SPINK1 c.194+2T>C IVS3+2T>C

Variant is in linkage with variant c.-215G>A

Citations:

Witt H, Luck W, Hennies HC, Classen M, Kage A, Lass U, Landt O, Becker M. (2000) **Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis.** Nat Genet 25, 213-216
1 affected

Pfützer RH, Barmada MM, Brunskill AP, Finch R, Hart PS, Neoptolemos J, Furey WF, Whitcomb DC. (2000) **SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis.** Gastroenterology 119, 615-623
3 affected

Rossi L, Pfützer RH, Parvin S, Ali L, Sattar S, Kahn AK, Gyr N, Whitcomb DC. (2001) **SPINK1/PSTI mutations are associated with tropical pancreatitis in Bangladesh. A preliminary report.** Pancreatology 1, 242-245
1 affected

Weiss FU, Simon P, Bogdanova N, Mayerle J, Dworniczak B, Horst J, Lerch MM. (2005) **Complete cystic fibrosis transmembrane conductance regulator gene sequencing in patients with idiopathic chronic pancreatitis and controls.** Gut 54, 1456-1460
1 affected

Kume K, Masamune A, Mizutamari H, Kaneko K, Kikuta K, Satoh M, Satoh K, Kimura K, Suzuki N, Nagasaki Y, Horii A, Shimosegawa T. (2005) **Mutations in the serine protease inhibitor Kazal Type 1 (*SPINK1*) gene in Japanese patients with pancreatitis.** Pancreatology 5, 354-360
9 affected (3 homozygous), 1 also carried p.N34S

Schneider A, Barmada MM, Slivka A, Martin JA, Whitcomb DC. (2004) **Clinical characterization of patients with idiopathic chronic pancreatitis and *SPINK1* mutations.** Scand J Gastroenterol 39, 903-904
1 affected; possible overlap with Pfützer et al. (2000); not counted

Keiles S, Kammesheidt A. (2006) **Identification of *CFTR, PRSS1*, and *SPINK1* mutations in 381 patients with pancreatitis.** Pancreas 33, 221-227
1 affected

Shimosegawa T, Kume K, Masamune A. (2006) ***SPINK1* gene mutations and pancreatitis in Japan.** J Gastroenterol Hepatol 21 Suppl 3, S47-51
10 affected (3 homozygous), possible overlap with Kume et al. (2005); counted as 1 affected heterozygous

Kume K, Masamune A, Kikuta K, Shimosegawa T. (2006) **[-215G>A; IVS3+2T>C] mutation in the SPINK1 gene causes exon 3 skipping and loss of the trypsin binding site.** Gut 55, 1214
2 affected (1 homozygous), 1 unaffected

Snabboon T, Plengpanich W, Sridama V, Sunthornyothin S, Suwanwalaikorn S, Khovidhunkit W. (2006) **A *SPINK1* gene mutation in a Thai patient with fibrocalculous pancreatic diabetes.** Southeast Asian J Trop Med Public Health 37, 559-562
1 affected

Kalinin VN, Kaifi JT, Schwarzenbach H, Sergeyev AS, Link BC, Bogoevski D, Vashist Y, Izbicki JR, Yekebas EF. (2006) **Association of rare *SPINK1* gene mutation with another base substitution in chronic pancreatitis patients.** World J Gastroenterol 12, 5352-5356
3 affected
Allele specific PCR was used to verify linkage with c.-215G>A

Masamune A, Kume K, Takagi Y, Kikuta K, Satoh K, Satoh A, Shimosegawa T. (2007) **N34S mutation in the *SPINK1* gene is not associated with alternative splicing.** Pancreas 34, 423-428
1 affected, likely overlap with Kume et al. (2006); did not count

Masamune A, Kume K, Shimosegawa T. (2007) **Differential roles of the *SPINK1* gene mutations in alcoholic and nonalcoholic chronic pancreatitis.** J Gastroenterol 42 Suppl 17, 135-140
9 affected (4 homozygous); likely overlap with Shimosegawa et al. (2006); counted 1 homozygous affected

Shimosegawa T, Kume K, Masamune A. (2008) ***SPINK1*, *ADH2*, and *ALDH2* gene variants and alcoholic chronic pancreatitis in Japan.** J Gastroenterol Hepatol 23 Suppl 1, S82-S86
11 affected (3 homozygous), 2 also carried p.N34S; likely overlap with Shimosegawa et al. (2006); 2 heterozygous affected counted

Oh HC, Kim MH, Choi KS, Moon SH, Park do H, Lee SS, Seo DW, Lee SK, Yoo HW, Kim GH. (2009) **Analysis of *PRSS1* and *SPINK1* mutations in Korean patients with idiopathic and familial pancreatitis.** Pancreas 38, 180-183
11 affected (1 homozygous); 1 also carried p.N34S

Chang YT, Wei SC, L PC, Tien YW, Jan IS, Su YN, Wong JM, Chang MC. (2009) **Association and differential role of PRSS1 and SPINK1 mutation in early-onset and late-onset idiopathic chronic pancreatitis in Chinese subjects.** Gut 58, 885
11 affected

Shimosegawa T, Kume K, Satoh K. (2009) **Chronic pancreatitis and pancreatic cancer: prediction and mechanism.** Clin Gastroenterol Hepatol 7 (11 Suppl), S23-S28
1 unaffected; with pancreatic cancer

Boulling A, Witt H, Chandak GR, Masson E, Paliwal S, Bhaskar S, Reddy DN, Cooper DN, Chen JM, Férec C. (2011) **Assessing the pathological relevance of *SPINK1* promoter variants.** Eur J Hum Genet 19, 1066-1073
9 affected, 1 unaffected, 1 affected may overlap with Witt et al. (2000); 8 affected counted
Variant was reported in footnote to Table 1

Baudry C, Rebours V, Houillier P, Hammel P, Ruszniewski P, Levy P. (2010) **Recurrent acute pancreatitis caused by association of a novel mutation of the calcium-sensing receptor gene and a heterozygous mutation of the *SPINK1* gene.** Pancreas 39, 420-421
1 affected, also carried *CASR* p.P682L and had hypercalcemia

Ota Y, Masamune A, Inui K, Kume K, Shimosegawa T, Kikuyama M. (2010) **Phenotypic variability of the homozygous IVS3+2T>C mutation in the serine protease inhibitor Kazal type 1 (*SPINK1*) gene in patients with chronic pancreatitis.** Tohoku J Exp Med 221, 197-201
3 affected (homozygous); 1 unaffected daughter of an affected homozygote

Lee YJ, Kim KM, Choi JH, Lee BH, Kim GH, Yoo HW. (2011) **High incidence of *PRSS1* and *SPINK1* mutations in Korean children with acute recurrent and chronic pancreatitis.** J Pediatr Gastroenterol Nutr 52, 478-481
10 affected (2 homozygous)

Masamune A, Ariga H, Kume K, Kakuta Y, Satoh K, Satoh A, Shimosegawa T. (2011) **Genetic background is different between sentinel and recurrent acute pancreatitis.** J Gastroenterol Hepatol 26, 974-978
1 affected; likely overlap with Shimosegawa et al. (2006, 2008); not counted

Kume K, Masamune A, Ariga H, Hayashi S, Takikawa T, Miura S, Suzuki N, Kikuta K, Hamada S, Hirota M, Kanno A, Shimosegawa T. (2012) **Do genetic variants in the *SPINK1* gene affect the level of serum PSTI?** J Gastroenterol 47, 1267-1274
10 affected (1 homozygous); two also carried p.N34S; likely overlap with Shimosegawa et al. (2006, 2008); 1 heterozygous affected counted
Five unaffected heterozygous family members with normal PSTI levels were only described in Discussion

Rosendahl J, Landt O, Bernadova J, Kovacs P, Teich N, Bödeker H, Keim V, Ruffert C, Mössner J, Kage A, Stumvoll M, Groneberg D, Krüger R, Luck W, Treiber M, Becker M, Witt H. (2013) ***CFTR, SPINK1, CTRC* and *PRSS1* variants in chronic pancreatitis: is the role of mutated *CFTR* overestimated?** Gut 62, 582-592
14 affected, 1 unaffected

Rho ES, Kim E, Koh H, Yoo HW, Lee BH, Kim GH. (2013) T**wo cases of chronic pancreatitis associated with anomalous pancreaticobiliary ductal union and *SPINK1* mutation.** Korean J Pediatr 56, 227-230
1 affected

Ceppa EP, Pitt HA, Hunter JL, Leys CM, Zyromski NJ, Rescorla FJ, Sandrasegaran K, Fogel EL, McHenry LW, Watkins JL, Sherman S, Lehman GA. (2013) **Hereditary pancreatitis: endoscopic and surgical management.** J Gastrointest Surg 17, 847-856
4 affected

Wang W, Sun XT, Weng XL, Zhou DZ, Sun C, Xia T, Hu LH, Lai XW, Ye B, Liu MY, Jiang F, Gao J, Bo LM, Liu Y, Liao Z, Li ZS. (2013) **Comprehensive screening for PRSS1, SPINK1, CFTR, CTRC and CLDN2 gene mutations in Chinese paediatric patients with idiopathic chronic pancreatitis: a cohort study.** BMJ Open 3, e003150
43 affected (10 homozygous)

Sun C, Liao Z, Jiang L, Yang F, Xue G, Zhou Q, Chen R, Sun S, Li Z. (2013) **The contribution of the SPINK1 c.194+2T>C mutation to the clinical course of idiopathic chronic pancreatitis in Chinese patients.** Dig Liver Dis 45, 38-42
53 affected (8 homozygous)

Hamoir C, Pepermans X, Piessevaux H, Jouret-Mourin A, Weynand B, Habyalimana JB, Leal T, Geubel A, Gigot JF, Deprez PH. (2013) **Clinical and morphological characteristics of sporadic genetically determined pancreatitis as compared to idiopathic pancreatitis: higher risk of pancreatic cancer in CFTR variants.** Digestion 87, 229-239
1 affected
Variant was also described incorrectly as 403+2T>C

Masson E, Chen JM, Audrézet MP, Cooper DN, Férec C. (2013) **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 8, e73522
1 affected; likely overlap with Boulling et al. (2011); not counted

Witt H, Beer S, Rosendahl J, Chen JM, Chandak GR, Masamune A, Bence M, Szmola R, Oracz G, Macek M Jr, Bhatia E, Steigenberger S, Lasher D, Bühler F, Delaporte C, Tebbing J, Ludwig M, Pilsak C, Saum K, Bugert P, Masson E, Paliwal S, Bhaskar S, Sobczynska-Tomaszewska A, Bak D, Balascak I, Choudhuri G, Nageshwar Reddy D, Rao GV, Thomas V, Kume K, Nakano E, Kakuta Y, Shimosegawa T, Durko L, Szabó A, Schnúr A, Hegyi P, Rakonczay Z Jr, Pfützer R, Schneider A, Groneberg DA, Braun M, Schmidt H, Witt U, Friess H, Algül H, Landt O, Schuelke M, Krüger R, Wiedenmann B, Schmidt F, Zimmer KP, Kovacs P, Stumvoll M, Blüher M, Müller T, Janecke A, Teich N, Grützmann R, Schulz HU, Mössner J, Keim V, Löhr M, Férec C, Sahin-Tóth M. (2013) **Variants in *CPA1* are strongly associated with early onset chronic pancreatitis.** Nat Genet 45, 1216-1220
Witt, 20 affected; 12 also carried p.N34S, likely overlap with Rosendahl et al. (2013); 6 affected counted

Masamune A. (2014) **Genetics of pancreatitis: the 2014 update.** Tohoku J Exp Med 232, 69-77
18 affected (3 homozygous); likely overlap with Shimosegawa et al. (2006, 2008); 7 affected heterozygous counted

Schubert S, Traub F, Brakensiek K, von Kopylow K, Marohn B, Maelzer M, Gaedcke J, Kreipe H, Stuhrmann M. (2014) ***CFTR, SPINK1, PRSS1,* and *CTRC* mutations are not associated with pancreatic cancer in German patients.** Pancreas 43, 1078-1082
4 affected; 1 also had pancreatic cancer

Singh S, Choudhuri G, Agarwal S. (2014) **Frequency of CFTR, SPINK1, and cathepsin B gene mutation in North Indian population: connections between genetics and clinical data.** Scientific World Journal, 2014:763195
10 affected, 1 unaffected

Chang MC, Jan IS, Liang PC, Jeng YM, Yang CY, Tien YW, Wong JM, Chang YT. (2014) **Human cationic trypsinogen but not serine peptidase inhibitor, Kazal type 1 variants increase the risk of type 1 autoimmune pancreatitis.** J Gastroenterol Hepatol 29, 2038-2042
1 affected

Sun C, Liu MY, Liu XG, Hu LH, Xia T, Liao Z, Li ZS. (2015) **Serine protease inhibitor Kazal type 1 (SPINK1) c.194+2T>C mutation may predict long-term outcome of endoscopic treatments in idiopathic chronic pancreatitis.** Medicine (Baltimore) 94, e2046
58 affected, homozygotes not specified

Hegyi E, Geisz A, Sahin-Tóth M, Derikx M, Németh BC, Balázs A, Hritz I, Izbéki F, Halász A, Párniczky A, Takács T, Kelemen D, Sarlós P, Hegyi P, Czakó L. (2016) ***SPINK1* promoter variants in chronic pancreatitis.** Pancreas 45, 148-153
3 affected

Cho SM, Shin S, Lee KA. (2016) ***PRSS1, SPINK1, CFTR,* and *CTRC* pathogenic variants in Korean patients with idiopathic pancreatitis.** Ann Lab Med 36, 555-560
12 affected

Saito N, Suzuki M, Sakurai Y, Nakano S, Naritaka N, Minowa K, Sai JK, Shimizu T. (2016) **Genetic analysis of Japanese children with acute recurrent and chronic pancreatitis.** J Pediatr Gastroenterol Nutr 2016 Jun 21. [Epub ahead of print]
13 affected

Dai LN, Chen YW, Yan WH, Lu LN, Tao YJ, Cai W. (2016) **Hereditary pancreatitis of 3 Chinese children: Case report and literature review.** Medicine (Baltimore) 95, e4604
2 affected, 2 unaffected

Functional studies:

Kume K, Masamune A, Kikuta K, Shimosegawa T. (2006) **[-215G>A; IVS3+2T>C] mutation in the *SPINK1* gene causes exon 3 skipping and loss of the trypsin binding site.** Gut 55, 1214

Masamune A, Kume K, Takagi Y, Kikuta K, Satoh K, Satoh A, Shimosegawa T. (2007) **N34S mutation in the *SPINK1* gene is not associated with alternative splicing.** Pancreas 34, 423-428

Kereszturi E, Király O, Sahin-Tóth M. (2009) **Minigene analysis of intronic variants in common *SPINK1* haplotypes associated with chronic pancreatitis.** Gut 58, 545-549

Kume K, Masamune A, Ariga H, Hayashi S, Takikawa T, Miura S, Suzuki N, Kikuta K, Hamada S, Hirota M, Kanno A, Shimosegawa T. (2012) **Do genetic variants in the *SPINK1* gene affect the level of serum PSTI?** J Gastroenterol 47, 1267-1274

Zou WB, Boulling A, Masson E, Cooper DN, Liao Z, Li ZS, Férec C, Chen JM. (2016) **Clarifying the clinical relevance of *SPINK1* intronic variants in chronic pancreatitis.** Gut 65, 884-886