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Genetics of Acute and Chronic Pancreatitis

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Abstract

Purpose of review—Acute pancreatitis (AP), recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) are interrelated and progressive inflammatory disorders of the pancreas with highly variable and complex susceptibility, severity and outcomes. The role of genetics in AP, RAP and progression to CP within a new framework is needed.

Recent findings—The first genome-wide association study in pancreas has been published with genome-wide significance linked with non-coding variants at the *PRSS1-PRSS2* locus on chromosome 7 and the *CLDN2* locus on the X chromosome. A new personalized medicine paradigm is considered to facilitate organization of genetic and other susceptibility risk compared to risk of disease progression or resolution and risk of complications.

Summary—A new framework for organizing multiple, complex data sets is emerging. The role of genetics in the context of other variables, is important in understanding susceptibility to RAP and in the modification of disease severity and progression to CP. Questions of when to order testing, what to order and how to use the data in real time remains an area for future research and development.

Keywords

Acute Pancreatitis; Chronic Pancreatitis; genetics; next generation sequencing; personalized medicine

Introduction

Acute pancreatitis (AP) is a syndrome of sudden inflammation in the pancreas characterized by epigastric abdominal pain, elevated levels of pancreatic digestive enzymes in the blood and/or evidence of inflammatory changes of the pancreas on abdominal imaging studies.(1) AP is the leading cause of digestive system-related hospital admissions in the US with an annual health care cost of approximately 2.6 billion dollars.(2) The most common causes of AP include gallstones and alcohol which account for approximately two-thirds of cases.(3,

4) Other less common etiologies include; metabolic, drug-induced, infectious, anatomic anomalies or tumors, trauma, collagen-vascular disease, autoimmune and genetic causes, in addition to those that remain idiopathic.(4, 5) Patients in whom the underlying cause of AP is not addressed, or in whom the initial evaluation fails to identify a treatable etiology, are likely to develop recurrent acute pancreatitis (RAP)(4, 6), and eventually chronic pancreatitis (CP).(7)

The pancreas is an unusual organ in that a minor injury can lead to a large local, and in some cases, a systemic inflammatory response. Trypsin, one of the key enzymes that mediates this response, does so by catalyzing premature zymogen activation within the pancreas, resulting in tissue autodigestion and an acute inflammatory response.(8) Why inflammation is mild in some patients and more severe in others, with progression to a systemic process that can lead to organ failure and mortality remains unknown. It is also unclear as to why some individuals with gallstone disease or who consume large amounts of alcohol develop AP and others do not.(9) These observations lead to the question of whether genetic variants and/or other factors are responsible for the observed differences in susceptibility to AP in some patients, modify disease severity or determine progression to CP.

The medical management of such a complex disease involves an organized holistic approach. This process includes a thorough history and physical examination, laboratory studies and abdominal imaging in addition to possible genetic testing. In this review we will discuss the approach of faculty members within the Pancreas Center of Excellence at the University of Pittsburgh Medical Center, with a special focus on the various genetic etiologies of RAP and CP and the timing of genetic evaluation.

Features of AP

AP can have a highly variable clinical course ranging from a mild, self-limited disease to a more severe systemic inflammatory process that can lead to pancreatic necrosis, multi-organ failure, and possibly death.(1, 8) Prevention of repeated episodes of AP can be beneficial by reducing the inconvenience of mild RAP, preventing severe AP, or slowing progression to CP; a potentially disabling form of the disease.(7) The initial evaluation following the index episode should therefore help to identify the underlying etiologic factors to prevent disease recurrence and progression.(4, 6, 7)

Initial Evaluation and Management of AP

AP is defined by a combination of at least two the following criteria: (i) abdominal pain characteristic of AP; (ii) serum amylase and/or lipase 3 times the upper limit of normal; and/or (iii) characteristic findings of AP on abdominal CT scan.(1) The patient's history is very important, and should include the following: nature, duration and severity of symptoms, alcohol consumption, smoking, prior episodes of biliary colic, medication intake, abdominal trauma, personal history of diabetes mellitus (with subtype and treatment), hypercalcemia, hypertriglyceridemia or autoimmune disorders. Prior surgical and endoscopic history, particularly with regards to pancreatic surgery, cholecystectomy or biliary sphincterotomy is also critical. The initial clues to potential genetic risk include a family history of AP, RAP,

CP, cystic fibrosis (CF) and atypical CF (e.g. chronic sinusitis, male infertility), hypertriglyceridemia or pancreatic cancer.(4, 10)

Blood work is obtained as biomarkers of etiology, severity and for prognostications.(11) Physical exam should specifically include mental status testing, cardiovascular and fluid status, pulmonary edema, abdominal tenderness, presence of bowel sounds as part of the evaluation. Initial imaging studies to consider include a chest x-ray to detect pulmonary edema and/or pleural effusions which are consistent with vascular leak syndrome(12). Although a computed tomography (CT) scan is useful for diagnosis, identifying pancreatitis risk factors and for evaluating disease complications it is generally not required to make the diagnosis of AP and should be delayed.(4, 6) A careful assessment of signs of systemic inflammation and organ dysfunction with institution of supportive measures as needed represents the current standard of care.

Genetic variants affecting the severity of acute pancreatitis

It remains unclear as to why some patients progress from mild AP to severe AP and others do not. One potential factor could be the production of pro-inflammatory cytokines that are affected by genetic polymorphisms. Association studies of cytokine and chemokine gene polymorphisms with pancreatitis severity have shown differing results in different populations. Examples include monocyte chemoattractant Protein-1 (MCP-1), CC chemokine (also known as C-C motif ligand 2; CCL2) and IL-8.(13–15) Studies on the TNF- α promoter polymorphisms have been variable, with meta-analysis of –308G>A and –238G>A showing no association.(16–21) This is consistent with our own studies, however we also evaluated the –1031C and –863A alleles and found them to be associated with progression to multi-organ failure.(22)

Most of these genetic studies suffer from small sample size, limited variant analysis, different patient populations, and variable effect measures. Future studies should thus incorporate large numbers of well phenotyped patients with AP and its complications and focus on linking polymorphisms to proof of functional effects.

For these test to be useful in classifying patients into risk groups the testing must be performed prior to the episode of AP and available so that the results can be integrated into decision analysis. Next generation sequencing (NGS) is a new technology that provides sequencing of all exons, or the whole genome of a patient in a single test. This data is valid for the life of the patient. If NGS is done and stored, then current and future genetic risk information is already stored. The key to usefulness in the future will be rapid access and interpretation.

Treatment of acute pancreatitis

Given the absence of effective pharmacologic treatment, the management of AP remains supportive.(23) Some problem-specific treatments include endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy for impacted gallstones,(24) and treatment of hypertriglyceridemia from any cause.(25) Enteral feeding should be initiated as early as possible to help limit SIRS and reduce infections.(26) While genetic factors may

increase both the risk of developing AP(27) and predisposition to systemic inflammation(22) current management guidelines continue to be limited and primarily supportive.(1, 28)

Premise and Perspective for Use of Genetic Information in Managing Pancreatic Diseases

Technological breakthroughs such as high-speed computers, massive parallel DNA sequencing (i.e. NGS) and chip genotyping are considered *disruptive technologies* because the resulting massive data sets cannot be interpreted within the context of the current medical paradigm –a new paradigm is required. (29) The old paradigm is the “germ theory” of disease in which a single factor caused a complex disease, such as a germ causing inflammation, pain and organ dysfunction. However, many diseases have inflammation without infection, or dysfunction without pathology (e.g. functional disorders). We now know that complex disorders are associated with many genetic, metabolic and environmental factors that, alone, are neither necessary for the disease to develop, nor sufficient to cause the disease by themselves.(29) Furthermore, many attempts to find single agents to treat complex disorders have failed, with billions of dollars of investment resulting in few if any true breakthroughs.(30)

Personalized medicine is a new form of medicine that has the potential to utilize these new technologies by structuring large amounts of data in disease models based on genetic variants and other mechanistic factors rather than the resulting pathology or symptom complex (i.e. syndromes). (29) The power of such modeling and simulation is that disease etiology, progression and outcome predictions under various treatments options can be individualized. (31) These ideas however, have been difficult to apply in most complex diseases, except for the pancreas.

The pancreas is a simple organ that is protected from most environmental factors and therefore serves as an ideal organ for the development and application of the evolving concepts of personalized medicine. (29, 31, 32) Growing knowledge of the biology of acute and chronic pancreatitis, better patient phenotyping and classification systems, and new tools for rapidly assessing genetic variants and biomarkers can now be used to model these complex and dynamic processes. This can ultimately aid in the prediction of which treatments will lead to optimal outcomes. While the application of genetic information, including next generation sequencing, has not yet been applied to the severity or complications of the first episode of AP, it has become valuable in evaluating RAP and CP. (33)

The connections between AP, RAP and CP

AP can progress to CP at a variable rate based on the frequency and severity of insults to the pancreas and the type of immune response. (9) CP is frequently diagnosed based on imaging studies and pancreatic function testing although histologic evidence of irreversible damage of the pancreas in the setting of ongoing inflammation remains the most definitive means of diagnosis.(34, 35) Since CP is irreversible, physicians should focus on disease prevention, which requires knowledge of the underlying disease etiologies and mechanisms of

progression. The sentinel acute pancreatitis event (SAPE) hypothesis highlighted the importance of the index episode of AP as an early warning that the patient may be on a pathway towards CP.(9, 36) This inciting (sentinel) event is modeled as an episode of AP of sufficient severity to initiate an inflammatory process leading to infiltration of the pancreatic parenchyma by resident macrophages and activation of stellate cells. This is the “first hit” of a “two hit” model. The pancreas thus becomes primed for the development of fibrosis, which occurs with subsequent episodes of pancreatitis or oxidative stress (second hits) that propagate this inflammatory response resulting in the deposition of collagen.(9, 37) This model also allow for identification and modeling of risk factors that may be present in a pre-AP phase that are important in the development of CP; namely genetic variants, smoking, alcohol consumption.(9)

A recent population-based epidemiology study has provided strong supporting evidence regarding the progression from AP to RAP, and RAP to CP, with alcohol having the strongest effect, biliary etiology being the lowest, and genetic and idiopathic etiologies being intermediate.(7) Based on the SAPE hypothesis the sentinel episode of AP serves as a warning sign for the future development of RAP and CP and therefore warrants thorough investigation for preventable causes to help avoid repeated insults to the pancreas and subsequent development of CP.

Limiting progression from AP to RAP and CP

We believe that prompt attention to the underlying etiology and modifying factors in patients diagnosed with AP, in addition to successful interventions help limit the progression from AP to RAP and CP. New data supports this hypothesis.

Alcohol use and smoking

Data from the North American Pancreatitis Study 2 (NAPS2) and other large studies have clearly demonstrated that alcohol consumption and smoking are strong independent risk factors for both RAP and CP.(10) Furthermore, there is now evidence that incidence of RAP and progression to CP are significantly reduced if patients stop alcohol use or smoking.(38–40) Therefore, strong behavioral interventions aimed at smoking and alcohol cessation are strongly recommended.

Genetic and Metabolic causes of RAP and CP

Patients with genetic and other risk factors for AP spend the majority of their lives *not* experiencing AP. Individuals may live for many years with a high risk of pancreatic injury from genetic, metabolic or environmental factors prior to a sentinel episode of AP.(9) Susceptibility is often linked to a lower threshold for trypsin activation or sustained trypsin activity within the pancreas. The first direct evidence for this was the identification of rare gain-of-function mutations in the *PRSS1* gene that were associated with an increased risk of RAP and CP as is seen in hereditary pancreatitis.(41) Newer evidence of the overall importance of trypsin in RAP comes from a recent genome-wide association study (GWAS).(42) A gene locus that includes the *PRSS1-PRSS2* genes that encode both cationic and anionic trypsinogen was shown to be associated with reduced expression of trypsinogen and

a lower risk of developing RAP and CP.(42) These findings effectively validated the hypothesis that in many cases AP associates with trypsin gene expression and activity. Other genetic risk factors linked with trypsin activation and survival within the pancreas include the cystic fibrosis gene (*CFTR*), (43–45) the serum protease inhibitor Kazal type 1 gene (*SPINK1*), (46–48) the chymotrypsinogen C gene (*CTRC*) (49) and the calcium sensing receptor gene (*CASR*). (50) A new study confirmed a role for the gamma-Glutamyltransferase 1 Gene (*GGT1*) and risk for CP. (51) Blood group type has also been reported to affect risk of CP in patients with other risk factors (52), but this is yet to be confirmed. The details of these genetic factors in reference to pancreatitis have recently been reviewed. (27)

The finding of genetic variants in patients with AP or RAP has significant clinical implications for patients. Presence of gain-of-function *PRSS1* mutations such as p.N29I or p.R122H suggests that the patient has hereditary pancreatitis, and that a further invasive work-up may be unnecessary. Patients with pancreatitis and *PRSS1-PRSS2* low-risk genotype however, should likely undergo a more thorough evaluation for other putative etiologies of AP. Identification of high-risk genetic factors could therefore end additional clinical testing to determine the etiology of AP. Genetic results also have implications for future health and also potential risk for blood relatives. Genetic counselors play a central role in guiding these patients (53).

CFTR variants are more complex with compound heterozygous *CFTR* mutations resulting in atypical CF phenotypes. In other cases *CFTR* variants occur along with *SPINK1* mutations, (45) *CTRC* mutations, (54) *CASR* mutations, (27) or with pancreas divisum. (55) Patients with compound *CFTR* mutations may have atypical cystic fibrosis and referral to a CF center should be considered. New medications that can potentially restore *CFTR* molecule function (27, 56) are currently being evaluated^{27, 51} but remain expensive and untested in pancreatic disease.

A number of metabolic disorders also increase the risk of AP through various mechanisms. Obesity has been identified as a predictor of severe disease in patients with AP. Patients with higher BMIs (e.g. >30) are more prone to develop organ failure, pancreatic necrosis and mortality. (57) Mutations that lead to loss of function in the lipoprotein lipase (LPL) gene are the most common causes of hypertriglyceridemia and subsequently increase the risk for AP. (58) Other genetic variants that result in severe hypertriglyceridemia include mutations in the *APOA5*, *APOC2*, *GPIHBP1* and *LMF1* genes. (59) Although hypertriglyceridemia is a risk factor for AP, pancreatic injury appears to require the release of fatty acids, largely through the action of pancreatic lipase, which have pro-inflammatory effects that induce cell necrosis. (60) Hypercalcemia is also known to increase the risk for AP. Animal studies indicate that pancreatic stimulation is required for hypercalcemia to cause AP. (61) Loss-of-function mutations in *CASR* are associated with familial hypercalcemia syndromes and increased risk of AP in a small subset of patients. Felderbaur et al found that patients with familial hypercalcemia, only developed RAP/CP in the presence of *SPINK1* N34S mutations. (50) Others have identified an increased risk with *CASR* and *CFTR* mutations. (27) In contrast, Muddana et. al demonstrated that the gain-of-function *CASR* p.R990G

mutation increase the risk of developing CP with moderate to heavy alcohol consumption.
(62) Therapeutic trials to minimize the effects of these variants have not been reported.

Biliary Pancreatitis

Gallstones continue to represent the most common identifiable cause of AP.(7) Patients with AP in whom an ongoing biliary obstruction is suspected but not confirmed should be considered for a magnetic resonance cholangiopancreatography (MRCP) to identify and characterize the cause of obstruction.(63) Note that CT and MRI images use volume averaging, such that small filling defects may be invisible using these techniques. In recent years, endoscopic ultrasound (EUS) has also been utilized as a relatively non-invasive test for the evaluation of choledocolithiasis.(64) Due to its higher accuracy in detecting choledocolithiasis, EUS can be performed in patients with a suspected biliary etiology, even when an MRCP fails to revealing the etiology of biliary obstruction.(65) Moreover, EUS can help identify other potential etiologies for AP including pancreas divisum and pancreatic neoplasms.(66, 67) Patients found to have evidence of choledocolithiasis and/or cholangitis should be considered for endoscopic retrograde cholangiopancreatography with sphincterotomy and clearance of the duct.(24) Recent data also shows significant benefit for cholecystectomy during the index admission in patients with mild biliary pancreatitis due to the increased risk of recurrence.(68) No guidance is available for the role of cholecystectomy in patients with AP of uncertain etiology.

Several societies and consensus panels currently recommend that patients with mild AP undergo a cholecystectomy, or biliary sphincterotomy if poor surgical candidates, prior to discharge from the hospital.(1, 28) Although cholecystectomy is generally a safe procedure, it is not without inherent risks and adds significant cost to the management of AP. New studies are needed to objectively determine which patients would most benefit from cholecystectomy, and which patients would not. For example, patients with a genetic susceptibility to AP and RAP represent an interesting dilemma since gallstones or sludge may not be the underlying cause of specific episodes of AP. With the relative low cost of DNA sequencing using NGS technology, it is becoming reasonable to consider delaying cholecystectomy in selected patients until after genotyping results are available, as this data will help formulate a rational decision guided by the patient's overall clinical presentation and underlying risk factors.

Autoimmune pancreatitis—Autoimmune pancreatitis differs from other forms of AP in that the immune response is likely due to autoantigens rather than an acute inflammatory response to injury. These patients therefore rarely develop a sudden onset of severe pain with elevated levels of pancreatic digestive enzymes in the blood, or risk of multi-organ failure and death. This topic has been reviewed elsewhere.(69–71) Treatment of autoimmune pancreatitis is targeted at the immune system with the utilization of steroids and other immune-modulating drugs.

Rapid Progression from AP to CP

Yadav estimates that among AP patients with an alcohol etiology, 30–35% will develop RAP, and 15–20% will develop CP.(72) The rate of progression from the first episode of AP

to CP has also been calculated on a population basis.(7) The data suggest that the risk of RAP differs based on the etiology of AP, with alcohol providing the highest risk, idiopathic and genetic being intermediate and biliary being the lowest risk; likely due to early cholecystectomy. New genetic findings may shed some light onto the progression from AP to CP, especially in patients with alcoholism. Our recent GWAS identified a genetic variants at the Claudin-2 (*CLDN2*) locus that was strongly associated with CP, but not with RAP.(42) As risk variant was common, we interpreted the finding as a disease modifier that did not increase the risk of AP, but rather increased the rate of progression from AP to CP. The risk was also found to be strongly associated with alcoholic etiology in this recessive genetic model. Of note, *CLDN2* is located on the X chromosome such that the risk effect is *recessive* only in women, and appears as a *dominant* trait in men. This may partially explain the higher rate of alcoholic CP in men. The risk however is not limited to alcoholics, as individuals with this mutation and other etiologies of AP also appeared to be at increased risk.

The other well-known genetic risk factor for rapid progression to CP is the *SPINK1* N34S mutation.(73) Several studies suggest that *SPINK1* primarily increases the risk of developing RAP and CP, but not the first episode of AP.(74–76) Thus, heterozygous *SPINK1* variants could be considered moderate disease-modifying factors, while bi-allelic *SPINK1* variants produce a very high risk for progression. *SPINK1* N34S increased the risk of CP due to a variety of other etiologies, especially those that increase the risk of trypsin activation.(77)

Summary and conclusions

AP is a complex process that highlights the interplay of genetic, metabolic, anatomic and environmental elements. Although current management strategies for this disease remain fairly standardized the growing importance of underlying disease modifiers and their interactions with other factors set the stage for a paradigm shift in the management of this disease. Better understanding of the complex process and proactive, targeted therapies are anticipated to improve the outcomes of individual patients. As genetic testing results becomes more available it will help shape clinical decision-making by providing crucial information on susceptibility to disease and its progression. Preliminary data suggest that patients with AP vary in the likelihood of developing severe disease based, in part on genetics. If patient's global risks and disease mechanisms can be identified before they progress, then novel, targeted interventions can provide each patient with the best possible outcome.

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Key points

- Genetic factors influence susceptibility to acute pancreatitis
- The *PRSS1-PRSS2* locus minor allele haplotype includes non-protein coding variants that significantly protect patients for pancreatitis.
- Genetic modifying factors become important after the first episode of acute pancreatitis and may worsen the severity of acute pancreatitis, or increase the rate of progression to chronic pancreatitis.
- The *CLND2* locus minor allele on the X chromosome includes non-protein coding variants that increase the risk of progressing from acute pancreatitis to chronic pancreatitis, with highest risk in alcoholics and in males.
- New DNA sequencing technologies generate massive amounts of information from patients with complex disorders that requires a new paradigm of personalized medicine to interpret.