ORIGINAL ARTICLE

The N34S mutation of the SPINK1 gene and alcoholic chronic pancreatitis

Halina Cichoż-Lach[1], Małgorzata Michalak[2], Emilia Lis[1], Jacek Wojcierowski[3], Agnieszka Kowalik[1], Maria Słomka[1], Agnieszka Korolczuk[4]

1 Department of Gastroenterology, Medical University of Lublin, Lublin, Poland
2 Department of Genetics of Cancer, Medical University of Lublin, Lublin, Poland
3 Genetic Testing Laboratory in Lublin, Lublin, Poland
4 Department of Clinical Pathomorphology, Medical University of Lublin, Lublin, Poland

KEY WORDS

alcohol, chronic pancreatitis, SPINK1 gene

ABSTRACT

INTRODUCTION Recent studies have shown the key role of genetic factors in the development of chronic pancreatitis.

OBJECTIVES The aim of the study was to establish whether the frequency of the N34S mutation of serine protease inhibitor Kazal type 1 (SPINK1) gene differs between patients with alcoholic chronic pancreatitis, patients with nonalcoholic chronic pancreatitis, alcoholics without any digestive organ damage, and controls. We also sought to investigate whether the frequency of this mutation differs between women and men, and whether the mutation is associated with the age of patients at first diagnosis of chronic pancreatitis.

PATIENTS AND METHODS The study included 207 patients: 67 with alcoholic chronic pancreatitis, 35 with nonalcoholic chronic pancreatitis, 43 alcoholics with no damage to digestive organs, and 62 healthy volunteers who served as controls. The N34S mutation of the SPINK1 gene was detected with the polymerase chain reaction.

RESULTS The N34S mutation of the SPINK1 gene occurred in 15 of 207 patients (7.25%). The mutation was most frequent in patients with alcoholic chronic pancreatitis (10 patients, 16.39%) and was more frequent compared with the control group (2 patients, 3.23%) ($P = 0.047$). There were no statistically significant differences between the other groups: patients with nonalcoholic chronic pancreatitis (2 patients, 5.71%), alcoholics without digestive organ damage (1 patient, 2.33%), and controls. The mutation was more frequent in men than in women ($P = 0.043$). There were no differences between patients with and without the mutation in terms of the age at first diagnosis of chronic pancreatitis ($P > 0.05$).

CONCLUSIONS The N34S mutation of the SPINK1 gene seems to be significantly correlated with alcoholic chronic pancreatitis.

Correspondence to:
Prof. Halina Cichoż-Lach, MD, PhD, Katedra i Klinika Gastroenterologii, Uniwersytet Medyczny w Lublinie, ul. Jaczewskiego 8, 20-945 Lublin, Poland, phone/fax: +48-817-244-535, e-mail: lach.halina@wp.pl
Received: April 11, 2012.
Revision accepted: June 6, 2012.
Published online: June 6, 2012.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2012; 122 (6): 277-283

INTRODUCTION Chronic pancreatitis is becoming an increasingly common pathology with the incidence of 50 to 70 cases per 100,000 population.[1] Alcohol abuse is among the most common causes of chronic pancreatitis (about 60%–70%) in highly developed countries.[2] Alcoholic chronic pancreatitis occurs with various frequency in different populations and geographical and environmental factors seem to be implicated in its pathogenesis although their involvement has not been fully elucidated.[3] In Japan, half of all the reported cases of chronic pancreatitis is due to alcohol abuse,[4] in Korea – 63.4%.[5] Data from Brazil showed even higher rates – chronic alcoholism is reported there to account for 89.6% of the cases of chronic pancreatitis.[6] In Italy, the rate is 80.4%[7] and in Australia – 95%.[8] In China, the incidence of alcoholic chronic pancreatitis is surprisingly low (19%), but the tropical form of the disease prevails there (46.4%).[8]

From 20% to 30% of the cases of chronic pancreatitis are considered idiopathic. In 10% of the cases, the disease is related to other rare conditions such as hypoparathyroidism, malnutrition, bile duct disorders or abnormal morphology of the organ (pancreas divisum), scarring of the pancreatic ducts, and autoimmune diseases.[9-11] There are no precise data concerning hereditary pancreatitis, but it appears that its incidence is substantially lower than that of the above conditions.[12]

Only from 5% to 10% alcohol addicts develop chronic pancreatitis, and numerous patients who do not drink alcohol at all also suffer from the disease. Therefore, other factors must probably be involved in its pathogenesis which confer individual risk.[3,10,13] Recent studies have suggested the essential role of genetic factors. Studies assessing the role of the polymorphism of genes that code the enzymes involved in ethanol metabolism have provided different results. A number of investigators observed that various polymorphic forms correlated with susceptibility to alcoholic chronic pancreatitis. Nevertheless, the results still remain inconclusive.[14-16]

Among many genetic factors likely to be associated with various etiological forms of chronic pancreatitis are: mutations of the cationic trypsinogen gene (PRSS1), the serine protease inhibitor Kazal type 1 gene (SPINK1), the chymotrypsin gene (CTRC), the cystic fibrosis transmembrane conductance regulator gene (CFTR), the calcium-sensing receptor gene (CASR), and genes coding such cytokines as interleukins, tumor necrosis factor α, transforming growth factor $\beta 1$, and interferon γ, vascular endothelial growth factor, and intercellular adhesion molecule 1.[17] The pancreatic secretory trypsin inhibitor (PST1) is a 79 amino acid peptide encoded by the SPINK1 gene and it operates as an inhibitor of trypsin activity. Therefore, it acts as a barrier or first-line defense against accidental premature activation of trypsinogen in acinar pancreatic cells.[1,17] The N34S mutation in exon 3 of the SPINK1 gene was identified in patients with chronic pancreatitis. Many studies focused on the relation between chronic pancreatitis of various origin and the N34S mutation in different populations. However, this issue have been poorly investigated in the Polish population.

The purpose of the present study was to establish the differences in the frequency of the SPINK1 N34S mutation between patients with alcoholic chronic pancreatitis, nonalcoholic chronic pancreatitis, alcohol addicts (alcoholics) without any digestive organ damage, and controls in the Polish population. We investigated whether N34S mutations of the SPINK1 gene occur with different frequency among men and women and whether the mutations affect the age of disease onset.

PATIENTS AND METHODS

Patients

A group of 207 patients were included in the study: 67 patients with alcoholic chronic pancreatitis, 35 with nonalcoholic chronic pancreatitis, 43 alcoholics with no damage to digestive organs, and 62 healthy volunteers (the control group). Patients were recruited from the Department of Gastroenterology, Medical University of Lublin, Lublin, Poland. The group of alcohol addicts comprised patients from the Department of Therapy of Addiction to Alcohol at the Neuropsychiatric Hospital in Lublin.

Diagnosis of chronic pancreatitis was established based on routine criteria: history of recurrent episodes of acute pancreatitis and abnormalities detected by imaging studies (ultrasonography, abdominal computed tomography, endoscopic retrograde cholangiopancreatography) such as calcifications, parenchymal fibrosis, calcified deposits in the pancreatic ducts, or widened/irregular ducts. In 3 patients, alcoholic chronic pancreatitis was histologically confirmed. Alcoholic etiology was determined on the basis of medical history, i.e., consumption of more than 80 g of pure ethanol/day (men) and more than 40 g of pure ethanol/day (women) over at least 2 years. Of 67 patients with alcoholic chronic pancreatitis, 24 had diabetes. The group of patients with nonalcoholic chronic pancreatitis consisted of patients who had the disease but did not have a personal history of alcohol abuse or a family history of chronic pancreatitis. In 4 patients, autoimmune pancreatitis was diagnosed on the basis of elevated serum immunoglobulin G4 levels. In 2 patients, the biliary origin of chronic pancreatitis was observed. In the remaining 29 cases, toxic, metabolic, and obstruction factors of chronic pancreatitis were excluded so they were considered to have idiopathic chronic pancreatitis.

The group of alcoholics without digestive tract pathologies consisted of individuals who complied with the DSM-IV criteria for alcohol addiction but in whom diagnostic tests excluded digestive pathology.[18] In all of them, laboratory tests showed normal results and abdominal ultrasonography did not reveal any abnormalities. Clinically significant diseases of digestive, respiratory, and circulatory tracts were excluded. All patients showed normal renal function.

The control group included healthy volunteers who reported no or very occasional alcohol consumption below 10 g of pure ethanol/year, so the alcohol dose was assumed as 0 g/day. These data were collected by a face-to-face interview. Controls did not have any evidence of a chronic disease, no disease was diagnosed at physical examination, and they had normal results of laboratory tests and abdominal ultrasonography. They were recruited from among the students and personnel of the Medical University of Lublin.

All participants were Caucasians and were ethnically homogenous. The study was conducted in accordance with the ethical principles of the 1975 Helsinki Declaration, and the study protocol was approved by the Commission of Bioethics at the Medical University of Lublin. All participants signed informed consent to take part in the study. Patient groups are described in TABLE 1.

TABLE 1 Characteristics of the study groups

Patient groups	Number of patients	Women	Men	Age, y	Duration of alcohol consumption, y	Daily dose of pure alcohol consumed, g
ACP	67	9	58	44.19 ±9.04	13.00 ±6.65	136.53 ±41.83
NCP	35	21	14	38.00 ±9.44	0	0
alcoholics	43	10	33	43.53 ±11.27	10.60 ±6.54	172.44 ±52.67
controls	62	29	33	41.38 ±8.88	0	0

Data are presented as mean ± standard deviation.

Abbreviations: ACP – alcoholic chronic pancreatitis, NCP – nonalcoholic chronic pancreatitis

Methods Genomic DNA was extracted from peripheral blood using the spin microcolumns (Blood Mini, A&A Biotechnology, Poland). Purity and quality of the extracted DNA was verified by electrophoresis in 2% agarose gel (Sigma, United States) stained with ethidium bromide and visualized under ultraviolet light transiluminator (Biometra, Germany). For the detection of the N34S mutation (located within exon 3 of the SPINK1 gene), the polymerase chain reaction (PCR)–restriction fragment length polymorphism technique was used. The reaction mixture (25 µl) contained: 2.5 µl of 2 mM dNTP mix (MBI Fermentas, Lithuania), 2.5 µl of 10-fold concentrated reaction buffer (MBI Fermentas), 2.5 µl of 25 mM $MgCl_2$ (MBI Fermentas),10 pmol of primer F 5'-TTCTGTTTAATTCCATTTTTAGGCCAAATGCTGCA-3' (DNA Gdańsk, Poland), 10 pmol of primer R 5'-GGCTTTTATCATACAAGTGACTTCT-3' (DNA Gdańsk), 0.2 µl of Taq 5 U polimerase (MBI Fermentas), 4 µl of genomic DNA, 11.3 µl nuclease free water (Sigma). The PCR reaction was performed in Mastercycler personal (Eppendorf AG, Germany) under the following conditions: initial denaturation at 95°C for 5 minutes; then 35 cycles of denaturation at 94°C for 30 seconds, primer annealing at 60°C for 30 seconds, extension at 72°C for 1 minute; and 1 cycle of final extension at 72°C for 7 minutes. After amplification, each sample (25 µl) was divided into 3 parts each with 8 µl. The first part was subjected to electrophoresis in 3% agarose gel stained with ethidium bromide, voltage – 220V. Jules size marker (MBI Fermentas) was subjected with amplicifation products. If the product length of 325 bp was observed, the remaining 2 parts of this sample were digested with 1 µl PstI Fast Digest enzyme (MBI Fermentas) at 37°C for 30 minutes and 1 µl BsrDI Fast Digest enzyme (MBI Fermentas) at 55°C for 15 minutes and subjected to electrophoresis in 3% agarose gel stained with ethidium bromide. Products of digestion of PstI: wild-type sequence – 325 bp, heterozygote – N34S 325 bp and 290 bp. Products of digestion of BsrDI: wild-type sequence – 285 bp, heterozygote – N34S 325 bp and 285 bp.

Detected mutations were confirmed by sequencing. The steps of sequencing were as follows:

1 The amplification products were diluted 5-fold.

2 Sequential mixture contained 4 µl of BigDye Terminator v 3.1 (Applied Biosystems, country), 2 µl of Sequencing Buffer (Applied Biosystems), 3.2 pmol of primer R, and 1 µl of template DNA; all were completed with water to the volume of 10 µl. Sequencing was conducted in the Biometra thermocycler under the following conditions: initial denaturation at 96°C for 1 minute, then 25 cycles of denaturation at 96°C for 10 seconds, annealing at 50°C for 5 seconds, extension at 60°C for 4 minutes.

3 Sequencing products were purified on spin microcolumns (A&A Biotechnology).

4 Capillary electrophoresis of the sequencing products was performed in ABI Pism 3100 with the capillary length of 36 cm (Applied Biosystems) and polimer POP-6 (Applied Biosystems).

5 Results were analyzed by Sequencing Analysis (Applied Biosystems)[19] modified by Michalak (unpublished data).

Statistical analysis The characteristics of the study population were analyzed and the comparison of the age of disease onset was performed using the *t* test for independent samples. To compare the frequency of the SPINK1 N34S mutation between the study groups, the χ^2 test with Yates' correction was used. Statistical significance between the differences was assumed at the level of *P* less than 0.05. All calculations were performed using the STATISTICA PL software.

RESULTS In the study group of 207 subjects, the N34S mutation of the SPINK1 gene occurred with the frequency of 7.25%. All mutations were heterozygotic (FIGURES 1 and 2). TABLE 2 presents the frequency of the SPINK1 N34S mutation in the study groups. The mutation was most frequent in the group of patients with alcoholic chronic pancreatitis (16.39%) and was more frequent compared with the control group (P = 0.047). The differences between the other examined groups were statistically insignificant.

The N34S mutation of the SPINK1 gene was more frequent in the group of men than in the group of women (10.14% vs. 1.45%; χ^2 = 3.96; P = 0.043; odds ratio, 7.68; 95% confidence interval, 0.99–59.65).

The age of disease onset was similar in the groups of patients with and without the N34S mutation of the SPINK1 gene (TABLE 3).

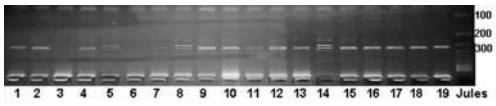

FIGURE 1 Products of digestion of the PstI enzyme subjected to electrophoresis in 3% agarose gel stained with ethidium bromide; lines 5, 8, 14: N34S mutations of the SPINK1 gene (N34S heterozygotes); the remaining lines present wild-type sequence

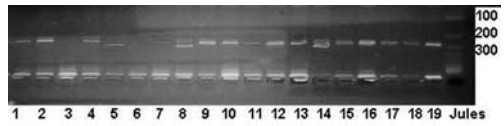

FIGURE 2 Products of digestion of the BsrDI enzyme subjected to electrophoresis in 3% agarose gel stained with ethidium bromide; lines 5, 8, 14: N34S mutations of the SPINK1 gene (N34S heterozygotes); the remaining lines present wild-type sequence

TABLE 2 Frequency of the SPINK1 N34S mutation in the study groups

	Number of patients	Mutation, n (%)		*P*	OR	95% CI
		yes	no			
ACP	67	10 (16.39)	57 (83.61)	0.295[a]	2.90[a]	0.60–14.02[a]
				0.068[b]	7.37[b]	0.91–59.81[b]
				0.047[c]	5.26[c]	1.11–25.07[c]
NCP	35	2 (5.71)	33 (94.29)	0.952[c]	1.82[c]	0.26–12.92[c]
CP (ACP + NCP)	102	12 (11.76)	90 (88.24)	0.108[c]	4.00[c]	0.86–18.5[c]
alcoholics	43	1 (2.33)	42 (97.67)	0.75[c]	0.71[c]	0.07–7.46[c]
controls	62	2 (3.23)	60 (96.87)			

Abbreviations: CI – confidence interval, CP – chronic pancreatitis, OR – odds ratio, others – see **TABLE 1**

a vs. NCP
b vs. alcoholics
c vs. controls

TABLE 3 Mean age (years) of disease onset in the study groups depending on the presence of the SPINK1 N34S mutation

	Number of patients	Mutation, n (%)		*P*
		yes	no	
ACP	67	36.4 ±8.04	42.84 ±9.01	U/H: t = 1.65, *P* >0.05
NCP	35	35.84 ±7.24	38.84 ±9.03	U/H: t = 0.45, *P* >0.05
CP (ACP + NCP)	102	35.98 ±8.24	41.72 ±8.99	U/H: t = 1.72, *P* >0.05

Abbreviations: see **TABLES 1** and **2**

DISCUSSION Methods of molecular genetics have been used to investigate the pathogenesis of chronic pancreatitis. Recent studies have provided controversial results suggesting the involvement of the N34S mutation of the SPINK1 gene, which occurs with varied frequency in particular populations of patients and plays a variable role in the etiology of different forms of chronic pancreatitis.

Our study is the first to have investigated the frequency of the SPINK1 N34S mutation in men and women. We observed that the mutation was more frequent in men than in women. Moreover, we revealed higher incidence of this mutation in Polish patients with alcoholic chronic pancreatitis (16.39%) and the control group (3.23%) compared with the results presented by other authors. This may suggest that the SPINK1 N34S mutation may affect the development of alcoholic chronic pancreatitis in Polish individuals. No such correlation was observed for nonalcoholic pancreatitis.

The findings concerning the N34S mutation of the SPINK1 gene and alcoholic chronic pancreatitis in the Polish population are in contrast with the study by Gąsiorowska et al.[20] who found no such correlations in the group of adult Polish patients. However, their study focused on idiopathic pancreatitis (P <0.05) and they investigated a smaller group of patients (34 with alcoholic pancreatitis and 14 with idiopathic pancreatitis), which may in part explain the discrepancy in the results.[20] We observed that all cases with the N34S mutation of the SPINK1 gene where heterozygous, which was in disagreement with the study by Gąsiorowska et al.[20] who observed 6 homozygous cases. On the other hand, our results are in line with their findings[20] on the high incidence of the SPINK1 N34S mutation of the gene among Polish patients with alcoholic chronic pancreatitis and among the controls (they reported 18% and 6.5%, respectively). Moreover, similarly to Gąsiorowska et al.,[20] we showed no effect of the mutation on the mean age of disease onset.

According to the European reports, the SPINK1 N34S mutation occurs with the frequency of 1% to 4% in the general population in the European countries, while it is substantially more frequent in cases of alcohol-related chronic pancreatitis (2.2%–10%) and in patients with idiopathic pancreatitis (25%).[1,21-24] The presence of this mutation was estimated to be between 0.8% and 2.6% in healthy individuals and 1.0% in alcoholics without chronic pancreatitis.[21] In our study, the incidence of the SPINK1 N34S mutation in the examined subjects was higher than in the majority of the European reports.

Similarly to our findings, the incidence of the mutation in Dutch and Finish populations showed a marked correlation with alcoholic chronic pancreatitis.[1,23] However, data from the studies on the British population showed no significant effect of the SPINK1 N34S mutation on alcoholic chronic pancreatitis.[22]

American studies reported the N34S mutation of the SPINK1 gene in 6.3% of the patients with alcoholic chronic pancreatitis, in 1.6% of the controls ($P > 0.05$), and in 10.3% of the patients with nonalcoholic chronic pancreatitis ($P < 0.005$), which is not in line with our findings. As in our study, they did not find any differences in the course of the disease or the onset age between the groups of patients with alcoholic and nonalcoholic pancreatitis.[25]

Based on a comprehensive literature research by Aoun et al.[26] (who investigated 24 case-control studies), a strong relationship between the N34S mutation of the SPINK1 gene and idiopathic and tropical pancreatitis and a slightly weaker correlation with alcoholic chronic pancreatitis can be postulated.

The studies conducted in the Far East reported different results in patients with alcoholic chronic pancreatitis. The N34S mutation of the SPINK1 gene was not observed among Japanese patients with alcoholic chronic pancreatitis; however, the mutation occurred significantly more frequently (21.1%) in patients with nonalcoholic pancreatitis than in controls (0.6%). The authors underlined a correlation between the mutation and idiopathic and familial chronic pancreatitis but the involvement of the mutation in alcoholic chronic pancreatitis was less evident. However, the role of the N34S mutation was confirmed in developing susceptibility to earlier age of disease onset.[27]

In India, the N34S mutation of SPINK1 gene was noted in 26.8% of the patients with alcoholic chronic pancreatitis compared with 2.76% in the control group ($P < 0.001$). It did not affect the course of pancreatitis and the age of disease onset.[28] Contrary to that, Korean studies found that the mutation did not affect the development of alcoholic chronic pancreatitis and occurred in 2.4% of the examined patients; surprisingly, the mutation was not observed in controls.[29]

The inconclusive results of numerous studies on the associations between the N34S mutation of the SPINK1 gene may result from small study cohorts, which is a crucial limitation in genetic studies.

In conclusion, the N34S mutation of the SPINK1 gene appears to be significantly correlated with alcoholic chronic pancreatitis in Polish individuals. No such correlation was found in patients with chronic pancreatitis of other etiology and among alcoholics without digestive pathology. This mutation is more common in men than in women and does not affect the age of disease onset.

Acknowledgements The major part of this study was supported by the Polish State Committee for Scientific Research, Grant No. N N402 244 635.

REFERENCES

1 Drenth JP, te Morsche R, Jansen JB. Mutations in serine protease inhibitor Kazal type 1 are strongly associated with chronic pancreatitis. Gut. 2002; 50: 687-692.

2 Yadav D, Whitcomb DC. The role of alcohol and smoking in pancreatitis. Nat Rev Gastrenterol Hepatol. 2010; 7: 131-145.

3 Yadav D, Papachristou GI, Whitcomb DC. Alcohol-associated pancreatitis. Gastroenterol Clin N Am. 2007; 36: 219-238.

4 Otsuki M. Chronic pancreatitis in Japan: epidemiology, prognosis, diagnosis criteria and future problems. J Gastroenterol. 2003; 38: 315-326.

5 Ryu JK, Lee JK, Kim YT, et al. Clinical features of chronic pancreatitis in Korea: a multicenter nationwide study. Digestion. 2005; 72: 207-211.

6 Dani R, Mott CB, Guarita DR, et al. Epidemiology and etiology of chronic pancreatitis in Brazil: a tale of two cites. Pancreas. 1990; 5: 474-478.

7 Pezzilli R, Morselli-Labate AM, Fantini L, et al. Assessment of the quality of life in chronic pancreatitis using Sf-12 and EORTC Qlq-C30 questionnaires. Dig Liver Dis. 2007; 39: 1077-1086.

8 Garg PK, Tandon RK. Survey on chronic pancreatitis in the Asia-Pacific region. J Gastrioenterol Hepatol. 2004; 19: 998-1004.

9 Etemad D, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001; 120: 682-707.

10 Lankisch PG, Lowenfels AB, Maisonneuve P. What is the risk of alcoholic pancreatitis in heavy drinkers? Pancreas. 2002; 25: 411-412.

11 Rydzewska G, Jedynak M. [The pathogenesis of alcoholic chronic pancreatitis]. Gastroenterol Pol. 1998; 5: 83-89. Polish.

12 Rosendahl J, Bödeker H, Mössner J, Teich N. Hereditary chronic pancreatitis. Orphanet J Rare Dis. 2007; 2: 1-10.

13 Niebisz-Cieślak AB, Karnafel W. Insulin sensitivity in chronic pancreatitis and features of insulin resistance syndrome Pol Arch Med Wewn. 2010; 120: 255-263.

14 Kimura S, Okabayashi Y, Inushima K, et al. Alcohol and aldehyde dehydrogenase polimorphism in Japanese patients with alcohol-induced chronic pancreatitis. Dig Dis Sci. 2000; 45: 2013-2017.

15 Shimosegawa T, Kume K, Masamune A. SPINK1, ADH2, and ALDH2 gene variants and alcoholic chronic pancreatitis in Japan. J Gastroenterol Hepatol. 2008; 23 Suppl 1: S82-S86.

16 Cichoż-Lach H, Partycka J, Nesina I, et al. Genetic polymorphism of alcohol dehydrogenase 3 in alcohol liver cirrhosis and in alcohol chronic pancreatitis. Alcohol Alcohol. 2006; 41: 14-17.

17 da Costa MZ, Guarita DR, Ono-Nita SK, et al. Genetic risk for alcoholic chronic pancreatitis. Int J Environ Res Public Health. 2011; 8: 2747-2757.

18 Grant BF, Hardford TC, Hasin DS. DSM-III-R and the proposed DSM-IV alcohol use disorders, United States 1988: a nosological comparison. Alcohol Clin Exp Res. 1992; 16: 215-221.

19 Diaconu BL, Ciobanu L, Mocan T, et al. Investigation of the SPINK1 N34S mutation in Romanian patients with alcoholic chronic pancreatitis. A clinical analysis based on the criteria of the M-ANNHEIM classification. J Gastrointestin Liver Dis. 2009; 18: 143-150.

20 Gąsiorowska A, Talar-Wojnarowska R, Czupryniak L, et al. The prevalence of cationic trypsinogen (PRSS1) and serine protease inhibitor, Kazal type 1 (SPINK1) gene mutations in Polish pateints with alcoholic and idiopathic chronic pancreatitis. Dig Dis Sci. 2011; 56: 894-901.

21 Witt H, Luck W, Becker M, et al. Mutation in the SPINK1 trypsin inhibitor gene, alcohol use, and chronic pancreatitis. JAMA. 2001; 285: 2716-2717.

22 Threadgold J, Greenhalf W, Ellis I, et al. The N34S mutation of SPINK1 (PSTI) is associated with a familial pattern of idiopathic chronic pancreatitis but does not cause the disease. Gut. 2002; 50: 675-681.

23 Lempinen M, Paju A, Kemppainen E, et al. Mutations N34S and P55S of the SPINK1 gene in patients with chronic pancreatitis or pancreatic

cancer and in healthy subjects: a report from Finland. Scand J Gastroenterol. 2005; 40: 225-230.

24 Perri F, Piepoli A, Stanziale P, et al. Mutation analysis of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the cationic trypsinogen (PRSS1) gene, and the serine protease inhibitor, Kazal type 1 (SPINK1) gene in patients with alcoholic chronic pancreatitis. Eur J Hum Genet. 2003 11: 687-692.

25 Schneider A, Pfützer R, Barmada MM, et al. Limited contribution of the SPINK1 N34S mutation to the risk and severity of alcoholic chronic pancreatitis: a report from the United States. Dig Dis Sci. 2003; 48: 1110-1115.

26 Aoun E, Chang CCH, Greer JB, et al. Pathways to injury in chronic pancreatitis: decoding the role of the high-risk SPINK1 N34S haplotype using meta-analysis. PloS ONE. 2008; 3: e2003.

27 Masamune A, Kume K, Shimosegawa T. Differential role of the SPINK1 gene mutations In alcoholic and nonalcoholic chronic panreatitis. J Gastroenerol. 2007; 42 Suppl 17: 135-140.

28 Chandak GR, Idris MM, Reddy DN, et al. Absence of PRSS1 mutations and association of SPINK1 trypsin inhibitor mutations in hereditary and non-hereditary chronic pancreatitis. Gut. 2004; 53: 723-728.

29 Lee KH, Ryu JK, Yoon WJ, et al. Mutation analysis of SPINK1 and CFTR gene in Korean patients with alcoholic chronic pancreatitis. Dig Dis Sci. 2005; 50: 1852-1856.

ARTYKUŁ ORYGINALNY

Mutacja N34S genu SPINK1 a alkoholowe przewlekłe zapalenie trzustki

Halina Cichoż-Lach[1], Małgorzata Michalak[2], Emilia Lis[1], Jacek Wojcierowski[3], Agnieszka Kowalik[1], Maria Słomka[1], Agnieszka Korolczuk[4]

1 Katedra i Klinika Gastroenterologii, Uniwersytet Medyczny w Lublinie, Lublin
2 Zakład Genetyki Nowotworów z Pracownią Cytogenetyczną, Uniwersytet Medyczny w Lublinie, Lublin
3 Laboratorium Badań Genetycznych w Lublinie, Lublin
4 Katedra i Zakład Patomorfologii Klinicznej, Uniwersytet Medyczny w Lublinie, Lublin

SŁOWA KLUCZOWE

alkohol, gen SPINK1, przewlekłe zapalenie trzustki

STRESZCZENIE

WPROWADZENIE Badania ostatnich lat dowodzą, że kluczową rolę w rozwoju przewlekłego zapalenia trzustki odgrywają czynniki genetyczne.

CELE Celem pracy było zbadanie czy istnieją różnice w częstości występowania mutacji N34S genu SPINK1 (*serine protease inhibitor Kazal type 1*) między chorymi z alkoholowym przewlekłym zapaleniem trzustki, niealkoholowym przewlekłym zapaleniem trzustki, alkoholikami bez uszkodzeń narządów układu pokarmowego a grupą kontrolną. Sprawdzano także czy istnieją różnice w częstości występowania tej mutacji między kobietami i mężczyznami oraz czy jej obecność miała wpływ na wiek pacjentów, w którym po raz pierwszy rozpoznano przewlekłe zapalenie trzustki.

PACJENCI I METODY Do badania zakwalifikowano 207 pacjentów: 67 z alkoholowym przewlekłym zapaleniem trzustki, 35 z niealkoholowym przewlekłym zapaleniem trzustki, 43 alkoholików bez uszkodzeń narządów układu trawienia i 62 zdrowych ochotników. Mutację N34S genu SPINK1 określano metodą reakcji polimerazy łańcuchowej.

WYNIKI Mutacja N34S genu SPINK1 występowała u 15 badanych (7,25%). Mutacja występowała najczęściej wśród chorych z alkoholowym przewlekłym zapaleniem trzustki (10 pacjentów; 16,39%) i występowała częściej w porównaniu z grupą kontrolą (2 pacjentów; 3,23%) ($p = 0,047$). Nie obserwowano istotnych statystycznie różnic między pozostałymi grupami: chorych z niealkoholowym przewlekłym zapaleniem trzustki (2 pacjentów; 5,71%), alkoholik bez uszkodzeń narządów układu trawienia (1 pacjent; 2,33%) i grupą kontrolną. Mutacja była obecna częściej wśród mężczyzn niż wśród kobiet ($p = 0,043$). Nie zaobserwowano różnic dotyczących wieku pacjentów, w którym postawiono pierwsze rozpoznanie przewlekłego zapalenia trzustki między chorymi, którzy posiadali i nie posiadali mutacji ($p > 0,05$).

WNIOSKI Mutacja N34S genu SPINK1 wydaje się mieć istotny związek z rozwojem przewlekłego alkoholowego zapalenia trzustki.

Adres do korespondencji:
prof. dr hab. med. Halina Cichoż-Lach, Katedra i Klinika Gastroenterologii, Uniwersytet Medyczny w Lublinie, ul. Jaczewskiego 8, 20-954 Lublin, tel./fax: 817-244-535, e-mail: lach.halina@wp.pl
Praca wpłynęła: 11.04.2012.
Przyjęta do druku: 06.06.2012.
Publikacja *online*: 06.06.2012.
Nie zgłoszono sprzeczności interesów.
Pol Arch Med Wewn. 2012; 122 (6): 277-283