Genetic Insights into Pancreatitis: Unveiling the Path of Genetic Determination

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ABSTRACT

Pancreatitis is a debilitating condition marked by inflammation of the pancreas, which can lead to substantial illness and death rates. While the etiology of pancreatitis is multifactorial, genetic factors have a considerable impact on disease development and evolution. Over the past few years, progress in molecular genetics and molecular biology has resulted in the discovery of numerous genetic variations that are linked to a higher likelihood of developing pancreatitis. This article reviews the current knowledge of the genetic underpinnings of pancreatitis and its impact on disease pathogenesis. We also discuss the potential clinical implications of genetic testing for pancreatitis, and the need for further research to identify new therapeutic targets and personalized treatment strategies for this complex disease.

INTRODUCTION

Pancreatitis being a heterogeneous disease[37], is a major contributor to illness and death on a global scale, with a reported incidence of 10-50 cases per 100,000 individuals per year[16]. Pancreatitis can be categorized into two distinct groups: acute pancreatitis (AP) and chronic pancreatitis (CP). AP entails the swift initiation of inflammation that can resolve spontaneously or progress to CP. CP, on the other hand, is a persistent inflammation of the pancreas resulting in fibrosis and a decline in pancreatic capability[60]. The etiology of pancreatitis is multifactorial, with several environmental and genetic factors implicated in disease development and progression[5]. This research article aims to investigate the extent to which genetic factors contribute to the development and progression of pancreatitis by reviewing existing literature on the subject, including studies on the genetic mutations and variations that have been associated with increased risk for pancreatitis, as well as those that may influence disease severity and response to treatment.

GENETICS AND PANCREATITIS: AN OVERVIEW

- **Genetic Factors in Pancreatitis**

The role of genetic factors in pancreatitis has been recognized for several decades. The discovery of the first

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genetic variant associated with pancreatitis, the cationic trypsinogen (PRSS1) gene mutation, was reported in 1996[43]. Since then, several genetic variants have been discovered which are linked to a heightened likelihood of developing pancreatitis. These variants are involved in various biological pathways, including pancreatic development, inflammation, and autophagy[48].

- **Common types of pancreatitis and their genetic associations**

1. **Hereditary pancreatitis**:

Hereditary pancreatitis is a rare genetic disorder that is characterized by repeated instances of inflammation within the pancreas, potentially resulting in damage and scarring of the organ over time[50]. This condition is caused by mutations in the PRSS1 gene, which imparts guidance for the production of a digestive enzyme called trypsin[2]. The PRSS1 gene is located on chromosome 7q35, and mutations in this gene are inherited in an autosomal dominant manner[43], implying that an individual requires just a single copy of the altered gene inherited from a single parent to manifest the condition. Each child of a parent with hereditary pancreatitis has a 50% chance of inheriting the mutated gene.

However, not all people who inherit the PRSS1 mutation will develop hereditary pancreatitis, and it is thought that additional genetic and environmental elements might also contribute to the emergence of the condition[3]. In addition to PRSS1 mutations, other genetic factors have been implicated in the development of hereditary pancreatitis. For example, mutations in the SPINK1 gene have been found in some people with hereditary pancreatitis[7]. The SPINK1 gene provides instructions for making a protein called pancreatic secretory trypsin inhibitor (PSTI), which regulates trypsin activity in the pancreas. Mutations in this gene can lead to decreased levels of PSTI, which may contribute to the development of hereditary pancreatitis[29].

Other genes that have been implicated in the development of hereditary pancreatitis include the cystic fibrosis transmembrane conductance regulator (CFTR) gene and the chymotrypsin C (CTRC) gene[3][68]. Mutations in the CFTR gene are associated with cystic fibrosis, a condition that can also affect the pancreas, while mutations in the CTRC gene have been linked to an increased risk of developing chronic pancreatitis.

2. **Familial pancreatitis**

Familial pancreatitis is used to depicts households in which the occurrence of pancreatitis exceeds what would be anticipated by random chance. To make a diagnosis, it is necessary to have a minimum of two or more immediate or extended family members who have idiopathic pancreatitis not caused by obstructions or environmental factors. It is necessary to consider and rule out other potential sources of pancreatitis, such as hereditary pancreatitis. Familial pancreatitis is also inherited in an autosomal dominant pattern with incomplete penetrance[66]

3. **Alcoholic pancreatitis**

Alcoholic pancreatitis is a condition where the pancreas, a gland that has a pivotal function in digestion and blood sugar regulation, becomes inflamed due to long-term alcohol abuse[37]. This inflammation can lead to severe abdominal pain, nausea, vomiting, and other complications. Alcohol consumption is a common cause of pancreatitis, but genetics can also play a role in its development[35]. Variations in genes such as the CYP2E1 gene and the ADH1B gene can affect how the body metabolizes alcohol, increasing the risk of developing alcoholic pancreatitis[41][67]. Another genetic factor that has been linked to alcoholic pancreatitis is a variant in the CTRB1 gene (encodes for the enzyme chymotrypsinogen B1, which is a

precursor to the digestive enzyme chymotrypsin), which codes for the enzyme chymotrypsinogen[51]. This variant has been found to be more prevalent among people with alcoholic pancreatitis compared to the overall populace and is thought to be associated with an increased risk of developing the condition. Other genetic factors that may play a role in the development of alcoholic pancreatitis include mutations in the CFTR gene, which is associated with cystic fibrosis[10].

4. **Idiopathic pancreatitis**

This type of pancreatitis has no known cause and may be due to a blend of genetic and environmental factors[3]. The prevailing consensus now acknowledges that genetic variants constitute the principal determinant for idiopathic chronic pancreatitis. Some studies have suggested that variations in genes such as the CFTR gene and SPINK1 gene have the potential to increase the risk of developing idiopathic pancreatitis[16].

Genetic Risk Factors for Pancreatitis

Numerous genetic markers have been pinpointed in relation to pancreatitis, and understanding these genes can provide valuable insights into the pathogenesis and potential treatment strategies for the disease. Here's a review of some key genes associated with pancreatitis:

PRSS1 (Protease Serine 1)

Studies have shown that over 60% of large families with multiple generations affected by HP have pathogenic mutations in the PRSS1 gene[33]. Currently, over 40 different mutations in the PRSS1 gene have been identified[22]. Among these mutations, R122H, N29I, and A16V are the most frequently occurring variations linked with the development of HP[50].

The R122H mutation is the predominant genetic variation found in cases of hereditary pancreatitis among all PRSS1 mutations[23].It results in the substitution of an arginine (R) amino acid with a histidine (H) at position 122 of the trypsinogen protein. This interferes with the natural process of CTRC-mediated trypsinogen degradation, preventing the normal breakdown of trypsinogen[30]. On the other hand, the N29I mutation involves the substitution of an asparagine (N) amino acid with an isoleucine (I) at position 29 of the trypsinogen protein. This mutation alters the protein's structure, potentially affecting its enzymatic activity and stability and has several distinct effects on the biochemistry of trypsinogen, all of which contribute to a significant production of trypsinogen autoactivation[2]. Additionally, The A16V mutation results in the substitution of an alanine (A) amino acid with a valine (V) at position 16 of the trypsinogen protein leading to the enhancement of the sensitivity of trypsinogen's activation peptide to CTRC-mediated processing, thereby promoting an increased level of autoactivation[28].

The PRSS1 gene is the precursor of trypsin, a major digestive enzyme in the pancreas[43]. Under normal conditions, the pancreas has protective mechanisms to prevent excessive trypsin activation. However, abnormal PRSS1 variants result in the production of trypsin that is turned on too early or not easily broken down, promoting a spike in autoactivation of defective trypsinogens and a markedly raised trypsin function within the pancreas. The majority of disease-causing PRSS1 variants in hereditary pancreatitis impact the regulatory regions of trypsin. These regions consist of calcium-binding sites that play a role in activating and shaping its structure[29]. Proper control of trypsin activity is crucial in defending against pancreatitis development.

Multiple European studies on hereditary pancreatitis (HP) revealed that among 418 individuals with HP, 78% had PRSS1 mutations, while 17% were negative and 5% were untested[22]. In a French survey, HP prevalence was 0.3/100,000, and 68% of eligible individuals were PRSS1 carriers, with the R122H variant

being most common[49]. Patients without PRSS1 mutations suggest additional genetic factors contribute. In a Danish cohort, PRSS1 mutations were identified in 15% of individuals with pancreatitis of unknown origin. Overall mutation prevalence was 38%, including other gene mutations[25]. PRSS1-related hereditary pancreatitis typically starts between 10 and 12 years old[64]. Acute pancreatitis occurs in 69% of carriers, progressing to chronic pancreatitis by ages 22-25[29] where calcification arises in about 61% of patients[50]. R122H carriers manifest at a younger age with more pronounced symptoms, with higher rates of exocrine and endocrine failure[22].

PRSS2 (Anionic trypsinogen)

Despite PRSS1 and PRSS2 having about 90% amino acid in common, no HP inducing variants of PRSS2 have been found[30][67]. PRSS2 mutation rather plays a crucial function in safeguarding the pancreas by reducing PRSS1 expression, resulting in a lower risk of recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP)[65]. CP does not exhibit any PRSS2 mutations could most likely be due to the swift breakdown of anionic trypsinogen by CTRC inhibiting the activation of enzymes within the pancreas[24]. Additionally, a protective variant known as p.G191R has been identified. This variant functions by enhancing the degradation of anionic trypsinogen by trypsin, thereby providing a safeguard against the onset of chronic pancreatitis[31].

SPINK1 (Serine Protease Inhibitor Kazal Type 1)

The SPINK1 protein plays a crucial role in suppressing the premature activation of zymogen, which helps protect the pancreas from self-digestion[70]. When functioning correctly, it has the ability to suppress approximately 20% of pancreatic trypsin activity [26]. Over 30 different mutations in the SPINK1 gene have been documented so far since it was first discovered in 1948[29]. In studies conducted in the United States and Europe found that N34S followed by P55S are commonest SPINK1 gene mutations[42]. Interestingly, the connection between the prevalent p.N34S SPINK1 mutation and CP was establish since the year 2000[66].

Worldwide, about 2% of people were found to have SPINK1 mutation[15]. When specifically considering European populations, p.N34S variant significantly raises the risk of chronic pancreatitis (CP) by factor 10[13]. It's worth noting that less than 1% of individuals who carry one copy of the SPINK1 gene mutation develop CP without the presence of additional influencing elements, indicating that multiple factors contribute to the development of pancreatitis[29][62]. While SPINK1 mutations are infrequently linked to hereditary pancreatitis (HP), they rather have the potential to elevate the likelihood of contracting the disease by 23%[48]. Researchers, such as Witt et al.[66] proposed that the manner in which traits of SPINK1 mutations are passed down follows an autosomal recessive pattern. Several research studies indicate that individuals carrying either two copies (homozygous) or one copy (heterozygous) of the N34S variant in the SPINK1 gene experience similar ages of disease onset and severity[47]. CFTR gene and others harmful genetic variants however increase disease severity and onset[53].

CTRC (Chymotrypsin C)

CTRC gene produces chymotrypsin C, which is an enzyme that facilitates the breakdown of trypsin by specifically cleaving the amino acid bonds at various locations[42]. The early activation of trypsin can be eliminated by CTRC through its interaction with calcium-bound particles[4]. CTRC mutations hence interfere with the elimination of trypsin and diminish its protective role in reducing the likelihood of developing chronic pancreatitis[58].

Roughly 4% of individuals diagnosed with chronic pancreatitis (CP) harbor mutations in the CTRC gene. However, it is worth noting that CTRC gene mutations do not directly cause CP; instead, they must be

combined with other genetic mutations, such as CFTR or SPINK1, in order to contribute to the development of CP[52]. G60G is the most common CTRC genetic variation and is significantly associated with the transition from recurrent acute pancreatitis (RAP) to CP, particularly among individuals who smoke[32].

CFTR (Cystic Fibrosis Transmembrane Conductance Regulator)

The groundbreaking discovery by two separate investigations of the correlation between CFTR mutations and CP dates back to 1998[9][55]. Genetic mutations in individuals with cystic fibrosis (CF) result in either the absence or dysfunction of the CFTR protein. This, in turn, leads to the production of thick and sticky mucus, which can block the pancreatic ducts[44]. Consequently, the normal flow of pancreatic enzymes from the pancreatic gland to the small bowel, where they are vital for digestion, becomes hindered[44].

Despite the identification of over 1600 CFTR mutations up until now[11], approximately 1.5% of CF patients actually develop pancreatitis[48]. Where the presence of additional mutations like SPINK1 or CTRC significantly increases the susceptibility to pancreatitis[57]. Cystic Fibrosis (CF) is frequently observed in individuals of Northern European heritage, affecting over 1 in every 2500 people[54]. Interestingly, CFTR mutations alone that is without PRSS1 mutation was found in about 35% of families with CF affected by pancreatitis[11].

Even in cases where CFTR mutations do not lead to typical cystic fibrosis or exhibit low penetrance, they still enhance the likelihood of pancreatitis by 2 to 5 times[3][9]. F508del stands out as the predominant CFTR mutation related to CF[45], found in 70% of CF cases and contributing up to 40% of CFTR variants in individuals with hereditary pancreatitis[29]. Several studies have shed light on the relationship between CFTR mutations and pancreatitis. For instance, in a study conducted in Germany, when comparing 67 individuals diagnosed with idiopathic pancreatitis, researchers identified 25 abnormal CFTR alleles[61]. Meanwhile, a Polish study conducted on children with CP revealed that 16.5% of them carry CFTR mutations[67].

CLDN2 (Claudin-2)

Claudin-2 is a protein that plays a crucial role in the formation and regulation of tight junctions, which are specialized structures that seal the gaps between cells in various tissues[64]. These tight junctions control the transfer of ions and molecules among neighboring cells, helping to preserve the structure and permeability of tissues.

Research conducted on animal models has provided evidence that the Claudin-2 (CLDN2) gene can be activated in acinar cells under conditions of stress[39]. While genetic variations in the CLDN2 locus are not directly associated with an elevated risk of acute pancreatitis (AP) and recurrent acute pancreatitis (RAP), they rather do play a significant role in the progression from RAP to chronic pancreatitis (CP)[40]. It is noteworthy that these genetic variations are mostly associated with CP caused by alcohol consumption[29]. Notably, this particular genetic difference presents a higher likelihood of pancreatitis resulting from alcohol consumption in males, about twice as higher compare to females[29][38].

CASR (Calcium-Sensing Receptor)

This mutation is seen as factors that influence CP, rather than being the primary reason behind it. The CASR gene encodes for the calcium-sensing receptor, which plays a crucial role maintaining the internal stability of calcium[29][36]. Mutations in this gene have been implicated in CP risk mostly in alcoholic patients in a study published in 2008[66] and many more studies. However, a more recent study conducted in 2021, which involved a Hungarian population comprising 337 patients and 840 controls, discovered that there was no association between CP and the two common mutations, namely p.A986S and p.R990G, as well as three

other minor mutations.[59]. Moreover, an additional study also published in 2021 about 339 French and 542 German who were afflicted with CP, along with 1025 German controls, arrived at the conclusion that the three primary CASR variants namely, p.A986S, p.R990G, and p.Q1011E do not elevate the risk of developing CP.[14].

In summary, the existing evidence does not substantiate a definite involvement of CASR variants in the development of CP.

CONCLUSION

Pancreatitis is a complex disease that is influenced by both genetic and environmental factors. Recent advances in genomics and molecular biology have led to the identification of several genetic variants that are associated with an increased risk of pancreatitis. The identification of these variants has provided insight into the underlying mechanisms of disease development and progression and has significant clinical implications for disease management and personalized treatment strategies. Further research is needed to identify new genetic variants and biological pathways involved in pancreatitis and to develop new therapeutic targets for this debilitating disease.

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