Association between the TP53BP1 rs2602141 A/C Polymorphism and Cancer Risk: A Systematic Review and Meta-Analysis

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Abstract

Background: The p53-binding protein 1 (TP53BP1) gene may be involved in the development of cancer through disrupting DNA repair. However, investigation of associations between TP53BP1 rs2602141 A/C polymorphism and cancer have yielded contradictory and inconclusive outcomes. We therefore performed a meta-analysis to evaluate the association between the TP53BP1 rs2602141 A/C polymorphism and cancer susceptibility.

Materials and Methods: Published literature from PubMed, Medline, the Cochrane Library, EMBase, Web of Science, Google (scholar), CBMDisc, Chongqing VIP database, and CNKI database were retrieved. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed or random-effects models. Publication bias was estimated using funnel plots, Begg’s and Egger’s test. Results: A total of seven studies (3,018 cases and 5,548 controls) were included in the meta-analysis. Our results showed that the genotype distribution of TP53BP1 rs2602141 A/C was not associated with cancer risk overall. However, on subgroup analysis, we found that TP53BP1 rs2602141 A/C was associated with cancer risk within an allele model (A vs C, OR=1.14, 95% CI: 1.01-1.29) and a codominant model (AA vs CC, OR=1.36, 95% CI: 1.06-1.74) in Asians rather than in Caucasians. Subgroup analysis by cancer type, genotype, and with or without adjustment for controls showed no significant association.

Conclusions: The findings suggested an association between rs2602141 A/C polymorphism in TP53BP1 gene and increased risk of cancer in Asians.

Keywords: TP53-binding protein 1 - cancer - polymorphism - gene - meta-analysis
Web of Science, Google (scholar), Chinese Biological Medicine, China National Knowledge Infrastructure, Wang Fang Data and Chongqing VIP database (last search was updated on December 15, 2013) using the terms “p53-binding protein 1 or TP53BP1 or 53BP1”, “Gln1136 Lys or rs26028140 or K1136Q”, “cancer or tumor or carcinoma” and “polymorphism, variant, mutation or SNP”. The search was done without restriction on language, but we only included published articles written in English or Chinese. We used the PubMed option “Related Articles” for each study to retrieve additional potentially relevant articles. Reference lists were checked and researchers contacted for additional literatures.

Selection criteria

Studies were selected if they met the following criteria: (1) association study with a case-control or cohort design; (2) the study investigated the association between rs2602141 polymorphisms of TP53BP1 and the risk of cancer; (3) in the case of multiple publications from the same study group, the most complete and recent results were used.

Exclusion criteria

The exclusion criteria were defined as: 1) abstracts, reviews and animal studies; 2) useless data reported, genotype number or frequency not included; 3) study without sufficient data for meta-analysis; and 4) genotype distribution in the control population not consistent with HWE. If more than one study was published by the same author using the same case series, only the most recent study or the study with the largest size of samples was included in our meta-analysis.

Data extraction

Two reviewers (Lei Liu and Dong Zhang) independently scrutinized studies on the associations between TP53BP1 rs2602141 A/C polymorphisms and cancer. When discrepancies were appeared, all investigators were recruited to assess the data. The following information was collected: First author, year of publication, location, ethnicity, characteristics, sample sizes of patients and controls, genotype numbers, \( p \) value for HWE.

The reviewers developed a quality assessment scale (Table 1), which was modified from previous studies (Camargo et al., 2006; Liu et al., 2011; Gao et al., 2011), to evaluate the quality of eligible studies.

The review and analysis were guided to conduct by the PRISMA statement for preferred reporting of systematic reviews and meta-analysis (Moher et al., 2009).

Statistical analysis

Odds ratio (ORs) with 95% confidence intervals (CIs) for genotypes and alleles were used to assess the strength of association between TP53BP1 rs2602141 A/C polymorphisms and risk of cancer. The ORs were performed for the allele contrasts, additive genetic model, as well as recessive genetic model and dominant genetic model, respectively. Heterogeneity was examined with the \( I^2 \) statistic interpreted as the proportion of total variation contributed by between-study variation. We also measured the effect of heterogeneity using a quantitative measure, \( F^2 = 100\times (Q-d f)/Q \). If there was a statistical difference in terms of heterogeneity (\( p<0.10, F^2>50\% \)), the random effects model would be used to estimate the pooled ORs (DerSimonian et al., 1986; 2007). Otherwise, the pooled ORs were estimated by the fixed effects model (Mantel et al., 1959). Sensitivity analysis was carried out by deleting one single study each time to examine the influence of individual data set on the pooled ORs. The possible publication bias was assessed with funnel plots and Egger’s test. An asymmetric plot suggests a possible publication bias and the \( p \) value of Egger’s test less than 0.05 was considered representative of statistically significant publication bias (Egger et al., 1997). All statistical tests were performed with RevMan version 5.0 (Review Manager, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2010) and Comprehensive Meta-Analysis software version 2.0 (Biostat, Englewood Cliffs, I.N.J., USA). All \( p \) values were two sided and a \( p \) value of smaller than 0.05 for any test was considered to be statistically significant.

Results

Study inclusion and characteristics

The study by He et al. (He et al., 2010) was divided into three studies according to cancer type. As showed in Figure 1, a total of 7 studies were included in the meta-analysis including 3,018 cases and 5,548 controls (Frank et al., 2005; Ma et al., 2006; Chen et al., 2007; He et al., 2010; Zhang et al., 2013). The studies identified and their main characteristics were summarized in Table 2 and Table 3. Genotype distribution of any polymorphism did not differ from Hardy-Weinberg equilibrium with in both groups (all were greater than 0.05).

Quantitative data synthesis

As showed in Table 4, meta-analysis of the total

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Figure 1. Flow Chart Demonstrating Those Studies That were Processed for Inclusion in the Meta-Analysis

Figure 2. Forest Plot of the Association between Cancer and the rs2602141 A/C Mutation in Asian Population (A vs C); (AA vs CC)

studies showed that there was no association between rs2602141 A/C polymorphism and risk of cancer under all five genetic models in overall population (OR=1.08, 95%CI=0.99-1.17 for A vs C; OR=1.22, 95%CI=1.01-1.47 for AA vs CC; OR=1.15, 95%CI=0.94-1.32 for AA vs AC; OR=1.12, 95%CI=0.95-1.31 for recessive model; OR=1.03; 95%CI=0.91-1.17 for dominant model).

Subgroup analyses were performed of rs2602141 A/C polymorphisms by ethnicity, showing that the rs2602141 A/C polymorphism was associated with elevated cancer risk in Asian (Figure 2) population (A vs C, OR =1.14, 95%CI =1.01-1.29; AA vs CC, OR =1.36, 95%CI =1.06-1.74) rather than in Caucasian.

In other subgroups analyses according to cancer type, adjusted with control or not, and genotyping methods, the results suggested that rs2602141 A/C polymorphisms were not associated with the risk of cancer (Table 4). The graphical funnel plots (Figure 3) and the results of Begg’s and Egger’s test (Begg, p=0.18; Egger, p=0.53) did not show any evidence of publication bias.

Sensitivity analysis

In order to examining the influence of the individual data set to the pooled ORs, we deleted every single study each time in this meta-analysis. According to sensitivity analysis, we found that there was no
substantial modification of estimates after exclusion of individual studies, indicating that the results were stable (data not shown).

Discussion

TP53BP1 gene has played an important role in both DNA repair and cell cycle control and also mediates the DNA damage checkpoint through cooperation with damage sensors and signal transducers (Miwa et al., 2013). The TP53BP1 contains two BRCA1 C-terminal (BRCT) domains, which is essential for tumor suppressor functions (Williams et al., 2001). The SNPs for TP53BP1 gene may play an important role in the etiology of cancer because of a direct role of TP53BP1 in the cellular response to DNA damage.

To the best of our knowledge, some researches that aim at the role of rs2602141 A/C polymorphism in cancer risk have been performed, but the results are controversial. This is the first meta-analysis to evaluate on the association between the rs2602141 A/C polymorphisms and cancer risk. Although we have not found a significant association between TP53BP1 rs2602141 A/C polymorphism and cancer risk in overall population, we performed subgroups analyses based on different ethnicity, adjusted with control or not, genotyping methods and cancer type factors. Interestingly, the results showed us that rs2602141 A/C polymorphisms were associated with the risk of cancer in Asian population rather than that in Caucasian, suggesting that this polymorphism might be biologically functional in ethnicity. The genotype distributions of rs2602141 A/C in different ethnicity might account for this.
When stratified by adjusted with control or not, genotyping methods and cancer type factors, the results showed no significant association between rs2602141 A/C polymorphism and cancer risk in all comparison models tested. That may be because only one study (Zhang et al., 2013) reported that the rs2602141 A/C polymorphism was associated with a risk of cancer. Therefore, further studies are needed to confirm our results.

Some studies indicate that TP53BP1 variants may have protective effects on squamous cell carcinoma of the head and neck (SCCHN) risk but such effects were confined to TP53 variant allele/haplotype carriers (Chen et al., 2007; Zhang et al., 2013). As the reason for few studies were performed and there were many meta-analysis related on TP53 gene polymorphism and cancer risk (Weng et al., 2012; Zhao et al., 2013), we could not use meta-analysis to analyze the relationship between TP53BP1 rs2602141 A/C polymorphism combined with TP53 gene polymorphism and cancer. In addition, Rudd et al. (Rudd et al., 2006) and Truong et al. (Truong et al., 2010) found that rs2602141 polymorphism was associated with lung cancer risk. However, because lack of sufficient data from these two studies, we could not include these studies in this meta-analysis. That may be another reason for the conclusion in this meta-analysis.

There are several limitations in this meta-analysis that should be considered. First, cancer is a multifactorial disease from complex interactions between environmental exposure and genetic factors. In this meta-analysis, we had insufficient data to perform an evaluation of such interactions for the independent role of TP53BP1 rs2602141 A/C polymorphisms in cancer development. Second, the number of current studies is relative small. Thus, more studies are needed to further identify this association more comprehensively. Third, we did not consider studies published in languages other than English/Chinese or data presented in abstracted form; thus, publication and potential language biases may occur.

In conclusion, the findings suggested an association between rs2602141 A/C polymorphism in TP53BP1 gene and increased risk to cancer in Asian population. To verify these results, large scale case-control studies with detailed individual information are needed.

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References


