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Contribution of long noncoding RNA *HOTAIR* variants to preeclampsia susceptibility in Iranian women

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ABSTRACT

Objective: To investigate the possible association of lncRNA *HOTAIR* rs920778 and rs874945 polymorphisms with preeclampsia risk in a sample from the Iranian population.

Method: The study subjects included 250 preeclamptic women and 250 healthy women. The genotyping for rs920778 and rs874945 polymorphisms were performed using the TP-ARMS-PCR method.

Results: HOTAIR rs920778 increased the risk of preeclampsia under the dominant and recessive inheritance patterns (OR = 4.84, 95% CI: 3.30–7.10, $P < 0.0001$; OR = 6.86, 95% CI: 3.51–13.42, $P < 0.0001$; respectively).

Conclusion: This study confirmed the association of *HOTAIR* rs920778 polymorphism with preeclampsia in Iranian women. Further studies should be performed to confirm our findings.

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KEYWORDS
Preeclampsia; *HOTAIR*; genetic association study; single nucleotide polymorphism; long noncoding-RNA

Introduction

Preeclampsia (PE) is a systemic disease that affects 2–8% of all pregnancies and is diagnosed by *de novo* onset of hypertension and proteinuria after 20 weeks gestation (1,2). Although PE is the leading cause of maternal and perinatal mortality, the exact etiology of pathogenetic mechanisms is not fully understood (3). A wide range of risk factors is associated with PE, including genetic, environmental, and social factors. Among these, genetic susceptibility plays an important role in the pathogenesis of preeclampsia (4). To date, several candidate genes, including coding and noncoding, are associate with PE (5–9). Long noncoding RNAs (lncRNAs) are the tissue-specific class of RNA defined as transcribed RNA molecules ranging from 200 to 100,000 nucleotides that do not code for any protein (10,11). LncRNAs such as *HOTAIR, H19, MEG3, SPRY4-IT1, ZEB2-AS1, FLT1P1, TUG1*, and *MALAT1* has been suggested to contribute to the behavior of trophoblasts in PE (6). The *HOX Transcript Antisense Intergenic RNA* (*HOTAIR*) manipulates the expression of various genes and also could epigenetically silence target genes by binding to specific gene sites. *HOTAIR* is deregulated in many diseases, including PE (6,8,12). Previous studies have revealed the role of *HOTAIR* in the placental trophoblast function and potentially the development of preeclampsia. *HOTAIR* is significantly up-regulated in PE; however, data about the cause of over-expression are scarce (6,8). Multiple single-nucleotide variants in the *HOTAIR* gene have recently been identified to be significantly associated with a wide range of diseases. Hence, in the current study, we explored the effect of *HOTAIR* rs920778 and rs874945 variants on the genetic susceptibility of PE in a sample of Iranian women.

Materials and methods

Subjects

In this case–control study, a total of 500 participants consisted of 250 preeclamptic pregnant women, and

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250 healthy pregnant women were recruited from Arash hospital, Tehran, Iran between March 2017 and October 2018. The average age was 33.68 ± 4.50, and 31.33 ± 3.15 years in the patients and controls, respectively. Participants with a maternal history of high blood pressure, cardiovascular disease, intrauterine growth restriction (IUGR), diabetes, renal disorders were excluded from the study. Preeclampsia was defined as blood pressure of ≥140/90 with new onset of proteinuria ≥300 mg after 20 weeks of gestation in women without any history of hypertension. The women were of Iranian descent, and informed about the study objectives, and signed informed consent. The study protocol was approved by the ethics committee of the Shahid Beheshti University of Medical Sciences (SBMU) (Code No: IR.SBMU.RETECH.REC.1398.330).

DNA extraction and genotyping

Peripheral blood samples were collected in EDTA tubes from all subjects, and genomic DNA was extracted by using salting-out method (13). We used tetra-primer amplification refractory mutation system polymerase chain reaction method (TP-ARMS-PCR) to perform genotyping for rs920778 and rs874945 variants. Primer1 online tool was utilized to design primers for genotyping of the mentioned polymorphisms (14). The TP-ARMS-PCR was performed on a GeneTouch thermocycler (BIOER, Hangzhou, China) in a 25 μL volume, containing 1 μL (10 pmol) of each primer, 12.5 μL Taq DNA Polymerase 2X Master Mix Red (Amplicon, Odense, Denmark), 1 μL genomic DNA and 7.5 PCR-grade water. The PCR conditions were as follows: initial denaturation at 95°C for 3 min; denaturation at 95°C for 45 s, annealing at 54°C for 1 min, and extension at 72°C for 45 s, in a total of 32 cycles, and a final extension at 72°C for 5 min. The list of primer sequences used for genotyping of rs920778 and rs874945 polymorphisms are shown in Table 1.

After PCR amplification, 2% agarose gel electrophoresis containing RedSafe stain (iNtRON, Gyeong- gi-do, Korea) in 0.5X tris/borate/EDTA (TBE) was used to separate the amplified products. Sanger sequencing was performed to confirm the accuracy of genotyping in 10% of the samples using an ABI 3500 DNA analyzer (Genomin, Tehran, Iran).

Bioinformatics analysis

To estimate the possible biological function of *HOTAIR* rs920778 and rs874945 variants, we performed *in silico* analysis using ORegAnno (15), HaploReg (16), RegulomeDB (17), and PROMO (18) online tools.

Statistical analysis

The differences between clinical characteristics and demographic variables in PE patients and healthy controls were examined by a χ^2 test or an independent t-test whenever appropriate. We used χ^2 test in SNPStats (19) and MEDCALC (20) online software for calculating allele and genotype frequencies and estimation of Hardy–Weinberg equilibrium (HWE). The association of selected polymorphisms with PE was investigated in recessive and dominant models of inheritance. *P* value less than 0.05 was considered to be statistically significant.

Results

Table 2 describes the demographic variables and clinical characteristics of the studied subjects. PE patients had a significantly higher body mass index (BMI), but with the lower fetal weight of neonates compared with the controls (both $P < 0.001$). As expected, the mean systolic and diastolic blood pressure values were significantly higher in the PE patients compared with controls (both $P < 0.001$). Family history of hypertension and a history of pregnancy loss was higher in the

Table 1. Primer sequences for genotyping HOTAIR rs920778 and rs874945 variants, and the related amplicon size.

SNP	Primer	Primer Sequence	Amplicon size (bp)
rs920778	Forward outer	GTAAAACGCTTCTGTCGCACTTTCCT	353
	Reverse outer	ATATCTCCCAGTCTTCTGTACCTCTCGC	
	Forward inner	TACCGCCTTGTTTTCTGAAGGAACCT	219 (T allele)
	Reverse inner	CGTGTACAGCTTAAATGTCTGAATGTTCCG	189 (C allele)
rs874945	Forward outer	TCCAGCTGTGTTTGGTCTTGTCG	390
	Reverse outer	CTGGTCTCCTCCGGAGGGC	
	Forward inner	ATTAAGACTCCAGCCGCTCTTGTAG	182 (G allele)
	Reverse inner	GAATCCCTGTGAGTGTGAGAGCCT	256 (A allele)

Table 2. Clinical characteristics and demographic variables in PE patients and healthy controls.

Characteristics	Patients N = 250	Controls N = 250	OR (95%CI)	*P* value
Age (years)	33.68 ± 4.50	31.33 ± 3.15		0.08
Body mass index (kg/m^2)	32.3 ± 5.13	29.30 ± 4.70		<0.001
Fetal weight (kg)	2.4 ± 0.90	3.3 ± 0.6		<0.001
Systolic blood pressure (mmHg)	146.15 ± 16.1	113.09 ± 5.1		<0.001
Diastolic blood pressure (mmHg)	96.32 ± 15.8	78 ± 5.56		<0.001
Family history of hypertension (n (%))	91 (36.4)	49 (19.60)	2.35 (1.57–3.52)	<0.0001
History of pregnancy loss (n (%))	78 (31.2)	31 (12.40)	3.20 (2.02–5.08)	<0.0001
Preeclampsia type				
- Mild	160 (64)			
- Severe	90 (36)			

CI: confidence interval, OR: odds ratio

patients compared with control subjects (both $P < 0.0001$).

We analyzed the genotype and allele frequencies of the *HOTAIR* rs920778 and rs874945 polymorphisms from 250 PE patients and 250 control subjects. The distribution of *HOTAIR* rs920778 genotypes was in the Hardy–Weinberg equilibrium in the control group ($P> 0.05$). Table 3 describes the allele and genotype frequencies for the rs920778 in the studied groups. The frequency of the rs920778C allele was significantly higher in PE patients compared with the healthy controls (OR = 2.27, 95% CI: 1.71–3.03, $P < 0.0001$). The frequency of CT and CC genotypes were significantly different between the cases and controls (both $P< 0.0001$). We further investigated the association of *HOTAIR* rs920778 polymorphism with PE risk in recessive and dominant inheritance models. The results showed the risk of preeclampsia was dramatically increased in both dominant and recessive modes of inheritance (OR = 4.84, 95% CI: 3.30–7.10,

Table 3. Distribution of *HOTAIR* rs920778 alleles and genotypes in PE patients and healthy controls.

Genotype/Allele	Case N (%)	Control N (%)	OR (95% CI)	P-value
T/T	63 (25.2)	155 (62)	1 (reference)	
C/T	127 (50.8)	84 (33.6)	3.72 (2.49–5.56)	<0.0001
C/C	60 (24)	11 (4.4)	13.42 (6.62–27.19)	<0.0001
C/T + C/C vs TT			4.84 (3.30–7.10)	<0.0001
CC vs T/T + C/T			6.86 (3.51–13.42)	<0.0001
T	253 (50.6)	394 (78.8)	1 (reference)	
C	247 (49.4)	106 (21.2)	2.27 (1.71–3.03)	<0.0001

Abbreviations: CI, confidence interval; OR, odds ratio.

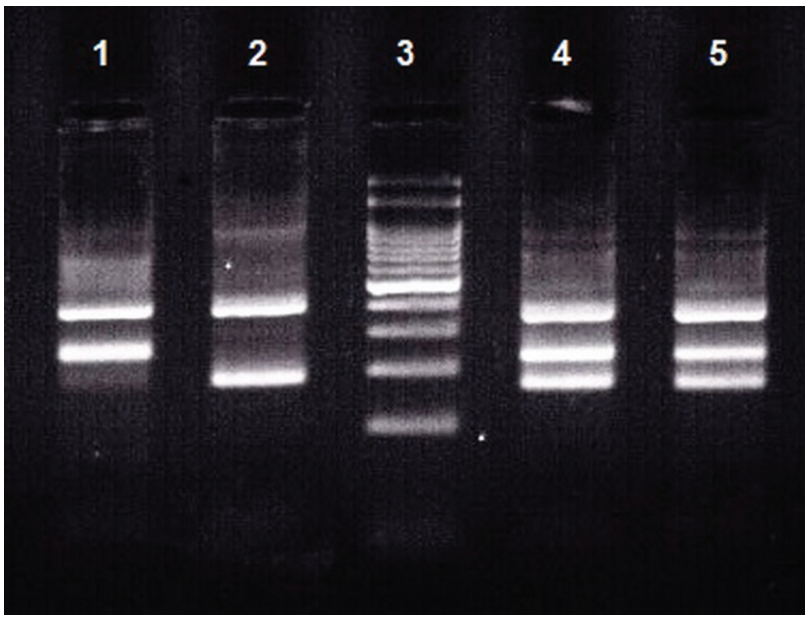

Figure 1. A representative 2% agarose gel electrophoresis of for identification of the HOTAIR rs920778 genotypes. Lanes 1: TT genotype; lane 2: CC genotype; lanes 4 and 5: CT genotype; and lane 3: DNA size marker (100 bp).

$P < 0.0001$; OR = 6.86, 95% CI: 3.51–13.42, $P < 0.0001$; respectively). Figure 1 represents 2% agarose gel electrophoresis for the identification of the *HOTAIR* rs920778 genotypes.

The distribution of *HOTAIR* rs874945 genotypes was not in Hardy–Weinberg equilibrium in both cases and controls. Table 4 shows the allele and genotype distributions for rs874945 in PE patients and controls. Although the frequency of the rs874945G allele was higher in the patients; however, the observed difference was not statistically significant (P= 0.08). The distribution of the AG genotype differed significantly between the cases and controls (P = 0.0007). The rs874945 was associated with the risk of PE in the dominant mode of inheritance (OR = 2.16, 95% CI: 1.37–3.40, P= 0.0009). Figure 2 represents 2% agarose gel electrophoresis for the identification of the *HOTAIR* rs874945 genotypes.

In silico analysis revealed that both rs920778 and rs874945 serve as the putative binding site for several transcription factors. PRDM14, EZH2, SUZ12, DRMT5, and NF-AT2 transcription factors have an affinity for binding to rs920778 locus. RegulomeDB assigns a score of 2b for rs920778. It means that the mentioned variant likely affects the binding of transcription factors (17). CTCF, RAD21, SUZ12, EZH2, and STAT-4 transcription factors has a binding affinity for rs874945 locus. RegulomeDB assigns a score of 4 for rs874945, which means that there is a minimal binding evidence for this variant (17). According to the PROMO, a virtual laboratory for the study of transcription factor binding sites in DNA sequences, Figures 3 and 4 describe the possible effects of rs920778 and rs874945 alleles on the binding of transcription factors, respectively.

Discussion

Preeclampsia is a systemic disorder and is still one of the leading causes of maternal, fetal, and neonatal morbidity and mortality worldwide (1,2). Several

Table 4. Distribution of HOTAIR rs874945 alleles and genotypes in PE patients and healthy controls.

Genotype/Allele	Case N (%)	Control N (%)	OR (95% CI)	P-value
AA	35 (14)	65 (26)	1 (reference)	
AG	213 (85.2)	180 (72)	2.20 (1.39–3.47)	0.0007
GG	2 (0.8)	5 (2)	0.74 (0.14–4.03)	0.74
GG+AG vs AA			2.16 (1.37–3.40)	0.0009
GG vs AA+AG			0.40 (0.08–2.06)	0.27
A	283 (56.6)	310 (62)	1 (reference)	
G	217 (43.4)	190 (38)	1.25 (0.97–1.61)	0.08

Abbreviations: CI, confidence interval; OR, odds ratio.

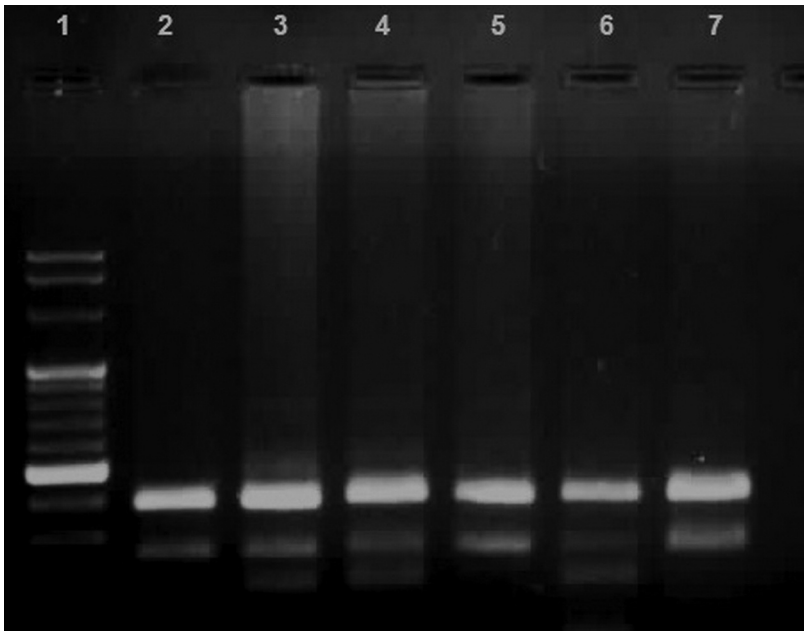

Figure 2. A representative 2% agarose gel electrophoresis of for identification of the HOTAIR rs874945 genotypes. Lane 1: 100 bp DNA ladder, lanes 2, 5 and 7: AA genotype; lanes 3, 4, and 6: AG genotype.

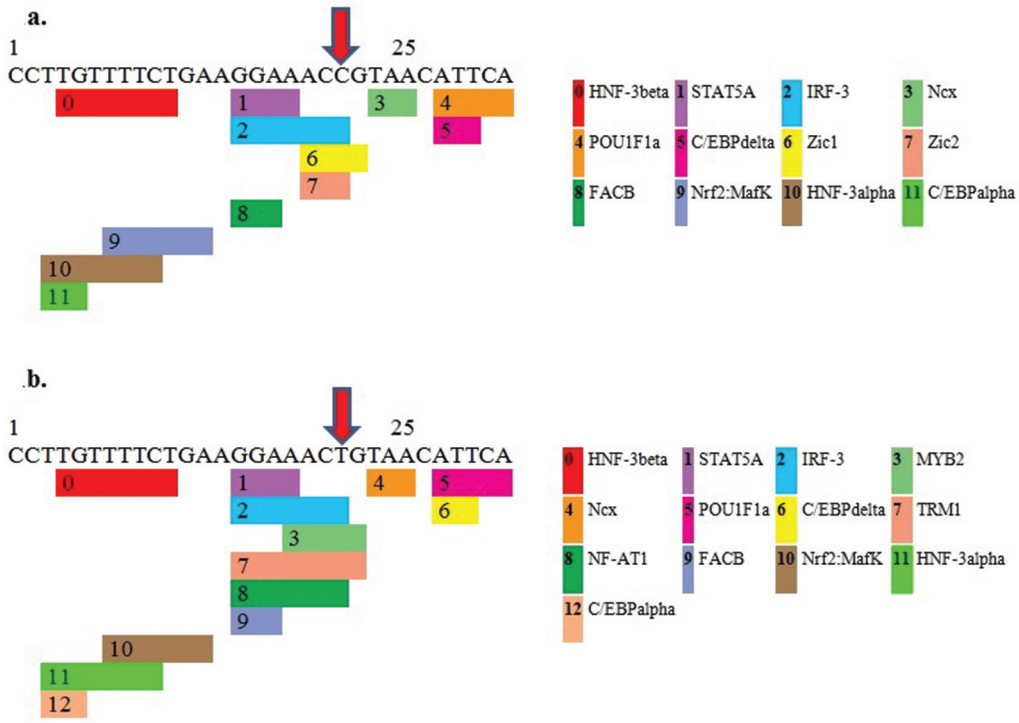

Figure 3. Schematic picture describes the effect of rs920778 alleles on the binding of transcription factors at the variant location: a. rs920778C allele; b. rs920778T allele.

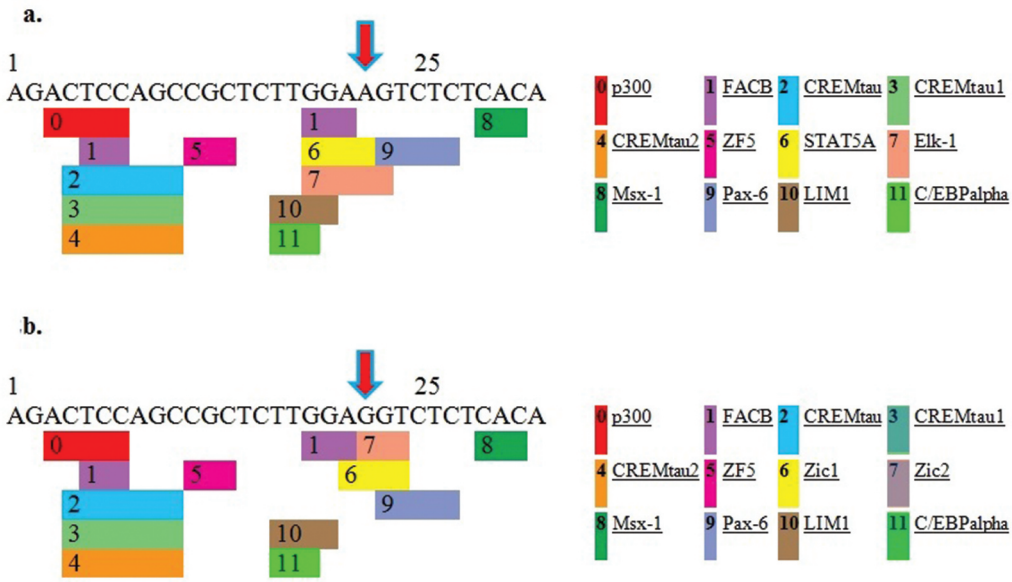

Figure 4. Schematic picture describes the effect of rs874945 alleles on the binding of transcription factors at the variant location: a. rs874945A allele; b. rs874945G allele.

studies confirmed that lncRNAs deregulation occurs in pregnancy complications, including PE (6–8,21). However, the precise molecular mechanism remains to be clarified entirely. Several studies have indicated the up-regulation of lncRNA *HOTAIR* in a variety of human diseases, including preeclampsia, breast cancer, hepatocellular carcinoma, pancreatic cancer, lung cancer, and colorectal cancer (6,8,12,22–24). Moreover,

previous studies have confirmed the role of *HOTAIR* in pregnancy disorders including, recurrent miscarriage and PE (8,21). Zou et al. revealed that *HOTAIR* is overexpressed in placental tissues from PE patients and concluded that deregulation of this lncRNA contributes to abnormal proliferation, invasion, and apoptosis of trophoblastic cells (8). It is suggested that *HOTAIR* promotes trophoblastic invasion by activating the PI3K-AKT signaling pathway (21). Therefore, any alteration in the gene expression may result in the deregulation of molecular pathways involved in a healthy pregnancy.

Functional single nucleotide polymorphisms (SNPs) located in the *HOTAIR* gene affect the gene expression level and are associated with various diseases susceptibility in diverse populations (5,25–28). In the present study, we found that *HOTAIR* rs920778, located within the gene intron 2, increased the risk of preeclampsia in both dominant and recessive models (both $P < 0.0001$). We performed an *in silico* analysis using ORegAnno (15), HaploReg (16), RegulomeDB (17), and PROMO (18) online tools which revealed that rs920778 is the putative binding site for PRDM14, EZH2, SUZ12, DRMT5, and NF-AT2 transcription factors. As an epigenetic and transcription regulator, *the PRDM14* gene plays a significant role in trophoblast differentiation (29,30). Many epigenetic events occur at the location of *HOTAIR* rs920778, and this region is considered as an intronic enhancer element for *HOTAIR* expression regulation (31). Inconsistent with our results, *HOTAIR* rs920778 was reported to have a significant association with cancer susceptibility (26–28,32). In contrast to our findings, Mohammadpour-Gharehbagh et al. did not find any association between *the HOTAIR* rs920778 variant and the PE risk in a sample of the Iranian population (5). This discrepancy may be due to the differences in the genetic background of the studied population. The allele frequency of the rs920778 variant differs between diverse ethnic populations based on HapMap data (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=920778).

In our study, we observed that rs874945 was associated with PE risk in the dominant mode of inheritance ($P= 0.0009$); however, the deviation from HWE was detected in both cases and control groups. According to the *in silico* analysis using ORegAnno (15), HaploReg (16), RegulomeDB (17), and PROMO (18), rs874945 is located at HOTAIR 3′UTR region and is a putative binding site for CTCF, RAD21, SUZ12, EZH2, and STAT-4 transcription factors. Previous studies have suggested that *HOTAIR* regulates the expression of several genes via its interaction with EZH2 (33–35). EZH2 serves as the catalytic subunit of the polycomb repressive complex 2 (PRC2) and transcriptionally represses the target genes via methylation of lysine 27 of histone 3. Zhao et al. confirmed that the HOTAIR-EZH2 complex represses the expression of miR-106a in the placenta and therefore contributes to the PE pathogenesis (35).

Although we observed the significant association between *HOTAIR* rs920778 polymorphism and PE risk, however, additional work is required to address several potential limitations of our case–control study. Because of the nature of PE as a polygenetic hereditary disease, the interaction of genetic and environmental factors such as diet, obesity, and stress should be considered. Additionally, relatively more extensive prospective studies and different ethnicities may be required to further validate the associations of the studied SNPs with the risk of PE. Taken together, for the first time, our results suggest that *the HOTAIR* rs920778 variant might contribute to the susceptibility of PE in an Iranian population.

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Disclosure statement

There are no conflicts of interest.

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