $\leq$20 years of age (OR: 18.8). Notably, 20% of patients with these defective variants also carried *SPINK1* N34S, further highlighting the complexity of genetics in CP.

PANCREATIC CANCER

The etiology of pancreatic cancer in the setting of HP or FP is multifactorial, although the true risk of pancreatic cancer is uncertain because studies are limited by referral, ascertainment, and other biases. CP itself is a strong risk factor for pancreatic cancer due to longstanding inflammation.[75] *PRSS1*, *SPINK1,* and *CFTR*, which all cause pancreatic cell injury, are known to significantly increase cancer risks.[76,77] For example, a French study found a standardized incidence ratio (SIR) of 87 in HP with *PRSS1* mutations.[76] In a study of symptomatic and asymptomatic white *PRSS1* carriers in the US, the age- and sex-adjusted SIR was 59.[25] In a cohort of patients with *SPINK1* carriers, the cumulative risk of developing pancreatic cancer was significantly higher (HR: 12.0) than in controls. Notably, there is also higher tobacco consumption in the patients who developed pancreatic cancer (15 pack-years) than the entire study population (8 pack-years).[38] *CFTR*-related CP is also associated with increased risk of pancreatic cancer (SIR: 26.5). However, all of the patients with cancer had a smoking history and CP was not more prevalent in the *CFTR* variant carriers than noncarriers.[30,78] In addition, smoking independently doubled the risk of pancreatic cancer in patients with CP, with earlier development of cancer and accounted for 25% to 30% of all pancreatic tumors.[79] More recent data, however, suggest that there may be a lower cumulative risk of pancreatic cancer (7%) reported for patients with CP with *PRSS1* mutations at age 70.[25] It is possible that more stringent regulations leading to decreased tobacco exposure have resulted in a birth cohort effect, resulting in a lower risk of *PRSS1*-associated pancreatic cancer in more recent years.

EVALUATION

Diagnosis of HP requires a comprehensive review of personal and family history, blood tests, and imaging studies, as well as a detailed discussion on the role of genetic

testing. Patients with idiopathic pancreatitis, RAP, or CP in the absence of typical inciting factors should undergo evaluation for a hereditary etiology for their pancreatitis. The young age of onset may also prompt genetic risk assessment. For example, one study demonstrated that patients with unexplained first episode of acute pancreatitis less than 35 years are more likely to carry pathogenic mutations when undergoing a four-gene panel test for *PRSS1*, *SPINK1*, *CFTR, and CRTC* than patients with CP without RAP or having later disease onset.[80]

Current guidelines recommend genetic testing for pancreatitis susceptibility genes in patients with pancreatitis and one or more of the following characteristics: an unexplained pancreatitis episode as a child; idiopathic CP with onset before 25 years of age; family history of CP, RAP, or childhood pancreatitis with unknown cause in a first- or second-degree relative; and RAP without an identifiable cause.[81,82]

In children less than the age of 16, genetic testing is recommended for an episode of pancreatitis of unknown etiology and severe enough for hospitalization; 2 or more episodes of pancreatitis of unknown etiology; an episode of pancreatitis in a child with a relative carrying an HP mutation; high suspicion of HP in a child with recurrent abdominal pain; or high suspicion of HP in a child with CP of unknown etiology.[83] The INSPPIRE(International Study Group of Pediatric Pancreatitis: In search for a cuRE) Consortium strongly recommends testing for *PRSS1* mutations and for CF in pediatric patients with RAP and CP. If children with RAP and CP have a sweat chloride less than 60 mmol/L, expanded *CFTR* mutation testing should be performed. Testing for *SPINK1* and *CTRC* may also be considered.[84]

Given the complex, often non–Mendelian, inheritance patterns in patients with HP should undergo pre and posttest genetic counseling.[77,85] Current germline testing often includes *PRSS1*, *SPINK1*, *CFTR*, *CEL*, *CRTC*, and *CPA1*.[86] If a variant has been previously identified in the family, patients may consider testing only for the familial variant or they may choose to interrogate a broader panel of genes associated with HP.

MANAGEMENT

Once a diagnosis of HP has been confirmed, treatment should be initiated to slow disease progression and development of complications. Lifestyle modifications, particularly tobacco and alcohol cessation, are recommended for all patients with RAP, CP, and HP, as they increase risks of symptom progression and cancer. Other factors, such as stress and dehydration, may also exacerbate pancreatitis.[85] Practitioners should be aware of the importance of these and destigmatize patients as alcoholics or substance users.[25,85] Patients at various stages of HP often experience significant pain. A multidisciplinary team should be involved to provide pain management, which may include antioxidant treatment, celiac plexus neurolysis, pancreatic enzyme replacement, counseling on psychosocial well-being, and potential intervention for drug addiction.[87] Families should additionally receive comprehensive counseling and support.[85]

Patients who develop EPI should undergo malnutrition evaluation and evaluation for osteoporosis.[88] Appropriate pancreatic enzyme and fat-soluble vitamin supplementation should be initiated. For patients with endocrine disorder, insulin is the first-line therapy for advanced disease.[88]

Select germline carriers may ultimately consider a total pancreatectomy with islet autotransplantation (TP-IAT) in a high-volume center under multidisciplinary care. Although the primary objective of this procedure is pain relief, it may improve glycemic control and quality of life in selected patients. However, age and prolonged course of

pancreatitis adversely affected TP-IAT outcomes, so the patient population needs to be carefully selected.[88,89]

Currently, there have been few therapeutic options targeting specific genetic mutations. The mainstay of treatment focuses on lifestyle modifications based on known risks factors associated with certain mutations. For example, patients with high-risk variants in *PRSS1*, *CLDN2,* or *CTRC* should be counseled for alcohol and tobacco cessation.[11,56] Given several of the HP-causing genes are well characterized, it is to be hoped that new technologies such as preimplantation genetic testing for monogenic disorders (PGT-M) would provide new targeted treatment options in the future.[19,90,91]

SUMMARY

HP and FP highlight a complex multigene, non–Mendelian disorder with environmental interactions. Early identification through genetic evaluation and proper interdisciplinary management may give patients the opportunity to control symptoms and prevent complications.

CLINICS CARE POINTS

- Patients with unexplained RAP or CP should undergo detailed screening for the family history of pancreatic diseases and genetic testing.
- All patients with HP should be counseled on tobacco and alcohol cessation.
- Patients who develop EPI should undergo malnutrition evaluation and evaluation for osteoporosis.
- Total pancreatectomy with islet autotransplantation (TP-IAT) may be indicated to provide pain relief and may improve glycemic control in selected patients.

DISCLOSURES

The authors have nothing to disclose.

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