

# Genetic Abnormalities in Pancreatitis

Subjects: Gastroenterology & Hepatology

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Hereditary pancreatitis (HP) has been defined as either two or more individuals within a family exhibiting pancreatitis for two or more generations, or pancreatitis linked to mutation of the *PRSS1* gene. In 2000, a mutation in the serine protease inhibitor gene (*Kazal* type 1: *SPINK1*) was reported to be related to sporadic pancreatitis of unknown etiology.

Keywords: genetic mutations ; chronic pancreatitis ; pancreatic exocrine insufficiency ; diabetes mellitus ; pancreatic cancer

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## 1. Introduction

When the patients with acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) show an autosomal dominant pattern of inheritance, they have been characterized as having hereditary pancreatitis (HP). HP caused by cationic trypsinogen (serine protease 1; *PRSS1*) gene mutation results in ARP and CP in both children and adults with high penetrance<sup>[1][2]</sup>. Currently, HP has been defined as either, two or more individuals within a family exhibiting pancreatitis for two or more generations, or pancreatitis linked to mutation of the *PRSS1* gene. On the other hand, familial pancreatitis is a broader term used to describe families in which pancreatitis occurs with a greater incidence than expected by chance alone in the general population. Patients with HP usually present clinically with recurrent bouts of acute pancreatitis (AP) in the first two decades of life. HP prevalence ranges depending on the region, from 0.3 to 0.57 per 100,000 people, according to national cohort data<sup>[3][4][5]</sup>. Progression to CP occurs in the late teenage years and early adult life. As damage to the pancreas progresses, malabsorption occurs due to pancreatic exocrine insufficiency, and diabetes mellitus develops due to pancreatic islet cell damage<sup>[3]</sup>. Several pancreatitis susceptibility genes have been identified so far (See “History” below). The mechanisms of developing pancreatitis due to genetic abnormalities are mainly classified into three genetic pathways, classified as: the trypsin-dependent pathway, misfolding and consequent endoplasmic reticulum stress, and related to the ductal pathway<sup>[6]</sup>. Compared to the other causes of ARP and CP, genetic pancreatitis has some unique clinical characteristics. Recently, several cohorts showed the natural history of patients with serine protease inhibitor gene (*Kazal* type 1: *SPINK1*) germline-related pancreatitis and HP caused by *PRSS1* gene mutation, indicating a high progression rate of pancreatic exocrine insufficiency and diabetes mellitus, as well as a significantly increased risk of pancreatic cancer<sup>[3][7]</sup>.

## 2. Genetic Abnormalities

### 2.1. CFTR Gene

The *CFTR* gene has been identified as a causative gene of cystic fibrosis<sup>[10]</sup>, and it is also reported to be a gene associated with pancreatitis<sup>[11][12]</sup>. About 1–4% of the overall cystic fibrosis population will have an episode of pancreatitis. Mutation causes a defect in the CFTR protein that causes abnormal HCO<sub>3</sub><sup>-</sup> transport, leading to defective pancreatic secretion<sup>[39]</sup>. As a result of impaired pancreatic juice alkalization and water secretion, protein plugs form in the pancreas and/or pancreatic duct<sup>[40]</sup>. Regarding the relationship with CP, it has been reported that splicing efficiency and channel function decrease due to poly T polymorphism, TG repeat polymorphism, and p.Q1352H polymorphism<sup>[11][12][41]</sup>. Some *CFTR* mutations can be inherited in a complex-type pattern. The *CFTR* gene is considered to be a high-risk for developing CP when it is associated with other multiple mutations (complex heterozygotes mutation), especially *SPINK1* gene mutations<sup>[42][43][44]</sup>.

### 2.2. PRSS1 Gene

Mutations in *PRSS1*, which encodes cationic trypsinogen, the most abundant isoform of trypsinogen in human pancreatic juice, can occur. In 1996, the p.R122H in the *PRSS1* gene was first identified as a cause of HP<sup>[4]</sup>. In the following years, the p.N29I mutation was detected as a new mutation in HP patients<sup>[45]</sup>. The p.R122H mutation is the most common (~65%), followed by p.N29I mutation (~25%), and p.A16V. Increased trypsin levels are generated at the onset of

pancreatitis, but not through the same biological mechanism. The p.R122H mutation (autolysis site) inhibits trypsin self-destruction, resulting in increased trypsin stability and a high level of trypsin in the pancreas, leading to pancreatic autodigestion and pancreatitis<sup>[46]</sup>. The p.A16V mutation (activation site) increases N-terminal processing of the trypsinogen activation peptide by CTRC, which in turn enhances autoactivation<sup>[46][47]</sup>. The p.N29I mutation affects both degradation and autoactivation in trypsinogen biochemistry<sup>[46]</sup>.

Alternatively, a subset of *PRSS1* mutations can cause misfolding and endoplasmic reticulum stress<sup>[48]</sup>. In 2009, the p.R116C mutation found in HP families with incomplete penetrance was first reported as a cause of CP by a mis-folding-dependent pathway. Since then, several variants such as p.D100H, p.C139F, p.K29N, p.S124F, and p.G208A have been reported, likely involving this pathway, but the detailed pathogenic mechanism is still unclear<sup>[49]</sup>.

### 2.3. SPINK1 Gene

*SPINK1* encodes a pancreatic secretory trypsin inhibitor, and mutations interfere with the protective function, and predispose a person to pancreatitis, possibly via increased intrapancreatic trypsin activity. SPINK1, together with the protease inhibitors  $\alpha_1$ -antitrypsin and  $\alpha_2$ -macroglobulin, binds to activated trypsin and inhibits its activity. SPINK1 inhibits about 20% of total trypsin activity, and acts as a primary defense mechanism<sup>[50][51]</sup>. The trypsin binding site is encoded on exon 3. The most common mutation is the p.N34S mutation. According to the first report by Witt et al., the p.N34S variant was found in 18 of 85 (21%) children with idiopathic pancreatitis<sup>[13]</sup>. However, the p.N34S mutation is even present in 0–2% of otherwise healthy persons, suggesting that this mutation is thought to be a disease-modifying factor rather than a causative factor, when additional risk factors for pancreatic inflammation such as alcohol, tobacco consumption, or genetic factors are present<sup>[51][52]</sup>. Actually, the p.N34S variation had no effect on the secretion of SPINK1 protein from transfected cells and trypsin inhibitory activity of the mutant protein was also unchanged<sup>[53][54]</sup>. Recently, the p.N34S mutation was found in 20% of patients carrying the functionally defective TRPV6 variants<sup>[24]</sup>, suggesting that the combination of mutated TRPV6 and *SPINK1* p.N34S results in predisposition to pancreatitis, as well as the *CFTR* gene. The next most frequent mutation is the c.194 + 2T > C mutation, which has often been reported in Asian persons in Japan, China, and South Korea<sup>[55][56][57]</sup>. In the c.194 + 2T > C mutation, because exon 3 is skipped, due to a splicing aberration, trypsin activation cannot be inhibited, and pancreatitis occurs<sup>[58]</sup>.

### 2.4. CTRC Gene

Following the finding that CTRC specifically degrades trypsin, the association between *CTRC* mutations and pancreatitis was investigated<sup>[18]</sup>. *CFTR* mutations have been shown to occur in 0.7% of healthy controls and 2.9% of adults with CP<sup>[18]</sup>. In a recent cohort from the International Study Group for Pediatric Pancreatitis: In Search of a Cure (INSPPIRE), it was reported that early-onset pancreatitis below 6 years of age was likely associated with genetic abnormalities, particularly *PRSS1* (43%) or *CTRC* (14%) mutations<sup>[2]</sup>. CTRC serves as a second line defense against premature activation of trypsinogen isoforms<sup>[48]</sup>. Mutations of *CTRC* cause loss of function by several mechanisms, which include severe reduction of CTRC secretion (p.A73T), inactive CTRC (p.K247\_R254del), promotion of degradation by trypsin (p.R254W), decreased CTRC activity (p.V235I), or decreased CTRC mRNA (p.G60 →)<sup>[18][59][60]</sup>. Of note, only *CTRC* pathogenic variants do not seem to cause CP, but rather they are seen in combination with other variants, such as *CTRC* or *SPINK1* mutations<sup>[18][43][60]</sup>, or with anatomic anomalies of the pancreaticobiliary system<sup>[33][61]</sup>.

### 2.5. CPA1 Gene

The mechanism by which a *CPA1* mutation confers an increased risk of pancreatitis involves misfolding-induced endoplasmic reticulum stress, rather than increased trypsin activity<sup>[20]</sup>. *CPA1* mutations with less than 20% apparent activity of the CPA1 protein have been observed to be significantly overrepresented in patients with CP. The functionally impaired *CPA1* variants with less than 20% functionality were found in 3.1% of non-alcoholic CP patients (29/944) and 0.1% of controls (5/3938) ( $p < 0.01$ ). The most frequent functionally impaired variant was p.N256K, and it was observed in 0.7% (7/944) of patients and 0% (0/3938) of controls. The risk for pancreatitis was 38-fold greater in patients younger than 20 years old and 84-fold greater in patients younger than 10 years old. The associations between *CPA1* mutations and non-alcoholic CP patients have also been reported in additional cohorts from Europe (1.3% (8/600) and 0.4% (9/2432) ( $p < 0.01$ )), India (2.5% (6/239) and 0.3% (1/340) ( $p < 0.05$ )), and Japan (2.0% (5/247) and 0% (0/341) ( $p < 0.05$ ))<sup>[20]</sup>.

### 2.6. TRPV6 Gene

TRPV6 is a member of the transient receptor potential vanilloid ion channel superfamily<sup>[62]</sup>. TRPV6 promotes high  $\text{Ca}^{2+}$  entry in absorptive and secretory tissues. It is mainly expressed in  $\text{Ca}^{2+}$ -transporting epithelia. In the pancreas, TRPV6 expression is nearly 6-times higher in ductal cells than in acinar cells<sup>[63]</sup>. More recently, Masamune et al. reported that impaired  $\text{Ca}^{2+}$  uptake caused by *TRPV6* variants was associated with early-onset CP<sup>[24]</sup>. Interestingly, 6 out of 30

(20%) patients with functionally defective *TRPV6* variants were trans-heterozygous for *SPINK1* p.N34S [24], indicating that CP is a complex multigenic disease, and a cumulative genetic handicap seems to be crucial for the development of early-onset CP.

## 2.7. Others

CASR, first characterized in the bovine parathyroid[64], expressed in the pancreas can respond to high calcium concentrations in the pancreatic juice by increasing ductal fluid secretion, thereby preventing stone formation and pancreatitis[65]. An association between developing CP and variants in the *CASR* gene has been reported [14][15][16][17], but the evidence remains uncertain.

PRSS2 is another major trypsinogen isoform constituting the bulk of secreted trypsinogen in humans[66]. No pathogenic *PRSS2* variants have been identified in HP and sporadic pancreatitis[27]. The variant p.G191R introduces a trypsin cut site anionic trypsin, which reduces the overall activity of *PRSS2*, indicating that this variant confers protection from CP[27].

CLDN2 is expressed in the proximal pancreatic duct and promotes H<sub>2</sub>O and Na<sup>+</sup> transport to counter Cl<sup>-</sup> and HCO<sub>3</sub><sup>-</sup> secretion through CFTR[19]. *CLDN2* mutations, an X-chromosome locus gene, were found to be associated with alcohol-related and sporadic pancreatitis[19]. Since men are hemizygous for the X chromosome, the risk appears dominant, whereas it is inherited as a recessive pattern in women.

Mutations in *CEL* cause maturity-onset diabetes of the young type 8 (MODY8), as well as pancreatic exocrine dysfunction[25]. A hybrid *CEL* allele (*CEL-HYB1*), formed by nonallelic homologous recombination between *CEL* and its adjacent pseudo-gene *CELP*, was enriched approximately 5-fold in patients with idiopathic CP[21]. This hybrid protein was poorly secreted due to intracellular retention, leading to endoplasmic reticulum stress and apoptosis in an in vitro experiment [21].

The changes in the balance of chymotrypsin isoforms, namely inversion at the *CTRB1* and *CTRB2* locus, that affect trypsin degradation slightly increased the risk of alcoholic and non-alcoholic CP[22][67]. In addition, several variants of *PNLIP* gene, particularly p.F300L, were associated with early onset and non-alcoholic CP in the European population, but the mechanism remains unclear[23].

## 3. Conclusions

Clinicians need to know the characteristics of ARP and CP with genetic abnormalities. Genetic testing for patients with unknown etiology is useful by analyzing *CEL*, *CFTR*, *CPA1*, *CTRC*, *PRSS1*, and *SPINK1* genes, after the major causes of AR and CP have been excluded. In addition, testing for protective variants of *PRSS2* gene is not useful clinically. The clinical usefulness of testing mutations of the genes encoding *CLDN2*, *CTRB1*, *CTRB2*, and *PNLIP* is limited due to their high frequency and narrow range of clinical symptoms. Genetic counseling prior to and after testing is required in all patients. Clinicians should carefully follow ARP and CP patients with genetic mutations, since they have a potentially high risk of developing pancreatic exocrine insufficiency, diabetes mellitus, and pancreatic cancer.

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