Pancreatitis associated with genetic risk factors

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INTRODUCTION

Risk factors that may contribute to acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) can be categorized with the mnemonic "TIGAR-O": **T**oxic-metabolic, **I**diopathic (when no risk factor is identified), **G**enetic, **A**utoimmune, **R**ecurrent/Severe pancreatitis, **O**bstructive [1]. In many cases, more than one factor is needed to result in pancreatitis.

Genetic risk factors were previously thought to be a minor factor in ARP and CP but are increasingly recognized as cofactors in the complex etiology of these conditions. Testing for genetic risk factors has become important both to understand the individual patient's risk for future disease and to establish a basis for future treatment.

Issues related to genetic risk factors for ARP and CP will be reviewed here. Identification and management of other risk factors for ARP and CP are discussed in other topic reviews:

- (See "Clinical manifestations and diagnosis of chronic and acute recurrent pancreatitis in children".)
- (See "Causes and contributing risk factors for chronic pancreatitis in children and adolescents".)
- (See "Chronic pancreatitis: Clinical manifestations and diagnosis in adults".)
- (See "Overview of the complications of chronic pancreatitis".)

- (See "Chronic pancreatitis: Management".)

TERMINOLOGY AND CATEGORIES OF PANCREATITIS

- **Acute pancreatitis (AP)** – AP is a syndrome of sudden pancreatic inflammation, regardless of etiology. While the majority of cases of AP heal completely, approximately one-third of patients with AP develop acute recurrent pancreatitis. Among those with acute recurrent pancreatitis, approximately one-third develop chronic pancreatitis [2,3].

- **Acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP)** – ARP refers to repeated episodes of pancreatitis with good health in between. CP is a fibrosing condition with almost constant symptoms and the increased risk of both endocrine and exocrine pancreatic insufficiency. (See "Causes and contributing risk factors for chronic pancreatitis in children and adolescents" and "Etiology and pathogenesis of chronic pancreatitis in adults".)

- **Hereditary pancreatitis** – The term "hereditary pancreatitis" was previously used to refer to an autosomal dominant form of CP caused by the *PRSS1* gene. "Familial pancreatitis" was used to refer to other forms of inherited pancreatitis. The reader may find these terms in older literature, but the complexity of the genetic risk factors for ARP and CP generally puts these terms out of use. Instead, the disorders should be described by the specific gene defect (eg, *PRSS1*-associated pancreatitis).

EPIDEMIOLOGY

The epidemiology of genetic risk factors for acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) varies greatly between different cities, regions, countries, and ancestral groups, likely because of founder effects and migration patterns. Furthermore, the true incidence of these risk factors, even among patients with acute pancreatitis (AP), ARP, and CP, is not known, because deep sequencing of all the important genes has not been done in most populations. For example, in 2011, it was estimated that strong genetic contributors were present in fewer than 10 percent of children with AP [4] but up to 30 to 80 percent of those with ARP or CP, depending on the genes tested and ethnicity of the population [5,6]. However, a subsequent single-center study found genetic etiology in 42 percent of children with the first attack of AP, and more than one genetic factor was identified in a substantial proportion of those with CP [7].

It is increasingly clear that genetic factors may interact with other risk factors for ARP and CP. As examples, genetic factors may influence the development of toxic-metabolic pancreatitis. A large

multicenter study demonstrated an association of known genetic risk factors for pancreatitis with some cases of asparaginase-associated pancreatitis [8]. A study from China suggests that major genetic variants for *SPINK1* or *PRSS1* are present in nearly 40 percent of individuals with pancreatitis that had been classified as "alcohol related" [9]. (See "Causes and contributing risk factors for chronic pancreatitis in children and adolescents", section on 'Genetic'.)

GENETICS

Inheritance patterns — There are at least three different inheritance patterns for acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) (see "Causes and contributing risk factors for chronic pancreatitis in children and adolescents", section on 'Genetic'). In addition, cases of pancreatitis without a family history may have a genetic basis (simplex case).

- **Autosomal dominant** – Autosomal dominant inheritance is most often associated with gain-of-function variants in the *PRSS1* gene on chromosome 7q35, which encodes trypsin-1 (cationic trypsinogen) [10-12]. Rarely, autosomal dominant-appearing pancreatitis is identified in a kindred that does not have an identifiable *PRSS1* mutation [13-15]. (See 'PRSS1 gene' below.)

- **Autosomal recessive** – Mutations in *SPINK1* may present in an autosomal recessive pattern. *CFTR*-associated disorders include CP with minimal lung disease, and this gene may present in multiple family members. (See 'CFTR gene' below.)

- **Complex mechanisms** – Multiple family members may have ARP or CP associated with a combination of genetic and environmental factors. This is the case for patients with heterozygous *SPINK1* mutations, in which the *SPINK1* mutation probably acts as a disease modifier, lowering the threshold for developing pancreatitis from other genetic (eg, *CFTR* mutations) [16,17] or environmental factors (see 'SPINK1 gene' below). Some apparently sporadic cases of pancreatitis have complex genetic risk.

***PRSS1* gene** — Gain-of-function variants in *PRSS1*, which encodes cationic trypsinogen, are present in up to 80 percent of patients with autosomal dominantly inherited pancreatitis [5,18-22]. *PRSS1* variants are also occasionally identified in cases of apparently idiopathic ARP or CP [23,24]. In two case series, approximately 10 percent of children with ARP had a pathogenic *PRSS1* variant [7,25]. (See "Pathogenesis of acute pancreatitis" and "Causes and contributing risk factors for chronic pancreatitis in children and adolescents", section on 'Idiopathic'.)

- **Molecular mechanisms** – Cationic trypsin is the most abundant form of trypsin produced by the pancreas and is the primary catalyst for the conversion of pancreatic zymogens into

pancreatic digestive enzymes after they are secreted into the duodenum. Premature activation of digestive enzymes in the pancreas is a major cause of pancreatic injury and immune system activation, leading to ARP and later CP. The primary defense against pancreatitis is to control trypsin activity, either through prevention of premature activation of trypsinogen to trypsin or by the destruction, inhibition, or elimination of trypsin from the pancreas. These defenses are weakened by pathogenic variants in *PRSS1* or in genes coding for molecules that protect the pancreas from active trypsin (eg, *SPINK1*, *CTRC*, *CFTR*) [26].

Trypsin has two regulatory regions that are controlled by corresponding calcium-binding pockets, one regulating the activation site (changing trypsinogen into trypsin with the release of trypsinogen activation peptide) and the other regulating the autolysis site (leading to trypsin destruction). Nearly all of the pathogenic genetic variants associated with pancreatitis are clustered in these two regions.

- **Pathogenic variants** – The most common pancreatitis-associated variants in *PRSS1* are p.R122H (at the autolysis site) and p.N29I [11,12,18,22]. As an example, in a national series of 200 patients from 78 families with suspected *PRSS1*-associated pancreatitis in France, pathogenic *PRSS1* variants were detected in 68 percent; among these patients, p.R122H and p.N291 were present in 78 and 12 percent, respectively [18]. The estimated population-prevalence of *PRSS1*-associated pancreatitis in this study was at least 0.3 per 100,000. A research website on CP genetics maintains and updates a list of *PRSS1*, *PRSS2*, and carboxypeptidase A1 (*CPA1*) variants including functional studies to help classify the mutations [27].

  The p.R122H and p.N291 variants have high penetrance (80 and 93 percent in two series) [18,28]. It remains unclear why some family members with these variants do not develop CP. A possible contributing factor for the occasionally decreased penetrance of pancreatitis is the presence of variants that protect against the development of CP. One such variant has been described in the *PRSS2* gene (anionic trypsinogen), resulting in the loss of trypsin activity [29]. (See 'Genetic variants conferring protection from pancreatitis' below.)

  Other kindreds carry pathogenic *PRSS1* variants, which modify cationic trypsinogen in different ways. New variants continue to be described [23,30-34]. These variants may not have the same high penetrance that has been seen with p.R122H and p.N291 variants.

  Risk of pancreatitis is also associated with copy number variants. Copy number variants are uncommon. Cases have been reported in both Europe [35] and the United States [15]. The risk appears to be a dose-effect since decreased *PRSS1* expression is associated with a reduced risk of pancreatitis [36].

Two synonymous variants in *PRSS1* (p.Asp162= [rs6666] and p.Asn246= [rs6667]) are important because they are linked with a risk haplotype associated with CP, especially in alcohol-drinking patients, known as the *PRSS1-PRSS2* risk haplotype [36]. This haplotype is characterized by a large insertion/deletion variant that contains additional trypsinogen pseudogenes, a *PRSS2* promoter and multiple T cell receptor beta gene transcripts that may increase susceptibility to pancreatitis and alter the immune response [37].

- **False-positive results** – *PRSS1* variants that were identified through exome or genome sequencing should be confirmed through another methodology. Exome and genome sequencing may result in a *PRSS1* false positive because of high homology between *PRSS1* and other trypsinogen genes and pseudogenes.

  In addition, there is a major technical problem in the diagnosis of *PRSS1* gene variants, and especially *PRSS1* p.N29I, when using next-generation "shot gun" sequencing due to an error in the human DNA reference sequence build 37 where *PRSS2* was not included. Thus, the normal *PRSS2* p.I29 cannot be mapped to the reference build 37 template. Because the sequenced fragments best fit the *PRSS1* sequence, the normal *PRSS2* p.I29 is misinterpreted as a *PRSS1* p.N29I variant, resulting in an erroneously high estimate for this rare variant. We are aware of a number of patients that were incorrectly diagnosed with hereditary pancreatitis based on this error. Furthermore, next-generation sequencing genotyping was also complicated by a large insertion/deletion that requires the use of the alternate contig-containing trypsinogen genes *PRSS1*, *PRSS3P1*, *PRSS3P2*, *TRY7*, and *PRSS2* rather than only *PRSS1*, *PRSS3P1*, and *PRSS2* for proper sequence fragment alignment and correct mutation calls [38,39]. If an apparent *PRSS1* p.N29I mutation is identified, the accuracy of the result should be verified with another testing method prior to any medical decision-making.

***SPINK1* gene** — *SPINK1* (**s**erine **p**rotease **in**hibitor **K**azal type **1**) encodes a pancreatic secretory trypsin inhibitor that is regulated as an acute phase reactant. It is expressed in pancreatic acinar cells during an inflammatory process where it normally serves as a critical suicide inhibitor of trypsin. Pathogenic variants in *SPINK1* interfere with this protective action and predispose to pancreatitis [19]. Thus, pathogenic variants in *SPINK1* are of minimal consequence, unless there is premature and excessive activation of trypsin and inflammation. *SPINK1* variants can cause pancreatitis with an autosomal recessive pattern in families in which both parents have a pathogenic variant. However, the majority of patients with *SPINK1* variants and CP are heterozygous, resulting in complex inheritance patterns.

Pathogenic *SPINK1* variants are fairly common in the general population (2 percent of healthy individuals carry a "high-risk" variant) [40], but less than 1 percent of carriers develop pancreatitis [41]. Nonetheless, variants in *SPINK1* increase the risk for CP approximately 12-fold over the

general population. In four series of patients with apparent idiopathic CP, pathogenic variants in *SPINK1* were detected in 15 to 23 percent [7,33,42,43]. In one of these reports, *SPINK1* variants were more common in patients with idiopathic ARP or CP than in controls (19.5 versus 2.6 percent) [43]. A *SPINK1* high-risk haplotype containing p.N34S is the most common variant in the United States and Europe, while a *SPINK1* IVS3 +2T>C variant is also common in Japan, China, and Korea [44]. *SPINK1* variants have been linked to idiopathic pancreatitis, alcohol-related pancreatitis, familial pancreatitis, and tropical pancreatitis [45].

Patients with heterozygous *SPINK1* variants and pancreatitis typically have complex genetics (eg, gene x gene, gene x environment) since *SPINK1*, as a specific trypsin inhibitor, is only required if there is an upstream problem causing recurrent trypsin activation [45]. Thus, the *SPINK1* variant probably acts as a disease modifier, lowering the threshold for developing pancreatitis from other genetic or environmental factors. The most common genetic variant seen with *SPINK1* is *CFTR*, which is described below [16,17].

***CFTR* gene** — Pathogenic variants in the *CFTR* gene can be associated with pancreatitis with or without associated pulmonary manifestations of cystic fibrosis (CF). Over 2000 different genetic variants in *CFTR* have been identified, and disease manifestations depend on the severity of the variant and zygosity [46]. *CFTR* gene variants and the conditions associated with them are catalogued in the CFTR 2 database maintained by the Cystic Fibrosis Foundation and Johns Hopkins [47]. (See "Cystic fibrosis: Clinical manifestations and diagnosis", section on 'Pancreatic disease'.)

- **Patients with CF** – CF is an autosomal recessive genetic disorder caused by severe variants in the *CFTR* gene. Approximately 85 percent of people with CF have two severe *CFTR* variants [48], such as F508del/F508del (the most common allele causing disease), resulting in minimal or absent functional CFTR protein on epithelial cells of the respiratory system, digestive system, reproductive organs, and skin. Patients with these genotypes have abnormal sweat chloride measures (≥60 mmol/L) and typically develop pancreatic insufficiency early in life [49]. They rarely develop pancreatitis.

  In patients with CF, the risk of acute pancreatitis (AP) is linked with less severe *CFTR* variants, milder phenotype, and pancreatic sufficiency [50]. Homozygous or compound heterozygous genotypes in which at least one of the *CFTR* gene copies is a functionally "mild" variant (or variants of variable clinical significance) result in some retained CFTR function and milder or limited pulmonary features of CF. (See "Cystic fibrosis: Clinical manifestations and diagnosis".)

- **Patients without CF** – In addition, there is an increased risk of ARP and CP among patients with one or two CFTR variants but who do not meet clinical criteria for a diagnosis of CF.

CFTR-related disorder is a monosymptomatic clinical entity (eg, congenital bilateral absence of the vas deferens, pancreatitis, or bronchiectasis) associated with CFTR dysfunction [51]. Patients have less than two severe *CFTR* variants, and the clinical and functional evidence (ie, sweat chloride values are between 30 and 59 mmol/L) does not meet diagnostic criteria for CF. A study of a commercial claims database evaluated the prevalence of a variety of conditions that were associated with 19,800 CFTR carriers, each of which were matched with five controls [52]. Fifty-seven conditions were associated with *CFTR* variants including pancreatitis, male infertility, bronchiectasis, diabetes, constipation, cholelithiasis, short stature, and growth faltering. Thus, identification of CFTR-associated pancreatitis should alert the clinician of the risk for other CFTR-related disorders. (See "Cystic fibrosis: Clinical manifestations and diagnosis", section on 'CFTR-related disorder'.)

Individuals who carry a single pathogenic *CFTR* variant have a risk for CP that is increased three- to fourfold over the general population, although 99 percent of the carriers are healthy [53-55]. Those who do develop CP have a very high rate of coexisting *SPINK1*, *CTRC*, or more complex genotypes [16,17]. Heterozygous *CFTR* variants may also contribute to pancreatitis in the presence of pancreatic divisum [56,57].

Several studies have shown that carriage of one pathogenic *CFTR* variant, including uncommon and mild variants, is more common among patients with idiopathic CP than among controls [49,53,58]. However, in studies of populations known to be CF carriers (eg, parents of patients with CF), the prevalence of CP is only slightly increased [53,54,59]. In a longitudinal case series of children with AP, carriage of one pathogenic *CFTR* variant was associated with a greater risk for progression from AP to CP [7]. Together, these observations suggest that pancreatitis develops among carriers of a pathogenic *CFTR* variant primarily in the presence of additional genetic or environmental disease modifiers. Thus, testing is more useful in determining the etiology of early pancreatitis than for predicting pancreatitis in an asymptomatic person.

***CTRC* gene** — Pathogenic variants in the *CTRC* gene confer a moderate risk for CP, usually in conjunction with other heterogeneous pancreatitis susceptibility variants, such as *CFTR* or *SPINK1* [17,60-63]. Chymotrypsin C is a digestive enzyme that cooperates with active trypsin in solutions with lower calcium concentrations to degrade trypsin [64]. Thus, it is an intrapancreatic antitrypsin protective mechanism that complements *SPINK1*. Several rare variants in *CTRC* have been linked with CP in children [61-63], while the common p.G60G risk haplotype (where the synonymous amino acid code change is on the same chromosome as one or more variants that diminish gene expression) is associated with CP in adults, especially smokers [62].

Additional genes associated with acute recurrent and chronic pancreatitis — Two genes have been reported that are associated with chronic alcohol-related pancreatitis and pediatric idiopathic CP, respectively. These are important because the mechanism is not dependent on trypsin activation and because they are either common modifier genes or confer very high risk.

- ***CLDN2* gene** – The most important are the high-risk haplotype at the *CLDN2* locus associated with CP, especially in patients with alcohol-related CP [65-67]. It confers no or small risk of AP. Instead, these variants appear to accelerate progression from AP to CP. The high-risk locus is on the X chromosome, with the haplotype-defining variant rs12688220 C in 26 percent of control alleles. Since males are hemizygous for the X chromosome, the risk appears dominant, whereas it is inherited as a recessive trait in females. If 16 percent of males and 10 percent of females are at-risk alcohol drinkers, it suggests that 4 percent of males (0.16 × 0.26) are at high risk of alcohol-related CP, compared with 0.7 percent of females (0.10 × 0.26 × 0.26).

- ***CPA1* gene** – Carboxypeptidase A1, encoded by the *CPA1* gene, is a pancreatic digestive enzyme that is second in abundance in pancreatic secretions after trypsinogen. Variants in *CPA1* are linked to nonalcoholic CP, especially with early age of onset [68]. Risk of CP is unrelated to trypsin activation or failed inhibition. In a study involving 944 cases and 3938 controls in Germany, investigators performed standard DNA sequencing of all ten *CPA1* exons and identified 35 novel or rare variants [68]. Functional studies showed that many of the variants had less than 20 percent of expected activity and were not secreted from experimental cells. This suggests that the mutated peptides were misfolding, causing stress inside of the endoplasmic reticulum. The low-activity variants were found in 3.1 percent of cases compared with 0.1 percent of controls (odds ratio = 25). The finding was replicated in three other groups and found to be especially prevalent in children with idiopathic CP. Newer studies of families with an autosomal dominant pancreatitis inheritance pattern in Poland and in the United States found that they had novel *CPA1* p.Ser282Pro [69] or *CPA1* p.K374E variants [70], further extending this association of genetics and pancreatitis.

- **Other genes** – Ongoing candidate gene and association studies with larger national and international cohorts continue to identify genetic variants associated with pancreatitis.

  - One important gene is *CEL* (carboxyl-ester lipase), in which an important hybrid splice variant between *CEL* and the pseudogene *CELP* is associated with autosomal dominant pancreatitis and diabetes mellitus (MODY type 8), caused by an endoplasmic reticulum stress mechanism [71,72]. *CEL* has complex genetics in a region of DNA that is challenging to sequence, thereby limiting replication studies and genetic testing [71-74].

- Variants in the *CASR* gene (calcium-sensing receptor) are also associated with pancreatitis as a cofactor of a more complex genotype, likely associated as an activator of CFTR when duct calcium levels are too high [75,76]. The *PNLIP* gene (pancreatic lipase) has several variants associated with CP, especially p.F300L that is associated with pancreatitis risk in Germany and France, but it has not yet been seen in India, Japan, or the United States [77].

- Variants in the *GGT1* gene (gamma-glutamyltransferase 1) are associated with CP [78] and pancreatic cancer [79]. This gene protects duct cells against oxidative stress. Variants in the *UBR1* gene are associated with pancreatitis in Germany [80], although these appear to be cofactors since they are not pancreas-specific genes. *UBR1* is part of the protein quality control mechanism to identify and eliminate secreted proteins that are misfolded or in the wrong cellular compartment, including zymogens in the acinar cell.

- Variants in the *TRPV6* gene, which encodes a Ca(2+)-selective ion channel, were associated with early-onset idiopathic pancreatitis (before 20 years of age) in Japanese and European subjects [81].

Other genetic variants continue to be described.

Genetic variants conferring protection from pancreatitis — There are at least two genetic variants that protect people from pancreatitis. The first is the *PRSS2* p.G191R variant. This introduces a trypsin cut site into anionic trypsin so that overall activity is reduced. This may be present in up to 3 percent of some populations [29,82]. Second, a protective haplotype at the *PRSS1-PRSS2* locus was found that is present in approximately 42 percent of controls but only 38 percent of cases with pancreatitis, suggesting that risk was reduced by up to 40 percent [36,65]. The difference between that risk and protective haplotype in *PRSS1-PRSS2* depends on which variant/haplotype is designated as the reference, with the alternative being either protective or risk.

CLINICAL PRESENTATION

Patients with genetic risk factors present similarly to other forms of pancreatitis, but some genetic risk factors may increase the chances of early-age presentation. Early-onset idiopathic chronic pancreatitis (CP) in adults is associated with the presence of genetic risk factors for pancreatitis more commonly than late-onset presentations [83]. Children presenting with acute recurrent pancreatitis (ARP) or CP before age six years more commonly had a *PRSS1* or *CRTC* mutation [84].

The clinical presentation of patients with genetic risk factors for pancreatitis can begin with episodes of acute pancreatitis (AP) or with CP. The clinical features are similar to those seen in other causes of CP and are discussed in detail elsewhere. The primary manifestations are abdominal pain, maldigestion due to pancreatic exocrine dysfunction, and diabetes mellitus due to islet cell damage. (See "Clinical manifestations and diagnosis of chronic and acute recurrent pancreatitis in children" and "Chronic pancreatitis: Clinical manifestations and diagnosis in adults".)

The following findings were noted in the national series of 418 patients with suspected *PRSS1*-associated pancreatitis from 112 families in 14 European countries [13] and 200 patients from 78 families in France [18]:

- The median ages at first symptom and diagnosis were 10 and 19 years, respectively [13,18]. Similar findings have been noted in other studies in which disease onset may be before age five [28,85]. The first symptoms occurred at a slightly older age in patients with N29I or without identified *PRSS1* variants [13].
- In the French series, pancreatic pain, AP, and pseudocysts were present in 83, 69, and 23 percent, respectively, with pancreatic calcifications noted on radiologic examination in 61 percent [18].
- Exocrine pancreatic insufficiency eventually developed in 37 and 34 percent, respectively [13,18], and presented at a mean age of 29 years [18].
- Diabetes mellitus eventually developed in 48 and 26 percent, respectively [13,18], and presented at a mean age of 38 years [18]. Patients who develop diabetes typically require insulin therapy. However, the diabetes is different from typical type 1 diabetes in that the pancreatic alpha cells, which produce glucagon, are also affected (type 3c diabetes mellitus) [86]. As a result, there is an increased risk of hypoglycemia, both treatment-related and spontaneous.
- There were no differences in clinical and morphologic data according to genetic status.

The most common presentation of *PRSS1*-associated pancreatitis is ARP [13,18,28,87,88]. After recovery from the acute episode, affected patients may remain well for a significant duration. Some patients may present with CP without episodes of AP.

PANCREATIC CANCER

Cancer risk — *PRSS1*-associated pancreatitis is associated with a significantly increased risk of pancreatic cancer, although *PRSS1*-associated pancreatitis patients account for a very small fraction of all cases of pancreatic cancer [13,18,89,90]. Although the risk of pancreatic cancer is high compared with that of the general population, the true risk is not known, because studies are limited by referral bias and estimates have wide confidence intervals. (See "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer".)

The best available evidence suggests a cancer risk between 7 and 20 percent [13,91]. A study from the United States, representing up to 20 years for prospective follow-up of the originally identified families with *PRSS1*-associated pancreatitis, suggested that the risk of pancreatic cancer was indeed significantly greater than age- and sex-matched data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry (standardized incidence ratio [SIR] 59, 95% CI 19-138) but that the cumulative risk was only 7.2 percent (95% CI 0.0-15.4) at 70 years [91]. In a study of 112 families in Europe, the cumulative risk of developing pancreatic cancer was 18.8 percent (95% CI 8.6-29.0) at 70 years (SIR 67, 95% CI 50-82). In both studies, the risk increased markedly after age 50 [13]. Of note, pancreatic cancer is also a disease seen in older patients, and the incidence of pancreatic cancer continues to increase beyond 70 years of age.

Earlier studies suggested a much higher incidence of pancreatic cancer among patients with *PRSS1*-associated pancreatitis. In 1997, an international study of 246 patients (175 from the United States, 60 from Europe, and 11 from Japan) reported a cumulative risk of pancreatic cancer to age 70 years of 40 percent (SIR 53, 95% CI 9-71) [89]. These conclusions are limited because (1) the patients were seen at referral centers, (2) only five patients reached age 70 years, and (3) only two of five developed pancreatic cancer. In a separate series from France that included 200 patients from 78 families with *PRSS1*-associated pancreatitis, the cumulative risk of pancreatic cancer in affected family members was 10, 19, and 54 percent at ages 50, 60, and 75 years, respectively [18]. The SIR for pancreatic cancer compared with the general population was 87 (95% CI 42-113). The risk was highest in smokers and in individuals with diabetes mellitus and was much lower in nonsmokers and patients without diabetes.

The higher risk of pancreatic cancer in the older studies may be associated with a high prevalence of smoking in earlier generations, with a marked change in prevalence of smoking after the associated risks were discovered in the late 1990s. Smoking increases the risk of pancreatic cancer approximately twofold in patients with *PRSS1*-associated pancreatitis, which is similar to the increase in risk in the general population [92]. However, among patients with *PRSS1*-associated pancreatitis, smokers developed pancreatic cancer 20 years earlier than nonsmokers. (See "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer", section on 'Cigarette smoking'.)

To minimize their cancer risk, patients with all forms of chronic pancreatitis (CP) should be urged not to smoke and follow healthy lifestyles (see 'Avoidance of alcohol and tobacco' below). When pancreatic cancer does occur, it is typically in late adulthood. There is no evidence to support prophylactic procedures such as total pancreatectomy for cancer prevention.

Cancer screening — Several consensus panels have recommended screening for pancreatic cancer in individuals with *PRSS1*-associated pancreatitis [93-96]. These recommendations are guided largely by expert opinion since no well-powered studies have been performed to determine if screening in these patients is effective. Guidelines on screening for the familial pancreatic cancer syndrome patient that rely on imaging studies, such as magnetic resonance imaging (MRI) and/or endoscopic ultrasound, are not easily applied to *PRSS1*-associated pancreatitis, since the morphology of the pancreatic gland is markedly altered by CP. Nonetheless, these guidelines typically suggest initiating imaging surveillance starting at age 40 [96] or 50 [95].

Issues related to screening for pancreatic cancer in high-risk individuals with genetic risk factors for CP, including those with *PRSS1*-associated pancreatitis, are discussed in detail elsewhere. (See "Familial risk factors for pancreatic cancer and screening of high-risk patients", section on 'Pancreatic cancer screening'.)

GENETIC TESTING

Genetic testing is an important component of the evaluation for many patients with acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP). Testing for genetic risk factors be overseen by a qualified genetic counselor with expertise in this area [40,97,98]. (See "Etiology and pathogenesis of chronic pancreatitis in adults", section on 'Idiopathic' and "Causes and contributing risk factors for chronic pancreatitis in children and adolescents", section on 'Idiopathic'.)

Indications for genetic testing

- **Symptomatic patients** – Genetic testing for pancreatitis susceptibility genes is medically necessary and should be performed in patients with pancreatitis **and** one or more of the following [40,99,100]:
  - A second episode of pancreatitis in a person under age 35 years old (including children) despite appropriate therapeutic interventions (eg, clearing the biliary tree in gallstone-associated pancreatitis)
  - A family history of ARP, idiopathic CP, or childhood pancreatitis without a known cause

- Relatives known to carry gene variants associated with pancreatitis (eg, *PRSS1* variants)
- ARP and CP
- Evidence of a CFTR-associated disorder (eg, male infertility or bronchiectasis)
- Unexplained exocrine or endocrine pancreatic insufficiency
- Patients eligible for approved research protocols

Practice varies regarding genetic testing for patients with ARP or CP and other risk factors (eg, heavy alcohol use, duct obstruction, or medications). Some clinicians defer genetic testing for this group. However, genetic testing is increasingly included in the evaluation, recognizing that multiple risk factors can contribute to disease expression. Most clinicians do not test for genetic factors in individuals with a single episode of acute pancreatitis (AP), although some may do so if there is a family history of pancreatitis, pancreatic cancer, or previous episodes of undiagnosed severe abdominal pain.

- **Asymptomatic patients** – Testing of asymptomatic individuals (predictive testing) can be considered for individuals who have a first-degree relative with a known pathologic *PRSS1* variant but should only be undertaken after expert genetic counseling. Predictive testing is generally not recommended for asymptomatic individuals under 16 years of age [100]. If a family carries a known pathogenic variant, negative test results in a family member essentially eliminate the risk of *PRSS1*-associated pancreatitis in that individual [101]. A positive test result confers approximately 80 percent risk of developing pancreatitis. If an individual remains free of symptoms, the residual risk of developing pancreatitis is 25 percent at age 20 and 10 percent at age 30 [102].

  By contrast, predictive testing of *SPINK1* or *CFTR* variants in asymptomatic individuals is of minimal value because pathogenic variants are common and most patients with these variants do not develop disease [40].

Testing strategy and interpretation — Most laboratories that offer genetic testing for pancreatic diseases include the major variants for Mendelian disorders linked to *PRSS1*, *SPINK1*, *CFTR*, and *CTRC*. More comprehensive tests that include over a dozen genes are also available to detect additional risk genes and variants in gene regulatory elements. An updated list of laboratories that perform this testing is available at the Genetic Testing Registry website.

All patients in whom genetic testing is performed should be offered genetic counseling prior to and after testing. An overview of the issues to be addressed by genetic counselors has been

published [100,103].

Interpretation is as follows:

- ***PRSS1*** – The most common autosomal dominant, gain-of-function variants in *PRSS1* include p.A16V, p.N29I, p.R122H, and p.R122C, with p.A16V having a low penetrance. In addition, *PRSS1* copy number variants are associated with autosomal dominant pancreatitis. Other *PRSS1* gene variants may also be associated with pancreatitis because of protein misfolding in the endoplasmic reticulum of Golgi including p.D19A, p.D22G, p.K23R, p.K23I, p.K23I_I24insIDK, p.N29I, p.N29T, p.V39A, p.D100H, p.L104V or P, p.R116C, p.R122H, p.R122C, p.S124F, p.C139F, and p.G208A [104]. Co-inheritance of other risk alleles appears to increase risk and worsen severity. Knowledge of the type of *PRSS1* variant may affect choice of treatment, either focused on limiting trypsin activity or on managing the unfolded protein response.

- ***CFTR*** – Genetic testing for *CFTR* variants is also indicated in patients with unexplained ARP and CP or those with signs/symptoms of a CFTR-related disorder. Many clinicians would start with sweat chloride testing, if not already done. CFTR-associated pancreatitis includes the variants that cause cystic fibrosis (CF) but also gene variants previously thought to be benign (eg, R75Q). Therefore, complete gene sequencing should be considered, especially if the patient has recurrent sinusitis or male infertility. Interpretation of results must be done in the context of clinical setting. Patients with two severe *CFTR* variants, or a severe and mild-variable *CFTR* variant, should be referred to a CF center for formal testing because management requires a structured, multidisciplinary approach. Of note, patients with types IV and V and some other variants appear to be responsive to CFTR potentiators [105-107].

- ***SPINK1*** – Pathogenic *SPINK1* variants are believed to limit the inflammation-associated feedback inhibition of intrapancreatic trypsin activity. Heterozygous *SPINK1* variants are benign, unless there is a problem causing recurrent intrapancreatic trypsin activation. Homozygote or compound heterozygote *SPINK1* variants cause sufficient loss of trypsin inhibiting function to explain the etiology of recurrent pancreatitis. Heterozygous *SPINK1* variants typically cause pancreatitis only if they are associated with another predisposing factor, such as pathogenic variants in *CFTR*, *CaSR*, or *CTRC* [75], or biliary obstruction. Patients with pathogenic *SPINK1* variants typically have a more severe clinical course compared with those with other causes of ARP and a more rapid progression from ARP to CP [7,108]. Inactivating variants in *CaSR* also cause familial hypocalciuric hypercalcemia, which is also associated with pancreatitis when present with pathogenic *CFTR* variants, heavy alcohol use, or other risks. (See "Disorders of the calcium-sensing receptor: Familial

hypocalciuric hypercalcemia and autosomal dominant hypocalcemia", section on 'Familial hypocalciuric hypercalcemia'.)

Only a minority of patients with unexplained pancreatitis have a genotype that is a sufficiently strong risk factor to explain their condition. These may include *PRSS1* p.R122*H*, *CFTR* p.F508del with a class IV or V variant, or homozygo*us SPINK1* pN34S haplotypes.

The majority of patients with unexplained pancreatitis will have complex genotypes in which none of the factors alone are necessary or sufficient to cause pancreatitis by themselves but in combination are pathogenic. These patients may have a genetic risk factor as well as an obstructive or toxic metabolic risk factor. In this case, the data are best interpreted with a precision medicine paradigm, where the focus is on the underlying mechanistic disorders in specific cells or systems where symptoms of a disorder arise from a combination of genetic variant-associated alterations in normal function and environmental, metabolic, or lifestyle stressors [109]. The goal is to diagnose the underlying disorder (e*g, CFTR* dysfunction) and provide targeted holistic treatment before the disorder causes sufficient pathology to meet consensus criteria for irreversible CP [110]. Thus, clinical context, biomarkers, and information from an adequate gene-sequencing panel are needed for interpretation of complex disorders from a precision medicine perspective and to provide guidance beyond a typical "genetic report" of classic Mendelian diseases.

MANAGEMENT

Management of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) follows many of the principles for CP of other causes. However, some therapies may be contraindicated in individuals with genetic risk factors. (See "Chronic pancreatitis: Management".)

Avoidance of alcohol and tobacco — We suggest that any patient with a genetic risk factor for ARP and CP abstain from alcohol and tobacco for life, although data are limited.

The best data for these risk factors are for individuals with *PRSS1*-associated pancreatitis (eg, the *PRSS1* variants p.R122H, p.N29I), members of affected families, and individuals in whom a specific pathogenic *PRSS1* variant has been identified. Alcohol intake has been associated with exacerbations, and there is no known quantity of alcohol that is safe for this group of patients [18,88]. Other possible triggers for exacerbations include emotional stress and dietary fat. In addition, smoking is a strong independent risk factor for CP [111,112] and increases the risk of pancreatic cancer [92].

Alcohol and tobacco use also increase the risk of progressing to end-stage CP for patients with risk variants in the *CLDN2* gene locus, the high-risk *PRSS1-PRSS2* haplotype, or *CTRC* p.G60G risk haplotypes [36,62]. (See 'Genetics' above.)

CFTR modulator therapy — Several small molecules are now available that modulate the CFTR protein to make it a more effective transmembrane conduction regulator. These molecules may hold promise for individuals with CFTR-associated pancreatitis. Case series have demonstrated that some people with CF and recurrent episodes of pancreatitis have experienced relief of pancreatitis episodes while on modulators [105,113]. These patients probably had moderately impaired pancreatic function at baseline and modulator therapy improved CFTR function sufficiently to put the patient out of the risk range for pancreatitis [50]. Conversely, a few people with CF have developed pancreatitis on modulators [114,115]. These patients had more severe pancreatic insufficiency at baseline and modulator therapy improved CFTR function, moving them into the risk range for pancreatitis. Both effects are likely the result of increased CFTR function in the pancreatic acinus. Clinicians managing people with CF should be aware of these possibilities. Clinical trials are necessary to determine whether CFTR modulators have a role in therapy of patients with ARP or CP. (See "Cystic fibrosis: Treatment with CFTR modulators" and "Cystic fibrosis: Hepatobiliary disease", section on 'Considerations related to CFTR modulator therapy'.)

Endoscopic retrograde cholangiopancreatogram and pancreatic surgery — Endoscopic retrograde cholangiopancreatogram (ERCP) procedures may relieve pain in individuals with pancreatitis associated with genetic risk factors, although the effect may not be permanent [116]. If repeated ERCP procedures are needed for pain relief, an alternative strategy is pancreatectomy with islet autotransplantation. Surgical draining procedures or other surgical interventions should be used judiciously in people with genetic risk factors for pancreatitis. There is a high risk of pancreatitis recurrence in the remaining pancreatic tissue.

Pancreatectomy

- **Pancreatectomy with islet autotransplantation** – We generally offer pancreatectomy with islet autotransplantation for younger patients with severe features of ARP or CP.

  This procedure is most likely to be beneficial for younger patients who have functional islet cells, for whom it may preserve islet function and relieve intractable, narcotic-dependent pancreatic pain [117,118]. Outcomes based on case series show moderate levels of success. As an example, in a series of 75 children undergoing this procedure, 90 percent experienced sustained improvement in pancreatic pain and almost all of these patients were successfully weaned from narcotics [119]. Insulin independence was achieved in 41 percent of patients (31 of 75 subjects). Insulin independence was typically achieved during the first 12 months

after the transplant procedure and was sustained for at least three years in most (28 of 31 subjects). Factors predicting insulin independence included younger age (<12 years), male sex, and the number of islets transplanted. In a small series of younger children (ages three to eight years), outcomes were somewhat better, with 82 percent achieving insulin independence with median follow-up 2.2 years and all patients experiencing pain relief [120]. These outcomes are generally better than in series of adults undergoing the same procedure [117,118].

Arguments against this procedure are that it is irreversible, is associated with multiple risks, and has not been proven to protect islet cells and delay development of diabetes. Furthermore, the risk of cancer occurs late in life; the published risk may be higher than real risk because of selection bias. Finally, new treatments are being evaluated that may further reduce risk of pancreatitis and pancreatic cancer. Enthusiasm for doing this procedure should therefore be tempered with caution.

Two conferences were held to debate the role of total pancreatectomy with islet autotransplantation in management of disabling ARP or painful CP, and these produced recommendations for follow-up of these patients [121,122].

- **Pancreatectomy without islet transplantation** – Pancreatectomy without islet autotransplantation is occasionally performed if there is a risk of malignant cells being infused with islets. This may be the case in older patients with long-standing CP (eg, those who have had CP for 20 years or more) to treat pain or reduce the risk of developing pancreatic cancer. Screening for pancreatic cancer in these high-risk patients can be particularly difficult because the pancreas is scarred and disfigured [93]. However, most such patients can be managed with islet autotransplantation if there are functioning islet cells and there is judged to be little or no cancer risk; if successful, the islet infusion will reduce the severity of postoperative diabetes. No cases of pancreatic cancer have yet been reported after islet autotransplantation [123].

PROGNOSIS

The mortality rate compared with the general population is significantly increased in patients with genetic risk factor-associated pancreatitis who develop pancreatic cancer [124]. In contrast, mortality does not appear to be increased in patients without pancreatic cancer.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Chronic pancreatitis and pancreatic exocrine insufficiency".)

SUMMARY AND RECOMMENDATIONS

- **Genes involved in pancreatitis**
  - Autosomal dominant hereditary pancreatitis is usually caused by pathogenic variants in *PRSS1*. In some cases, the *PRSS1* variant may promote premature activation of trypsinogen or interfere with the inactivation of trypsin. (See 'PRSS1 gene' above.)
  - Other forms of pancreatitis with a genetic basis are associated with homozygous or compound heterozygous variants in *SPINK1*, *CFTR*, *CTRC*, or other genes such as *CPA1* in children and *CLDN2* in adults, especially in men with alcohol-related pancreatitis. (See 'Genetics' above.)
- **Clinical presentation** – Most patients with pancreatitis associated with genetic risk factors present before 20 years of age with acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP). As many as one-third of patients progress to develop pancreatic insufficiency and/or diabetes mellitus. Affected individuals have increased risk of developing pancreatic cancer, especially if they smoke or have diabetes mellitus. (See 'Clinical presentation' above and 'Pancreatic cancer' above.)
- **Symptomatic patients** – Clinical indications for genetic testing in patients with pancreatitis include:
  - ARP or CP, particularly if beginning <35 years of age
  - Pancreatitis in a patient with a family history of pancreatitis or pancreatic cancer
  - Pancreatitis and clinical evidence of a CFTR-associated disorder (eg, male infertility or bronchiectasis)

  Such patients should be tested for variants in *PRSS1*, *SPINK1*, *CFTR*, and *CTRC* as a minimum, plus additional risk genes if the inheritance pattern is less clear and if no other etiology can be identified. (See 'Indications for genetic testing' above.)
- **Asymptomatic patients** – For children under age 16 with a family history of CP but no clinical symptoms, we suggest **not** performing genetic testing (**Grade 2C**). For patients older than age 16, genetic testing for *PRSS1* can be considered if there is a family history of a

known pathogenic *PRSS1* variant and if testing is desired by the patient after expert genetic counseling. For patients without clinical symptoms suggestive of pancreatic disease, testing for *SPINK1* or *CFTR* is not clinically useful, because a heterozygous variant for one of these genes only slightly increases the risk for CP. However, *CFTR* variant carriers may also be at increased risk for a variety of other disorders as well. (See 'Indications for genetic testing' above and 'CFTR gene' above.)

- **Management of CP**

  - **Supportive care** – Management of genetic risk factor-associated pancreatitis is similar to that for other causes of ARP and CP. Affected individuals should exercise, focus on a healthy lifestyle, and avoid consuming alcohol and smoking cigarettes. (See 'Management' above and "Chronic pancreatitis: Management".)

  - **Pancreatectomy** – In children or adults with severe pain and high opioid use associated with ARP or CP, but with residual islet function, we suggest pancreatectomy with islet autotransplantation (**Grade 2C**). Pancreatectomy can markedly improve the quality of life in selected patients, but the procedure is irreversible, is associated with significant perioperative risk, has uncertain long-term consequences related to islet cell function in the liver, and results in complete pancreatic exocrine insufficiency that requires lifelong, full-dose pancreatic enzyme replacement therapy. (See 'Pancreatectomy' above.)

  - **Cancer risk and surveillance** – CP associated with genetic risk factors is associated with a significantly increased risk of pancreatic cancer. The cumulative risk of developing pancreatic cancer within 70 years appears to be between 7 and 20 percent (with wide confidence intervals), but this statistic includes patients with other risk factors for pancreatic cancer, including smoking, diabetes, and a family history of cancer. Smokers from pancreatic cancer-prone families develop cancer on average a decade earlier than nonsmokers. Patients who do not smoke and have not developed diabetes likely have less than a 20 percent chance of developing pancreatic cancer. Consensus panels have recommended screening for pancreatic cancer in individuals with CP, but there is no consensus as to the optimal age to start screening. (See 'Pancreatic cancer' above.)

    In older patients with long-standing inflammation and diabetes mellitus, pancreatectomy with or without islet autotransplantation should be considered if the patient has a high level of concern about pancreatic cancer. (See 'Pancreatectomy' above.)

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REFERENCES

1. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001; 120:682.
2. Sankaran SJ, Xiao AY, Wu LM, et al. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015; 149:1490.
3. Fonseca Sepúlveda EV, Guerrero-Lozano R. Acute pancreatitis and recurrent acute pancreatitis: an exploration of clinical and etiologic factors and outcomes. J Pediatr (Rio J) 2019; 95:713.
4. Bai HX, Lowe ME, Husain SZ. What have we learned about acute pancreatitis in children? J Pediatr Gastroenterol Nutr 2011; 52:262.
5. Schwarzenberg SJ, Bellin M, Husain SZ, et al. Pediatric chronic pancreatitis is associated with genetic risk factors and substantial disease burden. J Pediatr 2015; 166:890.
6. Poddar U, Yachha SK, Mathias A, Choudhuri G. Genetic predisposition and its impact on natural history of idiopathic acute and acute recurrent pancreatitis in children. Dig Liver Dis 2015; 47:709.
7. Abu-El-Haija M, Valencia CA, Hornung L, et al. Genetic variants in acute, acute recurrent and chronic pancreatitis affect the progression of disease in children. Pancreatology 2019; 19:535.
8. Wolthers BO, Frandsen TL, Patel CJ, et al. Trypsin-encoding PRSS1-PRSS2 variations influence the risk of asparaginase-associated pancreatitis in children with acute lymphoblastic leukemia: a Ponte di Legno toxicity working group report. Haematologica 2019; 104:556.
9. Wang Y-C, Zou W-B, Tang D-H, et al. High Clinical and Genetic Similarity Between Chronic Pancreatitis Associated With Light-to-Moderate Alcohol Consumption and Classical Alcoholic Chronic Pancreatitis. Gastro Hep Adv 2023; 2:186.
10. Whitcomb DC, Preston RA, Aston CE, et al. A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996; 110:1975.
11. Whitcomb DC, Gorry MC, Preston RA, et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996; 14:141.

12. Gorry MC, Gabbaizedeh D, Furey W, et al. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology 1997; 113:1063.
13. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2004; 2:252.
14. LaFemina J, Roberts PA, Hung YP, et al. Identification of a novel kindred with familial pancreatitis and pancreatic cancer. Pancreatology 2009; 9:273.
15. LaRusch J, Barmada MM, Solomon S, Whitcomb DC. Whole exome sequencing identifies multiple, complex etiologies in an idiopathic hereditary pancreatitis kindred. JOP 2012; 13:258.
16. Schneider A, Larusch J, Sun X, et al. Combined bicarbonate conductance-impairing variants in CFTR and SPINK1 variants are associated with chronic pancreatitis in patients without cystic fibrosis. Gastroenterology 2011; 140:162.
17. Rosendahl J, Landt O, Bernadova J, et al. CFTR, SPINK1, CTRC and PRSS1 variants in chronic pancreatitis: is the role of mutated CFTR overestimated? Gut 2013; 62:582.
18. Rebours V, Boutron-Ruault MC, Schnee M, et al. The natural history of hereditary pancreatitis: a national series. Gut 2009; 58:97.
19. DiMagno MJ, DiMagno EP. Chronic pancreatitis. Curr Opin Gastroenterol 2005; 21:544.
20. Applebaum-Shapiro SE, Finch R, Pfützer RH, et al. Hereditary pancreatitis in North America: the Pittsburgh-Midwest Multi-Center Pancreatic Study Group Study. Pancreatology 2001; 1:439.
21. Howes N, Greenhalf W, Stocken DD, Neoptolemos JP. Cationic trypsinogen mutations and pancreatitis. Gastroenterol Clin North Am 2004; 33:767.
22. Whitcomb DC. Value of genetic testing in the management of pancreatitis. Gut 2004; 53:1710.
23. Witt H, Luck W, Becker M. A signal peptide cleavage site mutation in the cationic trypsinogen gene is strongly associated with chronic pancreatitis. Gastroenterology 1999; 117:7.
24. Creighton J, Lyall R, Wilson DI, et al. Mutations of the cationic trypsinogen gene in patients with chronic pancreatitis. Lancet 1999; 354:42.
25. Vue PM, McFann K, Narkewicz MR. Genetic Mutations in Pediatric Pancreatitis. Pancreas 2016; 45:992.
26. Whitcomb DC. Genetic aspects of pancreatitis. Annu Rev Med 2010; 61:413.
27. Pancreas genetics website: Genetic risk factors in chronic pancreatitis. Available at: https://pancreasgenetics.org/ (Accessed on May 05, 2023).

28. Sossenheimer MJ, Aston CE, Preston RA, et al. Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype. The Midwest Multicenter Pancreatic Study Group (MMPSG). Am J Gastroenterol 1997; 92:1113.
29. Witt H, Sahin-Tóth M, Landt O, et al. A degradation-sensitive anionic trypsinogen (PRSS2) variant protects against chronic pancreatitis. Nat Genet 2006; 38:668.
30. Kereszturi E, Szmola R, Kukor Z, et al. Hereditary pancreatitis caused by mutation-induced misfolding of human cationic trypsinogen: a novel disease mechanism. Hum Mutat 2009; 30:575.
31. Sahin-Tóth M. Hereditary pancreatitis-associated mutation asn(21) --> ile stabilizes rat trypsinogen in vitro. J Biol Chem 1999; 274:29699.
32. Teich N, Ockenga J, Hoffmeister A, et al. Chronic pancreatitis associated with an activation peptide mutation that facilitates trypsin activation. Gastroenterology 2000; 119:461.
33. Teich N, Bauer N, Mössner J, Keim V. Mutational screening of patients with nonalcoholic chronic pancreatitis: identification of further trypsinogen variants. Am J Gastroenterol 2002; 97:341.
34. Grocock CJ, Rebours V, Delhaye MN, et al. The variable phenotype of the p.A16V mutation of cationic trypsinogen (PRSS1) in pancreatitis families. Gut 2010; 59:357.
35. Le Maréchal C, Masson E, Chen JM, et al. Hereditary pancreatitis caused by triplication of the trypsinogen locus. Nat Genet 2006; 38:1372.
36. Whitcomb DC, LaRusch J, Krasinskas AM, et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet 2012; 44:1349.
37. Fu D, Blobner BM, Greer PJ, et al. Pancreatitis-Associated PRSS1-PRSS2 Haplotype Alters T-Cell Receptor Beta (TRB) Repertoire More Strongly Than PRSS1 Expression. Gastroenterology 2023; 164:289.
38. Lou H, Xie B, Wang Y, et al. Improved NGS variant calling tool for the PRSS1-PRSS2 locus. Gut 2023; 72:210.
39. Mastromatteo S, Chen A, Gong J, et al. High-quality read-based phasing of cystic fibrosis cohort informs genetic understanding of disease modification. HGG Adv 2023; 4:100156.
40. Fink EN, Kant JA, Whitcomb DC. Genetic counseling for nonsyndromic pancreatitis. Gastroenterol Clin North Am 2007; 36:325.
41. Pfützer RH, Barmada MM, Brunskill AP, et al. SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. Gastroenterology 2000; 119:615.

42. Witt H, Luck W, Hennies HC, et al. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet 2000; 25:213.
43. Schneider A, Barmada MM, Slivka A, et al. Clinical characterization of patients with idiopathic chronic pancreatitis and SPINK1 Mutations. Scand J Gastroenterol 2004; 39:903.
44. Shimosegawa T, Kume K, Masamune A. SPINK1, ADH2, and ALDH2 gene variants and alcoholic chronic pancreatitis in Japan. J Gastroenterol Hepatol 2008; 23 Suppl 1:S82.
45. Aoun E, Chang CC, Greer JB, et al. Pathways to injury in chronic pancreatitis: decoding the role of the high-risk SPINK1 N34S haplotype using meta-analysis. PLoS One 2008; 3:e2003.
46. Rowntree RK, Harris A. The phenotypic consequences of CFTR mutations. Ann Hum Genet 2003; 67:471.
47. Clinical and Functional Translation of CFTR (CFTR2). Available at: https://cftr2.org/ (Accessed on August 24, 2023).
48. Cystic Fibrosis Foundation. CFTR Mutation Classes. Available at: https://www.cff.org/research-clinical-trials/types-cftr-mutations (Accessed on August 24, 2023).
49. Cohn JA, Friedman KJ, Noone PG, et al. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med 1998; 339:653.
50. Ooi CY, Dorfman R, Cipolli M, et al. Type of CFTR mutation determines risk of pancreatitis in patients with cystic fibrosis. Gastroenterology 2011; 140:153.
51. Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017; 181S:S4.
52. Miller AC, Comellas AP, Hornick DB, et al. Cystic fibrosis carriers are at increased risk for a wide range of cystic fibrosis-related conditions. Proc Natl Acad Sci U S A 2020; 117:1621.
53. Weiss FU, Simon P, Bogdanova N, et al. Complete cystic fibrosis transmembrane conductance regulator gene sequencing in patients with idiopathic chronic pancreatitis and controls. Gut 2005; 54:1456.
54. Cohn JA, Neoptolemos JP, Feng J, et al. Increased risk of idiopathic chronic pancreatitis in cystic fibrosis carriers. Hum Mutat 2005; 26:303.
55. LaRusch J, Whitcomb DC. Genetics of pancreatitis. Curr Opin Gastroenterol 2011; 27:467.
56. Bertin C, Pelletier AL, Vullierme MP, et al. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. Am J Gastroenterol 2012; 107:311.
57. Gelrud A, Sheth S, Banerjee S, et al. Analysis of cystic fibrosis gener product (CFTR) function in patients with pancreas divisum and recurrent acute pancreatitis. Am J Gastroenterol 2004; 99:1557.

58. Sharer N, Schwarz M, Malone G, et al. Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Engl J Med 1998; 339:645.

59. Lowenfels A, Maisonneuve P, Palys B. Re: Ockenga et al.--mutations of cystic fibrosis gene in patients with pancreatitis. Am J Gastroenterol 2001; 96:614.

60. Rosendahl J, Witt H, Szmola R, et al. Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis. Nat Genet 2008; 40:78.

61. Masson E, Chen JM, Scotet V, et al. Association of rare chymotrypsinogen C (CTRC) gene variations in patients with idiopathic chronic pancreatitis. Hum Genet 2008; 123:83.

62. LaRusch J, Lozano-Leon A, Stello K, et al. The Common Chymotrypsinogen C (CTRC) Variant G60G (C.180T) Increases Risk of Chronic Pancreatitis But Not Recurrent Acute Pancreatitis in a North American Population. Clin Transl Gastroenterol 2015; 6:e68.

63. Grabarczyk AM, Oracz G, Wertheim-Tysarowska K, et al. Chymotrypsinogen C Genetic Variants, Including c.180TT, Are Strongly Associated With Chronic Pancreatitis in Pediatric Patients. J Pediatr Gastroenterol Nutr 2017; 65:652.

64. Beer S, Zhou J, Szabó A, et al. Comprehensive functional analysis of chymotrypsin C (CTRC) variants reveals distinct loss-of-function mechanisms associated with pancreatitis risk. Gut 2013; 62:1616.

65. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology 2013; 144:1292.

66. Derikx MH, Kovacs P, Scholz M, et al. Polymorphisms at PRSS1-PRSS2 and CLDN2-MORC4 loci associate with alcoholic and non-alcoholic chronic pancreatitis in a European replication study. Gut 2015; 64:1426.

67. Masamune A, Nakano E, Hamada S, et al. Common variants at PRSS1-PRSS2 and CLDN2-MORC4 loci associate with chronic pancreatitis in Japan. Gut 2015; 64:1345.

68. Witt H, Beer S, Rosendahl J, et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. Nat Genet 2013; 45:1216.

69. Kujko AA, Berki DM, Oracz G, et al. A novel p.Ser282Pro CPA1 variant is associated with autosomal dominant hereditary pancreatitis. Gut 2017; 66:1728.

70. Németh BC, Orekhova A, Zhang W, et al. Novel p.K374E variant of CPA1 causes misfolding-induced hereditary pancreatitis with autosomal dominant inheritance. Gut 2020; 69:790.

71. Fjeld K, Weiss FU, Lasher D, et al. A recombined allele of the lipase gene CEL and its pseudogene CELP confers susceptibility to chronic pancreatitis. Nat Genet 2015; 47:518.

72. Xiao X, Jones G, Sevilla WA, et al. A Carboxyl Ester Lipase (CEL) Mutant Causes Chronic Pancreatitis by Forming Intracellular Aggregates That Activate Apoptosis. J Biol Chem 2016;

291:23224.

73. Raeder H, Johansson S, Holm PI, et al. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. Nat Genet 2006; 38:54.
74. Molven A, Fjeld K, Lowe ME. Lipase Genetic Variants in Chronic Pancreatitis: When the End Is Wrong, All's Not Well. Gastroenterology 2016; 150:1515.
75. Felderbauer P, Hoffmann P, Einwächter H, et al. A novel mutation of the calcium sensing receptor gene is associated with chronic pancreatitis in a family with heterozygous SPINK1 mutations. BMC Gastroenterol 2003; 3:34.
76. Muddana V, Lamb J, Greer JB, et al. Association between calcium sensing receptor gene polymorphisms and chronic pancreatitis in a US population: role of serine protease inhibitor Kazal 1type and alcohol. World J Gastroenterol 2008; 14:4486.
77. Popescu O, Allison MJ, Brown RW. Effect of intravenous L-isoleucine infusion upon concentration of free isoleucine in milk. J Dairy Sci 1976; 59:1752.
78. Brand H, Diergaarde B, O'Connell MR, et al. Variation in the γ-glutamyltransferase 1 gene and risk of chronic pancreatitis. Pancreas 2013; 42:836.
79. Diergaarde B, Brand R, Lamb J, et al. Pooling-based genome-wide association study implicates gamma-glutamyltransferase 1 (GGT1) gene in pancreatic carcinogenesis. Pancreatology 2010; 10:194.
80. Sukalo M, Fiedler A, Guzmán C, et al. Mutations in the human UBR1 gene and the associated phenotypic spectrum. Hum Mutat 2014; 35:521.
81. Masamune A, Kotani H, Sörgel FL, et al. Variants That Affect Function of Calcium Channel TRPV6 Are Associated With Early-Onset Chronic Pancreatitis. Gastroenterology 2020; 158:1626.
82. Santhosh S, Witt H, te Morsche RH, et al. A loss of function polymorphism (G191R) of anionic trypsinogen (PRSS2) confers protection against chronic pancreatitis. Pancreas 2008; 36:317.
83. Lewis MD, Talluri J, Wilcox CM, et al. Differences in Age at Onset of Symptoms, and Effects of Genetic Variants, in Patients With Early vs Late-Onset Idiopathic Chronic Pancreatitis in a North American Cohort. Clin Gastroenterol Hepatol 2021; 19:349.
84. Giefer MJ, Lowe ME, Werlin SL, et al. Early-Onset Acute Recurrent and Chronic Pancreatitis Is Associated with PRSS1 or CTRC Gene Mutations. J Pediatr 2017; 186:95.
85. Keim V, Bauer N, Teich N, et al. Clinical characterization of patients with hereditary pancreatitis and mutations in the cationic trypsinogen gene. Am J Med 2001; 111:622.
86. Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. Pancreatology 2011; 11:279.

87. Whitcomb DC. Genetic predispositions to acute and chronic pancreatitis. Med Clin North Am 2000; 84:531.
88. Sibert JR. Hereditary pancreatitis in England and Wales. J Med Genet 1978; 15:189.
89. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 1997; 89:442.
90. Whitcomb DC, Applebaum S, Martin SP. Hereditary pancreatitis and pancreatic carcinoma. Ann N Y Acad Sci 1999; 880:201.
91. Shelton CA, Umapathy C, Stello K, et al. Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer. Am J Gastroenterol 2018; 113:1376.
92. Lowenfels AB, Maisonneuve P, Whitcomb DC, et al. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA 2001; 286:169.
93. Ulrich CD, Consensus Committees of the European Registry of Hereditary Pancreatic Diseases, Midwest Multi-Center Pancreatic Study Group, International Association of Pancreatology. Pancreatic cancer in hereditary pancreatitis: consensus guidelines for prevention, screening and treatment. Pancreatology 2001; 1:416.
94. Brand RE, Lerch MM, Rubinstein WS, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut 2007; 56:1460.
95. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015; 110:223.
96. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013; 62:339.
97. Solomon S, Whitcomb DC. Genetics of pancreatitis: an update for clinicians and genetic counselors. Curr Gastroenterol Rep 2012; 14:112.
98. Kumar A, Ajilore O, Zhang A, et al. Cortical thinning in patients with late-life minor depression. Am J Geriatr Psychiatry 2014; 22:459.
99. Gardner TB, Adler DG, Forsmark CE, et al. ACG Clinical Guideline: Chronic Pancreatitis. Am J Gastroenterol 2020; 115:322.
100. Ellis I, Lerch MM, Whitcomb DC, Consensus Committees of the European Registry of Hereditary Pancreatic Diseases, Midwest Multi-Center Pancreatic Study Group, International Association of Pancreatology. Genetic testing for hereditary pancreatitis: guidelines for indications, counselling, consent and privacy issues. Pancreatology 2001; 1:405.

101. Whitcomb DC. Hereditary disease of the pancreas. In: Textbook of Gastroenterology, 4th ed, Yamada T, Alpers DH, Laine L (Eds), Lippincott, Williams and Wilkins, 2002. p.2147.

102. Ellis JH, Greenhalf W, Howes N, et al. Clinical and molecular findings of cationic trypsinogen mutations in 60 families with hereditary pancreatitis on the EUROPAC Register (abstract). Digestion 2000; 61:266.

103. Shelton C, Solomon S, LaRusch J, Whitcomb DC. PRSS1-related hereditary pancreatitis. In: GeneReviews, Adam MP, Ardinger HH, Pagon RA, et al (Eds), University of Washington, Seattle 1993 (updated April 2019).

104. Genetic risk factors in chronic pancreatitis database. Available at: www.pancreasgenetics.org/ (Accessed on November 16, 2015).

105. Carrion A, Borowitz DS, Freedman SD, et al. Reduction of Recurrence Risk of Pancreatitis in Cystic Fibrosis With Ivacaftor: Case Series. J Pediatr Gastroenterol Nutr 2018; 66:451.

106. Johns JD, Rowe SM. The effect of CFTR modulators on a cystic fibrosis patient presenting with recurrent pancreatitis in the absence of respiratory symptoms: a case report. BMC Gastroenterol 2019; 19:123.

107. Han ST, Rab A, Pellicore MJ, et al. Residual function of cystic fibrosis mutants predicts response to small molecule CFTR modulators. JCI Insight 2018; 3.

108. Aoun E, Muddana V, Papachristou GI, Whitcomb DC. SPINK1 N34S is strongly associated with recurrent acute pancreatitis but is not a risk factor for the first or sentinel acute pancreatitis event. Am J Gastroenterol 2010; 105:446.

109. Whitcomb DC. Primer on Precision Medicine for Complex Chronic Disorders. Clin Transl Gastroenterol 2019; 10:e00067.

110. Whitcomb DC, Shimosegawa T, Chari ST, et al. International consensus statements on early chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. Pancreatology 2018; 18:516.

111. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med 2009; 169:1035.

112. Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clin Gastroenterol Hepatol 2016; 14:738.

113. Akshintala VS, Kamal A, Faghih M, et al. Cystic fibrosis transmembrane conductance regulator modulators reduce the risk of recurrent acute pancreatitis among adult patients with pancreas sufficient cystic fibrosis. Pancreatology 2019; 19:1023.

114. Sadras I, Cohen-Cymberknoh M, Kerem E, et al. Acute pancreatitis in pancreatic-insufficient cystic fibrosis patients treated with CFTR modulators. J Cyst Fibros 2023; 22:777.

115. Gould MJ, Smith H, Rayment JH, et al. CFTR modulators increase risk of acute pancreatitis in pancreatic insufficient patients with cystic fibrosis. J Cyst Fibros 2022; 21:600.

116. Kitano M, Gress TM, Garg PK, et al. International consensus guidelines on interventional endoscopy in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. Pancreatology 2020; 20:1045.

117. Chinnakotla S, Radosevich DM, Dunn TB, et al. Long-term outcomes of total pancreatectomy and islet auto transplantation for hereditary/genetic pancreatitis. J Am Coll Surg 2014; 218:530.

118. Chinnakotla S, Beilman GJ, Dunn TB, et al. Factors Predicting Outcomes After a Total Pancreatectomy and Islet Autotransplantation Lessons Learned From Over 500 Cases. Ann Surg 2015; 262:610.

119. Chinnakotla S, Bellin MD, Schwarzenberg SJ, et al. Total pancreatectomy and islet autotransplantation in children for chronic pancreatitis: indication, surgical techniques, postoperative management, and long-term outcomes. Ann Surg 2014; 260:56.

120. Bellin MD, Forlenza GP, Majumder K, et al. Total Pancreatectomy With Islet Autotransplantation Resolves Pain in Young Children With Severe Chronic Pancreatitis. J Pediatr Gastroenterol Nutr 2017; 64:440.

121. Bellin MD, Gelrud A, Arreaza-Rubin G, et al. Total pancreatectomy with islet autotransplantation: summary of a National Institute of Diabetes and Digestive and Kidney diseases workshop. Pancreas 2014; 43:1163.

122. Bellin MD, Freeman ML, Gelrud A, et al. Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. Pancreatology 2014; 14:27.

123. Blondet JJ, Carlson AM, Kobayashi T, et al. The role of total pancreatectomy and islet autotransplantation for chronic pancreatitis. Surg Clin North Am 2007; 87:1477.

124. Rebours V, Boutron-Ruault MC, Jooste V, et al. Mortality rate and risk factors in patients with hereditary pancreatitis: uni- and multidimensional analyses. Am J Gastroenterol 2009; 104:2312.

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