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A meta-analysis of *MDR1* polymorphisms rs1128503 and rs1045642 and susceptibility to hepatocellular carcinoma

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Abstract

Objective: A relationship between polymorphisms rs1128503 and rs1045642 in the multidrug resistance 1 gene (*MDR1*) and susceptibility to hepatocellular carcinoma (HCC) has been reported but is inconclusive. This study was performed to explore the significance of *MDR1* polymorphisms rs1128503 and rs1045642 in screening and diagnosis of HCC.

Methods: Studies of association analyses between *MDR1* gene polymorphisms rs1128503 and rs1045642 and HCC were selected from three foreign language databases (PubMed, Cochrane, and Embase) and three Chinese databases (Wanfang, China National Knowledge Infrastructure, and China Knowledge Network) and subjected to meta-analysis.

Results: We found no significant relationship between the rs1128503 polymorphism and susceptibility to HCC in 4 cohorts and no significant relationship between the rs1045642 polymorphism and susceptibility to HCC in 3 cohorts.

Conclusions: There was no relationship between polymorphisms rs1128503 or rs1045642 of the *MDR1* gene and susceptibility to HCC.

Keywords

Hepatocellular carcinoma (HCC), meta-analysis, multidrug resistance 1 (MDR1), polymorphism, susceptibility, P-glycoprotein

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Introduction

Hepatocellular carcinoma (HCC) has a high degree of malignancy and a poor prognosis. The highest worldwide incidences of HCC are in Asia and Africa; about 75% of HCCs occur in Asia.[1] Chronic hepatitis B and hepatitis C virus infections are major risk factors for HCC, but only 10% of individuals infected with these viruses eventually develop HCC.[2,3] Therefore, genetic and environmental factors may be involved in the occurrence and development of HCC.

The human multidrug resistance 1 gene (*MDR1*) is located on the long arm of chromosome 7 and contains 28 exons. The intron and exon junctions conform to the classical A/G rule and have a full length of 4.5 kb. An open reading frame encoding a 1280-amino acid polypeptide is glycosylated to form a 170-kDa membrane glycoprotein (P-glycoprotein), which plays a physiological role in protecting cells from toxin and metabolite damage.[4] Recent studies have found that *MDR1* polymorphism is not only an important genetic factor affecting the response of cancer patients to chemotherapy drugs but is also related to patients' susceptibility to disease and clinical manifestations.[5–7]

A relationship between polymorphism rs1128503 or rs1045642 of the *MDR1* gene and susceptibility to HCC has been reported but the conclusions are inconsistent. Therefore, we performed this study to objectively evaluate the relationship between HCC and *MDR1* polymorphisms rs1128503 and rs1045642 by meta-analysis. We aimed to explore the significance of *MDR1* polymorphisms rs1128503 and rs1045642 in HCC screening and diagnosis.

Material and methods

Inclusion and exclusion criteria

The inclusion criteria for this study were as follows: (1) a case control study; (2) clinical study to evaluate the relationship between rs1128503 and rs1045642 polymorphisms of *MDR1* and the risk of HCC; and (3) sufficient data, including the number of subjects and gene frequency.

The exclusion criteria for this study were as follows: (1) meeting summary, case report, or review article; (2) relationship between *MDR1* rs1128503 and rs1045642 polymorphisms and HCC risk was not detected; or (3) a study with repeatedly reported data or unclear data.

Literature retrieval

Three foreign language databases, PubMed, Cochrane, and Embase, and three Chinese databases, Wanfang, China National Knowledge Infrastructure (CNKI), and China Knowledge Network, were comprehensively searched by the method of retrospection. The retrieval date ended on August 23, 2018. We used the following combined keywords and MeSH terms: "ABCB1, C3435T, C1236T, rs1128503, rs1045642, MDR1, MDR-1, p-glycoprotein, P-gp" and "polymorphism, SNP, variation, variants, locus, mutation" and "liver cancer, liver tumor, liver tumour, liver malignance, liver carcinoma, liver neoplasm, hepatocellular carcinoma, HCC, intrahepatic cholangiocarcinoma, ICC, hepato-cholangio-carcinoma, HCC-CC, hepatoma".

Literature extraction and filtering and evaluation of data quality

Evaluation of the extracted publications was carried out by two independent researchers; if there was disagreement, a third researcher was included in the evaluation until consensus was reached. The retrieved publications were screened according to the preset inclusion and exclusion criteria, reviewing title, abstract, and full text systematically. Data extracted included first author, publication year,

country, number of subjects and gene distribution, type of adverse reactions, source of controls, ethnicity, and Hardy-Weinberg equilibrium (HWE) test. The quality of the included studies was assessed using the Newcastle-Ottawa scale (NOS).

Statistical analysis

Statistical analysis was performed using Stata 13.0 (StataCorp LLC, College Station, TX, USA) for data processing, and heterogeneity among the studies was analyzed using the Q test and *P*-value, and heterogeneity was evaluated by I^2. When $P \geq 0.1$ or $I^2 \leq 50\%$, there was no statistical heterogeneity among the studies and the fixed-effect model was used for combined analysis. When $P < 0.1$ or $I^2 > 50\%$, there was statistical heterogeneity among studies, and the combined analysis was performed using the random-effect model. The odds ratio (OR) value and 95% confidence interval (CI) were analyzed as the combined effect value with a test level $\alpha = 0.05$. Potential publication bias was analyzed by using Egger's test, and sensitivity analysis was performed if necessary.

Results

Literature search and screening results

According to the search strategy, 290 publications were initially retrieved. After 47 duplicates were excluded, 213 unrelated articles and 25 publications with insufficient data or non-*MDR1* polymorphisms and HCC risk were excluded by reading the title, abstract, and full text. A total of 5 qualified publications were screened and included in the meta-analysis[8–12] (Figure 1).

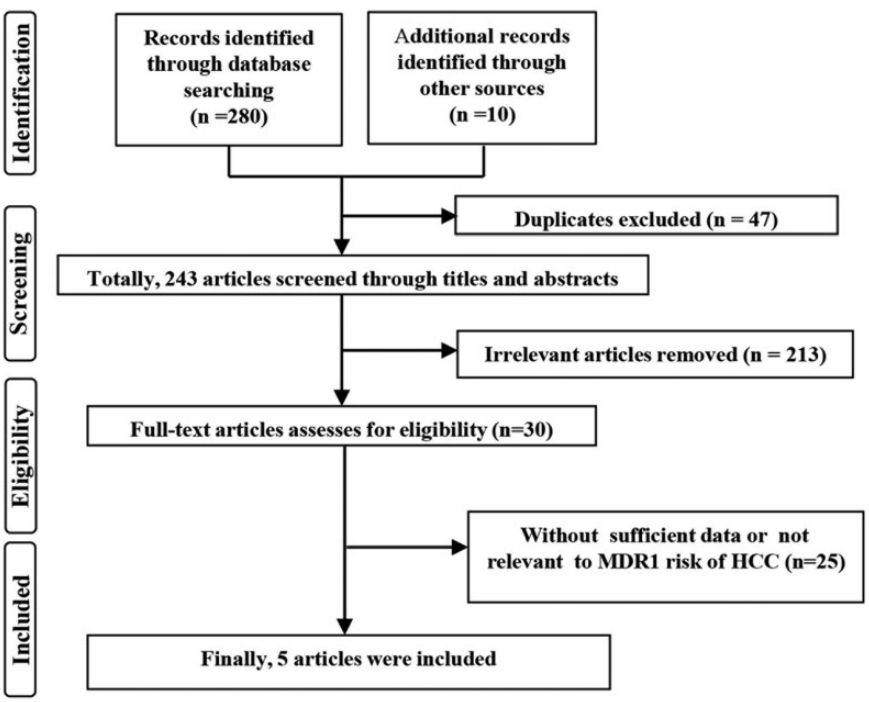

Figure 1. Flow diagram of study selection process.

Basic characteristics and quality evaluation of the included studies

After the studies included in the literature were integrated and differentiated, 7 studies were available from 5 publications for analysis in this study. Of these, 4 studies were on the rs1128503 polymorphism and HCC susceptibility, and 3 studies were on the rs1045642 locus. The quality of the studies was scored using the NOS, and the results ranged from 5 to 9 points, indicating that the included studies were of medium to high quality (Table 1, Figure 2).

Meta-analysis

The association between susceptibility to HCC and two *MDR1* polymorphism sites (rs1128503 and rs1045642) was analyzed in an allele model (C vs. T), a homozygous model (CC vs. TT), a heterozygous model (CT vs. TT), a recessive model (CC vs. CT + TT), and a dominant model (CC + CT vs. TT), respectively. Four studies were included and we found no significant relation between *MDR1* rs1128503 polymorphism and susceptibility to HCC under the five genetic models (Table 2, Figure 3). Meta-analysis of *MDR1* rs1045642 polymorphism and susceptibility to HCC from 3 studies also showed no significant relation (Table 2, Figure 4). Racial subgroup analysis showed a relation between *MDR1* rs1128503 polymorphism and HCC risk in Caucasians (CC vs. TT: OR = 0.64, 95% CI = 0.42–0.98, $P = 0.039$, $I^2 = 12.4\%$; CT vs. TT: OR = 0.64, 95% CI = 0.44–0.94, $P = 0.024$, $I^2 = 48.2\%$; CC + CT vs. TT: OR = 0.64, 95% CI = 0.45–0.93, $P = 0.017$, $I^2 = 47.4\%$). A subgroup analysis of control species showed a relation between *MDR1* rs1128503 polymorphism and HCC risk in patients with hepatitis virus infection and gallstones (CT vs. TT: OR = 0.51, 95% CI = 0.30–0.86, $P = 0.011$, $I^2 = 0.0\%$) (Table 3).

Table 1. Characteristics of studies on the associations between rs1128503 (T > C) and rs1045642 (T > C) polymorphisms in *MDR1* and hepatocellular cancer.

Author	Year	Country	Ethnicity	*MDR1* type	Source of controls	Control type	Cases	Controls	Cases			Controls			HWE	NOS
									WH	WM	MH	WH	WM	MH		
De	2017	Italy	Caucasian	rs1128503	HB	HBV/HCV	192	167	46	92	54	22	93	52	0.15	7
		Italy	Caucasian	rs1128503	PB	Healthy	192	192	46	92	54	39	95	58	1.00	7
Dong	2013	China	Asian	rs1045642	PB	Healthy	109	109	16	45	48	22	47	40	0.50	8
Jing	2013	China	Asian	rs1128503	PB	Healthy	109	109	36	54	19	39	48	22	0.60	9
Chen	2011	China	Asian	rs1128503	HB	Cholecyst	36	50	15	6	15	24	14	12	0.02	6
		China	Asian	rs1045642	HB	Cholecyst	36	50	8	10	18	11	12	27	<0.01	6
Fukuda	2010	Japan	Asian	rs1045642	PB	Healthy	58	61	13	29	16	8	39	14	0.08	6

HBV, hepatitis B virus; HCV, hepatitis C virus; HB, hospital-based; PB, population-based; WH, wild homozygous genotype; WM, wild/mutant heterozygous genotype; MH, mutant homozygous genotype; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale.

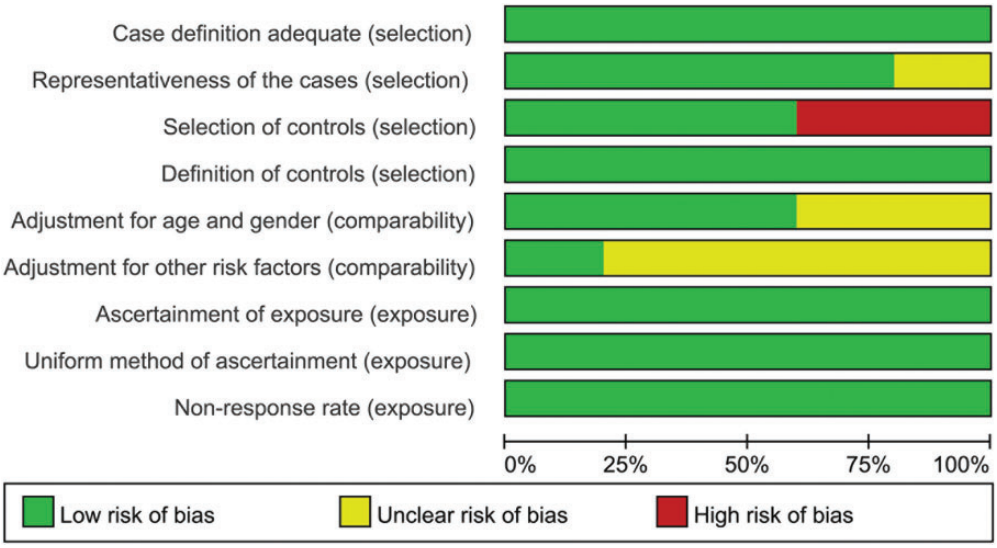

Figure 2. Quality assessment scale of eligible studies.

Table 2. OR and 95% CI for hepatocellular cancer and rs1128503 or rs1045642 polymorphism in *MDR1* under different genetic models.

Genetic models	n	OR (95% CI)	*P* (OR)	Analysis model	I^2 (%)	*P*(H)	*P* (Egger)	*P* (Begg)
rs1128503 T>C								
Allele (C vs. T)	4	0.91 (0.76, 1.08)	0.260	F (M-H)	42.8	0.155	0.082	0.308
Homozygous model (CC vs. TT)	4	0.80 (0.57, 1.12)	0.193	F (M-H)	46.2	0.134	0.225	0.308
Heterozygous model (CT vs. TT)	4	0.77 (0.56, 1.04)	0.093	F (M-H)	40.5	0.169	0.914	1.000
Recessive model (CC vs. CT+TT)	4	0.95 (0.73, 1.25)	0.729	F (M-H)	19.1	0.295	0.230	0.734
Dominant model (CC+CT vs. TT)	4	0.81 (0.61, 1.07)	0.137	F (M-H)	48.5	0.120	0.592	0.734
rs1045642 T>C								
Allele (C vs. T)	3	1.10 (0.83, 1.45)	0.505	F (M-H)	0	0.435	0.293	1.000
Homozygous model (CC vs. TT)	3	1.16 (0.67, 2.01)	0.587	F (M-H)	0	0.421	0.100	0.296
Heterozygous model (CT vs. TT)	3	0.93 (0.55, 1.60)	0.800	F (M-H)	29.2	0.243	0.755	1.000
Recessive model (CC vs. CT+TT)	3	1.21 (0.81, 1.80)	0.354	F (M-H)	0	0.660	0.481	0.296
Dominant model (CC+CT vs. TT)	3	1.01 (0.62, 1.65)	0.962	F (M-H)	30.3	0.238	0.450	1.000

OR, odds ratio; CI, confidence interval; *P*(OR), probability for odds ratio; *P*(H), *P* for heterogeneity; n, number of the included studies; F, fixed-effect model; M-H, Mantel-Haenszel method.

Publication bias and sensitivity analysis

On the basis of the results of Egger's test, there was no publication bias in this study (Table 2). To evaluate the stability of this meta-analysis, we excluded the included studies one by one and compared the differences between the effect values before and after each elimination. This analysis showed that the results were stable.

Discussion

The *MDR1* rs1128503 and rs1045642 polymorphisms are synonymous mutations in

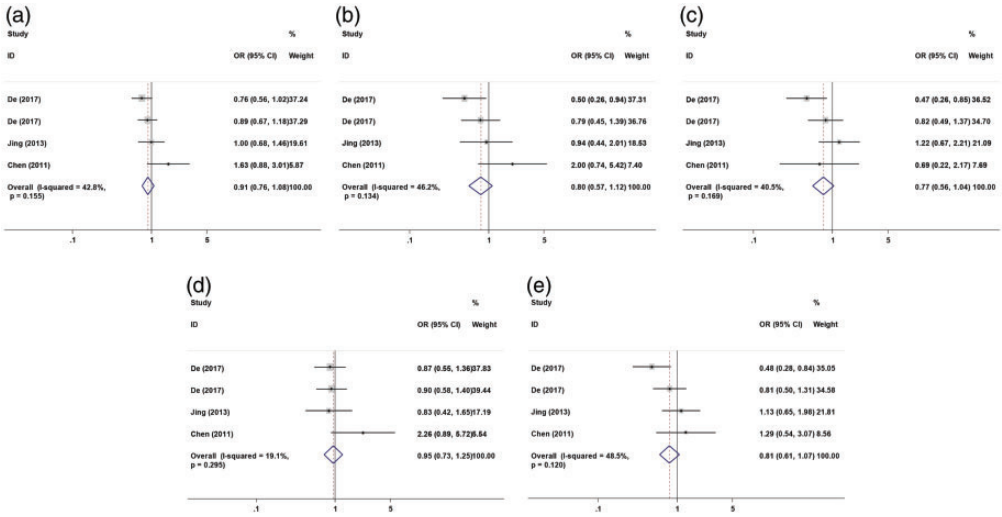

Figure 3. Forest plot of hepatocellular cancer risk associated with rs1128503 (C>T) models. (a) allele model; (b) homozygous model; (c) heterozygous model; (d) recessive model; (e) dominant model. The horizontal line indicates the lower and upper limits of the 95% CI; the square indicates the OR, with the size of the square indicating the weight of the study and the dotted red line indicating the combined OR value. The diamond represents the combined effect size, and the larger the diamond, the larger the confidence interval. A cross between the diamond and the ineffective line indicates no statistical correlation between the factors studied and the outcome; if the diamond falls on the left side of the invalid vertical line, it indicates a protective factor; if the diamond falls on the right side of the line, it indicates a risk factor. OR, odds ratio; CI, confidence interval.

exon 26 and exon 12,[13] respectively, and the CC genotype in the mutation site is considered the wild type.[14] The wild-type P-glycoprotein not only pumps drugs out of cells but, synergistically with immune function, also inhibits tumorigenesis and development.[15] Some studies have found that P-glycoprotein can delay the apoptosis cascade of tumor cells by inhibiting caspase.[16] Five relevant studies were included in this meta-analysis, and the results showed that the rs1128503 polymorphism may be related to HCC risk in Caucasian individuals and in patients with hepatitis virus infection or gallstones.

A previous meta-analysis showed that mutations in the *MDR1* gene are associated with susceptibility to HCC and are risk factors for HCC.[17] The different results between that meta-analysis and the current meta-analysis may be explained by two factors. First, in the early study, the association analysis between *MDR1* polymorphisms and susceptibility to HCC was based on pooled results from 11 mutation sites in *MDR1*. In the current meta-analysis, the relation analysis between *MDR1* polymorphism and susceptibility to HCC was conducted for only two polymorphic sites. Second, the subjects included in the previous study were Asian (Japanese and Chinese), whereas those in the current analysis were Asian (Japanese and Chinese) and Caucasian (Italian). Compared with the previous study, a more appropriate detailed analysis of the relation between *MDR1* mutation and hepatocarcinogenesis, involving different populations, was performed in this meta-analysis, and the results were shown to be reliable.

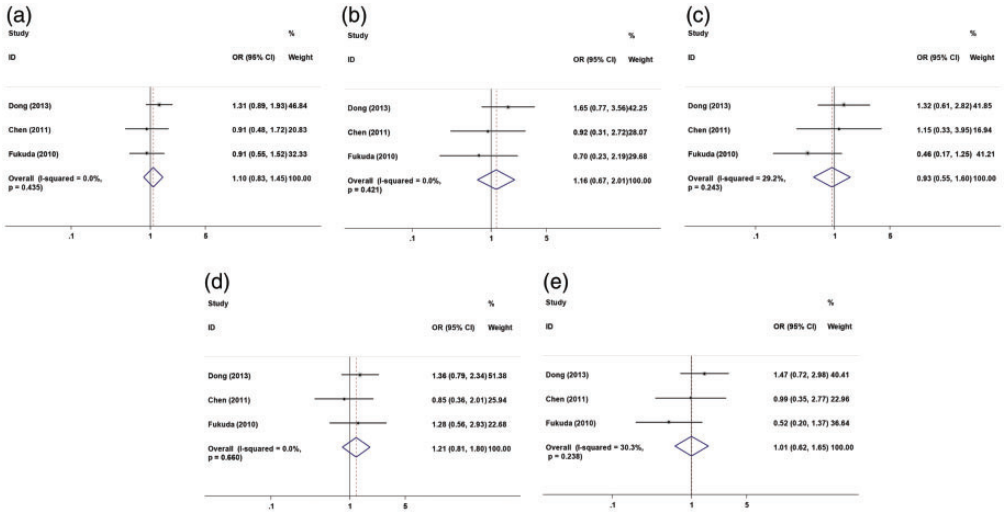

Figure 4. Forest plot of hepatocellular cancer risk associated with rs1045642 (C>T) models. (a) allele model; (b) homozygous model; (c) heterozygous model; (d) recessive model; (e) dominant model. The horizontal line indicates the lower and upper limits of the 95% CI; the square indicates the OR, with the size of the square indicating the weight of the study and the dotted red line indicating the combined OR value. The diamond represents the combined effect size, and the larger the diamond, the larger the confidence interval. A cross between the diamond and the ineffective line indicates no statistical correlation between the factors studied and the outcome; if the diamond falls on the left side of the invalid vertical line, it indicates a protective factor; if the diamond falls on the right side of the line, it indicates a risk factor. OR, odds ratio; CI, confidence interval.

The occurrence of HCC is a complex pathological process, involving multiple genes and environmental factors.[18–20] Hepatitis virus infection,[21,22] smoking,[23,24] drinking,[25,26] and genetic factors are non-negligible causes of HCC. These risk factors may cause chronic inflammation and accumulation of toxic products in the liver, leading to HCC.[27,28] The protein encoded by *MDR1* is involved in the elimination of endogenous and exogenous harmful substances.[29] Polymorphisms in *MDR1* will alter the structure or expression of the encoded protein, thereby affecting its efflux effect on carcinogens and the normal physiological functions of hepatocytes.[30] However, abnormal protein expression of *MDR1* also affects the sensitivity of cancer cells to drugs, thereby affecting the development of HCC.[31] In this meta-analysis, we analyzed the relationship between two mutations of *MDR1* and susceptibility to HCC without considering the influence of other factors. However, the number of subjects included in the current meta-analysis was limited, and the control group was included with different standards. Therefore, further stringent analyses with larger sample sizes are necessary to confirm the results of this meta-analysis.

In conclusion, this meta-analysis showed that *MDR1* polymorphism rs1128503 may be related to HCC risk in Caucasians and in patients with hepatitis viral infection or gallstones. A better understanding of the effect of *MDR1* gene polymorphisms on HCC risk by analyzing the relation between rs1128503 or rs1045642 and HCC might improve our understanding of the role of genetic factors in HCC risk.

Table 3. Stratified analyses of relation between hepatocellular cancer and rs1128503 or rs1045642 polymorphism in *MDR1* under different genetic models.

		Allele (C vs. T)			Homozygous model (CC vs. TT)			Heterozygous model (CT vs. TT)			Recessive model (CC vs. CT + TT)			Dominant model (CC + CT vs. TT)		
Subgroup	N	OR (95% CI)	*P* (OR)	I^2 (%)	OR (95% CI)	*P* (OR)	I^2 (%)	OR (95% CI)	*P* (OR)	I^2 (%)	OR (95% CI)	*P* (OR)	I^2 (%)	OR (95% CI)	*P* (OR)	I^2 (%)
rs1128503 T>C																
Ethnicity																
Asian	2	1.15 (0.83, 1.58)	0.409	43.4	1.24 (0.68, 2.26)	0.484	29.0	1.06 (0.64, 1.82)	0.784	0.0	1.18 (0.69, 2.03)	0.543	65.3	1.18 (0.74, 1.88)	0.499	0.0
Caucasian	2	0.82 (0.67, 1.01)	0.063	0.0	0.64 (0.42, 0.98)	0.039	12.4	0.64 (0.44, 0.94)	0.024	48.2	0.89 (0.65, 1.21)	0.449	0.0	0.64 (0.45, 0.93)	0.017	47.4
Control type																
Healthy	2	0.93 (0.74, 1.17)	0.524	0.0	0.84 (0.53, 1.32)	0.447	0.0	0.97 (0.66,1.43)	0.883	0.0	0.88 (0.61, 1.28)	0.510	0.0	0.93 (0.65, 1.34)	0.710	0.0
Others	2	0.88 (0.67, 1.14)	0.324	79.6	0.75 (0.44, 1.26)	0.269	81.3	0.51 (0.30, 0.86)	0.011	0.0	1.04 (0.70, 1.57)	0.835	69.9	0.64 (0.40, 1.01)	0.058	71.7
rs1045642 T>C																
Controls type																
Healthy	2	1.15 (0.84, 1.56)	0.379	20.2	1.26 (0.67, 2.36)	0.473	32.7	0.89 (0.49, 1.61)	0.702	63.0	1.33 (0.85, 2.10)	0.214	0.0	1.02 (0.58, 1.78)	0.946	65.1
others	1	0.91 (0.48, 1.72)	0.774	NU	0.92 (0.31, 2.72)	0.876	NU	1.15 (0.33, 3.95)	0.829	NU	0.85 (0.36, 2.01)	0.714	NU	0.99 (0.35, 2.77)	0.980	NA

N, number of comparisons; OR, odds ratio; CI, confidence interval; NU, null, NA, not available.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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