Association Between Apolipoprotein Gene Polymorphisms and Hyperlipidemia: A Meta-analysis

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Abstract

Background: Hyperlipidemia plays an important role in the etiology of cardio-cerebrovascular disease. Over recent years, a number of studies have explored the impact of apolipoprotein genetic polymorphisms in hyperlipidemia, but considerable differences and uncertainty have been found in their association for different populations from different regions.

Objective: To correlate apolipoprotein gene expression with hyperlipidemia through a systematic review of case-control studies.

Methods: Comprehensive identification of relevant articles in Pubmed, Web of Science, ScienceDirect, CNKI, Wangfang, and VIP published to June 9, 2020. A systematic review of hyperlipidemia case-control studies was conducted to evaluate the quality of data in articles included in the review, and a meta-analysis was conducted using Stata 11 software.

Results: A total of 59 articles were included, containing in total 13843 hyperlipidemia patients in the case group and 15398 healthy controls in the control group. Meta-analysis of the data indicated that APOA5-1131T>C, APOA1 -75bp, APOB Xba^{II} and APOE gene polymorphisms were significantly associated with hyperlipidemia, with OR values of 1.996, 1.228, 1.444 and 1.710, respectively, for allele models. All P values were less than 0.05.

Conclusions: Meta-analysis of the data indicated that the C allele of APOA5 1131T>C, the A allele at APOA1-75bp, the APOB Xba^{II} T allele, and the ε4 allele of APOE were each a risk factor for susceptibility for hyperlipidemia.

Background

Cardio-cerebrovascular disease is the leading cause of death among urban and rural residents in China, and also the disease with the highest mortality and morbidity globally ^[1]. Recently, studies have shown that the fatality rate from cardio-cerebrovascular disease accounts for approximately 30% of the total global death toll ^[2]. Hyperlipidemia is a chronic non-communicable disease caused by an imbalance in the structure of plasma lipids caused by a fat metabolism disorder ^[3]. It is the primary risk factor for atherosclerosis, the pathological basis for cardio-cerebrovascular disease ^[4]. In addition, a large number of manuscripts have demonstrated that hyperlipidemia is a pathogenic factor of digestive and urinary diseases such as diabetes, hepatopathy, pancreatitis. Hyperlipidemia can be divided into hypercholesteremia, hypertriglyceridemia, mixed hyperlipidemia, and low density lipoproteinemia, *etc.* Medical research has established that the mechanism of hyperlipidemia is not only determined by environmental factors, such as long-term consumption of large amounts of saturated fatty acids, cholesterol, and sugar, it is also influenced by genetic factors at gene loci. There are multiple academic reports that apolipoprotein (APO) gene mutations are closely related to disorders of blood lipid metabolism ^[5]. APO is an important component of lipoprotein. So far, more than 20 forms of APO have been identified, including APOA, APOB, APOC, APOD, APOE, APOH, APOM, *etc.* ^[6].

Single nucleotide polymorphisms (SNPs) are changes to a single nucleic acid in a protein caused by the insertion, deletion, or substitution of a single nucleotide base in the gene sequence. Of the existing apolipoprotein candidate genes, researchers have correlated APOA1, APOA5, APOB, and APOE gene polymorphisms with hyperlipidemia. APOA1 and APOA5 genes are located in the long arm region of chromosome 11. APOA1 is located in the APOA1-C3-A4 gene cluster, the principal site controlling the expression of lipids and lipoproteins ^[7]. APOA5 is located downstream of APOA4, and its distance from the APOA1/C3/A4 gene cluster is approximately 30 kb. The APOA5 gene is most commonly altered at the - 1131T > C site, this polymorphism closely associated with a number of diseases, such as hypertriglyceridemia and coronary heart disease ^[8]. The APOB gene is located in the short arm of chromosome 2 and contains 29 exons and 28 introns. The cleavage sites Msp^I and Xba^I are located on exon 26 of the APOB gene. The EcoR^I cleavage site is located in exon 29 ^[9]. A number of studies have clearly indicated that the APOB gene affects lipid metabolism to a certain extent. The APOE gene is located on chromosome 19 with a polymorphic gene structure. The isomers are encoded by three alleles ε2, ε3, and ε4 ^[10], forming 6 genotypes E2/2, E3/3, E4/4, E2/3, E2/4 and E3/4, among which E3/3 is the most common within the population.

Over recent years, there have been multiple studies that have explored the correlation between genetic polymorphism and hyperlipidemia for the apolipoprotein gene loci described above, but there are great differences and uncertainties in different populations from different regions. Therefore, in the present review, we systematically searched the literature and reviewed case-control studies of hyperlipidemia. A meta-analysis was conducted to explore the relationship between APOA (A1-75 bp, A1 + 83 bp, A5-1131T>C), APOB (Msp^I, Xba^I, EcoR^I), APOE with hyperlipidemia in order to provide an evidence-base for the prevention and control of hyperlipidemia.

Methods

Literature search strategy

The Pubmed, Web of Science, ScienceDirect, CNKI, Wangfang, and VIP manuscript databases were searched to identify studies that evaluated the association of APO gene polymorphisms with the risk of hyperlipidemia, where publication date was prior to June 9, 2020. The keywords “apolipoprotein”, “APO”, “hyperlipidemia”, “dyslipidemias”, “hypercholesteremia”, “hypertriglyceridemia”, “mixed hyperlipidemia”, “low density lipoproteinemia”, “APOA”, “APOB”, “APOC”, “APOD”, “APOE”, “APOA5-1131T>C”, “rs662799”, “APOA1-75bp”, “rs670”, “APOA1+83bp”, “rs5069”, “APOB Msp^I”, “rs1801701”, “APOB Xba^I”, “rs693”, “APOB EcoR^I”, “rs1042031”, “gene”, “polymorphism”, and “genetic polymorphism” were searched. The references of all eligible studies were also searched manually in order to find other studies missed in the main search activity.

Identification of studies to include

The inclusion criteria for the present meta-analysis were as follows: (1) studies that evaluated the association between APO and risk of hyperlipidemia; (2) studies with an appropriate statistical design and selection methods; (3) case-control and RCT studies; (4) diagnostic criteria for dyslipidemia were clear and uniform^[11]; (5) the distribution of APO genotypes in controls group were consistent with the Hardy-Weinberg equilibrium (HWE); (6) allele typing methods were accurate; (7) data included in studies were complete, and there were no omissions. Duplicated data, reviews, abstracts, case reports, animal studies, and studies that did not meet the inclusion criteria were excluded.

Data extraction

Two reviewers (XNZ and QS) independently conducted literature screening and evaluation. The following information was extracted from each study included in the review: first author, year of publication, area, age, source of control, sample size of controls and cases, genotyping method, Hardy-Weinberg equilibrium (HWE), the distribution of genotypes and frequencies of alleles in cases and controls. Any disputes were resolved by discussion with a third investigator.

Quality evaluation

The quality of the selected case-control studies was evaluated according to the NOS (Newcastle-Ottawa Scale)^[12], in which data with a score higher than 7 were considered high quality^[13].

Statistical analyses

The included hyperlipidemia data were analyzed by meta-analysis using Stata 11 software. The correlation between apolipoprotein gene polymorphism and hyperlipidemia was expressed by odds ratio (OR) and 95% confidence intervals (CI). In order to better evaluate the presence of heterogeneity between the studies, an I^2 test was also used. Where homogeneity ($I^2 < 50\%$) was identified in the meta-analysis, a fixed-effects model was adopted; otherwise, a random-effects model was used to integrate incorporated data. The data was assessed using Egger's and Begg's tests to evaluate publication bias. Sensitivity analysis was conducted, delete the data with large deviation shown by the analysis results, and recalculate the OR value. All P -values were two-sided, with a significance threshold set at $\alpha = 0.05$.

Results

Study characteristics

A total of 3706 selected articles were obtained from Chinese and English databases, of which 59 articles were finally selected, including 22 that analyzed APOA, 28 APOB, and 30 APOE. Three sites in the APOA gene were studied: A5-1131T>C was included in 10 case-control studies, including 1211 cases and 1495 controls; A1-75bp was included in 5 case-control studies, including 1284 cases and 1312 controls; and A1+83bp was included in 7 case-control studies, including 1452 cases and 1620 controls. The APOB gene was investigated at three sites: MspI was studied in 6 case-control studies, including a hyperlipidemia group of 1155 cases and 1043 controls; XbaI was studied in 12 case-control studies, including 1900 cases and 1836 controls; and EcoRI in 10 case-control studies, including 1633 cases and 1686 controls. The APOE gene is co-coded by the three $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ alleles, and 30 case control studies were included, including 5208 cases in the hyperlipidemia group and 6406 cases in the control group. No NOS score of any studies included in the review was less than 7. The comparison between case and control groups was highly credible. The specific process for literature retrieval is displayed in Figure 1.

Meta-analysis result of APOA5-1131T>C(rs662799)

This gene locus was included in 10 case-control studies, involving a total of 2706 subjects, including 1211 in the hyperlipidemia group and 1496 in the control group. The baseline data and quality evaluation of each study are displayed in Table 1. Analysis of the relationship between C vs T alleles and hyperlipidemia (allele model) revealed heterogeneity ($I^2 = 73.9\%$, $P < 0.000$), so a random-effects model was used to analyze the combined effects. Individuals with the C allele had a higher risk of hyperlipidemia than those with the T allele, a difference that was statistically significant (OR=1.996, 95% CI=1.529-2.606, $P < 0.000$) (Figure 2). Other gene models at this site showed consistent results, suggesting that a single nucleotide polymorphism of APOA5-1131T>C is associated with hyperlipidemia, with the C allele posing a risk factor for hyperlipidemia susceptibility (Table 2).

Meta-analysis result of APOA1-75bp(rs670)

This site on APOA was included in 5 case-control studies, involving a total of 2596 subjects, of which 1284 were in the hyperlipidemia group and 1312 in the control group. Baseline data and quality evaluation are displayed in Table 1. Analysis of the relationship between A vs G alleles and hyperlipidemia (allele model) indicated no significant heterogeneity ($I^2 = 1.2\%$, $P = 0.400$), and so a fixed-effects model was used to combine the effects. Individuals with the A allele had a higher risk of hyperlipidemia than those with the G allele, a difference that was statistically significant (OR=1.228, 95% CI=1.067-1.413, $P = 0.004$) (Figure 3). The recessive model of this locus indicated that the difference was not statistically significant ($P = 0.066$). Other gene models at this site demonstrated consistent results, suggesting that the single nucleotide polymorphism of APOA1-75bp is associated with hyperlipidemia, and the A allele is a risk factor for hyperlipidemia susceptibility (Table 2).

Meta-analysis result of APOA1+83bp(rs5069)

This site was included in 7 case-control studies, involving a total of 3072 subjects, including 1452 in the hyperlipidemia group and 1620 in the control group. The baseline data and quality evaluation of each study are shown in Table 1. Analysis of the relationship between A vs G alleles and hyperlipidemia (allele model) indicated that there was no significant heterogeneity ($I^2 = 0.0\%$, $P = 0.472$). Therefore, a fixed-effects model was selected to analyze the pooled effect. There was no significant difference in risk among individuals carrying the T and C alleles (OR=0.928, 95% CI=0.771-1.116, $P = 0.425$) (Figure 4). Other gene

models of this locus indicated that the *P* values were all higher than 0.05, suggesting that there was no significant difference. It was considered that an association between APOA1+83bp gene polymorphism and hyperlipidemia susceptibility did not exist (Table 2).

Meta-analysis of APOB MspI(rs1801701)

This gene locus was included in 6 case-control studies, involving a total of 2198 subjects, including 1155 in the hyperlipidemia group and 1043 in the control group. Baseline data and quality evaluation are shown in Table 3. Analysis of the association between M- vs M+ alleles and hyperlipidemia (allele model) indicated heterogeneity ($I^2 = 0.0\%$, $P = 0.731$), therefore, a fixed-effects model was selected to analyze the pooled effects. There was no significant difference in risk among individuals carrying M- and M+ alleles (OR=0.892, 95% CI=0.756-1.053, $P = 0.178$). The *P* values of other gene models at this site were also higher than 0.05, indicating that there was no significant difference. Thus, no association between genetic polymorphism of APOB MspI and risk of hyperlipidemia was found (Table 4).

Meta-analysis of APOB XbaI(rs693)

This site was included in 12 case-control studies, involving a total of 3736 subjects, including 1900 in the hyperlipidemia group and 1836 in the control group. Baseline data and quality evaluation are shown in Table 3. Analysis of the association between T vs C alleles and hyperlipidemia (allele model) indicated heterogeneity ($I^2 = 72.4\%$, $P < 0.000$) and so a random-effects model was used to analyze the pooled effects. The risk of hyperlipidemia in the T allele population was higher than that in the C allele population, the difference of which was statistically significant (OR=1.444, 95% CI=1.061-1.966, $P = 0.020$) (Figure 5). There was no significant difference between the dominant and codominant models of this locus, with *P* values of 0.100 and 0.140, respectively. The results of other gene models were consistent with those of the allele model. Therefore, it is considered that there is an association between APOB XbaI gene single nucleotide polymorphism and hyperlipidemia and that the T allele is a risk factor for hyperlipidemia (Table 4).

Meta-analysis of APOB EcorI(rs1042031)

This site was included in 10 case-control studies, involving a total of 3319 subjects, including 1633 in the hyperlipidemia group and 1686 in the control group. Baseline data and quality evaluation are shown in Table 3. Analysis of the association between A vs G alleles and hyperlipidemia (allele model) indicated heterogeneity ($I^2 = 70.0\%$, $P < 0.000$), so the pooled effects were analyzed using a random-effects model. There was no significant difference in risk among people carrying A and G alleles (OR=1.333, 95% CI=0.942-1.885, $P = 0.104$). Other gene models at this site provided consistent results, and so no association between the genetic polymorphism of APOB EcorI and susceptibility to hyperlipidemia (Table 4) can be considered to exist.

Meta-analysis of APOE

This site was included in 30 case-control studies, involving a total of 11614 subjects, including 5208 in the hyperlipidemia group and 6406 in the control group. The baseline data and quality evaluation of various studies are displayed in Table 5. The APOE ε3 allele was used as a reference to analyze the relationship between alleles and hyperlipidemia. Analysis of ε2 ($I^2 = 63.0\%$, $P < 0.000$) and ε4 ($I^2 = 73.3\%$, $P < 0.000$) data indicate that there was heterogeneity between them, so the pooled effects were analyzed using a random-effects model. The difference in risk between individuals with ε2 and ε3 alleles was not statistically significant (OR=1.167, 95% CI=0.955-1.426, $P = 0.131$). The risk of hyperlipidemia in people with the ε4 allele higher than that in those with the ε3 allele, a difference that was statistically significant (OR= 1.710, 95% CI=1.405-2.083, $P < 0.000$) (Figure 5).

Correlations in the APOE genotype (E2/E2, E2/E3, E2/E4, E3/E4, E4/E4) and hyperlipidemia were analyzed using the wild type E3/E3 genotype as a reference. The heterogeneity and OR values and 95% CI of these data are shown in Table 6. The significance level was adjusted to $\alpha' = \alpha / (k-1) = 0.01$. There was a significant difference in the risk of hyperlipidemia between carriers of genotypes E2/E4, E3/E4, or E4/E4 with carriers of genotype E3/E3, *P* values all less than 0.01. It can be concluded that APOE gene polymorphism is closely related to hyperlipidemia and that the ε4 allele is a risk factor for hyperlipidemia.

Publication bias and sensitivity analysis

There was no apparent asymmetry in each Begg's funnel plot (Figure 6), indicating that publication bias was slight. In addition, from the statistical analysis of the symmetry of the Begg's funnel plot using an Egger's test, the publication bias of each gene locus indicated that the *P* values were all higher than 0.05, and that no apparent publication bias existed.

For groups with a large deviation shown in the analysis, after excluding the associated manuscripts, the meta analysis was performed again and OR and *P* values re-calculated. When the literature^[21] for the APOA5-1131T>C allele model with the largest OR value deviation was excluded, the results were similar to those of the original data and consistent with the original conclusions (OR= 1.800, 95% CI=1.454-2.229, $P < 0.000$). The results of the APOA1-75bp and APOA1+83bp allele models were stable, with no literature having excessive deviation found.

For the APOB XbaI locus allele model, exclusion of the literature with the largest OR value deviation^[35] provided conclusions of the meta-analysis consistent with the original conclusions (OR= 1.365, 95% CI=1.001-1.862, $P = 0.049$). Exclusion of the corresponding APOB EcorI literature^[32] indicated differences in meta-analysis that were not statistically significant, consistent with the original conclusions (OR= 1.260, 95% CI=0.892-1.779, $P = 0.190$). For the APOB MspI loci alleles model, the results were stable and no manuscripts with excessive deviation was found.

When the manuscript^[68] having the maximum deviation for data of the ε2 allele of APOE was eliminated, the meta-analysis concluded that the ε2 allele was not associated with hyperlipidemia (OR= 1.150, 95% CI=0.943-1.402, $P = 0.167$). Correspondingly, exclusion of the literature with the largest deviation for the APOE ε4 allele^[68], resulted in conclusions consistent with those originally made following recalculation, so carrying the ε4 allele is considered a risk factor for

hyperlipidemia (OR= 1.657, 95% CI=1.365-2.012, $P < 0.000$). To summarize, we conclude that no apparent problems existed among the literature that would overturn our original conclusions, with good reliability.

Discussion

The APOE gene, located on chromosome 19, contains 4 exons and 3 introns, with 3 isomers, and has the function of regulating plasma total cholesterol (TC) and lipoprotein metabolism. APOE3 is the most common phenotype. A principal function is to bind low-density lipoprotein receptor (LDL-R) and APOE receptor as a ligand^[69]. Compared with APOE3, the ability of APOE4 to bind to its receptor is relatively strong, causing the metabolism of chylomicron (CM) and very low-density lipoprotein (VLDL) residues to be accelerated and the conversion of VLDL to LDL to increase. Additionally, the rate of liver internalization and catabolism of CM and VLDL residues is accelerated, resulting in increased free cholesterol in hepatocytes and feedback causing a down-regulation of LDL-R on their surface, resulting in a decrease in the metabolic rate of LDL^[70]. Furthermore, the low intestinal cholesterol absorption capacity of $\epsilon 4$ carriers also increases, resulting in higher plasma levels of TC and LDL. This is consistent with the conclusion that the $\epsilon 4$ allele is a risk factor for hyperlipidemia in the present review, although the protective effects of the $\epsilon 2$ allele on blood lipid levels were not observed. This might be related to the heterogeneity of the study population and the small number of $\epsilon 2$ alleles included. The existence of a medical mechanism to explain why the $\epsilon 2$ allele did not protect blood lipid levels could not be ruled out.

APOB is the principal protein component of LDL and plays a role in transporting endogenous cholesterol to maintain its balance within the body. The APOB gene is located in region 23-24 of the short arm of human chromosome 2. The APOB gene plays a key role in the production, transport, and removal of LDL and VLDL from plasma and regulates the concentration of plasma cholesterol^[71]. The polymorphism of the APOB XbaI restriction site is due to a mutation of nucleotide C→T at position 7673 of the APOB gene cDNA, which changes the codon sequence at position 2488 (ACC→ACT), thus producing an XbaI endonuclease recognition site. The T allele may be related to a reduction in LDL degradation rate mediated by the receptor^[9]. A number of studies have also speculated that a single nucleotide polymorphism at this locus is a genetic marker and has linkage disequilibrium with other nearby DNA sequence variants that affect cholesterol levels^[72]. This molecular mechanism could explain the result that the T allele was a risk factor for hyperlipidemia. Other studies further confirm the conclusions that this polymorphism of the APOB XbaI gene might increase the risk of cerebral infarction, and that the T allele is such a risk factor^[73]. The T allele was associated with lower levels of HDL-C, which might be associated with incidence of coronary heart disease^[74].

The APOA1 gene is located in the terminal region of the long arm of chromosome 11 and consists of 3 introns and 4 exons. APOA1 is the main apolipoprotein that creates high-density lipoprotein (HDL), maintaining the stability and integrity of the HDL structure, and promoting cholesterol (TC) esterification^[75]. The APOA1-75bp polymorphism not only destroys the endonuclease recognition site but also changes the GGGCCGG sequence which can activate transcription. A change to the sequence may affect the synthesis of APOA1^[76]. This mechanism was consistent with the conclusion that there was an association between the A1-75bp gene single nucleotide polymorphism and hyperlipidemia. The APOA5 gene, located in 23 regions of the long arm of chromosome 11, has 1889 bp and consists of 4 exons, 2 introns and 4 silencing molecules. APOA5 can reduce triglyceride (TG) and increase HDL, and represents a protective factor for coronary heart disease^[77]. Some manuscripts also clearly state that the mutation APOA5-1131T > C is closely related to increased triglyceride levels^[78] and that the CC genotype of this locus was positively correlated with serum TG levels and negatively correlated with APOA5 levels^[79].

A meta-analysis can effectively make up for the lack of statistical efficacy and other problems within a single study. However, although the present review developed a scientifically-based and comprehensive search strategy with strict unified screening criteria, limitations still remain^[80]: (1) There were few relevant Chinese and English manuscripts on the acquisition of particular gene loci, such as APOA1 and APOB MspI, so the number of case-control studies included in the analysis was small, possibly reducing the effectiveness of the Egger's and Begg's tests, in addition to sensitivity analysis; (2) The data included in the review could not unify racial and ethnic information, also leading to heterogeneity to some extent; (3) It is unknown whether there were statistical differences in sex and age among individuals included in the study; (4) The effects of gene-environmental interactions and genetic linkage disequilibrium were not considered. In the future, we shall include more reliable data in this respect and update the meta-analysis, thereby providing a more reliable evidence base for the prevention and control of hyperlipidemia from the perspective of the apolipoprotein gene.

Conclusions

The results of this present meta-analysis revealed that the C allele of APOA5 1131T>C, the A allele at APOA1-75bp, the APOB XbaI T allele, and the $\epsilon 4$ allele of APOE might represent genetic risk factors for susceptibility for hyperlipidemia. In addition, we find it is consistent with the current study on the pathological mechanisms of hyperlipidemia. However, there is a need for further larger-scale studies, including larger case-control study and analysis of other loci of the APO genes, to confirm our conclusions and elucidate the influence of gene-environment interactions.

Abbreviations

APO: Apolipoprotein; SNPs: Single nucleotide polymorphisms; HWE: Hardy-Weinberg Equilibrium; NOS: Newcastle-Ottawa Scale; TC: Total cholesterol; LDL-R: Low-density lipoprotein receptor; CM: Chylomicron; VLDL: Very low-density lipoprotein; HDL: High-density lipoprotein.

Declarations

Ethics approval and consent to participate

This work has been approved by the Ethics Committee of The University Town Hospital of Guizhou Medical University.

Consent for publication

All author have read and agreed with the published version of the paper.

Availability of data and material

Data openly available in a public repository that issues datasets with DOIs.

Competing interests

We declare that none of the work contained in this manuscript is published in any language or currently under consideration at any other journal, and there are no conflicts of interest to declare.

Author Contribution

Writing-Original draft preparation: XNZ, QS, Methodology and data curation: QS, XNZ, Writing-review and editing: YQC, XR and XNZ, Supervision: YC, QS.

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Tables

Table 1: Main characteristics of studies of APOA included in the review.

SNP	First author	Year	Area	Sample size		Age (y)		Source of control	Genotyping method	Cases	
				Case	Control	Case	Control			TT/GG/CC	CT/GA/C'
APOA5-1131 T/C	Zhao DD ^[14]	2007	Beijing, China	172	80	NR	NR	HB	PCR-RFLP	63	86
	Niu ZB ^[15]	2016	Shanghai, China	156	262	NR	NR	PB	MALDI-TOF	68	68
	Huang M ^[16]	2008	Taiwan, China	76	240	59.57±10.2	60.98±13.58	PB	PCR-RFLP	15	41
	Long SY ^[17]	2013	Hunan, China	95	102	61 ± 12	62 ± 12	HB	PCR-RFLP	46	36
	Maria ^[18]	2014	Napoli, Italian	165	142	47.5 ± 12.2	43.9 ± 9.6	HB	TaqMan	111	49
	Cláudia ^[19]	2012	Minas Gerais, Brazil	108	107	48.4±6.8	46.7±6.6	PB	PCR-RFLP	52	52
	Brito ^[20]	2010	Belo Horizonte, Brazil	53	77	10.4 ± 2.7	11.2 ± 3.4	HB	PCR-RFLP	34	14
	ZK Liu ^[21]	2009	Hongkong, China	56	176	49.6±12.3	50.1±9.4	HB	PCR	9	27
	Peter H ^[22]	2008	Netherlands	254	240	NR	NR	HB	PCR	142	72
	Han Y ^[8]	2012	Hunan, China	109	117	60.3±12.1	62.9±12.0	HB	PCR-RFLP	52	43
APOA1-75bp	Huang G ^[23]	2011	Xinjiang, China	275	252	47.7±7.9	48.23±7.6	HB	PCR-RFLP	135	102
	Feng DW ^[7]	2016	Xinjiang, China	365	370	46.8±15.9	45.21±16.4	PB	PCR	248	104
	Feng DW ^[7]	2016	Xinjiang, China	345	391	43.9±14.3	41.5±13.3	PB	PCR	250	87
	Chi YH ^[24]	2012	Xinjiang, China	200	200	58.5±11.8	58.3±11.5	PB	PCR-RFLP	116	82
	Bora K ^[2]	2017	Assam, India	100	100	43.1±11.6	43.0±11.6	PB	PCR-RFLP	62	35
APOA1+83bp	Xie YJ ^[25]	2011	Xinjiang, China	150	150	56.8±10.8	58.1±10.5	HB	PCR-RFLP	126	24
	Ou HJ ^[5]	2014	Xinjiang, China	241	246	49.1±0.7	48.3±0.8	HB	MALDI-TOF	160	80
	Feng DW ^[7]	2016	Xinjiang, China	365	370	46.8±15.9	45.2±16.4	PB	PCR	317	48
	Feng DW ^[7]	2016	Xinjiang, China	345	391	43.91±14.27	41.51±13.28	PB	PCR	299	44
	Zhu H ^[26]	2001	Sichuan, China	134	255	54.7±12.6	51.7±10.9	PB	PCR	123	11
	Jia LQ ^[27]	2005	Sichuan, China	118	109	58.1±8.9	54.5±9.6	NR	PCR	105	13
	Bora K ^[2]	2017	Assam, India	100	100	43.12 ± 11.64	42.95 ± 11.60	PB	PCR-RFLP	89	11

SNP: single nucleotide polymorphism; PB: population-based; HB: hospital-based; HWE: Hardy-Weinberg equilibrium; NR: not reported.

Table 2: Summary of the meta-analysis of the association of APOA gene polymorphisms and hyperlipidemia.

SNP	Analysis model	Genotype model	Heterogeneity I^2/P	OR [95% CI]	<i>P</i>	Publication bias <i>P</i>
APOA5-1131T/C	A	C vs T	73.9%/ 0.000	1.996 [1.529~2.606]	0.000	0.353
	D	TC+CC vs TT	71.2%/ 0.000	2.179 [1.565~3.035]	0.000	0.258
	R	CC vs TC+TT	5.5%/ 0.390	2.790 [2.055~3.789]	0.000	0.991
	C	CC vs TT	45.7%/ 0.056	3.604 [2.589~5.017]	0.000	0.899
		TC vs TT	67.2%/ 0.001	1.932 [1.395~2.674]	0.000	0.465
APOA1-75bp	A	A vs G	1.2%/ 0.400	1.228 [1.067~1.413]	0.004	0.086
	D	AA+GA vs GG	0.0%/ 0.704	1.246 [1.056~1.471]	0.009	0.067
	R	AA vs GA+GG	15.9%/ 0.313	1.458 [0.976~2.180]	0.066	0.086
	C	AA vs GG	17.4%/ 0.304	1.520 [1.008~2.291]	0.046	0.086
		GA vs GG	0.0%/ 0.828	1.212 [1.020~1.439]	0.029	0.221
APOA1+83bp	A	T vs C	0.0%/ 0.472	0.928 [0.771~1.116]	0.425	0.440
	D	TT+TC vs CC	0.0%/ 0.478	0.950 [0.780~1.157]	0.607	0.371
	R	TT vs TC+CC	0.0%/ 0.799	0.310 [0.076~1.271]	0.104	0.315
	C	TT vs CC	0.0%/ 0.775	0.308 [0.075~1.259]	0.101	0.346
		TC vs CC	0.0%/ 0.607	0.967 [0.793~1.180]	0.740	0.466

A: allelic model; D: dominant model; R: recessive model; C: codominant model; Publication bias *P*: using Begg's or Egger's tests.

Table 3: Principal characteristics of the studies of APOB included in the review.

SNP	First author	Year	Area	Sample size		Age (y)		Source of control	Genotyping method	Cases		
				Case	Control	Case	Control			M-M-/TT/AA	M+M-/CT/AG	M-/G
APOB Msp	Cao WJ ^[28]	2009	Xinjiang, China	100	90	46±11	44±11	HB	PCR-RFLP	0	4	9
	Chi YH ^[29]	2012	Xinjiang, China	247	221	48.7±7.7	47.3±6.2	HB	PCR-RFLP	9	70	1
	Huang G ^[23]	2011	Xinjiang, China	275	252	47.7±7.9	48.2±7.6	HB	PCR-RFLP	25	68	1
	Jin YN ^[30]	2015	Chongqing,China	157	180	48.1±3.8	49.1±4.2	HB	DNA chips	0	26	1
	Chi YH ^[24]	2012	Xinjiang, China	200	200	58.5±11.8	58.3±11.5	PB	PCR-RFLP	6	66	1
	Selma ^[31]	2000	Sao Paulo, Brazil	177	100	58	44	HB	PCR	2	25	1
APOB XbaI	Qian J ^[32]	2010	Yunnan, China	91	76	46.9±11.4	47.5±8.1	HB	DNA chips	0	7	8
	Feng JS ^[33]	1997	Guangdong, China	108	128	40-70		HB	DNA probe	0	8	1
	Ma ZZ ^[34]	2012	Guangdong, China	250	250	45.50±13.20		PB	PCR-RFLP	0	52	1
	Chi YH ^[29]	2012	Xinjiang, China	247	221	48.7±7.7	47.3±6.2	HB	PCR-RFLP	4	54	1
	Xie YJ ^[25]	2011	Xinjiang, China	150	150	56.8±10.8	58.1±10.5	HB	PCR-RFLP	2	29	1
	Jin YN ^[30]	2015	Chongqing,China	157	180	48.1±3.8	49.1±4.2	HB	DNA chips	0	28	1
	Zhang PZ ^[35]	2015	Beijing, China	100	100	60.0±5.0		HB	PCR	0	20	8
	Ou HJ ^[5]	2014	Xinjiang, China	241	246	49.1±0.7	48.3±0.8	HB	MALDI-TOF	0	19	2
	Selma ^[31]	2000	Sao Paulo, Brazil	177	100	58	44	HB	PCR	30	94	5
	Philippa ^[36]	1987	London, U.K.	133	62	NR		HB	PCR-RFLP	43	59	3
	Gong LG ^[37]	2003	Liaoning, China	115	150	54.2±11.7	52.5±13.1	HB	PCR-RFLP	1	29	8
	CHOONG ^[38]	1999	Singapore	131	173	NR		HB	PCR-RFLP	0	25	1
APOB EcorI	Qian J ^[32]	2010	Yunnan, China	91	76	46.9±11.4	47.5±8.06	HB	DNA chips	0	13	7
	Ma ZZ ^[34]	2012	Guangdong, China	250	250	45.5±13.2		PB	PCR-RFLP	0	41	2
	Huang G ^[23]	2011	Xinjiang, China	275	252	47.7±7.9	48.2±7.6	HB	PCR-RFLP	12	73	1
	Xie YJ ^[25]	2011	Xinjiang, China	150	150	56.8±10.8	58.1±10.5	HB	PCR-RFLP	1	55	9
	Jin YN ^[30]	2015	Chongqing,China	157	180	48.1±3.8	49.11±4.2	HB	DNA chips	0	12	1
	Zhang PZ ^[35]	2015	Beijing, China	100	120	60.0±5.0		HB	PCR	1	19	8
	Ou HJ ^[5]	2014	Xinjiang, China	241	246	49.1±0.7	48.3±0.8	HB	MALDI-TOF	1	29	2
	Chi YH ^[24]	2012	Xinjiang, China	200	200	58.5±11.8	58.3±11.5	PB	PCR-RFLP	6	52	1
	CHOONG ^[38]	1999	Singapore	131	173	NR		HB	PCR-RFLP	0	9	1
	Timirci O ^[39]	2010	Capa-Istanbul, Turkey	38	39	11.5±3.6	11.4±3.2	HB	PCR	0	4	3

SNP: single nucleotide polymorphism; PB: population-based; HB: hospital-based; HWE: Hardy-Weinberg equilibrium; NR: not reported.

Table 4: Summary of meta-analysis results of the association of APOB gene polymorphisms and hyperlipidemia.

SNP	Analysis model	Genotype model	Heterogeneity I^2/P	OR 95% CI	<i>P</i>	Publication bias <i>P</i>
APOB Msp	A	M- vs M+	0.0%/ 0.731	0.892 0.756~1.053	0.178	0.452
	D	M-M-/M+M- Vs M+M+	0.0%/0.716	0.868 0.716~1.053	0.152	0.707
	R	M-M-vs M+M-/M+M+	0.0%/ 0.513	0.932 0.596~1.456	0.757	0.908
	C	M-M- vs M+M+	0.0%/ 0.555	0.903 0.574~1.421	0.660	0.883
		M+M- vs M+M+	0.0%/ 0.654	0.864 0.705~1.057	0.156	0.746
APOB Xba	A	T vs C	72.4%/ 0.000	1.444 1.061~1.966	0.020	0.732
	D	TT+CT vs CC	73.5%/ 0.000	1.360 0.943~1.962	0.100	0.945
	R	TT vs CT+CC	0.0%/ 0.747	1.613 1.022~2.545	0.040	0.707
	C	TT vs CC	0.0%/ 0.774	1.432 0.851~2.411	0.017	0.724
		CT vs CC	73.5%/ 0.000	1.322 0.912~1.917	0.140	0.837
APOB Ecor	A	A vs G	70.0%/ 0.000	1.333 0.942~1.885	0.104	0.474
	D	AA+AG Vs GG	72.9%/ 0.000	1.366 0.924~2.020	0.118	0.283
	R	AA vs AG+GG	0.0%/ 0.942	1.183 0.628~2.229	0.603	0.221
	C	AA vs GG	0.0%/ 0.886	1.166 0.617~2.202	0.637	0.086
		AG vs GG	72.6%/ 0.000	1.356 0.913~2.015	0.131	0.371

A: allelic model; D: dominant model; R: recessive model; C: codominant model; Publication bias *P*: using Begg's or Egger's tests.

Table 5: Main characteristics of studies of APOE included in the review.

First author	Year	Area	Sample size		Age (y)		Source of control	Genotyping method	Cases			
			Case	Control	Case	Control			E2/E2	E2/E3	E2/E4	E3/E4
Liang JP ^[40]	2008	Beijing,China	210	94	58.48	NR	HB	PCR-RFLP	2	19	2	155
Wu XH ^[41]	2007	Xinjiang,China	100	91	48.7±10.5	43.1±10.8	HB	PCR-RFLP	0	9	0	69
Zhao DD ^[14]	2007	Beijing,China	172	80	NR		HB	PCR-RFLP	1	18	2	124
Hu HN ^[42]	2007	Hubei,China	165	108	60.5±8.3	63.8±6.2	HB	ARMS-PCR	0	26	0	109
Zeng ZW ^[43]	2001	Guangdong,China	163	87	56.4±3.2	58.0±2.4	HB	PCR-RFLP	0	22	5	104
Zeng WY ^[44]	1996	Beijing,China	133	122	41-60		PB	PCR	5	17	4	88
Wang R ^[45]	2005	Sichuan,China	206	250	52	51	HB	PCR-RFLP	0	46	2	135
Zhu CL ^[46]	2005	Hubei,China	113	108	62.5±7.2	63.8±6.2	HB	ARMS-PCR	0	16	0	74
Tian Y ^[47]	2005	Sichuan,China	103	146	56.9±8.5	56.3±9.8	PB	PCR-RFLP	2	23	1	64
Zhang YH ^[48]	2004	Beijing,China	160	328	47.3±13.8	40.1±13.5	PB	PCR-RFLP	0	13	5	114
Jiang WM ^[49]	2013	Jiangsu,China	102	100	48.4±9.7	50.2±15.1	HB	DNA sequencing	1	9	2	64
Qian J ^[50]	2011	Jiangsu,China	212	100	54.6±11.9	50.2±15.1	HB	DNA sequencing	2	21	6	127
Liu YL ^[51]	2006	Shanxi,China	72	95	NR		HB	ARMS-PCR	2	8	3	45
Zhan CY ^[52]	2007	Beijing,China	96	95	60.0±8.3	NR	HB	PCR	0	9	0	75
Luo R ^[53]	2006	Hubei,China	164	156	58.3±7.1	53.1±4.7	HB	PCR-RFLP	1	27	1	101
Zhang XM ^[54]	2001	Sichuan,China	74	230	56.8±12.4	51.3±10.3	PB	PCR-RFLP	0	10	2	56
Jiang WM ^[55]	2013	Jiangsu,China	93	100	56.0±11.85	50.2±15.1	HB	DNA sequencing	1	7	2	57
Jiang WM ^[56]	2012	Jiangsu,China	212	100	54.6±11.85	50.2±15.1	HB	DNA sequencing	2	21	6	127
Long SY ^[57]	2004	Sichuan,China	112	73	58.2±7.9	55.1±9.7	PB	PCR-RFLP	1	21	4	68
Zhang XM ^[58]	2001	Sichuan,China	225	230	53.0±15.5	51.3±10.3	PB	PCR-RFLP	1	37	5	156
ALBERT ^[59]	2003	Amsterdam, Netherlands	450	2018	10.8	NR	HB	PCR	0	50	10	243
Turky H.A ^[60]	2018	Riyadh, Saudi Arabia	104	100	57.8±9.9	44.0±6.3	HB	TaqMan	1	7	2	74
Corella ^[61]	2000	Valencia, Spain	330	330	38.8±9.1	37.6±8.4	PB	PCR	0	17	5	237
Kobori ^[62]	1988	Kumamoto, Japan	447	188	30-69		HB	SRID	9	49	7	323
Cenarro ^[63]	2016	Zaragoza, Spain	288	220	47.9±11.5	44.8±16.0	HB	RT-PCR	0	9	1	186
Kiran ^[64]	2011	New Delhi, India	219	352	42.0 ± 7.9	35.2 ± 9.6	HB	PCR-RFLP	0	8	4	143
SolanasB ^[65]	2012	Zaragoza, Spain	312	264	48.4±9.7	43.5±16.9	HB	PCR	11	25	5	189
N.Ferreira ^[66]	2010	Minas Gerais, Brasil	109	107	48.4±6.8	46.7±6.6	HB	PCR-RFLP	0	10	0	77
FUMERON ^[67]	1988	Paris, France	59	113	NR		HB	PCR	0	5	1	35
T Kuusi ^[68]	1988	Helsinki, Finland	21	21	45.2±0.8	46.7±1.5	HB	PCR	0	1	3	2

SNP: single nucleotide polymorphism; PB: population-based; HB: hospital-based; HWE: Hardy-Weinberg equilibrium; NR: not reported; SRID: single radial immunodiffusion.

Table 6: Summary of the meta-analysis of the association of APOE gene polymorphisms and hyperlipidemia.

Genotype model	Heterogeneity I^2/P	OR 95% CI	<i>P</i>	publication bias <i>P</i>
E2/E2	0.0%/0.634	1.746 1.081~2.819	0.023	0.131
E2/E3	50.3%/0.001	1.076 0.883~1.311	0.467	0.400
E2/E4	0.0%/0.790	1.693 1.227~2.336	0.001	0.054
E3/E4	67.8%/0.000	1.578 1.276~1.951	0.000	0.073
E4/E4	2.7%/ 0.424	2.346 1.723~3.195	0.000	0.851

Publication bias *P*: using Begg's or Egger's tests.

Figures

Figure 1

Flow diagram of the meta-analysis.

Figure 2

Pooled calculated OR for the association between APOA5-1131T>C allele and hyperlipidemia.

Figure 3

Pooled calculated OR for the association between the APOA1-75bp allele and hyperlipidemia.

Figure 4

Pooled calculated OR for the association between APOB XbaI allele and hyperlipidemia.

Figure 5

Pooled calculated OR for the association between the APOE allele and hyperlipidemia.

Figure 6

Begg's funnel plot for the APOE $\epsilon 4$ allele.