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ORIGINAL RESEARCH

Polymorphism of IFN-γ +874T/A associated with production of IFN-γ affects human papillomavirus susceptibility in rural women from Luohe, Henan, China

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Qing-wei Zhang[1]
Jia-yu Song[2]
Jiang-hua Yu[1]
Ming-zhen Sun[2]
Si-yuan Tang[1]
Shao-zhe Yang[1]
Lei-jia Cao[1]
Hui-fen Wang[1]
Li-na Cui[1]
Xiu-hong Fu[1]

[1]Department of Obstetrics and Gynaecology, Luohe Central Hospital, Luohe, 462000, Henan, China; [2]Department of Pharmacology, Luohe Medical College, Luohe, 462000, Henan, China

Purpose: In this paper, the association between polymorphisms of IFN-γ+874T/A (rs2430561), IFN-γR1 −56 T/C (rs2234711), IFN-γR1 +95 C/T (rs7749390), and IFN-γR1 −611A/G (rs 1327474) and human papillomavirus (HPV) susceptibility was investigated in rural women from Luohe, Henan, China.

Patients and methods: A total of 520 rural women were enrolled from Luohe, including 260 with HPV infection and mild dysplasia or less and 260 without HPV infection. Single-nucleotide polymorphisms (SNPs) of IFN-γ+874T/A, IFN-γR1 −56 T/C, IFN-γR1 +95 C/T and IFN-γR1 −611A/G were genotyped using TaqMan Pre-Designed SNP Genotyping Assays. Serum IFN-γ levels were measured using Human IFN-γ Quantikine ELISA Kit. Multivariate logistic regression analysis was performed to identify the SNPs associated with HPV susceptibility. Serum IFN-γ levels were compared between different genotypes.

Results: The polymorphism of IFN-γ +874T/A was associated with HPV susceptibility and +874A carriers had an increased risk. Moreover, the odds ratio was higher in +874 AA carriers than in +874 AT carriers (1.672 vs 2.874). Serum IFN-γ levels were highest in IFN-γ +874 TT carriers, intermediate in AT carriers, and lowest in AA carriers (2.86±1.14 vs 1.57±0.79 vs 0.41±0.22 pg/mL, all $P<0.05$).

Conclusion: The polymorphism of IFN-γ+874T/A was associated with HPV susceptibility in rural women from Luohe, Henan, China, and +874A carriers had an increased risk. The possible mechanism was that +874A carriers had a low production of IFN-γ.

Keywords: single-nucleotide polymorphisms, IFN-γ, IFN-γR1, human papillomavirus, susceptibility

Introduction

As one of the most common cancers in women around the world,[1,2] cervical cancer led to >266,000 deaths in 2012 alone.[3] In China, cervical cancer is the second most common gynecologic cancer among women, with an increasing incidence and mortality.[4,5]

Human papillomavirus (HPV) is a typical risk factor for cervical cancer as the only confirmed cancer-inducing virus so far.[6] Cervical HPV infection is common,[7,8] with a lifetime risk of 80%–90%.[9] Although most HPV infections are transitory,[10] 5%–10% of women with persistent infections remain at an increased risk for the development of cervical intraepithelial neoplasia (CIN) 3 and, less commonly, cervical cancer.[11]

The immune system of hosts has an important role in controlling HPV infection. Immunosuppressed women have an increased incidence of HPV infection.[12,13] The imbalance

Correspondence: Jia-yu Song
Department of Pharmacology, Luohe Medical College, No 148, University Road, Yuanhui, Luohe, 462000, Henan, China
Tel/fax +86 395 296 9417
Email songjiayu1986@21cn.com

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of local inflammatory cytokines, including interferon-gamma (IFN-γ), interleukin (IL)-12 and tumor necrosis factor-alpha, is associated with persistent HPV infection.[14–16] INF-γ has a role in both innate and adaptive immunity,[17] and can induce cellular resistance to HPV infection.[18] Both IFN-γ and its receptor (IFN-γR1) genes are key immune response genes.[19] The IFN-γ gene is located on chromosome 12q24.1 and encodes IFN-γ.[20] The polymorphism of IFN-γ +874T/A (rs2430561) may affect the production of IFN-γ.[21] The IFN-γR1 gene locates on chromosome 13q31.3–32.1 and encodes the ligand-binding chain of the IFN-γ receptor.[22]

In this paper, the association between the polymorphisms of IFN-γ +874T/A (rs2430561), IFN-γR1 −56 T/C (rs2234711), IFN-γR1 +95 C/T (rs7749390) and IFN-γR1 −611A/G (rs 1327474) and HPV susceptibility was investigated in rural women from Luohe, Henan, China. The aim was to identify susceptible genotypes to HPV infection and, thus, provide useful information for vaccination.

Patients and methods

Sampling and randomization strategy

This case–control study employed a multistage randomized sampling strategy. One district was selected from five districts in Luohe using computer-generated random selection, and five villages were selected from this selected district. All women meeting the inclusion criteria in these selected villages were detected for HPV infection. The inclusion criteria included: 1) voluntary participation, 2) age ranging from 22 to 70 years and 3) a sexual history of >3 years. The exclusion criteria included having a medical history of CIN, or cervical cancer, or hysterectomy.

Participants

A total of 260 women were randomly selected and allocated to the case group from the screened women with HPV infection and mild dysplasia or less. The case group was matched by the control group (n=260) according to age and village at a ratio of 1:1. This study was permitted by the ethics committee of Luohe Central Hospital (201402016), and all participants provided written informed consent.

HPV infection testing

Cervical tissue cells were collected >3 days after menstruation and 72 hours after sexual life or vaginal medication from all participants. The sampling brush was rotated softly in the cervical canals to take specimens, and specimens were then stored in a refrigerator at a temperature of 4°C. The HPV infection status in the cervical tissue was tested with Hybrid Capture 2 (HC-2) detector developed by QIAGEN (Hilden, Germany).

Single-nucleotide polymorphism genotyping

DNA for single-nucleotide polymorphism (SNP) genotyping was extracted from the peripheral blood of participants using salting out method according to Hashemi et al.[23] SNPs of IFN-γ +874T/A, IFN-γR1 −56 T/C, IFN-γR1 +95 C/T and IFN-γR1 −611A/G were genotyped with TaqMan Pre-Designed SNP Genotyping Assays (Applied Biosystems, Carlsbad, CA, USA). Polymerase chain reaction amplification and allelic discrimination were performed according to product specifications using the ABI 7500 Fast real-time polymerase chain reaction system (Applied Biosystems).

Measurement of serum IFN-γ levels

Serum IFN-γ levels were measured with Human IFN-γ Quantikine ELISA Kit (R&D Systems Europe, Ltd., Abingdon, UK) in all participants, according to the instructions of the manufacturer.

Statistical analysis

For all SNPs, Hardy–Weinberg equilibrium test, allele frequencies and genotype frequencies were computed with the SNPstats software (a web tool for the analysis of association studies: net/SNPstats).[24] All factors, including general data and all SNPs, were compared with a chi-squared test between the case group and the control group. The factors with a P-value <0.10 in univariate analysis were included in the multivariate analysis with a backward stepwise logistic regression model. Multivariate logistic regression analysis was then performed to identify the SNPs associated with HPV susceptibility. Serum IFN-γ levels were compared with analysis of variance between different genotypes. The SPSS version 22.0 for Windows (IBM Corporation, Armonk, NY, USA) was employed to perform all statistical analyses. Significance was set at $P<0.05$.

Results

General data

The average age of all participants was 41.58±9.46 years. According to the results of univariate analysis, annual family income, education level and occupation were statistically different between the case group and the control group, and race, and marital, drinking and smoking status were not statistically different (Table 1).

Table 1 General data of the case group and the control group

Variables	Case group (n=260)	Control group (n=260)	χ^2	*P*-value
Race				
Han	251 (96.54%)	250 (96.15%)	0.055	>0.05
Hui/Mongol/Manchu	9 (3.46%)	10 (3.85%)		
Educational level				
Primary school and below	79 (30.38%)	56 (21.54%)	28.626	<0.001
Junior high school	144 (55.38%)	115 (44.23%)		
Senior high school and above	37 (14.24%)	89 (34.23%)		
Occupation				
Farmer	218 (83.85%)	177 (68.08%)	18.001	<0.001
Worker	29 (11.15%)	53 (20.38%)		
Civil servant/teacher/doctor	13 (5.00%)	30 (11.54%)		
Annual family income (RMB)				
<10,000	199 (76.54%)	148 (56.92%)	26.01	<0.001
10,000–20,000	42 (16.15%)	60 (23.08%)		
>20,000	19 (7.31%)	52 (20.00%)		
Marital status				
Married	245 (94.23%)	249 (95.77%)	0.648	>0.05
Unmarried/divorced	15 (5.77%)	11 (4.23%)		
Drinking status				
Yes	234 (90.00%)	239 (91.92%)	0.585	>0.05
No	26 (10.00%)	21 (8.08%)		
Smoking status				
Yes	228 (87.69%)	238 (91.54%)	2.066	>0.05
No	32 (12.31%)	22 (8.46%)		

Note: Case group, women with HPV infection and mild dysplasia or less; control group, women without HPV infection.
Abbreviations: HPV, human papillomavirus; RMB, Renminbi.

SNP analysis

The success rates of genotyping of all SNPs were 100% in both the control group and the case group. The genotype frequencies of all SNPs did not deviate significantly from those expected under Hardy–Weinberg equilibrium (Table 2). According to the results of univariate analysis, the genotype frequencies of IFN-γ +874T/A and IFN-γR1 −56 T/C were statistically different between the case group and the control group ($P<0.05$), and those of IFN-γR1 +95 C/T and IFN-γR1 −611A/G were not statistically different ($P>0.05$).

Multivariate analysis

Multivariate logistic regression analysis was performed to determine the association between different genotypes of

Table 2 Allele and genotype frequencies of the case group and the control group

Single-nucleotide polymorphisms	Allele frequency		Genotype frequency			HWE *P*-value
IFN-γ +874T/A	T	A	TT	AT	AA	
Case group*	224	296	72	80	108	>0.05
Control group	302	218	119	79	62	>0.05
IFN-γR1 −56 T/C	T	C	TT	CT	CC	
Case group*	251	269	64	123	73	>0.05
Control group	225	295	41	143	76	>0.05
IFN-γR1 +95 C/T	C	T	CC	CT	TT	
Case group	252	268	67	118	75	>0.05
Control group	249	271	62	125	73	>0.05
IFN-γR1 −611A/G	A	G	AA	AG	GG	
Case group	467	53	218	31	11	>0.05
Control group	458	62	213	32	15	>0.05

Note: *$P<0.05$, vs genotype frequency of the control group.
Abbreviations: HWE, Hardy–Weinberg equilibrium; IFN, interferon.

Table 3 Association between polymorphism of IFN-γ +874T/A, IFN-γR1 −56 T/C, IFN-γR1 +95 C/T, IFN-γR1 −611A/G and HPV susceptibility

Genotypes	Regression coefficient	Standard error	Wald	OR	95% CI	*P*-value
IFN-γ +874			10.668			0.003
TT				–	–	Ref=1
AT	0.316	0.167	8.639	1.672	1.0912–2.563	0.014
AA	0.425	0.226	12.639	2.874	1.872–4.414	<0.001
IFN-γR1 −56			1.217			0.203
TT				–	–	Ref=1
CT	0.249	0.136	1.329	0.551	0.232–1.157	0.187
CC	0.273	0.148	1.208	0.615	0.396–1.398	0.209
IFN-γR1 +95			1.054			0.264
CC				–	–	Ref=1
CT	0.357	0.192	1.145	0.874	0.491–1.586	0.241
TT	0.282	0.159	0.967	0.951	0.619–1.835	0.318
IFN-γR1 −611			0.987			0.296
AA				–	–	Ref=1
AG	0.174	0.126	0.871	0.946	0.608–1.826	0.349
GG	0.225	0.137	1.238	0.717	0.401–1.479	0.195

Abbreviations: HPV, human papillomavirus; IFN, interferon; OR, odds ratio; Ref, reference.

IFN-γ+874T/A and IFN-γR1 −56 T/C and HPV susceptibility, adjusting for age, annual family income, education level, occupation and smoking status (Table 3). According to the results of multivariate analysis, the polymorphism of IFN-γ +874T/A was associated with HPV susceptibility, and +874A carriers had an increased risk of HPV infection. Moreover, the odds ratio (OR) was higher in +874 AA carriers than in +874 AT carriers (Figure 1).

Serum IFN-γ levels

The results of analysis of variance showed that serum IFN-γ levels were highest in IFN-γ +874 TT carriers, intermediate in AT carriers and lowest in AA carriers (Table 4).

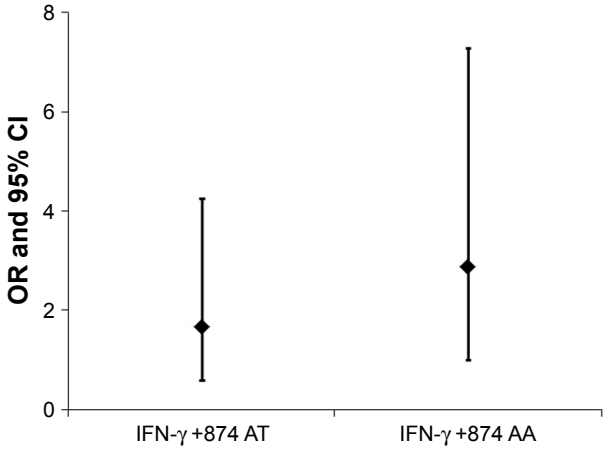

Figure 1 Association between IFN-γ +874T/A polymorphism and human papillomavirus susceptibility.
Note: IFN-γ +874 TT was used as Ref.
Abbreviations: IFN, interferon; OR, odds ratio; Ref, reference.

Discussion

Cytokines have a pivotal role in establishing and maintaining immune responses against virus infection.[25] Polymorphisms of regulating regions of cytokine genes, including *IFN-γ*, *IL-6*, *IL-10*, *transforming growth factor beta 1* (*TGF-β1*) and *TNF* genes, have been associated with their production, which lead to difference in susceptibility to virus infection.[26–30] HPV infection is very common among women. However, the virus is eliminated in most infected women (70%–90%) 12–24 months after the initial diagnosis without any intervention.[31,32]

The exact mechanism associated with the clearance of HPV infection remains uncertain. Both the innate and adaptive immune responses are involved in the clearance, persistence or progression of HPV infection.[33] The innate immune response is thought to be critical in early control of HPV infection as the first line of defense against invading pathogens.[34] It can coordinate the host responses to prevent

Table 4 Serum IFN-γ levels in different genotypes of IFN-γ +874T/A

Genotypes	Different genotypes (n)	Serum IFN-γ levels (pg/mL)
IFN-γ +874 TT	72	2.86±1.14
IFN-γ +874 AT	80	1.57±0.79*
IFN-γ +874 AA	108	0.41±0.22*,‡
F		8.947
P-value		<0.001

Notes: *$P<0.05$, vs IFN-γ +874 TT. ‡$P<0.05$, vs IFN-γ +874 AT.
Abbreviation: IFN, interferon.

or reduce viral replication and spread, until the adaptive immune system is established.[35] Most cervical HPV infections are eliminated or suppressed through cell-mediated immunity with CD4+ and CD8+ T cells as the major effector cells,[36] and the Th1 response is associated with clearance of the HPV infection.[37]

As a T-helper 1 proinflammatory cytokine, IFN-γ is produced during virus infection. IFN-γ has a pivotal role in defense against HPV through inducing cell-mediated inflammatory responses.[38,39] Telesheva et al found that the outcome of HPV infection is correlated with the interferon component of the immune response.[40] A persistent HPV infection is characterized by decreased levels of IFN-α, and transient infection is associated with increased levels of IFN-γ and IFN-α. Song et al investigated 57 women with high-risk HPV (HR-HPV) infection and untreated mild dysplasia or less. After a follow-up period of 12 months, HPV was not detectable in 93.3% (28/30) of women who were IFN-γ positive and in 66.7% (18/27) of women who were IFN-γ negative. Multivariate analysis showed that IFN-γ-positive status was significantly associated with clearance of HR-HPV (OR: 8.26; 95% CI: 1.24–54.94). Therefore, they concluded that IFN-γ may be a prognostic marker for clearance of HR-HPV.[15]

As the encoding gene of IFN-γ, *IFN-γ* gene may affect the production of IFN-γ through an SNP located in the first intron at the 5′ end adjacent to a CA repeat region (+874T/A polymorphism).[21] IFN-γ +874 TT genotype produces a high level of IFN-γ and helps the host's defense against viral infection. Conversely, the genotypes AA and AT cause low IFN-γ production, which may increase the risk of viral infection.[41–45]

According to our results, the polymorphism of IFN-γ +874T/A was associated with HPV susceptibility, and +874A carriers had an increased risk of HPV infection. Moreover, the OR was higher in +874 AA carriers than in +874 AT carriers. The serum levels of IFN-γ were +874 TT carriers>AT carriers>AA carriers. Therefore, the polymorphism of IFN-γ +874T/A affected HPV susceptibility through modulating the production of IFN-γ. Meanwhile, the polymorphisms of IFN-γR1 −56 T/C, IFN-γR1 +95 C/T and IFN-γR1 −611A/G were not associated with HPV susceptibility, and the serum levels of IFN-γ were not statistically different between different genotypes.

Conclusion

The polymorphism of IFN-γ +874T/A was associated with HPV susceptibility in rural women from Luohe, Henan, China, and +874A carriers had an increased risk of HPV infection. The possible mechanism was that +874A carriers had a low production of IFN-γ.

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Disclosure

The authors report no conflicts of interest in this work.

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