**SPINK1**  
c.101A>G  
p.N34S  
exon 3

rs17107315

Linked with variants  
c.-4141G>T, c.56-37T>C, c.87+268A>G, c.195-606G>A,  
c.195-66_65insTTTT and c.*16201A>C

Genetic studies:

Number of CP carriers reported: 1889 (238 hm)  
Number of non-CP carriers reported: 402 (9 hm)

1 family with unspecified number of affected and 3 unaffected; counted as 1 affected  
Variant was described at the protein level as N11S

18 affected (6 homozygous)

29 affected (7 homozygous), 3 unaffected

Chen JM, Mercier B, Audrezet MP, Raguenes O, Quere I, Ferec C. (2001) **Mutations of the pancreatic secretory trypsin inhibitor (PSTI) gene in idiopathic chronic pancreatitis.** Gastroenterology 120, 1061-1064  
17 affected (5 homozygous), 3 unaffected

9 affected (1 homozygous)

6 affected (1 homozygous)

3 affected


3 affected


146 affected (20 homozygous), 40 unaffected (2 homozygous)

Figure 1 shows the 2 unaffected homozygous family members


4 affected (1 homozygous)


37 affected (11 homozygous), 7 unaffected (1 homozygous)


10 unaffected; including 2 with pancreatic cancer


59 affected (11 homozygous); 18 affected (6 homozygous) likely overlap with Witt et al. (2000); 41 affected (5 homozygous) counted


1 family with 1 affected and 3 unaffected; 1 affected and 1 unaffected also carried CASR c.518T>C (p.L173P)


23 unaffected (3 homozygous); including 11 with diabetes (3 homozygous)


3 affected (1 homozygous), 1 heterozygous also carried CFTR p.L997F
1 affected

6 affected, 3 unaffected; likely overlap with Pfützer et al. (2000); 2 affected counted

5 affected, 7 unaffected (4 with pancreatic cancer and 3 with cholecystitis)

5 affected, 2 unaffected; all carried PRSS1 p.R122H

7 affected (2 homozygous); 1 homozygous and 1 heterozygous who also carried p.R67C were reported in 2001; 5 affected counted (1 homozygous)

9 affected, likely overlap with Kuwata et al. (2001, 2003); homozygotes not specified; not counted

2 affected (also HIV positive), 2 unaffected

5 unaffected including 2 with chronic parotitis

75 affected (15 homozygous), 8 unaffected, possible overlap with Chandak et al. (2002); 44 affected (7 homozygous) and 5 unaffected counted
1 family with 2 affected (homozygous, 1 also with pancreatic cancer) and 5 unaffected

1 family with 1 affected (pregnant) and 1 unaffected, plus 1 affected sister with heterozygous c.*32C>T but no p.N34S

5 affected; 1 also carried p.P55S, 3 unaffected, likely overlap with previous papers from same group; not counted

1 affected

1 affected

8 affected

14 affected (1 homozygous), 19 unaffected including 7 with pancreatic cancer

29 affected (1 homozygous), 12 unaffected, controls overlap with Lempinen et al. (2005); only affected counted

37 unaffected, includes 22 with diabetes
9 affected (1 homozygous), 1 unaffected

7 affected (1 homozygous), 1 unaffected; likely overlap Lemppinen et al. (2005) and/or Tukiainen et al. (2005); not counted

22 affected

11 affected (1 homozygous), 1 unaffected; possible overlap with Kume et al. (2005); 2 affected heterozygous counted

4 affected, 2 unaffected
Text and Table 4 contradict; text value was counted

134 affected; likely overlap with Chandak et al. (2002, 2004); homozygotes not specified; 59 affected counted as heterozygous

52 affected, 3 unaffected, likely overlap with Chandak et al. (2002, 2004) and Mahurkar et al. (2006); homozygotes not specified; not counted

66 affected (7 homozygous), 38 unaffected

14 affected (2 homozygous)
10 affected

2 affected (homozygous)

11 affected (1 homozygous), 1 unaffected; likely overlap with Shimosegawa et al. (2006); not counted

PaCa44 and PancTu-1 cell lines are heterozygous; not counted

1 family with 1 affected who also carried p.G48E and 1 unaffected

2 affected

2 unaffected

Aoun E, Slivka A, Papachristou DJ, Gleeson FC, Whitcomb DC, Papachristou GI. (2007) Rapid evolution from the first episode of acute pancreatitis to chronic pancreatitis in human subjects. JOP 8, 573-578
2 affected (1 homozygous)

48 affected, likely overlap with Chandak et al. (2002, 2004), Mahurkar et al. (2006) and Bhaskar et al. (2006); homozygotes not specified; not counted

12 affected (2 homozygous), 2 unaffected; likely overlap with Shimosegawa et al. (2006); 1 affected (homozygous) counted

11 affected, mutation not specified; counted as heterozygous p.N34S

148 affected; likely overlap with Chandak et al. (2002, 2004), Mahurkar et al. (2006, 2007) and Bhaskar et al. (2006), homozygotes not specified; 14 affected counted as heterozygous

4 affected

3 unaffected; with hyperenzymemia

24 affected (1 homozygous), 18 unaffected

57 affected, 21 unaffected, possible overlap with Pfützer et al. (2000), homozygotes not specified; 28 affected and 18 unaffected counted as heterozygous

5 affected

6 affected, 6 unaffected

67 affected (13 homozygous), 10 unaffected


2 unaffected (homozygous); with fatty liver disease
Oddly, homozygotes found only; no heterozygous carriers


5 affected


1 family with 2 affected (1 homozygous) and 1 unaffected


6 affected

Oh HC, Kim MH, Choi KS, Moon SH, Park do H, Lee SS, Seo DW, Lee SK, Yoo HW, Kim GH. (2009) **Analysis of PRSSI and SPINK1 mutations in Korean patients with idiopathic and familial pancreatitis.** Pancreas 38, 180-183

3 affected


47 affected (7 homozygous), 7 unaffected


5 affected, 1 unaffected


1 affected; mutation not specified; counted as heterozygous p.N34S

22 affected (4 homozygous); 2 heterozygous and 2 homozygous with pancreas divisum, 1 unaffected


19 affected (6 also with pancreatic cancer), 5 unaffected (3 with pancreatic cancer)

Paper also describes family previously reported by Masamune et al. (2004)

Aoun E, Muddana V, Papachristou GI, Whitcomb DC. (2010) \textit{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 105, 446-451

9 affected (3 homozygous), 19 unaffected, possible overlap with Pfützer et al. (2000) and Muddana et al. (2008); not counted


1 affected (with PanINs), also carried \textit{CFTR 2789+5G>A} and \textit{IVS-5T}

Maruyama K, Harada S, Yokoyama A, Mizukami S, Naruse S, Hirota M, Nishimori I, Otsuki M. (2010) \textit{Association analyses of genetic polymorphisms of GSTM1, GSTT1, NQO1, NAT2, LPL, PRSS1, PSTI, and CFTR with chronic alcoholic pancreatitis in Japan}. Alcohol Clin Exp Res 34 Suppl 1, S34-S38

Unclear what, if anything, was found


2 affected


4 affected (1 homozygous)


48 affected (8 homozygous), 4 unaffected; possible overlap with Garg et al. (2009); 26 affected (4 homozygous) and 3 unaffected counted


haplotypes and susceptibility to chronic pancreatitis and congenital bilateral absence of the vas deferens. Hum Mutat 32, 912-920
97 affected (13 homozygous), 7 unaffected, likely overlap with Witt et al. (2000, 2001) and Truninger et al. (2002); 73 heterozygous (7 homozygous) affected counted

13 affected

8 affected, 2 unaffected

10 affected (5 homozygous), 3 unaffected (1 homozygous); study highly problematic; not counted

6 affected
Mutation not specified; counted as heterozygous p.N34S

12 affected (1 homozygous); likely overlap with prior papers from the Shimosegawa group; not counted

4 affected

2 affected, 2 unaffected

25 affected, mutations not specified, not counted

15 affected, 2 unaffected


3 affected


2 affected


1 family with 1 affected and 1 unaffected


107 affected (17 homozygous), 26 unaffected. Possible overlap with Witt et al. (2000); Keim et al. (2003) and Steiner et al. (2011); 10 affected (4 homozygous) counted; 19 unaffected counted


1 family with 1 affected and 1 unaffected


3 affected


1 affected


1 affected

8 affected

20 affected, likely overlap with previous Chandak papers, homozygotes not specified; not counted

14 affected (1 homozygous), 1 also carried CFTR p.F508del, 1 also carried CFTR p.L997F

38 affected (14 homozygous; 1 also carried homozygous p.R65Q); likely overlap with Chen et al. (2000, 2001); 16 affected (9 homozygous) counted

3 affected, 1 unaffected


3 affected, 1 unaffected

1 affected; also carried PRSS1 p.R122C, 3 unaffected, 1 also carried PRSS1 p.R122C
22 affected (1 homozygous), 4 unaffected

11 affected (2 homozygous), 1 unaffected

67 affected (5 homozygous), 3 unaffected

3 subjects; unclear if found in affected or unaffected subjects; counted as affected
Variant is indicated as G>A in Table 2

2 affected (1 homozygous), 5 unaffected (2 homozygous)

3 affected, 1 unaffected

3 affected

3 affected (1 homozygous); likely overlap with prior Whitcomb papers; not counted

12 affected, 1 unaffected
Unaffected control was calculated from percentage given in Discussion
6 affected, 1 unaffected

26 affected (5 homozygous), 1 unaffected

1 affected; heterozygosity not specified

1 affected (homozygous)

3 affected, 1 unaffected

Moran RA, Quesada-Vazquez N, Sinha A, de-Madaria E, Singh VK. (2016) High penetrance of the PRSS1 A16V mutation in a kindred with SPINK1 N34S and CFTR TG11-5T co-mutations. Pancreas 45, e2-4
3 affected (2 homozygous), 1 unaffected; 1 affected heterozygous and 1 homozygous and the 1 unaffected also carried PRSS1 p.A16V

168 affected (33 homozygous); likely overlap with prior Chandak papers; 38 affected (18 homozygous) counted

2 affected

5 affected, 1 unaffected
10 affected

3 affected

19 affected (1 homozygous)

1 affected; also had pancreatic cancer

Midha S, Sreenivas V, Kabra M, Chattopadhyay TK, Joshi YK, Garg PK. (2016) Genetically determined chronic pancreatitis but not alcoholic pancreatitis is a strong risk factor for pancreatic cancer. Pancreas 45, 1478-1484
16 affected; also had pancreatic cancer

1 affected, also carried c.194+2T>C

13 unaffected, 1 pancreatic cancer patient, 12 controls

20 affected

23 affected
1 affected

6 affected, 3 unaffected

1 affected, also carried p.Y54H

10 affected, mutation not specified, counted as p.N34S

18 affected (2 homozygous), mutation not specified, counted as p.N34S

23 affected (3 homozygous), 2 unaffected

Heterozygous variant was found in the PaCa44 and PancTu-I pancreatic cancer cell lines; counted as 2 unaffected

207 affected (41 homozygous), 17 unaffected; unclear overlap with previous reports; all counted
Reported in Supplementary Table S2

26 affected, p.N34S and c.194+2T>C reported together; not counted
1 homozygous affected (no clinical symptoms!), 2 heterozygous unaffected parents

25 affected, homozygotes not specified, likely overlap with Masamune et al. (2014); not counted
Data taken from Table 2

GWAS, tagging SNP c.*16201A>C (rs146437551) was studied; not counted

Functional studies:


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


Boulling A, Chen JM, Callebaut I, Férec C. (2012) **Is the SPINK1 p.Asn34Ser missense mutation per se the true culprit within its associated haplotype?** WebmedCentral GENETICS 2012; 3, WMC003084

Marchbank T, Mahmood A, Playford RJ. (2013) **Pancreatic secretory trypsin inhibitor causes autocrine-mediated migration and invasion in bladder cancer and phosphorylates the EGF receptor, Akt2 and Akt3, and ERK1 and ERK2.** Am J Physiol Renal Physiol 305, F382-389


Wu H, Boulling A, Cooper DN, Li ZS, Liao Z, Férec C, Chen JM. (2017) **Analysis of the impact of known SPINK1 missense variants on pre-mRNA splicing and/or mRNA stability in a full-length gene assay.** Genes (Basel) 8(10)