Genetics of Pancreatitis: Are There Differences between Korea and Other Countries?

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In the initial genetic studies about pancreatitis in Korea, gene mutations were thought to be rare. However, the recent findings of PRSS1, SPINK1, and CFTR mutations in patients with idiopathic chronic pancreatitis or inherited cases of chronic pancreatitis are much more common than originally predicted. Therefore, it is important to identify underlying genetic background in idiopathic chronic pancreatitis to avoid progression and development of complications. In addition, concentrated and strict follow-up must be given to the patients because of very high risk of pancreatic cancer. However, it is also true that studies about genetics in pancreatitis were not enough to compare with Western studies. Accordingly, further large scale studies are necessary to find other unknown possible genes that could be related to the chronic and hereditary pancreatitis.

Keywords: Genetics, Pancreatitis, PRSS1, SPINK1, CFTR

INTRODUCTION

No apparent underlying causes of chronic pancreatitis (CP) can be identified in 10-30% of the patients. Many studies indicate that a significant percentage of the patients with CP, as well as classical hereditary pancreatitis (HP), have a genetic basis for their disorder. A genetic background for chronic HP, revealed as a PRSS1 defect later, was first described in a pedigree with an obviously autosomal dominant inheritance pattern in 1952. Recently, genetics has appeared as a crucial part in evaluation and management of CP. Importance of genetic evaluation can be suggested as follows. First, identification of main genetic factors in a patient with recurrent acute pancreatitis provides the clinician an opportunity for early intervention to prevent the progression. Second, concentrated and strict follow-up must be given to the patients because of very high risk of pancreatic cancer. Third, some
customized medication in accordance with genetic defects could help to attenuate the progression of pancreatitis. \(^3\) In addition, an association between a mutated gene and alcoholic CP has been described.\(^5\)

Earlier studies in Korea, in contrast to Western countries, showed that PRSS1 mutations were not detected in patients with chronic idiopathic pancreatitis,\(^6\) and that SPINK1 and CFTR mutations were also uncommon in chronic alcoholic pancreatitis.\(^7\) However, recent studies in Korea revealed that PRSS1, SPINK1 and CFTR mutations are not rare in Korean patients with idiopathic and familial pancreatitis.\(^8,9\)

This review delineates the prevalence of three major and two minor variants of gene mutation and clinical differences in patients with CP in Korea, compared with other Asian and Western countries.

**Cationic Trypsinogen (protease, serine, 1: PRSS1)**

A genetic defect was first identified in 1996 by Whitcomb et al, who found a substitution of arginine by histidine at residue 122 (R122H mutation) in exon 3 of the cationic trypsinogen (protease, serine, 1: PRSS1) gene.\(^10\) The discovery of mutations in PRSS1 in HP not only provided insights into the molecular mechanisms of pancreatitis, but also opened a new era in the field of CP. Various other PRSS1 alterations have been reported in subsequent studies. Other PRSS1 alterations including A16V, N29T, R116C, R122C and several other genetic alterations have been reported in families with suspected HP or in patients without a family history. Until now, the R122H and N29I mutations of the PRSS1 gene have been identified as the most common disease associated mutations.\(^11\)

It is known that there are ethnic differences in PRSS1 mutation. Detection rates of PRSS1 mutations were 52% and 81% in North American and European studies in which classic criteria for HP were used, whereas the detection rate was 44% in a Japanese study in which broader criteria were used.\(^12-14\) No PRSS1 mutation was found in the Indian population.\(^15\)

In Korea, there is controversy about the prevalence of PRSS1 mutation in idiopathic and familial pancreatitis. In first study, PRSS1 mutation was not found in idiopathic CP.\(^6\) However, a recent study in 2009 showed that PRSS1 mutation was found in 12.8% (6/47) in idiopathic and familial pancreatitis.\(^8\) Another study in 2011 also documented that 4 of 32 Korean children (12.5%) with acute recurrent pancreatitis or CP had mutation in the PRSS1 gene.\(^9\)

Although the prevalence of PRSS1 mutations and HP in Korea were not as high as in Western countries and Japan, it is also true that PRSS1 mutations are not rare in Korean patients with idiopathic and familial pancreatitis. Most common mutated allele is known to be R122H.\(^8,9\)

**Serine Protease Inhibitor, Kazal Type 1 (SPINK1)**

SPINK1, also known as pancreatic secretory trypsin inhibitor, is a potent anti-protease that is a major inactivation factor of intrapancreatic trypsin activity. Mutations in SPINK1 interfere with this protective action and predispose to pancreatitis. Most common type of SPINK1 mutation in Western counties is known to be N34S.\(^16,17\)

Approximately 2% of individuals in the general population exhibit high-risk nucleotide variants in the SPINK1 gene, but less than 1 percent of carriers develops pancreatitis. Nonetheless, mutations in SPINK1 increase the risk for CP about 12-fold over the general population. Thus, the SPINK1 mutation probably acts as a disease modifier, lowering the threshold for developing pancreatitis from other genetic or environmental factors.\(^18\)

In Western study, the prevalence rate of SPINK1 mutations was 20% in familial pancreatitis, 7% in alcoholic pancreatitis, and 21% in idiopathic pancreatitis.\(^19\) Another prevalence report of the mutations in familial and idiopathic pancreatitis was 25.9% (29/112) in a conjoined study of North America and Europe,\(^20\) and 28.8% (17/59,
23.4% in idiopathic, 50.0% in familial) in a Japanese study. In Indian study, SPINK1 gene mutations were also common. N34S mutation was observed in the SPINK1 gene in the majority of HP patients (73%, 27/37), 26.8% (11/41) of alcoholic CP, and 32.5% (39/120) of idiopathic CP patients also had SPINK1 mutations. In initial Korean study, only one patient (2.1%, 1/47) with alcoholic CP was a heterozygote for SPINK1 (N34S) mutation. However, in a recent study of children with acute recurrent pancreatitis or CP, 34.4% (11/32) of the patients carried either the IVS3+2T>C or N34S mutation of the SPINK1 gene. In another study, the overall prevalence of SPINK1 mutations (N34S or IVS3+2T>C) was 31.7% (13/41) among 41 patients without PRSS1 mutations. Interestingly, the observed prevalence of IVS3+2T9C mutation in Korea was 26.8% (11/41), which was much higher than that of N34S heterozygous mutation (7.3%, 3/41) which is the most common mutation in Western countries.

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

Pancreatic duct obstruction induced by a defective cAMP-regulated chloride channel, as a result of mutations in the CFTR gene, such as F508del, R117H, and N1303K, is the cause of pancreatic insufficiency in patients with cystic fibrosis. In the pancreas, CFTR plays a pivotal role in the apical HCO₃⁻ transport in duct cells. Accordingly, mutations in the CFTR can cause pancreatitis with or without associated manifestations of cystic fibrosis. Over 1700 different genetic polymorphisms in CFTR have been identified, and disease manifestations depend on the severity of the mutation and zygosity. F508del is the most frequent and R117H is the second frequent mutation of CFTR in Western population. However, cystic fibrosis is a rare disease in East Asia, and mutations of F508del and R117H are rare in Korean and Japanese populations. Nonetheless, the prevalence of CFTR gene mutations in idiopathic CP was reported as a range of 9-21% in Asian countries including Japan, China and India, which was similar to Western countries.

In Korea, there is also controversy about the prevalence of CFTR mutation in CP. An earlier study detect only 1 case of CFTR Q1352H mutation in alcoholic CP. However, another study reported that the new CFTR Q1352H mutation was found in 19% of Korean patients with idiopathic chronic pancreatitis. These findings provided the definite evidence on the association of CFTR mutations with CP in Korean.

Chymotrypsinogen C (CTRC)

CTRC, also known as caldecrin, was first isolated from porcine pancreas in 1992. The gene was initially studied as a candidate gene for pancreatitis because it appears to be able to degrade trypsin, and therefore protect the pancreas from trypsin-related injury. A recent study reported an increased frequency of CTRC variants in patients with CP compared to control subjects. Analyzing a large European cohort of over 900 patients (mostly German) with idiopathic or hereditary CP by DNA sequencing of all 8 exons of the 8.2-kb-long CTRC, several CTRC variants were detected. The two most frequent variants, p.R254W and p.K247_R254del were found in affected individuals with a frequency of 2.1 and 1.2%, respectively. Taken together, the two alterations were significantly over-represented in the pancreatitis group (30/901, 3.3%) compared to controls (21/2,804, 0.7%). However, Masson et al did not associate p.R254W or p.K247_R254del with CP in patients in France but did associate them with multiple rare, newly identified mutations in CTRC. In brief, the functional analyses of the CTRC variants revealed impaired activity and reduced secretion, indicating that alterations in CTRC predispose to pancreatitis by diminishing its protective trypsin-degrading activity. Unfortunately, there have
been no studies about CTRC in patients with pancreatitis in Korea.

**Calcium sensing receptor (CASR)**

The CASR is a seven exon, 1078 amino acid, plasma membrane-bound G protein coupled receptor that senses extracellular calcium levels and is expressed in many cells and tissues. The CASR is now known to play a central role in calcium homeostasis primarily through regulation of parathyroid hormone (PTH) secretion.

CASR is expressed on the luminal side of the ducts and increases cyclic-AMP and activate bicarbonate secretion through CFTR. Thus, CASR is a monitor and regulator of pancreatic juice calcium concentration by triggering ductal electrolyte and fluid secretion when levels are elevated. This action would wash out duct fluid with high concentrations of calcium, which increases risk of trypsinogen activation and stabilization of trypsin, which in turn causes acute pancreatitis.

The association between CP and CASR gene mutation was initially reported in patients with familial hypocalciuric hypercalcemia, a condition caused by loss-of-function mutations in CASR. In a study of 338 subjects, Muddana et al associated pancreatitis with the gain-of-function R990G variant of CASR. The risk of CP was not associated with SPINK1 variants but was associated with moderate to heavy alcohol consumption.

More than 70 CASR variants have been classified and are included in the calcium-sensing receptor locus-specific database. They have been associated with familial (benign) hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcemia. CASR p.R990G is a common polymorphism that has been identified in CP. There is evidence that loss-of-function variants of CASR, in association with SPINK1 and CFTR variants, affect duct cell function, whereas gain-of-function variants in CASR that are associated with alcoholic pancreatitis affect acinar cell functions. Sadly, there have been no studies about CASR in patients with pancreatitis in Korea.

**CONCLUSIONS**

In the initial genetic studies about pancreatitis in Korea, gene mutations were thought to be rare. However, the recent findings of PRSS1, SPINK1, and CFTR mutations in patients with idiopathic CP or inherited cases of CP are much more common than originally envisioned. Combinations of genetic factors and the other factors such as alcohol are known to increase the risk of RAP and CP. Accordingly, it is important to identify underlying genetic background in ICP to avoid progression and development of complications. A characteristic feature of HP is a prominently increased risk of pancreatic cancer, and it is important to identify underlying cause so that chronic pancreatitis with all of its complications can be avoided. Accordingly, further large scale studies are needed to find other unknown possible genes that could be related to the CP and HP.

**CONFLICTS OF INTEREST**

The authors have no conflicts to disclose.

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