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Genetic Mutations, Polymorphisms and Pancreatitis



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INTRODUCTION

Hereditary chronic pancreatitis is a rare form of pancreatitis with a typical early onset and a slow progression of disease. The significant increase of pancreatic cancer in this patient population is very concerning. While its clinical features, including the course, pathology, and laboratory findings are similar to other etiologies of chronic pancreatitis, the underlying pathophysiologic mechanisms are based on genetic mutations. In 1952, Comfort and Steinberg¹ pointed out a familial accumulation of chronic pancreatitis, hence suggestive of a possible genetic etiology to the disease.¹ It was not until 1996 that several groups identified a genetic link to hereditary chronic pancreatitis on chromosome 7.^{2,3} The underlying mutations were further characterized the same year by Whitcomb et al³ as an R122H mutation in the cationic trypsinogen gene (PRSS1). Since then, there has been remarkable progress in understanding the genetic basis of chronic pancreatitis with the identification of several additional genetic polymorphisms, including mutations in the anionic trypsinogen gene (PRSS2), the serine protease

inhibitor Kazal type 1 gene (SPINK1), and the cystic fibrosis transmembrane conductance regulator gene (CFTR). In this paper, we will review these underlying genetic factors and their link to chronic pancreatitis.

PRSS1 Mutations and Hereditary Pancreatitis

Hereditary pancreatitis is an autosomal dominant genetic disorder with incomplete penetrance and highly variable disease expression. About half of the affected individuals tend to progress to chronic pancreatitis at a young age.^{4,5} The discovery of cationic trypsinogen gene mutation and their link to pancreatitis provided evidence that trypsinogen is an essential player in the pathophysiology of the disease. Patients with hereditary pancreatitis can start showing symptoms in childhood or adolescence, and with time, exocrine and endocrine insufficiency may develop. The diagnosis of hereditary pancreatitis should be considered in patients who present with recurrent pancreatitis and with a family history of pancreatic disease.⁶ In a clinical setting, however, it is very hard to establish accurate pedigrees. Therefore, the criteria for diagnosis of hereditary pancreatitis continue to evolve. In 1997, the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC) based the diagnosis on two first-degree relatives or three or

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more second-degree relatives, in two or more generations with recurrent acute and/or chronic pancreatitis with no evidence of other known etiologies.⁴ These criteria differ across various clinical centers. Although hereditary pancreatitis only represents approximately 2%–3% of all cases of chronic pancreatitis, it is important to establish diagnosis as early as possible because it provides clinical insight into acute, recurrent acute, and chronic pancreatitis, in addition to pancreatic cancer.⁷ Even then, it is very common for patients to remain undiagnosed for years. Aside from young age and slow progression, the presentation of hereditary pancreatitis is indistinguishable from other causes of acute and chronic pancreatitis. In fact, with more genes and polymorphisms being discovered, the line between idiopathic and genetic-related pancreatitis is becoming unclear and such a differentiation may become obsolete.

In 1996, the discovery of the hereditary pancreatitis gene, cationic trypsinogen (PRSS1)—specifically chromosome 7q35—led to important insights into the pathophysiology of acute and chronic pancreatitis.⁸ There are two main PRSS1 mutations associated with hereditary pancreatitis. The most common is the R122H mutation that results from a substitution of the amino acid histidine (H) for arginine (R) at position 122.^{8–10} The second mutation, known as N291, results from a substitution of isoleucine (I) for asparagine (N) at position (N291). These mutations lead to an increase in the autocatalytic conversion of trypsinogen to trypsin causing premature intrapancreatic trypsinogen activation.⁹ There are other PRSS1 alterations identified as well in the trypsinogen activation peptide region which include A16V, D22G, K23R, N29T and R122C.⁹

Clinical Presentation

PRSS1 mutations are detected in more than 50% of families with hereditary pancreatitis. However, only 80% of patients carrying the N291 or the R122H mutations express the chronic pancreatitis phenotype. The reason behind this incomplete penetrance remains unclear and likely involves the interaction with other environmental factors such as smoking, alcohol, and lack of antioxidants.^{5, 11} While both alcoholic and PRSS1-related chronic pancreatitis have very similar clinical laboratory features, histopathology, and imaging findings, patients with PRSS1-related pancreatitis typically present at a younger age and tend to have a lower incidence of calcifications and diabetes.¹² The presentation of hereditary pancreatitis

can vary significantly between individuals and families. Children tend to present with recurrent acute abdominal pain associated with vomiting that can last up to 2–3 days. Other patients present with vague abdominal pain during their teens and now present with chronic pancreatitis.⁸ In some patients, the disease can be severe enough to lead to diabetes, pancreatic pseudocysts, bile duct and duodenal obstruction, and pancreatic cancer. The lifetime risk of developing pancreatic cancer in these patients is about 50-fold higher than the normal population and is even higher than that of patients with alcoholic chronic pancreatitis, which is 20-fold higher than the general population.^{13, 14}

SPINK1/PSTI

Serine Protease Inhibitor Kazal type 1 (SPINK1)/Pancreatic Secretory Trypsin Inhibitor (PSTI) is the second gene that has been found to be associated with pancreatitis. PSTI is a 56-amino acid polypeptide secreted in the pancreatic juice that inhibits trypsin by binding to it and forming a stable complex, thus rendering the enzyme inactive. It plays an important protective role by preventing the trypsin activation of other zymogens as well. It is believed that intrapancreatic PSTI concentrations are able to inhibit about 20% of intrapancreatic trypsin.¹⁵ SPINK1 is an acute-phase protein whose gene expression and protein concentrations are markedly up-regulated by inflammation.^{16–18} SPINK1 gene mutations are thought to diminish protection against prematurely activated trypsin, and are thereby linked to trypsin-related pancreatic injury.¹⁹

Multiple studies have looked at the association between SPINK1 mutations and chronic pancreatitis, and there has been a wide variation along with significant heterogeneity noted across the board. Indeed, odds ratios for this association have ranged from 0 to 80. In 2008, a meta-analysis of this association was conducted based on different etiologies of chronic pancreatitis.²⁰ It was found that there was an overall strong association between the N34S haplotype and chronic pancreatitis in general regardless of etiology with an odds ratio of 11. Interestingly, the association between such polymorphisms varied greatly depending on the underlying etiology. The weakest association was noted in patients with alcohol-related chronic pancreatitis (odds ratio 4.98), while patients with idiopathic and tropical pancreatitis had a significantly higher association (odds ratio 14.97 and 19.15, respectively).

These findings suggested that the pathophysiology of alcohol-related chronic pancreatitis may follow a different pathway that is largely trypsin independent.²⁰

The association of SPINK1 polymorphisms with acute pancreatitis was studied in 188 patients with acute pancreatitis and 670 controls.²¹ SPINK1 N34S polymorphism was detected in 1 of 232 alleles in patients with sentinel AP, 11 of 144 alleles in patients with recurrent acute pancreatitis, and in 19 of 1,340 control alleles. There was no difference in the prevalence of the polymorphism between sentinel attack patients and controls. Patients with the polymorphism were more prone to develop recurrent attacks with an odds ratio of 19.1. These findings suggested that the N34S polymorphism is not associated with the sentinel acute pancreatitis attack, but that its presence substantially increases the risk of recurrent attacks.²¹

Cystic Fibrosis Transmembrane Conductance Regulator Gene (CFTR)

Cystic fibrosis is the most common heritable cause of pancreatic insufficiency. CFTR functions as an anion channel and as a regulator of other ion transport proteins. It plays a key role during normal exocrine pancreatic function. Located on the apical side of the duct cells, it promotes cAMP-regulated bicarbonate and fluid secretion.²² It is believed that CFTR contributes to normal pancreatic secretions by alkalinizing and diluting the pancreatic juice, hence preventing proteinaceous plugs from obstructing the small pancreatic ductules.²³ Several findings suggested an association between chronic pancreatitis and CFTR gene mutation. First, early ductal plugging is a common feature of chronic pancreatitis.²⁴ Second, patients with chronic pancreatitis can have false-positive sweat tests,²⁵ and finally, patients with cystic fibrosis were noted to have a higher incidence of pancreatitis.²⁶

In 1998, two separate articles published in the *New England Journal of Medicine* reported a strong association between idiopathic chronic pancreatitis and mutations in the CFTR gene.^{27,28} Over 1500 mutations of the CFTR gene have so far been described in the literature. However, the exact underlying mechanisms that lead to chronic pancreatitis are not well understood.⁷ The increased risk of developing chronic pancreatitis seems to be in the compound heterozygote state where patients have one cystic fibrosis severe mutation (CFsev) and one cystic fibrosis mild-variable mutation (CFm-v). In one specific study involving 39 patients,

compound heterozygotes were found to have a 40-fold increase in the risk of developing pancreatitis. The addition of the N34S SPINK1 polymorphism to the compound heterozygote state increased the risk substantially further.²⁹

Management

The treatment of pancreatitis resulting from a genetic predisposition does not differ substantially from that of other forms of pancreatitis. It is recommended that patients abstain from any form of alcohol and tobacco consumption. Chronic pain with persistent dilation of the main pancreatic duct in patients with hereditary pancreatitis can be addressed surgically.⁷ Surgical interventions in the pediatric population should be performed with caution. Overall, the consequences for treatment and follow-up for patients with mutations of PRSS1, SPINK1 or CFTR are limited. There is a 40% chance of increased pancreatic cancer risk in patients with the PRSS1 mutation by the age of 70 years.

CONCLUSION

The genetic basis of pancreatitis and its implications present a fascinating perspective in our understanding and approach at assessing and treating the disease. Much more remains to be discovered about the interactions between these genes and other environmental risk factors. With no cure for the disease, medical management at this time focuses on symptom-based treatment and lifestyle changes that may reduce the risk of potential complications including the development of pancreatic cancer. Further research is warranted in order to better understand the pathogenesis behind these polymorphisms in pancreatitis patients.

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