RESEARCH ARTICLE

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

Lei Liu¹,⁵*, Dong Zhang², Jing-Hua Jiao³, Yu Wang⁴, Jing-Yang Wu¹, De-Sheng Huang⁵

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

Asian Pac J Cancer Prev, 15 (6), 2917-2922

Introduction

It was reported that there was about 12.7 million new cancer cases and 7.6 million cancer deaths throughout the world in 2008 (Ferlay et al., 2010). However, the etiology of cancer remains unknown and disease-modifying treatments are limited.

Previous researches suggested a more direct role of p53-binding protein 1 (TP53BP1) in the cellular response to DNA damage (Schultz et al., 2000; Rappold et al., 2001). In addition, studies suggested that TP53BP1 was a positive regulator of the BRCA1 promoter (Rauch et al., 2005) and a key transducer of the DNA damage checkpoint signal (Wang et al., 2002) and that it constitutively played an important role in the etiology of human cancers (DiTulio et al., 2002).

Since the involvement of cytokines in cancer was hypothesized, there were many candidate genes approach in designing a case-control association study of single nucleotide polymorphisms (SNPs) including TP53BP1. Previous researches have revealed that no association between the variant genotype of the TP53BP1 rs2602141 A/C SNPs and cancer risk (Frank et al., 2005; Ma et al., 2006; Chen et al., 2007; He et al., 2010), but Zhang et al. (2013) reported that the rs2602141 genotype increased lung cancer risk (Zhang et al., 2013). So published data were contradictory, and the association between TP53BP1 rs2602141 A/C polymorphism and cancer risk was still inconclusive. Therefore, we conducted a systematic review and meta-analysis to get a more precise estimate of the association between TP53BP1 rs2602141 A/C polymorphism and cancer susceptibility.

Materials and Methods

Selection of eligible studies

We searched PubMed, Medline (US National Library of Medicine, Bethesda, MD), Embase, the Cochrane Library,
As showed in Table 4, meta-analysis of the total
quantitative data synthesis
was more powerful for detecting a possible publication bias and the
plots and Egger’s test. An asymmetric plot suggests
the possible publication bias was assessed with funnel
plots and Egger’s test. An asymmetric plot suggests
the effect of heterogeneity using a quantitative measure,
F^2=100%×(Q-d f)/Q. If there was a statistical difference
in terms of heterogeneity (p<0.10, F>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 seven 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
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=1.11, 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=1.11, 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).

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.

**Table 3. Distributions of TP53BP1 Genotype and Allele Among Cases and Controls**

<table>
<thead>
<tr>
<th>First author</th>
<th>Study groups</th>
<th>Distribution of TP53BP1 genotypes (n)</th>
<th>Frequency of TP53BP1 alleles (n)</th>
<th>HWE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>AC</td>
<td>CC</td>
<td>AA+CC</td>
</tr>
<tr>
<td>Chen K</td>
<td>Case</td>
<td>430</td>
<td>322</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>433</td>
<td>330</td>
<td>58</td>
</tr>
<tr>
<td>Frank B</td>
<td>Case</td>
<td>158</td>
<td>144</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>148</td>
<td>396</td>
<td>94</td>
</tr>
<tr>
<td>Ma H</td>
<td>Case</td>
<td>139</td>
<td>194</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>175</td>
<td>234</td>
<td>59</td>
</tr>
<tr>
<td>Zhang H</td>
<td>Case</td>
<td>112</td>
<td>322</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>144</td>
<td>338</td>
<td>203</td>
</tr>
<tr>
<td>He C</td>
<td>melanoma</td>
<td>389</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>389</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>He C</td>
<td>SCC</td>
<td>389</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>389</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>He C</td>
<td>BCC</td>
<td>389</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA: not applicable; HWE: Hardy-Weinberg equilibrium; SCC: squamous cell carcinoma; BCC: basal cell carcinoma

**Table 4. Summary ORs and 95% CI of the rs2602141 Polymorphism in the TP53BP1 Gene and Cancer Risk**

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Variables</th>
<th>Allele Model</th>
<th>Codominant Model</th>
<th>Dominant model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A vs C</td>
<td>AA vs CC</td>
<td>AA vs AC</td>
<td>AA vs AC+CC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(fixed model)</td>
<td>(model)</td>
<td>(model)</td>
</tr>
<tr>
<td></td>
<td>OR(95% CI)</td>
<td>Ph</td>
<td>I2%</td>
<td>OR(95% CI)</td>
</tr>
<tr>
<td>Overall</td>
<td>4</td>
<td>1.08(0.99-1.17)</td>
<td>0.57</td>
<td>0.76</td>
</tr>
<tr>
<td>Caucasian</td>
<td>4</td>
<td>1.07(0.96-1.21)</td>
<td>0.25</td>
<td>0.14</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>1.19(1.01-1.39)</td>
<td>0.24</td>
<td>0.84</td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>1.06(0.95-1.20)</td>
<td>0.31</td>
<td>0.81</td>
</tr>
<tr>
<td>Study with matching</td>
<td>2</td>
<td>1.08(0.97-1.20)</td>
<td>0.32</td>
<td>0.82</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>1.07(0.95-1.21)</td>
<td>0.09</td>
<td>0.81</td>
</tr>
<tr>
<td>Genotyping</td>
<td>PCR</td>
<td>2</td>
<td>1.08(0.97-1.20)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>Taqman</td>
<td>2</td>
<td>1.07(0.95-1.21)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*The study by He et al was included; Ph: p value for test of heterogeneity; PCR: polymerase chain reaction; OR: odds ratio; CI: confidence interval; F: fixed-effects model; R: random-effects model
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 multi-factorial 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.

Acknowledgements

Thanks to Xiaomei Wu, Ph.D, Professor of the Department of Clinical Epidemiology and Evidence Medicine in the First Affiliated Hospital of China Medical University. Thanks to the editors and anonymous reviewers.

References


DOI:http://dx.doi.org/10.7314/APJCP.2014.15.6.2917
Lei Liu et al

*PLoS One, 7, 45820.*

