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Genetic polymorphisms in interleukin 13 gene with the susceptibility to nasopharyngeal carcinoma in a Chinese population

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ABSTRACT

Although inflammation is emerging as a candidate risk factor in tumorigenesis of nasopharyngeal carcinoma (NPC). In particular, Interleukin (IL) 13 involved inflammatory diseases and cancers. Single nucleotide polymorphisms in *IL-13* have been associated with multiple cancers. The study analyzed genetic polymorphisms in *IL-13* aiming to investigate its' potential susceptibility with the NPC. The genotyping of polymorphisms (rs20541, rs1295687 and rs2069744) was examined by Snapshot SNP and DNA sequencing. All SNPs were within Hardy-Weinberg equilibrium and each appeared in three genotypes in NPC and controls. Adjusted logistic regression showed that the TT genotype of rs20541 increased the risk of lymph node metastasis (TT vs. CC: OR = 2.87, 95%CI, 1.33–6.18, $P = 0.007$). CT/CC genotypes were associated with the decreased the risk of lymph node metastasis in NPC (CT/CC vs. TT: OR = 0.32, 95%CI, 0.16–0.65, $P = 0.002$). The concentration of IL-13 was significantly elevated in NPC patients compared with controls ($P = 0.012$). Moreover, significant differences were detected in the T-C-T haplotype distribution between NPC patients and controls (OR = 2.47, 95%CI, 1.06–5.78, $P = 0.031$). Our results, the first report, provide evidence that rs20541 polymorphisms may affect the lymph node metastasis of NPC patients in Chinese population.

1. Introduction

Nasopharyngeal carcinoma (NPC) is a highly invasive malignant tumor of the head and neck from the mucosal epithelium, which is a disease with obvious differences in racial and ethnic aspects [1,2]. NPC mainly occurs in a few defined populations countries. China and Southeast Asia region are highest incidence rates (30–50/100,000 and 9–12/100,000, respectively). Environmental factors, including Epstein Barr virus, alcohol consumption, smoking play significant roles in the etiology of NPC [3,4]. Although the etiological study of NPC in recent years has been improved, it remains a highly prevalent and dead cancer in China [5]. The susceptibility association was verified in the many genes and the risk of NPC [6–10]. But looking for more susceptibility biomarkers of NPC is insistent and critical.

In the last decade, many studies have been launched to understand the mechanisms how the immune system impacts the development of cancers. Interestingly, cytokines produced by inflammatory cells can involve growth of tumor cells or the mechanisms of immune surveillance directed by tumors. Interleukin-13 (IL-13) is an important member of T-helper type 2 (Th2) cytokines. Many cells, such as mononuclear phagocytes, natural killer cells, T-helper-2 cells, and B lymphocytes, can produce IL-13 [11,12]. IL-13 is a structural and functional cytokine that regulates the proliferation and the activation of lymphocytes and can also directly impact proliferation in tumor [13]. Furthermore, binding of IL-13 and type II IL-4R can lead to activation of the inflammation pathway, which induces the proliferation and apoptosis resistance [14,15].

Human *IL-13* gene stands on chromosome 5q23.31, which contains several single nucleotide polymorphisms (SNPs). Recently, many studies have reported the association of SNPs in *IL-13* with Glioma [16–19], renal cell carcinoma [20], colorectal cancer [21,22], bladder cancer [23], breast cancer [24], non-Hodgkin lymphoma [25]. Whether polymorphisms of *IL-13* also influence NPC risk? Until now, no studies addressing the relationship of *IL-13* polymorphisms and NPC and their clinical features have been conducted. Here, this work aimed to test three SNPs (rs20541, rs1295687 and rs2069744) in *IL-13* and analyzed the relationship of them with NPC risk in a Chinese population.

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2. Materials and methods

2.1. Subjects and SNPs selection

The study population included 319 NPC patients (139 women and 180 men) diagnosed clinical and histological examination. Meanwhile, healthy controls consisted of 325 age- and gender-matched (128 women and 197 men) without no individual and family history of any tumors; attending a health examination at the same period. The patients and healthy individuals were recruited from the Affiliated Hospital of Youjiang Medical University for Nationalities during the same period. The ethics committees of the above institution approved this study. Informed consent was obtained from all participants. The candidate SNPs were chosen by the following aspects: (1) minor allele frequency (MAF) > 5% of Han Chinese data. (2) The position and potential function of SNPs. (3) Tagging SNPs. (4) the existence of cancers and SNPs in previous papers. Finally, rs20541, rs1295687 and rs2069744 of the *IL-13* gene were selected in the current study.

2.2. DNA isolation and genotyping

To acquire genomic DNA in samples, peripheral blood samples were extracted by standard manufacturer's protocols of blood genome DNA isolation kit (Tiangen Inc., Beijing, China) and stored at −20 °C. The genotyping of three SNPs (rs20541, rs1295687 and rs2069744) was performed using Snapshot SNP technique. The PCR primers were designed by professional primer 3.0 software (http://primer3.ut.ee/). The primers designed for rs20541, rs1295687 and rs2069744 were presented in Table 1. Furthermore, in order to confirm the genotyping results, a method of DNA sequencing was used to prove the results.

2.3. Serum IL-13 level determination

Samples were collected from patients with NPC and controls. The serum was separated after clot at room temperature, and stored until use. Serum IL-13 concentration was measured by commercial enzyme linked immunosorbent assay (ELISA) (eBioscience, California, USA) according the product's guideline. The detectable concentration of the ELISA kits was the range of 1.6–100.0 pg/mL. The calculated overall intra-assay coefficient of variation and inter-assay coefficient of variation are 6.0% and 4.6%. Developed color reaction was tested as 450 nm wave length on an ELISA reader (RT-6000, China).

2.4. Statistical analysis

Data were analyzed by IBM SPSS 17.0 software. Differences in age and gender in NPC group and controls were calculated with Student's *t*-test and χ^2 test. A goodness-of-fit χ^2 test was executed to evaluate Hardy-Weinberg equilibrium (HWE) among the control individuals. The association of genotype and allele frequencies with the NPC risk was performed by adjusted odds ratios (AORs) and 95% confidence intervals (95%CIs) after controlling for other covariates (containing age, gender, smoking, and drinking). We estimated the common haplotypes analysis by the SHEsis software (http://analysis.bio-x.cn/myAnalysis.php). *P* value of < 0.05 was considered to be statistically significant.

Table 2
General characteristics of the NPC patients and control subjects.

Characteristics	NPC (%)	Controls (%)	
Age (years) Mean (± SD)	46.56 ± 11.40	48.06 ± 12.83	0.117
Gender			
Male	180(56.4)	197(60.6)	0.281
Female	139(43.6)	128(39.4)	
Smoking status			
Yes	205(64.3)	187(57.5)	0.080
No	114(35.7)	138(42.5)	
Drinking status			
Yes	111(34.8)	95(29.2)	0.130
No	208(65.2)	230(70.8)	
Tumor stage (%)			
I + II	97(30.4)		
III + IV	222(69.6)		
Lymph node metastasis (%)			
Yes	145(45.4)		
No	174(54.6)		
Distant metastasis (%)			
Yes	111(34.8)		
No	208(65.2)		

3. Results

3.1. Basic characteristics of the subjects

In control group, the average age was 48.1 ± 12.8 years, while NPC group had a mean age 46.6 ± 11.4 years. Table 2 shows the basic characteristics of patients with NPC and controls. For age, no significant difference was found between cases and controls (*P* = 0.117). There was no statistical difference in the gender of patients and controls (*P* = 0.281). In addition, other variables such as smoking status, drinking status and TNM stage were obtained.

3.2. Genetic polymorphisms of SNPs and NPC risk

The results of genotypes in two methods was concordant and all of SNPs have three genotypes (Fig. 1). The genotype and allele frequencies of the candidate SNPs in NPC patients and controls and their associations with NPC risks are summarized in Tables 3 and 4. No significant difference was existed between three SNPs (rs20541 rs1295687,

Table 1
The primer sequences for *IL-13* genotyping.

SNP ID	PCR primers
rs20541	F: 5′-TGGAAAGCCCCTGGTTTGTG-3′ R: 5′-TCCCGCCTACCCAAGACATTTT-3′ E:5′-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGCTTTCGAAGTTTCAGTTGAAC -3′
rs1295687	F: 5′-TTTGCCAACTGGATTTTGACCA-3′ R: 5′-TCTGATGGTGAGGGAACACTGC-3′ E:5′-TTTTTTTTTTTTTTTTTTTTTTTTTTTTTGGGCAAGGA GCGGACTCTACTAA-3′
rs2069744	F: 5′-TTTGCCAACTGGATTTTGACCA-3′ R: 5′-TCTGATGGTGAGGGAACACTGC-3′ E: 5′-TTTTTTGCCTGGCCAACACCAGAGTGT-3′

SNP, single nucleotide polymorphism. F, forward. R, reverse. E, extension.

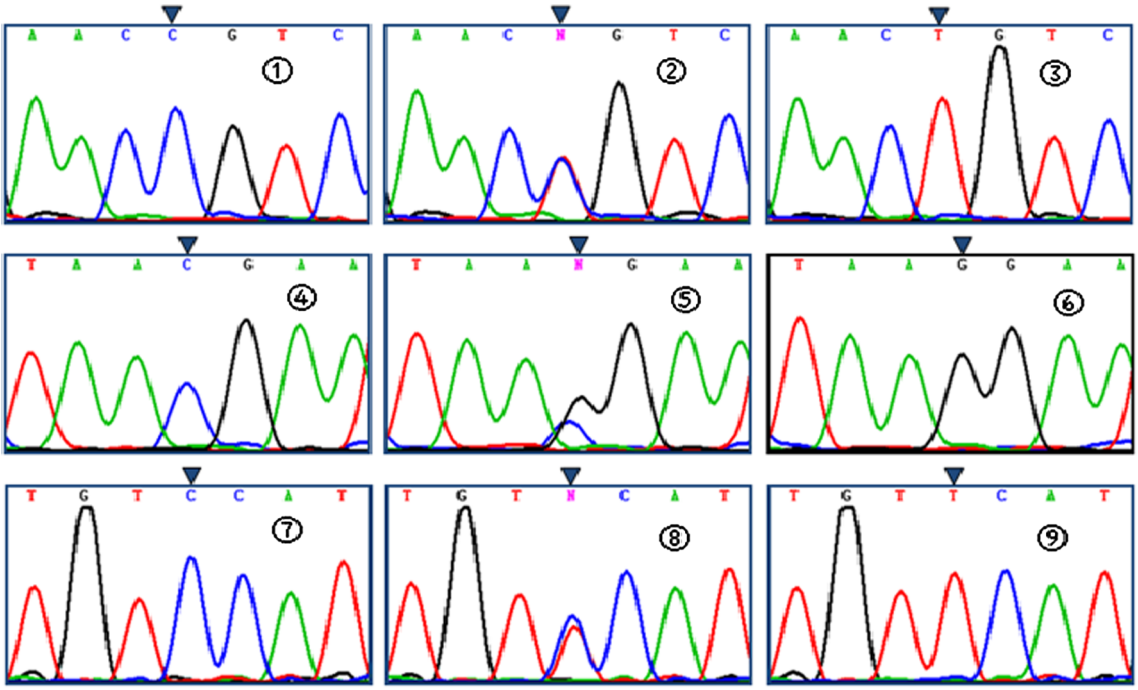

Fig. 1. Sequencing map of three SNPs for *IL-13* gene. Note: ①–③ represent CC, CT and TT genotypes for rs20541; ④–⑥ represent CC, CG and GG genotypes for rs1295687; ⑦–⑨ represent CC, CT and TT genotypes for rs2069744, respectively.

rs2069744) and NPC risk ($P > 0.05$).

3.3. Haplotype analysis of the SNPs

To analyze the common haplotypes of three SNPs, we used the online SHEsis software program and results presented in Table 5. The maximum haplotype (C-G-C) occupied for 43.0% and 46.3% in NPC and controls, respectively. We found that there is a significant difference in the T-C-T haplotype distribution between NPC patients and controls (OR = 2.47, 95%CI, 1.06–5.78, $P = 0.031$).

3.4. rs20541 polymorphism and clinical features

We conducted an analysis to investigate the potential genetic association and the clinical features of NPC and summarized the results in Table 6. Results indicate that the TT genotype of rs20541 increased the risk of lymph node metastasis (TT vs. CC: OR = 2.87, 95%CI, 1.33–6.18, $P = 0.007$). Contrarily, CT/CC genotypes were associated with the decreased the risk of lymph node metastasis in NPC (CT/CC vs. TT: OR = 0.32, 95%CI, 0.16–0.65, $P = 0.002$). No significant association between other two sites and clinical features of NPC was observed ($P > 0.05$).

3.5. Serum IL-13 level and polymorphisms

As shown in Fig. 2A, serum level analyses of IL-13 were examined in NPC patients and controls. The analysis showed that the levels of IL-13 were higher in NPC patients compared with controls ($P = 0.012$).

Table 3
Polymorphism distributions of SNPs in *IL-13* between NPC and controls.

Polymorphisms	NPC (%)	Controls (%)	OR (95%CI)	AOR (95%CI)†	*AP*†
rs20541					
CC	109(34.1)	128(39.4)	1.00(Ref)		
CT	169(53.0)	158(48.6)	1.26(0.90–1.76)	1.24(0.89–1.74)	0.209
TT	41(12.9)	39(12.0)	1.24(0.74–2.05)	1.27(0.76–2.12)	0.365
CT/TT			1.26(0.91–1.73)	1.25(0.90–1.73)	0.182
CT/CC			0.93(0.58–1.48)	0.90(0.567–1.44)	0.647
rs1295687					
GG	210(65.8)	227(69.8)	1.00(Ref)		
CG	92(28.8)	84(25.8)	1.18(0.83–1.68)	1.19(0.83–1.69)	0.341
CC	17(5.4)	14(4.4)	1.31(0.63–2.73)	1.39(0.66–2.90)	0.385
CG/CC			1.20(0.86–1.67)	1.22(0.87–1.70)	0.253
CG/GG			0.80(0.39–1.65)	0.76(0.37–1.58)	0.458
rs2069744					
CC	188(58.9)	200(61.5)	1.00(Ref)		
CT	112(35.1)	103(31.8)	1.16(0.83–1.62)	1.12(0.80–1.58)	0.495
TT	19(6.0)	22(6.7)	0.92(0.48–1.75)	1.00(0.52–1.93)	0.998
CT/TT			1.12(0.81–1.53)	1.10(0.80–1.52)	0.545
CT/CC			1.15(0.61–2.16)	1.04(0.55–1.99)	0.897

Note: OR, odds ratio. 95% CI, 95% confidence interval. Ref, reference. AOR: adjusted OR value; AP: adjusted *P* value.
† Adjusted by age, gender, smoking and drinking.

Table 4
Polymorphism distributions of SNPs in *IL-13* between NPC and controls.

Polymorphisms	NPC (%)	Controls (%)	OR (95%CI)	AOR (95%CI)†	*AP*†
rs20541					
C	387(60.7)	414(63.6)	1.00(Ref)		
T	251(39.3)	236(36.4)	1.14(0.91–1.43)	1.14(0.91–1.44)	0.248
rs1295687					
G	512(80.3)	538(82.8)	1.00(Ref)		
C	126(19.7)	112(17.2)	1.18(0.89–1.57)	1.20(0.90–1.60)	0.208
rs2069744					
C	488(76.5)	503(77.4)	1.00(Ref)		
T	150(23.5)	147(22.6)	1.05(0.81–1.36)	1.06(0.82–1.38)	0.657

Note: OR, odds ratio. 95% CI, 95% confidence interval. Ref, reference. AOR: adjusted OR value; A*P*: adjusted *P* value.
† Adjusted by age, gender, smoking and drinking.

Table 5
Haplotype analysis of the *IL-13* polymorphisms with risk of NPC.

Haplotypes	NPC	Controls	OR (95%)	*P*
C-G-C	274(43.0)	301(46.3)	1.00(Ref)	
C-G-T	51(8.0)	49(7.6)	1.14(0.75–1.75)	0.536
C-C-T	21(3.3)	243.7)	0.92(0.51–1.69)	0.794
C-C-C	41(6.5)	40(6.1)	1.13(0.71–1.79)	0.617
T-G-T	60(9.3)	66(10.1)	1.00(0.69–1.47)	0.995
T-G-C	127(19.9)	122(18.8)	1.14(0.85–1.54)	0.377
T-C-T	18(2.9)	8(1.2)	2.47(1.06–5.78)	0.031
T-C-C	46(7.1)	40(6.2)	1.26(0.80–1.99)	0.312

Unfortunately, we further detected that no difference of level was existed among genotypes in the three SNPs ($P > 0.05$, Fig. 2B–D).

4. Discussion

In the current hospital study, we assessed the association between three SNPs in *IL-13* and NPC susceptibility in a Chinese population and found no significant risk role of them in NPC. But it is noticeable that polymorphism distributions of rs20541 were related with the clinical features of NPC. Concretely, TT genotype of rs20541 increased the risk of lymph node metastasis and CT/CC genotypes were associated with the decreased risk of lymph node metastasis in NPC. Moreover, T-C-T haplotype was significantly associated with a higher risk of NPC. So far, this is the first study to describe the possible role of *IL-13* gene polymorphisms in NPC and found that rs20541 might be related to the risk of NPC.

The rs20541, a missense SNP, changes glutamine to arginine. rs20541 was most widely reported in the tumor population. Nevertheless, the results of those association studies remain argument. Previous studies showed that rs20541 was associated with glioma and non-Hodgkin lymphoma [16,26]. Meta-analysis conducted in glioma patients and controls identified these findings of *IL-13* rs20541 as a risk role of glioma [17,27]. Urayama KY et al. [28] conducted a genome-wide association study, which provide strong evidence that an association between EBV-negative classical Hodgkin lymphoma and rs20541. Hildebrandt MA et al. [29] indicated that rs20541 polymorphism increased the risk of non-small cell lung cancer. On the other hand, Krsteski J et al. [30] observed the TT genotype of rs20541 was significantly associated with decreased risk of uterine leiomyomas (ULM) compared to both the CC and CT genotypes. Deng et al. [31] identified that the functional rs20541 polymorphism may account for the risk of hepatocellular carcinoma (HCC) and it acts as a protective role for HCC population. However, Bao et al. [32] reported that no significant associations were observed between rs20541 and Non-Small Cell Lung Cancer (NSCLC). We found no association between NPC patients and normal controls in the SNP. The possible reason may be that SNPs play various roles in different cancers, especially in different ethnicities.

No association has been observed between rs1295687 with susceptibility to Chinese asthma [33]. Consistent with these data, In the present study, our results also demonstrated that no association was found between rs1295687 polymorphism and NPC risk in the Chinese population. Regrettably, there are no reports about the association between rs2069744 and the risk of diseases.

Table 6
Genotype frequencies of rs20541 in relation to clinical parameters of NPC patients.

Items	NPC (%)		OR (95% CI)	AOR (95%CI)	*AP*
Tumor stage	I + II	III + IV			
CC	28(28.9)	81(36.5)	1.00(Ref)	1.00(Ref)	
CT	56(57.7)	113(50.9)	0.70(0.41–1.19)	0.66(0.38–1.13)	0.129
TT	13(13.4)	28(12.6)	0.75(0.34–1.63)	0.73(0.33–1.63)	0.447
CT/TT			0.71(0.42–1.19)	0.67(0.40–1.13)	0.136
CT/CC			1.07(0.53–2.17)	1.05(0.51–2.14)	0.901
Lymph node metastasis	Positive	Negative			
CC	48(33.1)	61(35.1)	1.00(Ref)	1.00(Ref)	
CT	69(47.6)	100(57.5)	0.88(0.54–1.43)	0.88(0.54–1.43)	0.594
TT	28(19.3)	13(7.4)	2.74(1.28–5.85)	2.87(1.33–6.18)	0.007
CT/TT			1.09(0.69–1.74)	1.10(0.69–1.75)	0.704
CT/CC			0.34(0.17–0.68)	0.32(0.16–0.65)	0.002
Distant metastasis	Positive	Negative			
CC	33(29.7)	76(36.5)	1.00(Ref)	1.00(Ref)	
CT	60(54.1)	109(52.4)	1.27(0.76–2.12)	1.29(0.76–2.16)	0.344
TT	18(16.2)	23(11.1)	1.80(0.86–3.78)	1.83(0.86–3.87)	0.115
CT/TT			1.36(0.83–2.23)	1.38(0.84–2.27)	0.208
CT/CC			0.64(0.33–1.25)	0.64(0.33–1.25)	0.193

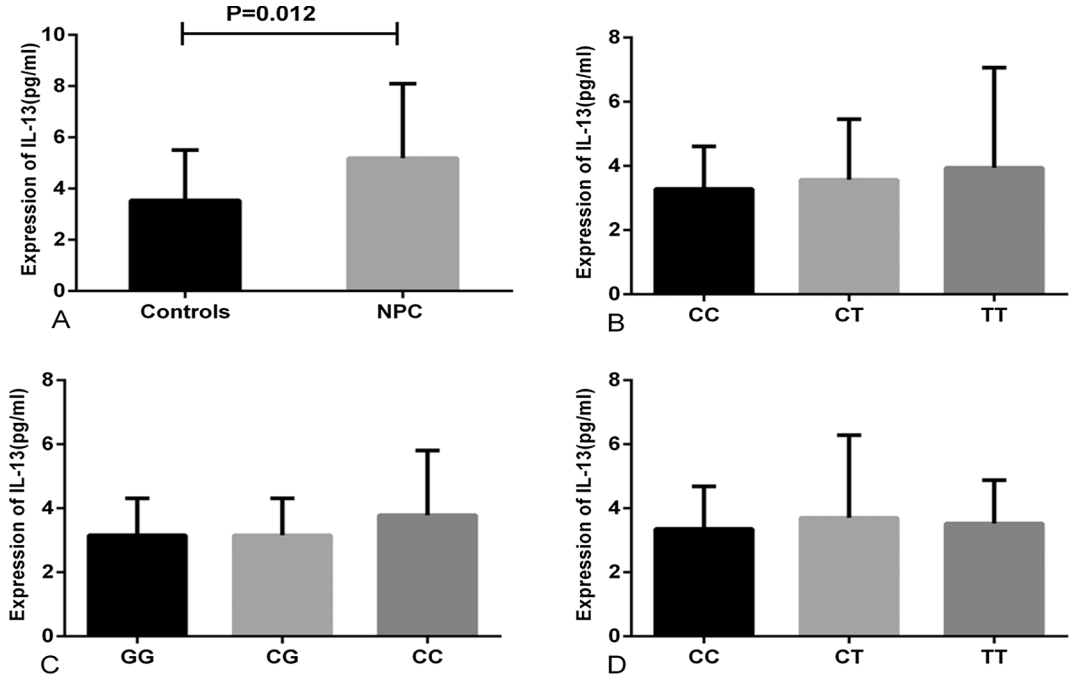

Fig. 2. ELISA detection of IL-13 expression. (A) Serum level of IL-13 in NPC patients and controls. (B) Serum level of IL-13 of patients in rs20541 ($P = 0.906$; $P = 0.807$). (C) Serum level of IL-13 of patients in rs1295687 ($P = 0.754$; $P = 0.727$). (D) Serum level of IL-13 of patients in rs2069744 ($P = 0.684$; $P = 0.776$).

The prevailing view is that the development of cancer is often associated with the inflammatory response [34]. *IL-13* encodes IL-13, a cytokine of immune regulatory produced chiefly by Th2 cells. As closely relevant genes, IL-4 and IL-13 use a shared IL-4Rα subunit that is essential for signaling. Now, studies found that IL-4 was associated that the proliferation of head and neck carcinomas [35]. However, no study explores the role of IL-13 in NPC. The strength of this present study is to analyze the association of IL-13 and NPC. Some potential limitations should be discussed. The first is that information in smoking and drinking are categorized in “Yes“ and “No”. Therefore, more detailed information based on amount is not available. Furthermore, the functional role of IL-13 polymorphism in tumor growth of NPC is worth for further investigation, so which will be included in our future work.

In conclusion, our results firstly provides new evidence of rs20541 genotypes in the *IL-13* with lymph node metastasis of NPC. Studies involving diverse populations are warranted to confirm our results. Furthermore, functional assay should be carried out the mechanism of *IL-13* in NPC.

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Conflict of interest

The authors have declared that no conflict of interest exists.

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