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Review article

Genetic susceptibility factors for alcohol-induced chronic pancreatitis

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ABSTRACT

Chronic pancreatitis is a progressive inflammatory disease of the pancreas and frequently associated with immoderate alcohol consumption. Since only a small proportion of alcoholics eventually develop chronic pancreatitis genetic susceptibility factors have long been suspected to contribute to the pathogenesis of the disease. Smaller studies in ethnically defined populations have found that not only polymorphism in proteins involved in the metabolism of ethanol, such as Alcohol Dehydrogenase and Aldehyde Dehydrogenase, can confer a risk for developing chronic pancreatitis but also mutations that had previously been reported in association with idiopathic pancreatitis, such as SPINK1 mutations. In a much broader approach employing genome wide search strategies the NAPS study found that polymorphisms in the Trypsin locus (PRSS1 rs10273639), and the Claudin 2 locus (CLDN2-RIPPLY1-MORC4 locus rs7057398 and rs12688220) confer an increased risk of developing alcohol-induced pancreatitis. These results from North America have now been confirmed by a European consortium. In another genome wide approach polymorphisms in the genes encoding Fucosyltransferase 2 (FUT2) non-secretor status and blood group B were not only found in association with higher serum lipase levels in healthy volunteers but also to more than double the risk for developing alcohol-associated chronic pancreatitis. These novel genetic associations will allow to investigate the pathophysiological and biochemical basis of alcohol-induced chronic pancreatitis on a cellular level and in much more detail than previously possible.

Alcoholism and chronic pancreatitis

Alcoholism has a high impact on the social and health care systems in both, the industrialized and developing countries. In Germany estimates show that around 10 million of the country's 82 million inhabitants are problem drinkers and 1.8 million addicted to alcohol [1]. Of the 19 million German hospital inpatients in 2012 a total of 345,034 patients were admitted for mental disorders caused by alcoholism [2]. This number would be much higher when all disorders caused by ethanol abuse were taken into account.

Chronic pancreatitis is a progressive inflammatory disease that is characterized by a loss of intact exocrine and endocrine tissue, progressive acinar cell atrophy and replacement by fibrous and fatty tissue. Pancreatic pain is the predominating syndrome and patients regularly develop exocrine and endocrine pancreatic insufficiency in advanced disease stages [3,4].

As early as 1878 alcohol was suggested to represent a risk factor for pancreatitis and it is now well established that immoderate alcohol consumption may trigger an episode of acute pancreatitis but also increases the susceptibility to develop chronic pancreatitis [5,6]. There are several pathophysiological routes that connect alcohol consumption to pancreatic damage including direct acinar cell and organellar injury, intracellular protease activation, initiation of parenchymal cell death and activation of inflammatory mediators [7–10]. Furthermore, alcohol and its metabolites promote activation of pancreatic stellate cells and extracellular matrix production that are prerequisites for pancreatic fibrosis [11,12]. In-vivo and ex-vivo experiments also indicate that the effect of alcohol alone may not be sufficient to induce pancreatitis but that its role is in sensitizing the organ to damaging stimuli and inflammatory processes that would otherwise be harmless [3]. This also implies that other factors exist that predispose the pancreas to the harmful effects of alcohol. Historically, immoderate alcohol consumption was considered to be the predominant etiological factor for chronic pancreatitis in the majority of cases (60–90%) in Western countries [13]. A dose-dependent linear correlation

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between the amount of alcohol consumed and the risk of chronic pancreatitis was proposed. However, unlike in alcohol associated liver disease, data regarding a safe threshold level for pancreatic tolerance are sparse and so far no minimal toxic dose for the development of chronic pancreatitis has been established [6].

Yadav et al. reported a significant increase in the risk of chronic pancreatitis at or above the threshold of 5 alcoholic drinks per day [14] (1 drink = 14 g of alcohol). Two meta-analyses reported a relative risk of 1.3, 1.8 and 3.2 fold for a daily alcohol intake of 25 g, 50 g and 100 g, respectively [15] or a relative risk of 2.5 when more than 4 drinks were consumed on a daily basis [16]. Some studies are limited by the small number patients included and thus were inadequately powered for a conclusive analysis. Another limiting factor for the generalizability of drinking habits as a causative factor is the fact that alcohol abuse often occurs in conjunction with cigarette smoking, another recently established risk factor for chronic pancreatitis [13,14].

Interestingly, less than 5% of heavy drinkers ultimately develop pancreatitis and recent studies suggested a lower prevalence of heavy drinkers among patients with chronic pancreatitis than previously assumed. In this context a clarification for the term "heavy" alcohol consumption requires definition. Data from the NAPS2 cohort show that only 38.4% of men and 11% of women with chronic pancreatitis were heavy drinkers, when heavy drinking was defined as a consumption of between 2 and 5 daily drinks for women and between 3 and 5 drinks for men. Even when the threshold for heavy drinking was lowered the proportion of 'moderate' and 'heavy' drinkers among patients with chronic pancreatitis was lower than reported in previous studies [14]. Results from an Italian study (PanCroInf) also reported a less frequent association of heavy alcohol intake (defined as consumption of >80 g/day for more than 5 years) with chronic pancreatitis and identified this aetiology in only 34% of cases [4].

Taken together these observations suggest that the contribution of alcohol to the pathogenesis of pancreatitis has been overestimated and other susceptibility or cofactors are likely to be required for the clinical disease onset. Several of these potential cofactors have been discussed and the most frequently investigated were obesity, dietary habits, smoking, infectious agents and genetic risk [17,18]. Furthermore, the incidence of alcohol-associated chronic pancreatitis is often clustered in families and this could further suggest a genetic predisposition [19]. Methodically, in the majority of studies the identification and characterization of potential risk genes is based on the investigation of individuals with alcohol abuse who either develop chronic pancreatitis or remain unaffected by that disorder. This means that, ideally, patients with alcoholism only differ in the variable of chronic pancreatitis.

In the last decades much progress has been made regarding the role of genetic changes in recurrent acute and chronic pancreatitis. After the initial report by Comfort and Steinberg in 1952 of an extended family, in which chronic pancreatitis followed an apparent autosomal dominant inheritance pattern and the discovery that a mutation in the cationic trypsinogen (PRSS1) gene is associated with the pancreatitis phenotype in this family [20,21], it is now well established that a variety of germline genetic changes are either causes of pancreatitis or susceptibility factors that increase the risk of developing the disease (Table 1 and Fig. 1).

In experimental animal models of acute pancreatitis it was established that premature activation of pancreatic digestives proteases is involved in the pathophysiology of the disease onset [22–25]. The suggested initiator protease trypsin, is activated by limited proteolysis from its precursor trypsinogen. Under physiological conditions this activation occurs in the small intestine but in experimental pancreatitis it begins inside of acinar cells, the

Table 1
Genetic susceptibility factors in alcoholic chronic pancreatitis.

Mutation/polymorphism	Detection method	Reference
PRSS1–PRSS2 locus		
rs10273639	GWAS (two-stage)	Whitcomb DC, Nat Genet 2012; Derikx M, Gut 2014
CLDN2-RIPPLY1-MORC4 locus		
rs7057398, rs12688220	GWAS (two-stage)	Whitcomb DC, Nat Genet 2012; Derikx M, Gut 2014
SPINK1		
p.N34S	DNA sequencing specific for N34S	Witt H, JAMA 2001
CTRC		
p.R254W, p.K247_R254del	DNA sequencing of all CTRC exons	Rosendahl J, Nat Genet 2008
ABO locus		
rs8176693	GWAS (two-stage), SNP analysis	Weiss FU, Gut 2014
FUT2 locus		
rs632111	GWAS (two-stage), SNP analysis	Weiss FU, Gut 2014
rs601338	GWAS (two-stage), SNP analysis	Weiss FU, Gut 2014

smallest functional units of the exocrine pancreas. Three isoforms of trypsinogen in the human pancreas are classified on the basis of their mobility in an electric field as cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2) and mesotrypsinogen (PRSS3). Cationic and anionic trypsinogen represent approximately two thirds and one third, respectively, whereas mesotrypsinogen accounts for only 5% of the human trypsinogens [26,27]. Trypsin can activate other zymogens in a cascade-like fashion and is therefore likely to play a central role in the initiation of an intracellular proteolytic cascade. The fact that trypsin mutations are associated with inherited forms of pancreatitis appears to support the assumption of a central role of trypsin in pancreatitis.

Using linkage and candidate gene approaches six major genes have been identified who target either acinar cells through a trypsin-dependent pathway (PRSS1, PRSS2, CTRC, CASR, SPINK) or duct cells (CFTR).

Cationic trypsinogen

Since activation of trypsinogen to trypsin has been proposed to be a critical event in the initiation of acute pancreatitis it was readily regarded as a promising candidate gene for studies exploring genetic risk factors for pancreatitis. The breakthrough publication by Whitcomb at al. in 1996 identified a mutation in exon 3 of the cationic trypsinogen (p.R122H) gene in patients with hereditary pancreatitis and proposed that this amino acid exchange renders trypsin more resistant to degradation [21]. Shortly thereafter, another trypsinogen-mutation in the same exon (p.N29I) was found in patients with recurrent acute and chronic pancreatitis [28]. Both mutations appear to be inherited in an autosomal-dominant fashion and are found in the majority of hereditary pancreatitis families [29]. The p.R122H mutation has also been reported in patients with sporadic idiopathic pancreatitis and patients carrying the p.R122H mutation were significantly younger at disease onset (mean age: 14 ± 3 years) than the remaining cohort (38 ± 2 years) [30]. Meanwhile more PRSS1 mutations have been identified in association with hereditary pancreatitis [31–34]. Taken together these observations support a critical role of the protease/antiprotease system, and trypsin in particular, in the pathogenesis of pancreatitis and would be in line with observations from experimental animal models of the disease.

Data on the potential role of mutations of the cationic trypsinogen gene as a cofactor for alcoholic chronic pancreatitis are more

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