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ORIGINAL PAPER

Matrix Metalloproteinase-1 (*MMP1*) Polymorphism is Associated with Lowered Risk of Nasopharyngeal Carcinoma in Asian Population

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Abstract Data on the association between −1607 1G > 2G polymorphism in the promoter region of matrix metalloproteinase-1 (*MMP1*) and nasopharyngeal carcinoma (NPC) are conflicting. The aim of this study was to confirm whether this polymorphism was a causative factor of NPC. We searched PubMed, Embase, and China National Knowledge Infrastructure (CNKI) for studies on the present topic. A total of four publications (1,044 NPC patients and 1,284 healthy control subjects) were included and meta-analysis was performed to assess the association between −1607 1G > 2G polymorphism and NPC risk. Odds ratio (OR) with 95 % confidence interval (95 % CI) was calculated for 1G1G versus 2G2G, 1G1G + 1G2G versus 2G2G, 1G1G versus 1G2G + 2G2G, 1G versus 2G, and 1G2G versus 2G2G contrast models. Meta-analysis results showed significantly reduced risk of NPC associated with the 1G1G versus 2G2G, 1G versus 2G and 1G2G versus 2G2G contrast models (OR = 0.61, 95 % CI 0.49–0.77; OR = 0.78, 95 % CI 0.65–0.92; OR = 0.86, 95 % CI 0.74–0.99, respectively). When we continued to perform subgroup analysis by ethnicity, the significant association persisted in Asian population and was most pronounced under the 1G2G versus 2G2G model (OR = 0.85, 95 % CI 0.73–0.99). These data suggested that *MMP1* −1607 1G > 2G polymorphism was associated with reduced risk of NPC, particularly in the population of Asian descent.

Keywords Matrix metalloproteinase-1 · Polymorphism · Nasopharyngeal carcinoma

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Introduction

Nasopharyngeal carcinoma (NPC) is a generally rare cancer worldwide, with the incidence rate of 1 per 100,000 people each year. Southern China, nevertheless, is suffering an obviously higher prevalence rate. The average incidence increases to 30 per 100,000 people [1, 2]. Environmental factors, such as Epstein-Barr virus, tobacco use, dietary habits, and occupational exposure to poisonous chemicals accelerate the development of NPC [3], but only a small fraction of individuals who are exposed to these factors develop NPC, implicating an effective role of genetic susceptibility in this cancer. Familial aggregation is a remarkable epidemiological feature of NPC. There is sufficient evidence for a positive association between high-incidence families and high-incidence [4–6].

Matrix metalloproteinase-1 (*MMP1*) is a member of MMP family that is characterized by breaking down

extracellular matrix components and basement membranes, and facilitating cell invasion and metastasis [7]. *MMP1* affects many stages of tumorigenesis, promoting tumor growth through stimulating cellular proliferation, invasion and migration, angiogenesis, and suppressing tumor cells apoptosis [8–10]. Molecular and biochemical expression of *MMP1* are relevant to clinical outcomes of numerous cancers. High expression could lead to a poor prognosis of colorectal cancer, head and neck squamous cell cancer and lung cancer [11–13]. Single nucleotide polymorphisms (SNPs) in the promoter region serve as mediators for *MMP1* expression. 1G/2G polymorphic site at the 1,607 locus is a common deletion/insertion polymorphism. *MMP1* expression can be up-regulated by insertion of −1607 2G, consequently resulting in increased cancer risk [14–17].

Recently, −1607 1G > 2G polymorphism (rs1799750) within the promoter region of *MMP1* has been extensively investigated in the field of NPC, but reported with controversial results [18, 19]. Most importantly, as far as we know, no previous meta-analysis has reported the association of −1607 1G > 2G polymorphism and NPC. In view of these problems, we performed a meta-analysis to confirm whether this polymorphism was a causative factor of NPC.

Materials and Methods

Publication Search

To cover all publications on the relationship between −1607 1G > 2G polymorphism and NPC risk, two investigators systematically searched

PubMed (http://www.ncbi.nlm.nih.gov/pubmed).
Embase (http://www.elsevier.com/online-tools/embase).
China National Knowledge Infrastructure (CNKI, http://www.cnki.net/) using the keywords: ''nasopharyngeal carcinoma,'' ''NPC,'' ''Matrix metalloproteinase-1,'' ''*MMP1,*' ''polymorphism,'' "polymorphisms," "genotypes," and "variants." We updated the last search on February, 2014. All eligible studies were retrieved and their bibliographies were manually screened for additional relevant publications.

Inclusion Criteria

Selection of studies eligible for the current meta-analysis was based on

(a) Publication date was prior to December, 2013;
(b) The association of −1607 1G > 2G polymorphism and NPC risk must be addressed;
(c) Healthy unrelated subjects were selected as control population;
(d) The author must publish allele and genotype frequency that could estimate the risk of NPC.

When the same case series was repeatedly studied in more than one publication, the one with more complete data was considered.

Data Extraction

A standardized form according to the inclusion criteria was designed before data extraction, which was performed by two investigators independently. Information gathered from the studies included (a) last name of the first author; (b) publication year; (c) study country; (d) ethnicity; (f) matching criteria; (g) source of controls; and (h) genotype frequencies of −1607 1G > 2G polymorphism. In a case that a single study contained two or more independent case–control populations, we retrieved them separately and categorized them into their own ethnic groups.

Statistical Analysis

In order to demonstrate if the studies deviated from Hardy–Weinberg equilibrium (HWE), we evaluated HWE for the control populations using the goodness-of-fit χ^2 test. Association strength of −1607 1G > 2G polymorphism and NPC risk was measured by an odds ratio (OR) with 95 % confidence interval (95 % CI). The ORs were calculated for 1G1G versus 2G2G, 1G1G + 1G2G versus 2G2G, 1G1G versus 1G2G + 2G2G, 1G versus 2G, and 1G2G versus 2G2G contrast models. Heterogeneity assumption was evaluated by the χ^2-based Q test and I^2 index [20, 21], with a P value above 0.10 or $I^2 < 50$ % being considered non-significant. To assess the effective size for each study, the fixed-effect model (the Mantel-Haenszel method) was employed if the studies were homogeneous [22]. Otherwise, the ORs were summarized using the random-effect model (the DerSimonian and Laird method) [23]. To further detect the heterogeneity, subgroup analyses were performed by ethnicity. Stability of the combined results was determined by performing sensitivity analysis. Publication bias in the literature was estimated by funnel plot and Egger's linear regression test [24]. Asymmetric funnel plots or P values of Egger's test below 0.10 were suggestive of significant publication bias. STATA version 12.0 software (Stata Corporation, College Station, TX) was used to deal with all statistical data. All tests were two-sided and $P < 0.10$ was deemed statistically significant.

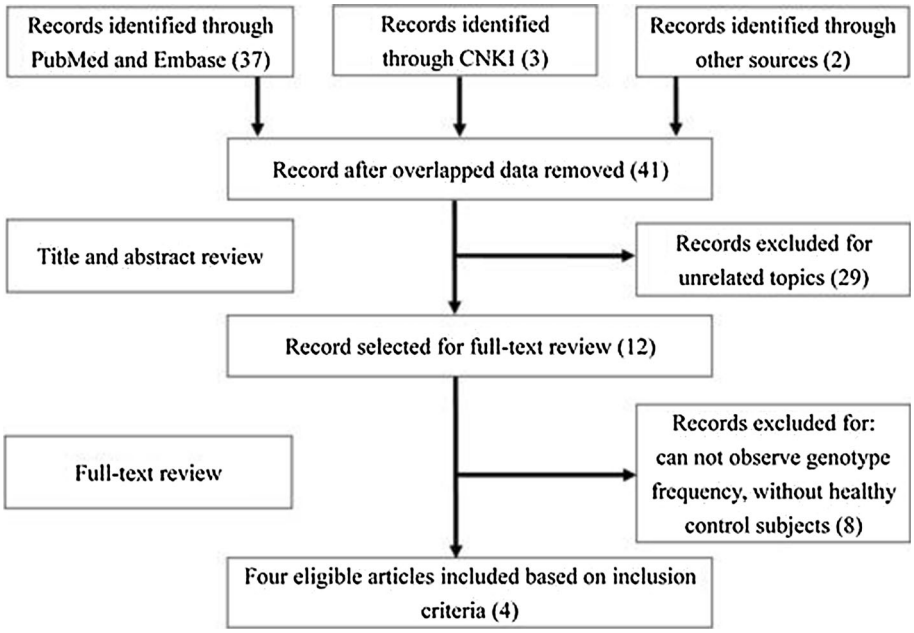

Fig. 1 Flow chart for primary selection

Table 1 Description of studies included in the meta-analysis for MMP1 −1607 1G > 2G polymorphism

Author-year of publication		Control source	Country	Cases	Control	Matching	HWE
Asian	Kondo	Population	Japan	44	59	Age/sex	Yes
	Kondo	Population	Japan	39	23	Age/sex	Yes
	Zhou	Population	China	317	479	Age/residential area	Yes
	Zhou	Population	China	238	280	Age/residential area	Yes
	Gao	Population	China	232	272	Age/sex	Yes
African	Nasr	Population	Tunisia	174	171	ND	No

Results

Characteristics of the Included Studies

We initially retrieved 42 publications matching the search terms. We then verified their eligibility according to the pre-described inclusion criteria, and finally selected 4 full-text articles with complete data [18, 19, 25, 26]. The selection process is described in Fig. 1.

Table 1 summarizes the characteristics of the four publications, including all extracted information listed previously (data extraction). In the studies of Kondo et al. [25] and Zhou et al. [19], the genotype frequencies were completely presented for two independent case–control populations; thus, our meta-analysis included six case–control studies involving 1 044 NPC patients and 1,284 healthy control subjects. All of these studies were carried out in Asian countries except for Nasr et al. [18], who initiated their study in Africa. This was the only study deviating from HWE.

Meta-Analysis Results

We first compared the minor allele (1G) frequency between patients and controls. The 1G allele frequency was 0.26 in cancer patients, which was lower compared to the control subjects (0.35). Main meta-analysis results are shown in Table 2. As obvious heterogeneity was observed in part of the contrast models, both the fixed-effect model and the random-effect model were performed for pooled ORs. Overall, we observed significantly reduced NPC risk related to −1607 1G > 2G polymorphism under the 1G1G versus 2G2G, 1G versus 2G and 1G2G versus 2G2G contrast models (OR = 0.61, 95 % CI 0.49–0.77; OR = 0.78, 95 % CI 0.65–0.92; OR = 0.86, 95 % CI 0.74–0.99, respectively) (Fig. 2).

Since data were sufficiently provided for Asians, we then evaluated the effects in subgroup of Asian population and obtained an OR of 0.63 under the 1G1G versus 2G2G contrast model (OR = 0.63, 95 % CI 0.49–0.80) (Fig. 2). The results also provided an OR of 0.77 for the 1G versus

Table 2 Result of meta-analysis for MMP1 −1607 1G > 2G polymorphism and nasopharyngeal carcinoma

Study groups	No. of studies	Cases/controls	OR (95 % CI)	P_h	I^2 (%)	Model
Total	6	1,044/1,284				
1G1G versus 2G2G	6		0.61 (0.49, 0.77)[a]	0.143	39.7	FEM
1G1G + 1G2G versus 2G2G	6		0.91 (0.61, 1.34)	<0.001	86.5	REM
1G1G versus 1G2G + 2G2G	6		0.71 (0.41, 1.23)	<0.001	78.8	REM
1G versus 2G	6		0.78 (0.65, 0.92)[a]	0.060	52.9	REM
1G2G versus 2G2G	6		0.86 (0.74, 0.99)[a]	0.616	0	FEM
Asian	5	870/1,113				
1G1G versus 2G2G	5		0.63 (0.49, 0.80)[a]	0.095	49.5	FEM
1G1G + 1G2G versus 2G2G	5		0.91 (0.57, 1.45)	<0.001	88.6	REM
1G1G versus 1G2G + 2G2G	5		0.76 (0.41, 1.41)	<0.001	81.5	REM
1G versus 2G	5		0.77 (0.62, 0.95)[a]	0.032	62.0	REM
1G2G versus 2G2G	5		0.85 (0.73, 0.99)[a]	0.482	0	FEM

P_h, P value of Q test for heterogeneity, *REM* random-effect model, *FEM* fixed-effect model

[a] Statistically significant result

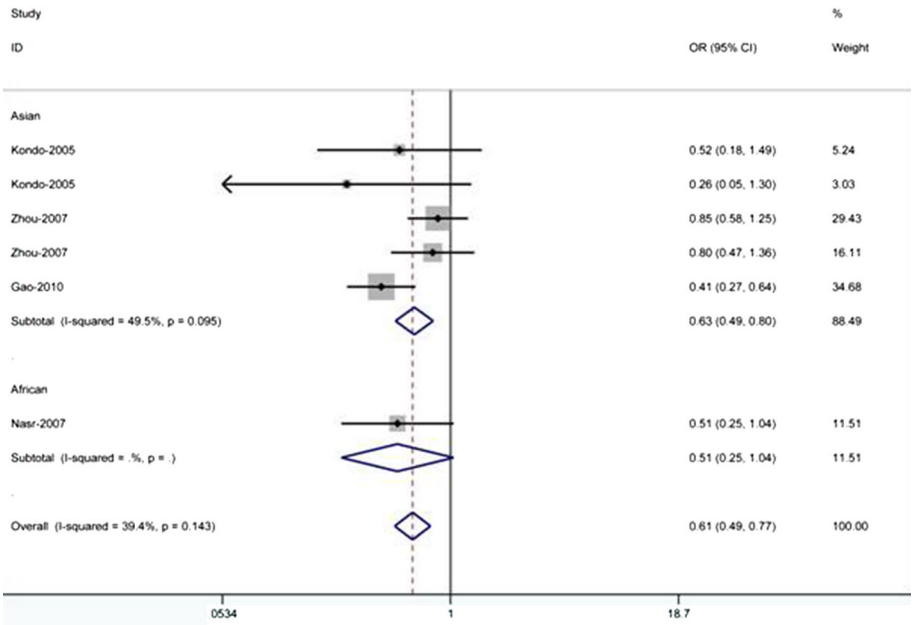

Fig. 2 Forest plot of nasopharyngeal carcinoma (NPC) risk associated with *MMP1* −1607 1G > 2G polymorphism stratified by ethnicity under 1G1G versus 2G2G model. The *boxes* and *horizontal lines* represent the OR and the corresponding 95 % CI. The area of the *boxes* indicates the weight (inverse of the variance). The *diamond* correspond to the summary OR and 95 % CI. Significant association between *MMP1* −1607 1G > 2G polymorphism and NPC risk was observed

2G contrast model (OR = 0.77, 95 % CI 0.62–0.95) and 0.85 for the 1G2G versus 2G2G contrast model (OR = 0.85, 95 % CI 0.73–0.99).

We observed obvious heterogeneity between studies in overall comparisons and subgroup analyses (Table 2). Sensitivity analysis was subsequently carried out and identified the Guangxi population studied by Zhou et al. [19] as the origin. The heterogeneity decreased drastically when we removed the study from meta-analysis. In addition, we found that the primary ORs were significantly altered (data not shown).

Publication Bias

By performing Begg's test and Egger's test, we evaluated publication bias across studies. Neither asymmetry was indicated in the funnel plots nor the P values of Egger's test less than 0.10 were observed, indicating no significant publication bias in this meta-analysis ($P > 0.10$). Figure 3 shows the funnel plot for the 1G1G versus 2G2G contrast model.

Discussion

It is well established that NPC susceptibility is determined by environmental factors. For example, a meta-analysis of six case–control studies associated preserved vegetable consumption in adulthood with NPC risk, and suggested 2.04 fold higher risk compared to the lowest intake. Conversely, fresh vegetables intake decreased the risk of NPC by nearly 40 % [27]. However, the etiology of NPC is still

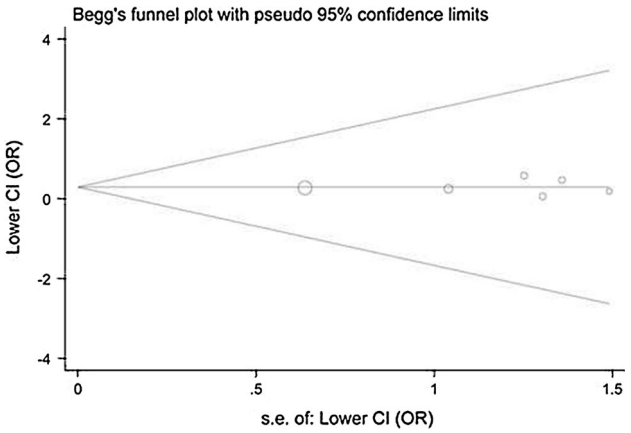

Fig. 3 Begg's funnel plot for *MMP1* −1607 1G > 2G polymorphism. Log OR is plotted versus standard error of Log OR for each included study. Each *circle dot* represents a separate study for the indicated association between *MMP1* −1607 1G > 2G polymorphism and NPC risk under 1G1G versus 2G2G model

incompletely understood. In the past decade, much attention has been directed to the research of host genetic factors and initiation of NPC. A number of susceptibility genes, such as *Interleukin-18*, *NFKB1*, *Cyclin D1*, and *HSP70-2*, have been investigated across different populations and recognized as risk factors [28–31]. Therefore, identification of candidate genes may facilitate an extended understanding of pathogenesis of this malignancy.

Several population-based, clinical, and physiological studies have investigated the relation of −1607 1G > 2G polymorphism and NPC risk. Evidence from these studies, however, failed to suggest a definitive role. Nasr et al. investigated the *MMP1* polymorphism in 174 patients with NPC and 171 healthy control subjects, and found a significantly increased risk of NPC associated with the 2G2G genotype [18]. Afterward, a replication study conducted by Zhou et al. who genotyped two larger independent case–control populations (593 patients with NPC and 480 controls; 239 patients and 286 controls, respectively) reported no association [19]. Several possible factors may cause the discordance, such as insufficient sample size, diverse genetic backgrounds, and different laboratory methods used for each study.

In the present study, we summarized all data from four research publications and performed a meta-analysis in an attempt to examine the relationship between −1607 1G > 2G polymorphism in the promoter region of the *MMP1* gene with the risk of NPC. The overall comparisons showed obviously reduced risk of NPC in the carriage of 1G1G genotype or 1G2G genotype or 1G allele compared to 2G2G genotype and 2G allele. When we continued to perform subgroup analysis by ethnicity, the significant association persisted in Asian population. A recent meta-analysis of head and neck cancer risk detected significant increased risk associated with −1607 1G > 2G polymorphism [32]. Head and neck cancer comprises multiple types of tumors, and NPC is one of them. The etiology of NPC is polygenic in nature and a single genetic polymorphism is typically inadequate to predict the risk of the malignancy. Moreover, the present sample limits us to derive a precise estimate; hence, the association remains to be further verified.

In our meta-analysis, we included four research publications involving six independent case–control studies. But the insufficient sample for overall comparisons as well as subgroup analysis may lack statistical power to precisely detect the association. Besides, heterogeneity was observed between studies. Even though heterogeneity was drastically deceased when eliminating the source, the original combined effects were significantly changed. Also, we did not assess the impact of gene–gene or gene-environment interactions on the development of NPC, because no usable data were allowed for extraction. So now we look forward to performing larger studies to confirm the association in the near future.

To draw a conclusion, this meta-analysis suggested that −1607 1G > 2G polymorphism within the promoter region of *MMP1* could reduce the risk of NPC in the population of Asian descent. Additional research in thousands of subjects with various ethnicities is warranted to further validate the findings in the present study.

Conflict of interest The authors have not declared any conflict of interest.

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