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Genetics of acute pancreatitis

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1. Introduction

It becomes increasingly apparent that acute pancreatitis (AP), recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) represent overlapping phenotypes of a single disease entity and the latter may begin in the guise of the former. Accordingly the genetic risk factors that have been identified for chronic pancreatitis have also been found to be of some relevance in acute and recurrent acute pancreatitis. Other inherited factors have been found to not influence disease susceptibility but rather the disease severity of AP. The most prominent in this category are genes that regulate cytokines and inflammatory response proteins. This chapter reviews the genetic changes that confer disease susceptibility as well as severity in patients with acute pancreatitis.

2. Definition and Diagnosis

Acute pancreatitis is a syndrome of a sudden pancreatic inflammation with unpredictable severity, duration, complications and outcome.
The diagnosis of acute pancreatitis requires two of the following three features: 1) *abdominal pain* consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); 2) serum *lipase activity (or amylase activity) at least three times greater than the upper limit of normal*; and 3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography (9).

The main etiologic causes of acute pancreatitis are gallstones and alcohol abuse but other rare causes include trauma, endoscopic interventions, infections and drugs or toxins. Also conditions such as hypercalcemia or hypertriglyceridemia have been suggested to increase the risk for acute pancreatitis. The onset of a “first” AP episode is caused by an acute injury of pancreatic tissue that rapidly disrupts its normal physiologic function and initiates an acute inflammatory response. Histologic damage occurs as a consequence of intra-acinar activation of digestive enzymes and a subsequent infiltration of pancreatic tissue with inflammatory cells. This pro-inflammatory cascade is normally self-limited and followed by anti-inflammatory responses which may include the activation of pancreatic stellate cells and the start of fibrosis. Clinical recovery from AP episodes is attained in most cases within 3-5 days. The etiology of acute pancreatitis can be established in approximately 75 percent of patients, leaving one in four patients with so called idiopathic acute pancreatitis. In contrast to AP as a consequence of environmental factors, inherited forms present with an earlier onset of acute or recurrent acute pancreatitis that eventually will progress to chronic disease. Here we discuss genetic mutations that have been associated with acute pancreatitis and influence the phenotype of the disease.

3. Acute, recurrent acute and chronic pancreatitis.

CP is a progressive inflammatory disease that may develop from acute to recurrent and chronic disease states. Historically, chronic pancreatitis has been associated with alcoholism and many CP patients are suspected of alcohol abuse, often unjustly (3). Today growing evidence suggests that genetic risk factors contribute substantially to the pancreatitis risk in CP patients (35, 43). In contrast to sporadic attacks of gallstone or alcohol-induced pancreatitis, hereditary forms of pancreatitis (HP) typically present in childhood with attacks of acute pancreatitis (AP) that become recurrent. Over time, HP patients with recurrent episodes of pancreatitis in the absence of precipitating factors may develop the same common complications as alcoholic CP patients, including pancreatic fibrosis, pseudocyst formation, pancreatic exocrine insufficiency (PEI) and diabetes mellitus. Large cohort studies on pancreatitis have established complex interactions between multiple genetic and environmental factors in the progression from RAP to CP. Clinical implications of genetic risk factors have not been established due to prognostic or therapeutic limitations of current genetic testing modalities.

4. Acute pancreatitis in children

There have been several studies in the last years reporting increasing incidences of acute pancreatitis among pediatric patients (49, 55, 59, 64). Current estimates range from 3.6-13.2 cases per 100,000 children, which is close to the incidence of AP in adults (59). Underlying causes may involve increased testing of amylase and lipase serum levels, more frequent emergency department visits and improved clinical awareness. The rising incidence of obesity in children may also contribute as an independent risk factor for acute biliary pancreatitis, which was once not a common etiology among children (44). A recent national survey of 55,000 hospitalized children (1-20 years old) with acute pancreatitis in the United States revealed that AP occurs more frequently in children older than 5 years (62.8% were older than 15 years) and slightly more frequently in girls (63%) than in boys (58). Hepatobiliary disease was the comorbidity condition with the greatest association with AP in this study, whereas other studies claim that the change in incidence of AP is primarily due to an increase of cases with systemic diseases and those with an unidentified (idiopathic) etiology (55).

Considerable differences exist in the etiology of AP in adults and children. Whereas 70% of cases in adults can be attributed to the gallstones or alcohol abuse, the causes of AP in children are more diverse. In a recent study by Bai et al. (7) the top 5 etiologies of acute pancreatitis in children were biliary, medications, idiopathic, systemic disease, and trauma, followed by infectious, metabolic, and hereditary causes. Not surprisingly, alcohol was not reported as a common cause of pancreatitis in children and genetic mutations were identified in about 5-8% of patients. Mutations were most commonly found in the cationic trypsinogen gene (*PRSS1*), the pancreatic secretory trypsin inhibitor gene (*SPINK1*), and the cystic fibrosis transmembrane conductance regulator gene (*CFTR*). A hereditary etiology is nearly indistinguishable clinically or by imaging from other causes of AP. Early onset, and recurrent events occurring during the first decade of life in combination with a family history may be the best indication for a genetic background of AP.

In a retrospective genetic analysis of 69 children with recurrent acute pancreatitis (RAP) or CP, Vue et al. identified 48% as a carrier of at least 1 mutation in one of the known risk genes of chronic pancreatitis: *PRSS1, CFTR* and *SPINK1* (73). Patients with mutations were more likely to have a family history but otherwise could not be identified by any mutation-specific phenotypic differences. Similar results were obtained by Palermo et al. in

a genetic analysis of 45 pediatric AP patients, of which 60% carried a least one mutation in one of the pancreatitis risk genes *PRSS1, SPINK1, CTRC* and *CFTR*. Even though the study cohort has not been completely genotyped, the authors claim that they identified a higher frequency of CFTR mutations in CP patients in comparison to RAP patients. A multinational cross-sectional study of 301 children with RAP and CP has been performed by the INSPPIRE consortium (40). 84% of children with CP reported prior recurrent episodes of AP. Sequencing analysis identified at least one mutation in pancreatitis-related genes in 48% of patients with RAP vs 73% of patients with CP. Children with PRSS1 or SPINK1 mutations were more likely to develop CP, but also ethnic differences seem to affect the disease phenotype and disease progression. A higher disease burden in CP patients might justify early genetic testing in pediatric AP patients which may also help to optimize therapeutic strategies to stop disease progression in these patients

5. Risk genes

Two decades of worldwide screening efforts have confirmed a complex network of gene-environment interactions that control or influence the development and progression of pancreatic diseases including acute, recurrent acute and chronic pancreatitis. While acute pancreatitis in most cases can be attributed to environmental factors such as gallstones or alcohol abuse, in 20-25% the etiology remains unclear. In these idiopathic AP patients genetic risk factors are found to play a major role in the onset of the disease. Most CP patients report prior episodes of AP or RAP and also hereditary chronic pancreatitis starts in most mutation carriers with a first attack of acute pancreatitis. The known genetic risk factors of CP therefore also play a role in the onset of acute and recurrent acute pancreatitis episodes and are identified in genetic association studies of AP patients, however at a lower incidence rate when compared to patients diagnosed with idiopatic CP. Most identified genetic risk factors to date are involved in the regulation and control of protease activity, starting with the initial identification of an autosomal dominant mutation in the cationic trypsinogen (*PRSS1*) in 1996 by Whitcomb (75). Candidate-gene approaches and validation studies in multiple cohorts have increased the number of pancreatitis-related risk genes, which include *CFTR, SPINK1 and CTRC* (16, 66, 69, 78, 79). Significant association with pancreatitis has also been demonstrated for sequence variants in *CPA1, CASR, and CEL (29, 50, 78).* Preliminary reports which await further validation include CLDN2 (76), CTSB (46), MYO9B (54) and UBR1 (83) or the association of an increased pancreatitis risk with ABO blood group and the so-called “secretor status”, which is determined by a mutation of the Fucosyl-transferase gene FUT2 (74). With the exception of the dominant PRSS1 mutations, most variant alleles of these risk genes are not single factor causes, but predisposing to pancreatitis and may lower the threshold for pancreatitis attacks. They predispose not only to acute pancreatitis, but to recurrent episodes or the progression to chronic disease. Additional environmental or metabolic factors are operative and relevant in the complex gene-environmental interactions that determine the disease phenotype in each individual patient.

Metabolic causes of pancreatitis are less common, but also constitute an important component of the etiologic factors of AP. They include hypercalcemia, hypertriglyceridemia, diabetes mellitus and rarely Wilson’s disease (39). Familial Hypocalciuric Hypercalcemia (FHH) was first described in the 1970s (30), which led to the subsequent cloning of the calcium-sensing receptor (*CASR*) and the discovery of its pivotal role in disorders of calcium homeostasis like FFH (61). The CaSR plays a central role in calcium homeostasis primarily by regulation of parathyroid hormone (PTH) secretion and calcium reabsorption in the renal tubular system. Pearce et al. reported in 1996 three FHH kindreds with recurrent pancreatitis and in all patients the disease was associated with missense mutations in the extracellular domain of the CaSR (60). In

acinar cells low calcium concentrations are prevalent in the cytosol, which constitutes one fail-safe mechanism in the prevention of intra-acinar trypsinogen activation. Hypercalcemia-related pancreatitis can also be secondary to primary hyperparathyroidism (PHPT) and was first reported by Cope et al. in 1957 (17). PHPT represents a non-physiological overproduction of parathyroid hormone, caused by adenoma of the parathyroid gland or multiple endocrine neoplasia (MEN) types 1 and 2A. Genetic studies provide evidence that inherited mutations in pancreatitis-related genes SPINK1 and CFTR, but not CASR were identified in 36% of hyperparathyroidism patients who developed AP (26, 27, 42). A recent review of the literature by Bai et al. (6) confirmed an association of PHPT with pancreatitis and implicates hypercalcemia, but the functional role of CaSR mutations in the context of pancreatitis has yet to be elucidated. Apparently PHTP requires multiple genetic and environmental influences to induce pancreatitis.

Another minor but significant etiologic factor of acute pancreatitis are familial disorders, including lipoprotein lipase deficiency, apolipoprotein C-II deficiency or common hypertriglyceridemia that lead to plasma accumulations of chylomicrons or triglycerides. Lipoprotein lipase catalyzes the hydrolysis of triglyceride from chylomicrons and very low density lipoprotein (VLDL) and therefore plays a central role in the regulation of the energy metabolism. Familial lipoprotein lipase deficiency prevents the enzyme from effectively breaking down triglycerides in the bloodstream and leads to chylomicronemia and consequently very severe hypertriglyceridemia. As a result, triglycerides attached to lipoproteins accumulate in plasma and tissues, leading to inflammation of the pancreas (pancreatitis), enlarged liver and spleen (hepatosplenomegaly), and fatty deposits in the skin (eruptive xanthomas). Triglyceride levels above 2,000 mg/dl should be considered a significant risk factor of developing pancreatitis (12).

The most common familial disorders associated with chylomicronemia are the type I and type V hyperlipoproteinemias (10). Hyperlipoproteinemia type I is caused by loss-of function mutations in the *LPL* gene or in the gene of its co-factor ApoC2 (18) and is inherited in an autosomal recessive pattern. The frequency of LPL deficiency in the general population is estimated to be about 1-2 per million (13). More than 100 *LPL* sequence variants have been described, most of them associated with a loss of catalytic activity (48, 63). LPL deficient patients are homozygote or compound heterozygote for these mutations and work on a systematic classification of *LPL* gene variants is ongoing (65). Also, rare mutations in other genes like the apoA5, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1) or lipase maturation factor 1 (LMF1) have been reported to affect LPL acitivity and were found to associate with chylomicronemia (1, 38).

Plasma triglyceride levels are also elevated as a result of hepatic over-production of VLDL or heterozygous *LPL* deficiency in familial hypertriglyceridemia Type IV. This monogenic familial hypertriglyceridemia is associated with only mild hypertriglyceridemia. Additional increases of plasma lipid levels in these predisposed patients may arise from unrelated risk factors like plasmocytoma, systemic lupus erythematosus and lymphomatous disease and further enhance the risk of developing pancreatitis.

Another very rare autosomal recessive metabolic disorder with associated acute pancreatitis is the congenital lipodystrophy, or Berardinelli-Seip congenital lipodystrophy (BSCL) [OMIM 269700], which has an estimated prevalence of one in 10 million. Affected patients have a generalized muscular appearance due to the nearly complete absence of fat tissue (11) and present with tryglyceridemia, hepatomegaly, mental retardation, insulin-resistant diabetes mellitus and hypertrophic cardiomyopathy (32). Hypertriglyceridemia seems to be the

predisposing factor for the development of acute pancreatitis, however the pathophysiology and genetic background of the disease have not been completely resolved. Linkage analysis identified mutations in the 1-acylglycerol-3-phosphateO-acetyltransferase 2 (*AGPAT2*), a key enzyme in the biosynthesis of triacyglycerol and glycerophospholipids (2) and in a second locus, *BSCL2/seipin* at 11q13 (45), with sequence homology to a murine guanine nucleotide-binding protein γ3-linked gene (Gng3lg). BSCL patients are homozygous or compound heterozygous carriers of loss-of function mutations.

6. Disease Severity and Prognostic Marker

Acute pancreatitis has an annual incidence of 10-30 per 100,000 population (4, 23). 80% of AP episodes have a mild course, without significant morbidity or mortality. However, in 20% of cases the disease is severe with a mortality rate of 25% to 30%.(41, 52) Increased serum levels of TNF-α, IL-1, IL-6, IL-8 and their (soluble) receptors in AP patients demonstrate an important role of these major early cytokines (14, 20) which mediate the systemic inflammatory response. Interleukin secretion is regulated at the transcriptional level which makes SNPs in the promoter region of these inflammatory mediators likely risk factor candidates for the development of systemic inflammatory response syndrome (SIRS) and organ failure. Variants *TNF*-α -238G>A, and -308G>A have been identified as transcriptional enhancers, leading to higher *TNF*-α levels (8, 77). In a recent meta-analysis on more than 1500 patients and 1330 controls from 12 published case-control studies Yang et al demonstrated that the common *TNF*-α polymorphisms (-238, -308) do not alter the risk of pancreatitis nor have they any influence on disease severity (shown only for the -308 SNP) (80).

Also some polymorphisms in the promoter regions of IL-1β, (-511C>T, -31C>T, +3954C>T), IL-6 (-634C>G, -174G>C), IL-8 (-251T>A), and IL-10 (-1082A>G, -819C>T, -592C>A) were identified to affect transcriptional activities and therefore were considered as potential risk factors for disease severity (24, 28, 51, 57). The second intron of the IL1Ra gene (IL1RN) contains in addition a variable number of tandem repeats (VNTR) of 86 nucleotides and carriers of allele 2, containing 2 repeats, face increased production of IL1Ra protein. Some genetic association studies have suggested that different IL1RN alleles are associated with specific disease risks for sepsis (25), ulcerative colitis (47) or increase the susceptibility to gastric cancer (85) . A number of limited genetic association studies have investigated these polymorphisms in different population cohorts of acute pancreatitis patients, but showed inconclusive results (19, 62, 72). The IL-1 gene cluster had been implicated in acute pancreatitis by a study of Smithies et al in 2000, but they found no association of the IL-1β+3954C>T polymorphism in a cohort of British AP patients (70). Also the IL-10 -1082A>G, -819C>T and -592C>A polymorphisms did not associate with AP among British AP patients (67). In contrast, Hofner reported a significant association of the IL-8 -251T>A polymorphism with the risk for AP (34). In a recent meta-analysis in 2013 Yin and colleagues evaluated 10 studies on IL gene polymorphisms and their susceptibility to AP (81). Their study suggests that indeed the IL-8 -251T>A polymorphism is associated with an increased risk of AP. However, no risk association could be confirmed for any of the gene polymorphisms in IL-1β, IL-6 or IL-10.

IL-1 constitutes actually a group of cytokines produced by a wide range of cells including macrophages, monocytes, fibroblasts and dendritic cells and elicits the acute phase response of the body against infection. IL-1α and IL-1β are the most analyzed members which have a natural antagonist (IL1Ra) and they all bind to the same type I IL-1 receptor (IL-1RI). Polymorphisms in IL-1 genes have been found associated with some cancers and Grave's disease (22). In a meta-analysis of 37 studies Ying recently reported that IL-1β-31C>T

polymorphism might confer susceptibility to gastric cancer in the presence of H.pylori infection, indicating gene-environment interaction in gastric carcinogenesis (82). Another analysis of 11 case-control studies by Chen et al. confirmed significant protection of the IL-1b-511C>T polymorphism from Grave's Disease in Asians, but not in Caucasians (15). These results may indicate that the pancreatitis risk evaluation of IL polymorphisms is more complex than previously thought and future studies should be carefully designed to consider genetic background differences, as well as additional gene-environment interactions.

The interleukin 1 family is also closely linked to the innate immune response and the cytoplasmic region of the type I IL-1 receptor is highly homologous to the cytoplasmic domains of the Toll-like receptors (TLRs).

TLRs play a critical role in the development of pancreatic diseases as they mediate interactions between environmental stimuli and the innate immune response. They belong to a larger family of so-called pattern-recognition receptors (PRRs) which are activated by either pathogen-associated or damage-associated molecular patterns (PAMPs or DAMPs) (37), released by activated or necrotic cells in response to stress or cell damage. TLR signaling involve Myeloid differentiation primary response protein (MyD88)-dependent pathways and upregulate the transcription of pro-inflammatory genes through the activation of NFκB (36). TLR3 and TLR4 can further activate in addition the TRIF pathway leading to the synthesis of interferon-α/β (56).

Sequence variations in TLR genes are capable of influencing the susceptibility to infectious diseases (53, 68) and the common TLR4 polymorphisms p.D299G and p.T399I were the first identified risk factors for the development of sepsis in patients (5). Variant TLR4 receptors show reduced interaction with lipopolysaccharide which may result in higher infection with Gram-negative bacteria. A first limited genetic association study by Hofner (34) did not find an association of these TLR4 polymorphisms with the incidence or severity of acute pancreatitis, but several subsequent studies in Caucasian and Asian patient cohorts had inconsistent results (31, 33, 71, 84). A meta-analysis by Zhou on 1255 cases and 998 controls did not confirm a risk factor role of TLR4 D299G and T399I polymorphisms for AP susceptibility (86). A number of additional genetic analyses have been performed, which reported significant association of TLR2 intronic mutation with susceptibility and severity of AP in Japan (71), and a risk factor role of Mannose-binding lectin (MBL) promoter variants with disease severity in Chinese patients (84). These studies await confirmation.

Also, the role of pattern-recognition receptors in the pathophysiology of mucosal barrier failure in acute pancreatitis has currently not been resolved. A disturbance of the mucosal barrier plays an essential role in the development of severe acute pancreatitis, as it allows bacterial translocation from the gut into the blood stream, which may trigger infectious complications. Nijmejier et al. performed a candidate gene approach in more than 500 AP patients from the Netherlands and Germany and reported that sequence variants in myosin IXB (*MYO9B*), a protein which seems to play a role in tight junction assembly, do not only associate with inflammatory bowel disease (IBD) and celiac disease (CD), but also with acute pancreatitis (54). Myosin IXB variants may confer a higher risk of intestinal barrier dysfunction in AP.

7. Identification of additional Risk factors

After the publication of the first pancreatitis-associated risk gene in 1996 by Whitcomb et al. the identification of genetic risk factors in pancreatitis followed for two decades mainly candidate gene approaches. These efforts were successful and contributed significantly to our current understanding of the molecular details of

pancreatic pathophysiology. Powerful new screening technologies include Genome-wide association analyses and Next Generation Sequencing studies. These techniques are rather expensive and require large cohorts of clinically well-defined individuals but they are ideally suited to identify new risk factors outside the already known or suspected signaling pathways or regulatory mechanisms involved in the pancreas physiology. To date few GWA studies have been performed, mainly in CP and RAP patients, and the study by Whitcomb et al. was able to identify one new susceptibility locus in the Claudin-2 gene (*CLDN2*) (76). A second SNP found in the *PRSS1-PRSS2* locus seems to further confirm the importance of this established risk locus for the development of pancreatitis. In a replication GWA study on European patients with alcoholic and non-alcoholic CP, Derikx and colleagues were able to confirm these findings (21). A third GWA was done by Weiss et al. on high serum lipase values in a population-based cohort of healthy individuals (74). The study reported an association of blood group B (*ABO-B*) and the non-secretor allele of the fucosyltransferase-2 locus (*FUT2*) with elevated lipase activities in asymptomatic individuals. Both loci were also identified to associate with CP. Also this study awaits confirmation in larger replication cohorts involving different ethnic populations.

These new findings and upcoming reports from current candidate-free genetic screening approaches may open the route for studies on pathological mechanisms outside the known protease-antiprotease homeostasis network. More GWA studies and NGS-data will significantly contribute to expand our current understanding of pancreatic pathophysiology and pancreatic disease and hopefully will help to identify new therapeutic strategies.

8. References

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