doi:10.4149/neo_2018_170720N491

Meta-analysis of the association of IGFBP3 and IGF1 polymorphisms with susceptibility to colorectal cancer

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Received July 20, 2017 / Accepted November 3, 2017

The aim of this study is to comprehensively evaluate the associations of *IGFBP3* and *IGF1* polymorphisms with susceptibility to colorectal cancer (CRC). We searched the English and Chinese databases and recruited case-control studies based on strict inclusion and exclusion criteria. The statistical analysis was performed by the Comprehensive Meta-analysis 2.0 (CMA 2.0) software and this initially identified 251 studies. We then recruited 10 English studies to this meta-analysis detailed review which includes 9,415 CRC patients and 14,179 healthy controls. Our results demonstrated that *IGFBP3* rs2854746 C>G polymorphism increases susceptibility to the CRC (allele model: OR=1.167, 95% CI=1.095~1.244, p<0.001 and to the dominant gene model: OR=1.226, 95% CI=1.113~1.350, p<0.001); but *IGFBP3* rs2854744 A>C has no significant association with the CRC susceptibility (allele model: OR=0.970, 95% CI=0.932~1.010, p=0.138; dominant gene model: OR=0.995, 95% CI=0.936~1.057, p=0.874). Also, *IGF1* rs35767 C>T polymorphism decreases susceptibility to CRC (allele model: OR=0.785, 95% CI=0.726~0.850, p<0.001 and also the dominant model: OR=0.730, 95% CI=0.661~0.806, p<0.001). However, *IGFBP3* rs2854746 C>G is considered the susceptible CRC polymorphism and *IGF1* rs35767 C>T is CRC protective.

Key words: IGFBP3, IGF1, rs2854746 C>G, rs35767 C>T, polymorphism, colorectal cancer

Both colon and colorectal cancer (CRC) originate from uncontrolled cell proliferation in the gastrointestinal epithelial cell lining [1]. CRC is the third most common cancer worldwide with a global incidence exceeding 1.2 million new cases and 600,000 deaths per year, and the mortality rate is lower in men than in women [2, 3]. The progression of CRC from benign adenoma to malignant adenocarcinoma and distant metastasis, normally takes a long time and CRC can therefore be cured if detected at an early stage However, two thirds of patients with CRCs are diagnosed at a more advanced stage because early-stage disease is mostly asymptomatic [4]. Therefore, screening and early diagnosis are more preferable to efficiently relieving the burden of disease [5]. Although the etio-pathogenesis of CRC is adventitious, epigenetic alterations of both proto-oncogenes and tumor suppressor genes are critical in tumorigenesis mechanisms [6]. As decisive factors in proliferation and apoptosis, the insulin-like growth factor (IGF) axis and functional insulin deregulation are considered the potential mechanisms explaining colorectal carcinogenesis [7].

IGF1, a protein encoded by the *IGF1* gene located on chromosome 12 [8], exerts biological effects through activating the insulin-like growth factor type 1 receptor (IGF-1R), but the relationship between expressions of IGF1 and IGF-1R and CRC clinical-pathological factors remains unclear [9]. IGF1 and members of the IGF-binding protein family (IGFBPs) are essential for cell cycle regulation [10].

IGF1, as a peptide growth factor, can improve cell proliferation and restrain apoptosis and it is also regulated by the insulin-like growth factor binding protein IGFBP3 [11]. Extant studies show that IGF1, IGFBP3 and insulin significantly influence the pathogenesis of colon cancer through regulating cell growth and proliferation [12, 13]. Moreover, the insulin level, IGF1 level, IGF1/IGFBP3 ratio and reduction of IGFBP3 may be related to the initiation of CRC, but not to the progression and outcome of the disease [12]. The *IGF1* gene comprises a highly conservative sequence with 6 exons, which give rise to heterogeneous mRNA transcripts by combining multiple transcription initiation sites and alternative splicing [14]. The *IGFBP3* gene, on human chromo-

some 7, is integrated in four protein-coding exons and a 5th exon in the 3' untranslated region [15]. *IGFBP3* acts as a hypoxia-inducible gene and it regulates a series of cellular processes, including senescence, cell proliferation, epithelial-mesenchymal transition and apoptosis [16]. The activities of *IGF-1* are controlled by interaction of several high-affinity IGFBPs; especially *IGFBP3* which directly carries *IGF-1* to target tissues, prevents it from proteolytic degradation and regulates its interaction with IGF-1R. Its expression is negatively related to *IGF-1* expression [17, 18]. *IGF1* and *IGFBP3* gene polymorphisms may affect circulation levels of IGF1 and IGFBP3, and high IGF1 level but low IGFBP3 level contributes to increased cancer risk [7, 19]. In addition, IGFBP3 has an effect in its own IGF-independent apoptosis through mediation of a specific cell surface receptor [20]. These findings suggest that genetic variations in the *IGF1* and the *IGFBP3* genes play important roles in colorectal tumourigenesis [21, 22]. However, previous studies indicated that polymorphic variations in *IGF1* and *IGFBP-3* genes may have no association with the CRC risk [11, 23, 24]. This present study therefore investigates the relationship of *IGF1* and *IGFBP3* polymorphisms with colorectal cancer susceptibility.

Materials and methods

Search methods. We searched PubMed (1996~Aug. 2017), Cochrane Library (CEN-TRAL, 2017), Ovid (1948~Aug. 2017), Embase (1966~Aug. 2017), CNKI(1994~Aug. 2017) and Wanfang database (1986~Aug. 2017), following search terms: "Colorectal Neoplasms" or "Colorectal Neoplasm" or "Colorectal Tumor" or "Colorectal Carcinoma" or "Colorectal Cancer" or "Colorectal Cancer" and "Insulin-Like Growth Factor Binding Protein 3" or "IGFBP-3" or "IGF-Binding Protein 3" or "IGF Binding Protein 3" or "Protein 3, IGF-Binding" and "Polymorphism, Genetic" or "Genetic Polymorphism" or "Polymorphism (Genetics)"and "IGF1 protein, human". Then we manually searched the reference lists of the retrieved articles and reviews in other relevant studies.

Inclusion and exclusion criteria. Studies were based on the following inclusion criteria: (1) all studies had to be case-controlled, with participants divided into CRC and non-CRC groups; (2) the research topic was associated with the *IGFBP3* and *IGF1* gene polymorphism and susceptibility to CRC; (3) the outcome index ensured the studies provided the information for *IGFBP3* rs2854746 C>G, rs2854744 A>C and *IGF1* rs35767 C>T. The exclusion criteria were: (1) summaries and abstracts only; (2) duplicated studies and (3) insufficient statistics. Inclusion was discussed until consensus was reached.

Data extraction. Two independent investigators extracted the data from eligible studies. Two authors reviewed all articles that suited inclusion criteria. The information was collected as follows: surname and initials of the first author, year of publication, source country, language of publication, cases, demographic variables of the subjects, study designs, detective methods, single nucleotide polymorphisms (SNPs), and genotype frequencies; disagreement was solved by a third investigator.

Statistical analysis. Data analysis was performed by Comprehensive Meta-analysis 2.0 (CMA 2.0; Biostatic Inc., Englewood, New Jersey, USA). Hardy-Weinberg equilibrium (HWE) was assessed by χ^2 test in the control group of each study. Odds ratio (OR) and 95% confidence intervals (95% CI) for CRC were calculated by comparing differences in allele and genotype frequency of *TLR4* rs4986790A>G and rs4986791 C>T polymorphisms. The significance of overall effect sizes was evaluated by Z test [25]. Forest plots were applied to reflect the comparisons of ORs and 95% CI between the case study and controls. The heterogeneity between included trials was estimated by the Cochran's Q-statistic ($p<0.05$ was considered significant) and also the I^2 test (0%, no heterogeneity; 100%, maximal heterogeneity) [25, 26]. The fixed-effect model was applied to calculate parameters when heterogeneity was not an issue; otherwise the random effect model was used [27]. Meta-regression univariate analysis was applied to identify potential sources of heterogeneity and the Monte Carlo simulation for further confirmation [28–30]. Sensitivity analysis evaluated whether the removal of a single study would influence the overall outcome. The Egger's linear regression test, funnel plot and classic fail-safe-N analyzed publication bias [31–33]. All tests were two-sided, and $p<0.05$ indicated statistical significance.

Results

Selection of eligible studies. Our search identified 251 relative studies. After excluding duplicates (n=32), letters, reviews and meta-analysis (n=48), non-human studies (n=21) and studies irrelevant to research topics (n=70), we reviewed 80 full-text articles. Through detailed evaluation, we further excluded 67 studies (14 uncontrolled case studies, 18 studies irrelevant to *IGFBP3* or *IGF1*, 35 studies irrelevant to CRC) and 3 studies with irrelevant data. Finally, 10 eligible case-control studies from 2005~2012 [7, 13, 22, 23, 34–39] were incorporated in the study. They comprised 9,415 CRC patients and 14,179 healthy controls, and the sample size in each study ranged from 414 to 5,271. The flow chart of selection of eligible studies is shown in Figure 1. Eight studies were conducted in Caucasians and 2 in Asians. Polymerase chain reaction with the restriction fragment length polymorphism (PCR~RFLP) and TaqMan assay were applied for detection of SNP. In most eligible studies, the genotype distributions of studied loci were in accordance with the HWE (all $p>0.05$); except two studies with *IGF1* rs35767 C>T [23, 36] and one study with *IGFBP3* rs2854744 A>C [34]. The *IGFBP3* and *IGF1* gene loci-related information is summarized in Table 1.

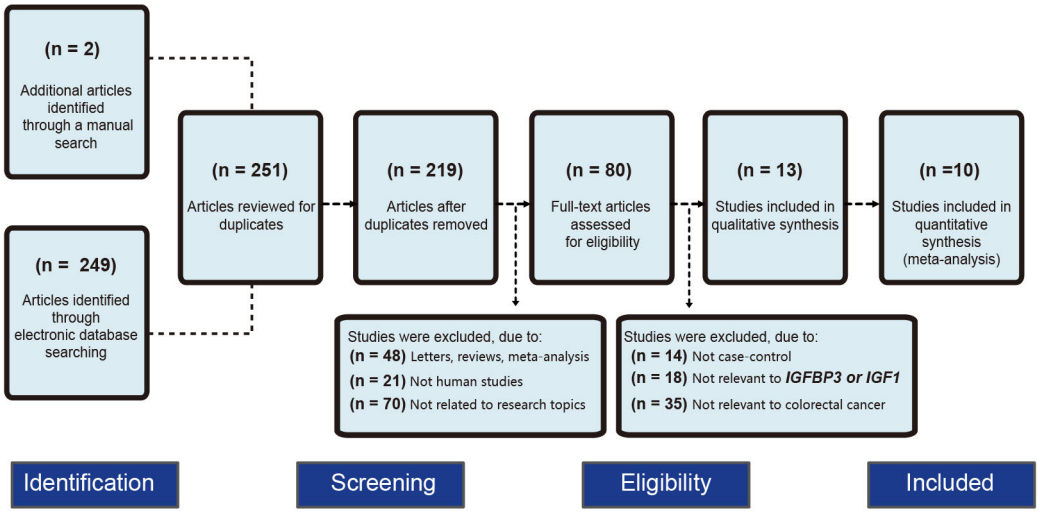

Figure 1. Flow chart of selected eligible studies. We searched 251 relative studies (249 studies from electronic databases and 2 from manual search). After excluding duplicates (n=32), letters, reviews or meta-analysis (n=48), non-human studies (n=21), unrelated to research topics (n=70), 80 full-text articles remained. Through further reading and evaluation, we rejected 67 studies (14 studies for not being case-controlled, 18 for irrelevance to *IGFBP3* or *IGF1* and 35 studies for irrelevance to CRC). A further 3 studies had irrelevant data so finally there were 10 eligible case-control studies from 2005–2012 included in our study [7, 13, 22, 23, 34–39].

Table 1. The *IGFBP3* and *IGF1* variants that have ever been reported in colorectal cancer and characteristics of studies included in this meta-analysis.

SNP	Author	Year	Country	Ethnicity	Genes	Study design	Source of controls	Genotype method	Sample size (case/control)	Adjusted factors	HWE	CASP score
rs2854746 (C>G)	Ollberding NJ [36]	2012	USA	Caucasians	IGFBP3	Case-Control	PB	TaqMan	1954/2587	1,2,3,4,5,6	0.100	10
rs2854746 (C>G)	Feik E [13]	2010	Austria	Caucasians	IGFBP3	Case-Control	PB	TaqMan	178/1795	1,2,3,4,5,6	0.450	9
rs2854746 (C>G)	Xiang H [22]	2009	China	Asians	IGFBP3	Case-Control	PB	TaqMan	202/212	1,2,3,4,5,6	0.717	8
rs2854746 (C>G)	Pechlivanis S [23]	2007	Germany	Caucasians	IGFBP3	Case-Control	PB	TaqMan	661/607	1,2,3,4,5,6	0.392	9
rs2854746 (C>G)	Morimoto LM [35]	2005	USA	Caucasians	IGFBP3	Case-Control	PB	PCR-RFLP	782/503	1,2,3,4,5,6	0.098	8
rs2854744 (A>C)	Ollberding NJ [36]	2012	USA	Caucasians	IGFBP3	Case-Control	PB	TaqMan	1954/2587	1,2,3,4,5,6	0.100	10
rs2854744 (A>C)	Keku TO [7]	2012	USA	Caucasians	IGFBP3	Case-Control	PB	TaqMan	552/873	1,2,3,4,5,6	0.255	9
rs2854744 (A>C)	Feik E [13]	2010	Austria	Caucasians	IGFBP3	Case-Control	PB	TaqMan	178/1795	1,2,3,4,5,6	0.450	9
rs2854744 (A>C)	Xiang H [22]	2009	China	Asians	IGFBP3	Case-Control	PB	TaqMan	202/212	1,2,3,4,5,6	0.717	8
rs2854744 (A>C)	Pechlivanis S [23]	2007	Germany	Caucasians	IGFBP3	Case-Control	PB	TaqMan	661/607	1,2,3,4,5,6	0.392	9
rs2854744 (A>C)	Slattery ML [38]	2006	USA	Caucasians	IGFBP3	Case-Control	PB	PCR-RFLP	2371/2972	1,2,3,4,5,6	0.844	8
rs2854744 (A>C)	Samowitz WS [37]	2006	USA	Caucasians	IGFBP3	Case-Control	PB	PCR-RFLP	1788/1981	1,2,3,4,5,6	0.325	9
rs2854744 (A>C)	Wong HL [39]	2005	Singapore	Asians	IGFBP3	Case-Control	PB	TaqMan	290/873	1,2,3,4,5,6	0.112	8
rs2854744 (A>C)	Le Marchand L [34]	2005	USA	Caucasians	IGFBP3	Case-Control	PB	PCR-RFLP	2298/2749	1,2,3,4,5,6	0.817	9
rs35767 (C>T)	Ollberding NJ [36]	2012	USA	Caucasians	IGF1	Case-Control	PB	TaqMan	1954/2587	1,2,3,4,5,6	0.100	10
rs35767 (C>T)	Feik E [13]	2010	Austria	Caucasians	IGF1	Case-Control	PB	TaqMan	178/1795	1,2,3,4,5,6	0.450	9
rs35767 (C>T)	Pechlivanis S [23]	2007	Germany	Caucasians	IGF1	Case-Control	PB	TaqMan	661/607	1,2,3,4,5,6	0.392	9

Notes: CASP, critical appraisal skill program; HWE, Hardy-Weinberg equilibrium; PB, population based; 1, Year; 2, Country; 3, Ethnicity; 4, Genotype method; 5, SNP; 6, Sample size.

Associations between IGFBP3 gene rs2854746 C>G polymorphism and CRC susceptibility. Five studies demonstrated the associations of *IGFBP3* gene rs2854746 C>G with susceptibility to CRC. The random effect model was adopted because of observed heterogeneity in the allele model and dominant gene model ($p<0.05$). Results demonstrated that *IGFBP3* gene rs2854746 C>G polymorphism increases susceptibility to CRC (allele model: OR=1.167, 95% CI=1.095~1.244, $p<0.001$; dominant gene model: OR=1.226, 95% CI=1.113~1.350, $p<0.001$) (Figures 2A, 2B, Table 2).

The subgroup analyses based on ethnicity determined that *IGFBP3* gene rs2854746 C>G polymorphism may increase the CRC susceptibility among both Asians and Caucasians (Asians: allele model: OR=1.448, 95% CI=1.058~1.982, p=0.021; dominant model: OR=1.554, 95% CI=1.052~2.296, p=0.027; Caucasians: allele model: OR=1.156, 95% CI=1.083~1.234, p<0.001; allele model: OR=1.207, 95% CI=1.092~1.334, p<0.001) (Figures 3A, B).

Table 2. Comparisons of genotype and allele frequencies between the case and the control groups.

SNP		rs2854746 C>G			rs2854744 A>C			rs35767 C>T		
		OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
M allele vs. W allele (Allele model)	Overall	1.167	1.095~1.244	<0.001	0.97	0.932~1.010	0.138	0.785	0.726~0.850	<0.001
WM + MM vs. WW (Dominant model)	Overall	1.226	1.113~1.350	<0.001	0.995	0.936~1.057	0.874	0.73	0.661~0.806	<0.001
MM vs. WW (Homozygous model)	Overall	1.3	1.150~1.470	<0.001	0.957	0.880~1.036	0.227	0.721	0.594~0.876	0.001
MM vs. WM (Heterozygous model)	Overall	0.891	0.795~0.999	0.048	0.963	0.816~1.136	0.656	1.155	0.947~1.408	0.115
MM vs. WW + WM (Recessive model)	Overall	1.191	1.072~1.324	<0.001	0.927	0.866~1.126	0.472	0.778	0.645~0.939	0.009

Notes: OR, odds ratio.

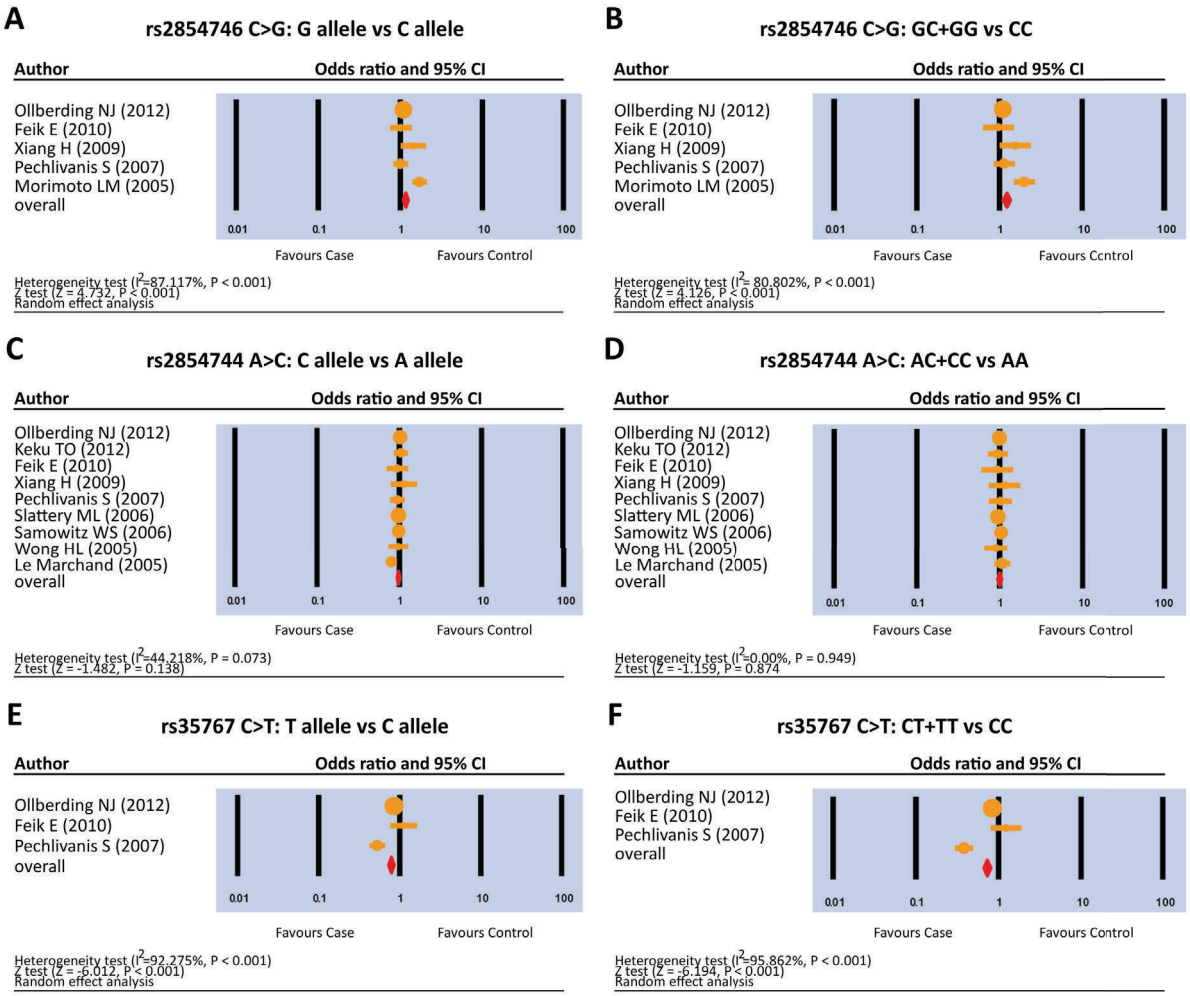

Figure 2. Forest plots for the association of *IGFBP3* gene rs2854746 C>G and rs2854744 A>C polymorphism and *IGF1* gene rs35767 C>T polymorphism with CRC susceptibility. Under allele mode and dominant model, *IGFBP3* gene rs2854746 C>G and *IGF1* gene rs35767 C>T polymorphism could increase the CRC susceptibility (all p<0.05, shown in A, B, E, F), while IGFBP3 gene rs2854744 A>C polymorphism had no significant influence on the susceptibility to CRC (all p>0.05, shown in C, D). The complete set of statistical data is in Supplementary Figure 1.

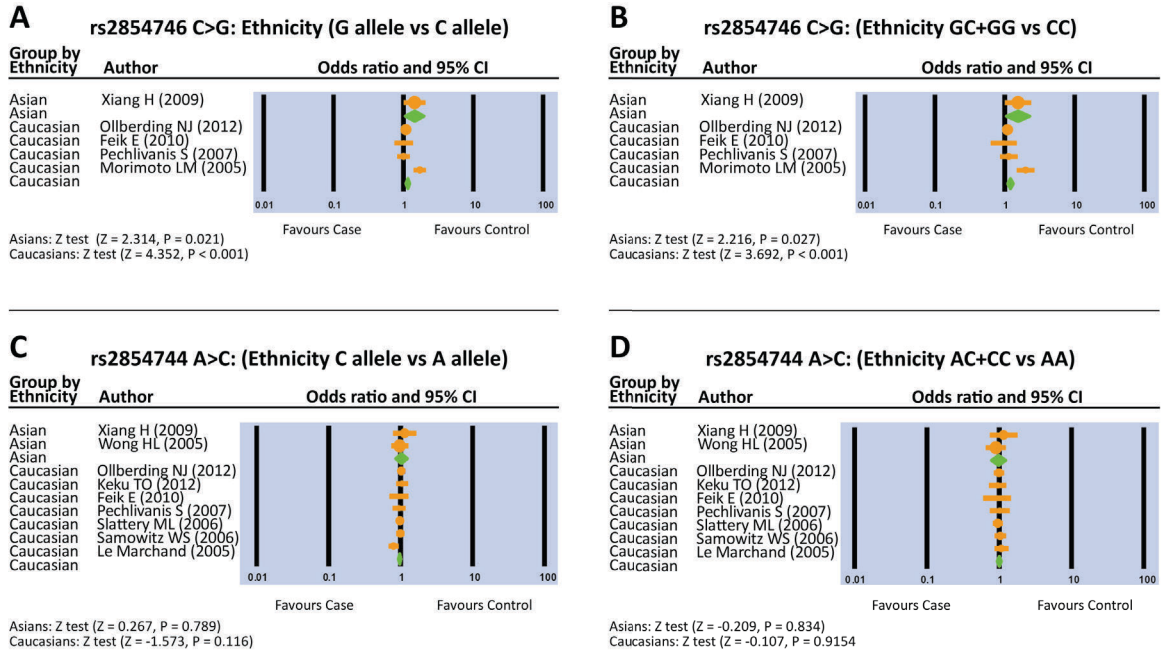

Figure 3. Subgroup analysis by ethnicity for the association of *IGFBP3* gene rs2854746 C>G and rs2854744 A>C polymorphism with CRC susceptibility. Under allele mode and dominant model, *IGFBP3* gene rs2854746 C>G polymorphism may increase the CRC susceptibility in both Asians and Caucasians (all p<0.05, shown in A, B), while IGFBP3 gene rs2854744 A>C polymorphism was not related to CRC susceptibility in either Asians or Caucasians (all p>0.05, shown in C, D). The complete set of statistical data is in Supplementary Figure 2.

Associations between IGFBP3 gene rs2854744 A>C polymorphism and CRC susceptibility

Nine studies demonstrated association of *IGFBP3* gene rs2854744 A>C with CRC susceptibility. The fixed effect model was adopted because no heterogeneity was observed in the allele model or dominant gene model (p>0.05). The results demonstrated that *IGFBP3* gene rs2854744 A>C polymorphism had no significant influence on susceptibility to CRC (allele model: OR=0.970, 95% CI=0.932~1.010, p=0.138; dominant model: OR=0.995, 95% CI=0.936~1.057, p=0.874) (Figures 2C, 2D, Table 2). The subgroup analyses based on ethnicity established that *IGFBP3* gene rs2854744 A>C polymorphism was unrelated to CRC susceptibility in both Caucasian and Asian subjects (p>0.05) (Figures 3C, D).

Associations between IGF1 gene rs35767 C>T polymorphism and CRC susceptibility. Three studies demonstrated the associations of *IGF1* gene rs35767 C>T polymorphism with susceptibility to CRC. The random effect model was adopted because of observed heterogeneity in the allele and dominant gene models (p<0.05). The results demonstrated that *IGF1* gene rs35767 C>T polymorphism decreased the CRC susceptibility (allele model: OR=0.785, 95% CI=0.726~0.850, p<0.001 and dominant model: OR=0.730, 95% CI=0.661~0.806, p<0.001) (Figures 2E, 2F, Table 2). No subgroup analysis was made on ethnicity because eligible studies only included Caucasians.

Sensitivity analysis and publication bias. Sensitivity analysis indicated that the *IGFBP3* gene rs2854746 C>G, rs2854744 A>C and *IGF1*gene rs35767 C>T showed no significant influences on pooled ORs of CRC (Figure 4). Publication year, country, ethnicity, SNPs, genotype methods and sample size were not the main sources of heterogeneity or crucial factors in the overall size of the effect. This was indicated by the univariate meta-regression analysis (all p>0.05) (Figure 5). The shape of funnel plots of genotype differences in *IGFBP3* gene rs2854746 C>G, rs2854744 A>C and *IGF1* gene rs35767 C>T did not show any evidence of symmetry and the statistical results did not show publication bias. No existence of obvious publication bias was found by Classic fail-safe N and Egger's linear regression test (all p>0.05) (Figure 6).

Discussion

We conducted this meta-analysis to investigate associations of IGFBP3 and IGF1 polymorphisms with susceptibility to colorectal cancer; and we finally concluded that *IGFBP3* rs2854746 C>G and *IGF1* rs35767 C>T correlated with CRC. Specifically, *IGFBP3* rs2854746 C>G is most likely

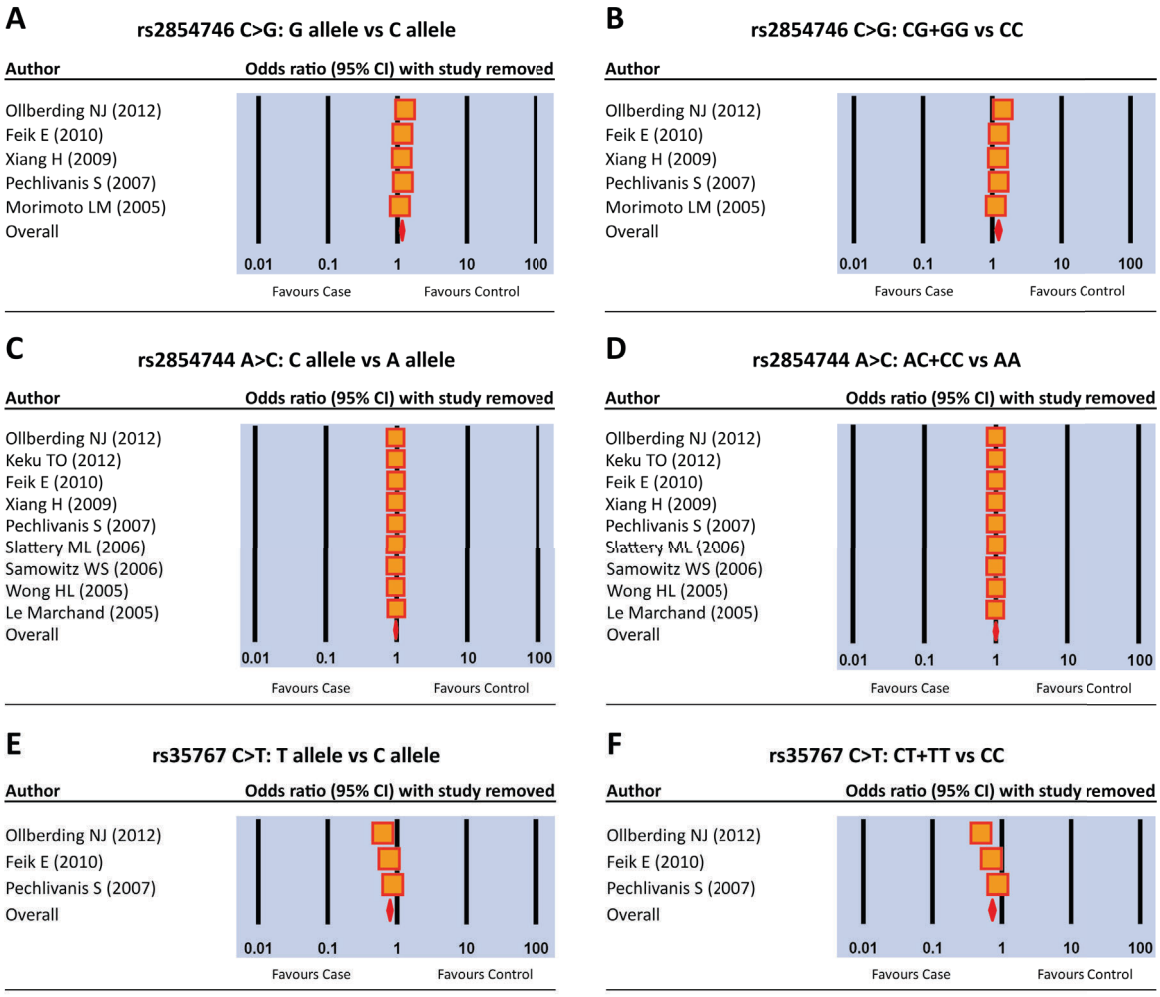

Figure 4. Sensitivity analysis for the association of *IGFBP3* gene rs2854746 C>G and rs2854744 A>C polymorphism and *IGF1* gene rs35767 C>T polymorphism with CRC susceptibility. Under allele mode and dominant model, the *IGFBP3* gene rs2854746 C>G, rs2854744 A>C and *IGF1* gene rs35767 C>T showed no significant influences on pooled ORs of CRC. The complete set of statistical data is shown in Supplementary Figure 3.

the susceptible CRC polymorphism and *IGF1* rs35767 C>T may be the protective CRC polymorphism.

Our overall findings demonstrated that *IGF1* rs35767 C>T polymorphism decreased the susceptibility to CRC while *IGFBP3* rs2854746 C>G polymorphism increased CRC susceptibility. The IGF family is expected to have an essential role in regulating cell proliferation, apoptosis, and transformation [11]. IGF1, widely regarded as a circulating growth factor, is normally produced by the liver and participates in mediating body growth through growth hormone effects [40], but it is fatal for the normal development and growth of cell maintenance and homeostasis [9].

A previous study also showed that IGF1 is expressed locally in many tissues, including skeletal muscle, thus implying that paracrine and autocrine effects of local IGF1 are a major mechanism controlling tissue growth [41]. Moreover, IGF1, a peptide growth factor, stimulates cell division and inhibits apoptosis and its abnormal expression could therefore contribute to cancer development and metastasis; including in CRC [11, 42].

To regulate cellular growth and differentiation, the IGF system and apoptosis circulate IGF family growth factors which bind IGFBP proteins and IGF receptors 1 and 2 cell surface receptors [36]. IGFBP3 has inherent anti-proliferative and pro-apoptotic ability, and the circulating IGF1 and IGFBP3 concentrations and down-stream signaling molecules may relate to CRC [43]. It has been reported that high levels of circulating IGF1 and/or low levels of IGFBP3 are associated with elevated CRC risk [44].

In addition, *IGFBP-3* rs2854744 was recently reported to be related to IGFBP-3 concentration, and its C allele may lower IGFBP-3 concentration [11]. This has attracted great atten-

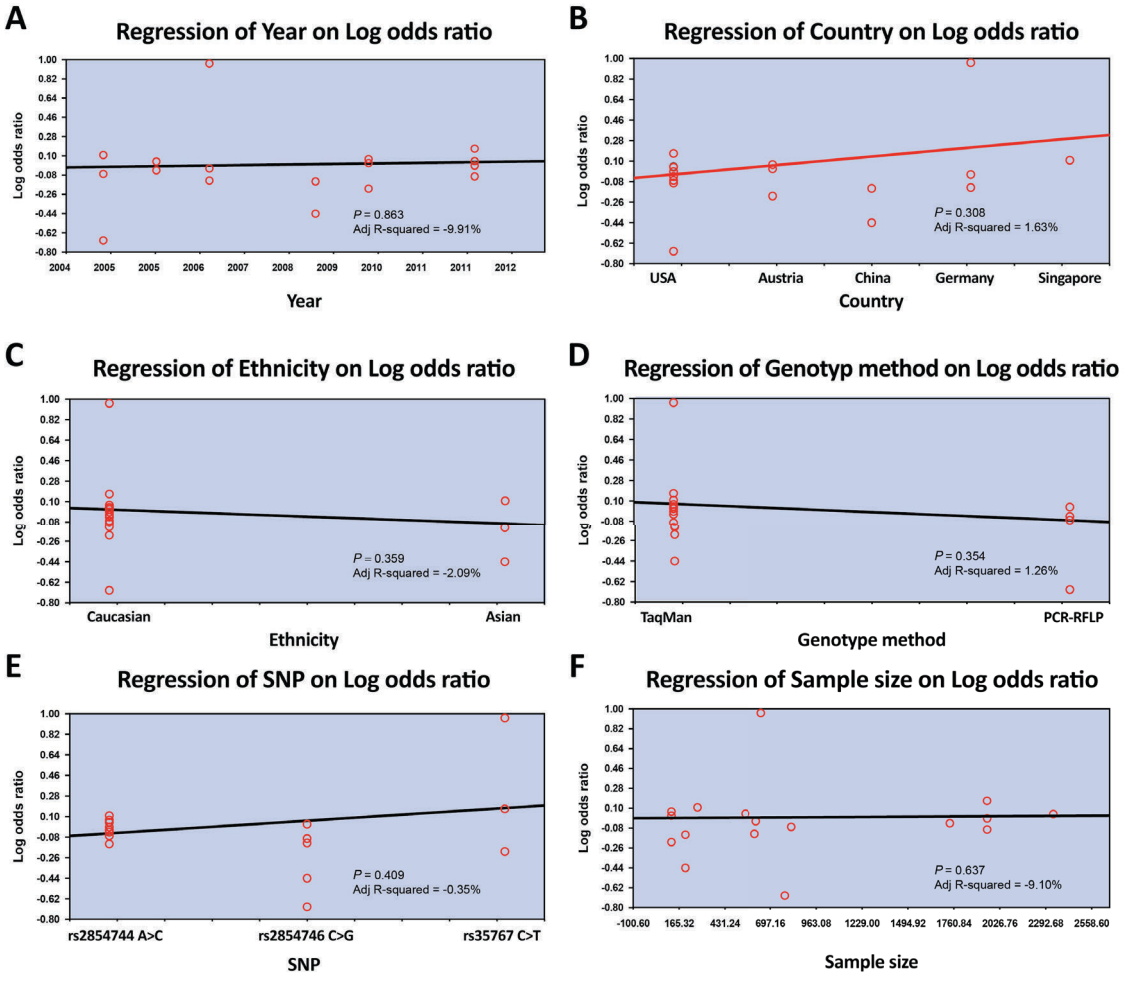

Figure 5. Meta-regression analysis for the association of IGFBP3 gene rs2854746 C>G and rs2854744 A>C polymorphism and IGF1 gene rs35767 C>T polymorphism with CRC susceptibility. Publication year, country, ethnicity, SNPs, genotype methods and sample size were not the main sources of heterogeneity or crucial factors in the overall size effect; as indicated in the univariate meta-regression analysis (all p>0.05).

tion. IGFBP-3 can modulate the mitogenic and metabolic effects of IGFs encoded by the *IGFBP-3* gene [16]. The IGFBP3 circulating level is significantly influenced by the *IGFBP3* gene rs2854746 C>G located at position –202 (rs2854744, A.C) as a transcription start-site affecting promoter activity and rs35767 C>T is regarded as a non-synonymous substitution with the Gly32Ala (rs2854746, G.C) site providing high affinity IGF1 binding [45]. Rare variant alleles of the functional G2133C, rs2854746 polymorphisms have consistently been associated with decreased circulating levels of IGFBP3, thus suggesting that the exon 1 G2133C missense variant in *IGFBP3* is critical in silencing its expression [7, 46]. This indicates that the *IGFBP3*rs2854746 SNP increases CRC risk by inhibiting the circulating level of IGFBP3. Previous studies support our findings by demonstrating that the exon 1 G2133C missense variant in *IGFBP3* may be a susceptibility factor for CRC in an allele dose-responsive manner [22, 34]. IGFBP3 is the binding protein for IGF1 that decreases cancer risk by mediating the bioavailability of freely circulating IGF1. This stimulates apoptosis and reduces cell proliferation in an IGF1–independent manner [36].

There are several limitations in our meta-analysis. We had no access to original data from included studies and this limited further research into potential interactions. The fact that only one rs2854746 study for Asian ethnicity was included may cause bias. Moreover, differing language in published studies could also cause bias in the overall estimates.

Subgroup analyses based on ethnicity were then conducted to consider the influence of ethnicity on the associations of *IGFBP3* gene rs2854746 C>G and *IGF1* gene rs35767 C>T polymorphisms with CRC. These ethnicity-stratified analyses revealed the influence of ethnicity on associations

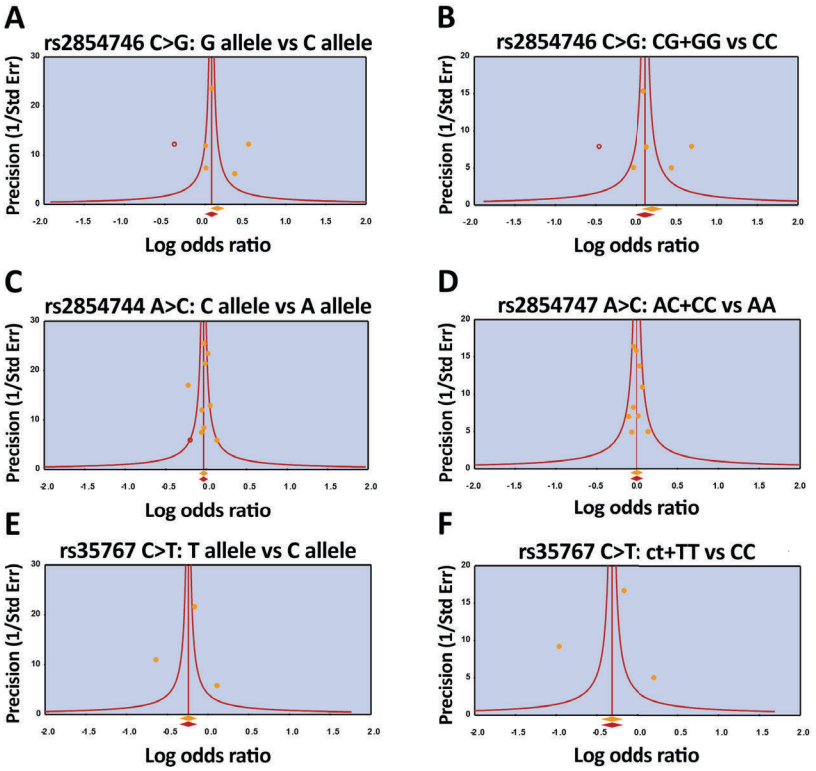

Figure 6. Funnel plot of publication bias in the association of IGFBP3 gene rs2854746 C>G and rs2854744 A>C polymorphism and IGF1 gene rs35767 C>T polymorphism with CRC susceptibility. The shape of funnel plots of genotype differences in IGFBP3 gene rs2854746 C>G, rs2854744 A>C and IGF1 gene rs35767 C>T did not show any evidence of symmetry and the statistical results did not show publication bias. No existence of obvious publication bias was found by Classic fail-safe N and Egger's linear regression test (all p>0.05). The complete set of statistical data is in Supplementary Figure 4.

between *IGFBP3* gene and CRC risk. The subgroup analysis suggested that *IGFBP3* gene rs2854746 C>G polymorphism increased susceptibility to CRC in both Asians and Caucasians. Moreover, no significant associations between *IGFBP3* gene rs2854744 A>C polymorphism and CRC susceptibility were observed in either Asians or Caucasians.

In conclusion, our study demonstrates that *IGFBP3* rs2854746 C>G is most likely the susceptible CRC polymorphism and *IGF1* rs35767 C>T is the protective polymorphism in colorectal cancer.

Supplementary information is available in the online version of the paper.

Acknowledgments: We are grateful to our instructors for their valuable advice.

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Meta-analysis of the association of IGFBP3 and IGF1 polymorphisms with susceptibility to colorectal cancer

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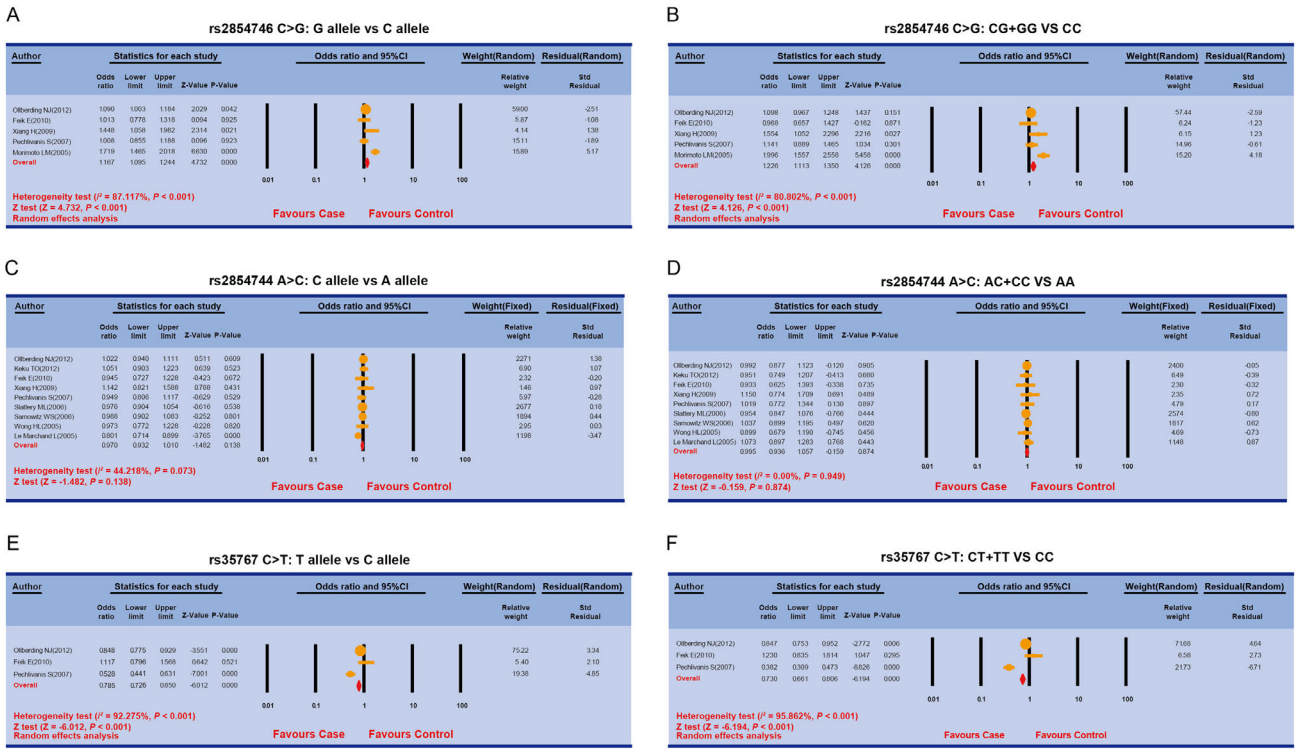
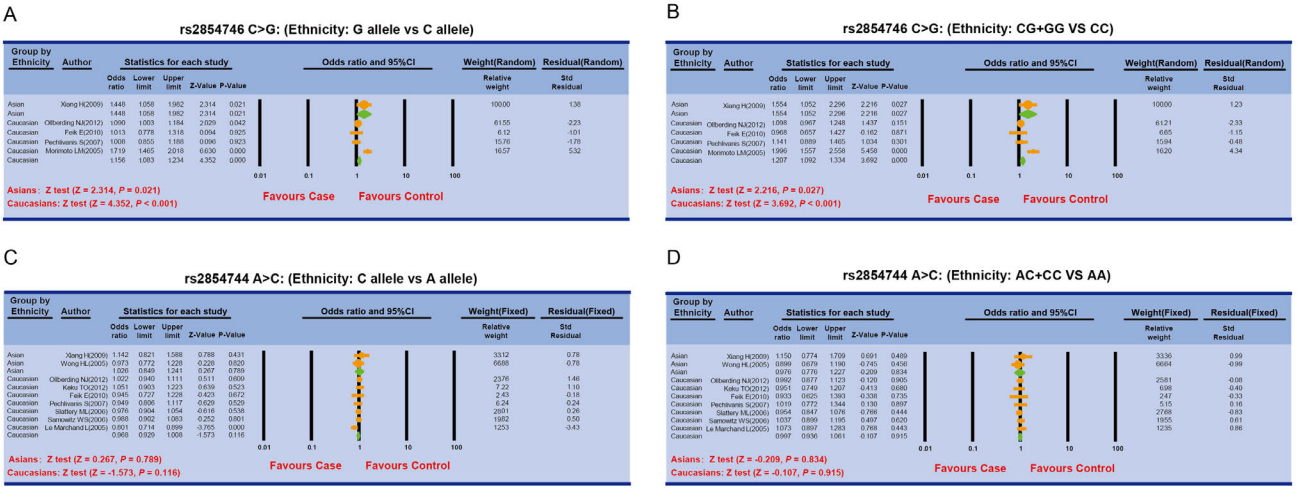
Supplemental Material



Supplementary Figure 1.



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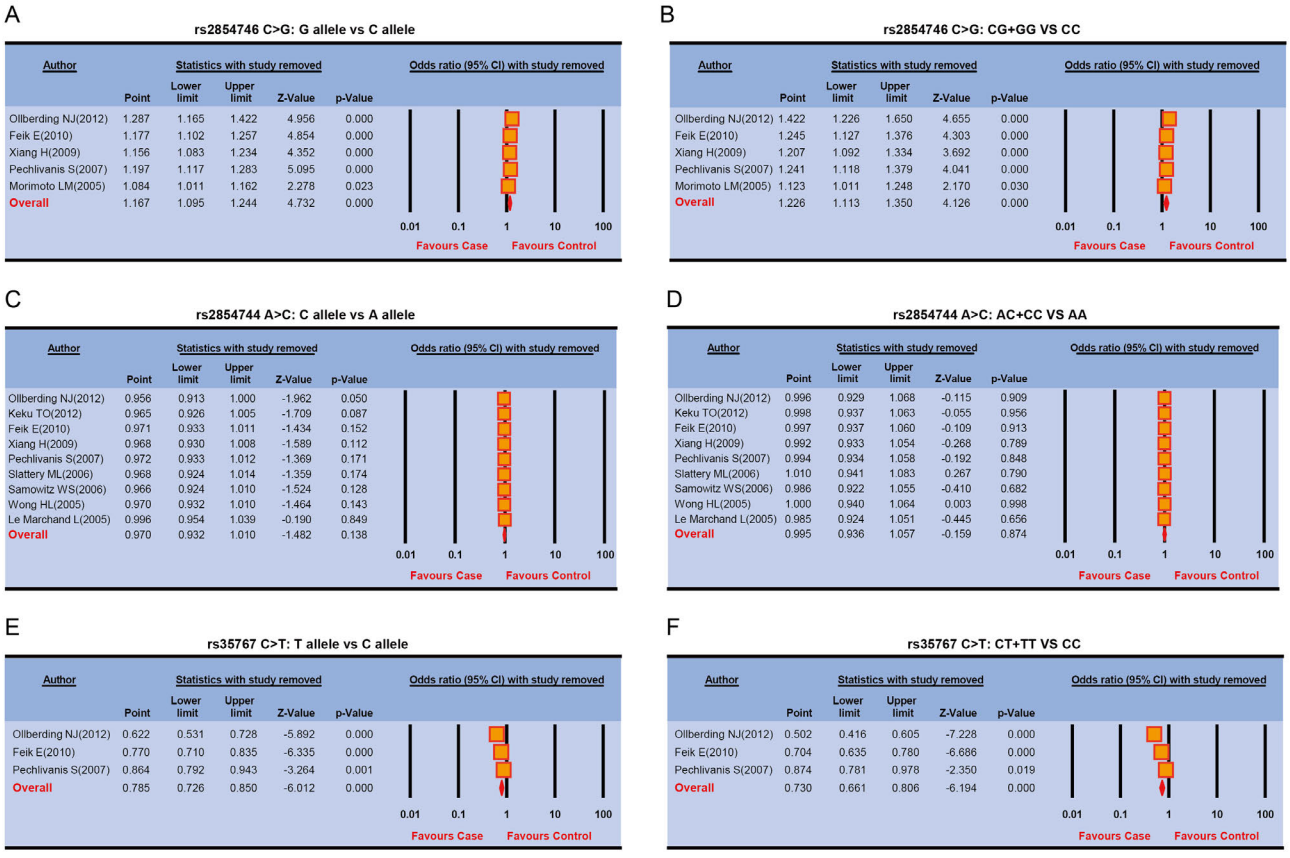
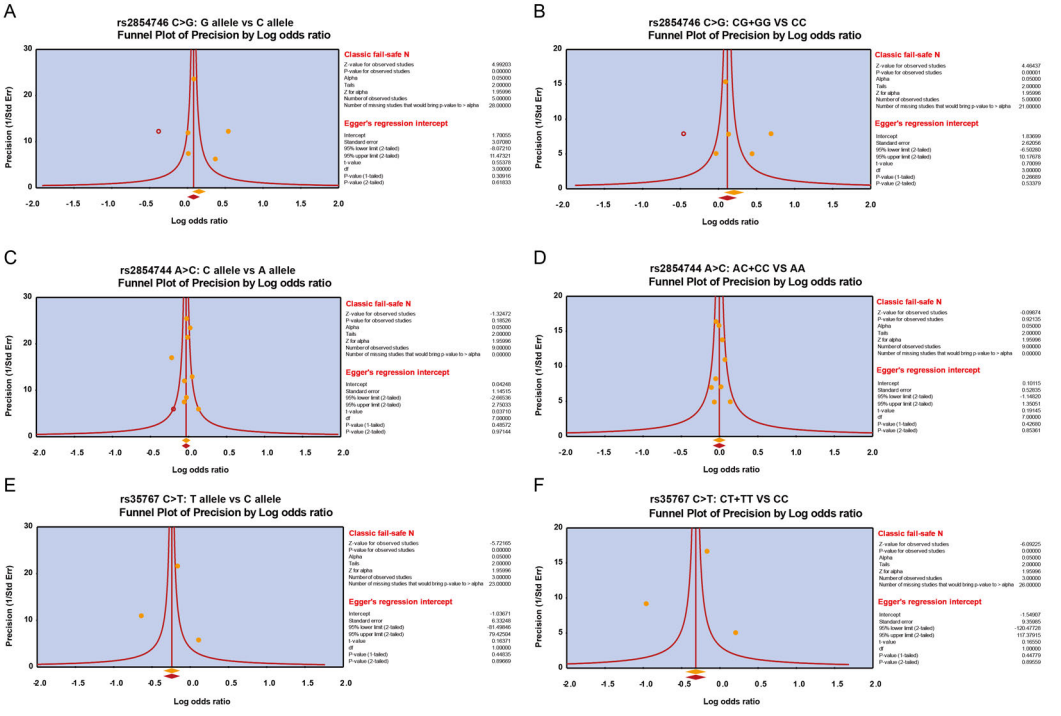


Supplementary Figure 3.



Supplementary Figure 4.