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Genetic Testing in Acute and Chronic Pancreatitis

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Abstract

Purpose of review Premature intracellular activation of pancreatic zymogens leads to the initiation of pancreatitis, which in up to 25% leads to chronic tissue destruction, exocrine and endocrine organ failure, and a moderate increased risk of pancreatic cancer development. Whereas in many cases, the trigger of organ damage is identified, diagnostic workup in a significant number of patients does not reveal the underlying etiology of pancreatic inflammation. In these cases, alterations in different pancreatic susceptibility genes have been described to be directly or indirectly involved in disease development. In this review, we want to give an update on the most important pancreatitis risk genes and their impact on clinical diagnostics and risk stratification as well as possible treatment options.
Recent findings Genetic testing is not routinely implemented in the diagnostic workup of acute or chronic pancreatitis, as most genetic variations are not considered causative for pancreatitis development but confer increased susceptibility and genetic testing rarely changes disease management. However, in patients with recurrent pancreatitis episodes of unknown etiology after intensive diagnostic work-up, in patients with a family history of pancreatitis, relatives of patients with hereditary pancreatitis, and patients with

disease onset at young age, genetic testing and counseling is recommended. Besides well-established susceptibility genes such as PRSS1, SPINK1, CPA1, and CFTR, additional genes such as TRPV6 and rare genetic alterations in established risk genes have been recently identified which significantly contribute to the risk of pancreatitis, involving different molecular mechanisms.

Summary When genetic testing is considered, we propose screening at least for PRSS1, SPINK1, CPA1, and CFTR gene variants. The emergence of next-generation sequencing methods could also render larger gene panels possible and clinically meaningful to detect rare variants with high-risk phenotypes. Here we summarize, evaluate, and convey in the form of practical recommendations the current level of knowledge with respect to definition, etiology, and genetic diagnostics of all forms of inherited pancreatitis.

Introduction

The paradigm that acute pancreatitis (AP), recurrent acute pancreatitis (RAP), and chronic pancreatitis (CP) represent different entities has been increasingly replaced by the concept of a disease continuum with different stages of the same disease spectrum [1]. Pancreatic inflammation is thought to be initiated by premature intracellular activation of zymogens causing pancreatic damage via diverse triggers, followed by complex gene-environment interactions that in up to 25% lead to an irreversible fibroinflammatory syndrome resulting in pancreatic fibrosis and tissue damage [2, 3]. Frequently, RAP represents an intermediate stage in the years between the first episode of AP and the development of CP [3]. Whereas AP and CP significantly overlap regarding clinical manifestations and phenotypes, they differ with regard to morphology and imaging appearance as well as organ function [3]. In AP, alcohol abuse and bile duct stones are the main etiology, whereas other triggers are rare and comprise metabolic alterations (hypertriglyceridemia, hypercalcemia), physical trauma, endoscopic interventions (ERCP, EUS, balloon enteroscopy), autoimmunity, infections (e.g., coxsackievirus), toxins, and certain drugs [4]. CP is particularly caused by noxious agents, especially alcohol and smoking, and the risk of CP development is further increased by simultaneous alcohol and tobacco abuse [3].

Besides the aforementioned etiologies that are caused by exogenous factors, growing evidence has emerged that also endogenous triggers in terms of genetic alterations in different risk genes can directly or indirectly result in acute and/or chronic pancreatitis [5]. In this review, we will highlight recent developments regarding established and novel pancreatitis risk genes and their current impact on clinical reasoning as well as potential future perspectives of genetics in the diagnostic workflow of pancreatitis patients.

Acinar cell–derived susceptibility genes

Pancreatic proenzyme synthesis and regulated enzyme secretion as well as safety mechanism to prevent premature activation are localized in pancreatic acinar cells (Fig. 1). In general, genetic alterations in acinar pancreatitis risk genes result from two pathophysiologically distinctly different mechanisms:

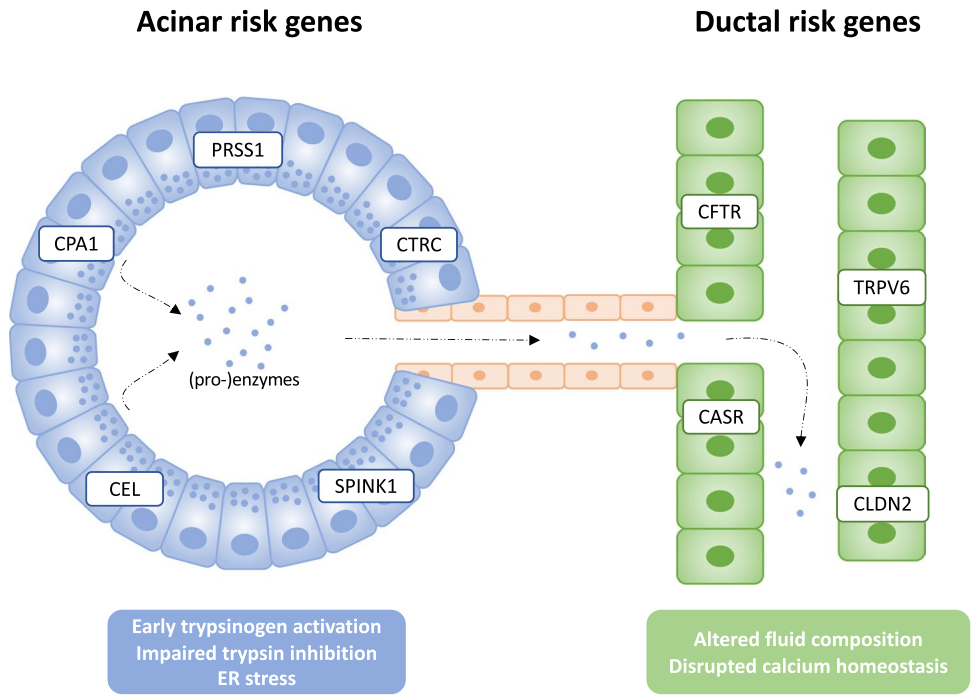

Fig. 1 Overview of acinar and ductal pancreatitis risk genes and their underlying disease-causing mechanisms (adapted from [6]).

1) Early trypsinogen activation or impaired trypsin inhibition can lead to autodigestion as it prematurely activates the pancreatic zymogene cascade. This mechanism is also referred to as "trypsinogen-dependent" risk factors (*PRSS1*, *SPINK1*, *CTRC*) [6].
2) Misfolding of proteins causes stress in the endoplasmic reticulum (ER), resulting in cell stress and an inflammatory response, referred to as "misfolding-dependent" risk factors (*CPA1*, *PRSS1*, *CELL-HYB1* allele) [7].

In the following, the different acinar genes involved in pancreatitis development and the evidence supporting their importance will be highlighted.

Cationic trypsinogen (PRSS1)

Changes in *PRSS1*, the cationic trypsinogen, can lead to pancreatitis via both mechanisms presented above. Mutations causing early autoactivation are by far the most common alterations of *PRSS1* and even account for up to 60–80% of all cases of hereditary pancreatitis [8]. Here the term hereditary pancreatitis highlights segregation or the PRSS1 gene in an autosomal dominant pedigree. Lately, different genetic variants with specific effector mechanisms have been highlighted. These comprise chymotrypsinogen C (CTRC)–dependent stimulation of trypsinogen autoactivation (p.N291) and inhibition of CTRC-dependent degradation of trypsinogen (p.R122C/p.R122H) [9], as well as direct, CTRC-independent activation of the enzyme

(multiple rare mutations, such as p.D19A and p.D21A) [10]. Misfolding, resulting in intracellular accumulation of the mutated trypsinogen and subsequent ER stress, has been also shown to represent a risk factor for CP in rare cases and is mostly detected in sporadic CP [11•, 12]. Recently, it was shown that in East Asia, about 4% of CP patients carry a mutation in the *PRSS1* gene associated with misfolding (p.G208A), whereas this mutation seems to be very rare in Europe [13, 14].

The significance of *PRSS1* gene alterations could be reproduced in a mouse model, where insertion of the most common pathogenic variation led to the progression of caerulein-induced AP into CP [15]. Mutations in the *PRSS1* gene can either cause autosomal-dominant hereditary pancreatitis (with incomplete penetrance, 80%) or in case of de novo mutations increase the risk for sporadic CP [16].

Interestingly, changes in anionic trypsinogen (*PRSS2*) are not linked to the development of CP [17]. Strikingly, even a protective variant (p.G191R), present in approximately 5% of the general population, was identified. The underlying pathogenesis is closely linked to increased inactivation and upregulated autocatalytic proteolysis due to a newly introduced trypsin cleavage site [17, 18].

Serine protease inhibitor Kazal-type 1 (SPINK1)

Variations in *SPINK1*, the gene encoding the most prevailing trypsin inhibitor predisposes to idiopathic chronic pancreatitis [19–21]. The most common variant, p.N34S, leads to severe CP in homozygous carriers and is regarded as causative [22]. In heterozygous carriers, a *SPINK1* mutation predisposes to pancreatitis and since 1% of the general population carry the variant, further triggers are required for disease manifestation [23]. Yet, the underlying mechanism has not been fully elucidated. For others, mostly rare or private, *SPINK1* mutations found in patients with CP, various effector mechanisms, such as diminished secretion, have been described increasing the risk of overt disease [24].

Carboxypeptidase A1 (CPA1)

Carboxypeptidases belong to the group of pancreatic metalloproteinases hydrolyzing C-terminal peptide bonds from dietary polypeptide chains. [25] Three different carboxypeptidases (CPA1, CPA2, CPB1) are known, each defined by its substrate specificity. In a patient cohort of CP, an increased mutational burden of *CPA1* was observed when compared to the general population, whereas variants of *CBP1* or *CPA2* were not associated with CP [26]. Mechanistically, in loss-of-function *CPA1* carriers, changes in trypsin activation or degradation could not be detected, but reduced CPA1 protein secretion and misfolding-dependent ER stress were identified as possible inflammatory triggers predisposing to pancreatitis [26].

The hypothesis of *CPA1* variants causing ER stress via protein misfolding as underlying mechanism of CP was further underlined in murine experiments. Here, artificial insertion of a variation (p.N256K) indeed leads to elevated ER stress markers and progressive pancreatitis [27].

Chymotrypsinogen C (CTRC)

CTRC serves as key factor in the degradation of all trypsin isoforms. Mutations in this protein either lead to decreased secretion (p.A73T), increased degradation (p.K247_R254del), or reduced enzymatic activity (p.V235I), resulting in trypsin-dependent CP [28, 29•]. Multiple risk genes have been recently identified which elevate the risk for CP and alcoholic CP by 5- to 19-fold [29•, 30]. Furthermore, a p.G60 = variant has been identified with surprisingly high frequency of up to 30% in CP [31, 32]. When a heterozygous alteration occurs, the risk of CP is elevated by 2.5-fold, whereas a homozygous mutation increases the probability by up to tenfold [32, 33]. Mechanistically, reduced *CTRC* mRNA expression levels possibly due to altered pre-mRNA splicing leading to diminished CTRC-dependent trypsin degradation were described as possible cause.

Carboxyl ester lipase (CEL-HYPB1 allele)

During tissue homeostasis, CEL is secreted into the duodenum to hydrolyze and facilitate absorption of lipid-soluble vitamin esters and cholesterol [34]. The enzyme is activated upon contact with bile salts. Non-allelic homologous recombination, also referred to as "cross-over," between *CEL* and *CELP*, its adjoining pseudogene, has been named hybrid allele *CEL-HYB1*. First described in 2015, a population-based study showed an increase of the risk gene in a German population of CP [35•]. Interestingly, allele distribution varied among different patient cohorts from Europe and additionally, the hybrid allele could not be detected in independent cohorts originating from Asia [36].

The molecular basis of the increased CP risk was highlighted in cell culture experiments, where secretion of the hybrid protein was reduced resulting in intracellular accumulation, thereby causing CP via the misfolding pathway and subsequent ER stress [35•].

Blood group antigens attached to the surface of the CEL protein and fucosyltransferase 2 (FUT2) non-secretor status (which affects the status of the ABO antigens, especially blood group B) was associated in a genome-wide association study (GWAS) [37]. However, in following studies, this association could not be confirmed apart from an association between blood group B and azathioprine-induced AP [38–40].

Ductal risk genes

Apart from pathogenic acinar gene variations causing alterations in pancreatic enzyme activation and protein misfolding, variants can also affect ductal cell function (Fig. 1). Mechanistically, these gene variants are particularly involved in the regulation of pancreatic juice composition and calcium homeostasis. In the following, the most important ductal genes involved in pancreatic inflammation will be highlighted.

Cystic fibrosis transmembrane conductance regulator (CFTR)

The CFTR protein is a cAMP-dependent ion channel localized in the apical plasma membrane of epithelial cells in different secretory organs such as airways, the pancreas and the gastrointestinal tract [41]. In these tissues, CFTR-mediated transport of chloride or bicarbonate anions is the critical step of transepithelial fluid secretion and thus fluid hydration as well as regulation of fluid pH [42]. Genetic alterations in the *CFTR* gene can lead to various clinical phenotypes. The corresponding phenotype of two *CFTR* alleles with severe mutations, which results in complete CFTR dysfunction, is cystic fibrosis (CF), a monogenetic disorder characterized by progressive lung disease, pancreatic insufficiency, and a variety of other organ manifestations [43]. When a severely mutated allele is compounded by a mild variant and CFTR function is preserved, atypical CF with a less pronounced phenotype is developed and typically patients remain pancreatic sufficient [43]. Furthermore, compound heterozygosity can also present with the clinical phenotype of idiopathic RAP or CP, without fulfilling the criteria for a CF diagnosis [44]. Finally, heterozygous carrier status of certain CFTR mutations increases the risk for pancreatitis development [44]. So far, around 2000 CFTR gene variants have been identified, and clinical course and severity of pancreatitis is dependent on zygosity as well as the specific variant(s) involved [45, 46]. Mechanistically, mutations in the *CFTR* gene can either lead to disruption of channel activity or reduction of CFTR membrane expression [43]. In the pancreatic duct, CFTR dysfunction results in reduction of intraluminal secrete alkalization, augmentation of fluid viscosity, and failure of zymogen washout, leading to intraluminal zymogen activation and pancreatic tissue digestion [47, 48], thereby causing pancreatitis.

First observations linking CFTR mutations and pancreatitis were reported in the late 1990s [49, 50]. Cohn and colleagues analyzed 27 patients with idiopathic CP and identified at least one abnormal CFTR allele in ten patients. The prevalence of having one CFTR-mutated allele was 11 times higher; the prevalence of two affected alleles was 80 times higher than in the control population, respectively. Sharer and colleagues analyzed 134 patients with classified or unclassified CP and detected CFTR mutations in about 13%, as compared to about 5% in the selected control population. Strikingly, CFTR

mutation carriers were younger at initial presentation, had predominantly no history of alcohol abuse, and were more likely to be non-smokers. The concept of different CFTR variants and their association with the risk to develop pancreatitis has been supported by a large number of follow-up studies in international cohorts [51–58]. When talking about specific CFTR variants, heterozygous carrier status of the severe delF508 mutation represents a small risk for CP (OR 2.5), whereas expression of the mild R117H variant increases CP risk by about fourfold [59]. The strongest risk for CP development is represented by compound heterozygous carrier state for one severe and one mild CFTR allele and may even be considered causative [56]. Interestingly, CFTR-related gene alterations have recently been demonstrated to be the most frequent mutations among all tested pancreatitis-associated gene variants in a cohort of RAP, patients with less than 35 years of age with an unexplained first episode of AP and idiopathic CP [60].

Since genetic defects in CFTR functionality have been associated with pancreatic inflammation and recent preclinical and clinical evidence also suggested that pancreatitis-causing triggers such as alcohol, smoking, or bile acids can strongly inhibit CFTR function, correction of CFTR function could be a promising therapeutic approach in pancreatitis [44, 61]. CFTR-modulating drugs have shown impressive clinical benefits in CF patients regarding respiratory function, exacerbation rate, and quality of life [62]. Two recent publications have demonstrated that risk of pancreatitis development among CF patients with pancreatic sufficiency was substantially diminished in patients treated with CFTR modulators [63, 64•], suggesting its clinical benefit. To our knowledge, there are no clinical trials investigating the role of CFTR modulation on the course of RAP and CP of different etiologies so far. Preclinical studies suggest that pharmacological rescue of ductal CFTR activity reduced tissue damage in a preclinical model of autoimmune pancreatitis and caerulein-induced AP [65, 66]. A recently published single case study reported a CFTR mutation carrier with methylmalonic acidemia and CP who was treated with the CFTR potentiator ivacaftor and subsequently experienced CP resolution [67]. Thus, initial preclinical studies and clinical observations regarding therapeutic CFTR targeting in pancreatitis are promising. Yet, further evidence is required to determine whether CFTR modulators can be effectively used as causal therapeutics to target reduction of CFTR functionality in genetic as well as other forms of RAP and CP.

Claudin-2 (CLDN2)

Claudins are a family of transmembrane proteins that represent crucial components of tight junctions between epithelial cells throughout the body, thereby regulating paracellular ion permeability and thus selectivity of the diffusion barrier [68]. CLDN2 is constitutively expressed at low levels in pancreatic duct cells and forms low-resistance cation-selective ion and water channels [69–71]. Besides being constitutively expressed, *CLDN2* gene expression as well as localization is extensively regulated, especially under conditions associated with stress or injury, as the *CLDN2* promotor region includes

a NFkB binding site [72–76]. From GWAS studies we learned that several single-nucleotide polymorphisms (SNPs) in the *CLDN2* locus are associated with a two-fold risk of CP [77–79]. This association was most pronounced in patients suffering from alcoholic CP. So far, there is no clear explanation of the pathophysiological role of *CLDN2* risk variants and their impact on CP development. As a putative pathomechanism, atypical localization of CLDN2 proteins due to *CLDN2* risk genes was proposed [77]. Whether this could lead to alterations in pancreatic ductal fluid composition and/or imbalance in calcium homeostasis with consecutive augmentation of CP risk still needs to be further investigated.

Calcium-sensing receptor (CASR)

The *CASR* gene encodes a G-protein-coupled plasma membrane receptor particularly expressed in calcitropic tissues such as the parathyroid gland and the kidneys. Here, it regulates systemic calcium homeostasis by detection of increasing calcium concentrations, leading to downstream signaling events that result in diminished parathyroid hormone secretion and reduced renal calcium reabsorption [80]. In the exocrine pancreas, *CASR* is preferentially expressed in epithelial cells of the pancreatic duct, where it might respond to high pancreatic juice calcium levels by increasing ductal bicarbonate and fluid secretion, thereby preventing calcium salt precipitation, pancreatic stone formation, and pancreatitis [81, 82]. The first observation linking *CASR* variants and CP development arose from a family with heterozygous *SPINK1* N34S polymorphism and clinical features of familial hypocalciuric hypercalcemia (FHH), a disease caused by heterozygous inactivating mutations in the *CASR* gene. While family members with a combination of the *CASR* L173P missense mutation and *SPINK1* gene mutation suffered from RAP episodes and progressed to CP, family members with isolated *CASR* mutation remained healthy [83]. Further studies were conducted which demonstrated conflicting results regarding genetic *CASR* variants and their association with pancreatitis. In an US-based cohort, the *CASR* exon 7 R990G polymorphism was shown to be associated with an about twofold higher risk of CP development, an effect that was even stronger when patients reported moderate or heavy alcohol consumption (OR 3.12) [84]. In a more recently published French study, rare *CASR* variants were overrepresented in idiopathic CP and a significant association between *CASR* alterations and CP was identified for the A986S variant, but only in homozygous carriers [85]. Controversially, the most recent study investigating the role of different *CASR* variants in a Hungarian cohort of 337 patients with alcoholic and non-alcoholic CP did not identify any association between *CASR* variants and CP risk modification [86]. Taken together, there is no clear evidence to consider *CASR* variants as risk genes for the development of pancreatitis so far. It is conceivable that specific *CASR* gene variants modulating intrapancreatic calcium homeostasis coincide with other environmental risk factors for pancreatic inflammation, putatively resulting in an increased pancreatitis risk. Further investigation in larger cohorts is required to clarify the impact of *CASR* gene variants on CP pathogenesis.

Transient receptor potential vanilloid superfamily member 6 (TRPV6)

The *TRPV6* gene encodes a constitutively active, highly selective calcium channel that regulates calcium absorption in different epithelial tissues, particularly in the intestine, placenta, prostate, and the exocrine pancreas [87]. In the human pancreas, TRPV6 is mainly expressed in ductal epithelial cells indicating a potential role in regulating ductal fluid calcium concentration, but its exact function has not been elucidated thus far [88, 89]. The concept that *TRPV6* mutations are associated with an augmented risk of CP development is rather novel. To our knowledge, the first study pointing towards *TRPV6* as CP risk gene was published in 2020 by Masamune and colleagues [90••]. They performed whole exome sequencing (WES) in a 34-year-old index patient with idiopathic CP and a history of RAP episodes with onset at the age of 25 years and compared identified gene variants with WES of his clinically unaffected parents. In doing so, they identified one rare heterozygous A210V variant inherited from the mother as well as one de novo D324N variant in the *TRPV6* gene in the index patient. In large Japanese and European validation cohorts, the authors could further demonstrate that loss-of-function *TRPV6* variants were strongly associated with non-alcoholic CP, which convincingly highlighted the role of *TRPV6* as novel high-impact CP susceptibility gene. These findings could be confirmed in a Chinese CP cohort and most recently a German and Polish early-onset CP cohort with comparable results [91, 92]. Furthermore, defective *TRPV6* variants could be detected in a significant number of patients with idiopathic, hereditary, and familial CP, with a notable cluster in hereditary and familial CP [93]. Besides confirming that *TRPV6* gene variants are important contributors to CP development, this study revealed that (co-)inherited *TRPV6* deficiency can also be a key driver in hereditary and familial CP. The discovery of *TRPV6* as genetic handicap for CP development also offers a putative novel target for therapeutic intervention. Particularly augmentation of TRPV6 membrane expression in variants causing reduced channel expression rather than mediating structural dysfunctionality might be a promising tool [89]. The fact that TRPV6 expression is positively regulated by 1a-,25-dihydroxyvitamin D3 renders therapeutic vitamin D administration a potential medication for prevention as well as therapy of *TRPV6*-mediated CP [94]. Still, further studies investigating the underlying mechanism linking defective *TRPV6* variants and augmented pancreatitis risk are required to profoundly understand the pathophysiology and to potentially use TRPV6 as a causal therapeutic target.

Genetic testing in diagnostic workup: current recommendations and potential future perspectives

Determining the underlying etiology in patients diagnosed with AP, RAP, and CP is critical for clinical management as well as follow-up. Unfortunately, the etiology causing pancreatitis remains unclear in a relevant

amount of patients with AP (around 15%) and CP (around 20%) [3, 95]. Thus, genetic testing and identification of gene variants directly or indirectly involved in pancreatitis development can be relevant for risk stratification, establishment of diagnostic and therapeutic measures, and follow-up recommendations (Table 1). So far, there is no clear evidence for testing of special gene variants and guideline recommendations are mainly based on expert consensus. The European guideline for CP recommends genetic testing especially in patients with a positive family history, pediatric patients, and patients before 20 years of age with so far idiopathic disease, as familial accumulation and early CP onset are suggestive for an inherited cause [96]. Patients should be offered genetic testing of PRSS1 (exons 2 and 3 to cover mainly p.A16V, p.N29I, and p.R122H), SPINK1 (all four exons, mainly p.N34S and IVS3 + 2 T > C in exon 3 and intron 3), CPA1 (several variants, mainly in exons 7, 8, and 10), CTRC (especially exon 7), and CEL (hybrid allele only) and may also be screened for variants in CFTR gene [96]. The American guidelines judge genetic testing to be indicated in patients with a positive family history for pancreatic diseases, in patients with persisting disease after therapeutic intervention (e.g., RAP after clearing the biliary system), and in patients with unclear etiology, especially when the patient is young (e.g., less than 35 years of age) [97]. They recommend evaluation of at least PRSS1, SPINK1, CFTR, and CTRC gene mutations. According to the recently updated German pancreatitis guideline, genetic testing can be performed in patients with a positive family history (at least one first-degree relative or two second-degree relatives) or patients with early disease onset (before 30 years of age) if no other etiology could be established [95]. The guideline recommends initial testing for PRSS1 (exons 2 and 3), SPINK1 (exon 3), and CPA1 (exons 7, 8, and 10) gene variants, with potential subsequent testing of other potential risk genes (e.g., CTRC, CEL, PNLIP, and CFTR) [95].

Since there is no clear definition for positive family history or early disease onset in the context of pancreatitis and since RCTs investigating the role of genetic testing in pancreatitis are lacking, the aforementioned recommendations are expert-based. Yet, there is a broad expert consensus to perform genetic testing in a certain subset of patients with idiopathic pancreatitis (young patients, positive family history) after other established causes and pancreatic cancer have been ruled out as underlying etiology. So far, identification of pancreatitis etiology may not necessarily lead to immediate therapeutic consequences, but still, performance of genetic testing and identification of potential risk genes can be important during diagnostics for many reasons. First of all, when common pancreatitis causes have been excluded, the identification of known pancreatitis-related risk genes can terminate or prevent other invasive and expensive diagnostic procedures. Furthermore, from a patient's point of view, resolution of the probable underlying cause of an initially undefined syndrome might support disease acceptance and mental health. Additionally, identification of high-impact gene variants associated with familial pancreatitis risk for carriers might also help family members and their physicians making clinical decisions and starting preventive measures such as nicotine and alcohol abstinence. Ultimately, genetic

Table 1 Summary of risk genes implicated in pancreatitis development (adapted from [96])

Pathogenic gene	Molecular/functional consequence	Clinical manifestations/phenotype
Acinar risk genes		
PRSS1	CTRC-dependent stimulation of trypsinogen activation, inhibition of CTRC-dependent trypsinogen degradation, and misfolding resulting in ER stress	Commonest mutation in hereditary CP (prevalence), elevation of risk for CP development and pancreatic cancer, cumulative life time risk up to 40%
CPA1	ER stress caused by protein misfolding and intracellular accumulation	Susceptibility gene. Elevated risk for CP development
CEL-HYPB1	Hybrid gene with reduced secretion of encoded protein resulting in intracellular accumulation and ER stress via misfolding pathway	Susceptibility gene. Elevated risk of CP development, especially non-alcoholic CP
SPINK1	Gene encoding for most prevailing trypsin inhibitor; hypothesis that reduced expression and/or activity leads to trypsinogen mediated autodigestion, precise effect not known to date	In homozygous carriers causative of CP (sometimes termed hereditary pancreatitis), in heterozygous carriers increased risk of CP
CTRC	Decreased secretion, inactive protein, or reduced enzyme activity of chymotrypsinogen	Elevated risk of CP and alcoholic CP, depending on site of mutation
Ductal risk genes		
CFTR	Channel dysfunction with reduction of secrete alkalization, augmented fluid viscosity, failure of zymogen washout, and intraluminal zymogen activation	Various phenotypes depending on zygosity and variant, elevated risk of RAP and CP mostly in pancreatic sufficient subjects
CLDN2	Unknown; possible imbalance in pancreatic fluid composition or intraluminal calcium homeostasis	Elevated risk of CP, especially alcoholic CP. Conflicting data from GWAS analysis
CASR	Imbalance in intraluminal calcium levels, calcium salt precipitation, pancreatic stone formation	Potential risk elevation of RAP and CP
TRPV6	Unknown; potential regulation of ductal fluid calcium concentration	Elevated risk of non-alcoholic, familial, and hereditary CP

AP acute pancreatitis, *RAP* recurrent acute pancreatitis, *CP* chronic pancreatitis; gene abbreviations: CTRC chymotrypsinogen C, *PRSS1* cationic trypsinogen, *CPA1* carboxypeptidase 1, *SPINK* 1 serine protease inhibitor Kazal-type 1, *CEL-HYPB1* carboxyl ester lipase hybrid allele, *CFTR* cystic fibrosis transmembrane conductance regulator, *CLDN2* claudin-2, *CASR* calcium sensing receptor, *TRPV6* transient receptor potential vanilloid superfamily member 6

testing might help defining the underlying pathogenetic disease mechanism and could thereby support the identification of potential therapeutic targets.

With regard to future perspectives, due to recent technological advances especially in next-generation sequencing (NGS), genetic testing of more variants than currently recommended seems to be meaningful, as many recently identified high-impact pancreatitis risk genes such as TRPV6 are not reflected by the current recommendations and also other rare genetic variants could exert clinical relevance as treatment targets. Potentially, the establishment of polygenetic risk scores for pancreatitis development could be a potent tool for pancreatitis risk stratification once risk variants will be determined in an untargeted gene analysis approach such as NGS [95]. NGS-based sequencing can nowadays be performed quite cost-effectively and be used for analysis of pancreatitis-related risk gene variants throughout the whole human genome. Since also NGS-based genome analysis may have its pitfalls, careful confirmation of results by Sanger sequencing might be of value [98]. In summary, it seems rational to extend genetic testing in young patients with RAP or CP of so far unknown etiology by performing NGS in the future to identify underlying genetic and pathophysiological pathways, to improve clinical and preventive reasoning and to potentially benefit in terms of novel therapeutic targets in this subset of patients.

Conclusions

Genetic testing still is no routine diagnostic measure in patients with AP, RAP, and CP, since only a minority of pancreatitis cases can be directly explained by genetic variants. However, as more and more susceptibility genes have emerged and been linked to pancreatitis risk, particularly younger patients with unknown etiology and patients with family history for pancreatitis should trigger screening and counseling for genetic risk variants. In the future, due to modern sequencing technologies, genetic screening of pancreatitis patients might become even more relevant in understanding the underlying pathophysiology and potentially identifying possible therapeutic targets.

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Declarations

Conflict of Interest
Ignazio Piseddu declares that he has no conflict of interest. Jakob Vielhauer declares that he has no conflict of interest. Julia Mayerle declares that she has no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:
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•• Of major importance

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