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META-ANALYSIS

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Association Between *TP53* Gene Codon 72 Polymorphism and Acute Myeloid Leukemia Susceptibility: Evidence Based on a Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEG 1 **Xiao-Lan Ruan**
BDEF 2,3 **Sheng Li**
BDF 2,3 **Peiliang Geng**
BCF 2,3,4 **Xian-Tao Zeng**
BCDF 2,3 **Guo-Zheng Yu**
BCD 2,3 **Xiang-Yu Meng**
A 1 **Qing-Ping Gao**
BD 1 **Xu-Bin Ao**

1 Department of Hematology, Targeted Biotherapy Key Laboratory of Ministry of Education, Renmin Hospital of Wuhan University, Wuhan, Hubei, P.R. China
2 Center for Evidence-Based and Translational Medicine, Zhongnan Hospital, Wuhan University, Wuhan, Hubei, P.R. China
3 Center for Evidence-Based and Translational Medicine, Wuhan University, Wuhan, Hubei, P.R. China
4 Center for Evidence-based Medicine and Clinical Research, Taihe Hospital, Hubei University of Medicine, Shiyan, Hubei, P.R. China

Corresponding Authors: Qing-Ping Gao, e-mail: gaoqingping2014@163.com; Xu-Bin Ao, e-mail: aoxubin@163.com
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Background: Many studies have reported that the p53 codon 72 polymorphism is associated with acute myeloid leukemia (AML) susceptibility; however, the conclusions are inconsistent. Therefore, we performed this meta-analysis to obtain a more precise result.

Material/Methods: We searched PubMed to identify relevant studies, and 6 published case-control studies were retrieved, including 924 AML patients and 3832 controls. Odds ratio (OR) with corresponding 95% confidence interval (95%CI) was applied to assess the association between p53 codon 72 polymorphism and AML susceptibility. The meta-analysis was performed with Comprehensive Meta-Analysis software, version 2.2.

Results: Overall, no significant association between p53 codon 72 polymorphism and AML susceptibility was found in this meta-analysis (Pro *vs.* Arg: OR=0.94, 95%CI=0.81–1.10; Pro/Pro *vs.* Arg/Arg: OR=0.93, 95%CI=0.71–1.22; Arg/Pro *vs.* Arg/Arg: OR=0.79, 95%CI=0.55–1.13; (Pro/Pro + Arg/Pro) *vs.* Arg/Arg: OR=0.84, 95%CI=0.62–1.13; Pro/Pro *vs.* (Arg/Arg + Arg/Pro): OR=1.06, 95%CI=0.83–1.35). Similar results were also found in stratified analysis according to ethnicity and source of controls.

Conclusions: Our meta-analysis demonstrates that p53 codon 72 polymorphism may not be a risk factor for AML, which should be verified in future studies.

MeSH Keywords: Genes, p53 • Leukemia, Myeloid • Meta-Analysis • Polymorphism, Genetic

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Background

The tumor suppressor p53 (TP53) is a principal mediator of multiple cellular functions, including cell cycle arrest, senescence, and apoptosis in response to cellular stresses [1]. Located on chromosome 17p13, the *TP53* gene has been considered as a significant determinant factor in human carcinogenesis [2]. The *TP53* codon 72 polymorphism Arg72Pro (rs1042522), an amino acid substitution of arginine (Arg)→proline (Pro) at position 72 [3], is one of the most investigated polymorphisms. Published meta-analyses have indicated that *TP53* Arg72Pro polymorphism is associated with increased risk of some malignancies, such as lung cancer [4], cervical cancer [5], bladder cancer [6], nasopharyngeal carcinoma [7], thyroid carcinoma [8], prostate cancer [9], and skin cancer [10]. However, other meta-analyses found no significant association between *TP53* Arg72Pro polymorphism and certain malignancies, like head and neck cancer [11], oral squamous cell carcinoma [1], ovary cancer [12], and sarcoma [13]. Obviously, the associations between the polymorphism and tumors vary in different types of malignancies.

Acute myeloid leukemia (AML) is a hematological malignancy involving genetic alterations. Hence, much attention has been paid to the issue of whether *TP53* Arg72Pro polymorphism is associated with AML risk. In 2000, Nakano et al. performed a case-control study and reported that this polymorphism might decrease the risk of AML in the Japanese population [14]. However, subsequent studies showed divergent results about *TP53* Arg72Pro polymorphism and AML susceptibility. In this case, a meta-analysis is needed to pool these controversial outcomes for a more precise result [15].

Material and Methods

Literature search

A comprehensive search was conducted in PubMed for studies detecting the association between p53 gene polymorphism and ML susceptibility up to December 11, 2014. Keywords were combined with Boolean operators "OR" and "AND", and contained the following MeSH or text words: (Tumor Suppressor Protein p53[MH] or "tumor protein p53" or genes, p53[MH] or "p53") and (polymorphism[MH] or polymorph* or "SNPs" or "SNP" or mutation[MH] or mutat* or Genetic Variation[MH] or varian*) and (leukemia, myeloid[MH] or "myeloid leukemia"). The search strategy used English and Chinese languages, and the bibliographies of the included studies and recent reviews were checked for additional relevant publications.

Study selection criteria

Every study included in this analysis had to meet the following criteria: (1) with case-control or cohort design; (2) investigating the association between *TP53* gene Arg72Pro polymorphism and the susceptibility to AML; (3) cases were enrolled from patients with ML, and controls were from healthy population. Both diagnosed cases and controls accorded with laboratory medicine and clinical criteria, 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 if they satisfied any of the following exclusion criteria: (1) abstracts or unpublished records; (2) studies in which the genotype frequencies were not reported and could not be calculated. As for overlapped publications, the most comprehensive one was selected.

Data extraction

Two reviewers were responsible for data extraction separately following the same standard. The principal information of included studies to be extracted included first author, publication year, country, ethnicity, source of controls, numbers of cases and controls, genotype distribution, genotyping method, and Hardy-Weinberg equilibrium (HWE). All discrepancies during this work were solved by discussion between the 2 reviewers.

Statistical analysis

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. Comprehensive Meta Analysis software (version 2.2; Biostat, Englewood, N.J., USA) [16,17] was used for forest plots, heterogeneity test, and other data analyses. Heterogeneity was evaluated by the Cochran's *Q* statistic [18] and the I^2 statistic [19]. If heterogeneity was significant ($P<0.1$ or $I^2>25\%$), the random-effects model was used, otherwise, the fixed-effects model was employed. Subgroup analysis was also conducted. In addition, the influence of every single study on the overall results was investigated by removing each study in turn so as to test the robustness of the main results. Potential publication bias was assessed by visual inspection of the funnel plots, and Egger's regression method provided corresponding statistical evidence ($P<0.05$ represented statistical significance) [20,21].

Results

Study characteristics

Of the 579 records found initially, 6 case-control studies [14,22–26] were ultimately included involving 924 cases and 3832 controls. A detailed flowchart of the selection process is shown in Figure 1. Table 1 exhibits the major characteristics

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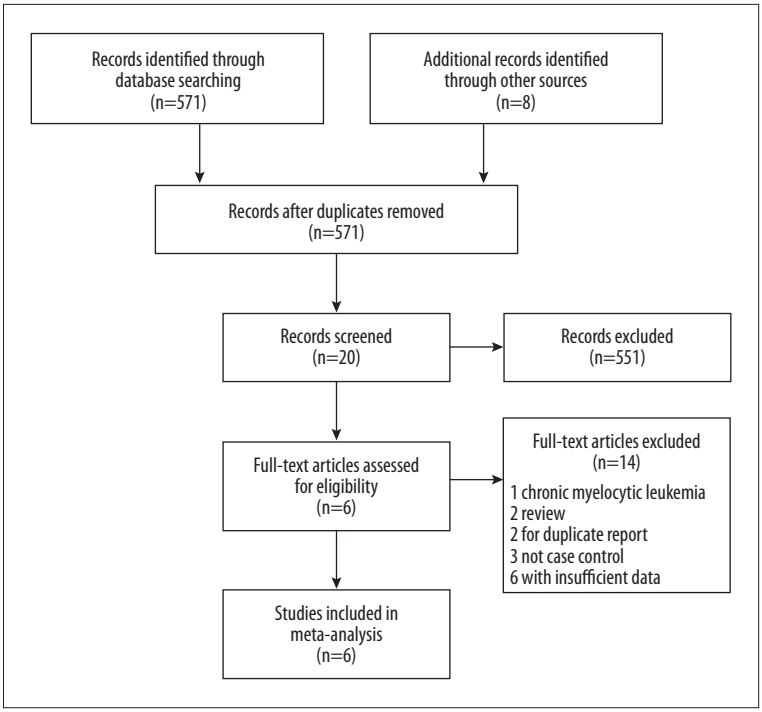

Figure 1. Flowchart of study selection.

Table 1. Characteristics of the studies included in the meta-analysis.

Reference	Country (Ethinicity)	Source of control	Case				Control				Genotype method	HWE
			Total	AA	AP	PP	Total	AA	AP	PP		
Nakano 2000	Japan (Asian)	PB	200	82	93	25	188	59	95	34	PCR-SSCP	0.77
Ellis 2008	USA/UK (Caucasian)	PB	171	95	66	10	3022	1714	1127	181	PCR-RFLP	0.85
Xiong 2009	China (Asian)	HB	231	52	127	52	128	39	64	25	PCR-RFLP	0.99
Chauhan 2012	India (Asian)	PB	131	38	71	22	199	51	112	36	PCR-RFLP	0.06
Dunna 2012	India (Asian)	PB	141	64	44	33	245	79	123	43	PCR-RFLP	0.68
El-Danasouri 2014	Egypt (Caucasian)	HB	50	20	20	10	50	14	31	5	PCR-RFLP	0.24

AA represents individuals who do not inherit a mutant allele; AP represents individuals who are heterozygote for the mutant allele; PP represents individuals who are homozygote for the mutant allele; HB – hospital based; PB – population based; HWE – Hardy-Weinberg equilibrium.

of the 6 case-control studies [14,22–26]. Four studies were conducted in Asian populations [14,23–25] and 2 in white populations [22,26]. In terms of source of controls, 2 studies recruited controls from hospital (HB) [23,26] and 4 from general population (PB) [14,22,24,25]. The genotype distributions of controls from all included studies were consistent with HWE.

Meta-analysis and sensitivity analysis

Table 2 shows the main results of meta-analysis. Overall, no significant association was observed between *TP53* Arg72Pro polymorphism and AML risk [Pro *vs.* Arg: OR=0.94, 95%CI=0.81–1.10; Pro/Pro *vs.* Arg/Arg: OR=0.93, 95%CI=0.71–1.22, Figure 2; Arg/Pro *vs.* Arg/Arg: OR=0.79, 95%CI=0.55–1.13; (Pro/Pro+Arg/Pro) *vs.* Arg/Arg: OR=0.84, 95%CI=0.62–1.13; Pro/Pro *vs.* (Arg/Pro+Arg/Arg): OR=1.06, 95%CI=0.83–1.35]. Similarly, in the succeeding stratified subgroup analysis, we also did not find any significant association (Table 2).

No substantial alterations occurred in results during sensitivity analysis through omitting 1 included study every time (Figure 3 shows the result for the Pro/Pro *vs.* Arg/Arg model), implying 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

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Table 2. Pooled ORs and 95% CIs for the association between p53 genetic polymorphism and AML susceptibility.

Overall and subgroups	N	Pro *vs.* Arg		ProPro *vs.* ArgArg		ArgPro *vs.* ArgArg		(ProPro + ArgPro) *vs.* ArgArg		ProPro *vs.* (ArgPro + ArgArg)	
		OR (95%CI)	I^2 (%)	OR (95%CI)	I^2 (%)	OR (95%CI)	I^2 (%)	OR (95%CI)	I^2 (%)	OR (95%CI)	I^2 (%)
Overall	6	0.94 (0.81–1.10)	30	0.93 (0.71–1.22)	21.55	0.79 (0.55–1.13)	69.2	0.84 (0.62–1.13)	60	1.06 (0.83–1.35)	23
Source of controls											
PB	4	0.88 (0.77–1.02)	6.37	0.80 (0.58–1.09)	0	0.74 (0.51–1.08)	67.3	0.78 (0.58–1.04)	51.36	0.97 (0.69–1.36)	30.46
HB	2	1.17 (0.90–1.54)	0	1.53 (0.87–2.69)	0	0.87 (0.27–2.78)	80.87	1.00 (0.40–2.52)	72.94	1.34 (0.82–2.17)	0
Ethnicity											
Asian	4	0.91 (0.73–1.14)	53.73	0.89 (0.58–1.38)	48.92	0.79 (0.49–1.27)	74.75	0.82 (0.54–1.24)	69.29	1.02 (0.72–1.44)	36.67
Caucasian	2	1.02 (0.81–1.28)	0	1.07 (0.59–1.94)	0	0.77 (0.34–1.72)	68.05	0.89 (0.54–1.49)	39.59	1.29 (0.59–2.78)	34.33

HB – hospital based; PB – population based; OR – odds ratio; CI – confidence interval; I^2 – test for heterogeneity.

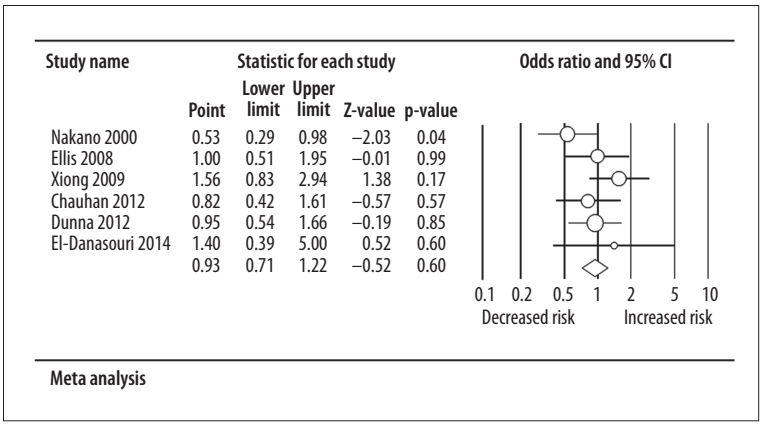

Figure 2. Overall ORs for AML susceptibility and p53 genetic polymorphism under Pro/Pro *vs.* Arg/Arg model with random-effects model.

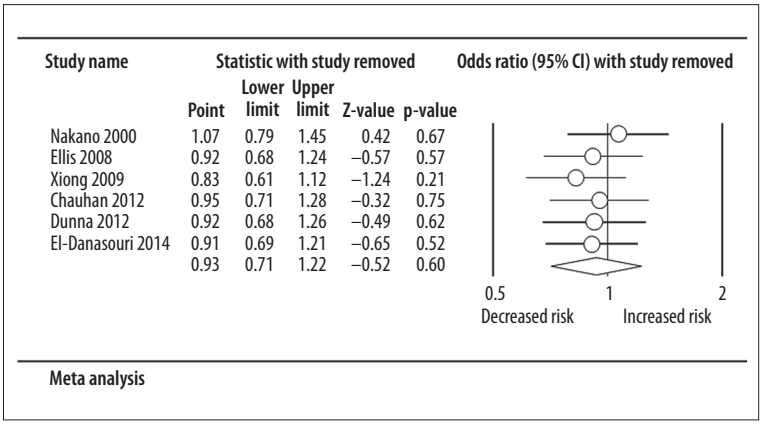

Figure 3. Forest plot of sensitivity analysis (Pro/Pro *vs.* Arg/Arg model).

vs. Arg/Arg model), which was confirmed with Egger's test [Pro *vs.* Arg, *P*=0.99; Pro/Pro *vs.* Arg/Arg, *P*=0.61; Arg/Pro *vs.* Arg/Arg, *P*=0.42; (Pro/Pro+Arg/Pro) *vs.* Arg/Arg, *P*=0.60; Pro/Pro *vs.* (Arg/Pro+Arg/Arg), *P*=0.50].

Discussion

AML is a multifactorial and complex disease, in which genetic effect has been considered as an important element. Many

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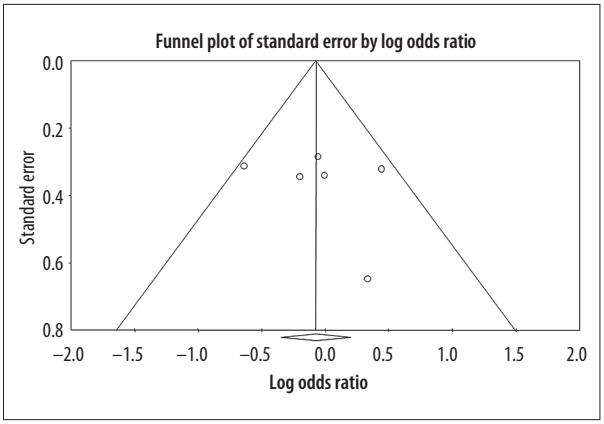

Figure 4. Funnel plot for publication bias (Pro/Pro *vs.* Arg/Arg mode).

studies reported the effects of *TP53* Arg72Pro (rs1042522) polymorphism on the susceptibility of myeloid leukemia. In 2004, for the first time, Bergamaschi et al. [27] reported that allele A1 (proline residue, Pro72) was more frequent in patients with CML than in controls, and among CML patients who had no cytogenetic response than among responders. However, the subsequent studies did not achieve the same or similar results, and the association between *TP53* Arg72Pro polymorphism and AML susceptibility is still controversial. This meta-analysis of 6 case-control studies was performed to assess the relationship between TP53 Arg72Pro polymorphism and AML susceptibility, but no significant association was found in overall analysis. Furthermore, similar results were also found in stratified analysis according to ethnicity and source of controls.

It should be noted that there are some limitations in the present study. Significant heterogeneity, for example, appeared among most of the genetic models. Inter-study heterogeneity may be frequent in the meta-analysis of studies on genetic association, but its occurrence also has certain relevance to some aspects, such as different enrollment criteria for study subjects, diverse environmental circumstances, multiple interactions among genes and environment factors, and various genotyping methods [28]. After stratification analyses by ethnicity, and source of control, the significance of heterogeneity still could not be eliminated completely. In addition, the number of included studies was limited, and the sample size was relatively small. Therefore, the evidence about the association in this meta-analysis may be less powerful. Furthermore, AML onset involves multiple genetic and environmental factors, and although p53 polymorphism showed no independently significant association with the risk of the disease, it may influence AML risk in combination with other elements, which was not analyzed in our study due to the lack of sufficient data. Despite the above limitations, the results in the present meta-analysis are reliable. First, there was no significant publication bias among selected studies. Second, no single included study had a crucial impact on the whole results, indicating the stability of the outcomes. Lastly, the meta-analysis itself presents a more powerful tool compared with any single study.

Conclusions

Although p53 gene polymorphism has been confirmed to be associated with increased risk of some malignancies, our meta-analysis suggests that p53 gene polymorphism may not be independently associated with AML risk. In the future, larger-scale case-control studies are needed to further investigate the exact correlation of the TP53 codon 72 polymorphism with AML susceptibility.

Conflict of interest

All authors declared there was none conflict of interest.

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