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An update meta-analysis and systematic review of TAP polymorphisms as potential biomarkers for judging cancer risk

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ABSTRACT

Objective: Transporter associated with antigen processing protein (TAP) is a heterodimer protein consist of TAP1 and TAP2, act a pivotal part in the immune surveillance. In recent days, controversial relationships were reported between *TAP* polymorphisms and cancer risk, thus, a systematic meta-analysis was performed to resolve this discrepancy.

Methods: We searched the PubMed, EMbase, Web of Science, CNKI and Wanfang databases, the cited references were also manually searched again, covering all the papers published until March 25, 2018. Quality assessment was conducted using the Newcastle–Ottawa Scale. All the meta-analysis was conducted with Stata version 12.0 software to assess the strength of the association.

Results: 4719 cases and 4215 controls from 24 case-control studies related to *TAP* polymorphisms were enrolled. There was no significant association between *TAP1-rs1135216, TAP1-rs4148873, TAP2-rs2228396, TAP2-rs241447 and TAP2-rs4148873* and cancer sensibility. Interestingly, a significant positive association was observed between TAP2 rs4148876 C/T polymorphism and increase cancer risk in homozygote and recessive models. Further in-silico results indicated the expression of TAP2 in cancer tissue is higher than that in normal tissue (cervical cancer, TPM = 70.2 vs. 24.0 respectively, $P < 0.01$; acute myeloid leukemia, TPM = 52.5 vs. 8.8 respectively, $P < 0.01$), and influence the survival time of acute myeloid leukemia patients (Log-rank $P < 0.05$).

Conclusions: Our finding suggested that *TAP1-rs1135216, TAP1-rs4148873, TAP2-rs2228396, TAP2-rs241447 and TAP2-rs4148873* might not be involved in cancer risk, but the T allele of *TAP2-rs4148876* might be a potential biomarker for judging cancer risk, and larger-scale studies are required to confirm our findings.

1. Introduction

Major histocompatibilitycomplex (MHC) class I molecules play a key role in the immune surveillance of infections and transformed cells, which could bind the intracellularly processed peptides and present them on the cell surface to cytotoxic T lymphocytes [1]. As a candidate peptide of MHC-I molecules, transporter associated with antigen processing protein (TAP), a heterodimer integral membrane protein of TAP1 and TAP2, could transport antigen peptide from cytoplasm into endoplasmic reticulum, and provide a supply of processed peptides to MHC-I [2,3]. Recently, twelve *TAP1* and *TAP2* polymorphisms have been reported according to the IPD-IMGT/HLA Database (http://hla.alleles.org), WHO Nomenclature Committee for Factors of the HLA System [4]. As polymorphisms of *TAP* genes coding regions may change the structure and function of the complex, making strong affection of immune surveillance and cancer susceptibility, *TAP1* and *TAP2* polymorphisms have been reported to be linked with various diseases, including tuberculosis [5], ankylosing spondylitis [6], leprosy [7], idiopathic bronchiectasis [8] and etc. Zou et al. [9] investigated the heterozygote of *TAP1-rs1135216* increases the susceptibility to esophageal squamous cell carcinoma (ESCC) in Kazakh populations. However, in a former study conducted by Cao et al. [10] reported that

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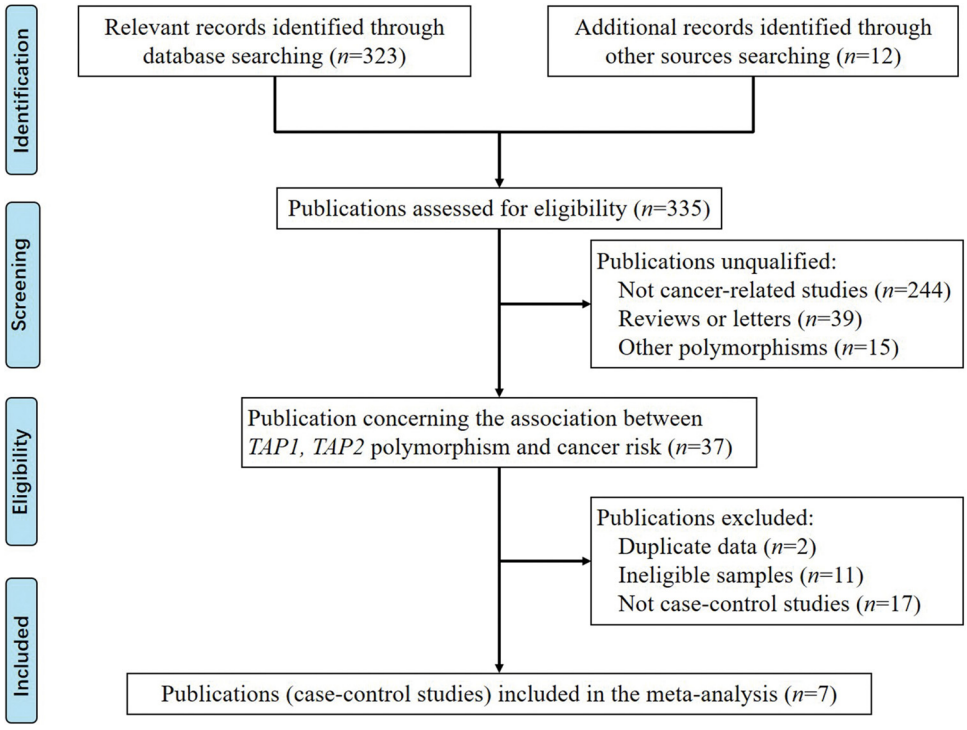

Fig. 1. Flow chart of studies selection in this meta-analysis.

TAP1-rs1135216 has no effect on the process of ESCC, while C allele of *TAP2-rs4148873* has a higher frequency in the patients than in the controls. *TAP1* and *TAP2* polymorphisms may be novel gene markers for the diagnosis and treatment of malignant tumors, however, the results remained controversial and ambiguous. Therefore, we enrolled all eligible case-control publications, performed a comprehensive updated meta-analysis to confirm the precise and latest association between *TAP* gene polymorphisms and tumors.

2. Material and methods

2.1. Identification and eligibility of relevant publications

We conducted a comprehensive literature search on the PubMed, EMbase, Web of Science, CNKI and Wanfang databases (the last search was performed at March 25, 2018) to pick out all eligible publications with the following search terms: (*TAP1* OR *TAP2)* AND (polymorphism OR SNP OR variant OR mutation OR allele) AND (cancer OR tumour OR carcinoma OR neoplasm OR malignancy), with no restriction of publication year or language. Two reviewers identified and extracted the eligible publications about cancers, and a manual retrieve of reference lists was also performed, covering all the relevant papers. However, if we found that the data were published in different reports, we selected the largest sample to record.

2.2. Inclusion criteria and exclusion criteria

Studies that were enrolled in this study should meet the following criteria: (a) case-control study design independently of human; (b) assess the correlation between *TAP* polymorphisms and cancers; (c) sufficient data of allele and genotype frequencies among cases and controls. On the contrary, studies were excluded if meet the following criteria: (a) meta-analyses, reviews, animal studies or case-only studies; (b) not concerning with cancer susceptibility. (c) no sufficient information on genetic data.

2.3. Data extraction and record

We extracted and record the following items from the study conformed to the inclusion criteria: first author's last name, year of publication, ethnicity, number of cases and controls with different genotypes, genotyping methods, source of control, cancer type, and Hardy–Weinberg equilibrium (HWE). Regarding the controls of eligible case-control studies, we distinguished it as either population-based (PB) or hospital-based (HB), while ethnicity was categorized as "Caucasian", "Asian" or "African". All discrepancies between the two investigators were discussed until consensuses were obtained.

2.4. Statistical analysis

The strength of correlation between *TAP1, TAP2* polymorphisms and cancer susceptibility in different models was analyzed in five models: allelic comparison, heterozygote comparison, homozygote comparison, dominant and recessive models, expressed as the odds ratios (ORs) with 95% confidence intervals (CIs). The statistical significance of the ORs was determined with the Z-test, Bonferroni corrections were also performed to adjust the results [11]. For example, the pooled ORs of *TAP1-rs4148880* polymorphisms were calculated by allelic contrast comparison (G vs. A), heterozygote comparison model (GA vs. AA), homozygote comparison model (GG vs. AA), dominant genetic model (GG + GA vs. AA) and recessive genetic model (GG vs. GA + AA). Additionally, stratified analyses were presented in the subgroup of source of control, genotyping methods, ethnicity, cancer type or HWE status. Heterogeneity assumption were evaluated by a χ^2-based Q-test [12]. The fixed effect model (Der-Simonian Laird) would be used to assess the point estimates and 95% CI, when the P-value > 0.10 for the Q-test indicated a lack of heterogeneity [13]. In addition, we carried out the one-way sensitivity analyses to access the stability of result. Publication bias was evaluated using Begg's funnel plot and Egger's test, $P < 0.05$ was considered statistically significant [14]. We used the Stata software (version 12.0; StataCorp LP, College Station, TX) to performed all the statistical analysis, and used the Power and Sample Size Calculation to evaluated the power of this study.