Review paper

# Genetic determination of pancreatitis

## *Determinacja genetyczna zapaleń trzustki*

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Medical Studies/Studia Medyczne 2018; 34 (1): 70-77
DOI: https://doi.org/10.5114/ms.2018.74823

**Key words:** acute pancreatitis, chronic pancreatitis, genetic mutations, risk factors.

**Słowa kluczowe:** ostre zapalenie trzustki, przewlekłe zapalenie trzustki, mutacje genetyczne, czynniki ryzyka.

**Abstract**

Pancreatitis is a complex disease with varied aetiology and clinical course. Genetic factors, in combination with environmental factors, may play a considerable role in the development of pancreatitis. Genetic studies may help in understanding the transition from acute pancreatitis to recurrent acute pancreatitis and progression to the chronic state. Various groups of genetic mutations may play a role in the pathogenesis of pancreatitis. Mutations in the cationic trypsinogen gene (*PRSS1*), anionic trypsinogen (*PRSS2*), the pancreatic secretory trypsin inhibitor gene (*SPINK1*), cystic fibrosis transmembrane conductance regulator gene (*CFTR*), chymotrypsinogen gene (*CTRC*), calcium-sensing receptor gene (*CASR*), and the protein claudin-2 (*CLDN2*) were found in different types of pancreatitis. The presented study demonstrates the role of the best recognised genetic mutations in the development of acute and chronic pancreatitis.
Summing up: Identification of patients with pathogenic genetic variants may change the approach to the factors related with lifestyle, such as alcohol consumption and cigarette smoking, and prevent or delay the occurrence of pancreatitis.

**Streszczenie**

Zapalenie trzustki jest złożoną chorobą o różnej etiologii i przebiegu klinicznym. Czynniki genetyczne w połączeniu z czynnikami środowiskowymi odgrywają znaczącą rolę w rozwoju zapaleń trzustki. Badania genetyczne pomagają zrozumieć przejście ostrego zapalenia trzustki do nawrotowego ostrego zapalenia trzustki i progresję do stanu przewlekłego. W patogenezie zapaleń trzustki mogą odgrywać rolę różne grupy mutacji genetycznych: w genie kodującym kationowy trypsynogen (*cationic trypsynogen/serine protease1 gen, PRSS1*), w genie trzustkowego inhibitora wydzielania trypsyny (*serine protease inhibitor, Kazal Type 1, SPINK1*), w genie kodującym białko tworzące kanał chlorkowy (*cystic fibrosis transmembrane conductance regulator, CFTR*), w genie chymotrypsyny C (*chymotrypsin C, CTRC*), w genie receptora rozpoznającego wapń (*calcium-sensing receptor gene, CASR*), w genie kodującym białko klaudynę 2 (*protein claudin-2, CLDN*). W pracy przedstawiono udział najlepiej poznanych mutacji genetycznych w rozwoju ostrego i przewlekłego zapalenia trzustki.
Podsumowanie: Identyfikacja osób z mutacjami w genach znanych jako patogenne dla zapalenia trzustki może zmienić podejście do czynników związanych ze stylem życia, takich jak picie alkoholu i palenie papierosów, i zapobiec lub opóźnić wystąpienie zapalenia trzustki.

## Introduction

Inflammatory conditions of the pancreas and pancreatic cancer are complex diseases with varied aetiology and clinical course, but they are mutually connected. Acute pancreatitis may be the first symptom of pancreatic cancer, and the risk was nine-times higher in patients in whom chronic pancreatitis developed in the future [1]. It was confirmed that pancreatic cancer frequently develops in the group of patients with CP [2–4]. Alcohol dominates among the causes of acute, as well as chronic pancreatitis [5–8]; nevertheless, in some patients the aetiology remains unknown [2, 6, 9, 10]. This proves the existence of other environmental and genetic factors that should be taken into consideration [11]. The advancement in the field of genetics and medical technologies that has been observed in recent years provides new opportunities for early evaluation of the risk factors of pancreatitis and pancreatic cancer. The discovery that genetic factors in combination with various environmental factors may be responsible for contracting inflamma-

tory conditions of the pancreas and pancreatic cancer has become a turning point in the understanding of the aetiology of these diseases. The study including 1000 patients with recurrent acute pancreatitis and chronic pancreatitis conducted within the *North American Pancreatitis Study 2* (NAPS2) brought us closer to understanding the complex environmental, metabolic, and genetic aetiology of the disease [12]. Genetic studies may also help to understand the transition from AP to RAP, and progression to CP. The potential genetic risk is specified based on the family history of AP, RAP, CP, cystic fibrosis, hypertriglyceridaemia, and pancreatic cancer [13]. The use of genetic information, including modern methods of DNA sequencing, such as next-generation sequencing (NGS), is still difficult to apply in order to explain the first episode of AP, but it has become a valuable source of information for the assessment of RAP and CP [13]. Various groups of genetic mutations may play a role in the pathogenesis of pancreatitis. Mutations in the cationic trypsinogen gene (*PRSS1*), anionic trypsinogen (*PRSS2*), pancreatic secretory trypsin inhibitor gene (*SPINK1*), cystic fibrosis transmembrane conductance regulator gene (*CFTR*), chymotrypsinogen gene (*CTRC*), calcium-sensing receptor gene (*CASR*), and the protein claudin-2 (*CLDN2*) were found in different types of pancreatitis [14–16]. Various mutations cause a different risk of pancreatitis. It may be estimated that mutation in the *PRSS1* gene increases the risk of contracting the disease by a factor of 1000-2000, p.*N34S homozygous mutation* increases this risk by a factor of about 500, and p.N34S heterozygous mutation in the SPINK1 gene and mutations in the *CFTR* gene are associated with 20–40-fold higher risk of pancreatitis [17].

## Acute and chronic pancreatitis

Pancreatitis may take an acute or chronic form. Chronic pancreatitis is the problem defined as an inflammatory condition of the pancreas diagnosed based on the presence of two out of three diagnostic criteria: acute abdominal pain, at least a three-fold elevation of serum amylase or lipase in the blood, and changes in imaging findings characteristic of acute pancreatitis [18, 19]. Poland is among the countries with the highest incidence rates [10]. Annually, more than 21,000 hospitalisations due to acute pancreatitis are registered by the Polish National Health Fund. The number of hospitalisations of patients with a severe form of AP is systematically increasing, from 3481 in 2010 to 5462 in 2016 [20]. High incidence rates are registered in Spain 72.5/100,000 [21], Finland 73.4/100,000, and Great Britain 56.5/100,000 population [9]. The main aetiological factors of AP are gallstones and alcohol, responsible for 60–75% of the causes of the disease [22]. In Polish studies, cholelithiasis was diagnosed in 30.1% of patients hospitalised due to AP, especially females at an older age, and alcohol-related cause in 24.1% of patients, mainly the young. It should be presumed that in a large group, 41.1% of unrecognised causes of the disease were also alcohol and gallstones [10, 23]. Recurrent AP occurred in nearly 15% of patients [24]. Alcohol consumption and impaired bile flow as a result of gallstones most frequently start a cascade of metabolic disorders, which ultimately lead to mild, moderate, or severe form of acute pancreatitis. Studies of the relationship between known aetiological factors of AP, such as alcohol and gallstones, and genetic factors also seem to be interesting. Despite common knowledge concerning the relationship between AP and alcohol consumption, the mechanism of this relationship remains unknown. Only 3% of those who consume large amounts of alcohol will develop AP. According to Yadav, 30–35% of patients with AP will develop RAP [25]. Acute episodes of alcohol-related AP lead to irreversible changes in the pancreas in the form of acute pancreatitis in approximately 15–20% of patients [25, 26]. Therefore, the majority of epidemiological studies pertaining to the effect of alcohol on diseases of the pancreas refer to AP [11].

Patients with gallstones and genetic susceptibility to AP are an especially interesting group. According to Mouzner [13], it seems justifiable to consider a delay in the performance of cholecystectomy in the group of patients with indications for genetic testing using the NGS technology until obtaining the results of genotyping. Also, the guidelines by the Polish Pancreatic Club recommend the performance of genetic tests (*PRSS1*, *CFTR*, *SPINK1*) in young patients with a family history of recurrent AP [19]. The data obtained may help to make rational clinical decisions with consideration of the risk factors.

The results of studies provide sufficient evidence that AP may progress to a chronic process with changeable speed, according to the frequency of recurrent acute episodes, severity of the course of the disease, and the type of immune response [13, 27]. The risk factors playing a special role in the progression of AP to CP are alcohol consumption and tobacco smoking, as well as various genetic variants [12, 28]. Many individuals exposed to risk factors, incuding genetic ones, will never contract AP [13].

Some studies focus on an attempt to establish in what way genetic risk affects the clinical course of AP. One of the potential risk factors of transition from mild to severe AP may be the production of proinflammatory cytokines, which depends on gene polymorphisms [29, 30]. The studies focused on genetic factors causing an increase in IL-8 during the inflammatory process. IL-8 plays a key role in the development of acute respiratory failure by activation of neutrophils, which is of basic importance for severe pancreatitis [30]. However, the results of these studies are unequivocal. In one of the studies, heterozygous

variants of *IL-8 A/T* mutation were more frequent in patients with severe AP, whereas a normal TT genotype was more often observed in patients with mild AP [29]. In turn, studies of *IL-8 251A/T* gene polymorphism in Chinese and Turkish populations did not show any significant correlations with the severity of the course of AP [30, 31]. The researchers concluded that IL-8-251 gene polymorphism may be related with ethnic differences, which exert an effect on the results of studies [31].

Chronic pancreatitis takes a course as a progressive destruction of the pancreatic parenchyma, leading to its atrophy and fibrosis. Exocrine and endocrine pancreatic insufficiency develops in the course of CP [2]. In European countries, the incidence remains within 6-7/100,000 population [32]. A known classification of the causes of CP is the TIGARO system: T – toxic-metabolic, I – idiopathic, G – genetic, A – autoimmune, R – recurrent and severe acute pancreatitis, O – obstructive [33]. Alcohol dominates among various causes of both acute and chronic pancreatitis [5–8]; however, in some patients the aetiology remains unknown [2]. In addition, in 10–25% of patients with CP the risk factors are unclear and are qualified as idiopathic pancreatitis (ICP) [34]. Recent studies suggest the presence of a relationship between tobacco smoking and the development of CP and pancreatic cancer [26, 35–39]. The development of CP is proportional to the dose and duration of alcohol consumption [40]. Although it has long been known that alcohol is the main cause of pancreatitis, only about 5–10% of individuals who consume large amounts of alcohol suffer from diseases of the pancreas [26, 40, 41]. This proves the existence of other environmental and genetic factors, which should be taken into consideration [11, 42, 43]. A family occurrence of chronic pancreatitis was described as early as in the 1950s [44]; however, the discovery of the mutation in the *cationic trypsinogen gene/serine protease 1 gene* (*PRSS1* R122H) was a breakthrough in understanding the aetiology of this disease [34]. During subsequent years, studies focused on proteases and anti-proteases, as well as the *CFTR* gene, the mutation in which is responsible for cystic fibrosis. The use of possibilities to investigate the whole genome (NAPS) indicated that polymorphisms at the trypsin locus (PRSS1 rs10273639) and Claudin 2 locus (CLDN2-RIPPLY1-MORC4 locus rs7057398 and rs12688220) cause an increased risk of alcohol-related pancreatitis [45].

Hereditary pancreatitis, which usually begins with recurrent episodes of acute pancreatitis in childhood or at a young age, is rarely diagnosed [46–48]. HP is defined as the occurrence of pancreatitis in two or more first-degree relatives, or three or more second-degree relatives in two or more generations with recurrent acute pancreatitis and/or chronic pancreatitis, for which no predisposing factors are identified [48]. It is an autosomal dominant inherited disease with approximately 80% penetrance for *PRSS1* [49].

## Genetic risk factors of acute and chronic pancreatitis

### *PRSS1*

The pancreas produces trypsinogen in the form of a pro-enzyme in three similar isoforms. Isoforms are encoded by separate genes: *PRSS1* (*cationic trypsinogen gene*), *PRSS2* (*anionic trypsinogen gene*), and *PRSS3* (*mesotrypsinogen*) [27, 50, 51]. Cationic trypsinogen gene represents 2/3 of total trypsinogen in the pancreatic juice [50]. The *PRSS1* located on the long arm of chromosome 7 (7q35) encodes cationic trypsinogen. Mutations may be located in various regions of the gene and result in a single amino acid substitution in the cationic trypsinogen. The changed pro-enzyme is more easily auto-activated inside pancreatic follicular cells. As a result of increased activity of proteolytic pancreatic enzymes self-digestion of the organ occurs. The mutations most frequently detected in the cationic trypsinogen gene (*PRSS1*) in patients with hereditary pancreatitis (HP) are: R122H [34], N29I [52], and A16V [53]. Pancreatitis in patients with R122H mutation is the result of impairment of the mechanism of Arg 122-Val123 autolytic peptide bond in trypsin, protecting the pancreas against premature activation of trypsin [34]. Approximately 70% of families with HP possess this mutation [47]. The p.R122H mutation increases the risk of recurrence of acute pancreatitis and chronic pancreatitis [54].

The N29I mutation is the second most common mutation (approximately 20%) [47]. An asparagine-isoleucine replacement at position 29 of cationic trypsinogen results in an increase in resistance to autolytic processes [55]. The A16V mutation is the third most frequent *PRSS1* mutation with changeable penetration, most often in the group of patients with idiopathic pancreatitis [47, 56]. The results of studies conducted by Nemoda [51] in 2006 confirmed that the A16V mutant protein, contrary to R122H and N29I, does not itself increase auto-activation of cationic trypsinogen; however, the stimulation of autoactivation by chymotrypsin C plays a role in chronic pancreatitis related with A16V mutation [51].

To date, nearly 30 *PRSS1* mutations have been identified that have been considered to be pathogenic [57]. The up-to-date list of investigated mutations and their clinical importance is available on the website: Genetic Risk Factors in Chronic Pancreatitis: http://www.pancreasgenetics.org.

Although *PRSS1* mutations are related with HP, they may also be found with changeable frequency of occurrence (0–19%) in idiopathic chronic pancreatitis [58–60]. However, no relationship was confirmed

with alcohol-related AP [61]. No *PRSS1* mutations were found in any patient with hereditary, idiopathic, or alcohol-related AP, nor in the control group among patients from India [15]. Studies of *PRSS1* mutation in the Polish population confirmed the relationship with CP. In the study conducted by Gąsiorowska *et al*. [60], *PRSS1* mutations were detected in 33% of Polish patients with alcohol-related CP, and in 21.4% of patients with ICP, significantly more frequently compared to the control group ($p < 0.001$). Kozieł *et al*. did not detect *PRSS1* mutation in any patient with AP, nor in the healthy controls [16]. The study published in 2017, which covered 136 children with CP (including 61 children with idiopathic CP), reported the occurrence of *PRSS1* mutation in 8% of patients [62]. Oracz *et al*. [63] showed that the Polish paediatric HP population has a different distribution of *PRSS1* mutations compared to populations from other countries, with p.R122H and p.R122C mutations being the most prevalent. Furthermore, it was also demonstrated that HP children with *PRSS1* mutations show significantly more severe clinical course of the disease than children without *PRSS1* mutation, despite the same age of CP onset. The most frequently mutated gene in Polish CP children was *SPINK1* (combined frequency 25.4%) followed by PRSS1 (13.1%) and CFTR (7.7%) [64].

### *PRSS2*

Anionic trypsinogen (*PRSS2*) constitutes approximately 30–40% [51]. The *PRSS2* mutation is the factor protecting the pancreas against the development of inflammation by decreased *PRSS1* expression [54]. Also, a lower risk of the development of RAP and CP was confirmed [54]. In patients with pancreatitis and the genotype *PRSS1-PRSS2* other causes of the disease should be sought [13] .

Total relative risk of the development of pancreatitis in this group of patients is estimated at 69 [65]. Although there exists a strong relationship between chronic pancreatitis and pancreatic cancer, within 20 years only about five per cent of patients with chronic pancreatitis will develop pancreatic cancer [65]. It has been proven that pancreatic cancer develops frequently in the group of patients with CP [2–4].

In PRSS1 hybrid alleles such as PRSS1-PRSS2 [66] and PRSS1-PRSS3P2 [67] generated by gene conversion events, although rare, are causative mutations in chronic pancreatitis.

### *SPINK1*

The pancreatic secretory trypsin inhibitor (*PSTI*). The role of SPINK1 protein consists of the prevention of premature activation of zymogen, and may inhibit up to 20% of pancreatic trypsin activity, thus protecting the pancreas against self-digestion [68]. To date, nearly 30 various types of *SPINK1* mutations have been reported. The complete list is available on the website: http://www.pancreasgenetics.org/. The most frequently observed *SPINK1* mutations are N34S and P55S, occurring mainly in Europe and the USA. Many studies provide evidence for the relationship between N34S mutation and chronic pancreatitis of varied aetiology, with a frequency of approximately 9.7% [15, 56, 69–71]. The mechanism combining *SPINK1* p.N34S mutation with pancreatitis remains unexplained [71]. The *SPINK1* mutations are rarely related with HP and may, in this case, increase the risk of contracting the disease by 23% [72]. Witt *et al*. [69] suggested an autosomal recessive inheritance pattern. Chandak *et al*. [15] found, in a large group, the presence of N34S mutation in 73% of patients with HP, in 26.8% with alcohol-related AP, and in 32.5% of patients with idiopathic AP [15]. The researchers suggested a dominant inheritance pattern with low level of penetration [15]. The *SPINK1* mutations are more frequently inherited in a heterozygous form, and contracting of pancreatitis depends on the presence of other genetic mutations and/or environmental factors [72]. The p.N34S mutation is strongly related with RAP; however, its effect on the risk of occurrence of the first episode of AP is under discussion [73–75]. In a study on Polish patients with AP, *SPINK1* mutation was significantly more often observed, compared to the control group (6.3% vs. 3.2%; $p < 0.05$) [16]. The *SPINK1* mutation was related with a more severe clinical course of AP ($p = 0.03$), but not with the cause of contracting the disease [16]. Gąsiorowska, in a group of 14 patients with ICP, discovered four patients (28.6%) with *SPINK1* mutation ($p < 0.05$). No relationship was found with alcohol-related CP, clinical course of the disease, and complications [60].

### *CLDN2*

Claudin-2 protein forms low-resistance, cation-selective ions, and water channels between endothelial cells [54]. It was confirmed on animal models that it may be expressed during stress in the acinar cells [76]. Genetic variants in the Claudin-2 locus (*CLDN2*) do not increase the risk of AP and RAP, but are strongly related with an increased risk of progression of RAP to CP [13, 54]. The total odds ratio for patients with alcohol-related AP and *CLDN2* mutation was higher, compared to non-alcoholic AP [54].

### *CFTR*

CFTR protein participates in the transport of sodium, chlorides, and carbohydrates in the epithelial cells of the respiratory system, sweat glands, and the pancreas [72]. The *CFTR* mutation (cystic fibrosis transmembrane conductance regulator gene) leads to cystic fibrosis, which may cause changes in the respi-

ratory, reproductive, gastrointestinal, and endocrine systems. To-date, more than 1600 CFTR mutations have been recognised [77]. More than 90% of patients with cystic fibrosis experience exocrine pancreatic insufficiency, while more than 50% experience diabetes. Approximately 1.5% of patients with cystic fibrosis contract pancreatitis [72]. This concerns patients with a milder phenotype of cystic fibrosis (molecular classes III, IV, or V), who develop chronic pancreatitis and pancreatic insufficiency considerably later than other patients with cystic fibrosis [78]. The risk of contracting the disease is higher when concomitant with other mutations, e.g. *SPINK1* or *CTRC* [78]. A strong relationship between *CFTR* mutations and chronic pancreatitis was first recognised and described in 1998 by Cohn *et al*. [79], and Sharer *et al*. [80]. LaRusch *et al*. [81] described nine *CFTR* mutations (CFTR R74Q, R75Q, R117H, R170H, L967S, L997F, D1152H, S1235R, and D1270N) considered as mild, which do not cause cystic fibrosis but do increase risk of chronic pancreatitis. Schneider *et al*. [78] observed three times more clearly occurrence of the *CFTR* variant p.R75Q in patients with pancreatitis, compared to the healthy controls. The risk of the disease increases in the case of the presence of other *CFTR* and *SPINK1* variants [78]. Rosendahl *et al*., who studied a group of 660 patients with idiopathic and hereditary CP and 1758 controls, did not confirm the relationship between *CFTR* p.R75Q and CP, and concluded that CFTR exerts a small effect on the development of CP [82]. Also, in our previously published study no relationship was found between CFTR mutation and acute pancreatitis [16]. In the above-mentioned study of Polish children with CP, *CFTR* mutation was identified in 18% of patients with CP. In two cases (1.5%) the *CFTR* mutation occurred in combination with mutation in the *SPINK1* or *PRSS1* gene [62].

### *CTRC*

*CTRC* protein encodes the enzyme chymotrypsin C, which is produced by the pancreatic follicular cells [68]. Chymotrypsin C promotes the degradation of trypsin by selective breaking of the bond between leucine at position 31, and glutamine at position 82, and subsequently by breaking the bond between arginine at position 122 and valine at position 123. Prematurely activated trypsin may be destroyed by *CTRC* through the action in the particle bonded with calcium [83]. The CTRC mutations may predispose for CP by ineffective degradation of trypsinogen/trypsin, ineffective activation of carboxypeptidase, and induction of the endoplasmic reticulum [82]. The degradation of trypsinogen with participation of CTRC takes place after the exhaustion of the protective mechanisms dependent on SPINK1 [84]. Pathogenic CTRC variants (p.A73T, p.V235I, p.R254W, and p.K247_R254del) were found in patients with CP, as well as healthy controls; therefore, they should be considered as risk factors [85]. The CTRC mutations occur in approximately 4% of patients with CP. Masson *et al*. [86] observed the presence of rare *CTRC* variants in 12% of patients with ICP. The majority of variants of heterozygous *CTRC* increase the risk of the disease by 5–10 times. A recently published Polish study also indicates that *CTRC* mutations, including c.180TT (p.Gly60Gly), are important risk factors for CP [62]. It was found that the c.493+51C>A variant is insufficiently represented in CP. The results suggest a protective role of this variant in the development of CP [62]. In our study of patients with AP published in 2017, three CTRC mutations were detected in exon 7: p.V235I (c.703 G>A), p.K247_R254del, p.R254W, known to be responsible for CP, and p.I259V, the importance of which has not been sufficiently recognised [87]. The frequent CTRC variant c.180T may exert an effect on the modification of the progression from RAP to CP, especially in patients with *CFTR* or *SPINK1* variant, who consume alcohol and are tobacco smokers [88]. The presence of the *SPINK1* and *CTRC* mutations causes a high risk of contracting pancreatitis and may be responsible for a more severe course of acute pancreatitis [84, 87].

## Conclusions

In order to establish the ultimate cause of pancreatitis, in some cases, it is necessary to take a comprehensive family history and perform molecular genetic tests. In recent years, many genetic factors have been identified, which, while modified by environmental factors, may be of importance in the development of pancreatitis, or exert an effect on the clinical course of the disease. Simultaneously, it should be emphasised that the presence of a single mutation does not determine the contraction of the disease. Whole genome sequencing (NGS) provides new opportunities with respect to the detection of changes and decreases the cost of genetic tests. Although, until today, routine population studies are not recommended, this should not lead to a lack of interest on the part of attending physicians in the referral of patients for genetic tests in justified cases. At present, according to the recommendations by the Polish Pancreatic Club, all patients with a positive history of hereditary pancreatitis should have genetic tests performed. The identification of patients with pathogenic genetic variants may change the approach to the factors related with lifestyle, such as alcohol consumption and cigarette smoking, and prevent or delay the occurrence of pancreatitis.

## Conflict of interest

The authors declare no conflict of interest.

**References**


1. Rijkers AP, Bakker OJ, Ali UA, Hagenaars J, van Santvoort HC, Besselink MG, Bollen TL, van Eijck CH, Dutch Pancreatitis Study G. Risk of Pancreatic Cancer After a Primary Episode of Acute Pancreatitis. Pancreas 2017; 46: 1018-1022.
2. Żuk K, Czkwianianc E, Degowska M, Durlik M, Gąsiorowska A, Ignyś I, Jurkowska G, Krasnodębski I, Lampe P, Małecka-Panas E et al. Zalecenia diagnostyczne i terapeutyczne w przewlekłym zapaleniu trzustki. Rekomendacje Grupy Roboczej Konsultanta Krajowego w dziedzinie Gastroenterologii i Polskiego Klubu Trzustkowego. Prz Gastroenterol 2011; 6: 339-352.
3. Lowenfels AB, Maisonneuve P, Whitcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. Med Clin North Am 2000; 84: 565-573.
4. Bhanot UK, Moller P. Mechanisms of parenchymal injury and signaling pathways in ectatic ducts of chronic pancreatitis: implications for pancreatic carcinogenesis. Lab Invest 2009; 89: 489-497.
5. Irving HM, Samokhvalov AV, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. JOP 2009; 10: 387-392.
6. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology 2017; 17: 155-165.
7. Samokhvalov AV, Rehm J, Roerecke M. Alcohol Consumption as a Risk Factor for Acute and Chronic Pancreatitis: A Systematic Review and a Series of Meta-analyses. EBioMedicine 2015; 2: 1996-2002.
8. Papachristou GI, Papachristou DJ, Morinville VD, Slivka A, Whitcomb DC. Chronic alcohol consumption is a major risk factor for pancreatic necrosis in acute pancreatitis. Am J Gastroenterol 2006; 101: 2605-2610.
9. Roberts SE, Akbari A, Thorne K, Atkinson M, Evans PA. The incidence of acute pancreatitis: impact of social deprivation, alcohol consumption, seasonal and demographic factors. Aliment Pharmacol Ther 2013; 38: 539-548.
10. Gluszek S, Koziel D. Prevalence and progression of acute pancreatitis in the Swietokrzyskie Voivodeship population. Pol Przegl Chir 2012; 84: 618-625.
11. Herreros-Villanueva M, Hijona E, Banales JM, Cosme A, Bujanda L. Alcohol consumption on pancreatic diseases. World J Gastroenterol 2013; 19: 638-647.
12. Whitcomb DC, Yadav D, Adam S, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, Bishop MD, Baillie J et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). Pancreatology 2008; 8: 520-531.
13. Mounzer R, Whitcomb DC. Genetics of acute and chronic pancreatitis. Curr Opin Gastroenterol 2013; 29: 544-551.
14. Solomon S, Whitcomb DC. Genetics of pancreatitis: an update for clinicians and genetic counselors. Curr Gastroenterol Rep 2012; 14: 112-117.
15. Chandak GR, Idris MM, Reddy DN, Mani KR, Bhaskar S, Rao GV, Singh L. Absence of PRSS1 mutations and association of SPINK1 trypsin inhibitor mutations in hereditary and non-hereditary chronic pancreatitis. Gut 2004; 53: 723-728.
16. Koziel D, Gluszek S, Kowalik A, Chlopek M, Pieciak L. Genetic mutations in SPINK1, CFTR, CTRC genes in acute pancreatitis. BMC Gastroenterol 2015; 15: 70.
17. Keim V. Role of genetic disorders in acute recurrent pancreatitis. World J Gastroenterol 2008; 14: 1011-1015.
18. Working Group IAPAPAAPG: IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology 2013; 13 (4 Suppl 2): e1-15.
19. Rosolowski M, Lipinski M, Dobosz M, Durlik M, Gluszek S, Kusnierz K, Lampe P, Malecka-Panas E, Nowakowska-Dulawa E, Nowak-Niezgoda M et al. Management of acute pancreatitis (AP) – Polish Pancreatic Club recommendations. Prz Gastroenterol 2016; 11: 65-72.
20. https://prog.nfz.gov.pl/app-jgp/AnalizaPrzekrojowaSzczegoly.aspx?id=520.
21. Mendez-Bailon M, de Miguel Yanes JM, Jimenez-Garcia R, Hernandez-Barrera V, Perez-Farinos N, Lopez-de-Andres A. National trends in incidence and outcomes of acute pancreatitis among type 2 diabetics and non-diabetics in Spain (2001-2011). Pancreatology 2015; 15: 64-70.
22. Farthing M, Roberts SE, Samuel DG, Williams JG, Thorne K, Morrison-Rees S, John A, Akbari A, Williams JC. Survey of digestive health across Europe: Final report. Part 1: The burden of gastrointestinal diseases and the organisation and delivery of gastroenterology services across Europe. United European Gastroenterol J 2014; 2: 539-543.
23. Kozieł D, Głuszek S. Epidemiology of acute pancreatitis in Poland – selected problems. Medical Studies/Studia Medyczne 2016; 32: 1-3.
24. Koziel D, Kozlowska M, Deneka J, Matykiewicz J, Gluszek S. Retrospective analysis of clinical problems concerning acute pancreatitis in one treatment center. Prz Gastroenterol 2013; 8: 320-326.
25. Yadav D. Recent advances in the epidemiology of alcoholic pancreatitis. Curr Gastroenterol Rep 2011; 13: 157-165.
26. Sand J, Lankisch PG, Nordback I. Alcohol consumption in patients with acute or chronic pancreatitis. Pancreatology 2007; 7: 147-156.
27. Whitcomb DC. Genetic risk factors for pancreatic disorders. Gastroenterology 2013; 144: 1292-1302.
28. Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. Nat Rev Gastroenterol Hepatol 2010; 7: 131-145.
29. Hofner P, Balog A, Gyulai Z, Farkas G, Rakonczay Z, Takacs T, Mandi Y. Polymorphism in the IL-8 gene, but not in the TLR4 gene, increases the severity of acute pancreatitis. Pancreatology 2006; 6: 542-548.
30. Anilir E, Ozen F, Yildirim IH, Ozemir IA, Ozlu C, Alimoglu O. IL-8 gene polymorphism in acute biliary and non biliary pancreatitis: probable cause of high level parameters? Ann Hepatobiliary Pancreat Surg 2017; 21: 30-38.
31. Chen WC, Nie JS. Genetic polymorphism of MCP-1-2518, IL-8-251 and susceptibility to acute pancreatitis: a pilot study in population of Suzhou, China. World J Gastroenterol 2008; 14: 5744-5748.
32. Jupp J, Fine D, Johnson CD. The epidemiology and socioeconomic impact of chronic pancreatitis. Best Pract Res Clin Gastroenterol 2010; 24: 219-231.
33. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology 2001; 120: 682-707.
34. Whitcomb DC, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, Martin SP, Gates LK, Jr., Amann ST, Toskes PP et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet 1996; 14: 141-145.

35. Hao L, Zeng XP, Xin L, Wang D, Pan J, Bi YW, Ji JT, Du TT, Lin JH, Zhang D et al. Incidence of and risk factors for pancreatic cancer in chronic pancreatitis: A cohort of 1656 patients. Digestive and Liver Disease 2017; 49: 1249-1256.
36. Lai Y, Yang H, Han W, Guo T, Lv H, Li J, Qian JM. Cigarette smoking associated with chronic pancreatitis: a case control study in China. Tobacco Induced Diseases 2017, 15.
37. Lee B, Zhao Q, Habtezion A. Immunology of pancreatitis and environmental factors. Current Opinion in Gastroenterology 2017; 33: 383-389.
38. Xu Z, Pothula SP, Lee ATK, Tran D, Pandol SJ, Pirola RC, Wilson JS, Apte MV. Smoking worsens the fibrosis of alcoholic chronic pancreatitis via activation of pancreatic stellate cells. J Gastroenterol Hepatol 2017; 32: 13-14.
39. Klein AP. Genetic susceptibility to pancreatic cancer. Mol Carcinog 2012, 51: 14-24.
40. Dufour MC, Adamson MD. The epidemiology of alcohol-induced pancreatitis. Pancreas 2003; 27: 286-290.
41. Grauvogel J, Daemmrich TD, Ryschich E, Gebhard MM, Werner J. Chronic alcohol intake increases the severity of pancreatitis induced by acute alcohol administration, hyperlipidemia and pancreatic duct obstruction in rats. Pancreatology 2010; 10: 603-612.
42. Hanck C, Schneider A, Whitcomb DC. Genetic polymorphisms in alcoholic pancreatitis. Best Pract Res Clin Gastroenterol 2003; 17: 613-623.
43. Whitcomb DC. Genetic polymorphisms in alcoholic pancreatitis. Dig Dis 2005; 23: 247-254.
44. Comfort MW, Steinberg AG. Pedigree of a family with hereditary chronic relapsing pancreatitis. Gastroenterology 1952; 21: 54-63.
45. Aghdassi AA, Weiss FU, Mayerle J, Lerch MM, Simon P. Genetic susceptibility factors for alcohol-induced chronic pancreatitis. Pancreatology 2015; 15 (4 Suppl): S23-31.
46. Rebours V, Levy P, Ruszniewski P. An overview of hereditary pancreatitis. Dig Liver Dis 2012; 44: 8-15.
47. Szmola R, Sahin-Toth M. Uncertainties in the classification of human cationic trypsinogen (PRSS1) variants as hereditary pancreatitis-associated mutations. J Med Genet 2010; 47: 348-350.
48. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, Truninger K, Ammann R, Cavallini G, Charnley RM, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2004; 2: 252-261.
49. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013; 144: 1252-1261.
50. Teich N, Rosendahl J, Toth M, Mossner J, Sahin-Toth M. Mutations of human cationic trypsinogen (PRSS1) and chronic pancreatitis. Hum Mutat 2006; 27: 721-730.
51. Nemoda Z, Sahin-Toth M. Chymotrypsin C (caldecrin) stimulates autoactivation of human cationic trypsinogen. J Biol Chem 2006; 281: 11879-11886.
52. Raty S, Piironen A, Babu M, Pelli H, Sand J, Uotila S, Nordback I, Herzig KH. Screening for human cationic trypsinogen (PRSS1) and trypsinogen inhibitor gene (SPINK1) mutations in a Finnish family with hereditary pancreatitis. Scand J Gastroenterol 2007; 42: 1000-1005.
53. Chen JM, Mercier B, Ferec C. Strong evidence that the N21I substitution in the cationic trypsinogen gene causes disease in hereditary pancreatitis. Gut 1999; 45: 916.
54. Whitcomb DC, LaRusch J, Krasinskas AM, Klei L, Smith JP, Brand RE, Neoptolemos JP, Lerch MM, Tector M, Sandhu BS et al. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet 2012; 44: 1349-1354.
55. Gasiorowska A, Malecka-Panas E. Znaczenie mutacji genetycznych w patogenezie przewlekłego zapalenia trzustki. Gastroenterol Pol 2012; 19: 30-36.
56. Chen JM, Piepoli Bis A, Le Bodic L, Ruszniewski P, Robaszkiewicz M, Deprez PH, Raguenes O, Quere I, Andriulli A, Ferec C. Mutational screening of the cationic trypsinogen gene in a large cohort of subjects with idiopathic chronic pancreatitis. Clin Genet 2001; 59: 189-193.
57. http://pancreasgenetics.org/e107_plugins/aacgc_itemlist/Item_List.php?det.1
58. Masson E, Chen JM, Audrezet MP, Cooper DN, Ferec C. A conservative assessment of the major genetic causes of idiopathic chronic pancreatitis: data from a comprehensive analysis of PRSS1, SPINK1, CTRC and CFTR genes in 253 young French patients. PLoS One 2013; 8: e73522.
59. Wang W, Sun XT, Weng XL, Zhou DZ, Sun C, Xia T, Hu LH, Lai XW, Ye B, Liu MY et al. Comprehensive screening for PRSS1, SPINK1, CFTR, CTRC and CLDN2 gene mutations in Chinese paediatric patients with idiopathic chronic pancreatitis: a cohort study. BMJ Open 2013; 3: e003150.
60. Gasiorowska A, Talar-Wojnarowska R, Czupryniak L, Smolarz B, Romanowicz-Makowska H, Kulig A, Malecka-Panas E. The prevalence of cationic trypsinogen (PRSS1) and serine protease inhibitor, Kazal type 1 (SPINK1) gene mutations in Polish patients with alcoholic and idiopathic chronic pancreatitis. Dig Dis Sci 2011; 56: 894-901.
61. Monaghan KG, Jackson CE, KuKuruga DL, Feldman GL. Mutation analysis of the cystic fibrosis and cationic trypsinogen genes in patients with alcohol-related pancreatitis. Am J Med Genet 2000; 94: 120-124.
62. Grabarczyk AM, Oracz G, Wertheim-Tysarowska K, Kujko AA, Wejnarska K, Kolodziejczyk E, Bal J, Koziel D, Kowalik A, Gluszek S et al. Chymotrypsinogen C Genetic Variants, Including c.180TT, Are Strongly Associated With Chronic Pancreatitis in Pediatric Patients. J Pediatr Gastroenterol Nutr 2017; 65: 652-657.
63. Oracz G, Kolodziejczyk E, Sobczynska-Tomaszewska A, Wejnarska K, Dadalski M, Grabarczyk AM, Kierkus J, Woynarowski M, Wertheim-Tysarowska K, Ryzko J, et al. The clinical course of hereditary pancreatitis in children – a comprehensive analysis of 41 cases. Pancreatology 2016; 16: 535-541.
64. Wejnarska K, Kolodziejczyk E, Wertheim-Tysarowska K, Dadalski M, Sobczynska-Tomaszewska A, Kierkus J, Bal J, Rygiel AM, Oracz G. The Etiology and Clinical Course of Chronic Pancreatitis in Children With Early Onset of the Disease. J Pediatr Gastroenterol Nutr 2016; 63: 665-670.
65. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol 2010; 24: 349-358.
66. Teich N, Nemoda Z, Kohler H, Heinritz W, Mossner J, Keim V, Sahin-Toth M. Gene conversion between functional trypsinogen genes PRSS1 and PRSS2 associated with chronic pancreatitis in a six-year-old girl. Hum Mutat 2005; 25: 343-347.

67. Rygiel AM, Beer S, Simon P, Wertheim-Tysarowska K, Oracz G, Kucharzik T, Tysarowski A, Niepokoj K, Kierkus J, Jurek M et al. Gene conversion between cationic trypsinogen (PRSS1) and the pseudogene trypsinogen 6 (PRSS3P2) in patients with chronic pancreatitis. Hum Mutat 2015; 36: 350-356.
68. Ravi Kanth V, Nageshwar Reddy D. Genetics of acute and chronic pancreatitis: An update. World J Gastrointest Pathophysiol 2014; 5: 427-437.
69. Witt H, Luck W, Hennies HC, Classen M, Kage A, Lass U, Landt O, Becker M. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet 2000; 25: 213-216.
70. Kume K, Masamune A, Mizutamari H, Kaneko K, Kikuta K, Satoh M, Satoh K, Kimura K, Suzuki N, Nagasaki Y et al. Mutations in the serine protease inhibitor Kazal Type 1 (SPINK1) gene in Japanese patients with pancreatitis. Pancreatology 2005; 5: 354-360.
71. Masamune A. Genetics of pancreatitis: the 2014 update. Tohoku J Exp Med 2014; 232: 69-77.
72. Raphael KL, Willingham FF. Hereditary pancreatitis: current perspectives. Clin Exp Gastroenterol 2016; 9: 197-207.
73. Masamune A, Ariga H, Kume K, Kakuta Y, Satoh K, Satoh A, Shimosegawa T. Genetic background is different between sentinel and recurrent acute pancreatitis. J Gastroenterol Hepatol 2011; 26: 974-978.
74. Aoun E, Chang CC, Greer JB, Papachristou GI, Barmada MM, Whitcomb DC. Pathways to injury in chronic pancreatitis: decoding the role of the high-risk SPINK1 N34S haplotype using meta-analysis. PLoS One 2008; 3: e2003.
75. Aoun E, Muddana V, Papachristou GI, Whitcomb DC. SPINK1 N34S is strongly associated with recurrent acute pancreatitis but is not a risk factor for the first or sentinel acute pancreatitis event. Am J Gastroenterol 2010; 105: 446-451.
76. Merilainen S, Makela J, Anttila V, Koivukangas V, Kaakinen H, Niemela E, Ohtonen P, Risteli J, Karttunen T, Soini Y et al. Acute edematous and necrotic pancreatitis in a porcine model. Scand J Gastroenterol 2008; 43: 1259-1268.
77. http://www.genet.sickkids.on.ca/app
78. Schneider A, Larusch J, Sun X, Aloe A, Lamb J, Hawes R, Cotton P, Brand RE, Anderson MA, Money ME et al. Combined bicarbonate conductance-impairing variants in CFTR and SPINK1 variants are associated with chronic pancreatitis in patients without cystic fibrosis. Gastroenterology 2011; 140: 162-171.
79. Cohn JA, Friedman KJ, Noone PG, Knowles MR, Silverman LM, Jowell PS. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med 1998; 339: 653-658.
80. Sharer N, Schwarz M, Malone G, Howarth A, Painter J, Super M, Braganza J. Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Engl J Med 1998; 339: 645-652.
81. LaRusch J, Jung J, General IJ, Lewis MD, Park HW, Brand RE, Gelrud A, Anderson MA, Banks PA, Conwell D et al. Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. PLoS Genet 2014; 10: e1004376.
82. Rosendahl J, Landt O, Bernadova J, Kovacs P, Teich N, Bodeker H, Keim V, Ruffert C, Mossner J, Kage A et al. CFTR, SPINK1, CTRC and PRSS1 variants in chronic pancreatitis: is the role of mutated CFTR overestimated? Gut 2013; 62: 582-592.
83. Szmola R, Sahin-Toth M. Chymotrypsin C (caldecrin) promotes degradation of human cationic trypsin: identity with Rinderknecht's enzyme Y. Proc Natl Acad Sci U S A 2007; 104: 11227-11232.
84. Hegyi E, Sahin-Toth M. Genetic Risk in Chronic Pancreatitis: The Trypsin-Dependent Pathway. Dig Dis Sci 2017; 62: 1692-1701.
85. Beer S, Zhou J, Szabo A, Keiles S, Chandak GR, Witt H, Sahin-Toth M. Comprehensive functional analysis of chymotrypsin C (CTRC) variants reveals distinct loss-of-function mechanisms associated with pancreatitis risk. Gut 2013; 62: 1616-1624.
86. Masson E, Chen JM, Scotet V, Le Marechal C, Ferec C. Association of rare chymotrypsinogen C (CTRC) gene variations in patients with idiopathic chronic pancreatitis. Hum Genet 2008; 123: 83-91.
87. Koziel D, Gluszek S, Kowalik A, Chlopek M. CTRC gene polymorphism (p.G60=; c.180 C > T) in acute pancreatitis. BMC Gastroenterol 2017; 17: 13.
88. LaRusch J, Lozano-Leon A, Stello K, Moore A, Muddana V, O'Connell M, Diergaarde B, Yadav D, Whitcomb DC. The Common Chymotrypsinogen C (CTRC) Variant G60G (C.180T) Increases Risk of Chronic Pancreatitis But Not Recurrent Acute Pancreatitis in a North American Population. Clin Transl Gastroenterol 2015; 6: e68.

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