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RESEARCH ARTICLE

Interactions of *miR-34b/c* and *TP-53* polymorphisms on the risk of nasopharyngeal carcinoma

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Abstract Growing evidence indicates that tumor suppressor gene *TP-53* and non-coding RNA miR-34b/c independently and/or jointly play crucial roles in carcinogenesis. We hypothesized that the polymorphisms of rs4938723 in the promoter region of pri-miR-34b/c and *TP-53* Arg72-Pro may be related to the risk of nasopharyngeal carcinoma (NPC). We performed a case–control study between 217 patients with NPC and 360 healthy controls in a Chinese population using polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) assay. A significantly increased risk of NPC was observed in the miR-34b/c rs4938723 CT/CC genotypes compared with the TT genotype (adjusted OR=1.44, 95 % CI 1.02–2.03, p=0.04), and also the C allele (adjusted OR=1.33, 95 % CI 1.04–1.70, p=0.03). The gene–gene interaction of miR-34b/c rs4938723 and *TP-53* Arg72-Pro showed that the combined genotypes of rs4938723CT/CC and *TP-53*CG/CC increased the risk of NPC (rs4938723CT/CC+*TP-53*CG/CC vs. rs4938723 TT+*TP-53* CG/CC: OR=1.58, 95 % CI 1.04–2.42, p=0.03). These findings suggest that miR-34b/c rs4938723 and *TP-53* Arg72Pro polymorphisms may singly or collaboratively contribute to the risk of NPC.

Keywords Nasopharyngeal carcinoma · miR-34b/c · *TP-53* · Genetic polymorphism

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Introduction

Nasopharyngeal carcinoma (NPC) is the most common head and neck tumor originating in the nasopharynx. The incidence is up to 50/100,000 in South China and South Asia but is rare in the Western world (1/100,000) [1–3]. The morbidity of NPC is still high among Chinese people who have migrated to North America, suggesting that genetic factors contribute to the pathogenesis of NPC [4].

p53 is a regulator response to genotoxic stress, such as DNA damage, DNA repair, and cell cycle regulation, which triggers apoptosis after cell injury [5]. The importance of p53 in preventing tumor formation is demonstrated by the presence of mutations in the p53 pathway in nearly all cancers [6]. Although *TP-53* mutation is rare in NPC, abundance studies have shown that p53 protein is overexpressed in NPC [7, 8], and studies focused on *TP53* polymorphism as a predisposing factor for different cancers are increasing. To date, the most studied point mutation in *TP-53* gene is at codon 72, where a polymorphism with an arginine (Arg CGC) residue replaces the proline (Pro CCC) [9]. It has been reported that the *TP-53* codon 72 polymorphism may influence the function of p53 protein and be involved in the susceptibility of several human cancers [10–14].

MicroRNAs (miRNAs) are endogenous non-coding RNA molecules with functions in cell proliferation,

differentiation, apoptosis, and metabolism, which play critical roles in human carcinogenesis. Previous studies have shown that miR-34 family was downregulated in NPC, and the downregulation of miR-34 family regulated several oncogenic signal pathways by binding to the target gene [15–17]. Given the important role the miR-34 plays in tumorigenesis, micro-variation in the regulation of progression or expression may have big effect on its action. The polymorphism of rs4938723C/T is located in the promoter region of pri-miR-34b/c, which is in the CpG island. The variation of rs4938723C to T may affect a predicted GATA-X transcription factor binding [18] and then affect the expression of many target genes related to tumor differentiation and carcinogenesis [19, 20]. Recently, Xu and coworkers reported that rs4938723 but not *TP-53* Arg72Pro polymorphism was associated with an increased risk of hepatocellular carcinoma (HCC) [18]. However, no association study has been explored between rs4938723 polymorphism and NPC susceptibility. In this study, we carried out a case–control study to investigate the relationship between rs4938723 and *TP-53* Arg72Pro polymorphisms and the risk of NPC in a Chinese population (Fig. 1).

Materials and methods

Study subjects

The case–control study included 217 NPC patients and 360 healthy controls. All the subjects were resident in the region of Southwest China. All cases were unrelated Chinese Han population, newly diagnosed (between July 2010 and March 2012 admitted to the Chongqing Cancer Hospital and the West China Hospital, Sichuan University) and histopathologically confirmed, while those who have family cancer history of NPC or recurrent ones were excluded from the study. The clinical stages and histological types were evaluated according to the 2002 American Joint Committee on Cancer staging system. At the same time, clinical pathology parameters were obtained from hospital clinical records. The mean age (SD) of the cases (158 males and 59 females) was 45.2 (11.5) years. The control subjects were genetically unrelated Chinese Han population and were also screened to rule out those who had ever been diagnosed with cancer or family cancer history. The controls were frequency-matched to patients based on gender, age, and ethnic background. The mean age (SD) of the controls (254 males and 106 females) was 44.7 (13.1) years (Table 1).

This study was approved by the ethics committee of the hospital. After informed consent was obtained, study subjects were interviewed to obtain epidemiology information on sociodemographic characteristics, and 2-mL venous blood was collected into an EDTA (disodium salt) tube.

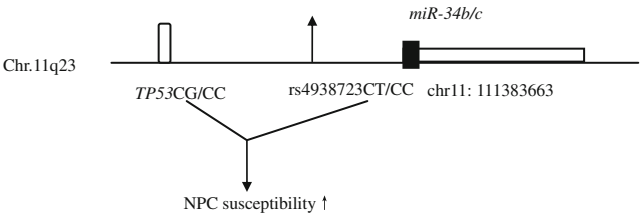

Fig. 1 The relationship between the combined genotypes of *TP53* and rs4938723 and NPC susceptibility

Genotyping

Genomic DNA was extracted from white blood cell using the Bioteke Blood Kit (Bioteke Corporation, Beijing, China) and stored at −20 °C. All the polymorphisms were assessed by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) technique. Primer sequences, reaction conditions, and restriction enzymes (New England BioLabs Inc., Beverly, MA, USA) have been described previously [18, 21]. To ensure quality control, each PCR reaction used sterile ddH_2O instead of DNA as a negative control, and more than 10 % of the samples were analyzed twice.

Statistical analysis

Differences in the distributions of demographic characteristics and frequencies of genotypes of miR-34b/c rs4938723 and *TP-53* Arg72-Pro polymorphisms between the cases and controls were evaluated using the *t* test (for continuous variables) or χ^2 test (for categorical variables). Hardy–Weinberg equilibrium (HWE) was tested using the software of Hardy–Weinberg for each polymorphism among control subjects. A 5 % level of significance was used in the

Table 1 Characteristics of patients with NPC and controls

Variable	Control (n=360)	NPC (n=217)	P value
Age (years, mean±SD)	44.7±13.1	45.2±11.5	NS
Gender (%)			
Male	254 (70.6)	158 (72.8)	NS
Female	106 (29.4)	59 (27.2)	
Clinical stages (%)			
I–II		46 (21.2)	
III–IV		171 (78.8)	
Histological type (%)			
Moderately differentiated cancer		32 (14.7)	
Poorly differentiated cancer		173 (79.7)	
Undifferentiated cancer		12 (5.5)	

NPC nasopharyngeal carcinoma, *SD* standard deviation, *NS* no significance

Table 2 Association between miR-34b/c rs4938723 and *TP-53* Arg72Pro polymorphisms and risk of NPC

Polymorphism	Control (n=360) (%)	NPC (n=217) (%)	Crude OR (95 % CI)	Adjusted OR (95 % CI)[a]	P value
rs4938723					
TT	168 (46.7)	82 (37.8)	1.0	1.0	
CT	155 (43.1)	104 (47.9)	1.38 (0.96–1.98)	1.37 (0.96–1.97)	0.09
CC	37 (10.3)	31 (14.3)	1.72 (0.995–2.96)	1.71 (0.99–2.95)	0.06
CT/CC	192 (53.3)	135 (62.2)	1.44 (1.02–2.03)	1.44 (1.02–2.03)	0.04
T	491 (68.2)	268 (61.8)	1.0	1.0	
C	229 (31.8)	166 (38.2)	1.33 (1.04–1.70)	1.33 (1.04–1.70)	0.03
TP-53 Arg72Pro					
GG	125 (34.7)	73 (33.6)	1.0	1.0	
CG	186 (51.7)	113 (52.1)	1.04 (0.72–1.51)	1.03 (0.71–1.50)	0.88
CC	49 (13.6)	31 (14.3)	1.08 (0.64–1.85)	1.09 (0.64–1.86)	0.75
G	436 (60.6)	259 (59.7)	1.0	1.0	
C	284 (39.4)	175 (40.3)	1.04 (0.81–1.32)	1.02 (0.79–1.32)	0.87

NPC nasopharyngeal carcinoma, *OR* odds ratio, *CI* confidence interval

[a] Adjusted for age and sex using the logistic regression model

analysis, and all statistical tests were two sided. Logistic regression analysis was used to calculate the odds ratio (OR) and 95 % confidence interval (CI) for the effect of miR-34b/c rs4938723 and *TP-53* Arg72-Pro polymorphisms on the risk of NPC adjusted for age and gender. Analysis of data was performed using the computer software SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Totally, 217 patients with NPC and 360 anonymous controls were enrolled in this study. Demographic information and other parameters for all the subjects are summarized in Table 1. No significant differences in age and gender were detected between cases and controls. We have determined the prevalence of miR-34b/c rs4938723 and *TP-53* Arg72-Pro polymorphisms in NPC patients and controls in order to evaluate its association with the risk of NPC (Table 2). Both polymorphisms followed the HWE in the control group (p=0.89 for rs4938723 and p=0.12 for *TP-53* Arg72-Pro). A significantly increased risk of NPC was found in the miR-34b/c rs4938723 CT/CC genotypes compared with the TT genotype (adjusted OR=1.44, 95 % CI 1.02–2.03, p=0.04), and also the C allele (adjusted OR=1.33, 95 % CI 1.04–1.70, p=0.03), while both genotypic and allelic prevalence of the *TP-53* Arg72-Pro polymorphism was remarkably similar between cases and controls. No significant effect on NPC risk was found for *TP-53* Arg72-Pro. Gene–gene interaction analysis showed that various combinations of the miR-34b/c rs4938723 and *TP*-53 Arg72-Pro polymorphisms increased the risk of NPC (rs4938723CT/CC+TP-53CG/CC vs. rs4938723 TT+TP-53 CG/CC: OR=1.58, 95 % CI 1.04–2.42, p=0.03) (Table 3).

Discussion

To our knowledge, this is the first study to investigate the association between the rs4938723 polymorphism in the promoter region of pri-miR-34b/c and NPC risk. We found that the CC/CT genotypes of miR-34b/c rs4938723 were associated with a significantly increased risk of NPC compared with the TT genotype. Gene–gene interaction analysis showed that the combined genotypes of rs4938723CT/CC and *TP-53*CG/CC increased the risk of NPC. We used QUANTO software version 1.2.4 to calculate the statistical power with an effective size of 1.8 under a dominant model, and the type II error was 0.1. These findings indicate that the miR-34b/c and *TP-53* may singly or collaboratively contribute to the etiology of NPC.

Table 3 Combined effects of miR-34b/c rs4938723 and *TP-53* Arg72Pro polymorphisms on NPC risk

NPC nasopharyngeal carcinoma, *OR* odds ratio, *CI* confidence interval

Variable	Control n (%)	NPC n (%)	OR (95 % CI)	P value
rs4938723 TT+*TP-53* CG/CC	111 (30.8)	52 (24.0)	1.0	
rs4938723 CT/CC+*TP-53* CG/CC	124 (34.4)	92 (42.4)	1.58 (1.04–2.42)	0.03
rs4938723 TT+*TP-53* GG	57 (15.8)	30 (13.8)	1.12 (0.65–1.95)	0.68
rs4938723 CT/CC+*TP-53* GG	68 (18.9)	43 (19.8)	1.35 (0.82–2.24)	0.24

miRNA genes have been reported to frequently lie in fragile sites and hot spots for chromosomal abnormalities or locate near cancer susceptibility loci that relate to tumorigenesis [22–24]. One of the most characterized cancer suppressor miRNAs is the miR-34 family. miR-34a is deleted in ~30 % of neuroblastomas, and the miR-34b/c promoter region is always silenced in metastatic cancer cell lines [22, 25–29]. Recently, the expression of miR-34 has been reported to be downregulated in NPC, and the downregulation is involved in the pathology of NPC through several signal pathways [15–17, 30]. The rs4938723C/T polymorphism, located within the CpG island of pri-miR-34b/c, was reported to create a predicted GATA binding site and influence the expression of miR-34b/c [18]. More recently, the polymorphism has been reported to be associated with an increased risk of HCC [18]. Similar to the result in this study, we also found that subjects carrying the CC/CT genotypes of rs4938723 had a 1.44-fold increased risk to develop NPC in the Chinese population. These findings suggest that the C allele of miR-34b/c rs4938723 may be a risk factor for the development of NPC. However, in our previous work, we found that the CC genotype of miR-34b/c rs4938723 was significantly associated with a decreased risk of intracranial aneurysm and colorectal cancer compared with the TT genotype [12, 21]. The possible reason for the conflicting result may be that the same polymorphism plays different roles in different types of cancers [31, 32].

The association between the *TP-53* Arg72Pro and the risk of NPC has been extensively investigated, but the results are controversial. In two independent researches performed in Taiwanese and Tunisians, the investigators found that individuals with Pro/Pro genotype were more prone to develop NPC [10, 33]. In contrast, Tiwawech and colleagues [34] reported that there was no significant association between the *TP-53* polymorphism and NPC risk in a Thai population. In another two studies performed in the south of China and Hong Kong, no association was found between the *TP-53* polymorphism and NPC susceptibility [35, 36]. Consistent with the negative result, we failed to find any association between the *TP-53* Arg72Pro polymorphism and the risk of NPC. Some possibilities should be considered to account for the conflicting results. It may be due to different genetic backgrounds. The positive result reported by Hadhri-Guiga and co-workers was observed in a Tunisian population [10] rather than in Asian populations. As for the other positive result, Tsai and colleagues presented a higher frequency of Pro/Pro genotype in Taiwanese NPC patients with very limited sample sizes, which may result in insufficient statistical power to detect the effect of *TP-53* Arg72-Pro on NPC risk [33]. Further studies, therefore, are necessary to confirm this finding.

When we analyzed the combined effects of miR-34b/c rs4938723 and *TP-53* Arg72-Pro polymorphisms on NPC risk, a significant difference was found between patients with NPC and controls. Individuals who carried the combined genotypes of rs4938723CT/CC and *TP-53*CG/CC had a 1.58-fold increased risk of NPC, suggesting that miR-34b/c interacting with *TP-53* participates in the development of NPC. This finding seems to be biologically plausible because of the interaction between miR-34b/c and p53 [37]. The participation of the miR-34 genes allows p53 to regulate the expression of many proteins, even after their transcripts have already been synthesized. In many types of sporadic and hereditary cancers, the miR-34 family is silenced either by functional inactivation of p53 or by its chromosomal deletion or epigenetic silencing, or both [22, 25, 38–41]. p53-induced mRNA targeting by miR-34 may be involved in the fine tuning of the p53 response and avoid an induced, uncontrolled, and irreversible response to p53 activation [42].

Although we found the association between polymorphisms in the promoter region of pri-miR-34b/c and *TP-53* and the risk of NPC, several limitations still exist in our study. Firstly, the small sample size may limit the statistic power of our study. Secondly, some clinical information of the subjects, such as the status of Epstein–Barr virus infection, is not available, which prevented our further analysis. Thirdly, the study subjects were all ethnic Han Chinese, and the results may not be extended directly to other ethnic groups. Further large-scale studies in different populations, therefore, needed to be done.

In conclusion, our study provides evidence that the polymorphisms of rs4938723 in the promoter region of pri-miR-34b/c and *TP-53* Arg72-Pro may singly or collaboratively contribute to the risk of NPC in the Chinese population. Larger well-designed epidemiological studies with ethnically diverse populations and functional evaluations are warranted to confirm these findings.

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Conflicts of interest None.

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