The Role of TP53 Gene Codon 72 Polymorphism in Leukemia

A PRISMA-Compliant Systematic Review and Meta-Analysis

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Abstract: The purpose of this meta-analysis was aimed to evaluate the association of tumor protein p53 (TP53) gene codon 72 polymorphism with leukemia susceptibility.

We searched PubMed to identify relevant studies, and 16 case-control studies from 14 published articles were identified as eligible studies, including 2062 leukemia patients and 5826 controls. After extracting data, odds ratio (OR) with the corresponding 95% confidence interval (95%CI) was applied to assess the association between TP53 codon 72 polymorphism and leukemia susceptibility. The meta-analysis was performed with the Comprehensive Meta-Analysis software, version 2.2.

Overall, no significant association between TP53 codon 72 polymorphism and leukemia susceptibility was found in this meta-analysis (Pro vs Arg: OR = 1.05, 95%CI = 0.90–1.21; Pro/Pro vs Arg/Arg: OR = 1.13, 95%CI = 0.84–1.52; Arg/Pro vs Arg/Arg: OR = 0.94, 95%CI = 0.76–1.15; [Pro/Pro + Arg/Pro] vs Arg/Arg: OR = 0.95, 95%CI = 0.80–1.21; Pro/Pro vs [Arg/Arg + Arg/Pro]: OR = 1.19, 95%CI = 0.93–1.51). Similar results were also found in subgroup analysis by ethnicity, source of controls, and types of leukemia (either acute myeloid leukemia or acute lymphocytic leukemia).

Our meta-analysis demonstrates that TP53 codon 72 polymorphism may not be a risk factor for acute leukemia; however, due to the limitations of this study, it should be verified in future studies.

INTRODUCTION

Leukemia is a group of hematological malignant clonal diseases involving genetic alterations.1,2 Generally, the overall incidence of leukemia appears to be rising.3,4 Multiple etiological factors have been revealed for leukemia, among which inherited DNA mutations and exposure to ionizing radiation, certain chemicals or cytotoxic therapy seem to be the most important internal and external contributors.5 DNA damage of hematopoietic progenitors induced by these factors may finally result in the development of leukemia, during which genetic variations corresponding to high-risk phenotypes are typically involved.6 As known, tumor protein p53 (TP53) plays a key role in preventing tumor formation through orchestrating a diversity of pathways such as activation of cell signaling transduction responses, DNA repair, and regulation of cell cycle progression and apoptosis.7,8 Generally, TP53 mutations are thought to be associated with carcinogenesis.9,10 Many studies have found that the TP53 played an important role during the development of leukemia.11–13 Among known TP53 polymorphisms, Arg72Pro (rs1042522), an amino acid substitution of arginine (Arg)—proline (Pro) at position 72, is one of the most widely studied polymorphisms.14 Hence, much attention has been paid to the issue whether TP53 Arg72Pro polymorphism is associated with leukemia susceptibility. In 2004, Bergamaschi et al reported that the allele A1 (proline residue, Pro72) was more frequent in patients with leukemia than in controls, and among leukemia patients who had no cytogenetic response than among responders.15 However, subsequent studies showed different results about TP53 Arg72Pro polymorphism and leukemia susceptibility. In this case, a meta-analysis is needed to pool these controversial findings.16

MATERIALS AND METHODS

Literature Search

A comprehensive search was conducted in PubMed databases for relevant published studies up to December 11, 2014 (updated on July 11, 2015). “Leukemia,” “Tumor Suppressor Protein p53,” and “polymorphism” were used as keywords.
Inclusion and Exclusion Criteria

Every study included in this meta-analysis had to meet the following criteria: (1) with case-control design; (2) investigating the association between TP53 gene Arg72Pro polymorphism and the susceptibility to leukemia, including acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML); (3) the case group consisted of patients with leukemia confirmed by both clinical and laboratory examinations, whereas the control group consisted of healthy individuals, and their details were clearly reported; (4) with sufficient data for estimating the odds ratios (ORs) and 95% confidence intervals (95%CIs). In addition, articles were excluded according to the following criteria: (1) abstracts or unpublished records; (2) studies on nonhuman subjects; (3) studies in which the genotype frequencies were not reported and could not be calculated. As for overlapped publications, the most comprehensive one would be selected.

Statistical Analysis

Relevant statistical analysis was performed using the Comprehensive Meta Analysis software (version 2.2; Biostat, Englewood, NJ).17,18 The OR and its 95% CI were used to assess the association under 5 genetic models: Pro vs Arg, Pro/Pro vs Arg/Arg, Arg/Pro vs Arg/Arg, Pro/Pro vs (Arg/Arg + Arg/Pro), and (Pro/Pro + Arg/Pro) vs Arg/Arg. Heterogeneity was evaluated by the Cochran’s $Q$ statistic19 and the $I^2$ statistic.20 Data were pooled using a random-effects model. Subgroup analyses were also conducted according to ethnicity, types of leukemia, and source of controls. And sensitivity analysis was performed using the individual exclusion method. Potential publication bias was assessed by visual inspection of the funnel plots, and Egger’s test provided corresponding statistical evidence ($P < 0.05$ represented statistical significance).21,22

RESULTS

Results of Search and Study Characteristics

Of the 1073 records found initially, 16 case-control studies involving 2062 cases and 5826 controls from 14 research papers15,23–35 were ultimately included. A detailed flowchart presenting the selection process is shown in Figure 1. Table 1 exhibits the major characteristics of these 16 case-control studies, which comprised seven studies23–28,33 on AML, six26,27,29,32,34,35 on ALL, one30 on CLL, one15 on CML, and one31 on acute leukemia (AL). Ten studies were conducted in Asian populations23,25–27,29,31,33,34 and six in Caucasian populations.15,24,28,30,32,35 In terms of source of controls, 3 studies recruited controls from hospital (HB)25,28,29 and
**TABLE 1. Characteristics of the Studies Included in the Meta-analysis**

| First Author (Year)          | Country (Ethnicity) | Type       | Source of Control | Total | AA | AP | PP | Total | AA | AP | PP | Genotype method | HWE  |
|-----------------------------|---------------------|------------|-------------------|-------|----|----|----|-------|----|----|----|----------------|------|
| Nakano 2000                 | Japan (Asian)       | AML        | PB                | 200   | 82 | 93 | 25 | 188   | 59 | 95 | 34 | PCR-SSCP        | 0.69 |
| Bergamaschi 2004            | Italy (Caucasian)   | CML        | PB                | 96    | 49 | 47 | 10 | 174   | 106| 61 | 7  | PCR-RFLP        | 0.63 |
| Takeuchi 2005               | Japan (Asian)       | ALL        | HB                | 87    | 33 | 38 | 16 | 89    | 32 | 37 | 20 | PCR-RFLP        | 0.15 |
| Kochethu 2006               | UK (Caucasian)      | CML        | PB                | 203   | 119| 62 | 22 | 97    | 44 | 40 | 13 | PCR-RFLP        | 0.42 |
| Ellis 2008                  | USA/UK (Caucasian)  | AML        | PB                | 171   | 95 | 66 | 10 | 302   | 171| 112| 181| Taqman/PCR-RFLP | 0.81 |
| Phang 2008                  | China (Asian)       | AL         | PB                | 44    | 13 | 25 | 6  | 160   | 56 | 72 | 32 | PCR-RFLP        | 0.32 |
| Xiong 2009                  | China (Asian)       | AML        | HB                | 231   | 52 | 127| 52 | 128   | 39 | 64 | 25 | PCR-RFLP        | 0.99 |
| Do 2009                     | USA (Caucasian)     | ALL        | PB                | 114   | 50 | 45 | 19 | 414   | 234| 154| 26 | Taqman/PCR-RFLP | 0.92 |
| Chauhan 2011                | India (Asian)       | AML        | PB                | 120   | 32 | 66 | 22 | 202   | 47 | 114| 41 | PCR-RFLP        | 0.07 |
| Dunna 2012a                 | India (Asian)       | AML        | PB                | 141   | 64 | 44 | 33 | 245   | 79 | 123| 43 | PCR-RFLP        | 0.68 |
| Dunna 2012b                 | India (Asian)       | ALL        | PB                | 147   | 59 | 67 | 21 | 245   | 79 | 123| 43 | PCR-RFLP        | 0.68 |
| Chauhan 2012a               | India (Asian)       | AML        | PB                | 131   | 38 | 71 | 22 | 199   | 51 | 112| 36 | PCR-RFLP        | 0.06 |
| Chauhan 2012b               | India (Asian)       | ALL        | PB                | 99    | 28 | 43 | 28 | 199   | 51 | 112| 36 | PCR-RFLP        | 0.06 |
| de Lourdes Perim 2013       | Brazil (Caucasian)  | ALL        | PB                | 54    | 33 | 18 | 3  | 58    | 46 | 11 | 1  | PCR-SSP         | 0.72 |
| Chen 2013                   | China (Asian)       | ALL        | PB                | 174   | 39 | 90 | 45 | 356   | 113| 183| 60 | PCR-RFLP        | 0.33 |
| El-Danasouri 2014           | Egypt (Caucasian)   | AML        | HB                | 50    | 20 | 20 | 10 | 50    | 14 | 31 | 5  | PCR-RFLP        | 0.24 |

AA = individuals who do not inherit a mutant allele; AP = individuals who are heterozygote for the mutant allele; PP = individuals who are homozygote for the mutant allele; AML = acute myeloid leukemia; ALL = acute lymphocytic leukemia; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; AL = acute leukemia; HB = hospital based; PB = population based; PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; PCR-SSCP = polymerase chain reaction-single strand conformation polymorphism; PCR-SSP = polymerase chain reaction-sequence-specific primer; HWE = Hardy–Weinberg equilibrium.
TABLE 2. Pooled ORs and 95% CIs for the Association Between TP53 Gene Polymorphism and Leukemia Susceptibility

| Subgroups | Pro vs Arg | Homozygous Model | Heterozygous Model | Dominant Model |
|-----------|------------|------------------|-------------------|---------------|
|            | N | OR(95%CI) | OR(95%CI) | OR(95%CI) | OR(95%CI) |
| Overall    | 16 | 1.06(0.90–1.21) | 0.94(0.76–1.15) | 0.77(0.64–0.94) | 0.96(0.79–1.15) |
| Ethnicity  |  |  |  |  |  |
| Asian      | 10 | 0.97(0.84–1.13) | 0.80(0.69–1.14) | 0.77(0.56–1.08) | 0.97(0.73–1.28) |
| Caucasian  | 6  | 1.22(0.88–1.69) | 1.06(0.81–1.40) | 0.93(0.69–1.26) | 1.12(0.81–1.54) |
| Alleles    | 16 | 1.06(0.90–1.21) | 0.94(0.76–1.15) | 0.77(0.64–0.94) | 0.96(0.79–1.15) |
|  | 7  | 1.24(0.93–1.65) | 1.12(0.80–1.57) | 0.93(0.62–1.40) | 1.01(0.64–1.60) |
|  | 3  | 1.03(0.62–1.65) | 1.00(0.55–1.85) | 0.95(0.50–1.79) | 0.95(0.59–1.57) |
|  | 3  | 1.08(0.86–1.36) | 0.92(0.77–1.11) | 0.95(0.72–1.28) | 0.95(0.72–1.28) |
|  | 13 | 1.03(0.88–1.25) | 0.94(0.80–1.13) | 0.95(0.74–1.24) | 0.93(0.74–1.24) |

| AMI-related AML | Acute myeloid leukemia, AML | Acute lymphocytic leukemia, ALL | Hospital-based population-based | Pro/Pro vs Arg/Arg | Pro/Pro vs Arg/Arg |
|-----------------|-----------------------------|---------------------------------|-------------------------------|--------------------|--------------------|
|                 |                | 71.38                          | 65.48                         | 0.95(0.80–1.13)    | 0.93(0.80–1.13)    |

13 from general population (PB).15, 23, 24, 26, 27, 30–35 The genotype distributions of controls from all the included studies were consistent with HWE.

Meta-Analysis

Table 2 summarizes the main results of meta-analysis. Overall, no significant association was observed between TP53 Arg72Pro polymorphism and leukemia susceptibility (Pro vs Arg: OR = 1.19, 95% CI = 0.93–1.51). In subsequent subgroup analyses, the results showed that the TP53 Arg72Pro polymorphism was not associated with either AML or ALL, and this negative association persisted in other subgroup analyses, for example, by ethnicity or sources of controls (Table 2).

Sensitivity Analysis

No substantial alterations occurred during sensitivity analysis through omitting 1 included study each time (Figure 3 shows the result for the Pro/Pro vs Arg/Arg model), which demonstrates the robustness of the results.

Publication Bias

Begg’s funnel plot seemed symmetric for each genetic model, showing no significant publication bias (Figure 4 for Pro/Pro vs Arg/Arg model), which was confirmed with Egger’s test (Pro vs Arg, P = 0.68; Pro/Pro vs Arg/Arg, P = 0.96; Arg/Pro vs Arg/Arg, P = 0.59; [Arg/Pro + Arg/Arg] vs Arg/Arg, P = 0.81; Pro/Pro vs [Arg/Pro + Arg/Arg], P = 0.76).

DISCUSSION

Leukemia is a multifactorial and complex disease, and the genetic effect has been considered as an important element for its development.36 Many studies reported the effects of TP53 Arg72Pro polymorphism on the susceptibility of leukemia. In 2000, for the first time, Nakano et al performed a case-control study and reported that this polymorphism might decrease the risk of AML in Japanese population.23 However, similar results were not achieved by subsequent studies, and the association between TP53 Arg72Pro polymorphism and leukemia susceptibility is still controversial. In the present study, we collected all available published studies and performed meta-analysis to assess the relationship between TP53 Arg72Pro polymorphism and leukemia susceptibility, but no significant association was found in overall analysis. Furthermore, similar results were also found in subgroup analyses according to ethnicity, types of leukemia (either AML or ALL), and source of controls.

We are aware of a relevant published meta-analysis indicating that TP53 Arg72Pro polymorphism is not associated with leukemia susceptibility (5 studies).37 When stratified by ethnicity, a protective effect of the TP53 codon 72 Pro allele was found in Asians even with a small number of studies (331 cases and 437 controls).37 Compared with the previous meta-analysis, this meta-analysis grouped subgroups with more accuracy, involved more studies, and provided a more accurate association estimation.

There are some limitations in the present study. Significant heterogeneity, for example, appeared in most of the genetic models. Intersubtype heterogeneity may be frequent in meta-analyses of genetic association studies. However, its occurrence
may have certain relevance to different enrollment criteria for study subjects, diverse environmental circumstances, multiple interactions among genes and environment factors, and various genotyping methods. After stratified analyses by types of leukemia, source of controls and ethnicity, the significance of heterogeneity still could not be eliminated completely. In addition, considering variant pathogenetic mechanisms underlying leukemia development, we attempted to perform a comprehensive subgroup analysis stratified by types of leukemia, unfortunately, because of the limited number of studies, we cannot get reliable information and findings concerning chronic leukemia, and only performed stratified analyses on the association between TP53 Arg72Pro polymorphism and risk of ALL (n = 6), risk of AML (n = 7), and risk of other types of leukemia (n = 3) (Table 2). Therefore, as data from emerging new studies become available, future meta-analysis should address separately the association between genetic variants and different types of leukemia. Lastly, since the leukemia onset involves multiple genetic and environmental factors, although TP53 Arg72Pro polymorphism showed no independent significant association with the susceptibility of this disease, it may have influence on leukemia susceptibility in combination with other elements, which was not analyzed in our study due to the lack of sufficient data.

| Study name        | Odds ratio  | Lower limit | Upper limit | Z-Value | Value |
|-------------------|-------------|-------------|-------------|---------|-------|
| Nakano 2000       | 0.529       | 0.288       | 0.979       | -2.028  | 0.043 |
| Bergamaschi 2004  | 3.090       | 1.110       | 8.600       | 2.161   | 0.031 |
| Takeuchi 2005     | 0.778       | 0.342       | 1.757       | -0.609  | 0.543 |
| Kochethu 2006     | 0.628       | 0.290       | 1.349       | -1.197  | 0.231 |
| Ellis 2008        | 0.997       | 0.510       | 1.947       | -0.009  | 0.993 |
| Phang 2008        | 0.808       | 0.280       | 2.332       | -0.395  | 0.693 |
| Xiong 2009        | 1.560       | 0.829       | 2.936       | 1.378   | 0.168 |
| Do 2009           | 3.420       | 1.758       | 6.865       | 3.620   | 0.000 |
| Chauhan 2011      | 0.788       | 0.397       | 1.564       | -0.681  | 0.496 |
| Dunna 2012a       | 0.947       | 0.541       | 1.660       | -0.189  | 0.850 |
| Dunna 2012b       | 0.854       | 0.351       | 1.217       | -1.340  | 0.180 |
| Chauhan 2012a     | 0.820       | 0.417       | 1.613       | -0.574  | 0.566 |
| Chauhan 2012b     | 1.417       | 0.721       | 2.784       | 1.010   | 0.312 |
| de Lourdes Perim 2013 | 4.182   | 0.416       | 42.000      | 1.216   | 0.224 |
| Chen 2013         | 2.173       | 1.278       | 3.695       | 2.865   | 0.004 |
| El-Danasouri 2014 | 1.400       | 0.392       | 4.997       | 0.518   | 0.604 |
|                  | 1.133       | 0.844       | 1.521       | 0.830   | 0.406 |

**Meta Analysis**

**FIGURE 2.** Overall ORs for leukemia susceptibility and TP53 gene polymorphism under the Pro/Pro versus Arg/Arg model with random effects model. ORs = odds ratio.

**FIGURE 3.** Forest plot of sensitivity analysis (Pro/Pro vs Arg/Arg model).
Despite the above-mentioned limitations, the results in the present meta-analysis still had certain reliability. First, there was no significant publication bias among selected studies. Second, none among included studies had crucial impact on overall results, which indicated the stability of the outcomes. And last, the meta-analysis itself presents a more powerful tool compared with any single study.

In conclusion, although TP53 gene polymorphism has been confirmed to be associated with increased risk of some malignancies, this meta-analysis suggests that TP53 codon 72 polymorphism may not be independently associated with leukemia susceptibility, especially for AML and ALL. In the future, larger-scale case-control studies are needed to further investigate the association between genetic variants and different types of leukemia separately.

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FIGURE 4. Funnel plot for publication bias (Pro/Pro vs Arg/Arg model).
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