

## RESEARCH COMMUNICATION

# Updated Meta-analysis of the TP53 Arg72Pro Polymorphism and Gastric Cancer Risk

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### Abstract

**Objective:** The p53 tumor suppressor pathway plays an important role in gastric cancer (GC) development. Auto-regulatory feedback control of p53 expression is critical to maintaining proper tumor suppressor function. So far, several studies between p53 Arg72Pro polymorphism and GC have generated controversial and inconclusive results. **Methods:** To better assess the purported relationship, we performed a meta-analysis of 19 publications. Eligible studies were identified by searching the Pubmed database. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess any link. **Results:** Overall, a significant association was detected between the p53 Arg72Pro polymorphism and GC risk (Pro-allele vs. Arg-allele: OR = 1.05, 95% CI = 1.01-1.08; Pro/Pro vs. Arg/Arg: OR = 1.13, 95% CI = 1.04-1.22). Moreover, on stratified analysis by race, significantly increased risk was found for Asian populations (Pro-allele vs. Arg-allele: OR = 1.06, 95% CI = 1.02-1.10; Pro/Pro vs. Arg/Arg: OR = 1.16, 95% CI = 1.07-1.26; Pro/Pro+Pro/Arg vs. Arg/Arg: OR = 1.58, 95% CI = 1.09-2.27). **Conclusions:** Our study provided evidence that the p53 72Pro allele may increase GC risk in Asians. Future studies with larger sample size are warranted to further confirm this association in more detail.

**Keywords:** P53 - gastric cancer- polymorphism- meta-analysis

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### Introduction

A 2005 analysis of the worldwide incidence of and mortality from cancer showed that 934,000 cases of gastric cancer (GC) occurred in 2002 and that 700,000 patients die annually of this disease (Parkin et al., 2002). Gastric carcinogenesis is a multi-step process, in which environmental and genetic factors interact. The response of the gastric mucosa to exogenous damaging agents is partly regulated by inhibitory and stimulatory factors, which are products of proto-oncogenes and tumour suppressor genes. Improper function of these inhibitory and stimulatory factors is associated with chronic damage of the gastric mucosa (Zhou et al., 2007).

Apoptosis is regulated by a variety of genes, including p53, which may play an important role to keep the homeostasis of the tissue dynamics (Etienne et al., 2002). TP53, which encodes p53, is a tumor suppressor gene and key player in the stress responses that preserve genomic stability, responding to a variety of insults, including DNA damage, hypoxia, metabolic stress and oncogene activation (Vogelstein et al., 2002; Vousden et al., 2007). Up to 50% of the patients with GC were reported to have p53 alterations (Levine, 1997).

Although p53 contains several polymorphic sites, only those in exon 4 have been examined in GC. Of these, the codon 72 polymorphism (rs1042522) is by

far more common, which results in the substitution of arginine (Arg) by proline (Pro) in the transactivating domain (Shepherd et al., 2007). Changes in its amino acid sequence can alter the ability of p53 to bind to response elements in target genes, alter recognition motifs for post-translational modifications or alter p53 stability and interactions with other proteins (Walker et al., 1996; Thomas et al., 1999; Bergamaschi et al., 2003; Li et al., 2007). Such changes may contribute to tumor progression and a poor prognosis (Katkoori et al., 2009).

Taking into consideration of the extensive role of p53 in GC, hence, to derive a more precise estimation of the association of Arg72Pro polymorphism between p53 gene and GC, we performed a meta-analysis of all eligible case-control studies (Hamajima et al., 2002; Hiyama et al., 2002; Zhang et al., 2003; Shen et al., 2004; Wu et al., 2004; Lai et al., 2005; Mu et al., 2005; Pérez-Pérez et al., 2005; Sul et al., 2006; Yi et al., 2006; Capellá et al., 2008; De Feo et al., 2009; Gomes de Souza et al., 2009; Kim et al., 2010; Mojtahedi et al., 2010; Shirai et al., 2010; Ihsan et al., 2011; Song et al., 2011; Zhu et al., 2012).

### Materials and Methods

#### *Selection of eligible studies*

PubMed database was searched with the keywords 'TP53' or 'p53', 'polymorphism' and 'gastric' or 'stomach'

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**Table 1. Characteristics of Studies of p53 Arg72Pro Polymorphism Included in This Meta-analysis**

First author	Year	Country	Ethnicity	Cases	Controls	MAF	HWE	Design	Genotype methods
Zhu	2011	China	Asian	140	125	0.472	0.307	HB	PCR-TaqMan
Song	2012	Korean	Asian	2213	1700	0.34	0.481	PB	PCR-TaqMan
Ihsan	2011	India	Asian	134	282	0.484	0.621	PB	PCR-RFLP
Mojtahedi	2010	Iran	Asian	92	163	0.407	0.778	PB	PCR-RFLP
Shirai	2010	Japan	Asian	389	419	0.365	0.812	PB	PCR-CTPP
Kim	2009	Korean	Asian	534	531	0.377	0.074	PB	PCR-RFLP
Feo	2009	Italy	European	114	295	0.254	0.13	HB	PCR-RFLP
Souza	2009	Brazil	Mixed	84	185	0.294	0.709	HB	PCR-RFLP
Capella	2008	Spain	European	245	1168	0.253	0.875	PB	PCR-SSCP
Sul	2006	USA	European	155	134	0.391	0.604	PB	PCR-RFLP
Yi	2006	Korea	Asian	292	216	0.349	0.474	PB	PCR-RFLP
Mu	2005	China	Asian	194	390	0.469	0.098	PB	PCR-RFLP
Perez	2005	Mexico	Mixed	65	182	0.385	0.773	HB	PCR-RFLP
Lai	2005	Taiwan	Asian	51	59	0.356	0.765	PB	PCR-RFLP
Wu	2004	Taiwan	Asian	89	192	0.456	0.971	HB	PCR-RFLP
Shen	2004	China	Asian	324	317	0.451	0.732	PB	PCR-RFLP
Zhang	2003	UK	European	120	277	0.316	0.197	HB	PCR-RFLP
Hiyama	2002	Japan	Asian	117	116	0.345	0.932	HB	PCR-RFLP
Hamajima	2002	Japan	Asian	144	239	0.402	0.232	HB	PCR-CTPP

HB, hospital-based; PB, population-based; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSCP, single strand conformation polymorphism; CTPP, confronting two-pair primers

and ‘cancer’ or ‘tumor’, last search updated on June 26 2011. The search was complemented with a perusal of the bibliographies of retrieved papers and review articles. Eligible studies had to meet the following criteria: (a) the study assessed the correlation between GC and the polymorphisms cited above; (b) case-control studies; (c) control subjects matched with case patients for age and gender and (d) only full-text manuscripts were included. Major exclusion criteria were a) no control population; b) no available genotype frequency; c) duplication of the previous publications and d) not English language source.

#### Data Extraction

The characteristics of selected studies were independently extracted through a standardized protocol by two investigators. Data were collected on the first author’s last name, year of publication, country of origin, ethnicity, subjects of cases and controls, study design, Minor Allele Frequency (MAF) and Hardy–Weinberg equilibrium (HWE) in control group and genotype methods.

#### Statistic analysis

For the purpose of this analysis, the raw data for genotype frequencies were used for calculation of the ORs and their 95% CIs, which were used to evaluate risk. Subgroup analysis stratified by race was performed first, which was categorized as European, Asian and Mixed (Brazilian and Mexican are two of the most heterogeneous populations in the world). Source of control subgroup analysis was performed on two classifications: population-based (PB) and hospital-based (HB).

The statistical significance of the summary OR was determined with the Z-test. Heterogeneity assumption was evaluated with a chi-square-based Q test among the studies. A P value of more than 0.05 for the Q-test indicated a lack of heterogeneity among the studies. If P heterogeneity >0.05 was detected, the random effects model was used

(Mantel et al., 1959), whereas P heterogeneity >0.05, the fixed effects model was chosen (DerSimonian et al., 1986). For p53 Arg72Pro polymorphism, we investigated the association between genetic variants and GC risk in dominant genetic model (Pro/Pro+Pro/Arg vs. Arg/Arg), using random effects model; homozygote comparison (Pro/Pro vs. Arg/Arg), using fixed effects model; allelic contrast (Pro-allele vs. Arg-allele), using fixed effects model. The possibility of publication bias was assessed by examining funnel plots and formally evaluated with the Begg adjusted rank correlation test and Egger regression asymmetry test (Egger et al., 1997). HWE was assessed by  $\chi^2$  test in controls using the Pearson chi-square test,  $P < 0.05$  was considered significant. All statistical tests were done with Stata software (version 10.0; StataCorp LP, College Station, TX).

## Results

#### Characteristics of studies

A total of 19 were retrieved based on the search criteria for risks of GC related to the p53 Arg72Pro polymorphism. Characteristics of studies of p53 Arg72Pro polymorphism are summarized in Table 1. Cases were diagnosed according to histopathology and cancer-free controls were used in all studies. Of these eligible studies, 13 were in Asian, 4 in European and 2 in Mixed populations. Hospital-based cases were used in eight studies. A classic polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was adopted in 14 of the 19 studies. Genotype distributions among the controls of all studies were in agreement with HWE.

#### Meta-analysis

Meta-analysis of the association between p53 Arg72Pro polymorphism and risk of GC included 19 studies with 5496 cases and 6990 controls. There was a wide variation in p53 72Pro allele frequencies in the

**Table 2. Stratified Analyses of p53 Arg72Pro Polymorphism on Gastric Cancer Risk**

Variables	N	Cases/ Controls	Pro-allele vs. Arg-allele		Pro/Pro vs. Arg/Arg		Pro/Pro+Pro/Arg vs. Arg/Arg	
			OR(95%CI)	P <sub>h</sub>	OR(95%CI)	P <sub>h</sub>	OR(95%CI)	P <sub>h</sub>
Total	19	5496/6990	1.05(1.01-1.08)	0.091	1.13(1.04-1.22)	0.133	1.11(0.75-1.62)	<0.001
Race								
Asian	13	4713/4749	1.06(1.02-1.10)	0.166	1.16(1.07-1.26)	0.099	1.58(1.09-2.27)	<0.001
Mixed	2	149/367	0.92(0.75-1.12)	0.121	0.91(0.55-1.50)	0.355	1.00(0.47-2.11)	0.048
European	4	634/1874	1.00(0.90-1.11)	0.174	0.93(0.69-1.26)	0.356	0.35(0.09-1.30)	<0.001
Source of control								
HB	8	873/1611	0.99(0.92-1.07)	0.209	1.03(0.87-1.23)	0.436	0.70(0.45-1.08)	<0.001
PB	11	4623/5379	1.06(1.02-1.10)	0.113	1.22(0.99-1.50)	0.041	1.57(0.77-3.20)	<0.001

P<sub>h</sub>, P-value for heterogeneity

control groups across different studies, ranging from 0.25 in an Italian population (De Feo et al., 2009) to 0.54 in a Taiwanese population (Wu et al., 2007). The mean Pro-allele frequencies were 0.30 in European and 0.33 in Mixed populations, respectively, and there was no significant difference ( $P > 0.05$ ). In addition, the Pro-allele frequency among Asians was 0.43, which was statistically significantly higher than above two races ( $P > 0.01$ ).

In the overall analysis, significantly increased association could be observed between GC risk and the variant genotypes of p53 Arg72Pro in two genetic models (Pro-allele vs. Arg-allele: OR = 1.05, 95% CI = 1.01-1.08, Pheterogeneity = 0.09,  $P = 0.01$ ; Pro/Pro vs. Arg/Arg: OR = 1.13, 95% CI = 1.04-1.22, Pheterogeneity = 0.13,  $P = 0.01$ , Table 2).

In the stratified analysis by race subgroup, a significant association between p53 Arg72Pro and GC was found in Asians (Pro-allele vs. Arg-allele: OR = 1.06, 95% CI = 1.02-1.10, Pheterogeneity = 0.17,  $P > 0.01$ ; Pro/Pro vs. Arg/Arg: OR = 1.16, 95% CI = 1.07-1.26, Pheterogeneity = 0.10,  $P > 0.01$ ; Pro/Pro+Pro/Arg vs. Arg/Arg: OR = 1.58, 95% CI = 1.09-1.27, Pheterogeneity = 0.01,  $P > 0.01$ ).

Similarly, in the subgroup of source of control, significantly increased relationship was found in PB (Pro-allele vs. Arg-allele: OR = 1.06, 95% CI = 1.02-1.10, Pheterogeneity = 0.11,  $P > 0.01$ , Table 2).

#### Publication bias

A funnel plot for visual assessment of publication bias was tested. Formal evaluations of publication bias using the Begg's test and Egger's test showed no statistical evidence for publication bias (Pro-allele vs. Arg-allele:  $t = -0.72$ ,  $P = 0.48$ ; Pro/Pro vs. Arg/Arg:  $t = -1.30$ ,  $P = 0.21$ ; Pro/Pro+Pro/Arg vs. A/rqArg:  $t = 0.34$ ,  $P = 0.74$ ).

## Discussion

In the present meta-analysis, we explored the association between the p53 Arg72Pro polymorphism and GC risk, involving 19 published case-control studies. We found that individuals with 72Pro allele or 72Pro/Pro genotype showed a increased risk of GC compared with those with the Arg72 allele or Arg/Arg72 genotype, respectively. Moreover, also a significantly increased GC risk was found among the Asian population. Furthermore, significantly increased GC risk was detected in HB source of control in the comparison of 72Pro allele vs. Arg72 allele.

p53 tumor suppressor plays a role in regulating the cell cycle, DNA repair and synthesis, and programmed cell death (Lane, 1992). Mutation of p53 leads to disruption of these pathways during tumor progression. Individuals homozygous for Pro have been reported to be more likely to develop lung cancer and experience a poor clinical outcome (Birgander et al., 1996; Wang et al., 1999). Similarly, the Pro allele has also been found to show an increased frequency in breast cancer patients (Själänder et al., 1997; Papadakis et al., 2000). These studies were consistent with our meta-analysis.

Some studies have reported conflicting findings on the association of p53 Arg72Pro polymorphism with the risk and prognosis of GC. There are two histologically distinct GC: the diffuse-type and intestinal-type. When GC was not classified by tissue type, the Arg/Arg genotype of p53 codon 72 was found to be related to the development of distal GC in the Mexican population (Pérez-Pérez et al., 2005) and the Arg allele with non-cardias GC in the Chinese (Shen et al., 2004). In addition, patients with cardiac cancer had a significantly higher frequency of the Arg/Arg genotype than chronic gastritis, DU and non-cardiac cancer in the UK (Zhang et al., 2004). In contrast, Pro allele carriers were indicated to show more progress to GC in China (Xi et al., 2004), similarly, Pro/Pro genotype was identified as a significant risk factor for GC in the USA (Sul et al., 2006).

To date, there have been two meta-analyses based on p53 Arg72Pro polymorphism and GC risk. Zhou et al. (2007) reported that a significant lower frequency of p53 72Arg allele in Asian gastric cancer patients. However, Gao et al. (2009) showed that p53 72Pro was associated with increased risk of diffuse type gastric cancer among Asians, but decreased risk of intestinal gastric cancer among Caucasians. Our meta-analysis confirmed the results with Gao et al. (2009), moreover, our study contains larger and well-designed multi-centric studies and all of included case-control studies were agreement with HWE.

Some limitations of our meta-analysis should be addressed. Although the mechanisms leading to GC are yet not clear, it seems that environmental, Helicobacter pylori-infection and dietary factors as well as genetic susceptibility play a role in the etiology of GC. The existence of gene-environment and gene-gene interactions may explain the discrepancy of results obtained in individual genetic association studies and additional work is needed to determine the functionality of the genetic variants. Second, our meta-analysis was based

on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other covariates including age, sex, family history, cancer stage and lifestyle. In spite of these, our meta-analysis also had four advantages. First, substantial number of cases and controls were from different studies, which significantly increased statistical power of the analysis. Second, the quality of case-control studies included in the current meta-analysis was satisfactory based on our selection criteria. Third, publication bias was not detected in all genetic models, suggesting that the results were relatively stable and powerful. Fourth, all of included studies were agreement with HWE.

In conclusion, our meta-analysis provides evidence that the p53 72Pro allele or Pro/Pro genotype is a risk factor for GC in Asians. Future studies should use standardized non-biased genotyping methods and homogeneous populations of patients with cancer in addition to well-matched controls and multiethnic groups. Furthermore, studies that investigate gene-gene and gene-environment interactions may help further elucidate the genetics of GC risk.

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The author(s) declare that they have no competing interests.

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