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Original Article

Association of 8q23-24 region (8q23.3 loci and 8q24.21 loci) with susceptibility to colorectal cancer: a systematic and updated meta-analysis

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Abstract: Background: Several single nucleotide polymorphisms (SNPs), rs16892766 in the 8q23.3 region and rs6983267, rs10505477, rs7014346 and rs7837328 in the 8q24.21 region, have been identified by genome-wide association studies (GWAS) and a number of case-control studies to be closely associated with risk of colorectal cancer (CRC). In the present study, a meta-analysis was performed to confirm if these loci are risk factors for susceptibility to CRC, taking heterogeneity of population into consideration. Methods: The whole literature search was conducted via database of MEDLINE and Embase, through which 33 articles with 49 studies (141,899 cases and 157,536 controls) were finally included in this meta-analysis to evaluate the association between the 5 polymorphisms and risk of CRC under allelic model. Results: A meta-analysis of the pooled data showed that the G allele of rs6983267, the A allele of rs7014346, the T allele of rs10505477, the C allele of rs16892766 and the A allele of rs7837328 were associated with significantly increased risk of CRC under allelic model. Additionally, subgroup analyses of four SNPs (rs7837328 excluded) by ethnicity witnessed a notable association between the G allele of rs6983267 and increased risk of CRC among Caucasians, Asians and Africans. Furthermore, the C allele of rs16892766 was strongly linked with elevated risk of CRC among Caucasians and Africans. However, the A allele of rs7014346 and T allele of rs10505477 only heightened risk for CRC among Caucasians and showed no effects among Asians. Conclusion: In summary, rs6983267 is a risk factor for CRC among Caucasians, Asians and Africans; rs7014346 and rs10505477 are risky genetic polymorphisms only among Caucasians; rs16892766 is a hazardous element among populations with Caucasian and African ancestry; and rs7837328 could elevate the susceptibility to CRC in a multinational group. However, more potential factors related with CRC risk should be investigated in further studies.

Keywords: Colorectal cancer (CRC), 8q23.3, 8q24.21, single nucleotide polymorphism (SNP), genome-wide association studies (GWAS), meta-Analysis

Introduction

Colorectal cancer (CRC), a malignant cancer developing between dentate line and rectosigmoid junction within the digestive tract, has been regarded as the fourth culprit for cancer-related mortality worldwide [1], injuring 1.23 million people and generating 0.6 million deaths globally [2]. While incremental risk of CRC could be explained partially by lifestyle factors (smoking, high protein and fat-rich diet, shortage of exercise etc.), genetic disorders also contribute to 35% of CRC cases as demonstrated by twin- and family- based studies [3]. High penetrance genes (DNA mismatch repair genes, *APC*, *SMAD4*, *BMPR1A*, *MUTYH* and *STK11*) are estimated to explain < 5% of total CRC, while much of the remaining genetic variation may be owing to multiple common alleles with low penetrance [2]. Until now, however, the molecular basis of CRC is still obscure, even more than 90% of the genetic pathogenesis for CRC remains unclear [4]. In fact, a significant aspect of the hereditary predisposition to CRC lies in the presence of single nucleotide polymorphisms (SNPs) [3].

Previously published genome-wide association studies (GWAS) have identified 5 SNPs located in the 8q24.21 (rs6983267, rs10505477, rs7837328, rs10505477) or 8q23.3 (rs16892766) chromosome region to show strong associations with the development of CRC [5-9]. Moreover, strong linkage disequilibrium (LD) were observed between rs6983267 and rs10505477 [10], rs6983267 and rs7837328 (r^2 = 0.71 among Caucasian population) [11], rs6983267 and rs7014346 (r^2 = 0.55 among European-American population) [12]; rs16892766 was also found to be in a high LD region [13]. Therefore, the 5 SNPs were selected as representative polymorphisms on the association studies of 8q23-24 region with risk of CRC.

Several replication studies targeting diverse ethnicities (British, American, Japanese, Chinese etc.) have also confirmed the association of 5 loci mentioned above with susceptibility to CRC [9, 14-16]. Nonetheless, heterogeneity of populations in certain studies makes it tough to deem 5 loci as risk factors for susceptibility to CRC confidently (**Table 1**). A series of meta-analyses have already been conducted to confirm the association of rs6983267 and rs10505477 polymorphisms with CRC risk [10, 17]. In the present study, a meta-analysis incorporating more related case-control studies (GWAS included) about a specific chromosome region (8q23-24) was carried out to confirm the association of rs16892766, rs7014346, rs7837328, rs6983267 and rs10505477 with susceptibility to CRC, through which the combined effects of 8q23-24 on CRC might be estimated.

Moreover, the incidence rate of CRC varies between populations partly because the variation of SNPs differs among distinct ethnicities [18]. However, there have been few reports about how to categorize 8q23-24 related SNPs identified by GWAS as common disease-common variants (CD-CV) and common disease-rare variants (CD-RV) among populations of different ethnicities. Therefore, subgroup analyses based on ethnicity are conducted to distinguish the susceptibility alleles that are frequent among population on a larger scale from those that are limited to specific ethnicities, in which way CRC risk could be predicted in different populations with identification of particular risk variants.

Methods

Search strategy and selection

A meta-analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [19]. Articles were searched by usage of the MeSH terms “colorectal cancer”, “SNP”, “rs6983267”, “rs10505477”, “rs7014346”, “7837328”, “16892766”, “8q24.21”, “8q23.3”, “case-control” and “meta-analysis” in MEDLINE and Embase without language limitations, with the latest search being updated in January 2015. The reference lists were sought for by hand for other pertinent publications.

Data extraction

Studies were included in the meta-analysis if they met the following criteria: (i) study patients were diagnosed with CRC at any tumorigenesis stage; (ii) availability of genotype or allele of both case and control groups or minor allele frequency (MAF) of patients and control groups or related odds ratio (OR) and confidence interval (95% CI) of the allelic model for CRC; and (iii) genotype frequencies were congruent with Hardy-Weinberg equilibrium (HWE) in the control group. Major exclusion criteria were as follows: (i) combined data of CRC with other cancers; (ii) no available genotype or allele frequencies or MAF or related OR; (iii) family-based studies; and (iv) abstracts and reviews.

Studies were screened by two investigators and information was extracted from all candidate publications independently. Disagreements were recorded and settled via discussion with a third author. The following characteristics were collected from each study: first author’s surname, year of publication, ethnicity of patients, genotyping method, total number of CRC patients and controls, methods of genotyping, loci, frequencies of genotype and allele, OR and 95% CI of allelic model.

Statistical analysis

A chi-squared (χ^2) test was performed when the frequencies of genotypes in controls satisfied HWE. Crude OR with 95% confidence interval (CI) and *P*-values were calculated to assess the stability of the results of the meta-analyses. Pooled ORs were calculated for the allelic model of rs6983267 (G vs. T), rs10505477 (T

Table 1. Main characteristics of studies selected in the meta-analysis

ID	First author	Year	Genotyping method	Country	Ethnicity	SNP				
						rs6983267	rs10505477	rs7014346	rs7837328	rs16892766
						Case/Cont	Case/Cont	Case/Cont	Case/Cont	Case/Cont
1	Gruber	2007	GeneChip	Northern Israel	Asian	--	1861/1937	--	--	--
2	Poynter	2007	PCR	Europe	Caucasian	1339/2191	1341/2193	--	--	--
3	Tomlinson	2007	Illumina	United Kingdom	Caucasian	7954/6202	--	--	--	--
4	Zanke	2007	TaqMan	Newfoundland, Canada	Caucasian	--	445/366	--	--	--
5	Zanke	2007	TaqMan	America	Caucasian	--	1859/1882	--	--	--
6	Zanke	2007	TaqMan	Scotland	Caucasian	--	2809/2912	--	--	--
7	Zanke	2007	TaqMan	France	Caucasian	--	1415/1656	--	--	--
8	Zanke	2007	TaqMan	Europe	Caucasian	--	761/749	--	--	--
9	Li	2008	TaqMan	America	Caucasian	527/679	--	--	--	--
10	Pittman	2008	PCR	United Kingdom	Caucasian	3583/2579	--	--	--	--
11	Schafmayer	2008	SNPlex	German	Caucasian	2712/2713	2713/2718	2713/2718	--	--
12	Tenesa	2008	Illumina	Scotland	Caucasian	--	--	2986/3059	--	--
13	Tenesa	2008	Illumina	Japan	Caucasian	--	--	4395/3179	--	--
14	Tenesa	2008	Illumina	Canada	Caucasian	--	--	1175/1183	--	--
15	Tenesa	2008	Illumina	England	Caucasian	--	--	2233/2248	--	--
16	Tenesa	2008	Illumina	Spain	Caucasian	--	--	349/292	--	--
17	Tenesa	2008	Illumina	Germany	Caucasian	--	--	3455/3563	--	--
18	Tenesa	2008	Illumina	Scotland	Caucasian	--	--	826/892	--	--
19	Tenesa	2008	Illumina	Israel	Caucasian	--	--	1517/1466	--	--
20	Tomlinson	2008	Illumina	United Kingdom	Caucasian	--	--	--	--	18831/18540
21	Tuupanen	2008	PCR	Finland	Caucasian	996/1012	--	--	--	--
22	Wokołorczyk	2008	RFLP-PCR	Poland	Caucasian	779/1910	--	--	--	--
23	Curtin	2009	SNPlex	United Kingdom	Caucasian	1069/1040	1071/1040	--	--	--
24	Kupfer	2009	Sequenom MassARRAY	America (European)	Caucasian	288/202	--	--	--	--
25	Matsuo	2009	TaqMan	Japan	Asian	476/961	--	--	--	--
26	Middeldorp	2009	PCR	Dutch	Caucasian	995/1340	--	--	--	--
27	Cui	2010	Illumina	Japan	Asian	6161/4494	--	--	6163/4494	--
28	Ghazi	2010	TaqMan	Sweden	Caucasian	511/1017	--	--	--	--
29	Holst	2010	TaqMan	Sweden	Caucasian	1737/1738	--	--	--	1755/1691
30	Hutter	2010	TaqMan	Iran	Asian	1962/2418	2089/2443	--	--	--
31	Kupfer	2010	Sequenom MassARRAY	America (European)	Caucasian	399/367	--	399/367	399/367	399/367
32	Kupfer	2010	Sequenom MassARRAY	America (African)	African	795/985	--	795/985	795/985	795/985

33	Xiong	2010	RFLP-PCR	China	Asian	2124/2124	--	--	--	--
34	He	2011	TaqMan	America (European)	Caucasian	1171/1543	--	--	--	1171/1543
35	He	2011	TaqMan	America (African)	African	382/510	--	--	--	382/510
36	He	2011	TaqMan	America (Native Hawaiians)	Caucasian	323/472	--	--	--	323/472
37	He	2011	TaqMan	America (Japanese)	Asian	1042/1426	--	--	--	1042/1426
38	He	2011	TaqMan	America (Latino)	Caucasian	393/524	--	--	--	393/524
39	Ho	2011	Sequenom MassARRAY	China	Asian	716/714	--	716/714	--	--
40	Li	2011	TaqMan	China	Asian	430/786	--	--	--	--
41	Lubbe	2011	PCR	United Kingdom	Caucasian	8878/6051	--	--	--	--
42	Daraei	2012	PCR–RFLP	Iran	Asian	110/120	--	--	--	--
43	Peters	2012	Illumina	--	Caucasian	4166/4990	--	--	--	7686/8977
44	Thean	2012	Affymetrix GeneChip	Singapore	Asian	1000/1000	--	--	--	991/993
45	Hong	2013	TaqMan	Korea	Asian	198/328	--	--	--	--
46	Nan	2013	TaqMan	America	Caucasian	807/1623	--	--	--	--
47	Wang	2013	Illumina	America (African)	African	1894/4703	1894/4703	1894/4703		1894/4703
48	Yang	2014	TaqMan	America	Caucasian	90/132	--	--	90/132	--
49	Yang	2014	Sequenom MassARRAY	Taiwan	Asian	705/1802	705/1802	705/1802	--	--

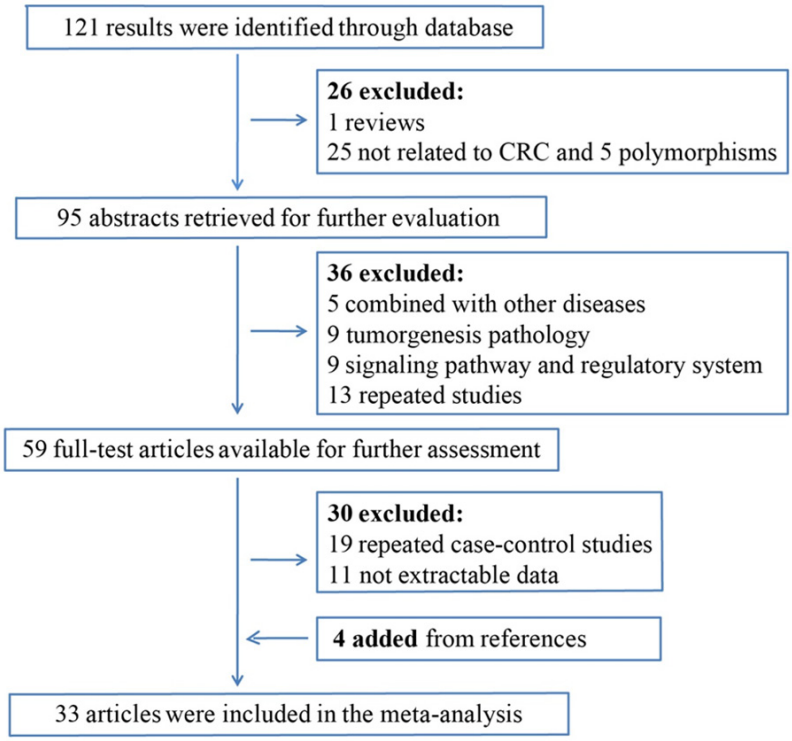

Figure 1. Selection of the related studies.

vs. C), rs7014346 (A vs. G), rs7837328 (A vs. G), rs16892766 (C vs. A). The statistical significance of pooled ORs was assessed by Z test. To measure the strength of genetic association, Cochran's Q test and Higgins's (I^2) test were used to assess between-study heterogeneity. In case of $I^2 < 50\%$ and $P > 0.1$, the fixed-effects model was employed to evaluate the pooled ORs; otherwise, the random-effects model was applied. Begg's funnel plots test and Egger's regression test were carried out to estimate publication bias. A value of $P < 0.1$ was regarded as statistically-significant publication bias. STATA software (version 12.0) was utilized to conduct statistical analyses, and a two-tailed P value less than 0.05 was considered to be statistically significant.

Results

Study characteristics

As shown in **Figure 1**, 121 reports were initially searched on account of the subject terms mentioned above. After excluding articles that described reviews, uncorrelated SNPs and diseases, 29 articles were finally selected for full assessment and another 4 studies were added through manual searching from references. On the whole, 33 articles containing 49 case-control studies were eligible for this meta-analysis study, among which the researches by Kupfer et al., Tenesa et al., Zanke et al. and He et al. contained 2, 9, 8 and 5 case-control studies, respectively [5, 8, 9, 11, 12, 14-18, 20-42]. The characteristics of the included studies were presented in **Table 1**. Moreover, the full-text reports of susceptibility to CRC were classified into Cauca-sian, Asian or African subgroups: of 34 studies on rs6983267 (56712 cases and 60691 controls), 20 studies were from Caucasian subjects (38317 cases and 38320 controls), 11 studies were from Asian subjects (14924 cases and 16173 controls) and 3 studies were from African subjects (3071 cases and 6198 controls); of 12 studies on rs10505477 (18962 cases and 24400 controls), 8 studies were from Caucasian subjects (12414 cases and 13516 controls), 3 studies were from Asian subjects (4654 cases and 6181 controls); of 14 studies on rs7014346 (24158 cases and 27171 controls), 8 studies were from Caucasian subjects (14136 cases and 14322 controls), 4 studies were from Asian subjects (7333 cases and 7161 controls); of 11 studies on rs16892766 (34620 cases and 39296 controls), 7 studies were from Caucasian subjects (30558 cases and 32105 controls) and 3 studies were from African subjects (3071 cases and 6198 controls).

Meta-analysis

The association results of 5 polymorphisms on the 8q23-24 genetic stripe with CRC in allelic model were shown in **Table 2**, and detailed analysis about the relationship between every specific SNP and susceptibility to CRC was demonstrated in Supplementary Figures 1, 2, 3, 4 and 5. A notable association between chromosome 8q23-24 (5 SNPs involved) and CRC

Table 2. Main results of meta-analysis of 5 polymorphisms on chromosome 8q23-24 (8q24.21 and 8q23.3) region and susceptibility to CRC

ID	SNP	Location (Hapmap)	Ethnicity	No. of studies	Case/Control	OR (95%CI)	Z	*P*-value	Model	I^2	P for Q-test	P*
1	rs6983267	8: 127,401,060	All	34	56712/60691	1.16 (1.12, 1.20)	56.43	< 0.001	Random	0.687	0.000	0.848
			Caucasian	20	38717/38320	1.15 (1.10, 1.21)	42.43	< 0.001	Random	0.750	0.000	0.719
			Asian	11	14924/16173	1.17 (1.09, 1.24)	32.14	< 0.001	Random	0.624	0.003	0.793
			African	3	3071/6198	1.20 (1.06, 1.34)	17.03	< 0.001	Fixed	0.063	0.344	0.180
2	rs10505477	8: 127,395,198	All	12	18962/24400	1.11 (1.06, 1.16)	43.84	< 0.001	Random	0.575	0.007	0.067
			Caucasian	8	12414/13516	1.15 (1.11, 1.19)	56.52	< 0.001	Fixed	0.402	0.110	0.122
			Asian	3	4654/6181	1.05 (0.94, 1.15)	19.28	< 0.001	Random	0.697	0.037	0.160
3	rs7014346	8: 127,412,547	All	14	24158/27171	1.12 (1.03, 1.21)	25.25	< 0.001	Random	0.880	0.000	0.628
			Caucasian	8	14136/14322	1.20 (1.16, 1.24)	57.61	< 0.001	Fixed	0.000	0.524	0.941
			Asian	4	7333/7161	1.01 (0.85, 1.17)	12.45	< 0.001	Random	0.874	0.000	0.209
4	rs7837328	8: 127,410,882	All	4	7447/5978	1.17 (1.11, 1.23)	38.45	< 0.001	Fixed	0.076	0.355	0.433
5	rs16892766	8: 116,618,444	All	11	34620/39296	1.23 (1.19, 1.28)	52.44	< 0.001	Fixed	0.000	0.961	0.720
			Caucasian	7	30558/32105	1.25 (1.20, 1.30)	46.81	< 0.001	Fixed	0.000	0.995	0.955
			African	3	3071/6198	1.16 (1.05, 1.26)	20.88	< 0.001	Fixed	0.000	0.758	0.987

P:* publication bias.

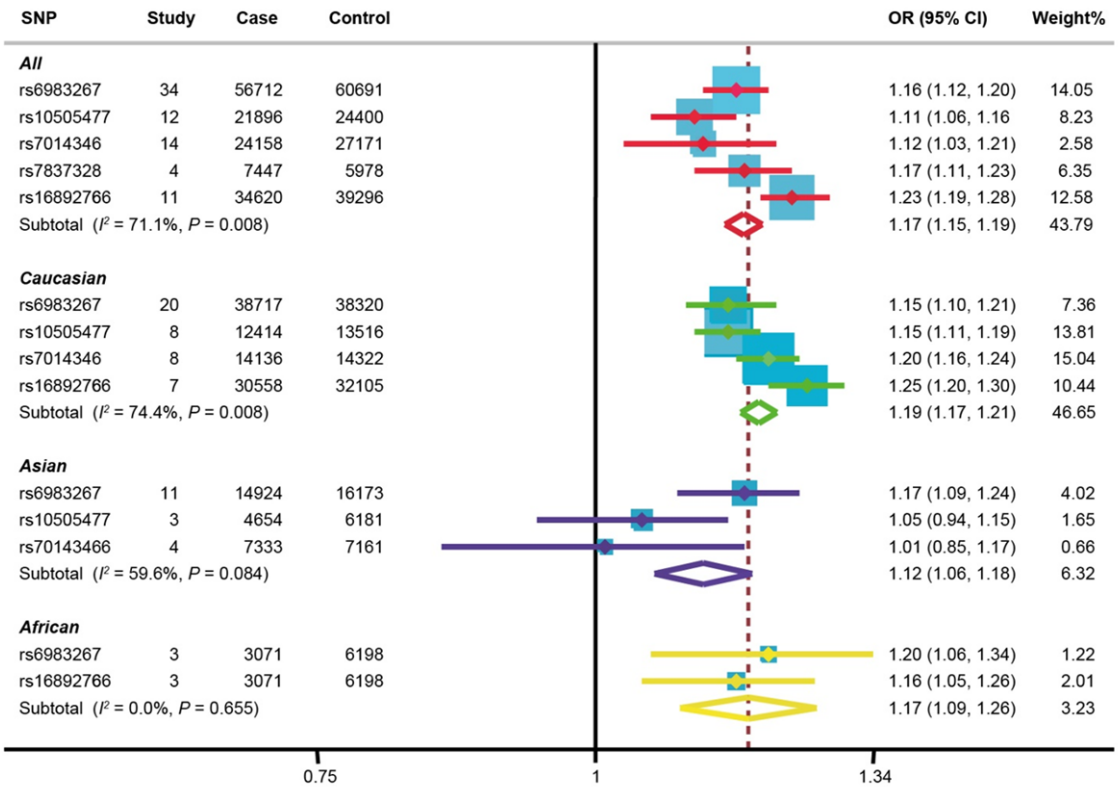

Figure 2. Forest plot presenting the meta-analysis of the association between 5 polymorphisms (rs6983267, rs10505477, rs7014346, rs7837328 and rs16892766) in 8q23.3 or 8q24.21 region and risk of CRC as well as subgroup analysis of 4 polymorphisms (rs7837328 excluded) by ethnicity in allelic model.

was also achieved on the foundation of meta-analysis of all related studies, including a total of 141899 cases and 157536 controls. As shown in **Figure 2**, the G allele of rs6983267 was associated with significantly increased risk of CRC under allelic model [OR = 1.16 (95% CI = 1.12-1.20), P < 0.001]. Furthermore, it was found that the A allele of rs7014346 remarkably increased CRC risk with OR of 1.12 (95% CI = 1.03-1.21, P < 0.001) and the T allele of rs10505477 could also elevate risk for CRC intensively [OR = 1.11 (95% CI = 1.06-1.16), P < 0.001]. Similarly, either the C allele of rs16892766 or the A allele of rs7837328 could promote CRC occurrence with OR of 1.23 (95% CI = 1.19-1.28, P < 0.001) and OR of 1.17 (95% CI = 1.11-1.23, P < 0.001), respectively.

Moreover, subgroup analyses of four SNPs (rs7837328 excluded) by ethnicity were further performed. **Figure 2** witnessed a remarkable association between the G allele of rs6983267 and increased risk of CRC among Caucasians [OR = 1.15 (95% CI = 1.10-1.21), P < 0.001], Asians [OR = 1.17 (95% CI = 1.09-1.24), P < 0.001] and Africans [OR = 1.20 (95% CI = 1.06-1.34), P < 0.001], which were consistent with the overall analysis. However, strong associations between the T allele of rs10505477 polymorphism and enhancive susceptibility to CRC were found only within Caucasians [OR = 1.15 (95% CI = 1.11-1.19), P < 0.001], and the results among Asians were not positive [OR = 1.05 (95% CI = 0.94-1.15), P < 0.001]. Likewise, the A allele of rs7014346 only elevated risk for CRC among Caucasians [OR = 1.20 (95% CI = 1.16-1.24), P < 0.001] and showed no effect among Asians. Regarding rs16892766, only meta-analysis of Caucasians and Africans were carried out due to shortage of Asian studies, revealing that the C allele of rs16892766 was closely related with increased risk of CRC among Caucasians [OR = 1.25 (95% CI = 1.20-1.30), P < 0.001] and Africans [OR = 1.16 (95% CI = 1.05-1.26), P < 0.001].

Publication bias

As revealed in **Table 2** and Supplementary Figure 6, no obvious asymmetry could be

observed in the shape of funnel plots (P = 0.848 for rs6983267, P = 0.067 for rs10505477, P = 0.628 for rs7014346, P = 0.433 for rs7837328 and P = 0.720 for rs16892766).

Discussion

There seems to exist potent associations between genetic markers at human chromosome 8q23.3 (rs16892766) or 8q24.21 (rs6983267, rs10505477, rs7014346 and rs7837328) and increased susceptibility to CRC [5-7, 9, 34]. This hypothesis was confirmed in the present study by conducting an allelic meta-analysis of involved association studies of the 5 polymorphisms worldwide, deriving consequences that the rs7014346 and rs10505477 polymorphisms were CRC-associated locus in both the Caucasians and the Asians while the rs6983267, rs16892766 and rs7837328 variants served as risk locus, respectively, among triple (Caucasian, Asian and African), double (Caucasian and African) and multi- ethnicities. The diverse magnitudes of increased risk of CRC in different populations (also shown as different values of I^2 in **Table 2**) conferred by the above genetic polymorphisms could be attributed to the discrepancy in allelic frequencies. Categorizing nearly all the case-control studies for each polymorphism on the basis of ethnicity, interesting results about allelic frequencies (case and control, respectively) are drawn as follows: Asian (0.54 and 0.56, respectively) > Caucasian (0.44 and 0.48, respectively) for T allele of rs6983267; Caucasian (0.46 and 0.50, respectively) ≈ Asian (0.46 and 0.47, respectively) for G allele of rs10505477; Caucasian (0.59 and 0.63, respectively) > Asian (0.40 and 0.46, respectively) for C allele of rs7014346; Caucasian (0.1171 and 0.1003, respectively) > Asian (0.0040 and 0.0005, respectively) for C allele of rs16892766. The possible reason might be that external environment would render one allele more frequent in one population than another, indicating that the allele could be associated with susceptibility to CRC [43]. Another probable explanation for the distinct proportion of different populations suffering from CRC could be clarified by diversified linkage disequilibrium (LD) structure [12, 44-47]. Various genotyping methods could also account for why the research results on a particular polymorphism are different from one another; for instance, SNPlex chemistry (Applied Biosystems, Foster City) [33], Sequenom MassARRAY platform [18, 41], Illumina [8, 34], PCR [37] were employed for the rs6983267 polymorphism in different published studies and distinct levels of risk for CRC were observed.

In fact, the characteristic function of 5 polymorphisms for CRC could be partly expatiated by the genomic organization, where the 5 SNPs reside. For instance, the 8q24.21 genomic region is featured by gene desert with 14807 bp away from pseudogene *POU5F1P1*, which is followed by oncogene *MYC* and the nearest proximal gene *FAM84B*. The above two genes, *MYC* and *FAM84B*, are respectively 335 kb and 849 kb from the rs6983267 polymorphism (the tag SNP in the 8q24.21 region) [37]. SNP rs6983267 is reported to either exert direct differential effects on *MYC* expression [48] or indirectly regulate expression of *MYC* through binding to some spicing forms of the transcription factor 7-like 2 (TCF7L2) [49]. According to Tuupanen et al., TCF7L2 is a main transcriptional effector of the Wnt signaling pathway, coactivating β-catenin in CRC [50]. Since the other three SNPs (rs7014346, rs7837328 and rs10505477) are in strong LD with rs6983267 [10-12], they might indirectly influence CRC through affiliation with cancer risk-associated rs6983267 polymorphism [10]. Hence, the four SNPs on the 8q24.21 region might carry an integrated and greater risk effect [11]. Still, clarification of the plausible regulatory role of these four loci and their LD in risk of CRC is required to be expatiated in further studies.

Besides, errors in meiotic cross-over events might also lead to chromosome abnormalities or non-disjunction, further causing loss of heterozygotes (LOH), which is closely associated with neoplastic progression [41, 51]. The meiotic cross-over events often take place in the recombination hotspots, where the locus are characteristic of higher exchange frequencies than others in the chromosome [51]. Certain variants harboring within the hotspots could thereby regulate hotspot activity and related recombination rate in the process of strand exchange; and the sequence variation might even cause distinctions in DNA topology, structure of chromatin, or chromosome domain organization [52, 53]. The rs10505477 polymorphism investigated in the present study

resides within a recombination hotspot and LD exists between the locus and other three locus (rs6983267, rs7014346, rs7837328) in the 8q24.21 region identified by GWAS, thus the four genetic variants might constitute part of hidden dangers for carcinogenesis. Additionally, the usage of recombination hotspots differs among populations [51], partly explaining the ethnic distribution of genetic variations. However, the possible effects of the four locus on the function of this hotspot and susceptibility to CRC demands more investigations.

The ultimately mentioned rs1982766, the tag SNP on chromosome 8q23.3, resides in an extended region with an anomalous and high LD [54]. The rs1982766 polymorphism has been demonstrated to display notable associations with CRC risk by means of repressing the expression of the eukaryotic translation initiation factor 3 subunit H (*EIF3H*) gene when interacting with the *EIF3H* promoter [55]. However, a succeeding assessment of ENCODE data and eQTLs implies that the expression level of the neighboring *UTP23* [small subunit (SSU) processome component, homologue (yeast)], instead of *EIF3H*, was markedly influenced by the rs1982766 variant and *UTP23* has become the most potential candidate gene associated with CRC in the 8q23.3 region [13, 54]. As reported by Lu et al., *UTP23* is a gene encoding *UTP23*, which is a conserved protein factor involved in the early assembly of ribosomal small subunit, affecting the precise identification of mRNA [56]. Since both *UTP23* and *EIF3H* share related functions in mRNA translation, it also appears to be conceivable that the double genes are collaborately regulated by the rs1982766 polymorphism in terms of susceptibility to CRC [54]. To elucidate how *EIF3H* or *UTP23*, or both, are associated with CRC etiology, additional work is necessitated [13].

Although some puzzles have been made more unambiguous by this meta-analysis, along with previous studies, several limitations should also be noted. First, the selection of case groups followed heterogeneous inclusion criteria for parameters, such as tumor stage and site. Second, the coverage of the clinical data (sex, age group, etc.) of the case and control groups was not all-sided. Third, MAF or OR (95% CI), rather than genotype and allele frequencies, were reported in some studies. Fourth, most of the studies did not identify whether people recruited in the control group are healthy or affected to other disease. Fifth, no enough case-control studies on Asian and African studies could be included in the meta-analysis, restraining further analysis of the association between 8q23-24 and CRC among more ethnicities. Despite these deficiencies, to the best of our knowledge, this is the first study to perform a systematic meta-analysis of 5 locus on the 8q23-24 genetic stripe which have been identified by GWAS, suggesting that the rs6983267 polymorphism was CRC associated locus in the Caucasians, Asians and Africans; rs7014346 and rs10505477 genetic variations showed positive results in both the Caucasians and the Asians; and rs16892766 served as risk locus in double (Caucasian and African) ethnicities while the rs7837328 variant was a risky factor in a multinational group. However, for in-depth understanding about the biological and clinical role of five polymorphisms seated in the 8q23.3 and 8q24.21 region in CRC risk, further investigation would be in urgent need.

Disclosure of conflict of interest

None.

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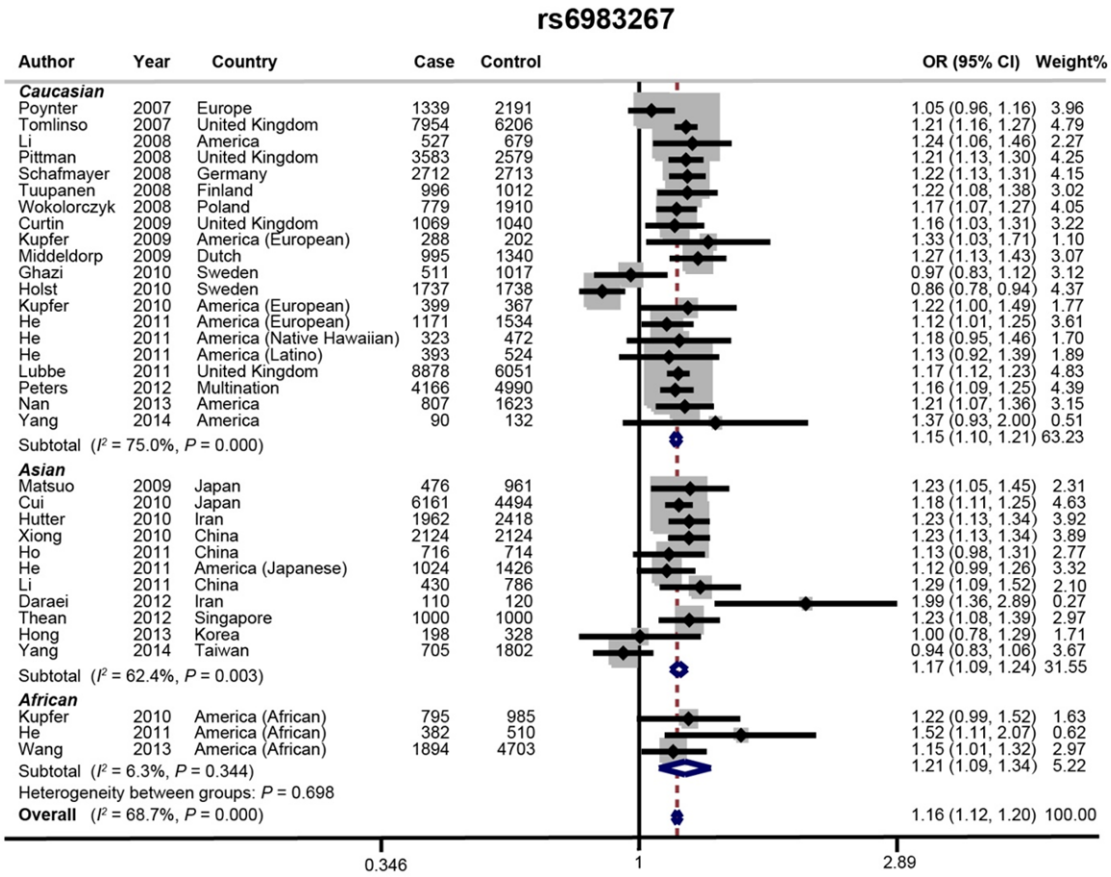
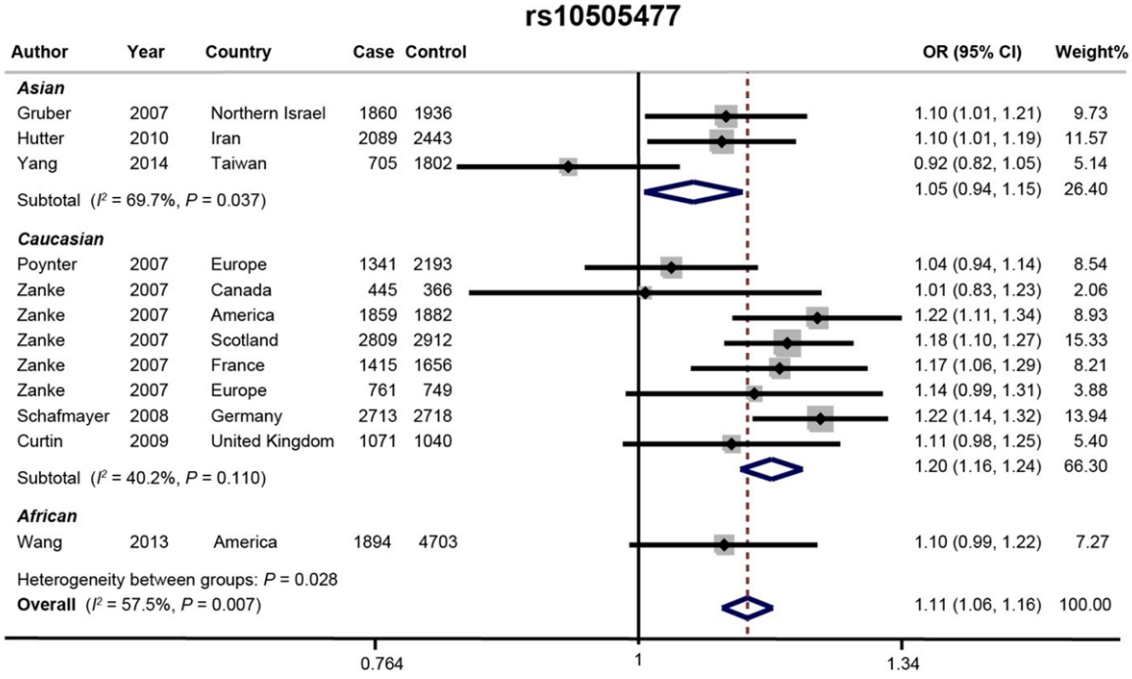
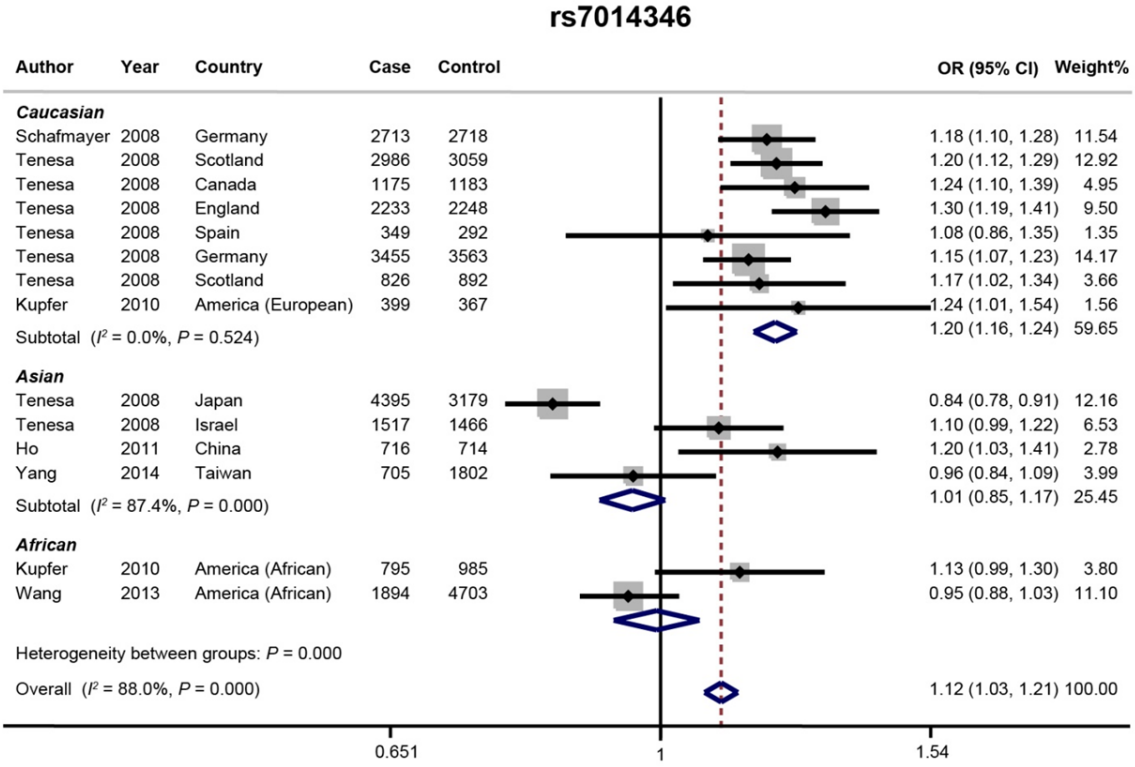


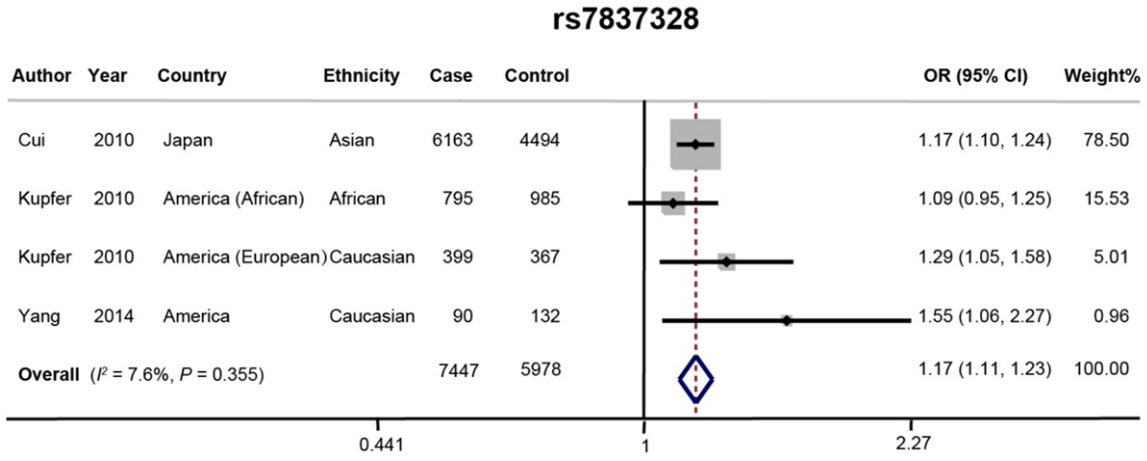
Supplementary Figure 1. Forest plot presenting the meta-analysis of the 34 association studies between rs6983267 mutation and CRC in allelic model. The horizontal lines represent 95% confidence intervals on estimating the outcome of the G allele vs. the T allele in the meta-analysis. Subgroup analysis were classified by ethnicity into Caucasians (20 studies), Asians (11 studies) and Africans (3 studies).



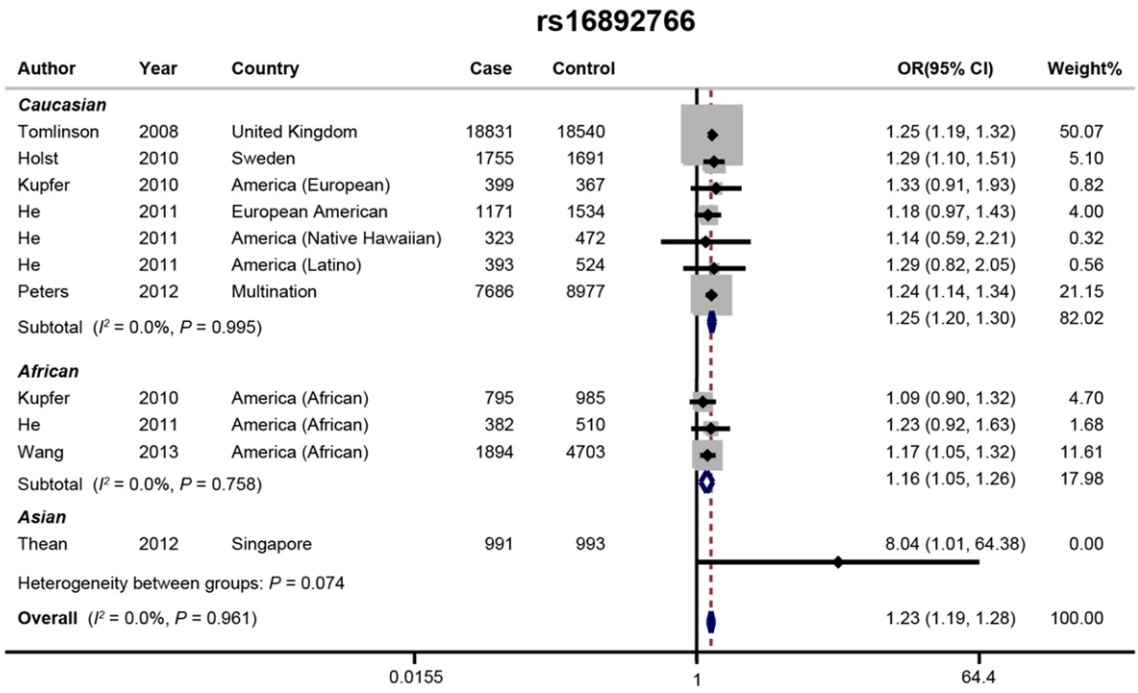
Supplementary Figure 2. Forest plot presenting the meta-analysis of the 12 association studies between rs10505477 mutation and CRC in allelic model. The horizontal lines represent 95% confidence intervals on estimating the outcome of the T allele vs. the C allele in the meta-analysis. Subgroup analyses were classified by ethnicity into Caucasians (8 studies) and Asians (3 studies).



Supplementary Figure 3. Forest plot presenting the meta-analysis of the 14 association studies between rs7014346 mutation and CRC in allelic model. The horizontal lines represent 95% confidence intervals on estimating the outcome of the A allele vs. the G allele in the meta-analysis. Subgroup analyses were classified by ethnicity into Caucasians (8 studies) and Asians (4 studies).

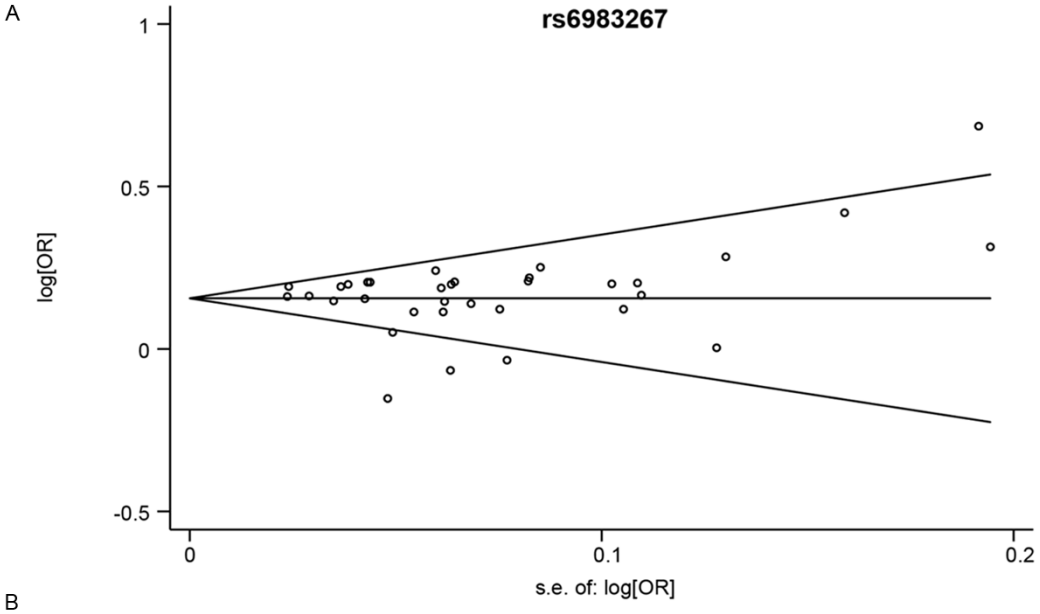


Supplementary Figure 4. Forest plot presenting the meta-analysis of the 4 association studies between rs7837328 mutation and CRC in allelic model. The horizontal lines represent 95% confidence intervals on estimating the outcome of the A allele vs. the G allele in the meta-analysis.



Supplementary Figure 5. Forest plot presenting the meta-analysis of the 11 association studies between rs16892766 mutation and CRC in allelic model. The horizontal lines represent 95% confidence intervals on estimating the outcome of the C allele vs. the A allele in the meta-analysis. Subgroup analyses were classified by ethnicity into Caucasians (7 studies) and Asians (3 studies).

A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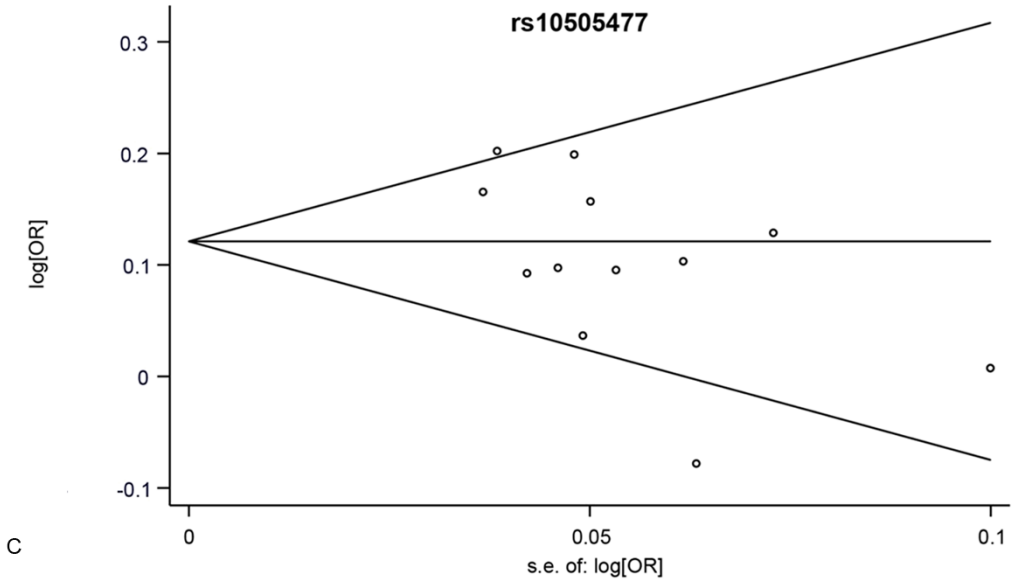
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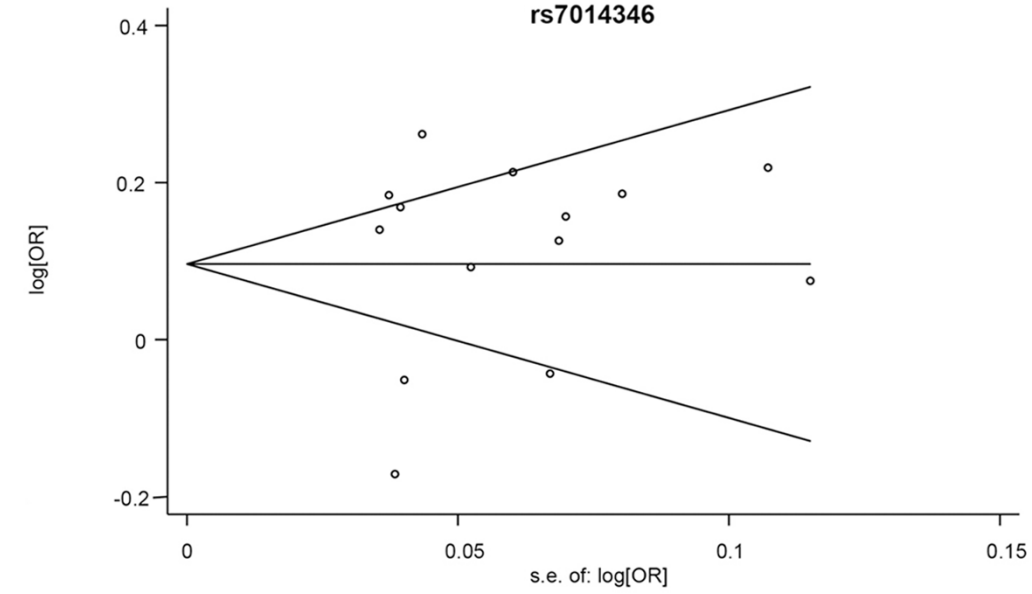
C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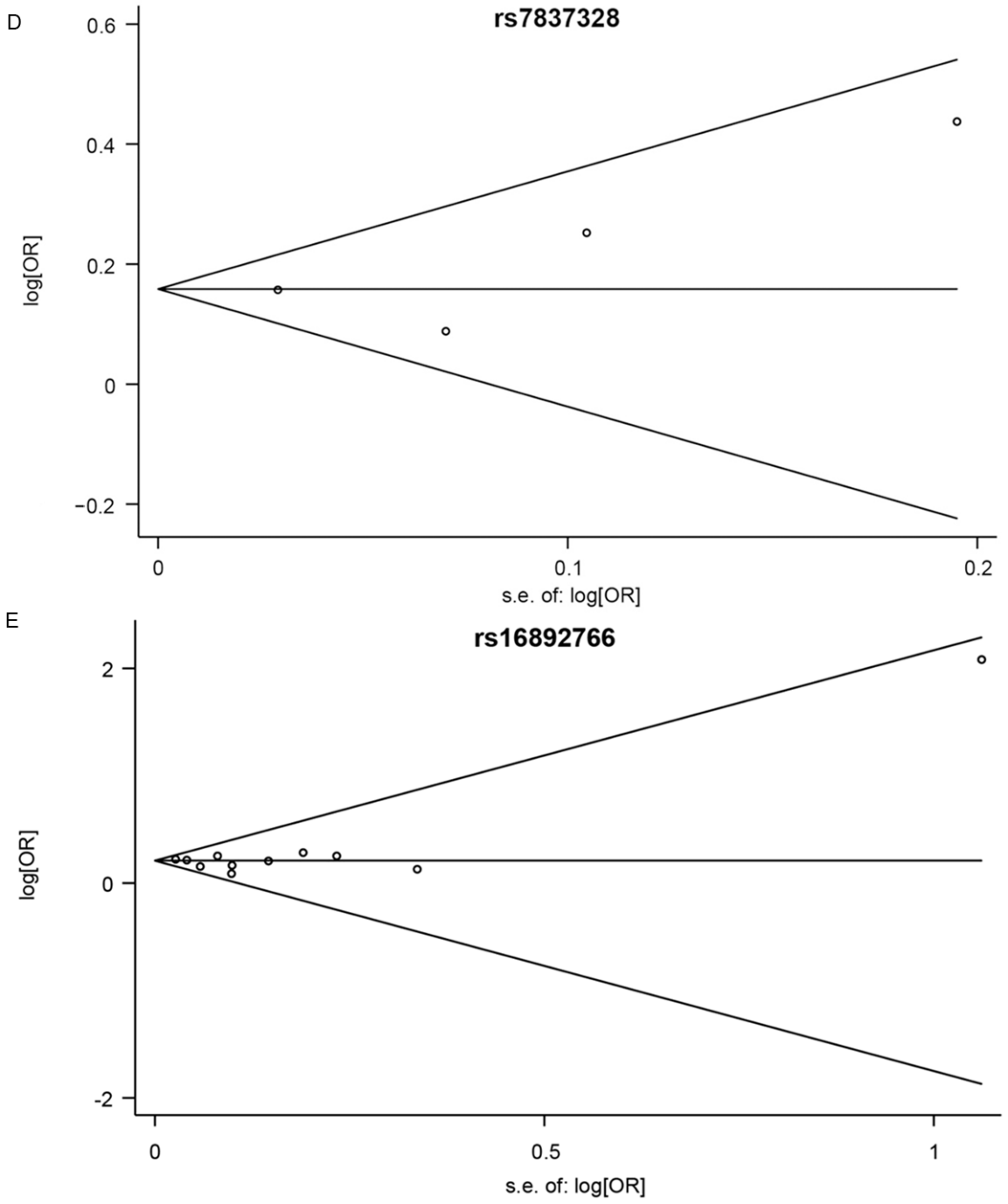
s.e. of: log[OR]



Supplementary Figure 6. Funnel plot for publication bias analysis of 5 genetic polymorphisms in CRC via allelic model. The funnel plot (A-E) are based on 34 studies for rs6983267, 12 studies for rs10505477, 14 studies for rs7014346, 4 studies for rs7837328 and 11 studies for rs16892766, respectively. The X-axis stands for standard error of the log[OR]s, and Y-axis is representative of the log[OR]s for each of the overall 75 studies. Egger's test and Begg's test were performed to assess the asymmetry of the funnel plots.