Asian Biomedicine Vol. 6 No. 1 February 2012; 1-7 DOI: 10.5372/1905-7415.0601.120

Review article

Relationship between the 308GA polymorphism of the tumor necrosis factor alpha gene and acute or chronic pancreatitis: a meta-analysis

Yun Sun[a,b], Hong Qi[a]

[a]The First Affiliated Hospital of Chengdu Medical College, Chengdu 610500; [b]Chongqing Medical University, Chongqing 400014, China

Background: Several studies have examined the association between G308A polymorphism of tumor necrosis factor alpha (TNF-α gene and acute or chronic pancreatitis, but the results are still controversial.

Objective: Assess whether a relationship exists between G308A polymorphism of TNF-α gene and acute or chronic pancreatitis using meta-analysis.

Methods: Relevant studies were identified from the electronic databases: MEDLINE, EMBASE, and Current Contents. This meta-analysis included 10 case-control studies, where 1,253 acute or chronic pancreatitis cases and 1,269 controls were included.

Results: The combined results based on all studies showed no relationship between the 308GA polymorphism of TNF-α gene and pancreatitis. When stratifying by types of disease, results were similar for both acute and chronic pancreatitis. Comparing severe with mild acute pancreatitis, we found no statistical association. When stratifying for race, results were similar among Asians and Caucasians.

Conclusion: There was no association between the 308GA polymorphism of TNF-α gene and acute or chronic pancreatitis.

Keywords: Gene polymorphism, meta-analysis, pancreatitis, tumor necrosis factor alpha

Acute pancreatitis is an inflammatory disease of the pancreas. Acute abdominal pain is the most common symptom, and increased concentrations of serum amylase and lipase confirm the diagnosis. Pancreatic injury is mild in 80% patients, who recover without complications. The remaining patients have a severe disease with local and systemic complications. Gallstone migration into the common bile duct and alcohol abuse are the most frequent causes of pancreatitis in adults. About 15 to 25% of pancreatitis episodes are of unknown origin [1]. The patients with severe acute pancreatitis have systemic inflammation characterized by activation of innate immune responses, which result in systemic release of pro-inflammatory mediators such as tumor necrosis factor alpha (TNF-α) [2, 3].

Correspondence to: Prof. Yun Sun, The First Affiliated Hospital of Chengdu Medical College, Xindu, Chengdu 610500, China. E-mail: yunsun10@hotmail.com

Chronic pancreatitis is the progressive and permanent destruction of the pancreas resulting in exocrine and endocrine insufficiency. The etiology is multifactorial. Alcoholism plays a significant role in adults [4], whereas genetic and structural defects predominate in children [5]. The inflammatory processes that characterize chronic pancreatitis are regulated by various cytokines, including TNF-α.

TNF-α is an important multifunctional cytokine secreted by macrophages and T lymphocytes with wide-ranging biological effects. These include protection from infection, surveillance against tumors and stimulation of inflammatory responses [6, 7]. Regulation of TNF-α production occurs at both transcriptional and posttranscriptional levels, with regulatory sequences within the 52 end of the gene controlling the rate of transcription. Single-nucleotide polymorphisms within TNF-α have the potential to cause structural changes within regulatory sites that could affect the function or regulation of TNF-α

production [8]. The best documented of this SNP is at position -308 of the TNF-α gene promoter and involves the substitution of guanine (G) for adenine (A) and the creation of two alleles (-308G and -308A) and three genotypes GG, GA, and AA [9].

Many case-control studies have investigated the association between TNF-α G-308A polymorphism and acute or chronic pancreatitis, but these studies have reported conflicting results. Most of the studies have been rather small with limited statistical power. In this study, we conducted meta-analysis to assess whether a relationship exists between TNF-α G-308A polymorphism and acute or chronic pancreatitis.

Methods

Searches were made on Medline (January 1966 to January 2010), Embase (January 1966 to January 2010), Current Contents (1998 to January 2010). The key words "tumour necrosis factor" or "TNF" were combined with "pancreatitis", and with "polymorphism genetics". The reference lists of relevant papers were scanned for further studies. All original articles were accepted, irrespective of language. If two articles described the same data, the most detailed paper was chosen. No attempts were made to identify unpublished studies.

To be eligible for inclusion, studies had to be case-control that reported genotypic frequencies for both case and control populations. Articles from peer-reviewed medical journals were included if they reported on studies using a case-control, cohort, nested case-control, or cross-sectional design and provided sufficient data to calculate an odds ratio (OR) and corresponding 95% confidence interval (CI). Interim analyses, overlapping study populations, and comparisons of laboratory methods were excluded. Titles and abstracts of all citations and retrieved studies were reviewed by two independent researchers.

Two of the authors extracted the data from each article using a structured sheet and entered them into a database. Study characteristics extracted from each paper included country, year of publication, design, ethnicity, setting, number of cases and controls, study period, genotyping method. Any disagreement between researchers was resolved by continuing discussions until a consensus was reached.

Statistical analysis

STATA software package version 9.2 (Stata Corporation, College Station, USA) was used. Heterogeneity was tested with Q-statistics, $P<0.1$ was considered statistically significant [10]. L'Abbe plots were used to assess statistical heterogeneity through visual examination [11]. The Mantel-Haenszel method for fixed effects and the Der-Simonian-Laird method for random effects were used to estimate pooled OR [12]. We used fixed-effects methods if the result of the Q-test was not significant. Otherwise, we calculated pooled estimates and CI assuming a random-effects model. While publication bias was not expected, we assessed this possibility using Begg funnel plots and Egger's bias test [13, 14].

Results

Forty-seven papers were relevant to the searching words. Seventeen studies were full publication reviews. Of these, seven were excluded (six did not report usable data [15-20], one was duplicate [21]). Thus 10 papers [22-31]. These included 1253 acute or chronic pancreatitis cases and 1269 controls, conforming to our inclusion criteria. Of these studies, eight reported on Caucasians, and two reported on Asians. Studies were conducted in USA, UK, China, Hungary, Brazil, and Finland. Characteristics of studies included in this meta-analysis are presented in **Table 1**.

The combined results based on all studies showed that there was no relationship between the 308GA polymorphism of the tumor necrosis factor alpha gene and pancreatitis (GG: OR=1.05, 95% CI=0.88, 1.26; GA: OR=0.99, 95% CI=0.81, 1.20; AA: OR=0.81, 95% CI=0.52, 1.28) as shown in **Figures 1-3**. When stratifying by types of disease, results were similar for both acute (GG: OR=1.00, 95% CI=0.80, 1.24; GA: OR=1.04, 95% CI=0.83, 1.31; AA: OR=0.80, 95% CI=0.48, 1.36) and chronic pancreatitis (GG: OR=1.19, 95% CI=0.85, 1.67; GA: OR=0.85, 95% CI=0.58, 1.24; AA: OR=0.85, 95% CI=0.35, 2.07).

Comparing severe with mild acute pancreatitis, we found no statistical association (GG: OR=0.91, 95% CI=0.69, 1.20; GA: OR=0.99, 95% CI=0.74, 1.33; AA: OR=1.85, 95% CI=0.92, 3.75). When stratifying for race, results were similar among Asians and Caucasians can be seen in **Table 2**.

No evidence of publication bias was found by Begg rank correlation method (P=0.59) and the Egger weighted regression method (P=0.91). Heterogeneity was not found through visual examination of L'Abbe plots. We also did not test the heterogeneity of the included studies with Q statistics (P=0.42).

Table 1. Characteristics of studies included in the meta-analysis.

Study (author, year)	Design	Study period	Population (country)	Genotyping method	Disease	No. of cases	No. of controls	GG of case	GG of control	GA of case	GA of control	AA of case	AA of control
Powell 2001	HCC	1996-1998	Caucasians (UK)	PCR	AP	190	102	122	65	60	32	8	5
Schneider 2003	HCC	DNR	Caucasians (USA)	PCR	CP	51	94	40	64	11	27	0	3
Zhang 2003	HCC	DNR	Asians (China)	PCR	AP	208	116	145	82	53	26	10	8
Zhang 2003	HCC	2001-2002	Asians (China)	PCR	AP	127	102	92	76	29	21	6	5
Schneider 2004	HCC	DNR	Caucasians (USA)	PCR-RFLP	CP	42	94	28	64	13	27	1	3
Balog 2005	HCC	2003-2004	Caucasians (Hungary)	PCR	AP	77	71	51	51	24	18	2	2
Bendicho 2005	HCC	2002-2004	Caucasians (Brazil)	PCR	CP	29	94	23	73	DNR	DNR	DNR	DNR
Howell 2005	HCC	DNR	Caucasians (UK)	PCR	CP	50	214	38	146	11	56	1	12
Farkas 2007	HCC	2003-2006	Caucasians (Hungary)	PCR-RFLP	CP	83	75	56	52	21	21	6	2
Tukiainen 2008	HCC	1998-2003	Caucasians (Finland)	PCR	AP	396	307	305	230	84	70	7	7

HCC: hospital-based case-control, DNR: data not reported, PCR: polymerase chain reaction, RFLP: restriction fragment length polymorphism, AP: acute pancreatitis, CP: chronic pancreatitis.

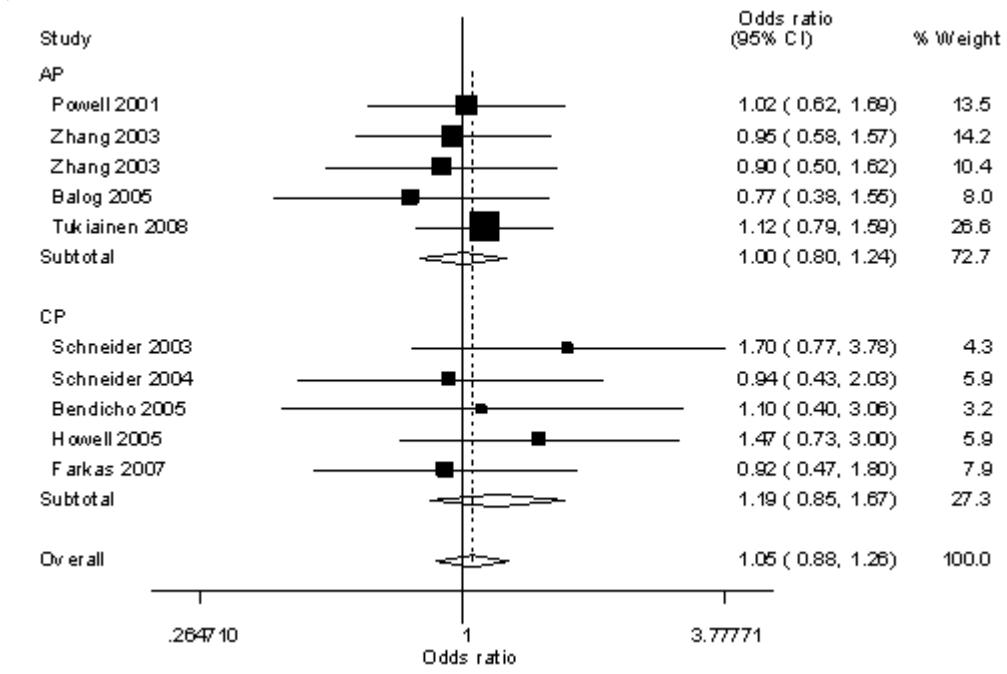

Figure 1. Meta-analysis of TNF-α-308GG and acute or chronic pancreatitis.

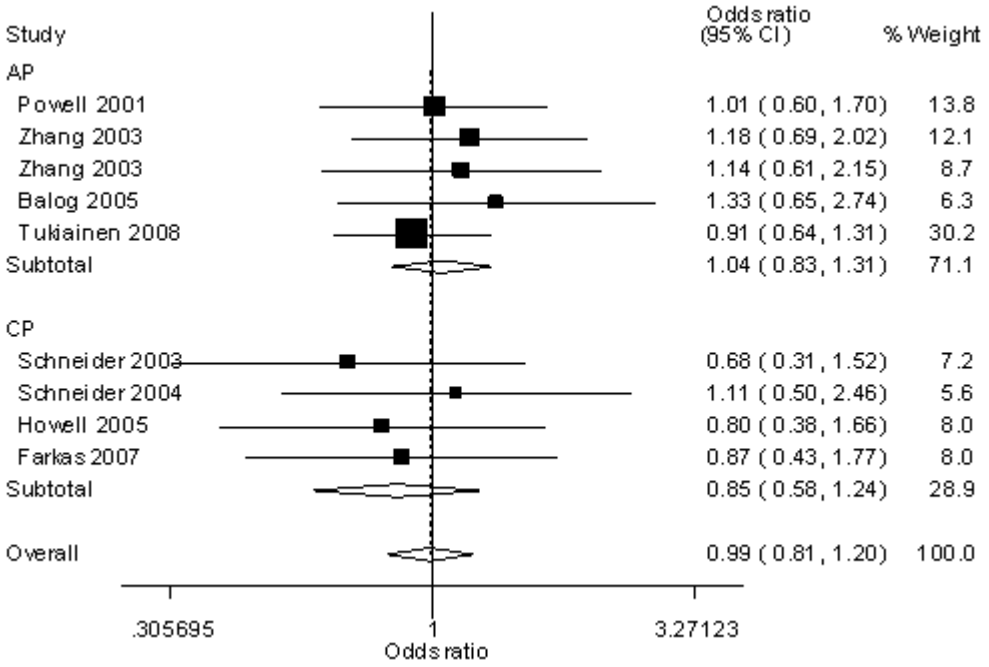

Figure 2. Meta-analysis of TNF-α-308GA and acute or chronic pancreatitis.

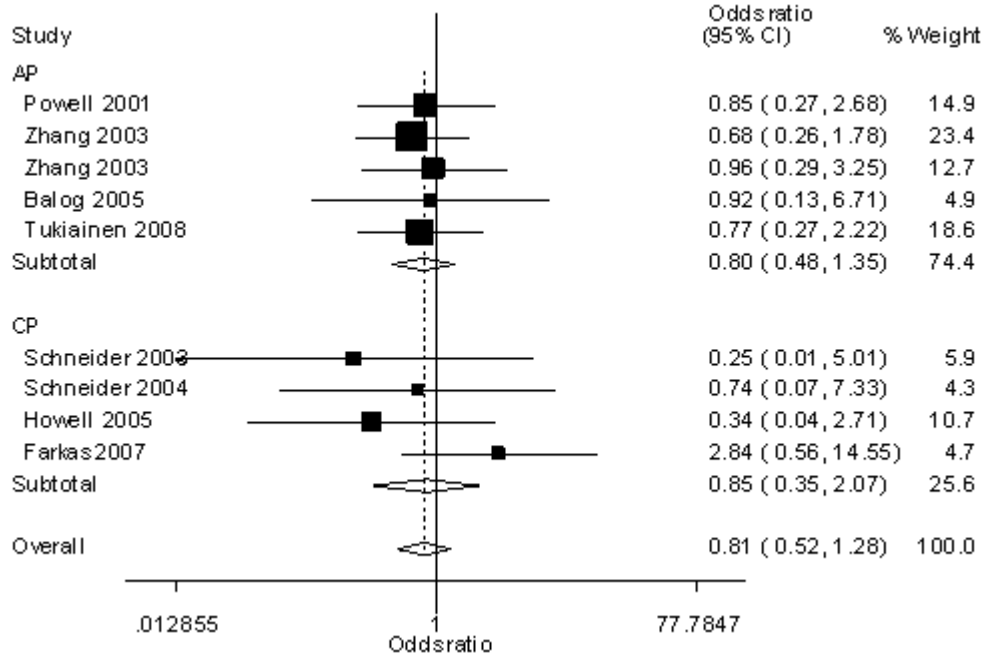

Figure 3. Meta-analysis of TNF-α-308AA and acute or chronic pancreatitis.

Table 2. Meta-analysis of TNF-α -308GA polymorphism and acute pancreatitis.

Stratification of acute pancreatitis	No. of studies	OR (95% CI) of GG	P for heterogeneity	OR (95% CI) of GA	P for heterogeneity	OR (95% CI) of AA	P for heterogeneity
Severity: severe vs mild	5	0.91 (0.69,1.20)	0.06	0.99 (0.74,1.33)	0.58	1.85 (0.92,3.75)	0.47
Asians	2	0.93 (0.58,1.49)	0.72	1.01 (0.61,1.65)	0.05	1.38 (0.50,3.79)	0.72
Caucasians	3	0.90 (0.63,1.28)	<0.001	0.98 (0.68,1.41)	0.19	2.46 (0.91,6.62)	0.48

OR: odds ratio, CI: confidence interval

Discussion

Acute pancreatitis is a relatively common disease. In USA, it affects about 300,000 patients per year with a mortality of about 7% [32]. In China, it affects about 650,000 patients per year with a mortality of about 5 to 10% [33].

Our meta-analysis suggests that there was no association between TNF-α G-308A polymorphism and acute or chronic pancreatitis. Chauhan et al. [34] conducted a systematic review and meta-analysis and suggested that the TNF-α G-308A polymorphism was not strongly associated with the risk of developing bronchopulmonary dysplasia in very preterm infants. Bombell et al. [35] conducted a meta-analysis of 16 case-control studies and suggested that the TNF-α G-308A polymorphism was not associated with pre-eclampsia/eclampsia [35]. However, some studies do not support our meta-analysis. Gao et al. [36] suggested that the TNF-α -308AA genotype confered a significant risk for developing asthma. Gorouhi et al. [37] suggested that TNF-□-308AA genotype was associated with a statistically significant increased risk of gastric cancer [37]. Li et al. [38] suggested that TNF-α gene polymorphisms at positions -308 (G-308A), -863 (C-863A), and -1031 (T-1031C) were associated with Graves' disease [38].

In our meta-analysis, no statistical association exists between TNF-α-308G/A polymorphism and severity of acute pancreatitis. However, in sepsis and other diseases, TNF-α-308G/A polymorphisms have been associated with morbidity and mortality of severe forms [39]. Zhang et al. [25] indicated that the TNF-α-308G/A polymorphism played no part in determination of disease severity or acute severe pancreatitis susceptibility. However, they are both strongly related to the development of septic shock in acute severe pancreatitis. TNF-α-308AA genotype was associated with death as a result of acute severe pancreatitis-associated septic shock. However, the role of genetic factors in influencing the incidence of severe sepsis awaits confirmation in further studies.

There are some limitations in our meta-analysis. Firstly, sources of bias were not controlled by the method. Secondly, the results were based on unadjusted estimates. Thirdly, since gallstone migration into the common bile duct and alcohol abuse are the most frequent causes of pancreatitis in adults, we could not assess these factors in our meta-analysis. Finally, study was lacked in non- Caucasians, only two studies reported on Asians.

In conclusion, our meta-analysis suggests no association between the 308GA polymorphism of TNF-α gene and acute or chronic pancreatitis.

The authors state that they have no conflict of interest.

References

1. Frossard JL, Steer ML, Pastor CM. Acute pancreatitis. Lancet. 2008; 371:143-52.
2. Zhang XP, Wang L, Zhou YF. The pathogenic mechanism of severe acute pancreatitis complicated with renal injury: a review of current knowledge. Dig Dis Sci. 2008; 53:297-306.
3. Zhang XP, Lin Q, Zhou YF. Progress of study on the relationship between mediators of inflammation and apoptosis in acute pancreatitis. Dig Dis Sci. 2007; 52: 1199-205.
4. Hanck C, Rossol S, Singer MV. Immunological changes of mild acute pancreatitis in late-stage alcoholic chronic pancreatitis. Dig Dis Sci. 1999; 44: 1768-73.
5. Nair RJ, Lawler L, Miller MR. Chronic pancreatitis. Am Fam Physician. 2007; 76:1679-88.
6. Rocha AC, Fernandes ES, Quintao NL, Campos MM, Calixto JB. Relevance of tumour necrosis factor-alpha for the inflammatory and nociceptive responses evoked by carrageenan in the mouse paw. Br J Pharmacol. 2006; 148:688-95.
7. Mahatma M, Agrawal N, Dajani EZ, Nelson S, Nakamura C, Sitton J. Misoprostol but not antacid

prevents endotoxin-induced gastric mucosal injury: role of tumor necrosis factor-alpha. Dig Dis Sci. 1991; 36:1562-8.
8. Achyut BR, Tripathi P, Ghoshal UC, Moorchung N, Mittal B. Interleukin-10 (-819 C/T) and tumor necrosis factor-alpha (-308 G/A) gene variants influence gastritis and lymphoid follicle development. Dig Dis Sci. 2008; 53:622-9.
9. Wilson AG, di Giovine FS, Blakemore AI, Duff GW. Single base polymorphism in the human tumour necrosis factor alpha (TNF alpha) gene detectable by NcoI restriction of PCR product. Hum Mol Genet. 1992; 1:353.
10. Rabinowitz D. Adjusting for population heterogeneity: a framework for characterizing statistical information and developing efficient test statistics. Genet Epidemiol. 2003; 24:284-90.
11. Song F. Exploring heterogeneity in meta-analysis: is the L'Abbe plot useful? J Clin Epidemiol. 1999; 52: 725-30.
12. Robins J, Greenland S, Breslow NE. A general estimator for the variance of the Mantel-Haenszel odds ratio. Am J Epidemiol. 1986; 124:719-23.
13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629-34.
14. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50:1088-101.
15. Sargen K, Demaine AG, Kingsnorth AN. Cytokine gene polymorphisms in acute pancreatitis. JOP. 2000; 1:24-35.
16. Zhang D, Li J, Jiang Z, Yu B, Tang X. Significance of tumor necrosis factor-alpha gene polymorphism in patients with acute severe pancreatitis (in Chinese). Zhonghua Yi Xue Za Zhi. 2002; 82:1529-31.
17. Zhang D, Li J, Jiang Z, Yu B, Tang X, Li W. The relationship between tumor necrosis factor-alpha gene polymorphisms and acute severe pancreatitis. Chin Med J (Engl). 2003;116:1779-81.
18. Kim MS, Lee DH, Kang HS, Park HS, Jung S, Lee JW, et al. [Genetic polymorphisms of alcohol-metabolizing enzymes and cytokines in patients with alcohol induced pancreatitis and alcoholic liver cirrhosis]. Korean J Gastroenterol. 2004; 43:355-63.
19. Chang MC, Chang YT, Tien YW, Liang PC, Jan IS, Wei SC, et al. T-cell regulatory gene CTLA-4 polymorphism/haplotype association with auto-immune pancreatitis. Clin Chem. 2007; 53:1700-5.
20. Chang YT, Chang MC, Su TC, Liang PC, Su YN, Kuo CH, et al. Association of cystic fibrosis transmembrane conductance regulator (CFTR) mutation/variant/haplotype and tumor necrosis factor (TNF) promoter polymorphism in hyperlipidemic pancreatitis. Clin Chem. 2008; 54:131-8.
21. Dianliang Z, Jieshou L, Zhiwei J, Baojun Y. Association of plasma levels of tumor necrosis factor (TNF)-alpha and its soluble receptors, two polymorphisms of the TNF gene, with acute severe pancreatitis and early septic shock due to it. Pancreas. 2003; 26:339-43.
22. Powell JJ, Fearon KC, Siriwardena AK, Ross JA. Evidence against a role for polymorphisms at tumor necrosis factor, interleukin-1 and interleukin-1 receptor antagonist gene loci in the regulation of disease severity in acute pancreatitis. Surgery. 2001; 129:633-40.
23. Schneider A, Pogue-Geile K, Barmada MM, Myers-Fong E, Thompson BS, Whitcomb DC. Hereditary, familial, and idiopathic chronic pancreatitis are not associated with polymorphisms in the tumor necrosis factor alpha (TNF-alpha) promoter region or the TNF receptor 1 (TNFR1) gene. Genet Med. 2003; 5:120-5.
24. Zhang D, Li J, Jiang ZW, Yu B, Tang X. Association of two polymorphisms of tumor necrosis factor gene with acute severe pancreatitis. J Surg Res. 2003; 112: 138-43.
25. Zhang DL, Li JS, Jiang ZW, Yu BJ, Tang XM, Zheng HM. Association of two polymorphisms of tumor necrosis factor gene with acute biliary pancreatitis. World J Gastroenterol. 2003; 9:824-8.
26. Schneider A, Barmada MM, Slivka A, Martin JA, Whitcomb DC. Analysis of tumor necrosis factor-alpha, transforming growth factor-beta 1, interleukin-10, and interferon-gamma polymorphisms in patients with alcoholic chronic pancreatitis. Alcohol. 2004; 32: 19-24.
27. Balog A, Gyulai Z, Boros LG, Farkas G, Takacs T, Lonovics J, et al. Polymorphism of the TNF-alpha, HSP70-2, and CD14 genes increases susceptibility to severe acute pancreatitis. Pancreas. 2005; 30:e46-50.
28. Bendicho MT, Guedes JC, Silva NN, Santana GO, dos Santos RR, Lyra AC, et al. Polymorphism of cytokine genes (TGF-beta1, IFN-gamma, IL-6, IL-10, and TNF-alpha) in patients with chronic pancreatitis. Pancreas. 2005; 30:333-6.
29. Howell WM, Pead PJ, Shek FW, Rose-Zerilli MJ, Armstrong T, Johnson CD, et al. Influence of cytokine and ICAM-1 gene polymorphisms on susceptibility to chronic pancreatitis. J Clin Pathol. 2005; 58:595-9.

30. Farkas G, Jr., Hofner P, Balog A, Takacs T, Szabolcs A, Farkas G, et al. Relevance of transforming growth factor-beta1, interleukin-8, and tumor necrosis factor-alpha polymorphisms in patients with chronic pancreatitis. Eur Cytokine Netw. 2007; 18:31-7.
31. Tukiainen E, Kylanpaa ML, Puolakkainen P, Kemppainen E, Halonen K, Orpana A, et al. Polymorphisms of the TNF, CD14, and HSPA1B genes in patients with acute alcohol-induced pancreatitis. Pancreas. 2008; 37:56-61.
32. Cappell MS. Acute pancreatitis: etiology, clinical presentation, diagnosis, and therapy. Med Clin North Am. 2008; 92:889-923.
33. Wang LW, Li ZS, Li SD, Jin ZD, Zou DW, Chen F. Prevalence and clinical features of chronic pancreatitis in China: a retrospective multicenter analysis over 10 years. Pancreas. 2009; 38:248-54.
34. Chauhan M, Bombell S, McGuire W. Tumour necrosis factor (-308A) polymorphism in very preterm infants with bronchopulmonary dysplasia: a meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2009; 94:F257-9.
35. Bombell S, McGuire W. Tumour necrosis factor (-308A) polymorphism in pre-eclampsia: meta-analysis of 16 case-control studies. Aust N Z J Obstet Gynaecol. 2008; 48:547-51.
36. Gao J, Shan G, Sun B, Thompson PJ, Gao X. Association between polymorphism of tumour necrosis factor alpha-308 gene promoter and asthma: a meta-analysis. Thorax. 2006; 61:466-71.
37. Gorouhi F, Islami F, Bahrami H, Kamangar F. Tumour-necrosis factor-A polymorphisms and gastric cancer risk: a meta-analysis. Br J Cancer. 2008; 98:1443-51.
38. Li N, Zhou Z, Liu X, Liu Y, Zhang J, Du L, et al. Association of tumour necrosis factor alpha (TNF-alpha) polymorphisms with Graves' disease: A meta-analysis. Clin Biochem. 2008; 41:881-6.
39. Mira JP, Cariou A, Grall F, Delclaux C, Losser MR, Heshmati F, et al. Association of TNF2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: a multicenter study. JAMA. 1999; 282:561-8.