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ORIGINAL RESEARCH ARTICLE

Association of Common Single Nucleotide Polymorphisms of Candidate Genes with Gallstone Disease: A Meta-Analysis

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Abstract Numerous studies have investigated the relationship between various candidate gene polymorphisms and gallbladder stone disease (GSD) across ethnic populations; however, the results are often inconsistent. This meta-analysis aims to comprehensively evaluate the influence of common ABCG8 T400K, ABCG8 D19H, ABCG8 C54Y, ApoB100 EcoRI, ApoB100 XbaI, ApoE HhaI, CETP TaqI, CYP7A1 Bsa, LRPAP1 I/D and TNF-α A308G polymorphisms on the risk of gallbladder stone disease. 33 Full-text articles with 9250 cases and 12,029 healthy controls (total 21,279 subjects) were analyzed using the RevMan software (V5.1) and the Comprehensive Meta-analysis software (Version 2.0, BIOSTAT, Englewood, NJ) a Random—effects model was applied. Begg's funnel plots, Fail-safe number, Egger's regression intercept and Begg and Mazumdar rank correlation tests were performed for the potential publication bias and sensitivity analysis. The studies were also sub-grouped into European and non-European groups to find out role of ethnicity, if any, on GSD risk. Studies included in quantitative synthesis were ABCG8 T400K rs4148217 (cases/controls, n = 671/1416) (4 studies), ABCG8 D19H rs11887534 (n = 1633/2306) (8 studies), ABCG8 C54Y rs4148211 (n = 445/1194) (3 studies), ApoB100 EcoRI rs1042031 (n = 503/390) (4 studies), ApoB100 XbaI rs693 (n = 1214/1389) (9 studies), ApoE HhaI rs429358 (n = 1335/1482) (12 studies), CETP TaqI rs708272 (n = 1038/1025) (5 studies), CYP7A1 Bsa rs3808607 (n = 565/514) (3 studies), LRPAP1 I/D rs11267919 (n = 849/900) (3 studies), TNF-α A308G rs1800629 (n = 997/1413) (3 studies). The combined results displayed significant association of ABCG8 D19H (GC + CC) [OR with 95%CI = 2.2(1.7–2.8); $p < 0.00001$], ABCG8 Y54C (GA + GG) [OR with 95%CI = 0.65(0.5–0.9); $p = 0.01$]. APOB100 EcoRI (GG vs. AA) [OR with 95%CI = 0.51(0.3–0.9); $p = 0.05$], (GG vs. GA) [OR with 95%CI = 0.6(0.4–0.9); $p = 0.04$], (GA + AA) [OR with 95%CI = 0.6(0.4–0.9); $p = 0.006$]. APOB Xba I (X^- vs. X^+) [OR with 95%CI = 0.53(0.3–0.8); $p = 0.006$. APOE Hha I (E4/E4 vs. E3/E3) [OR with 95%CI = 3.5(1.1–14.9); $p = 0.04$] and LRPAP1 I/D (ID + II) [OR with 95%CI = 1.27(1.0–1.6); $p = 0.03$] with the GSD risk. It was found that ABCG D19H was significantly associated with GSD in both European and Non-European populations. While APOB XbaI and LRPAP1 I/D markers were associated with gallstone disease only in Non- European population. Additionally, APOE HhaI and APOB 100 ECoRI were found to be associated with GSD only in European population. The results of quantitative synthesis suggest that the ABCG8 D19H polymorphism was associated with the increased risk of GSD in both European and Non-European populations, APOE Hha I and LRPAP1 I/D polymorphisms were associated with the increased risk of GSD in European and Non-European population respectively. However, no association was found in ABCG8 T400K, CETP Taq1, CYP7A1 Bsa and TNF-A308G polymorphisms with Gallstone Disease.

Keywords Gallstone disease · Genetic association · SNP · Polymorphism · Meta-analysis

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Introduction

Cholesterol Gallstone disease (CGD) corresponds to one of the most recurrent and costly gastroenterological disorder. It is a worldwide health problem representing 10–15% of the adult population in industrialized countries [1, 2] whereas a prevalence of 6% have been reported from North India [3]. Gallstone is classified into cholesterol stones and pigment stones according to their cholesterol content, and the cholesterol gallstone is more frequent than the pigment stone [4, 5]. The classical pathogenesis model of cholesterol gallstone formation included three defects: supersaturation of biliary cholesterol, imbalance of pro/anti-nucleation factors and impaired gallbladder motility [6]. Recently, genetic factors, such as the predisposition to gallstone disease and interaction with environmental factors, have drawn keen attention [7]. Katsika et al. [8], showed that genetic heredity contribute 25% of factors to gallstone formation after an elegant analysis of data from Swedish twins. Since late 1980 s', studies have been attempting to disclose susceptible genes associated with gallstone disease in different populations. The potential genes studied include apolipoprotein E [9–12], APOB [11, 12], cholesterol 7alpha-hydroxylase (CYP7A1) [11, 12], CETP etc. (Apo) E is a ligand for the low density lipoprotein family of receptors that plays a pivotal role in cholesterol metabolism [13, 14]. A large number of individually underpowered studies have been conducted on Apo E polymorphisms across different ethnic populations. However, the results are somewhat irreproducible and inconclusive. Apolipoprotein B-100 (ApoB-100) is a key protein involved in lipid metabolism. It is the sole component of LDL particles and plays an important role in the homeostasis of LDL cholesterol in plasma [15]. Numerous polymorphisms have been identified in ApoB-100, among which the XbaI polymorphism (22488C.T), a single base alteration in the exon 26, has been demonstrated to be associated with inter individual variability of lipid levels [16]. In addition, another polymorphism of ApoB-100 gene is EcoRI (24154G.A) [17]. In the last decade, with the understanding of ATP binding cassette (ABC) G5 and G8 as major cholesterol transporters in hepatic and intestinal cholesterol secretion and in regulating biliary cholesterol content and cholesterol absorption [18]. Studies on association of polymorphism of ABCG8 and gallstone disease have been published [19–28]. The most studied loci are D19H, T400K and Y54C. Cholesterol 7a-hydroxylase, a cytochrome P-450 enzyme, is the rate limiting in hepatic bile acid synthesis, with its activity regulated by bile acids, cholesterol and hormones [29]. Although the amino acid sequence of CYP7A between species is highly homologous (80–90% sequence identity), species respond differently to diet cholesterol [30]. As compared with control subjects, the activity of CYP7A varied in patients with gallstones [31–33] and diminished or elevated patterns were observed. The heterogeneity of activities of CYP7A in patients with GSD may be related to CYP7A polymorphisms. A linkage of A-204C single nucleotide polymorphism of the CYP7A gene promoter with plasma low density lipoprotein (LDL) cholesterol was found in studies of nuclear families [34] and within the general population [35]. Cholesteryl ester transfer protein (CETP) are associated with gallstone development [36]. CETP, also called plasma lipid transfer protein, is a plasma protein that facilitates transport of cholesteryl esters and triglycerides between lipoproteins. CETP collects triglycerides from VLDL or LDL and exchanges them for cholesteryl esters from HDL [37]. A 37-bp insertion/deletion polymorphism in intron 5 of LRPAP1 gene might also be associated with a variation in plasma lipid levels and hence gallstone disease [38, 39]. Since reproducibility of data is important in genetic association studies, the association of this polymorphism was also examined. The pro-inflammatory cytokine TNF-α may promote gallstone formation [40].

Due to difference in allele frequency at each polymorphic locus between different ethnicities, the associations between the SNPs with gallstone disease are somewhat not consistent. Thus, a meta-analysis approach to evaluate the association between each loci and gallstone disease was undertaken for the present study.

Objective

In this meta-analysis, we aimed to evaluate the association between polymorphisms of ABCG8 T400K [22, 23, 25, 26], ABCG8 D19H [[21–23, 25, 26, 41, 42, Chauhan T et al.], ABCG8 C54Y [23, 25, 26], ApoB100 EcoRI [43–45], ApoB100 XbaI [11, 12, 36, 43–47]. ApoE HhaI [9, 11, 12, 48–53], CETP TaqI [20, 36, 45, 54, 55], CYP7A1 Bsa [12, 56, 57]. LRPAP1 I/D [20, 58, 59] and TNF-α A308G [40, 60, 61] with cholesterol gallstone disease.

Methods

Literature Search

Publications were searched via public database PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (http://www.embase.com), with the last update as of February, 2019 The keywords used for the search were 'gallbladder stone disease' combined with 'genetic variants' or 'polymorphism', 'cholesterol gallstone disease', all of which were MeSH terms (Medical Subject Headings in the US

National Library of Medicine). The 'related articles' option in MEDLINE, as well as reference lists of all retrieved studies, were checked to search for other relevant publications that were not initially identified. As a prerequisite, only these published in English language were identified, and studies in human subjects. In addition, the full text of the retrieved articles were scrutinized to make sure the data of interest were included. If two or more studies shared the same cases or control subjects, the one with small sample size was abandoned. If more than one geographical or ethnic population were included in one article, each population was considered separately.

Inclusion/Exclusion Criteria

The included studies met the following criteria: (1) evaluated the associations between ABCG8 T400K, ABCG8 D19H, ABCG8 C54Y, ApoB100 EcoRI, ApoB100 XbaI, ApoE HhaI, CETP TaqI, CYP7A1 Bsa, LRPAP1 I/D and TNF-α A308G gene polymorphisms and the risks of GSD (2) case–control or cohort design, and (3) provided sufficient data for the calculation of odds ratios (ORs) with the corresponding 95% confidence interval (95% CI).The following information was extracted from each study: (1) name of the first author, (2) publication year, (3) country of origin, (4) ethnicity of the study population, (5) source of the control subjects, (6) numbers of cases and controls, (7) gender and age of the enrolled subjects, and (8) number of genotypes in the cases and controls. The data were extracted independently by 2 investigators who reached a consensus on all of the items.

Quality Score Assessment

The quality of each of the studies included in this meta-analysis (Ref) was rigorously evaluated independently by single author (Chauhan T), using the Newcastle–Ottawa quality assessment scale (NOS) [GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in Meta-analysis] and all disagreements were resolved through discussion. NOS is a star rating system in which each study is judged on standard criteria and subsequently categorized based on three facts: selection, comparability and exposure assessment with scores ranging from zero to nine stars. The studies with NOS score of 7–9, 4–6 and 1–3 stars are usually considered to be a high, intermediate and low methodological quality respectively.

Statistical Analysis

The associations between genotypes/alleles of ABCG8 T400K, ABCG8 D19H, ABCG8 C54Y, ApoB100 EcoRI, ApoB100 XbaI, ApoE HhaI, CETP TaqI, CYP7A1 Bsa, LRPAP1 I/D and TNF-α A308G polymorphisms with GSD were evaluated by using the software Review Manager (V5.1) for windows and the Comprehensive Meta-analysis software (Version 2.0, BIOSTAT, Englewood, NJ). In this meta-analysis, we used the Mantel–Haenszel Random effect model [62] to bring the individual effect-size estimates together and for the estimate of heterogeneity.

Heterogeneity was assessed by the I^2 statistic, which was documented for the percentage of the observed between-study variability due to heterogeneity rather than chance with the ranges of 0 to 100% [I^2 = 0–25%, no heterogeneity; I^2 = 25–50%, moderate heterogeneity; I^2 = 50–75%, large heterogeneity; I^2 = 75–100%, extreme heterogeneity] [63].

Begg's funnel plots and various tests namely Fail-safe number (the fail-safe number (N_{fs}) with the significance set at 0.05 for each Meta comparison. Specifically, if the calculated N_{fs} value was smaller than the number of observed studies, then the meta-analysis results might run the risk of having publication bias), Egger's regression intercept and Begg and Mazumdar rank correlation tests were performed to assess the potential publication bias [64]. A probability of less than 0.05 was judged to be significant except for the I^2 statistic. Sensitivity analysis was carried out to check if alteration of the inclusion criteria affects the results of the meta-analysis.

Hardy–Weinberg equilibrium (HWE) test of SNP was performed using Michael H. Court's (2005–2008) online calculator (http://www.tufts.edu/~mcourt01/Documents/Court%20lab%20-%20HW%20calculator.xls).

Results

As depicted in Fig. 1, 122 studies were initially identified through the database search. 28 studies were excluded by reading title and abstract. These included Chinese and Russian language studies, Mendelian randomization, duplicate sample studies, commentary, review etc. 94 Potential relevant records were screened but 62 were removed due to single study or just twice replicated studies. 33 Full-text articles were assessed for eligibility. Studies included in quantitative synthesis (meta-analysis) were as follows; (1) ABCG8 T400K (n = 4), (2) ABCG8

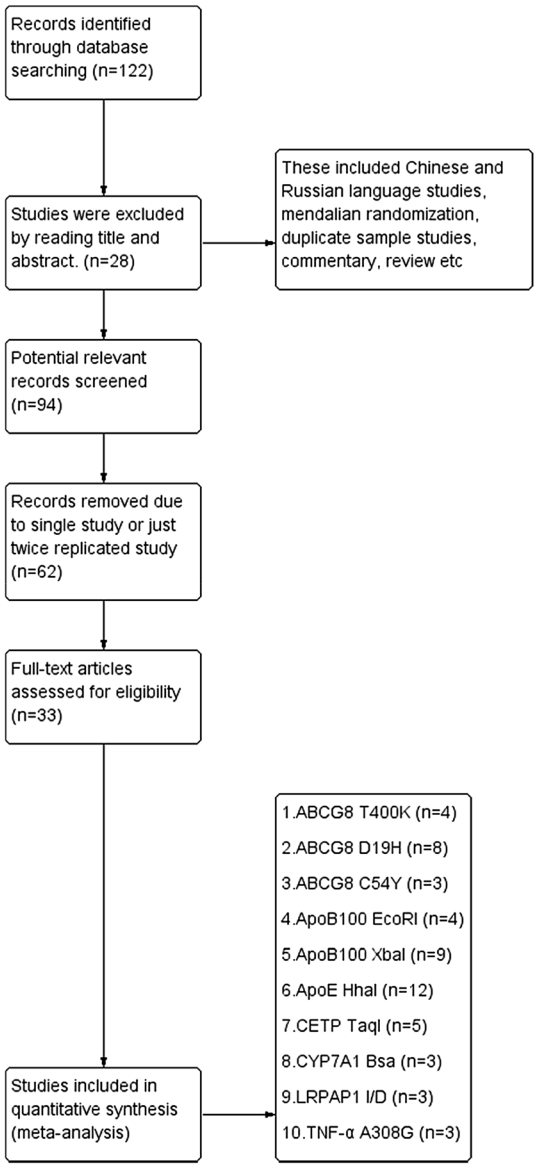


Fig. 1 Flow diagram of study selection in this meta-analysis. *n* Total number of studies

D19H (n = 8), (3) ABCG8 C54Y (n = 3), (4) ApoB100 EcoRI (n = 4), (5) ApoB100 XbaI (n = 9), (6) ApoE HhaI (n = 12), (7) CETP TaqI (n = 5), (8) CYP7A1 Bsa (n = 3), (9) LRPAP1 I/D (n = 3), (10) TNF-α A308G (n = 3). All the included studies used blood samples for DNA extraction. Polymerase chain reaction-restriction fragment length polymorphism (PCR-REFLP), PCR-dot blot hybridization, TaqMan genotyping assay, direct sequencing and MALDI-TOF mass spectrometry, amplification refractory mutation system–polymerase chain reaction methods and Sequenom based mass spectroscopy methods were used for genotyping. The detailed characteristics of the included studies are shown in Tables 1, 2, 3, 4, 5, 6 and 7.

Quality Assessment

According to the Newcastle–Ottawa quality assessment scale (NOS), the quality of all recruited case–control studies and their total quality scores are summarized in Supplementary Table 1. [a–j]. The quality scores ranged 7 and the average score of case–control studies was approximately 7.05. Thus, our NOS results indicated that most of these studies in our meta-analysis were of high quality (NOS score 6 or 7).

Quantitative Synthesis Pooled analysis

Analysis for ABCG8 T400K Fig. 2 polymorphism generated no association at all for any of the genetic models.

The forest plot for ABCG8 D19H polymorphism showed significant results in various genetic models. In genotypic model (GG vs. GC) OR with 95%CI = 2.2(1.7–2.9); $p < 0.00001$ (Fig. 3a), as well as Genotypic dominant model (GC + CC vs. GG) OR with 95%CI = 2.2(1.7–2.8); $p < 0.00001$ (Fig. 3b) assesed a high risk with GSD.

The forest plots for ABCG8 Y54C polymorphism revealed a low risk in genotypic recessive model (GA + GG vs. AA) OR with 95%CI = 0.65(0.5–0.9); $p = 0.01$ with Gallstone disease (Fig. 4).

APOB100 EcoRI polymorphism showed significant low risk in genotypic models (GG vs. AA) OR with 95%CI = 0.51(0.3–0.9); $p = 0.05$ (Fig. 5a) and (GG vs. GA) OR with 95%CI = 0.67(0.4–0.9); $p = 0.04$ (Fig. 5b). Genotypic dominant model (GA + AA vs. GG) also displayed a significant low risk OR with 95%CI = 0.6(0.4–0.9); $p = 0.006$ with GSD (Fig. 5c).

The analysis for APOB Xba I polymorphism revealed a significant low risk in allelic model (X^- vs. X^+) OR with 95%CI = 0.53(0.3–0.8); $p = 0.006$ with GSD risk (Fig. 6a).

In case of APOE Hha I polymorphism analysis revealed that in genotypic model (E4/E4 vs. E3/E3) a significant 4 fold associated risk was observed OR with 95%CI = 3.9(1.1–14.9); $p = 0.04$ with the GSD risk (Fig. 7a).

CETP Taq1 (Fig. 8) and CYP7A1 Bsa (Fig. 9) polymorphisms exposed no association at all for any of the genetic models.

Table 1 The detailed characteristics of the included studies for ABCG8 gene

Ref	Year	Country	Controls	Method	MAF % of		No. of		Sex m/f cases–controls
					Cases	Controls	Case	Control	
ABCG8 T400K rs4148217									
Wang [26]	2007	China	Patients	AD/PCR–RFLP	0.87	0.68	287	219	121/166–105/114
Kuo [23]	2008	China	Population	AD	4.2	1.0	74	905	810/95–70/4
Siddapuram [22]	2010	India	Patients	ARMS-PCR	8.2	3.8	226	222	98/128- –
Grunhage [25]	2007	Italy	Patients	AD	11.9	4.3	84	70	10/74–9/61
ABCG8 D19H rs11887534									
Kuo [23]	2008	China	Population	AD	4.2	1.0	74	905	810/95–70/4
Wang [26]	2007	China	patients	AD/PCR–RFLP	0.87	0.68	287	219	121/166–105/114
Siddapuram [22]	2010	India	Patients	ARMS-PCR	8.2	3.8	226	222	98/128- –
Srivastava [21]	2010	India	Patients	PCR–RFLP	5.2	2.5	230	220	83/47–77/143
Renner [41]	2013	Germany	Patients	MALDI-TOF MS	…	…	34	134	
Srivastava [42]	2008	India	Patients	PCR–RFLP	…	…	88	221	–/94/127
Frank Grunhage [25]	2007	Italy	Patients	AD	11.9	4.3	84	70	10/74–9/61
Chauhan et al.	2019	India	Patients	Sequenom	4.0	2.0	610	315	212/398–219/96
ABCG8 Y54C rs4148211									
Kuo [23]	2008	China	Population	AD	4.2	1.0	74	905	810/95–70/4
Grunhage [25]	2007	Italy	Patients	AD	11.9	4.3	84	70	10/74–9/61
Wang [26]	2007	China	Patients	AD/PCR–RFLP	0.87	0.68	287	219	121/166–105/114

Ref	Age cases/control	Allele freq Wild (1) and variant (2)				Genotype freq patients			Genotype freq controls			HW p	Matching criteria
		Cases 1–2		Controls 1–2		11	12	22	11	12	22		
ABCG8 T400K rs4148217													
Wang [26]	53.2 ± 0.8/55.1 ± 0.6	10.6	0	8.7	0	79.1	20.6	0.3	83.1	16.4	0.5	0.682	SM
Kuo [23]	45·8/51	…	…	…	…	58	15	0	739	134	2	0.277	SM
Siddapuram [22]	45.88/39.92	…	…	…	…	157	66	3	150	71	1	0.051	SM
Grunhage [25]	54/50	131	37	110	30	49	33	2	43	24	3	0.988	SM
ABCG8 D19H rs11887534													
Kuo [23]	45·8/51	…	…	…	…	66	6	0	851	18	0	0.954	SM
Wang [26]	53.2 ± 0.8/55.1 ± 0.6	..	0.9	…	0.7	98.3	1.7	0	98.6	1.4	0	0.999	SM
Siddapuram [22]	45.88/39.92	…	…	…	…	196	23	7	208	11	3	<0.001	SM
Srivastava [21]	48.611.9/49.09.8	436	24	429	11	206	24	0	209	11	0	0.930	NR
Renner [41]	61/57	…	…	…	…	23	11	0	115	19	0	0.677	NA
Srivastava [42]	53/52	143	33	391	5.1	55	32	1	170	50	1	0.411	SM
Frank Grunhage [25]	54/50	148	20	134	6	65	18	1	64	6	0	0.932	SM
Chauhan et al.	48/34	1120	58	515	19	533	54	2	249	17	2	0.05	NA
ABCG8 Y54C rs4148211													
Kuo [23]	45·8/51	…	…	…	…	54	18	2	747	152	6	0.847	SM
Grunhage [25]	54/50	108	60	97	43	36	36	12	35	27	8	0.735	SM
Wang [26]	53.2 ± 0.8/55.1 ± 0.6	11.5	0	11	0	77.4	22.3	0.3	79.9	18.3	1.8	0.999	SM

AD allelic discrimination; *ARMS* amplification refractory mutation system; *PCR* polymerase chain reaction; *RFLP* restriction fragment length polymorphism; *MAF* minor allele frequency; Genotypes: 11: DD; 12: DH; 22: HH: *m* male; *f* female; HW p: Hardy–Weinberg *p* value; *SM* sex matched; *NR* not reported; *NA* not applicable

Table 2 The detailed characteristics of the included studies for ApoB gene

Ref	year	country	Controls	Method	No. of		Sex m/f cases–contr	Age cases/control	Allele freq				Genotype freq patients			Genotype freq controls			HW p	Matching criteria
					Case	Control			Cases 1–2		Control 1–2		11	12	22	11	12	22		
ApoB100 EcoRI (E4154 K)rs1042031 or12669G > A																				
Kurzawski [43]	2007	Poland	Population	Pcr–rflp	240	217	59/181–102/115	61.9/63.9	–	–	–	–	172	63	5	128	74	15	0.639	NR
Rudzińska (F) [44]	2015	Poland	Hospital	Pcr–rflp	35	23	Female	9 ± 6.4/37 ± 5.4	52	18	34	12	20	12	3	13	8	2	0.895	NA
Rudzińska et al. (P) [44]	2015	Poland	Hospital	Pcr–rflp	59	58	Female	59 ± 5.5/61 ± 5.3	87	27	92	24	37	17	4	38	16	5	0.269	NA
Juvonen et al. [45]	1995	UK	Population	Pcr–rflp	169	92	??–23/69	56.0/55.0	0.772	0.23	0.777	0.223	55	32	5	55	33	4	0.943	SM
ApoB100 Xba I or 7673C > T or T2488T or exon 26 XbaI rs693																				
Sanchez-Cuén [12]	2010	Mexico	Hospital	Pcr–rflp	101	101	14/87–14/87	51.9/51.7	133-	69	118	84	41	51	9	34	50	17	0.982	SM
Kurzawski [43]	2007	Poland	Population	Pcr–rflp	240	217	59/181–102/115	61.9/63.9	–	–	–	–	63	129	48	61	122	34	0.112	NR
Dixit et al. [46]	2008	India	Population	Pcr–rflp	214	322	69/145–116/206	44.7/44.0	317	95	481	159	117	83	6	177	127	16	0.532	SM
Rudzińska (F) [44]	2015	Poland	Hospital	Pcr–rflp	35	23	Female	9 ± 6.4/37 ± 5.4	39	31	24	22	9	21	5	5	14	4	0.574	NA
Rudzińska (F) [44]	2015	Poland	Hospital	Pcr–rflp	59	58	Female	59 ± 5.5/61 ± 5.3	64	54	61	55	17	30	12	15	31	12	0.861	NA
Jiang [11]	2004	China	Population	Pcr–rflp	105	274	(78/27)–(184/90)	47.5/47.9	91.43	8.57	4.01	95.99	88	16	1	252	22	0	0.787	SM
Pandey [47]	2007	India	Population	Pcr–rflp	172	232	58/114–107/125	46.9/42.2	264	80	348	116	98	68	9	127	94	11	0.472	SM
Juvonen [45]	1995	UK	Population	Pcr–rflp	169	92	...–23/69	56.0/55.0	0.582	0.42	0.609	0.391	55	32	5	55	33	4	0.943	SM
Báez [36]	2010	Chile	Hospital	Taq man	119	70	Female	42.7/45.8	147	91	81	59	41	65	13	25	31	14	0.744	NA

PCR polymerase chain reaction; *RFLP* restriction fragment length polymorphism; *MAF* minor allele frequency; Genotypes: 11: DD; 12: DH; 22: HH: m: male; f: female; HW p: Hardy–Weinberg *p* value; *SM* sex matched; *NR* not reported; *NA* not applicable

Table 3 The detailed characteristics of the included studies for ApoE gene

Ref	Year	Country	Controls	Method	MAF % of		No. of		Sex m/f		Age m/f	
					Cases	Controls	Case	Control	Cases	Controls	Cases	Controls
ApoE Hha I rs429358 and rs7412 and e2,e3,e4												
Sanchez Cuén [12]	2010	México	Hospital	Pcr–rflp			101	101	13.90%/86.10%	13.90%/86.10%	51.93 ± 11.23	51.74 ± 10.99
Mella [48]	2007	Chile	population	Pcr–rflp			117	122	66 males, 168 Females		49 ± 12	40 ± 13
Mella [48]	2007	Germany	population	Pcr–rflp			184	184	162 males, 206 females		63 ± 13	63 ± 13
Pinheiro Júnior [55]	2012	Brazil	patients	Pcr–rflp			114	106	18/83	20/80	46.6 ± 11.2	40.6 ± 9.7
Dixit [49]	2006	India	population	Pcr–rflp			214	322	66/141	116/206	44.71 ± 13.20	43.98 ± 11.46
Hasegawa [50]	2003	Japan	hospital				79	53	55 ± 1	39 ± 1	37/42	32/21
Martinez Lopez [51]	2015	Mexico	Hospital	Pcr–rflp			90	371	8/82		40.6 ± 13.8	37.1 ± 11.5
Jiang [11]	2004	China	hospital	Pcr–rflp			105	274	78/27	184/90	47.53 ± 10.98	47.94 ± 12.21
Lin [52]	1997	China		Pcr–rflp			87	50	39/48	27/23	52	49
Antonia [9]	1996	Spain	Hospital				160	125	55/105	43/82	59 ± 1	58 ± 1
Niemi [53]	1999	Finland	Hospital	Pcr–rflp			54	47	Only female	53	54	
Niemi [53]	1999	Finland	Hospital	Pcr–rflp			30	17	Only male	51	54	

Ref	Allele freq						Genotype freq patients						Genotype freq controls						HW p			Matching criteria
	Cases			Controls			E2e2	E3e3	E4e4	E2e3	E2e4	E3e4	E2e2	E3e3	E4e4	E2e3	E2e4	E3e4	1	2	3	
ApoE Hha I rs429358 and rs7412 and e2,e3,e4																						
Sanchez Cuén [12]	9	173	20	12	158	32	0	74	1	8	1	17	1	64	2	6	4	24	0.95	0.90	0.98	SM
Mella [48]	0.07	0.79	0.13	0.08	0.67	0.24	0.008	0.79	0.017	0.051	0.008	0.12	0.001	0.67	0.016	0.082	0.000	0.23	0.99	0.99	0.99	NA
Mella [48]	0.08	0.79	0.13	0.08	0.80	0.12	0.000	0.63	0.016	0.14	0.027	0.20	0.000	0.64	0.011	0.13	0.022	0.20	0.99	0.99	0.99	NA
Pinheiro Júnior [55]	16	187	27	13	189	19	2	70	2	10	2	21	0	76	2	11	2	13	0.82	0.80	0.32	SM
Dixit [49]	19	360	35	30	560	54	0	158	2	16	3	28	1	247	1	21	7	45	0.75	0.25	0.78	SM
Hasegawa [50]	3.02	6.9	6.0	2.01	4.65	4.5	0	63	0	4	2	10	0	40	0	4	0	9	0.95	0.99	0.77	SM
Martinez Lopez [51]	10	22	68	7.8	8.4	83.8	0	43	2	13	8	32	0	72.1	0.5	10.6	2.9	12.9	0.84	0.57	0.77	NA
Jiang [11]	9.52	81.90	8.57	9.67	81.75	8.57	0	73	1	15	5	11	1	183	2	45	6	37	0.59	0.57	0.99	SM
Lin [52]	5.8	89.6	4.6	7	85.0	8		69		10	0	8		37		5	2	6	0.91	0.36	0.88	SM
Antonia [9]	0.050	0.850	0.100	0.036	0.924	0.040	0	71.3	0	8.8	1.3	18.8	0	86.4	0	5.6	1.6	6.4	0.96	0.44	0.94	SM
Niemi [53]						0	64	101	3	0	32	0	2	47	2	0	18		0.80	–	0.98	SM
Niemi [53]						0	25	1	2	1	18	0	9	1	0	1	6		–	0.89	1	SM

PCR polymerase chain reaction; *RFLP* restriction fragment length polymorphism; *MAF* minor allele frequency; Genotypes: 11: DD; 12: DH; 22: HH: m: male; f: female; HW p: Hardy–Weinberg *p* value. HW p for 1: (E2E2, E2E3, E3E3); 2: (E2E2, E2E4, E4E4); 3: (E3E3, E3E4, E4E4) groups; *SM* sex matched; *NR* not reported; *NA* not applicable

Table 4 The detailed characteristics of the included studies for CETP gene

Ref	year	country	Controls	Method	No. of		Sex m/f cases–contr	Age cases/control	Allele freq				Genotype freq patients			Genotype freq controls			HW p	Matching Criteria
					Case	Control			Cases 1–2		Control 1–2		11	12	22	11	12	22		
CETP TaqI rs708272																				
Juvonen [45]	1995	UK	Population	Pcr–rflp	169	92	– -23/69	56.0/55.0	0.898	0.10	0.929	0.071	74	19	0	82	7	3	< 0.05	SM
Dixit [54]	2006	India	Population	Pcr–rflp	206	310	69/138–107/203	44.7/44.0	–	–	–	–	54	107	45	78	167	65	0.377	SM
Pinheiro-Júnior [55]	2012	Brazil	Hospital	Pcr–rflp	114	106	20/94–21/85	46.6/40.6	135	93	132	80	35	65	14	36	60	10	0.108	SM
Xu [20]	2010	China	Population	Taq man	430	447	159/270–178/269	65/65	–	–	–	–	152	196	81	151	216	76	0.996	SM
Báez [36]	2010	Chile	Hospital	Taq man	119	70	Female	42.7/45.8	141	97	76	64	42	57	20	18	40	12	0.448	NA

PCR polymerase chain reaction; *RFLP* restriction fragment length polymorphism; *MAF* minor allele frequency; Genotypes: 11: DD; 12: DH; 22: HH: *m* male; *f* female; HW p: Hardy–Weinberg *p* value; *SM* sex matched; *NR* not reported; *NA* not applicable

Table 5 The detailed characteristics of the included studies for CYP7A1gene

Ref	year	country	Controls	Method	No. of		Sex m/f cases–contr	Age cases/control	Allele freq				Genotype freq patients			Genotype freq controls			HW p	Matching criteria
					Case	Control			Cases 1–2		Control 1–2		11	12	22	11	12	22		
CYP7A1 Bsa rs3808607 or G > T,-204AnC,-A204C or c.-278A > C																				
Sánchez-Cuén [12]	2010	México	Hospital	Pcr–rflp	101	101	13.90%/86.10%–13.90%/86.10%	51.93 ± 11.23/51.74 ± 10.99	150	52	146	56	59	32	10	56	34	11	0.274	SM
Juzyszyn [56]	2008	Poland	Hospital	Pcr–rflp	269	213	89/180–95/118	58.9 ± 15.2/61.3 ± 14.3	296	242	222	204	80	136	53	56	110	47	0.879	SM
Srivastava [57]	2010	India	Hospital	Pcr–rflp	195	200	64/131–75/125	49.44 ± 12.36/52.81 ± 10.77	215	175	241	159	62	91	42	70	101	21	0.221	SM

PCR polymerase chain reaction; *RFLP* restriction fragment length polymorphism; *MAF* minor allele frequency; Genotypes: 11: DD; 12: DH; 22: HH: *m* male; *f* female; HW p: Hardy–Weinberg *p* value; *SM* sex matched; *NR* not reported; *NA* not applicable

Table 6 The detailed characteristics of the included studies for LRPAP1 gene

Ref	year	country	Controls	Method	No. of		Sex m/f cases–contr	Age cases/control	Allele freq				Genotype freq patients			Genotype freq controls			HWp	Matching criteria
					Case	Control			Cases 1–2		Control 1–2		DD	ID	II	DD	ID	II		
LRPAP1 insertion/deletion or rs11267919																				
Juzyszyn [58]	2008	Poland	Hospital	Pcr–rflp	289	251	91/198–	59.8/	404	174	359	143	142	120	27	129	101	21	0.98	SM
Dixit [59]	2006	India	Population	Pcr–rflp	130	202	–	44.44 ± 12.05/ 44.45 ± 10.45	171	89	308	96	57	57	16	115	78	9	0.64	SM
Xu [20]	2010	China	Population	Taq man	430	447	159/270–178/ 269	65/65	–	–	–	–	112	222	95	135	221	89	0.99	SM

PCR polymerase chain reaction; *RFLP* restriction fragment length polymorphism; *MAF* minor allele frequency; *m* male; *f* female; HW p: Hardy–Weinberg *p* value; *SM* sex matched; *NR* not reported; *NA* not applicable

Table 7 The detailed characteristics of the included studies for TNFa gene

Ref	year	country	Controls	Method	No. of		Sex m/f cases–controls	Age cases/control	Allele freq				Genotype freq patients			Genotype freq controls			HW p	Matching criteria
					Case	Control			Cases 1–2		Control 1–2		11	12	22	11	12	22		
TNF-α -A308G rs*1800629*																				
Ebadi [40]	2013	Iran	Hospital	ARMS-PCR	158	254	41/117–81/ 173	41.22 ± 13.53/ 39.2 ± 11.3	228	28	374	134	98	32	17.73	163	48	43	< 0.05	NR
Hsing [60]	2008	China	Hospital	Taq man	774	959	224/449–305/ 481	55/55	–	–	–	–	582	78	2	510	66	6	0.08	SM
Vishnoi [61]	2007	India	Hospital	Pcr–rflp	65	200	19/46–82/118	49/50	118	12	350	50	54	10	1	153	44	3	0.996	SM

ARMS amplification refractory mutation system; *PCR* polymerase chain reaction; *RFLP* restriction fragment length polymorphism; *MAF* minor allele frequency; Genotypes: 11: DD; 12: DH; 22: HH: *m* male; *f* female; HW p: Hardy–Weinberg *p* value; *SM* sex matched; *NR* not reported; *NA* not applicable

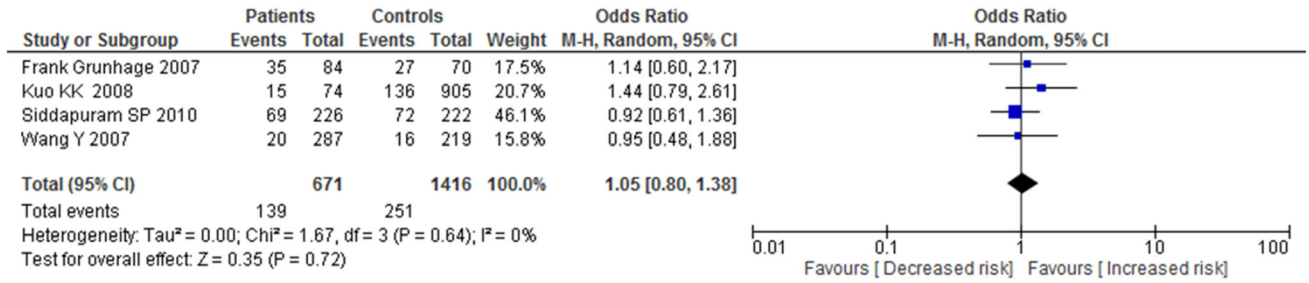


Fig. 2 Pooled random-effect-based odds ratio of gallstone disease for ABCG8 T400K polymorphism: A Genotypic Dominant model (TK + KK vs. TT)

In case of LRPAP1 I/D polymorphism the genotypic dominant model (ID + II) revealed a significant high risk OR with 95%CI = 1.27(1.0–1.6); $p = 0.03$ with GSD risk (Fig. 10). While, in TNF-A308G (Fig. 11) polymorphism no association was observed in any of the genetic models.

Summary of ORs for various contrasts on the association between polymorphisms of candidate genes and risk of gallstone disease is mentioned in Table 8.

Sub Group Analysis

To relate the difference between different ethnicity, we first divided the studies into White European and the rest dubbed as Non- European population groups. In ABCG8 D19H polymorphism in case of genotypic model (GG vs. GC) the sub groups for White European and the Non- European population a significant high risk was observed OR with 95%CI = 2.9 (1.5–5.5); $p = 0.001$ and OR with 95%CI = 2.08 (1.5–2.8); $p < 0.00001$ respectively (Fig. 3c). In case of genotypic Dominant model (GC + CC vs.GG) the subgroups for White European and Non- European population also showed high risk with GSD OR with 95%CI = 2.9(1.5–5.7); $p = 0.0009$ and OR with 95%CI = 2.0(1.5–2.7); $p < 0.00001$ respectively (Fig. 3d).

The analysis for APOB Xba I polymorphism revealed a significant low risk in allelic model (X^- vs. X^+) for the Non- European population with GSD OR with 95%CI = 0.53(0.3–0.8); $p = 0.01$ (Fig. 6b), in genotypic model (X^- X^- vs. X^+ X^+) for the Non- European population with GSD OR with 95%CI = 0.6(0.3–0.9); $p = 0.03$ (Fig. 6c), while White Europeans showed no association with GSD.

In case of APOE Hha I polymorphism analysis of genotypic model (E3/E4 vs. E3/E3) displayed that only the European population generated a significant high risk OR with 95%CI = 2.0(1.2–3.4); $p = 0.008$ with the GSD (Fig. 7b). While in genotypic recessive model (E4/E4 vs. E3/E4 + E3/E3) the European population showed significant low risk OR with 95%CI = 0.5(0.3–0.9); $p = 0.02$ with the GSD (Fig. 7c).

In case of LRPAP1 I/D polymorphism analysis of genotypic dominant model (DI + II vs. DD) displayed that only the Non- European population showed significant high risk OR with 95%CI = 1.3(1.0–1.8); $p = 0.03$ with the GSD (Fig. 10).

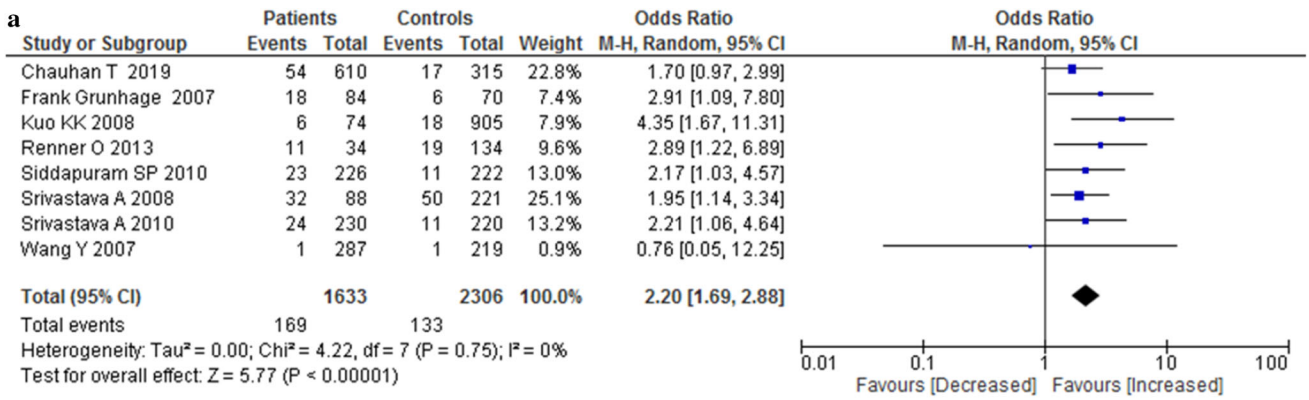
Overall, sub group analysis revealed that the ABCG8 D19H polymorphism might be more prominently associated with the increased risk of GSD in both European as well as Non-European populations, APOE Hha I polymorphism was observed to be associated with the increased risk of GSD in European population. Whereas LRPAP1 I/D polymorphism revealed association with the increased risk of GSD in Non-European population. However, APOB Xba I and ApoB100 EcoRI polymorphisms showed a low risk in both Non-European and European populations.

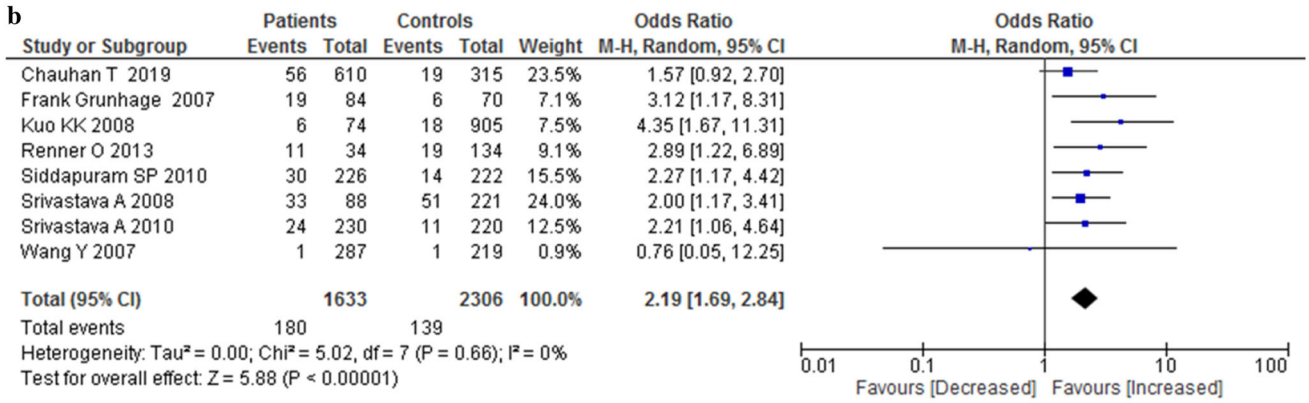
Test of Heterogeneity Source, Publication Bias and sensitivity analysis

Publication bias was detected by Funnel plots, Fail-safe number, Egger's regression intercept and Begg and Mazumdar rank correlation tests in various genetic model comparisons of total studies Table 9.

No between-study heterogeneity and publication bias was detected in the analysis of any of the associated genotypic models of ABCG8 D19H and Y54C polymorphisms with GSD risk.

A moderate heterogeneity was observed in the analysis of all the associated genotypic models of APOB100 EcoRI polymorphism with GSD risk ($I^2 < 50\%$) but in GG versus AA Fail safe number ($N_{fs} = 2$); Begg and Mazumdar rank correlation ($B_p = 0.04154$) and GG versus GA Fail safe number ($N_{fs} = 2$) reported the publication bias.





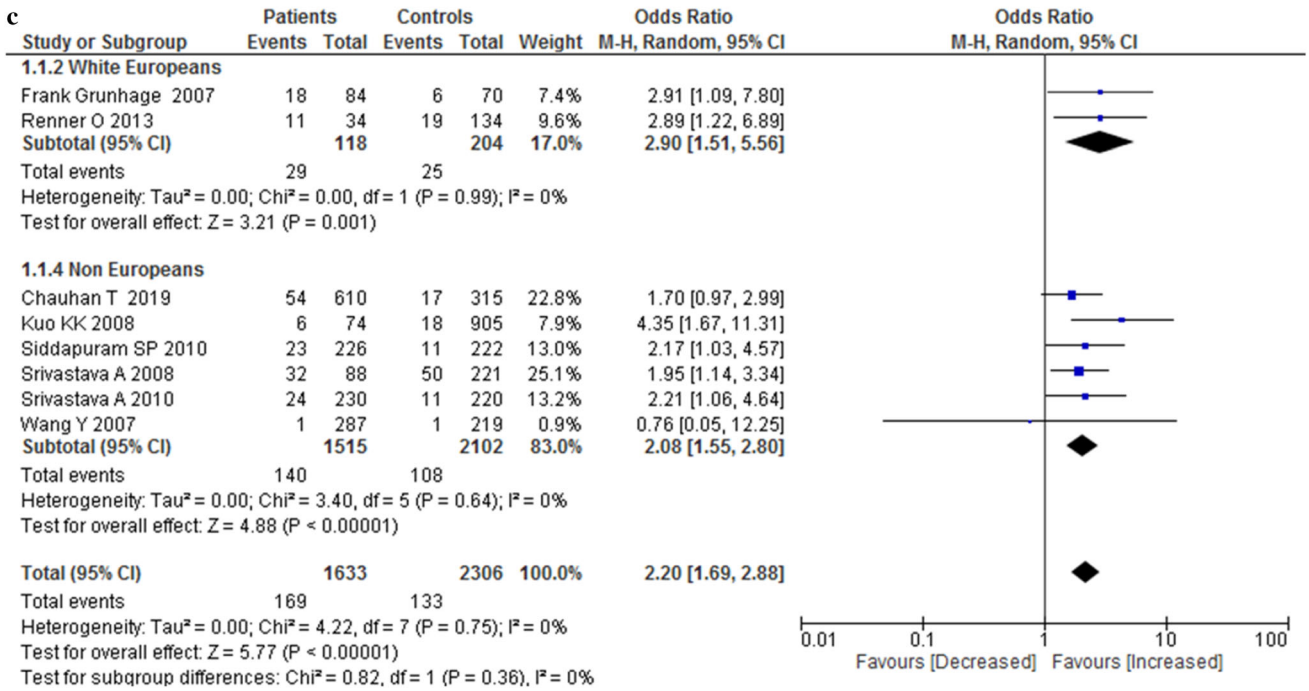


Fig. 3 **a** Pooled random-effect-based odds ratio of gallstone disease for ABCG8 D19H polymorphism: A Genotypic model (GG vs. GC). **b** Pooled random-effect-based odds ratio of gallstone disease for ABCG8 D19H polymorphism: A Genotypic Dominant model (GC + CC vs. GG). **c** Forest plot of comparison: Pooled random-effect-based odds ratio of gallstone disease for D19H polymorphism, outcome: A Genotypic model (GG vs. GC). **d** Forest plot of comparison: Pooled random-effect-based odds ratio of gallstone disease for D19H polymorphism, outcome: A Genotypic Dominant model (GC + CC vs. GG)

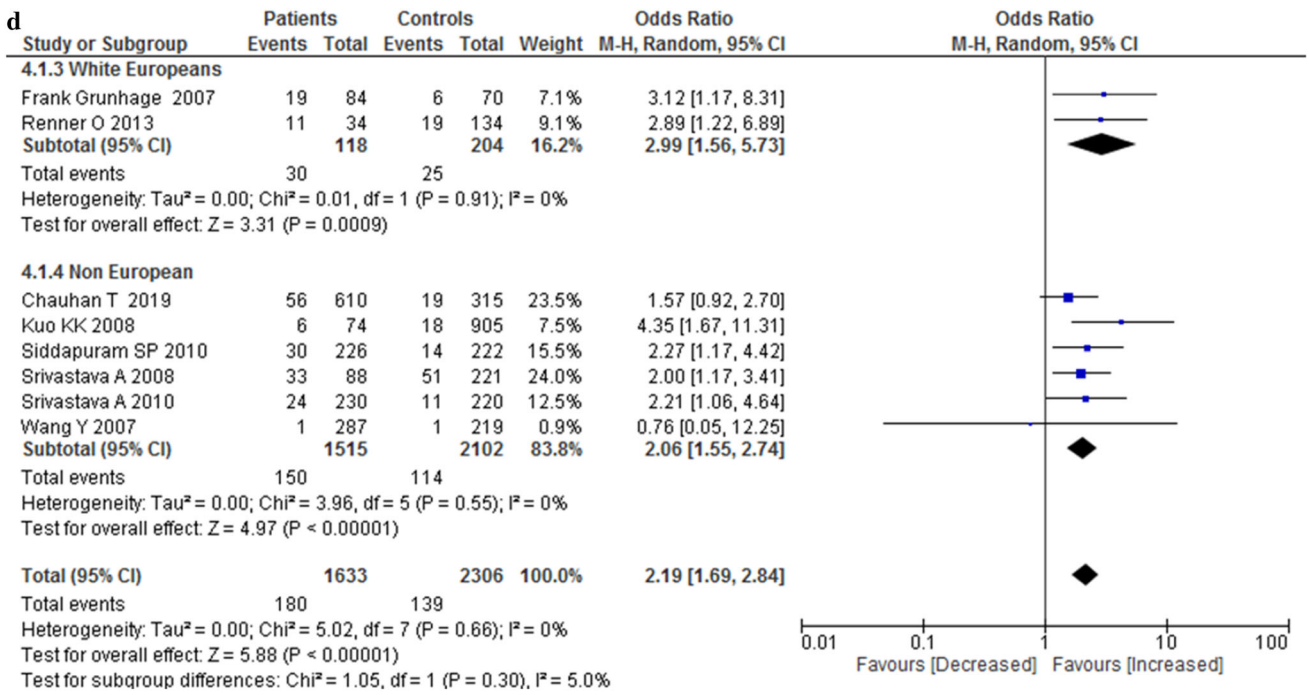


Fig. 3 continued

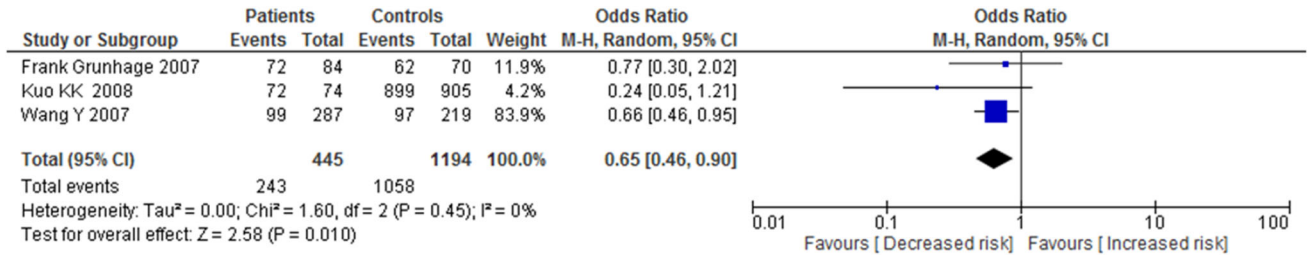


Fig. 4 Pooled random-effect-based odds ratio of gallstone disease for ABCG8 Y54C polymorphism: Genotypic Recessive model (GA + GG vs. AA)

A moderate heterogeneity was observed in the analysis of the associated allelic model [X^- vs. X^+] of APOB Xba I polymorphism and its Non-European subgroup with GSD risk ($I^2 > 50\%$) (Fig. 6d). On the other hand no between-study heterogeneity was observed in the analysis of the associated genotypic model [$X^- X^-$ vs. $X^+ X^+$] in its Non-European subgroup. No publication bias was reported in any of the genetic models of the total studies.

In APOE Hha I polymorphism a moderate between-study heterogeneity ($I^2 > 50\%$) was observed in the analysis of the associated genotypic model [E4/E4 vs. E3/E3]. While the White—European subgroup of genotypic model [E3/E4 vs. E3/E3] and [E4/E4 vs. E3/E4 + E3/E3] showed no between-study heterogeneity ($I^2 < 50\%$). No publication bias was reported in any of the genetic models of the total studies.

In LRPAP1 I/D polymorphism no between-study heterogeneity ($I^2 < 50\%$) was observed in the analysis of the associated genotypic model [DI + II vs. DD] and its Non-European subgroup. Publication bias was reported in this genetic model of the total studies in Fail safe number ($N_{fs} = 2$).

Discussion

In this study, we collected data from 33 papers which comprised of China, India, Italy, Germany, Poland, UK, Mexico, Chile, Brazil, Japan, Spain, Finland and Iran. The

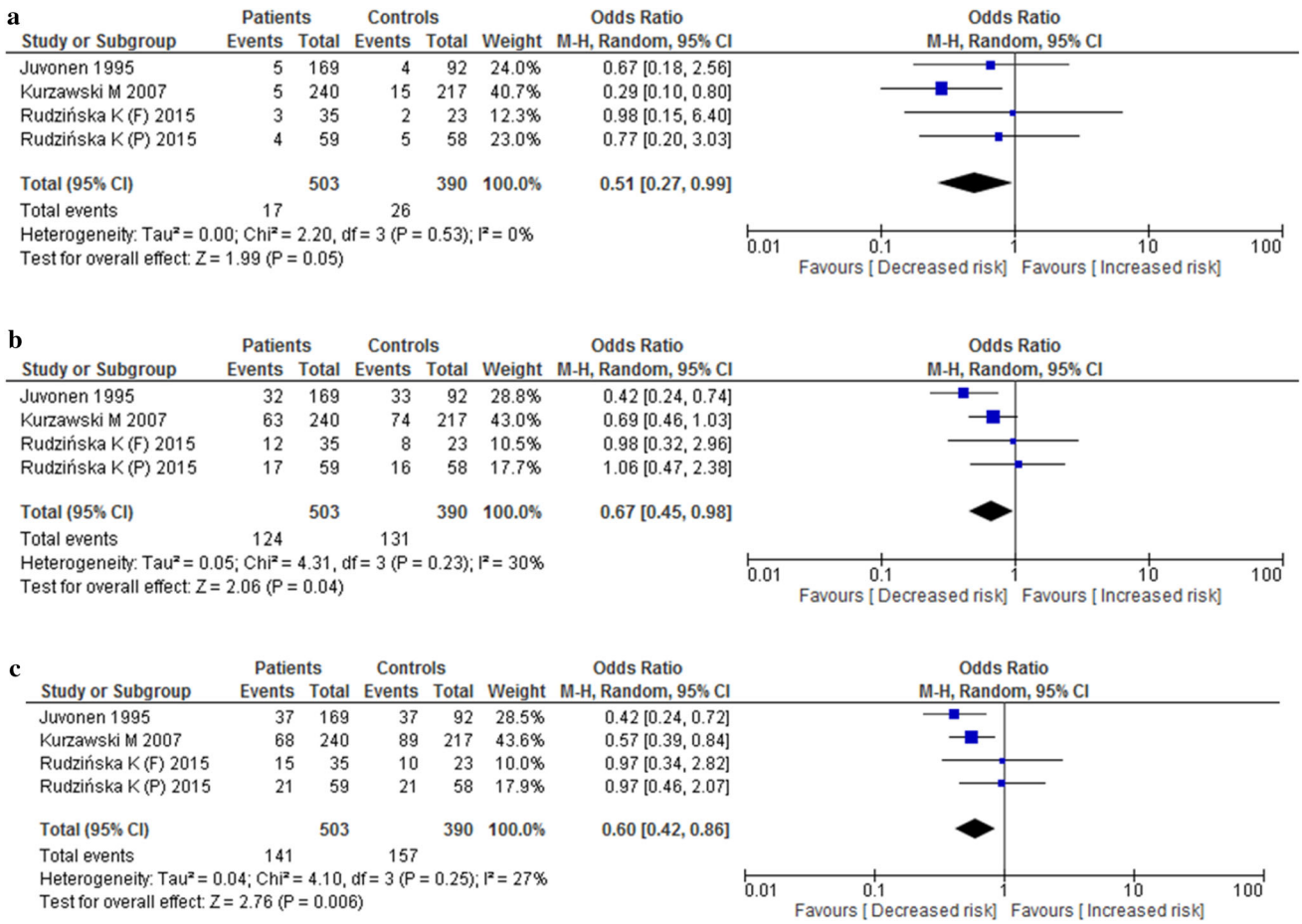
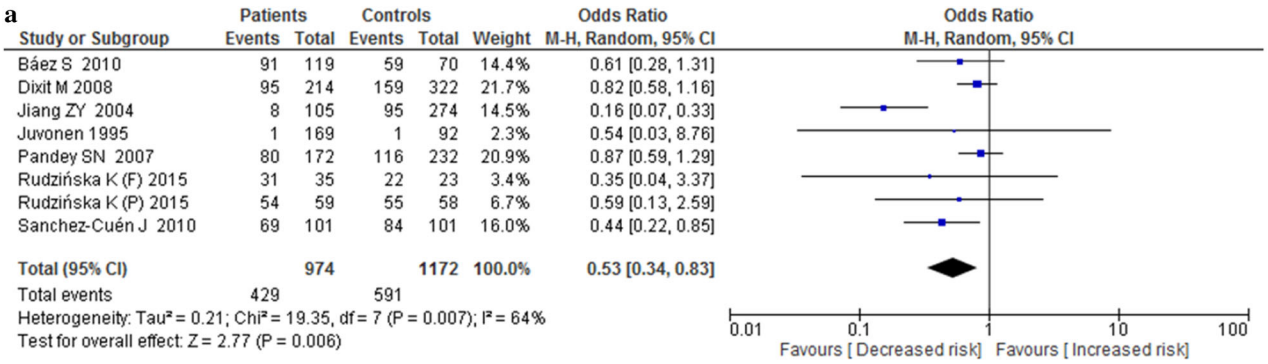


Fig. 5 **a** Pooled random-effect-based odds ratio of gallstone disease for APOB EcoRI polymorphism: A Genotypic model (GG vs. AA). **b** Pooled random-effect-based odds ratio of gallstone disease for APOB EcoRI polymorphism: A Genotypic model (GG vs. GA). **c** Pooled random-effect-based odds ratio of gallstone disease for APOB EcoRI polymorphism: A Genotypic Dominant model (GA + AA vs. GG). *Note* In APOB EcoRI all 4 included studies are that of White European population

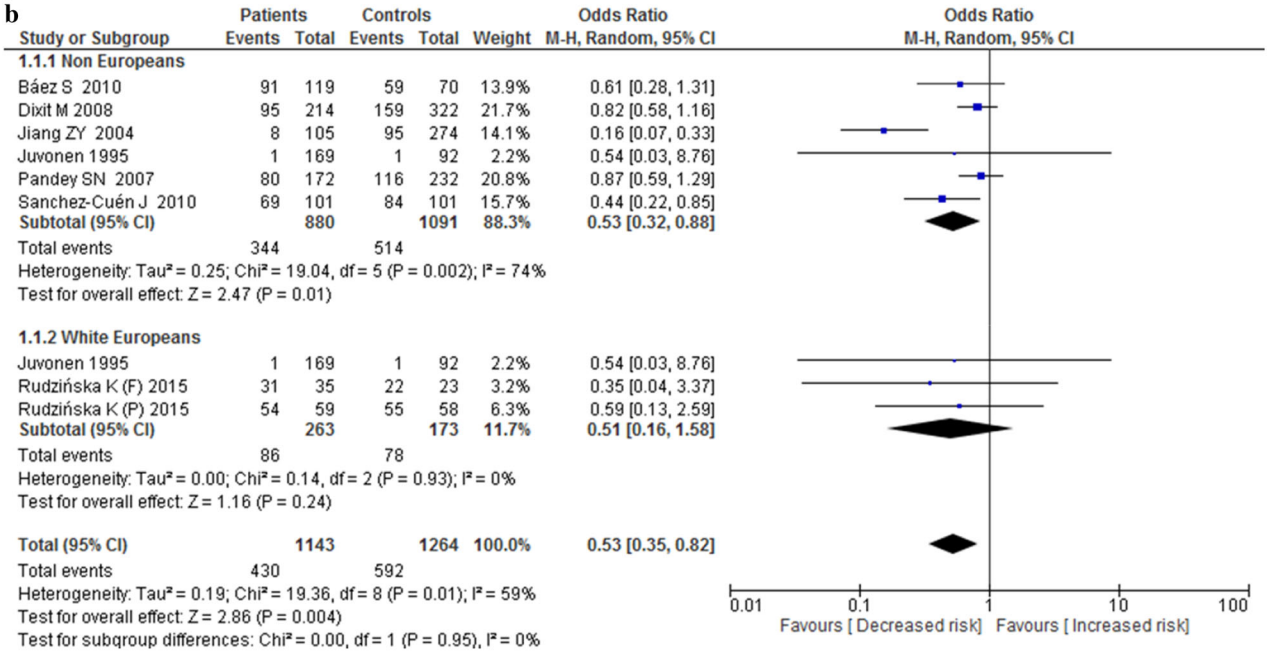
meta-analysis encompassed 7 genes from 3 different pathways. (1) Cholesterol metabolism: ABCG8, ApoE, CETP, LRPAP1, CYP7A1. (2) Lipid metabolism: APOB and (3) Signaling transduction pathway: TNFa and systematically evaluated the influence of a common ABCG8 T400K, ABCG8 D19H, ABCG8 C54Y, ApoB100 EcoRI, ApoB100 XbaI, ApoE HhaI, CETP TaqI, CYP7A1 Bsa, LRPAP1 I/D and TNF-α A308G polymorphisms on the risk of gallbladder stone disease and to relate the dissimilarity between different ethnicity, studies were divided into White European and Non-European (rest) populations.

ABCG8 T400K, D19H and C54Y are the most commonly studied polymorphisms in association with gallstone disease. In case of ABCG8 T400K polymorphism no association was found between any of the genetic models of our study. However, previous meta-analysis reported increased risk of gallstone in its allelic model. Therefore, results of this study are found to be contradictory with respect to its previous meta- analysis [65]. Two of the studies [19, 24] used large sample sizes. Buch et al. [24] showed that D19H polymorphism was associated with gallstone disease using GWAS approach. Another large sample size was all Danish studied by Stender et al. [19]. The samples sizes in rest of the studies were relatively small [8, 20–23, 25, 26]. A large-scale GWAS of gallstone disease by—Joshi AD et al., identified 4 loci in genes namely ABCG8 locus: rs11887534 and rs4245791 in TM4SF4 rs9843304 and rs2547231 in SULT2A1 that have putative functions in cholesterol metabolism and transport, and sulfonylation of bile acids or hydroxysteroids. Where,

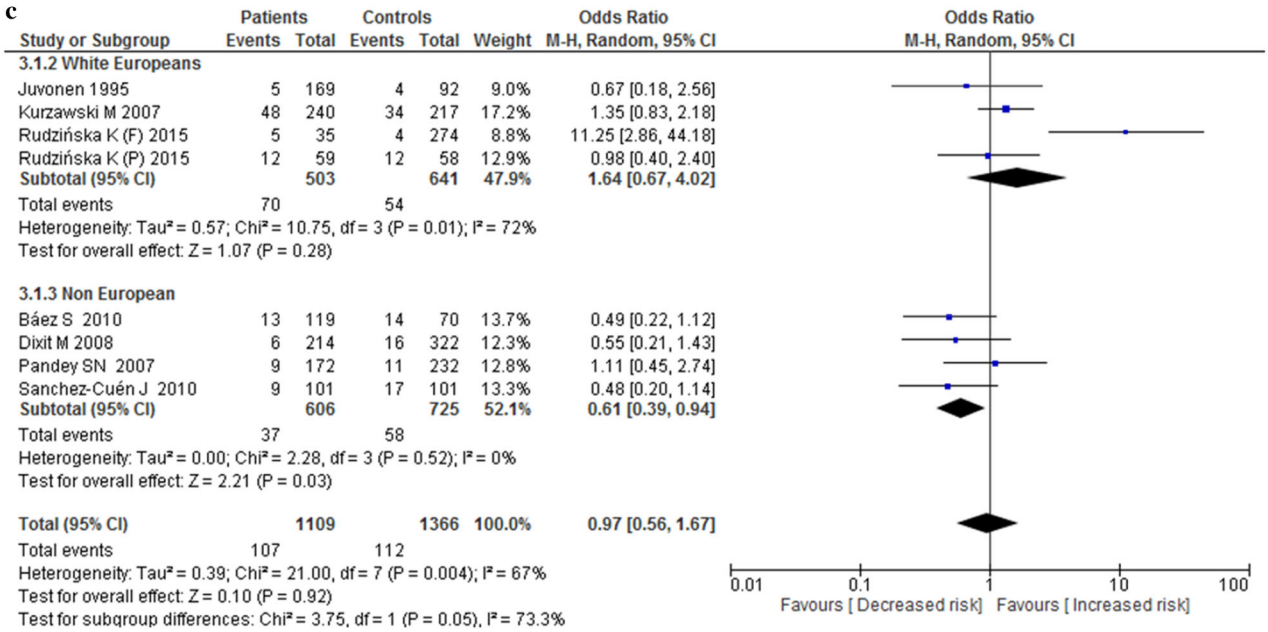
a


Patients
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Báez S 2010 91 119 59 70 14.4% 0.61 [0.28, 1.31]
Dixit M 2008 95 214 159 322 21.7% 0.82 [0.58, 1.16]
Jiang ZY 2004 8 105 95 274 14.5% 0.16 [0.07, 0.33]
Juvonen 1995 1 169 1 92 2.3% 0.54 [0.03, 8.76]
Pandey SN 2007 80 172 116 232 20.9% 0.87 [0.59, 1.29]
Rudzińska K (F) 2015 31 35 22 23 3.4% 0.35 [0.04, 3.37]
Rudzińska K (P) 2015 54 59 55 58 6.7% 0.59 [0.13, 2.59]
Sanchez-Cuén J 2010 69 101 84 101 16.0% 0.44 [0.22, 0.85]
Total (95% CI) 974 1172 100.0% 0.53 [0.34, 0.83]
Total events 429 591
Heterogeneity: Tau² = 0.21; Chi² = 19.35, df = 7 (P = 0.007); I² = 64%
Test for overall effect: Z = 2.77 (P = 0.006)
0.01 0.1 1 10 100
Favours [Decreased risk] Favours [Increased risk]

b


Patients
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 Non Europeans
Báez S 2010 91 119 59 70 13.9% 0.61 [0.28, 1.31]
Dixit M 2008 95 214 159 322 21.7% 0.82 [0.58, 1.16]
Jiang ZY 2004 8 105 95 274 14.1% 0.16 [0.07, 0.33]
Juvonen 1995 1 169 1 92 2.2% 0.54 [0.03, 8.76]
Pandey SN 2007 80 172 116 232 20.8% 0.87 [0.59, 1.29]
Sanchez-Cuén J 2010 69 101 84 101 15.7% 0.44 [0.22, 0.85]
Subtotal (95% CI) 880 1091 88.3% 0.53 [0.32, 0.88]
Total events 344 514
Heterogeneity: Tau² = 0.25; Chi² = 19.04, df = 5 (P = 0.002); I² = 74%
Test for overall effect: Z = 2.47 (P = 0.01)
1.1.2 White Europeans
Juvonen 1995 1 169 1 92 2.2% 0.54 [0.03, 8.76]
Rudzińska K (F) 2015 31 35 22 23 3.2% 0.35 [0.04, 3.37]
Rudzińska K (P) 2015 54 59 55 58 6.3% 0.59 [0.13, 2.59]
Subtotal (95% CI) 263 173 11.7% 0.51 [0.16, 1.58]
Total events 86 78
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.24)
Total (95% CI) 1143 1264 100.0% 0.53 [0.35, 0.82]
Total events 430 592
Heterogeneity: Tau² = 0.19; Chi² = 19.36, df = 8 (P = 0.01); I² = 59%
Test for overall effect: Z = 2.86 (P = 0.004)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%
0.01 0.1 1 10 100
Favours [Decreased risk] Favours [Increased risk]

c


Patients
Controls
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
3.1.2 White Europeans
Juvonen 1995 5 169 4 92 9.0% 0.67 [0.18, 2.56]
Kurzawski M 2007 48 240 34 217 17.2% 1.35 [0.83, 2.18]
Rudzińska K (F) 2015 5 35 4 274 8.8% 11.25 [2.86, 44.18]
Rudzińska K (P) 2015 12 59 12 58 12.9% 0.98 [0.40, 2.40]
Subtotal (95% CI) 503 641 47.9% 1.64 [0.67, 4.02]
Total events 70 54
Heterogeneity: Tau² = 0.57; Chi² = 10.75, df = 3 (P = 0.01); I² = 72%
Test for overall effect: Z = 1.07 (P = 0.28)
3.1.3 Non European
Báez S 2010 13 119 14 70 13.7% 0.49 [0.22, 1.12]
Dixit M 2008 6 214 16 322 12.3% 0.55 [0.21, 1.43]
Pandey SN 2007 9 172 11 232 12.8% 1.11 [0.45, 2.74]
Sanchez-Cuén J 2010 9 101 17 101 13.3% 0.48 [0.20, 1.14]
Subtotal (95% CI) 606 725 52.1% 0.61 [0.39, 0.94]
Total events 37 58
Heterogeneity: Tau² = 0.00; Chi² = 2.28, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)
Total (95% CI) 1109 1366 100.0% 0.97 [0.56, 1.67]
Total events 107 112
Heterogeneity: Tau² = 0.39; Chi² = 21.00, df = 7 (P = 0.004); I² = 67%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Chi² = 3.75, df = 1 (P = 0.05), I² = 73.3%
0.01 0.1 1 10 100
Favours [Decreased risk] Favours [Increased risk]

◀**Fig. 6** **a** Pooled random-effect-based odds ratio of gallstone disease for APOB Xba I polymorphism: An allelic model (X^- vs. X^+). **b** Forest plot of comparison: Pooled random-effect-based odds ratio of gallstone disease for APOB Xba I polymorphism, outcome: An allelic model (X^- vs. X^+). **c** Forest plot of comparison: Pooled random-effect-based odds ratio of gallstone disease for APOB Xba I polymorphism, outcome: A Genotypic model (X^- X^- vs. X^+ X^+). **d** Funnel plot of comparison: Publication bias on the APOB Xba I polymorphism (X^- vs. X^+) for Gallstone risk

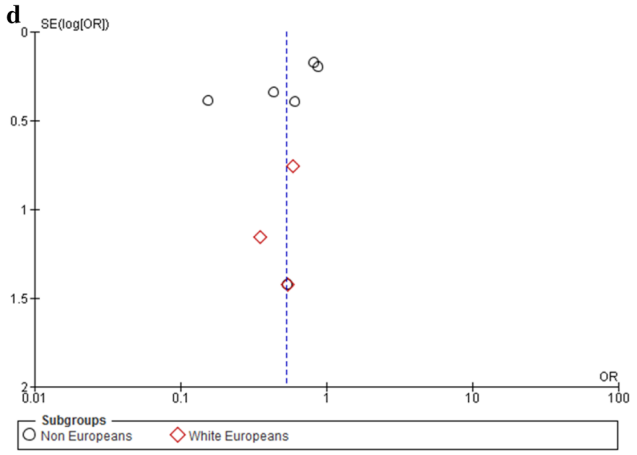


Fig. 6 continued

they found that amongst individuals of African American and Hispanic American ancestry, SNPs rs11887534 and rs4245791 were positively associated with gallstone disease risk, whereas the association for the rs1260326 SNP was inverse [66].

Our meta-analysis strongly verified the significant association between ABCG8 D19H polymorphism and gallstone disease risk. In case of its genotypic models our results are in concordance with the previous meta-analysis [65] of ABCG8 D19H gene polymorphism. However, in this study no association was found in its allelic model, which is a contradictory result with respect to its previous meta-analysis. In case of ABCG8 C54Y its genotypic model reported increased risk with the disease in its previous study [65] but our study showed a decreased risk with the gallstone disease.

ApoB100 as a candidate gene, is of a particular interest, as it is the major protein component of LDL [15]. In fact, few studies have also reported that individuals with the X^+X^+ genotype have significantly higher serum total cholesterol, LDL, and Apo-B levels compared to those with the wild-type X^-X^- genotype [67]. Thus, this ApoB-100 variant may be related to a higher incidence of GSD. In another meta-analysis study by—Gu W et al. it was reported that two of the genetic variants of APOB XbaI and EcoRI may be associated with serum lipids in Chinese population [68]. Unfortunately, earlier epidemiological studies and meta-analysis by—Yi Gong et al. [69] investigating the associations between ApoB-100 gene polymorphisms and the risks of GSD have yielded conflicting results. Discrepancy may be attributed to various factors, such as the ethnicity of the population and the sample size etc.

In case of ApoB 100 EcoRI all the included study were of European population. Therefore, this study reported that its genotypic models show a low risk with the gallstone disease in European population. No, association was reported in any of the genotypic models with GSD in its previous meta-analysis [69]. In case of ApoB 100 XbaI polymorphism our study showed a low risk of GSD in its allelic model. However, no association was found in any of the genetic models in its previous meta-analysis [69].

In case of ApoE HhaI polymorphism a genotypic model (E4/E4 vs. E3/E3) showed a significant fourfold associated risk with the GSD risk. However, a significant increased risk was observed in the dominant model of previous meta-analysis [10]. Earlier studies have shown that the presence of the E4 allele of Apo E is strongly associated with the risk of atherosclerosis [70] and Alzheimer's disease [71]. Earlier meta-analysis by Pei Xue et al. [10] also indicated that Apo e4 allele is a risk factor for the progression of gallstones. Different affinity of Apo E receptors, can eventually influence hepatic cholesterol processing by enhancing cholesteryl ester hydrolysis [72], and thereby increasing cellular free cholesterol availability for biliary secretion. Various evidences also tell that Apo E4 leads to more intracellular release of free cholesterol from internalized triglyceride-rich particle cholesteryl ester than does E3 [73]. A study by—Xue P et al. revealed Apo E gene ε4 allele to be a risk factor for gallbladder stone disease, particularly in older people and Chinese population [10]. Our meta-analysis also give a clear conclusion that E4 allele is a risk factor of gallbladder stone disease.

By contrast, the conclusion for E2 allele is equivocal. Through earlier studies and the present study, it seems that E2 allele can provide a protection against GSD in women. Nimei et al. [53] proposed that the protective effect of E2 may be due to the metabolic pathways leading to supersaturation, as subjects with the E2 allele show low

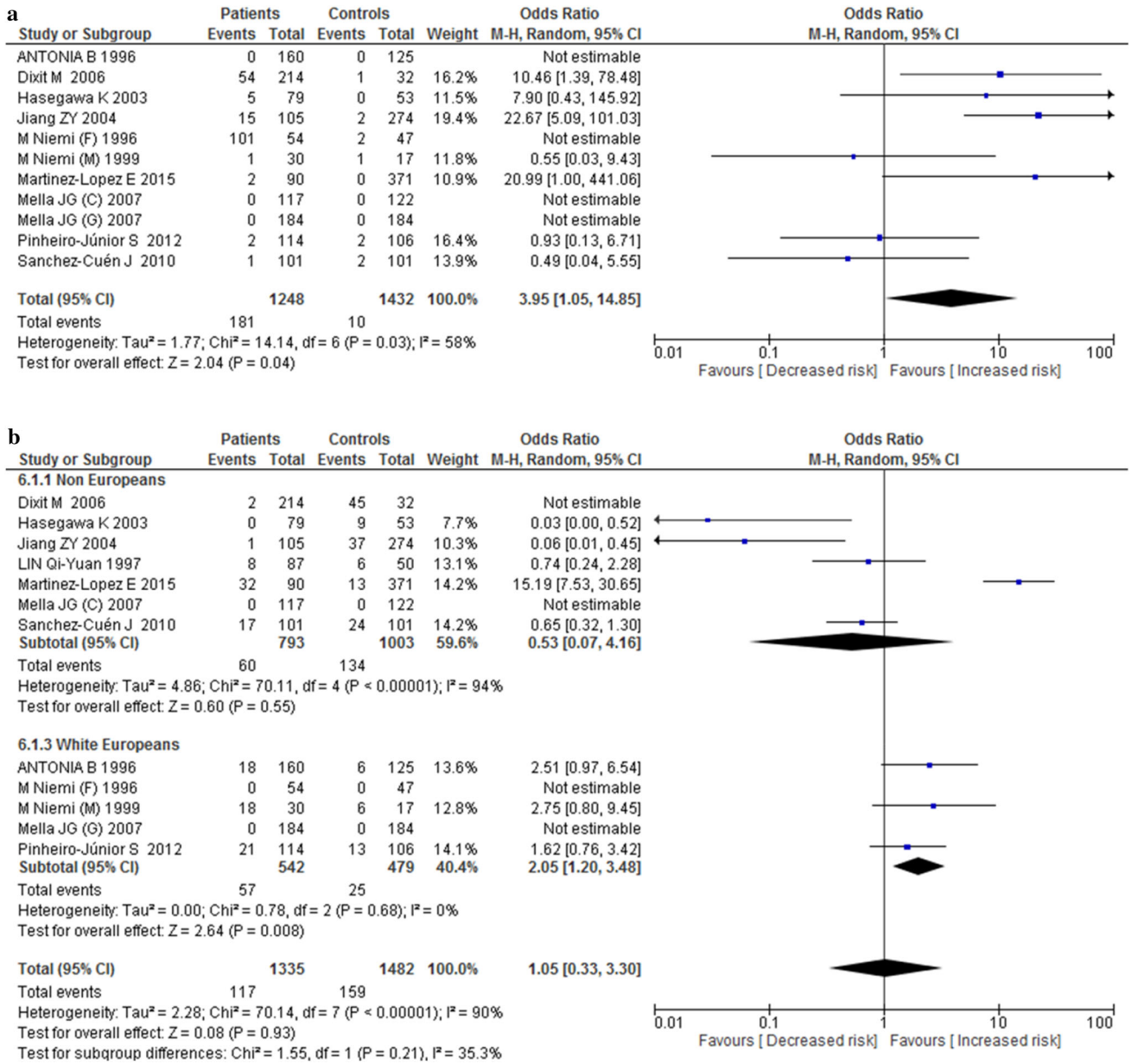


Fig. 7 **a** Pooled random-effect-based odds ratio of gallstone disease for APOE Hha I polymorphism: A Genotypic model (E4/E4 vs. E3/E3). **b** Forest plot of comparison: Pooled random-effect-based odds ratio of gallstone disease for APOE Hha I polymorphism, outcome: A Genotypic model (E3/E4 vs. E3/E3). **c** Forest plot of comparison: Pooled random-effect-based odds ratio of gallstone disease for APOE Hha I polymorphism, outcome: A Genotypic Recessive model (E4/E4 vs. E3/E4 + E3/E3)

cholesterol absorption and a high rate of bile salt synthesis [74].

In case of LRPAP1 IVS5 insertion/deletion polymorphism the genotypic dominant mode (ID + II) revealed a significant association with GSD risk. A previous study by Z. Juzyszyn et al. [58] did not observe any significant differences that could suggest an association of this polymorphism with GSD. In contrast the recent finding by Dixit et al. reported an increased risk of gallstone formation in individuals homozygous for the insertion (I) allele in an

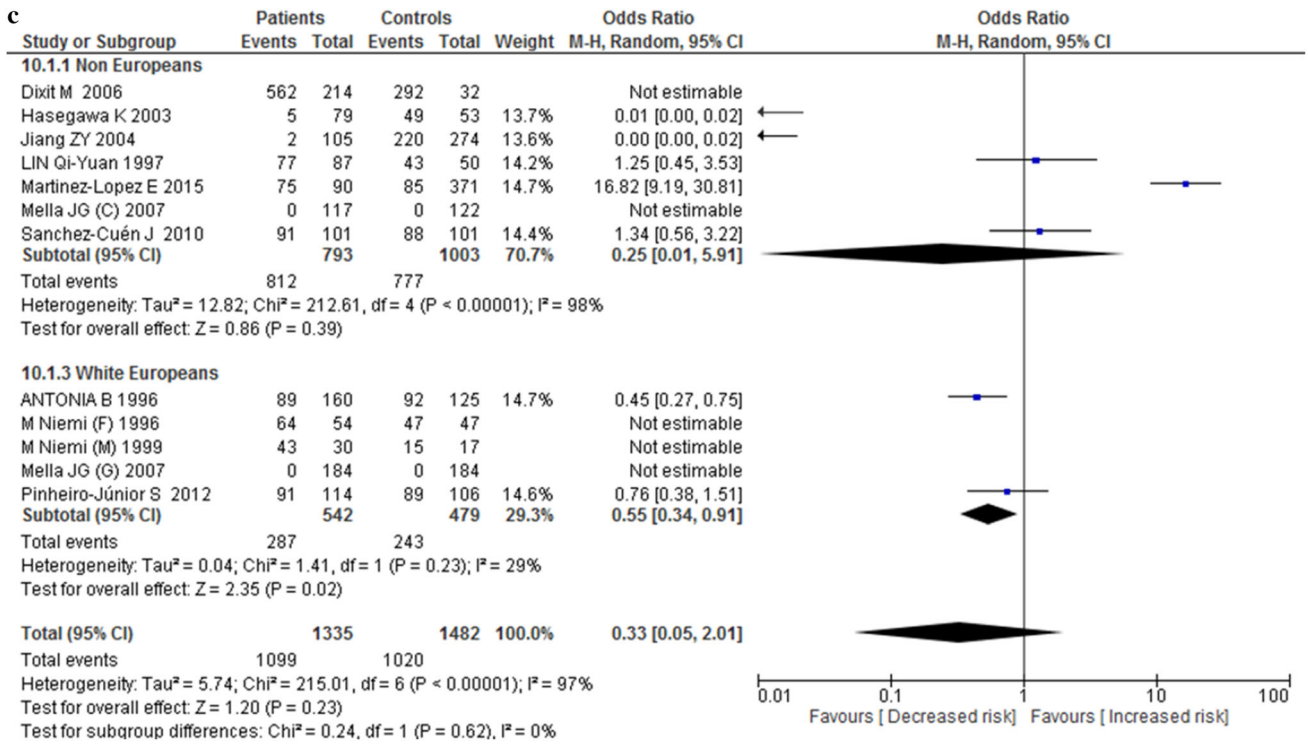


Fig. 7 continued

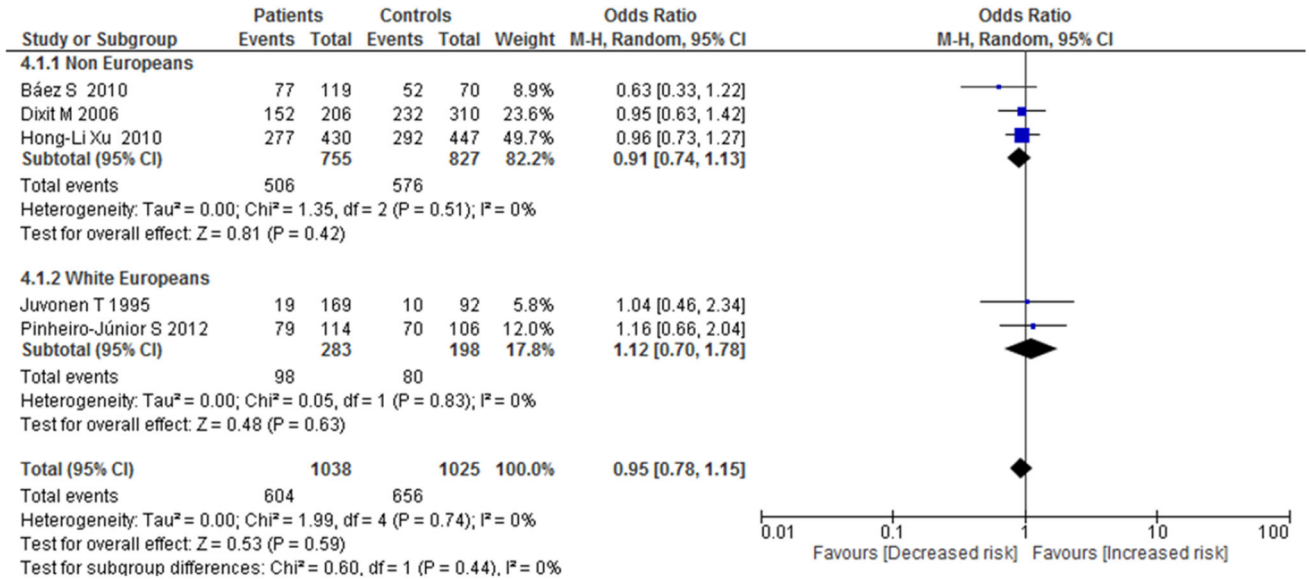


Fig. 8 Pooled random-effect-based odds ratio of gallstone disease for CETP Taq1 polymorphism, outcome: A Genotypic Dominant model (B1B2 + B2B2 vs. B1B1)

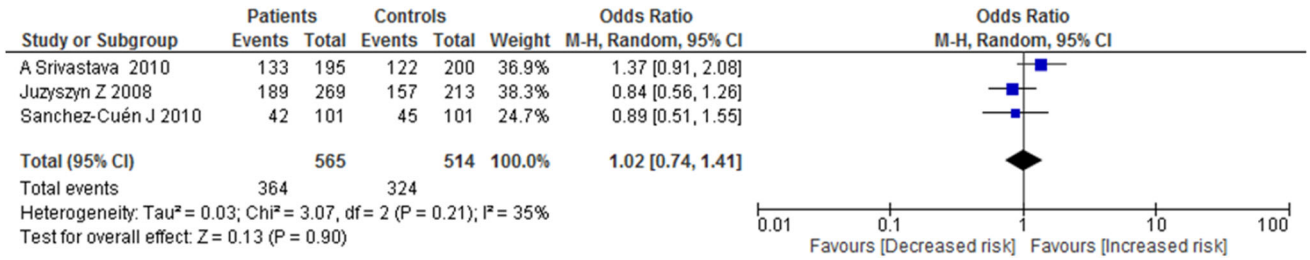


Fig. 9 Pooled random-effect-based odds ratio of gallstone disease for CYP7A1 Bsa polymorphism: A Genotypic Dominant model (AC + CC vs. AA)

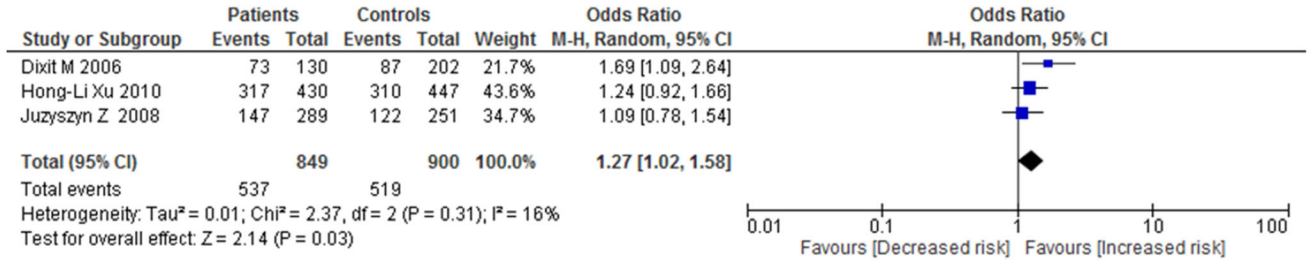


Fig. 10 Pooled random-effect-based odds ratio of gallstone disease for LRPAP1 I/D polymorphism: A Genotypic Dominant model (DI + II vs. DD)

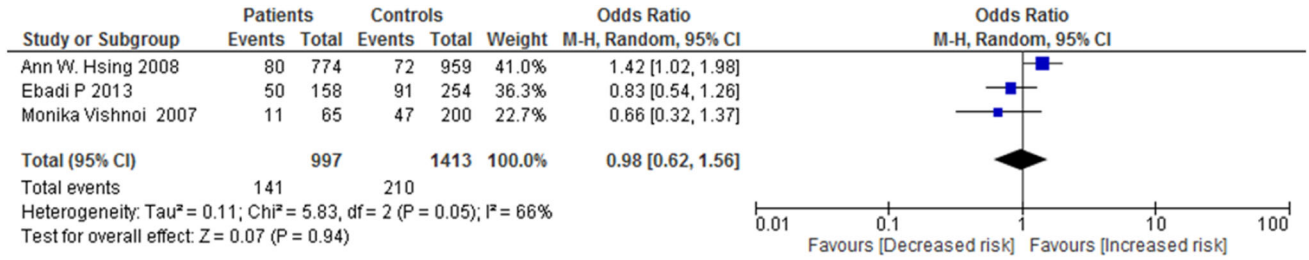


Fig. 11 Pooled random-effect-based odds ratio of gallstone disease for TNF-A308G polymorphism: A Genotypic Dominant model (GA + AA vs GG)

Indian population [54, 59]. In one of the above studies the authors revealed an increased risk of GSD among female carriers of the insertion allele (II) [54].

Some limitations of the present study should be noted in interpreting the results. This meta-analysis was based on unadjusted effect estimates and CIs as some studies did not provide age and sex adjusted ORs and 95% CI_s., GSD is a multifactorial disease, however, the gene–gene and gene-environment interactions were not addressed in the present meta-analysis, and the potential roles of the included polymorphisms might be masked or magnified by other gene–gene/gene-environment interactions. Many of the studies included hospital based controls and such case control studies have some selection biases because such controls might not be a representative of the general population. The possibility of a selection bias cannot be completely excluded as only published studies were considered for this study. Although we searched multiple databases, we might have still failed to include some papers, particularly from non-English publications.

In conclusion collectively, this Quantitative Synthesis approach, showed strong association of ABCG8 D19H rs11887534, ABCG8 C54Y rs4148211, ApoB100 EcoRI rs1042031, ApoB100 XbaI rs693, ApoE HhaI rs429358

Table 8 Summary of ORs for various contrasts on the association between polymorphisms of candidate genes and risk of gallstone disease

SNP	No. of studies	Sub-group	Test of association			Test of hetrogeneity	
			OR	95%CI	Z(P)[a]	I^2 (%)	*P* value
ABCG8 D19H rs11887534							
GG versus GC	8	All	**2.2**	**1.7–2.9**	**< 0.00001**	0	0.8
	2	White Europeans	**2.9**	**1.5–5.6**	**0.001**	0	0.99
	6	Non-Europeans	**2.1**	**1.5–2.8**	**< 0.00001**	0	0.64
GC + CC	8	All	**2.2**	**1.7–2.8**	**< 0.00001**	0	0.66
	2	White Europeans	**2.99**	**1.6–5.7**	**0.0009**	0	0.91
	6	Non-Europeans	**2.1**	**1.5–2.7**	**< 0.00001**	0	0.55
Y54C rs4148211							
GA + GG	3	All	**0.65**	**0.5–0.9**	**0.01**	0	0.45
APOB100 EcoRI rs1042031 (All 4 studies were of European population)							
GG versus AA	4	All	**0.51**	**0.3–0.9**	**0.05**	0	0.53
GG versus GA	4	All	**0.67**	**0.4–0.9**	**0.04**	30	0.25
GA + AA	4	All	**0.6**	**0.4–0.9**	**0.006**	27	0.25
APOB Xba I rs693							
X^- versus X^+	8	All	**0.53**	**0.3–0.8**	**0.006**	**64**	**0.007**
	3	White-Europeans	0.51	0.2–1.6	0.24	0	0.93
	6	Non- Europeans	**0.53**	**0.3–0.8**	**0.01**	**74**	**0.002**
$X^- X^-$ versus $X^+ X^+$	4	White-Europeans	1.6	0.6–4.0	0.28	72	0.01
	4	Non-Europeans	**0.61**	**0.4–0.9**	**0.03**	0	0.52
APOE Hha I rs429358							
E4/E4 versus E3/E3	11	All	**3.95**	**1.1–14.9**	**0.04**	**58**	**0.03**
E3/E4 versus E3/E3	5	White Europeans	**2.1**	**1.2–3.5**	**0.008**	0	0.68
	7	Non-Europeans	0.53	0.1–4.2	0.55	94	< 0.00001
E4/E4 versus E3/E4 + E3/E3	5	White Europeans	**0.55**	**0.3–0.9**	**0.02**	29	0.23
	7	Non-Europeans	0.25	0.01–5.9	0.39	98	< 0.00001
LRPAP1 I/D rs11267919							
ID + II	3	All	**1.27**	**1.0–1.6**	**0.03**	16	0.31
	2	Non-Europeans	**1.38**	**1.0–1.8**	**0.03**	24	0.25

Bold values are show significant association with gallstone disease

and LRPAP1 I/D rs11267919 polymorphisms with gallstone disease. In addition, sub group analysis reflected a prominent association of ABCG8 D19H rs11887534 marker in both European and Non-European populations. APOE Hha I polymorphism was found to be associated with gallstone disease in European population, whereas, LRPAP1 I/D rs11267919 polymorphism revealed association with the increased risk of GSD in Non-European population. Similarly, APOB Xba I rs693 and ApoB100 EcoRI rs1042031 polymorphisms revealed a low risk in Non-European and European populations respectively. However, ABCG8 T400K, CETP Taq1, CYP7A1 Bsa and TNF-A308G polymorphisms produced no association at all for any of the genetic models even after subgroup analysis. Our results suggest vital role of cholesterol and lipid metabolism pathways in the progression of gallstone formation.

Further studies on functional contribution of these polymorphisms in cholesterol and lipid metabolism will

Table 9 Publication bias and sensitivity analysis table

Gene/SNP	Fail-safe number	Egger's regression intercept *t* value and *p* value	Begg and Mazumdar rank correlation	Publication bias status
ABCG8 D19H rs11887534				
GG versus GC	57.0000	$t = 0.57088$; $p = 0.58881$	$P = 0.32230$	No
GC + CC	61.0000	$t = 0.70631$; $p = 0.50648$	$P = 0.21602$	No
Y54C rs4148211				
GA + GG	3	$t = 0.75710$; $p = 0.58745$	$P = 0.60151$	No
APOB100 EcoRI rs1042031				
GG versus AA	**0**	$t = 2.89859$; $p = 0.10126$	$P =$ **0.04154**	**Yes**
GG versus GA	**2.0000**	$t = 0.61268$; $p = 0.60247$	$P = 0.60247$	**Yes**
GA + AA	6.0000	$t = 1.12851$; $p = 0.37627$	$P = 0.49691$	No
APOB Xba I rs693				
X^- versus X^+	32	$t = 1.35798$; $p = 0.22332$	$P = 0.80457$	No
APOE Hha I rs429358				
E4/E4 versus E3/E3	9	$t = 1.20470$; $p = 0.27368$	$P = 1.00000$	No
LRPAP1 I/D rs11267919				
ID + II	**3**	$t = 1.14519$; $p = 0.45698$	$P = 0.60151$	**Yes**

Bold value show significant publication bias

provide more evidence on their roles to encourage gallstone formation.

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Author Contributions Conceived and extracted data: RDM, TC. Analyzed the data BM, TC. Wrote the paper TC, BM.

Compliance with Ethical Standards

Conflict of interest The author(s) declare that they have no conflict of interest.

Ethical Rules The Included Chauhan T. et al. (unpublished) is a case control study. Blood samples were collected after obtaining the informed consent of the enrolled individuals. All the DNA samples for this study were used after Institutional (Sanjay Gandhi Post Graduate Institute of Medical Sciences (SGPGIMS) Lucknow, UP India) Ethical Committee approval. Rest of the included studies are already published, so they are likely to have their own Institutional Ethical Committee approvals.

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