Genetic Abnormalities in Pancreatitis

Subjects: Gastroenterology

Submitted by: Mitsuyoshi Suzuki

Definition

Hereditary pancreatitis (HP) has been defined as either two or more individuals within a family exhibiting pancreatitis for two or more generations, or pancreatitis linked to mutation of the PRSS1 gene. In 2000, a mutation in the serine protease inhibitor gene (Kazal type 1: SPINK1) was reported to be related to sporadic pancreatitis of unknown etiology.

1. Introduction

When the patients with acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) show an autosomal dominant pattern of inheritance, they have been characterized as having hereditary pancreatitis (HP). HP caused by cationic trypsinogen (serine protease 1; PRSS1) gene mutation results in ARP and CP in both children and adults with high penetrance [1][2]. Currently, HP has been defined as either, two or more individuals within a family exhibiting pancreatitis for two or more generations, or pancreatitis linked to mutation of the PRSS1 gene. On the other hand, familial pancreatitis is a broader term used to describe families in which pancreatitis occurs with a greater incidence than expected by chance alone in the general population. Patients with HP usually present clinically with recurrent bouts of acute pancreatitis (AP) in the first two decades of life. HP prevalence ranges depending on the region, from 0.3 to 0.57 per 100,000 people, according to national cohort data[3][4][5]. Progression to CP occurs in the late teenage years and early adult life. As damage to the pancreas progresses, malabsorption occurs due to pancreatic exocrine insufficiency, and diabetes mellitus develops due to pancreatic islet cell damage[3]. Several pancreatitis susceptibility genes have been identified so far (See “History” below). The mechanisms of developing pancreatitis due to genetic abnormalities are mainly classified into three genetic pathways, classified as: the trypsin-dependent pathway, misfolding and consequent endoplasmic reticulum stress, and related to the ductal pathway[6]. Compared to the other causes of ARP and CP, genetic pancreatitis has some unique clinical characteristics. Recently, several cohorts showed the natural history of patients with serine protease inhibitor gene (Kazal type 1: SPINK1) germline-related pancreatitis and HP caused by PRSS1 gene mutation, indicating a high progression rate of pancreatic exocrine insufficiency and diabetes mellitus, as well as a significantly increased risk of pancreatic cancer[3][7].

2. Genetic Abnormalities

2.1. CFTR Gene

The CFTR gene has been identified as a causative gene of cystic fibrosis[10], and it is also reported to be a gene associated with pancreatitis[11][12]. About 1–4% of the overall cystic fibrosis population will have an episode of pancreatitis. Mutation causes a defect in the CFTR protein that causes abnormal HCO_3^- transport, leading to defective pancreatic secretion[39]. As a result of impaired pancreatic juice alkalinization and water secretion, protein plugs form in the pancreas and/or pancreatic duct[40]. Regarding the relationship with CP, it has been reported that splicing efficiency and channel function decrease due to poly T polymorphism, TG repeat polymorphism, and p.Q1352H polymorphism[11][12][41]. Some CFTR mutations can be inherited in a complex-type pattern. The CFTR gene is considered to be a high-risk for developing CP when it is associated with other multiple mutations (complex heterozygotes mutation), especially SPINK1 gene mutations[42][43][44].

2.2. PRSS1 Gene

Mutations in PRSS, which encodes cationic trypsinogen, the most abundant isoform of trypsinogen in human pancreatic juice, can occur. In 1996, the p.R122H in the PRSS1 gene was first identified as a cause of HP[1]. In the following years, the p.N29I mutation was detected as a new mutation in HP patients[45]. The p.R122H mutation is the most common (~65%), followed by p.N29I mutation (~25%), and p.A16V. Increased trypsin levels are generated at the onset of pancreatitis, but not through the same biological mechanism. The p.R122H mutation (autolysis site) inhibits trypsin self-destruction, resulting in increased trypsin stability and a high level of trypsin in the pancreas, leading to pancreatic

autodigestion and pancreatitis[46]. The p.A16V mutation (activation site) increases N-terminal processing of the trypsinogen activation peptide by CTRC, which in turn enhances autoactivation[46][47]. The p.N29I mutation affects both degradation and autoactivation in trypsinogen biochemistry[46].

Alternatively, a subset of PRSS1 mutations can cause misfolding and endoplasmic reticulum stress[48]. In 2009, the p.R116C mutation found in HP families with incomplete penetrance was first reported as a cause of CP by a misfolding-dependent pathway. Since then, several variants such as p.D100H, pC139F, p.K29N, p.S124F, and p.G208A have been reported, likely involving this pathway, but the detailed pathogenic mechanism is still unclear[49].

2.3. SPINK1 Gene

SPINK1 encodes a pancreatic secretory trypsin inhibitor, and mutations interfere with the protective function, and predispose a person to pancreatitis, possibly via increased intrapancreatic trypsin activity. SPINK1, together with the protease inhibitors α_1-antitrypsin and α_2-macroglobulin, binds to activated trypsin and inhibits its activity. SPINK1 inhibits about 20% of total trypsin activity, and acts as a primary defense mechanism[50][51]. The trypsin binding site is encoded on exon 3. The most common mutation is the p.N34S mutation. According to the first report by Witt et al., the p.N34S variant was found in 18 of 85 (21%) children with idiopathic pancreatitis[13]. However, the p.N34S mutation is even present in 0–2% of otherwise healthy persons, suggesting that this mutation is thought to be a disease-modifying factor rather than a causative factor, when additional risk factors for pancreatic inflammation such as alcohol, tobacco consumption, or genetic factors are present[51][52]. Actually, the p.N34S variation had no effect on the secretion of SPINK1 protein from transfected cells and trypsin inhibitory activity of the mutant protein was also unchanged[53][54]. Recently, the p.N34S mutation was found in 20% of patients carrying the functionally defective TRPV6 variants[24], suggesting that the combination of mutated TRPV6 and SPINK1 p.N34S results in predisposition to pancreatitis, as well as the CFTR gene. The next most frequent mutation is the c.194 + 2T > C mutation, which has often been reported in Asian persons in Japan, China, and South Korea[55][56][57]. In the c.194 + 2T > C mutation, because exon 3 is skipped, due to a slicing aberration, trypsin activation cannot be inhibited, and pancreatitis occurs [58].

2.4. CTRC Gene

Following the finding that CTRC specifically degrades trypsin, the association betweenCTRC mutations and pancreatitis was investigated[18]. CFTR mutations have been shown to occur in 0.7% of healthy controls and 2.9% of adults with CP[18]. In a recent cohort from the International Study Group for Pediatric Pancreatitis: In Search of a Cure (INSPPIRE), it was reported that early-onset pancreatitis below 6 years of age was likely associated with genetic abnormalities, particularly PRSS1 (43%) or CTRC (14%) mutations[2]. CTRC serves as a second lone defense against premature activation of trypsinogen isoforms[18]. Mutations of CTRC cause loss of function by several mechanisms, which include severe reduction of CTRC secretion (p.A73T), inactive CTRC (p.K247_R254del), promotion of degradation by trypsin (p.R254W), decreased CTRC activity (p.V235I), or decreased CTRC mRNA (p.G60 =)[18][59][60]. Of note, only CTRC pathogenic variants do not seem to cause CP, but rather they are seen in combination with other variants, such as CTRC or SPINK1 mutations[18][43][60], or with anatomic anomalies of the pancreaticobiliary system[33][61].

2.5. CPA1 Gene

The mechanism by which a CPA1 mutation confers an increased risk of pancreatitis involves misfolding-induced endoplasmic reticulum stress, rather than increased trypsin activity[20]. CPA1 mutations with less than 20% apparent activity of the CPA1 protein have been observed to be significantly overrepresented in patients with CP. The functionally impaired CPA1 variants with less than 20% functionality were found in 3.1% of non-alcoholic CP patients (29/944) and 0.1% of controls (5/3938) ($p < 0.01$). The most frequent functionally impaired variant was p.N256K, and it was observed in 0.7% (7/944) of patients and 0% (0/3938) of controls. The risk for pancreatitis was 38-fold greater in patients younger than 20 years old and 84-fold greater in patients younger than 10 years old. The associations between CPA1 mutations and non-alcoholic CP patients have also been reported in additional cohorts from Europe (1.3% (8/600) and 0.4% (9/2432) ($p < 0.01$)), India (2.5% (6/239) and 0.3% (1/340) ($p < 0.05$)), and Japan (2.0% (5/247) and 0% (0/341) ($p < 0.05$))[20].

2.6. TRPV6 Gene

TRPV6 is a member of the transient receptor potential vanilloid ion channel superfamily[62]. TRPV6 promotes high Ca^{2+} entry in absorptive and secretory tissues. It is mainly expressed in Ca^{2+}-transporting epithelia. In the pancreas, TRPV6 expression is nearly 6-times higher in ductal cells than in acinar cells[63]. More recently, Masamune et al. reported that impaired Ca^{2+} uptake caused by TRPV6 variants was associated with early-onset CP[24]. Interestingly, 6 out of 30 (20%) patients with functionally defective TRPV6 variants were trans-heterozygous for SPINK1 p.N34S [24], indicating that CP is a complex multigenic disease, and a cumulative genetic handicap seems to be crucial for the development of early-onset CP.

2.7. Others

CASR, first characterized in the bovine parathyroid[64], expressed in the pancreas can respond to high calcium concentrations in the pancreatic juice by increasing ductal fluid secretion, thereby preventing stone formation and pancreatitis[65]. An association between developing CP and variants in theCASR gene has been reported [14][15][16][17], but the evidence remains uncertain.

PRSS2 is another major trypsinogen isoform constituting the bulk of secreted trypsinogen in humans[66]. No pathogenic PRSS2 variants have been identified in HP and sporadic pancreatitis[27]. The variant p.G191R introduces a trypsin cut site anionic trypsin, which reduces the overall activity of PRSS2, indicating that this variant confers protection from CP[27].

CLDN2 is expressed in the proximal pancreatic duct and promotes H_2O and Na^+ transport to counter Cl^- and HCO_3^- secretion through CFTR[19]. CLDN2 mutations, an X-chromosome locus gene, were found to be associated with alcohol-related and sporadic pancreatitis[19]. Since men are hemizygous for the X chromosome, the risk appears dominant, whereas it is inherited as a recessive pattern in women.

Mutations in CEL cause maturity-onset diabetes of the young type 8 (MODY8), as well as pancreatic exocrine dysfunction[25]. A hybrid CEL allele (CEL-HYB1), formed by nonallelic homologous recombination between CEL and its adjacent pseudo-gene CELP, was enriched approximately 5-fold in patients with idiopathic CP[21]. This hybrid protein was poorly secreted due to intracellular retention, leading to endoplasmic reticulum stress and apoptosis in an in vitro experiment [21].

The changes in the balance of chymotrypsin isoforms, namely inversion at the CTRB1 and CTRB2 locus, that affect trypsin degradation slightly increased the risk of alcoholic and non-alcoholic CP[22][67]. In addition, several variants of PNLIP gene, particularly p.F300L, were associated with early onset and non-alcoholic CP in the European population, but the mechanism remains unclear[23].

3. Conclusions

Clinicians need to know the characteristics of ARP and CP with genetic abnormalities. Genetic testing for patients with unknown etiology is useful by analyzing CEL, CFTR, CPA1, CTRC, PRSS1, and SPINK1 genes, after the major causes of AR and CP have been excluded. In addition, testing for protective variants of PRSS2 gene is not useful clinically. The clinical usefulness of testing mutations of the genes encoding CLNN2, CTRB1, CTRB2, and PNLIP is limited due to their high frequency and narrow range of clinical symptoms. Genetic counseling prior to and after testing is required in all patients. Clinicians should carefully follow ARP and CP patients with genetic mutations, since they have a potentially high risk of developing pancreatic exocrine insufficiency, diabetes mellitus, and pancreatic cancer.

References

1. Whitcomb, D.C.; Gorry, M.C.; Preston, R.A.; Furey, W.; Sossenheimer, M.J.; Ulrich, C.D.; Martin, S.P.; Gates, L.K., Jr.; Amann, S.T.; Toskes, P.P.; et al. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat. Genet. 1996, 14, 141–145.
2. Giefer, M.J.; Lowe, M.E.; Werlin, S.L.; Zimmerman, B.; Wilschanski, M.; Troendle, D.; Schwarzenberg, S.J.; Poh, L.J.F.; Palermo, J.; Ooi, C.Y.; et al. Early-Onset Acute Recurrent and Chronic Pancreatitis Is Associated with PRSS1 or CTRC Gene Mutations. J. Pediatr. 2017, 186, 95–100.
3. Masamune, A.; Kikuta, K.; Hamada, S.; Nakano, E.; Kume, K.; Inui, A.; Shimizu, T.; Takeyama, Y.; Nio, M.; Shimosegawa, T. Nationwide survey of hereditary pancreatitis in Japan. J. Gastroenterol. 2018, 53, 152–160.

4. Joergensen, M.T.; Brusgaard, K.; Cruger, D.G.; Gerdes, A.M.; Schaffalitzky de Muckadell, O.B. Genetic; epidemiological; and clinical aspects of hereditary pancreatitis, a population-based cohort study in Denmark. Am. J. Gastroenterol. 2010, 105, 1876–1883.
5. Rebours, V.; Boutron-Ruault, M.C.; Schnee, M.; Ferec, C.; Le Marechal, C.; Hentic, O.; Maire, F.; Hammel, P.; Ruszniewski, P.; Levy, P. The natural history of hereditary pancreatitis, a national series. Gut 2009, 58, 97–103.
6. Mayerle, J.; Sendler, M.; Hegyi, E.; Beyer, G.; Lerch, M.M.; Sahin-Toth, M. Genetics, Cell Biology, and Pathophysiology of Pancreatitis. Gastroenterology 2019, 156, 1951–1968.e1.
7. Muller, N.; Sarantitis, I.; Rouanet, M.; de Mestier, L.; Halloran, C.; Greenhalf, W.; Ferec, C.; Masson, E.; Ruszniewski, P.; Levy, P.; et al. Natural history of SPINK1 germline mutation related-pancreatitis. EBioMedicine 2019, 48, 581–591.
8. Comfort, M.W.; Steinberg, A.G. Pedigree of a family with hereditary chronic relapsing pancreatitis. Gastroenterology 1952, 21, 54–63.
9. Gross, J.B.; Gambill, E.E.; Ulrich, J.A. Hereditary pancreatitis. Description of a fifth kindred and summary of clinical features. Am. J. Med. 1962, 33, 358–364.
10. Riordan, J.R.; Rommens, J.M.; Kerem, B.; Alon, N.; Rozmahel, R.; Grzelczak, Z.; Zielenski, J.; Lok, S.; Plavsic, N.; Chou, J.L.; et al. Identification of the cystic fibrosis gene, cloning and characterization of complementary DNA. Science 1989, 245, 1066–1073.
11. Cohn, J.A.; Friedman, K.J.; Noone, P.G.; Knowles, M.R.; Silverman, L.M.; Jowell, P.S. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N. Engl. J. Med. 1998, 339, 653–658.
12. 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.
13. Witt, H.; Luck, W.; Hennies, H.C.; 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.
14. Felderbauer, P.; Hoffmann, P.; Einwachter, H.; Bulut, K.; Ansorge, N.; Schmitz, F.; Schmidt, W.E. A novel mutation of the calcium sensing receptor gene is associated with chronic pancreatitis in a family with heterozygous SPINK1 mutations. BMC Gastroenterol. 2003, 3, 34.
15. Felderbauer, P.; Klein, W.; Bulut, K.; Ansorge, N.; Dekomien, G.; Werner, I.; Epplen, J.T.; Schmitz, F.; Schmidt, W.E. Mutations in the calcium-sensing receptor, a new genetic risk factor for chronic pancreatitis? Scand. J. Gastroenterol. 2006, 41, 343–348.
16. Muddana, V.; Lamb, J.; Greer, J.B.; Elinoff, B.; Hawes, R.H.; Cotton, P.B.; Anderson, M.A.; Brand, R.E.; Slivka, A.; Whitcomb, D.C. Association between calcium sensing receptor gene polymorphisms and chronic pancreatitis in a US population, role of serine protease inhibitor Kazal 1type and alcohol. World. J. Gastroenterol. 2008, 14, 4486–4491.
17. Masson, E.; Chen, J.M.; Ferec, C. Overrepresentation of Rare CASR Coding Variants in a Sample of Young French Patients with Idiopathic Chronic Pancreatitis. Pancreas 2015, 44, 996–998.
18. Rosendahl, J.; Witt, H.; Szmola, R.; Bhatia, E.; Ozsvari, B.; Landt, O.; Schulz, H.U.; Gress, T.M.; Pfutzer, R.; Lohr, M.; et al. Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis. Nat. Genet. 2008, 40, 78–82.
19. Whitcomb, D.C.; LaRusch, J.; Krasinskas, A.M.; Klei, L.; Smith, J.P.; Brand, R.E.; Neoptolemos, J.P.; Lerch, M.M.; Tector, M.; Sandhu, B.S.; 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.
20. Witt, H.; Beer, S.; Rosendahl, J.; Chen, J.M.; Chandak, G.R.; Masamune, A.; Bence, M.; Szmola, R.; Oracz, G.; Macek, M.; et al. Variants in CPA1 are strongly associated with early onset chronic pancreatitis. Nat. Genet. 2013, 45, 1216–1220.
21. Fjeld, K.; Weiss, F.U.; Lasher, D.; Rosendahl, J.; Chen, J.M.; Johansson, B.B.; Kirsten, H.; Ruffert, C.; Masson, E.; Steine, S.J.; et al. A recombined allele of the lipase gene CEL and its pseudogene CELP confers susceptibility to chronic pancreatitis. Nat. Genet. 2015, 47, 518–522.
22. Rosendahl, J.; Kirsten, H.; Hegyi, E.; Kovacs, P.; Weiss, F.U.; Laumen, H.; Lichtner, P.; Ruffert, C.; Chen, J.M.; Masso, N.E.; et al. Genome-wide association study identifies inversion in the CTRB1-CTRB2 locus to modify risk for alcoholic and non-alcoholic chronic pancreatitis. Gut 2018, 67, 1855–1863.
23. Lasher, D.; Szabo, A.; Masamune, A.; Chen, J.M.; Xiao, X.; Whitcomb, D.C.; Barmada, M.M.; Ewers, M.; Ruffert, C.; Paliwal, S.; et al. Protease-Sensitive Pancreatic Lipase Variants Are Associated With Early Onset Chronic Pancreatitis. Am. J. Gastroenterol. 2019, 114, 974–983.
24. Masamune, A.; Kotani, H.; Sorgel, F.L.; Chen, J.M.; Hamada, S.; Sakaguchi, R.; Masson, E.; Nakano, E.; Kakuta, Y.; Niihori, T.; et al. Variants That Affect Function of Calcium Channel TRPV6 Are Associated With Early-Onset Chronic Pancreatitis. Gastroenterology 2020, 158, 1626–1641.e8.
25. Raeder, H.; Johansson, S.; Holm, P.I.; Haldorsen, I.S.; Mas, E.; Sbarra, V.; Nermoen, I.; Eide, S.A.; Grevle, L.; Bjorkhaug, L.; et al. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. Nat. Genet. 2006, 38, 54–62.
26. Kujko, A.A.; Berki, D.M.; Oracz, G.; Wejnarska, K.; Antoniuk, J.; Wertheim-Tysarowska, K.; Kolodziejczyk, E.; Bal, J.; Sahin-Toth, M.; Rygiel, A.M. A novel p.Ser282Pro CPA1 variant is associated with autosomal dominant hereditary pancreatitis. Gut 2017, 66, 1728–1730.
27. Witt, H.; Sahin-Toth, M.; Landt, O.; Chen, J.M.; Kahne, T.; Drenth, J.P.; Kukor, Z.; Szepessy, E.; Halangk, W.; Dahm, S.; et al. A degradation-sensitive anionic trypsinogen (PRSS2) variant protects against chronic pancreatitis. Nat. Genet. 2006, 38, 668–673.
28. Banks, P.A. Epidemiology; natural history; and predictors of disease outcome in acute and chronic pancreatitis. Gastrointest. Endosc. 2002, 56, S226–S230.
29. Hegyi, P.; Parniczky, A.; Lerch, M.M.; Sheel, A.R.G.; Rebour, S.V.; Forsmark, C.E.; Del Chiaro, M.; Rosendahl, J.; de-Madaria, E.;

Szucs, A.; et al. International Consensus Guidelines for Risk Factors in Chronic Pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology; the American Pancreatic Association; the Japan Pancreas Society; and European Pancreatic Club. Pancreatology 2020, 20, 579–585.
30. DeBanto, J.R.; Goday, P.S.; Pedroso, M.R.; Iftikhar, R.; Fazel, A.; Nayyar, S.; Conwell, D.L.; Demeo, M.T.; Burton, F.R.; Whitcomb, D.C.; et al. Acute pancreatitis in children. Am. J. Gastroenterol. 2002, 97, 1726–1731.
31. Nydegger, A.; Couper, R.T.; Oliver, M.R. Childhood pancreatitis. J. Gastroenterol. Hepatol. 2006, 21, 499–509.
32. Suzuki, M.; Sait, O.N.; Naritaka, N.; Nakano, S.; Minowa, K.; Honda, Y.; Ohtsuka, Y.; Yamataka, A.; Shimizu, T. Scoring system for the prediction of severe acute pancreatitis in children. Pediatr. Int. 2015, 57, 113–118.
33. Saito, N.; Suzuki, M.; Sakurai, Y.; Nakan, O.S.; Naritaka, N.; Minowa, K.; Sai, J.K.; Shimizu, T. Genetic Analysis of Japanese Children With Acute Recurrent and Chronic Pancreatitis. J. Pediatr. Gastroenterol. Nutr. 2016, 63, 431–436.
34. Singh, V.K.; Yadav, D.; Garg, P.K. Diagnosis and Management of Chronic Pancreatitis, A Review. JAMA 2019, 322, 2422–2434.
35. Ellis, I.; Lerch, M.M.; Whitcomb, D.C.; Consensus Committees of the European Registry of Hereditary Pancreatic Diseases MM-CPSGIAoP. Genetic testing for hereditary pancreatitis, guidelines for indications; counselling; consent and privacy issues. Pancreatology 2001, 1, 405–415.
36. Fink, E.N.; Kant, J.A.; Whitcomb, D.C. Genetic counseling for nonsyndromic pancreatitis. Gastroenterol. Clin. North. Am. 2007, 36, 325–333.
37. Howes, N.; Lerch, M.M.; Greenhalf, W.; Stocken, D.D.; Elli, S.I.; Simon, P.; Truninger, K.; Ammann, R.; Cavallini, G.; Charnley, R.M.; et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin. Gastroenterol. Hepatol. 2004, 2, 252–261.
38. Suzuki, M.; Shimizu, T.; Kudo, T.; Suzuki, R.; Ohtsuka, Y.; Yamashiro, Y.; Shimotakahara, A.; Yamataka, A. Usefulness of nonbreath-hold 1-shot magnetic resonance cholangiopancreatography for the evaluation of choledochal cyst in children. J. Pediatr. Gastroenterol. Nutr. 2006, 42, 539–544.
39. Lee, M.G.; Ohana, E.; Park, H.W.; Yang, D.; Muallem, S. Molecular mechanism of pancreatic and salivary gland fluid and HCO3 secretion. Physiol. Rev. 2012, 92, 39–74.
40. Freedman, S.D. New concepts in understanding the pathophysiology of chronic pancreatitis. Int. J. Pancreatol. 1998, 24, 1–8.
41. Fujiki, K.; Ishiguro, H.; Ko, S.B.; Mizuno, N.; Suzuki, Y.; Takemura, T.; Yamamoto, A.; Yoshikawa, T.; Kitagawa, M.; Hayakawa, T.; et al. Genetic evidence for CFTR dysfunction in Japanese, background for chronic pancreatitis. J. Med. Genet. 2004, 41, e55.
42. Noone, P.G.; Zhou, Z.; Silverman, L.M.; Jowell, P.S.; Knowles, M.R.; Cohn, J.A. Cystic fibrosis gene mutations and pancreatitis risk, relation to epithelial ion transport and trypsin inhibitor gene mutations. Gastroenterology 2001, 121, 1310–1319.
43. Rosendahl, J.; Land, T.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.
44. Schneider, A.; Larusch, J.; Sun, X.; Aloe, A.; Lamb, J.; Hawes, R.; Cotton, P.; Brand, R.E.; Anderson, M.A.; Money, M.E.; 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.
45. Gorry, M.C.; Gabbaizedeh, D.; Furey, W.; Gates, L.K., Jr.; Preston, R.A.; Aston, C.E.; Zhang, Y.; Ulrich, C.; Ehrlich, G.D.; Whitcom, B.D.C. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology 1997, 113, 1063–1068.
46. Szabo, A.; Sahin-Toth, M. Increased activation of hereditary pancreatitis-associated human cationic trypsinogen mutants in presence of chymotrypsin C. J. Biol. Chem. 2012, 287, 20701–20710.
47. Nemoda, Z.; Sahin-Toth, M. Chymotrypsin C (caldecrin) stimulates autoactivation of human cationic trypsinogen. J. Biol. Chem. 2006, 281, 11879–11886.
48. Kereszturi, E.; Szmola, R.; Kukor, Z.; Simon, P.; Weiss, F.U.; Lerch, M.M.; Sahin-Toth, M. Hereditary pancreatitis caused by mutation-induced misfolding of human cationic trypsinogen, a novel disease mechanism. Hum. Mutat. 2009, 30, 575–582.
49. Schnur, A.; Beer, S.; Witt, H.; Hegyi, P.; Sahin-Toth, M. Functional effects of 13 rare PRSS1 variants presumed to cause chronic pancreatitis. Gut 2014, 63, 337–343.
50. Hedstrom, J.; Kemppainen, E.; Andersen, J.; Jokela, H.; Puolakkainen, P.; Stenman, U.H. A comparison of serum trypsinogen-2 and trypsin-2-alpha1-antitrypsin complex with lipase and amylase in the diagnosis and assessment of severity in the early phase of acute pancreatitis. Am. J. Gastroenterol. 2001, 96, 424–430.
51. Shimosegawa, T.; Kume, K.; Masamune, A. SPINK1 gene mutations and pancreatitis in Japan. J. Gastroentero. Hepatol. 2006, 21 (Suppl. 3), S47–S51.
52. Truninger, K.; Witt, H.; Kock, J.; Kage, A.; Seifert, B.; Ammann, R.W.; Blum, H.E.; Becker, M. Mutations of the serine protease inhibitor, Kazal type 1 gene, in patients with idiopathic chronic pancreatitis. Am. J. Gastroenterol. 2002, 97, 1133–1137.
53. Kuwata, K.; Hirota, M.; Shimizu, H.; Nakae, M.; Nishihara, S.; Takimoto, A.; Mitsushima, K.; Kikuchi, N.; Endo, K.; Inoue, M.; et al. Functional analysis of recombinant pancreatic secretory trypsin inhibitor protein with amino-acid substitution. J. Gastroenterol. 2002, 37, 928–934.
54. Kiraly, O.; Wartmann, T.; Sahin-Toth, M. Missense mutations in pancreatic secretory trypsin inhibitor (SPINK1) cause intracellular retention and degradation. Gut 2007, 56, 1433–1438.
55. Lee, Y.J.; Kim, K.M.; Choi, J.H.; Lee, B.H.; Kim, G.H.; Yoo, H.W. High incidence of PRSS1 and SPINK1 mutations in Korean children with acute recurrent and chronic pancreatitis. J. Pediatr. Gastroenterol. Nutr. 2011, 52, 478–481.

56. Kume, K.; Masamune, A.; Mizutamari, H.; Kaneko, K.; Kikuta, K.; Sato, H.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.
57. Oh, H.C.; Kim, M.H.; Choi, K.S.; Moon, S.H.; Park, D.H.; Lee, S.S.; Seo, D.W.; Lee, S.K.; Yoo, H.W.; Kim, G.H. Analysis of PRSS1 and SPINK1 mutations in Korean patients with idiopathic and familial pancreatitis. Pancreas 2009, 38, 180–183.
58. Masamune, A.; Kume, K.; Takagi, Y.; Kikuta, K.; Satoh, K.; Satoh, A.; Shimosegawa, T. N34S mutation in the SPINK1 gene is not associated with alternative splicing. Pancreas 2007, 34, 423–428.
59. Beer, S.; Zhou, J.; Szabo, A.; Keiles, S.; Chandak, G.R.; 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.
60. Masson, E.; Chen, J.M.; 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.
61. Suzuki, M.; Minowa, K.; Isayama, H.; Shimizu, T. Acute Recurrent and Chronic Pancreatitis in Children. Pediatr Int. 2020.
62. Fecher-Trost, C.; Wissenbach, U.; Weissgerber, P. TRPV6, From identification to function. Cell. Calcium. 2017, 67, 116–122.
63. Wissenbach, U.; Niemeyer, B.A.; Fixemer, T.; Schneidewind, A.; Trost, C.; Cavalie, A.; Reus, K.; Meese, E.; Bonkhoff, H.; Flockerzi, V. Expression of CaT-like; a novel calcium-selective channel; correlates with the malignancy of prostate cancer. J. Biol. Chem. 2001, 276, 19461–19468.
64. Brown, E.M.; Gamba, G.; Riccardi, D.; Lombardi, M.; Butters, R.; Kifor, O.; Sun, A.; Hediger, M.A.; Lytto, N.J.; Hebert, S.C. Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. Nature 1993, 366, 575–580.
65. Racz, G.Z.; Kittel, A.; Riccardi, D.; Case, R.M.; Elliott, A.C.; Varga, G. Extracellular calcium sensing receptor in human pancreatic cells. Gut 2002, 51, 705–711.
66. Kukor, Z.; Toth, M.; Sahin-Toth, M. Human anionic trypsinogen, properties of autocatalytic activation and degradation and implications in pancreatic diseases. Eur. J. Biochem. 2003, 270, 2047–2058.
67. Jancso, Z.; Hegyi, E.; Sahin-Toth, M. Chymotrypsin Reduces the Severity of Secretagogue-Induced Pancreatitis in Mice. Gastroenterology 2018, 155, 1017–1021.

Keywords

genetic mutations;chronic pancreatitis;pancreatic exocrine insufficiency;diabetes mellitus;pancreatic cancer