Research Article

The effect of *LTA* gene polymorphisms on cancer risk: an updated systematic review and meta-analysis

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**Purpose:** To provide a comprehensive account of the association of five Lymphotoxin-α (*LTA*) gene polymorphisms (rs1041981, rs2229094, rs2239704, rs746868, rs909253) with susceptibility to cancer.

**Methods:** A literature search for eligible candidate gene studies published before 28 February 2020 was conducted in the PubMed, Medline, Google Scholar and Web of Science. The following combinations of main keywords were used: (*LTA* OR Lymphotoxin alpha OR TNF-β OR tumor necrosis factor-beta) AND (polymorphism OR mutation OR variation OR SNP OR genotype) AND (cancer OR tumor OR neoplasm OR malignancy OR carcinoma OR adenocarcinoma). Potential sources of heterogeneity were sought out via subgroup and sensitivity analysis, and publication bias were estimated.

**Results:** Overall, a total of 24 articles with 24577 cases and 33351 controls for five polymorphisms of *LTA* gene were enrolled. We identified that rs2239704 was associated with a reduced risk of cancer. While for other polymorphisms, the results showed no significant association with cancer risk. In the stratified analysis of rs1041981, we found that Asians might have less susceptibility to cancer. At the same time, we found that rs2239704 was negatively correlated with non-Hodgkin lymphoma (NHL). While, for rs909253, an increased risk of cancer for Caucasians and HCC susceptibility were uncovered in the stratified analysis of by ethnicity and cancer type.

**Conclusion:** *LTA* rs2239704 polymorphism is inversely associated with the risk of cancer. *LTA* rs1041981 polymorphism is negatively associated with cancer risk in Asia. While, *LTA* rs909253 polymorphism is a risk factor for HCC in Caucasian population.

**Introduction**

Increasing studies have demonstrated that a number of proinflammatory cytokines could be associated with the development of cancer [1,2]. Lymphotoxin-α (*LTA*) is the predominant member of the tumor necrosis factor (TNF) ligand family, which responds to immune and inflammatory reaction and plays an important role in the pathogenesis of cancer [3,4]. The human *LTA* gene is located on the short arm of chromosome 6 (6p21.3) [5]. The presence of single nucleic polymorphism (SNP) may affect cytokine expression level, which might be an important mediator of cancer [6,7]. SNP rs1041981 is a mutation of *LTA* gene at the 804 (C/A) position of exon 3 in codon 26, causing the amino acid threonine to be asparagine, which may be related to the transcriptional regulation of *LTA*, then activate the lymphocytes and induce apoptosis [8]. While, SNP rs909253 is a mutation of *LTA* gene at 252 (A/G) position in intron 1, which may lead to increase in the transcriptional activities of *LTA* [1]. In addition, SNP rs2239704, rs746868 and rs2229094 are associated with the *LTA* expression, which may affect subsequent inflammatory responses and immunomodulatory diseases, including cancers [9,10].

There are ample evidences that have demonstrated the association between *LTA* polymorphisms and cancer [11-34]. However, these results are inconsistent and even contradictory, which might be due to the heterogeneity within cancer types, ethnicities, source of control, Hardy–Weinberg equilibrium (HWE),...
small sample sizes and so on. Huang et al. reported a meta-analysis about this topic, and they found that the \textit{LTA} rs1041981, rs2239704 and rs2229094 polymorphisms were associated with the increased risk of cancers \cite{35}. However, based on the current studies, we found that more studies were negatively correlated with \textit{LTA} polymorphisms and cancer \cite{11,13–15,18-24,27,28,31,32}. Therefore, we conducted the current updated systematic review and meta-analysis to accurately determine the association between genetic variation of \textit{LTA} gene and cancer susceptibility.

\textbf{Materials and methods}

\textbf{Literature search}

We conducted a systematic literature search on PubMed, Medline, Embase, Google Scholar and Web of Science to retrieve all eligible publications on the association between \textit{LTA} polymorphisms and the risk of cancer (up to 28 February 2020) with the following keywords: (\textit{LTA} OR Lymphotoxin alpha OR TNF-\textit{\beta} OR tumor necrosis factor-beta) AND (polymorphism OR mutation OR variation OR SNP OR genotype) AND (cancer OR tumor OR neoplasm OR malignancy OR carcinoma OR adenocarcinoma). The language of enrolled studies was restricted to English. After carefully screening, five polymorphisms were left for further investigation.

\textbf{Inclusion and exclusion criteria}

Articles enrolled in our meta-analysis satisfied the following inclusion criteria: (1) case–control studies that evaluated the association between \textit{LTA} polymorphisms and cancer risk; (2) publications focusing on population genetic polymorphisms; (3) articles with sufficient genotype data to assess odds ratios (ORs) and the corresponding 95\% CIs; (4) blood sample only for SNP analysis; (5) the control subjects satisfied HWE. The major exclusion criteria were: (1) case-only studies, case reports or reviews; (2) studies without raw data for the \textit{LTA} genotype.

\textbf{Data extraction}

Two investigators (Jingdong Li and Yaxuan Wang) independently extracted the data from each study. All the case–control studies satisfied the inclusion criteria and consensus for any controversy was achieved. The data from the eligible articles comprise the first author’s name, year of publication, ethnicity, source of control, cancer type and numbers of cases and controls in \textit{LTA} genotypes. Ethnicity was categorized as ‘Asian’, ‘Caucasian’, and ‘Mixed’.

\textbf{Statistical analysis}

The risk between the \textit{LTA} polymorphisms and cancer was evaluated using summary ORs and the corresponding 95\% CIs in allelic (\textit{B} vs. \textit{A}), dominant (\textit{BA + BB} vs. \textit{AA}), and recessive (\textit{BB} vs. \textit{BA + AA}) models (\textit{A}: wild allele; \textit{B}: mutated allele). The Cochrane’s Q-statistic test was used to assess the heterogeneity between studies, and the inconsistency was quantified with the $I^2$ statistic. The substantial heterogeneity was considered significant when $I^2 > 50\%$ or $PQ \leq 0.1$, then, a random-effects model was used; otherwise, the fixed-effects model was applied. Subgroup meta-analysis were performed by cancer type, ethnicity, genotyping, HWE and the source of control. We also conducted sensitivity analysis to assess stability of the results by omitting one study each time to exclude studies. HWE was estimated by the asymptotic test, and deviation was considered when $P < 0.05$. The potential publication bias of the eligible studies was evaluated by Begg’s and Egger’s regression test quantitatively. Trial sequential analysis (TSA) was performed as described by Xie et al. \cite{36}. The required information size was calculated after adopting a level of significance of 5\% for type I error and of 30\% for type II error. The data was analyzed using the Stata 14.0 software (version 14.0; State Corporation, College Station, Texas, U.S.A.). A two-tailed $P < 0.05$ was considered statistically significant.

\textbf{Results}

\textbf{Main characteristics of the enrolled studies}

The study selection processes were presented in Figure 1. For polymorphisms of \textit{LTA} gene (rs1041981, rs2229094, rs2239704, rs746868, rs909253), a total of 24 articles (including 43 case–control studies) with 24577 cases and 33351 controls met the inclusion criteria \cite{11–34}. Sixteen of these studies were performed in Asians, 17 studies were performed in Caucasians, 10 studies in Africans and the others were in mixed ethnic groups (including at least one race). Controls of 30 studies were population-based controls and 13 studies were hospital-based controls. All studies were in compliance with HWE except for two studies \cite{30,32}. Table 1 shows the characteristics of all the eligible studies and genotype frequency distributions of the five \textit{LTA} polymorphisms included in our meta-analysis. Newcastle–Ottawa scale (NOS) was used to evaluate the quality of the enrolled studies, as shown in Table 2.
Quantitative synthesis

rs1041981
The pooled results based on six included studies [11–16] (including 6427 cases and 9714 controls) indicated that no significant association between rs1041981 polymorphism and cancer risk was found. However, in the stratification analysis by ethnicity, we observed that Asian group was significantly related to a reduced risk of cancer in allelic contrast (B vs A: OR = 0.79, 95% confidence interval (CI) = 0.64–0.97, \( P = 0.027 \), Figure 2) and dominant model (BB+AB vs AA: OR = 0.67, 95% CI = 0.52–0.87, \( P = 0.002 \)). Moreover, when the subgroup analysis was performed based on source of controls, hospital-based control group was significantly related to a decreased risk of cancer in allelic contrast (B vs A: OR = 0.69, 95% CI = 0.55–0.87, \( P = 0.002 \)) and dominant model (BB+AB vs AA: OR = 0.58, 95% CI = 0.42–0.78, \( P = 0.000 \)) (Table 3).

rs2229094
The pooled results based on four included studies [11,17–19] (including 6227 cases and 8562 controls) indicated that no significant association between rs2229094 polymorphism and cancer risk was found. Further subgroup analysis by ethnicity also indicated that no significant result was uncovered (Supplementary Table S1).

rs2239704
The pooled results based on eight included studies [18–24] (including 3550 cases and 3962 controls) suggested that rs2239704 reduced the risk of cancer in allelic contrast (B vs A: OR = 0.90, 95% CI = 0.85–0.97, \( P = 0.003 \)), dominant
Table 1 Characteristics of the enrolled studies

| SNP     | First author | Year | Ethnicity | Source of control | Cancer type | Case | Control | HWE |
|---------|--------------|------|-----------|-------------------|-------------|------|---------|-----|
| rs1041981 | Abbas        | 2010 | Caucasian | PB, OC            | AA          | 1498  | 1317  | 332 | 2481  | 2399  | 607 | Y     |
|         | Castro       | 2009 | Caucasian | PB, OC            | AA          | 154   | 456   | 341 | 337   | 813   | 557 | Y     |
|         | Lee          | 2004 | Asian     | PB, GC            | AA          | 109   | 156   | 63  | 74    | 132   | 47  | Y     |
|         | Niwa         | 2005 | Asian     | HB, OC            | BB          | 60    | 59    | 12  | 107   | 165   | 48  | Y     |
|         | Niwa         | 2007 | Asian     | HB, OC            | BB          | 51    | 43    | 16  | 71    | 114   | 35  | Y     |
|         | Sainz        | 2012 | Caucasian | PB, OC            | BB          | 833   | 729   | 198 | 794   | 760   | 173 | Y     |
| rs2229094 | Abbas        | 2010 | Caucasian | PB, OC            | AA          | 1686  | 1199  | 251 | 2965  | 2153  | 359 | Y     |
|         | Madeleine    | 2011 | Mixed     | PB, OC            | AA          | 444   | 329   | 75  | 475   | 334   | 57  | Y     |
|         | Mahajan      | 2008 | Caucasian | PB, GC            | BB          | 206   | 74    | 21  | 247   | 150   | 18  | Y     |
|         | Wang         | 2009 | Mixed     | PB, NHL           | BB          | 1043  | 751   | 148 | 978   | 702   | 124 | Y     |
| rs2239704 | Cerhan       | 2008 | Mixed     | HB, NHL           | BB          | 169   | 217   | 55  | 170   | 225   | 79  | Y     |
|         | Ennas        | 2008 | Caucasian | PB, OC            | AA          | 14    | 17    | 7   | 36    | 53    | 23  | Y     |
|         | Gu           | 2014 | Asian     | PB, NHL           | BB          | 33    | 50    | 10  | 82    | 96    | 25  | Y     |
|         | Gu           | 2014 | Asian     | PB, NHL           | BB          | 30    | 21    | 13  | 82    | 100   | 47  | Y     |
|         | Lan          | 2006 | Mixed     | PB, NHL           | BB          | 165   | 189   | 63  | 186   | 226   | 87  | Y     |
|         | Mahajan      | 2008 | Caucasian | PB, GC            | BB          | 85    | 138   | 76  | 105   | 223   | 85  | Y     |
|         | Purdue       | 2007 | Caucasian | PB, NHL           | BB          | 202   | 240   | 64  | 162   | 229   | 72  | Y     |
| rs746888  | Crusius      | 2008 | Caucasian | PB, GC            | BB          | 151   | 205   | 72  | 398   | 545   | 181 | Y     |
|         | Garcia-Gonzalez | 2007 | Caucasian | PB, GC            | BB          | 135   | 194   | 75  | 142   | 191   | 71  | Y     |
|         | Gu           | 2014 | Asian     | PB, NHL           | BB          | 85    | 107   | 27  | 76    | 102   | 27  | Y     |
|         | Mahajan      | 2008 | Caucasian | PB, GC            | BB          | 83    | 143   | 74  | 108   | 220   | 84  | Y     |
| rs809253  | Cerhan       | 2008 | Mixed     | HB, NHL           | BB          | 179   | 208   | 53  | 207   | 217   | 51  | Y     |
|         | Cheng        | 2015 | Asian     | HB, NHL           | BB          | 45    | 71    | 9   | 95    | 149   | 56  | Y     |
|         | Crusius      | 2008 | Caucasian | PB, GC            | BB          | 168   | 218   | 38  | 533   | 472   | 121 | Y     |
|         | Ennas        | 2008 | Caucasian | PB, OC            | BB          | 29    | 10    | 1   | 85    | 24    | 4   | Y     |
|         | Garcia-Gonzalez  | 2007 | Caucasian | PB, GC            | BB          | 238   | 127   | 39  | 222   | 154   | 28  | Y     |
|         | Gu           | 2014 | Asian     | PB, NHL           | BB          | 42    | 39    | 11  | 69    | 98    | 36  | Y     |
|         | Gu           | 2014 | Asian     | PB, NHL           | BB          | 27    | 29    | 8   | 104   | 97    | 28  | Y     |
|         | Gunter       | 2006 | Mixed     | HB, OC            | BB          | 90    | 101   | 35  | 88    | 92    | 29  | Y     |
|         | Jeng         | 2014 | Asian     | PB, HCC           | BB          | 46    | 65    | 39  | 98    | 42    | 10  | Y     |
|         | Lankhanpal   | 2016 | Asian     | HB, OC            | BB          | 14    | 59    | 47  | 39    | 24    | 37  | N     |
|         | Lan          | 2006 | Mixed     | PB, NHL           | BB          | 240   | 218   | 59  | 274   | 254   | 65  | Y     |
|         | Lee          | 2004 | Asian     | PB, GC            | BB          | 112   | 152   | 64  | 77    | 131   | 46  | Y     |
|         | Liu          | 2013 | Asian     | PB, NHL           | BB          | 111   | 151   | 29  | 95    | 149   | 56  | Y     |
|         | Mahajan      | 2008 | Caucasian | PB, GC            | BB          | 137   | 135   | 29  | 201   | 174   | 38  | Y     |
|         | Mou          | 2015 | Asian     | HB, GC            | BB          | 105   | 75    | 14  | 57    | 48    | 28  | N     |
|         | Niwa         | 2005 | Asian     | HB, OC            | BB          | 60    | 59    | 12  | 107   | 165   | 48  | Y     |
|         | Niwa         | 2007 | Asian     | HB, OC            | BB          | 51    | 43    | 16  | 71    | 114   | 35  | Y     |
|         | Purdue       | 2007 | Caucasian | HB, NHL           | BB          | 205   | 265   | 68  | 198   | 233   | 63  | Y     |
|         | Tsai         | 2017 | Asian     | PB, HCC           | BB          | 45    | 66    | 39  | 98    | 42    | 10  | Y     |
|         | Wang         | 2009 | Mixed     | PB, NHL           | BB          | 778   | 857   | 262 | 788   | 766   | 219 | Y     |
|         | Yri          | 2013 | Caucasian | PB, NHL           | BB          | 157   | 247   | 76  | 394   | 479   | 136 | Y     |

Abbreviations: GC, gastric cancer; HB, hospital-based; HCC, hepatocellular carcinoma; N, no; NHL, non-Hodgkin lymphoma; OC, other cancer; PB, population-based; Y, yes.

model (BB+AB vs AA: OR = 0.88, 95% CI = 0.80–0.96, P = 0.006) and recessive model (BB vs AA+AB: OR = 0.88, 95% CI = 0.77–0.99, P = 0.040). Furthermore, in the stratification analysis by cancer type, we observed that rs2239704 reduced the risk of NHL in allelic contrast (B vs A: OR = 0.89, 95% CI = 0.83–0.96, P = 0.001, Figure 3), dominant model (BB+AB vs AA: OR = 0.88, 95% CI = 0.80–0.97, P = 0.011) and recessive model (BB vs AA+AB: OR = 0.83, 95% CI = 0.72–0.95, P = 0.006). Moreover, when the subgroup analysis was performed based on ethnicity, source
Table 2 Methodological quality of the enrolled studies according to the NOS

| SNP    | First author        | Adequacy definition | Representativeness of the cases | Control definition | Control cases/controls | Comparability | Exposure ascertainment | Same method ascertainment | Non-response rate |
|--------|---------------------|---------------------|---------------------------------|-------------------|------------------------|---------------|------------------------|--------------------------|------------------|
| rs1041981 | Abbas et al.       | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Castro et al.       | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Lee et al.          | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Niwa et al.         | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Niwa et al.         | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Sainz et al.        | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
| rs2229094 | Abbas et al.       | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Madeleine et al.    | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Mahajan et al.      | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Wang et al.         | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
| rs2239704 | Cerhan et al.      | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |
|         | Ennas et al.        | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Gu et al.           | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Gu et al.           | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Lan et al.          | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Mahajan et al.      | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Purdue et al.       | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Wang et al.         | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
| rs746868  | Crusius et al.     | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |
|         | Garcia-Gonzalez et al. | * | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Gunter et al.       | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |
|         | Mahajan et al.      | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
| rs909253  | Cerhan et al.      | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |
|         | Cheng et al.        | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Crusius et al.      | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |
|         | Ennas et al.        | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Garcia-Gonzalez et al. | * | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Gu et al.           | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |
|         | Gu et al.           | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Gunter et al.       | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Jeng et al.         | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Lakhanpal et al.    | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |
|         | Lan et al.          | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Lee et al.          | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Liu et al.          | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Mahajan et al.      | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Mou et al.          | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |
|         | Niwa et al.         | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Niwa et al.         | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Purdue et al.       | *                   | *                               | *                 | NA                     | *             | *                      | *                        | *                |
|         | Tsai et al.         | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Wang et al.         | *                   | *                               | *                 | *                      | *             | *                      | *                        | *                |
|         | Yri et al.          | *                   | *                               | NA                | *                      | *             | *                      | *                        | *                |

A study can be awarded a maximum of one star (*) for each numbered item within the Selection and Exposure categories. A maximum of two stars (**) can be given for Comparability. Abbreviations: NA, not applicable.

of control and genotyping, we found mixed ethnicity was significantly related to a reduced risk of cancer in allelic contrast (B vs A: OR = 0.89, 95% CI = 0.83–0.97, P = 0.006), dominant model (BB+AB vs AA: OR = 0.89, 95% CI = 0.79–1.00, P = 0.042) and recessive model (BB vs AA+AB: OR = 0.82, 95% CI = 0.71–0.96, P = 0.013) (Table 4).
Table 3 Meta-analysis of rs1041981

| Variables          | n  | Allelic contrast | Dominant model | Recessive model |
|--------------------|----|------------------|----------------|----------------|
|                    |    |                  | P, OR (99% CI) | P (Q test), I^2 |
|                    |    |                  | P, OR (99% CI) | P (Q test), I^2 |
|                    |    |                  | P, OR (99% CI) | P (Q test), I^2 |
| Total              | 6  | 0.307, 0.94 (0.84, 1.06) | 0.002, 73.1% | 0.002, 73.1% | 0.002, 73.1% |
|                    |    | 0.002, 73.1% | 0.163, 0.89 (0.75, 0.95) | 0.002, 73.1% | 0.607, 1.03 (0.91, 1.17) | 0.214, 29.4% |
| Ethnicity          |    | 0.002, 73.1% | 0.002, 73.1% | 0.607, 1.03 (0.91, 1.17) | 0.214, 29.4% |
| Asian              | 3  | 0.027, 0.79 (0.64, 0.97) | 0.192, 39.4% | 0.002, 73.1% | 0.002, 73.1% | 0.002, 73.1% |
| Caucasian          | 3  | 0.782, 1.02 (0.91, 1.14) | 0.009, 78.7% | 0.009, 78.7% | 0.009, 78.7% | 0.009, 78.7% |
| Source of control  |    |                  | 0.951, 1.01 (0.85, 1.18) | 0.001, 78.7% | 0.001, 78.7% | 0.001, 78.7% |
| PB                 | 4  | 0.926, 1.00 (0.91, 1.11) | 0.022, 68.7% | 0.022, 68.7% | 0.022, 68.7% | 0.022, 68.7% |
| HB                 | 2  | 0.002, 0.69 (0.55, 0.87) | 0.774, 0.0% | 0.000, 0.58 (0.42, 0.78) | 0.813, 0.0% | 0.171, 0.72 (0.46, 1.15) | 0.336, 0.0% |

Abbreviations: HB, hospital-based; n, number; PB, population-based.

rs746868

The pooled results based on four included studies [18,25–27] (including 1351 cases and 2145 controls) indicated that no significant association between rs746868 polymorphism and risk of cancer was uncovered. Moreover, in the subgroup analysis by cancer type, ethnicity and source of control, similar results were found. (Supplementary Table S2).

rs909253

The pooled results based on 21 included studies [13–15,18–34] (including 7022 cases and 8968 controls) indicated that no significant association between rs909253 polymorphism and cancer risk was found. However, in the stratification analysis by cancer type, we observed that rs909253 polymorphism was significantly related to an increased risk of HCC in allelic contrast (B vs A: OR = 3.52, 95% CI = 2.73–4.54, P=0.000, Figure 4), dominant model (BB+AB vs AA: OR = 4.33, 95% CI = 3.07–6.09, P=0.000) and recessive model (BB vs AA+AB: OR = 4.92, 95% CI = 2.92–8.29,
Figure 3. Forest plot of LTA rs2239704 polymorphism and cancer risk in allelic contrast stratified by cancer type

Abbreviations: GC, gastric cancer; OC, other cancer.

Table 4 Meta-analysis of rs2239704

| Variables       | n  | Allele contrast | Dominant model | Recessive model |
|-----------------|----|-----------------|----------------|-----------------|
|                 |    | P, OR (99% CI)  | P (Q test), I² | P, OR (99% CI)  | P (Q test), I² |
| Total           | 8  | 0.003, 0.90 (0.85, 0.97) | 0.819, 0.0% | 0.006, 0.88 (0.80, 0.96) | 0.831, 0.0% | 0.040, 0.88 (0.77, 0.99) | 0.444, 0.0% |
| Cancer type     |    |                 |                |                 |                 |                 |                 |
| NHL             | 6  | 0.001, 0.89 (0.83, 0.96) | 0.876, 0.0% | 0.011, 0.88 (0.80, 0.97) | 0.626, 0.0% | 0.006, 0.83 (0.72, 0.95) | 0.958, 0.0% |
| GC              | 1  | 0.733, 1.04 (0.84, 1.28) | NA             | 0.371, 0.86 (0.61, 1.20) | NA             | 0.128, 1.32 (0.92, 1.87) | NA             |
| OC              | 1  | 0.605, 0.87 (0.51, 1.47) | NA             | 0.596, 0.81 (0.38, 1.75) | NA             | 0.778, 0.87 (0.34, 2.24) | NA             |
| Ethnicity       |    |                 |                |                 |                 |                 |                 |
| Asian           | 2  | 0.633, 0.94 (0.72, 1.22) | 0.264, 19.8% | 0.645, 0.92 (0.63, 1.33) | 0.084, 66.5% | 0.775, 0.93 (0.55, 1.55) | 0.791, 0.0% |
| Caucasian       | 3  | 0.227, 0.92 (0.81, 1.05) | 0.356, 3.3% | 0.061, 0.83 (0.68, 1.01) | 0.964, 0.0% | 0.924, 1.01 (0.79, 1.29) | 0.131, 50.8% |
| Mixed           | 3  | 0.006, 0.89 (0.83, 0.97) | 0.944, 0.0% | 0.042, 0.89 (0.79, 1.00) | 0.978, 0.0% | 0.013, 0.82 (0.71, 0.96) | 0.698, 0.0% |
| Source of control |   |                 |                |                 |                 |                 |                 |
| PB              | 6  | 0.033, 0.92 (0.85, 0.99) | 0.728, 0.0% | 0.029, 0.88 (0.79, 0.99) | 0.681, 0.0% | 0.258, 0.92 (0.80, 1.06) | 0.431, 0.0% |
| HB              | 2  | 0.022, 0.86 (0.75, 0.98) | 0.849, 0.0% | 0.095, 0.85 (0.71, 1.03) | 0.581, 0.0% | 0.029, 0.75 (0.58, 0.97) | 0.710, 0.0% |
| Genotyping      |    |                 |                |                 |                 |                 |                 |
| PCR             | 5  | 0.023, 0.91 (0.85, 0.99) | 0.546, 0.0% | 0.032, 0.89 (0.79, 0.99) | 0.548, 0.0% | 0.153, 0.90 (0.78, 1.04) | 0.174, 37.0% |
| TaqMan          | 3  | 0.041, 0.88 (0.77, 0.99) | 0.877, 0.0% | 0.087, 0.85 (0.71, 1.02) | 0.830, 0.0% | 0.110, 0.82 (0.64, 1.05) | 0.955, 0.0% |

Abbreviations: GC, gastric cancer; HB, hospital-based; n, number; NA, not applicable; OC, other cancer; PB, population-based; PCR, polymerase chain reaction.
Figure 4. Forest plot of LTA rs909253 polymorphism and cancer risk in allelic contrast stratified by cancer type
Abbreviations: GC, gastric cancer; HCC, hepatocellular carcinoma; OC, other cancer.

P=0.000). In addition, in the stratification analysis by ethnicity, we observed that rs909253 polymorphism was significantly related to an increased risk of Caucasian ethnicity in allelic contrast (B vs A: OR = 1.10, 95% CI = 1.02–1.20, P=0.019), and mixed ethnicity in allelic contrast (B vs A: OR = 1.09, 95% CI = 1.01–1.17, P=0.024), dominant model (BB+AB vs AA: OR = 1.11, 95% CI = 1.01–1.23, P=0.039). Moreover, in the stratification analysis by source of control, genotyping and HWE, null result was found (Table 5).

**Sensitivity analysis and publication bias**
Sensitivity analysis were performed to evaluate the influence of each separate case–control study. The results showed that there was no material alteration in corresponding pooled ORs for rs1041981, rs2229094, rs2239704, rs746868, rs909253 (Supplementary Figures S1–S5). In addition, Begg’s test and Egger’s regression test were performed to evaluate the publication bias. As for rs1041981, rs2229094, rs2239704, rs746868 and rs909253, no evidence of publication bias was identified (Supplementary Table S3).

**TSA**
To evaluate random errors, we performed TSA (Figure 5). This analysis showed that the cumulative z-curve did not cross the trial sequential monitoring boundary and the required information size, suggesting that more evidences are needed to verify the conclusions.

**Discussion**
In the present study, a total of 24 articles including 43 case–control studies were enrolled to validate the association between five LTA gene polymorphisms (rs1041981, rs2229094, rs2239704, rs746868, rs909253) and the risk of cancer. We identified that rs2239704 was inversely associated with the risk of cancer under different genetic models. However,
Figure 5. TSA for LTA rs909253 polymorphism under the allele contrast model

for LTA rs1041981, rs2229094, rs746868, rs909253 polymorphisms, no significant association with cancer risk was uncovered.

In subgroup meta-analysis stratified by cancer type, we found that rs2239704 was significantly reduced NHL susceptibility. Huang et al. reported rs2239704 polymorphism was correlated with cancer and positive association in North Americans [35]. However, they included studies that contained buccal samples for SNP analysis or insufficient data studies [37–39]. We strictly follow the inclusion and exclusion criteria to include the literature. And our results indicated that rs2239704 was significantly reduced cancer susceptibility in mixed ethnicity, hospital-based control and polymerase chain reaction (PCR) genotyping subgroups. Despite of several possible bias, we still could conclude that rs2239704 could reduce cancer susceptibility.

In the stratified analysis of rs1041981, we found that Asians might have less susceptibility to cancer. Unlike the study by Huang et al. [35], we excluded two studies, one of which was autopsy specimen for SNP analysis [10] and the other was a study of HIV-infected patients [40]. The literature thus incorporated has a better baseline consistency and is more reflective of the real situation. Our results were consistent with the results of Huang et al.[35]. Due to the small sample size, we were unable to evaluate the role of rs1041981 in Caucasians. Larger sample size studies are needed for further evaluation. However, based on the current studies, we might conclude that rs1041981 could reduce cancer susceptibility.

For LTA rs2229094 and rs746848, only four studies reported their relationship with cancer in each group. No significant results were found. Huang et al. reported positive association between rs2229094 and cancer risk [35], which could be the bias from report by Takei et al. [10]. Because of the small sample size, we could not draw any conclusions based on current literature.

Although the overall analysis of rs909253 indicated a null result for cancer risk, the risk of cancer for Caucasians and HCC susceptibility were significantly increased in the stratified analysis by ethnicity and cancer types. In addition, some of the control groups did not match HWE, we cannot exclude the possibility that may cause the bias. Then, subgroup analysis by HWE showed that HWE status did not cause the bias of results. Huang et al. did not report the relationship of rs909253 and cancer risk, because it might be present in high linkage disequilibrium with other four SNPs [8,9]. However, our results identified that the function of rs909253 was opposite to rs2239704 and rs1041981. So, further studies with larger sample size are required to identify the role of LTA rs909253 and the linkage disequilibrium with other SNPs.

In the present study, we have put great effort on carefully searching for eligible studies. In order to obtain more accurate and reliable results, we conducted a comprehensive search to verify more eligible studies. Then, we used NOS to evaluate the quality of the included studies, eliminate low-quality studies and improve overall research quality.
Table 5 Meta-analysis of rs909253

| Variables       | n | Allele contrast | Dominant model | Recessive model |
|-----------------|---|-----------------|----------------|-----------------|
|                 |   | P, OR (99% CI)  | P (Q test), I² | P, OR (99% CI)  | P (Q test), I² |
| Total           | 21| 0.349, 1.07 (0.93, 1.23) | 0.000, 86.5% | 0.198, 1.12 (0.94, 1.34) | 0.000, 84.2% | 0.993, 1.00 (0.81, 1.23) | 0.000, 73.9% |
| Cancer type     |   |                 |                |                 |
| NHL             | 9 | 0.717, 0.98 (0.87, 1.10) | 0.000, 68.2% | 0.599, 1.04 (0.91, 1.18) | 0.056, 47.3% | 0.360, 0.90 (0.71, 1.13) | 0.004, 64.2% |
| GC              | 5 | 0.567, 0.94 (0.78, 1.15) | 0.006, 72.6% | 0.775, 0.96 (0.74, 1.25) | 0.007, 71.6% | 0.511, 0.87 (0.57, 1.32) | 0.005, 73.4% |
| HCC             | 2 | 0.000, 3.52 (2.73, 4.54) | 0.969, 0.0% | 0.000, 4.33 (3.07, 6.09) | 0.928, 0.0% | 0.000, 4.92 (2.92, 8.20) | 1.000, 0.0% |
| OC              | 5 | 0.968, 0.99 (0.69, 1.43) | 0.001, 79.8% | 0.759, 1.11 (0.58, 2.13) | 0.000, 87.7% | 0.638, 0.93 (0.70, 1.25) | 0.555, 0.0% |
| Ethnicity       |   |                 |                |                 |
| Asian           | 11| 0.707, 1.07 (0.75, 1.54) | 0.000, 92.9% | 0.507, 1.17 (0.74, 1.86) | 0.000, 91.3% | 0.753, 0.92 (0.56, 1.52) | 0.000, 85.4% |
| Caucasian       | 6 | 0.019, 1.10 (1.02, 1.20) | 0.697, 0.0% | 0.064, 1.15 (0.99, 1.34) | 0.141, 39.6% | 0.470, 1.07 (0.90, 1.27) | 0.534, 0.0% |
| Mixed           | 4 | 0.024, 1.09 (1.01, 1.17) | 0.860, 0.0% | 0.039, 1.11 (1.01, 1.23) | 0.758, 0.0% | 0.136, 1.12 (0.96, 1.31) | 0.984, 0.0% |
| Source of control|   |                 |                |                 |
| PB              | 13| 0.066, 1.18 (0.99, 1.42) | 0.000, 88.4% | 0.069, 1.23 (0.98, 1.53) | 0.000, 85.4% | 0.225, 1.18 (0.90, 1.53) | 0.000, 75.7% |
| HB              | 8 | 0.370, 0.91 (0.73, 1.12) | 0.000, 80.3% | 0.858, 0.97 (0.71, 1.34) | 0.000, 81.8% | 0.119, 0.76 (0.54, 1.07) | 0.003, 67.3% |
| Genotyping      |   |                 |                |                 |
| PCR             | 18| 0.377, 1.08 (0.91, 1.27) | 0.000, 88.5% | 0.223, 1.14 (0.92, 1.40) | 0.000, 86.5% | 0.996, 1.00 (0.78, 1.27) | 0.000, 77.7% |
| TaqMan          | 3 | 0.706, 1.02 (0.90, 1.16) | 0.957, 0.0% | 0.649, 1.04 (0.88, 1.23) | 0.846, 0.0% | 0.929, 1.01 (0.78, 1.31) | 0.927, 0.0% |
| HWE             |   |                 |                |                 |
| Y               | 19| 0.304, 1.08 (0.94, 1.24) | 0.000, 85.8% | 0.292, 1.10 (0.92, 1.30) | 0.000, 82.5% | 0.643, 1.05 (0.85, 1.29) | 0.000, 71.5% |
| N               | 2 | 0.985, 1.01 (0.32, 3.21) | 0.000, 95.2% | 0.592, 1.72 (0.24, 12.6) | 0.000, 95.8% | 0.403, 0.58 (0.16, 2.10) | 0.003, 88.6% |

Abbreviations: GC, gastric cancer; HB, hospital-based; HCC, hepatocellular carcinoma; n, number; N, no; OC, other cancer; PB, population-based; PCR, polymerase chain reaction; Y, yes.

In order to provide the sources of heterogeneity, subgroup analysis was performed by ethnicity, cancer type, source of controls, genotyping and so on. In addition, sensitivity analysis was used to confirm the stability of the studies. Egger's and Begg's tests were used to assess publication bias. However, several limitations in our study should be noted. First, small sample size limits the reliability of the results for some polymorphisms. Second, we just included the studies published in English, which may influence the effects of the polymorphisms. Third, we mainly evaluated the relationship between LTA polymorphisms with various cancers, and we could not get enough data for some cancer types. Fourth, we did not assess the linkage disequilibrium, which might not reflect the real function correctly. In future, more well-designed case–control studies are needed to investigate the functions of LTA polymorphisms.

Conclusion
Our meta-analysis suggests that LTA rs2239704 polymorphism is inversely associated with the risk of cancer, as is LTA rs1041981 polymorphism in Asia. While, LTA rs909253 polymorphism is a risk factor for HCC in Caucasians. Further studies with larger sample size are needed to confirm these findings.

Competing Interests
The authors declare that there are no competing interests associated with the manuscript.

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Author Contribution
Zhenwei Han had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Zhenwei Han and Jingdong Li. Acquisition of data: Jingdong Li and Yaxuan Wang. Analysis and interpretation of data: Jingdong Li and Yaxuan Wang. Drafting of the manuscript: Jingdong Li and Zhenwei Han. Critical revision of the manuscript for important intellectual content: Jingdong Li, Yaxuan Wang and Xueliang Chang. Statistical analysis: Yaxuan Wang and Xueliang Chang.

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Abbreviations
CI, confidence interval; HWE, Hardy–Weinberg equilibrium; LTA, lymphotoxin-α; NHL, non-Hodgkin lymphoma; NOS, Newcastle–Ottawa scale; OR, odds ratio; SNP, single nucleic polymorphism; TNF, tumor necrosis factor; TSA, trial sequential analysis.

References
1 Bauer, J. et al. (2012) Lymphotoxin, NF-kB, and cancer: the dark side of cytokines. Dig. Dis. 30, 453–468, https://doi.org/10.1159/000341690
2 El-Ghany, H.M. et al. (2014) Stromal cell derived factor-1 (CXCL12) chemokine gene variant in myeloid leukemias. Clin. Lab. 60, 735–741, https://doi.org/10.7754/ClinLab.2013.130445
3 Aggarwal, B.B. (2003) Signalling pathways of the TNF superfamily: a double-edged sword. Nat. Rev. Immunol. 3, 745–756, https://doi.org/10.1038/nri11184
4 Lu, R. et al. (2012) A functional polymorphism of lymphotoxin-alpha (LTA) gene rs909253 is associated with gastric cancer risk in an Asian population. Cancer Epidemiol. 36, e380–e386, https://doi.org/10.1016/j.canep.2012.05.014
5 Carroll, M.C. et al. (1987) Linkage map of the human major histocompatibility complex including the tumor necrosis factor genes. Proc. Natl. Acad. Sci. U.S.A. 84, 8555–8559, https://doi.org/10.1073/pnas.84.23.8553
6 Aggarwal, B.B., Gupta, S.C. and Kim, J.H. (2012) Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. Blood 119, 651–665, https://doi.org/10.1182/blood-2011-04-329225
7 Heybaeck, J. et al. (2009) A lymphotoxin-driven pathway to hepatocellular carcinoma. Cancer Cell 16, 295–308, https://doi.org/10.1016/j.ccr.2009.08.021
8 Ozaki, K. et al. (2002) Functional SNPs in the lymphotoxin-alpha gene that are associated with susceptibility to myocardial infarction. Nat. Genet. 32, 650–654, https://doi.org/10.1038/ng1047
9 Knight, J.C., Keating, B.J. and Kwiatkowski, D.P. (2004) Allele-specific repression of lymphotoxin-alpha by activated B cell factor-1. Nat. Genet. 36, 394–399, https://doi.org/10.1038/ng1331
10 Yakei, K. et al. (2008) Lymphotoxin-alpha polymorphisms and presence of cancer in 1,536 consecutive autopsy cases. BMC Cancer 8, 235, https://doi.org/10.1186/1471-2407-8-235
11 Abbas, S. et al. (2010) Polymorphisms in the BRCA1 and ABCB1 genes modulate menopausal hormone therapy associated breast cancer risk in postmenopausal women. Breast Cancer Res. Treat. 120, 727–736
12 Castro, F.A. et al. (2009) Association of HLA-DRB1, interleukin-6 and cyclin D1 polymorphisms with cervical cancer in the Swedish population—a candidate gene approach. Int. J. Cancer 125, 1851–1858, https://doi.org/10.1002/ijc.24529
13 Lee, S.G. et al. (2004) TNF/LTA polymorphisms and risk for gastric cancer-duodenal ulcer in the Korean population. Cytokine 28, 75–82, https://doi.org/10.1016/j.cyto.2004.06.009
14 Niwa, Y. et al. (2005) Lymphotoxin-alpha polymorphism and the risk of cervical cancer in Japanese subjects. Cancer Lett. 218, 63–68, https://doi.org/10.1016/j.canlet.2004.09.021
15 Niwa, Y. et al. (2007) Lymphotoxin-alpha polymorphisms and the risk of endometrial cancer in Japanese subjects. Gynecol. Oncol. 104, 586–590, https://doi.org/10.1016/j.ygyno.2006.09.007
16 Sainz, J. et al. (2012) Effect of type 2 diabetes predisposing genetic variants on colorectal cancer risk. J. Clin. Endocrinol. Metab. 97, E845–E851, https://doi.org/10.1210/jc.2011-2565
17 Madeleine, M.M. et al. (2011) Genetic variation in proinflammatory cytokines IL6, IL6R, TNF-region, and TNFRSF1A and risk of breast cancer. Breast Cancer Res. Treat. 129, 887–899, https://doi.org/10.1007/s10549-011-1520-4
18 Mahajan, R. et al. (2008) Genetic variants in T helper cell type 1, 2 and 3 pathways and gastric cancer risk in a Polish population. Jpn. J. Clin. Oncol. 38, 626–633, https://doi.org/10.1093/jjco/hyn075
19 Wang, S.S. et al. (2009) Common gene variants in the tumor necrosis factor (TNF) and TNF receptor superfamilies and NF-kB transcription factors and non-Hodgkin lymphoma risk. PLoS ONE 4, e5360, https://doi.org/10.1371/journal.pone.0005360
20 Cerhan, J.R. et al. (2008) Genetic variation in tumor necrosis factor and the nuclear factor-kappaB canonical pathway and risk of non-Hodgkin’s lymphoma. Cancer Epidemiol. Biomark. Prev. 17, 3161–3169, https://doi.org/10.1158/1055-9965.EPI-08-0536
21 Ennas, M.G. et al. (2008) Interleukin-1β (IL1B) and interleukin-6 (IL6) gene polymorphisms are associated with risk of chronic lymphocytic leukaemia. Hematol. Oncol. 26, 98–103, https://doi.org/10.1002/hon.843
22 Gu, X. et al. (2014) Polymorphic variation of inflammation-related genes and risk of non-Hodgkin lymphoma for Uygur and Han Chinese in Xinjiang. Asian Pac. J. Cancer Prev. 15, 9177–83, https://doi.org/10.7314/APJCP.2014.15.21.9177

23 Lan, Q. et al. (2006) Cytokine polymorphisms in the Th1/Th2 pathway and susceptibility to non- Hodgkin lymphoma. Blood 107, 4101–4108, https://doi.org/10.1182/blood-2005-10-4166

24 Purdue, M.P. et al. (2007) Polymorphisms in immune function genes and risk of non-Hodgkin lymphoma: findings from the New South Wales non-Hodgkin Lymphoma Study. Carcinogenesis 28, 704–712, https://doi.org/10.1093/carcin/bgl200

25 Crusius, J.B. et al. (2008) Cytokine gene polymorphisms and the risk of adenocarcinoma of the stomach in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). Ann. Oncol. 19, 1894–1902, https://doi.org/10.1093/annonc/mdn400

26 García-Gonzalez, M.A. et al. (2007) Gastric cancer susceptibility is not linked to pro-and anti-inflammatory cytokine gene polymorphisms in whites: a nationwide multicenter study in Spain. Am. J. Gastroenterol. 102, 1878–1892, https://doi.org/10.1111/j.1572-0241.2007.01423.x

27 Gunter, M.J. et al. (2006) Inflammation-related gene polymorphisms and colorectal adenoma. Cancer Epidemiol. Biomark. Prev. 15, 1126–1131, https://doi.org/10.1158/1055-9965.EPI-06-0042

28 Cheng, S. et al. (2015) LTA + 252A >G polymorphism is associated with risk of nasal NK/T-cell lymphoma in a Chinese population: a case-control study. BMC Cancer 15, 480

29 Jeng, J.E. et al. (2014) Independent and additive interaction between tumor necrosis factor beta +252 polymorphisms and chronic hepatitis B and C virus infection on risk and prognosis of hepatocellular carcinoma: a case-control study. Asian Pac. J. Cancer Prev. 15, 10209–10215, https://doi.org/10.7314/APJCP.2014.15.23.10209

30 Lakhanpal, M. et al. (2016) Study of single nucleotide polymorphisms of tumour necrosis factors and HSP genes in nasopharyngeal carcinoma in North East India. Tumour Biol. 37, 271–281, https://doi.org/10.1007/s13277-015-3767-6

31 Liu, J. et al. (2013) Genetic variations in CTLA-4, TNF-alpha, and LTA and susceptibility to T-cell lymphoma in a Chinese population. Cancer Epidemiol. 37, 930–934, https://doi.org/10.1016/j.canep.2013.08.011

32 Mou, X. et al. (2015) Genetic variation of BCL2 (rs2279115), NEIL2 (rs804270), LTA (rs909253), PSCA (rs2294008) and PLCE1 (rs3765524, rs10509670) genes and their correlation to gastric cancer risk based on universal tagged arrays and Fe3O4 magnetic nanoparticles. J. Biomed. Nanotechnol. 11, 2057–2066, https://doi.org/10.1166/jbn.2015.2113

33 Tsai, J.F. et al. (2017) Interactive effects between Lymphotoxin alpha +252 polymorphism and habits of substance use on risk of hepatocellular carcinoma. Kaohsiung J. Med. Sci. 33, 334–338, https://doi.org/10.1016/j.kjms.2017.04.010

34 Yri, O.E. et al. (2013) Influence of polymorphisms in genes encoding immunoregulatory proteins and metabolizing enzymes on susceptibility and outcome in patients with diffuse large B-cell lymphoma treated with rituximab. Leuk. Lymphoma 54, 2205–2214, https://doi.org/10.3109/10428194.2013.774392

35 Huang, Y. et al. (2013) Four genetic polymorphisms of lymphotoxin-alpha gene and cancer risk: a systematic review and meta-analysis. PLoS ONE 8, e82519, https://doi.org/10.1371/journal.pone.0082519

36 Xie, S. et al. (2014) Relevance of UGA gene polymorphisms with cancer susceptibility: evidence from a meta-analysis. Sci. Rep. 4, 6630, https://doi.org/10.1038/srep06630

37 Wang, S.S. et al. (2006) Common genetic variants in proinflammatory and other immunoregulatory genes and risk for non-Hodgkin lymphoma. Cancer Res. 66, 9771–9780, https://doi.org/10.1158/0008-5472.CAN-06-0324

38 Liu, X. et al. (2006) Nonsteroidal anti-inflammatory drugs and decreased risk of advanced prostate cancer: modification by lymphotoxin alpha. Am. J. Epidemiol. 164, 984–989, https://doi.org/10.1093/aje/kwj294

39 Jacobs, E.J. et al. (2008) Polymorphisms in angiogenesis-related genes and prostate cancer. Cancer Epidemiol. Biomark. Prev. 17, 972–977, https://doi.org/10.1158/1055-9965.EPI-07-2787

40 Aissani, B. et al. (2009) The major histocompatibility complex conserved extended haplotype 8.1 in AIDS-related non-Hodgkin lymphoma. J. Acquir. Immune Defic. Syndr. 52, 170–179, https://doi.org/10.1097/QAI.0b013e3181b017d5