Apolipoprotein A5 Gene Promoter Region-1131T/C Polymorphism Is Associated with Risk of Ischemic Stroke and Elevated Triglyceride Levels: A Meta-Analysis

Yan Pi Lili Zhang Qingwu Yang Binghu Li Lu Guo Chuanqin Fang
Changyue Gao Jingzhou Wang Jing Xiang Jingcheng Li

Department of Neurology, Institute of Surgery Research, Daping Hospital, Third Military Medical University, Chongqing, PR China

Key Words

Apolipoprotein A5 · Ischemic stroke · Triglyceride · Polymorphism · Meta-analysis

Abstract

Background: The association between polymorphism -1131T/C in the promoter region of apolipoprotein A5 (APOA5) and ischemic stroke and plasma triglyceride (TG) levels remains controversial. To better clarify the association between APOA5-1131T/C and risk of ischemic stroke and plasma TG levels, we performed a meta-analysis to examine the allele and genotype of APOA5-1131T/C polymorphism in ischemic stroke cases and controls. **Methods:** Based on the search of PubMed, Embase, MEDLINE, CNKI (National Knowledge Infrastructure) and CBM (Chinese BioMedical Literature Database) databases, we identified and abstracted outcome data from all articles to evaluate the association between APOA5 and ischemic stroke/plasma TG levels. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were performed in dominant model (CC + TC vs. TT), recessive model (CC vs. TC + TT), homozygote comparison (CC vs. TT) and heterozygote comparison (TC vs. TT). The association between dominant model (CC + TC vs. TT) and plasma TG/total cholesterol/high-density lipoprotein cholesterol levels was measured by a weighted mean difference (WMD) with

its corresponding 95% CI. To evaluate the ethnicity-specific effects, subgroup analyses were performed by ethnic group. **Results:** A meta-analysis containing 2,294 ischemic stroke cases and 1,858 controls from 8 case-control studies was performed. The results showed that APOA5-1131T/C polymorphism was significantly associated with ischemic stroke in all comparison models (CC + TC vs. TT, OR = 1.70, 95% CI = 1.24–2.32; CC vs. TC + TT, OR = 1.36, 95% CI = 0.98–1.90; CC vs. TT, OR = 1.73, 95% CI = 1.34–2.23; TC vs. TT, OR = 1.67, 95% CI = 1.19–2.36). On subgroup analysis by ethnicity, similarly significant associations were found in both Asians and Europeans, and the Europeans possessed a higher risk of ischemic stroke, especially in CC versus TT model (OR = 4.47, 95% CI = 1.33–15.06). Significant association between the C allele and elevated TG levels was detected in both ischemic stroke cases and controls; the TG levels were higher in the ischemic stroke cases and controls carrying the APOA5-1131C allele than in the noncarriers (CC + TC vs. TT, cases WMD = 0.43, 95% CI = 0.27–0.59; controls WMD = 0.51, 95% CI = 0.35–0.66). Similar within-group comparison of the total cholesterol and high-density lipoprotein cholesterol levels did not show any difference. **Conclusions:** Our meta-analysis revealed that the APOA5-1131T/C polymorphism is associated

Y.P. and L.Z. contributed equally to this work as co-first authors.

with a significant risk of ischemic stroke and elevated TG levels. The CC genotype and C allele might be a genetic risk factor that increases susceptibility of ischemic stroke and elevates plasma TG levels, and might be a useful target for clinical therapeutic intervention. Copyright © 2012 S. Karger AG, Basel

Introduction

Stroke is the third leading cause of death and the leading cause of long-term disability worldwide [1]. The common sporadic form of ischemic stroke is underpinned by environmental and genetic risk factors [2]. Although environmental and clinical risk factors (such as hypertension, diabetes mellitus, hyperlipemia, atherosclerosis, smoking, excessive alcohol drinking, and so on) are considered important [3, 4], nowadays a growing spectrum of genetic susceptibility factors have been identified [5, 6]. With the help of robust genome-wide association studies, the biological plausibility and epidemiological evidence suggest that the elevated triglyceride (TG) level potentially contributes to an increased risk for ischemic stroke [7–9].

In 2001, a new apolipoprotein gene, apolipoprotein A5 (APOA5), was first reported [10] and found to be strongly associated with plasma TG levels [11]. The APOA5 gene is located on chromosome 11q23 and presents in the APOA1-C3-A4 gene cluster. Human and mouse data consistently show that APOA5 is a factor that apparently reduces plasma TG levels [10]. Compared with controls, transgenic mice overexpressed human APOA5 and produced one third lower plasma TG levels, while APOA5 knockout mice had fourfold higher plasma TG levels. APOA5-1131T/C, as a polymorphism site in the promoter region of APOA5, has been found to modify the susceptibility of ischemic stroke and shown to be associated with elevated TG levels [12–19].

A variety of molecular epidemiological studies have focused on the association between APOA5-1131T/C polymorphism and ischemic stroke and TG levels. However, results in different studies have been inconsistent. Two meta-analysis articles on the association between APOA5-1131T/C and coronary artery disease have just been performed [20, 21], but currently there is no meta-analysis article on APOA5-1131T/C and ischemic stroke. To draw a more stable and reliable conclusion about the association between APOA5-1131T/C and risk of ischemic stroke and plasma TG levels, we performed a meta-analysis to examine the allele, genotype of APOA5-1131T/C polymorphism in cases and controls.

Materials and Methods

Literature Search

Two independent investigators screened an electronic literature from PubMed, Embase, MEDLINE, CNKI (National Knowledge Infrastructure) and CBM (Chinese BioMedical Literature Database) databases up to 2011. The initial search used the MeSH terms ‘apolipoprotein A5’ OR ‘APOA5’, ‘ischemic stroke’ OR ‘cerebral infarction’ OR ‘stroke’ in combination with ‘polymorphism’ OR ‘variant’ OR ‘mutation’. We reviewed the bibliographies of all selection articles to identify additional relevant studies.

Inclusion and Exclusion Criteria

The inclusion criteria were: (1) case-control studies to evaluate the association between APOA5-1131T/C and risk of ischemic stroke, (2) useful data including genotype number or frequency given, (3) studies clearly describe ischemic stroke diagnoses and the sources of cases and controls, (4) studies written in English and Chinese with full-text, (5) genotype distribution of controls in Hardy-Weinberg equilibrium (HWE). The exclusion criteria were: (1) not case-control studies, (2) studies without available genotype number or frequency, (3) genotype distribution of controls not in HWE, (4) animal studies, reviews, case reports, abstracts and repeated literature.

Data Extraction

Two independent investigators extracted the following data: first author, year of publication, characteristics of cases and controls (age, gender, body mass index, total cholesterol (TC) levels, high-density lipoprotein cholesterol (HDL-C) levels and TG levels), study population, ethnicity, genotyping methods and genotype number in cases and controls. The results were compared, and disagreements were resolved by consensus. Different ethnicity descents were categorized as Asians and Europeans.

Statistical Analysis

Pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were used to assess the association between the polymorphism APOA5-1131T/C and risk of ischemic stroke. Four different genetic models, including dominant model (CC + TC vs. TT), recessive model (CC vs. TC + TT), homozygote comparison (CC vs. TT) and heterozygote comparison (TC vs. TT), were estimated in our analysis. The association between dominant model (CC + TC vs. TT) and plasma TG/TC/HDL-C levels was measured by a weighted mean difference (WMD) with its corresponding 95% CI. Heterogeneity assumption was assessed by the Q test and I^2 statistics. If the result of the Q test was $p_Q > 0.1$ and $I^2 < 50\%$, the fixed-effects model was used to calculate the pooled ORs [22]; otherwise, the random-effects model was used [23]. Moreover, Galbraith plot was used to detect the potential sources of heterogeneity. To evaluate the ethnicity-specific effects, subgroup analyses were performed by ethnic group. Publication bias was tested by Begg's funnel plot and Egger's test [24, 25]. All analyses were performed using Review Manager 5.0 and Stata 10.0. Statistical significance was set at two-sided $p < 0.05$.

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

Study	Country	Ethnicity	Genotyping method	Males in cases/controls, %	Mean age of cases/controls, years	IS cases				Controls			
						TT	TC	CC	total	TT	TC	CC	total
Havasi et al. [12]	Hungary	European	PCR-RFLP	52.98/54.33	NG/54.6 ± 13.3	237	60	5	302	261	27 ^a	1 ^a	289
Xu et al. [13]	China	Asian	PCR-RFLP	60.96/60.50	64.58 ± 11.83/61.85 ± 12.27	99	40	14	153	105	77	18	200
Zhang et al. [14]	China	Asian	PCR-RFLP	60.44/61.03	65.39 ± 10.94/61.17 ± 10.17	130	115	27	272	177	123	16	316
Li et al. [15]	China	Asian	PCR-RFLP	63.02/65.46	63.92 ± 9.90/62.25 ± 9.61	77	63	54	194	172	77	62	311
Maasz et al. [16]	Hungary	European	PCR-RFLP	39.68/31.30	66.1 ± 0.74/58.1 ± 1.51	309	58 ^a	11 ^a	378	119	11 ^a	1 ^a	131
Chen et al. [17]	China	Asian	PCR-RFLP	58.57/65.89	67.76 ± 10.86/65.54 ± 11.10	43	76 ^a	21 ^a	140	60	43 ^a	26 ^a	129
Járomi et al. [18]	Hungary	European	PCR-RFLP	40.35/28.49	65.1 ± 0.62/56.5 ± 1.20	434	68	11	513	159	12	1	172
Li et al. [19]	China	Asian	PCR-RFLP	55.56/56.13	65.35 ± 10.52/63.87 ± 11.23	125	181	36	342	167	115	28	310

PCR-RFLP = Polymerase chain reaction restriction fragment length polymorphism; NG = not given; IS = ischemic stroke.

^a Calculated value.

Results

Study Characteristics

The initial search identified fifty potentially relevant studies, eight of which met the inclusion criteria in the final, including 2,294 ischemic stroke cases and 1,858 controls (fig. 1). The main characteristics of the studies are summarized in table 1. Of the eight studies, five were conducted in Asians and three in Europeans. Six studies (1,828 cases and 1,231 controls) were available for the meta-analysis of APOA5-1131T/C polymorphism and TG levels [12, 13, 16–19].

All the cases of ischemic stroke were diagnosed based on the WHO criteria. Most of the controls received routine health examinations. In all of the selected studies, the genomic DNA was extracted from peripheral blood samples and the gene polymorphisms were detected by polymerase chain reaction restriction fragment length polymorphism. In all of the included studies, the χ^2 test was used to compare the different genotypes between groups, and the ORs derived from multiple logistic regression were used to evaluate the impact of the APOA5-1131T/C genotype on the risk of ischemic stroke at 95% CIs. Three of six studies used the Mann-Whitney test to assess the different TG levels between groups. In the remaining three studies, the unpaired Student's t test was used.

Meta-Analysis Results

The meta-analyses suggested that APOA5-1131T/C polymorphism was significantly associated with ischemic stroke in all comparison models (CC + TC vs. TT, OR = 1.70, 95% CI = 1.24–2.32; CC vs. TC + TT, OR =

Fig. 1. Flowchart of the current study selection.

1.36, 95% CI = 0.98–1.90; CC vs. TT, OR = 1.73, 95% CI = 1.34–2.23; TC vs. TT, OR = 1.67, 95% CI = 1.19–2.36). Forest plots on the basis of all studies are shown in figure 2. The results showed that the carriers of the C allele have higher risk of ischemic stroke than the noncarriers.

On subgroup analysis by ethnicity of study population, significant association between the C allele and ischemic stroke risk was detected in both Asians and Europeans. Compared with Asians, the Europeans had a higher risk of ischemic stroke, especially in CC versus TT (OR = 4.47, 95% CI = 1.33–15.06; table 2).

Fig. 2. Forest plot for APOA5-1131T/C polymorphism and risk of ischemic stroke in four different genetic models. **a** Dominant model (CC + TC vs. TT). **b** Recessive model (CC vs. TC + TT). **c** Homozygote comparison (CC vs. TT). **d** Heterozygote comparison (TC vs. TT).

Significant association between the C allele and elevated TG levels was detected in both ischemic stroke cases and controls (1,828 cases and 1,231 controls). The TG levels were higher in the ischemic stroke cases and controls carrying the APOA5-1131C allele than in the noncarriers (CC + TC vs. TT, cases WMD = 0.43, 95% CI = 0.27–0.59; controls WMD = 0.51, 95% CI = 0.35–0.66; fig. 3). Similar within-group comparison of the TC and HDL-C levels did not show any difference.

Heterogeneity Analysis

The heterogeneity of CC versus TT, TC versus TT, CC + TC versus TT and CC versus TC + TT was analyzed for eight case-control studies. The results in CC versus TT ($p_Q = 0.28$, $I^2 = 19$) and CC versus TC + TT ($p_Q = 0.17$, $I^2 = 33$) had no heterogeneity, the other two models (TC vs. TT, $p_Q < 0.0001$, $I^2 = 77$; CC + TC vs. TT, $p_Q = 0.0001$, $I^2 = 76$) indicated significant heterogeneity. To detect the source of heterogeneity, we performed subgroup analyses stratified by the characteristics of the

Fig. 3. Forest plot for APOA5-1131T/C polymorphism (CC + TC vs. TT) and TG levels in both ischemic stroke cases and controls.

Table 2. Subgroup analysis of APOA5-1131T/C polymorphism and risk of ischemic stroke in four genetic models

Category	CC + TC versus TT		CC versus TC + TT		CC versus TT		TC versus TT	
	OR (95% CI)	I ²	OR (95% CI)	I ²	OR (95% CI)	I ²	OR (95% CI)	I ²
Overall	1.70 (1.24, 2.32)	76	1.38 (1.08, 1.75)	33	1.73 (1.34, 2.23)	19	1.67 (1.19, 2.36)	77
Asians	1.45 (0.97, 2.18)	83	1.28 (1.00, 1.64)	42	1.61 (1.24, 2.09)	32	1.46 (0.91, 2.34)	85
Europeans	2.36 (1.70, 3.28)	0	4.09 (1.22, 13.72)	0	4.47 (1.33, 15.06)	0	2.22 (1.51, 3.12)	0

studies. When classified by ethnicity, the heterogeneity in the Europeans was ruled out. We determined that ethnicity might substantially influence the initial heterogeneity. By using Galbraith plot, one study [11] was identified as the main contributor of heterogeneity on TC versus TT and CC versus TC + TT (fig. 4). After excluding the outlier study, the heterogeneity was effectively removed or decreased. The pooled ORs were recalculated after removal of the outlier study, and the pooled ORs were similar to those when the outlier study was included (fig. 5).

Publication Bias

Publication bias was assayed by funnel plot inspection and Egger's test. The shape of the funnel plot did not reveal obvious asymmetry in dominant model (CC + TC vs. TT). Then, Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not indicate any evidence of publication bias ($p = 0.721$ for CC + TC vs. TT).

Fig. 4. Galbraith plot of APOA5-1131T/C polymorphism and risk of ischemic stroke in dominant model and heterozygote comparison. **a** The study by Xu et al. [11] was the outlier in dominant model (CC + TC vs. TT). **b** The study by Xu et al. [11] was the outlier in heterozygote comparison (TC vs. TT).

Fig. 5. Forest plot for APOA5-1131T/C polymorphism and risk of ischemic stroke after excluding the outlier study in dominant model and heterozygote comparison. **a** Dominant model (CC + TC vs. TT). **b** Heterozygote comparison (TC vs. TT).

Discussion

Ischemic stroke is a multifactorial and polygenic disorder disease which is thought to be the result of complex gene-gene and gene-environment interactions. Both environmental and common genetic factors lead to the development of ischemic stroke [26]. As demonstrated by previous studies, the elevated TG level may be an inde-

pendent risk factor for ischemic stroke [27, 28]. Human and animal data consistently show that the newly identified APOA5 gene may play an important role in the development of ischemic stroke and TG metabolism [12, 29, 30].

The association between APOA5 polymorphisms (*T-1131C*, *IVS3+G476A*, *C56G*, and *T1259C*) and the risk of ischemic stroke has been investigated, but the limited

data are available about the role of some polymorphisms (*IVS3+G476A*, *C56G*, and *T1259C*) [16, 30]. *APOA5-1131T/C*, as one polymorphism site of *APOA5*, has been widely studied in ischemic stroke susceptibility. However, inconclusive results have been obtained. Some studies supported the conclusion that risk for ischemic stroke was associated with the polymorphism, whereas other studies drew converse conclusions. To better explain the association between *APOA5-1131T/C* and risk of ischemic stroke and plasma TG levels, we performed a meta-analysis to examine the allele and genotype of *APOA5-1131T/C* polymorphism in cases and controls.

The results of our meta-analysis confirmed that the CC genotype and C allele of the *APOA5-1131T/C* polymorphism could increase the risk of ischemic stroke and elevate plasma TG levels. Compared with TT subjects, the CC had a 73% increased risk of ischemic stroke, the TC had a 67% increased risk, and the C carriers (CC + TC) had a 70% increased risk. As far as TG levels are concerned, there were 45 and 51% increased risks for C carriers (CC + TC) compared with TT subjects in both ischemic stroke cases and controls, respectively. This association was still significant after excluding the outlier study. When stratifying by ethnicity, we obtained similar results in both Asians and Europeans. Moreover, the association was more significant in Europeans. Thus, the C allele might be a genetic risk factor that increases susceptibility to ischemic stroke and elevates plasma TG levels; this finding is consistent with the results of previous studies [17, 19].

In view of the complex effect of genetic polymorphisms on disease progression, the mechanism behind the association between the *APOA5-1131T/C* polymorphism and ischemic stroke risk may be that the *APOA5-1131T/C* polymorphism influences the function of the protein transcript, which could modify secondarily the interaction of *APOA5* with the lipoprotein lipase and ultimately lead to increased circulating TG levels [10, 31, 32]. This process can be involved in the abnormal accumulation of lipids in the endothelial cells under pathologic conditions, eventually in the formation of atherosclerotic plaques that are elements in obstructive vascular diseases (such as ischemic stroke) [33, 34]. Prieur et al. [35] identified a peroxisome proliferator response element (PPRE) in the promoter region of the *APOA5* gene and demonstrated that the *APOA5* gene is a highly responsive peroxisome proliferator-activated receptor- α (PPAR α) target gene. The *APOA5* gene expression could be enhanced markedly by fibrates through the PPAR α pathway, whose signal transmission required the par-

ticipation of the PPRE. Considering this, it is hypothesized that *APOA5-1131T/C* might change the affinity of this or the binding of other unknown regulatory elements, leading to reductions of gene expression. The presence of naturally existing *APOA5-1131T/C* confers a risk for ischemic stroke through elevating plasma TG levels [29, 30].

Some limitations of our meta-analysis should be noted. First, the small number of studies and sample size limited the ability to draw more solid conclusions. So, more convincing evidence, such as larger sample size, number of studies, and ethnicity, is required to confirm our conclusions. Second, several human *APOA5* gene single-nucleotide polymorphisms have been identified; we only included the *APOA5-1131T/C* polymorphism in this meta-analysis because this polymorphism was most extensively studied. Meta-analyses that investigate the association of other polymorphisms of the *APOA5* gene with ischemic stroke and plasma TG levels should be performed later. Third, the influence of bias in this analysis could not be completely excluded; as it was very difficult to get full papers published in various languages, we only included the studies published in English and Chinese. Moreover, ischemic stroke is known to be a complex disease, and the gene-environment interactions should be considered.

In spite of the limitations, our meta-analysis has some key advantages. First, to the best of our knowledge, this is the first meta-analysis to explain the association between *APOA5-1131T/C* polymorphism and ischemic stroke. The results should be more reliable than those from a single study, as cases and controls were pooled from different studies, and statistical power of analysis was significantly increased. Second, no publication bias was found. After excluding one outlier study, the heterogeneity was effectively removed or decreased, no significant changes and reversal of results were found, which suggested the result of the present meta-analysis was stable and reliable.

In conclusion, our meta-analysis has revealed that the *-1131T/C* polymorphism in the promoter region of the *APOA5* gene was associated with a significant risk of ischemic stroke and elevated plasma TG levels. The CC genotype and C allele may have a promoting effect on ischemic stroke and elevated TG levels. These findings highlighted the importance of the *APOA5* gene in ischemic stroke and plasma TG levels, which might be a useful target for clinical therapeutic intervention.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (No. 30970998, 30800444) and Chongqing key Project of Science and Technologies (No. CSTC2010GGC502).

Disclosure Statement

None.

References

- Rothwell PM, Coull AJ, Silver LE, Fairhead JF, Giles MF, Lovelock CE, Redgrave JNE, Bull LM, Welch SJV, Cuthbertson FC, Binner LE, Gutnikov SA, Anslov P, Banning AP, Mant D, Mehta Z: Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet* 2005;366:1773–1783.
- Elbaz A, Amarenco P: Genetic susceptibility and ischaemic stroke. *Curr Opin Neurol* 1999;12:47–55.
- Hankey GJ: Potential new risk factors for ischemic stroke: what is their potential? *Stroke* 2006;37:2181–2188.
- Stankovic S, Majkic-Singh N: Genetic aspects of ischemic stroke: coagulation, homocysteine, and lipoprotein metabolism as potential risk factors. *Crit Rev Clin Lab Sci* 2010;47:72–123.
- Dichgans M: Genetics of ischaemic stroke. *Lancet Neurol* 2007;6:149–161.
- Markus HS: Stroke genetics. *Hum Mol Genet* 2011;20:R124–R131.
- Antonios N, Angiolillo DJ, Silliman S: Hypertriglyceridemia and ischemic stroke. *Eur Neurol* 2008;60:269–278.
- Pikija S, Milevic D, Trkulja V, Kidemet-Piskac S, Pavlice I, Sokol N: Higher serum triglyceride level in patients with acute ischemic stroke is associated with lower infarct volume on CT brain scans. *Eur Neurol* 2006;55:89–92.
- Tanne D, Koren-Morag N, Graff E, Goldbourt U: Blood lipids and first-ever ischemic stroke/transient ischemic attack in the Bezafibrate Infarction Prevention (BIP) registry: High triglycerides constitute an independent risk factor. *Circulation* 2001;104:2892–2897.
- Pennacchio LA, Olivier M, Hubacek JA, Cohen JC, Cox DR, Fruchart JC, Krauss RM, Rubin EM: An apolipoprotein influencing triglycerides in humans and mice revealed by comparative sequencing. *Science* 2001;294:169–173.
- Nilsson SK, Heeren J, Olivecrona G, Merkel M: Apolipoprotein A-V; a potent triglyceride reducer. *Atherosclerosis* 2011;219:15–21.
- Havasi V, Szolnoki Z, Talian G, Bene J, Komlosi K, Maasz A, Somogyvari F, Kondacs A, Szabo M, Fodor L, Bodor A, Melegh B: Apolipoprotein A5 gene promoter region T-1131C polymorphism associates with elevated circulating triglyceride levels and confers susceptibility for development of ischemic stroke. *J Mol Neurosci* 2006;29:177–183.
- Xu HW, Hu MY, Yuan L, Yuan CY, Wang YN, Zhang L: Relationship between T-1131C polymorphism of apolipoprotein A5 and cerebral infarction in Chinese Han population in Hunan. *J Apoplexy and Nervous Diseases* 2008;25:529–533.
- Zhang K, Qui F, Li L, Gu GY, Tao Y, Wang L, Luo XY, Xia YQ: The associated study on apolipoprotein A5 gene polymorphisms with carotid arteriosclerosis in patients with cerebral infarction. *Chin J of Med Genet* 2008;25:284–288.
- Li XP, Zhao SP, Nie S, Xiao ZJ, Lu W, Peng DQ: Relationship between A5-1131T>C polymorphism and strokes. *Chin J Neurology* 2008;7:928–931.
- Maasz A, Kisfali P, Jaromi L, Horvathovich K, Szolnoki Z, Csengei V, Safrany E, Sipeky C, Hadarits F, Melegh B: Apolipoprotein A5 gene IVS3+G476A allelic variant confers susceptibility for development of ischemic stroke. *Circ J* 2008;72:1065–1070.
- Chen W, Zhou MZ, Lu LX, Liu ZG, Ni PH, Ying YY: ApoA5-1131 T/C gene polymorphism in patients with ischemic stroke. *J of Shanghai Jiaotong University (Medical Science)* 2009;29:192–195.
- Jaromi L, Csengei V, Polgar N, Szolnoki Z, Maasz A, Horvathovich K, Farago B, Sipeky C, Safrany E, Magyari L, Kisfali P, Mohas M, Janicssek I, Lakner L, Melegh B: Functional variants of glucokinase regulatory protein and apolipoprotein A5 genes in ischemic stroke. *J Mol Neurosci* 2010;41:121–128.
- Li X, Su D, Zhang X, Zhang C: Association of apolipoprotein A5 gene promoter region-1131T>C with risk of stroke in Han Chinese. *Eur J of Intern Med* 2011;22:99–102.
- Zhai G, Li M, Zhu C: APOA5 -1131T/C polymorphism is associated with coronary artery disease in a Chinese population: a meta-analysis. *Clin Chem Lab Med* 2011;49:535–539.
- Zhang Z, Peng B, Gong RR, Gao LB, Du J, Fang DZ, Song YY, Li YH, Ou GJ: Apolipoprotein A5 polymorphisms and risk of coronary artery disease: a meta-analysis. *Biosci Trends* 2011;5:165–172.
- Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719–748.
- DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–188.
- Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–1101.
- Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–634.
- Szolnoki Z, Melegh B: Gene-gene and gene-environment interplay represent specific susceptibility for different types of ischaemic stroke and leukoaraiosis. *Curr Med Chem* 2006;13:1627–1634.
- Cho HJ, Kim YJ: Higher serum triglyceride levels are associated with less severe stroke and good outcome. *J Neurol Sci* 2009;285:S170–S171.
- Ogunrin OA, Unuigbo E: Serum lipids in patients with stroke – A cross sectional case-control study. *Cerebrovasc Dis* 2009;28:210.
- Pennacchio LA, Rubin EM: Apolipoprotein A5, a newly identified gene that affects plasma triglyceride levels in humans and mice. *Arterioscl Thromb Vas* 2003;23:529–534.
- Fadel W, Nassar H, Mourad H, Nagy H, Farouk G: The role of apolipoprotein A-V gene T1131C and C56G allelic variants in lipid regulation and susceptibility for development of ischemic stroke. *Cerebrovasc Dis* 2010;29:270–271.
- Yang Y, Ruiz-Narvaez E, Niu T, Xu X, Campos H: Genetic variants of the lipoprotein lipase gene and myocardial infarction in the Central Valley of Costa Rica. *J Lipid Res* 2004;45:2106–2109.
- Wright WT, Young IS, Nicholls DP, Patterson C, Lytle K, Graham CA: SNPs at the APOA5 gene account for the strong association with hypertriglyceridaemia at the APOA5/A4/C3/A1 locus on chromosome 11q23 in the Northern Irish population. *Atherosclerosis* 2006;185:353–360.
- Hachinski V, Graffagnino C, Beaudry M, Bernier G, Buck C, Donner A, Spence JD, Doig G, Wolfe BM: Lipids and stroke: a paradox resolved. *Arch Neurol* 1996;53:303–308.
- Hassan A, Markus HS: Genetics and ischaemic stroke. *Brain* 2000;123:1784–1812.
- Prieur X, Coste H, Rodriguez JC: The human apolipoprotein AV gene is regulated by peroxisome proliferator-activated receptor-(alpha) and contains a novel farnesoid X-activated receptor response element. *J Biol Chem* 2003;278:25468–25480.