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*Original Article*

# Correlation of NAMPT and FFR4 gene polymorphisms with preoperative chemotherapy efficacy for esophageal squamous cell carcinoma

Shouhua Zhao[1], Shuhui Li[2], Hong Zhao[1], Cunwei Qin[1], Peng Zhang[1], Changhua Wang[3]

*Departments of [1]Thoracic Surgery, [2]Gastroenterology, [3]CT-MRI, Tengzhou City Central People's Hospital Affiliated to Jining Medical College, Tengzhou 277500, Shandong Province, China*

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**Abstract:** Objective: This present study was designed to investigate correlation between nicotinamide phosphoribosyl transferase (NAMPT) and fibroblast factor receptor 4 (FFR4) gene polymorphisms and preoperative chemotherapy efficacy for patients, in China, with esophageal squamous cell carcinoma. Methods: This study recruited a total of 76 patients with esophageal squamous cell carcinoma receiving preoperative FOLFOX regimen chemotherapy from January 2008 to December 2012. Peripheral venous blood was collected, before chemotherapy, to obtain DNA. Afterward, single-nucleotide polymorphisms (SNP) of NAMPT and FFR4 were detected by restriction fragment length polymorphism (RFLP-PCR). The relationship between genotypes and preoperative chemotherapy efficacy was investigated. Results: Progression-free survival (PFS) was significantly associated with NAMPT genotype G/G (univariate and multivariate regression analysis, P=0.020, P=0.017). There was no correlation between FFR4 genotypes and mPFS (all P>0.05). Severe adverse events, especially thrombocytopenia, nausea, and vomiting, were seen more in patients with NAMPT genotype A/A or FFR4 genotype T/T (all P<0.05). Conclusion: SNP of NAMPT is associated with efficacy and safety of FOLFOX regimen in patients with esophageal squamous cell carcinoma.

**Keywords:** Esophageal squamous cell carcinoma, single nucleotide polymorphism, FOLFOX regimen, nicotinamide phosphoribosyl transferase, fibroblast factor receptor 4

## Introduction

The incidence of esophageal carcinoma accounts for approximately 10-15% of all cancers, ranking 4th in the world [1, 2]. The average recurrence rate of esophageal carcinoma, after surgery, is approximately 30-50% and 5-year survival rate is about 70% [3, 4]. In addition, most patients are diagnosed in middle or advanced stages, meaning that patients have missed the best opportunity to receive surgical treatment. In the advanced stage, outcome of surgery has been unsatisfactory because of cancer metastasis. Even if patients receive an operation, it is local palliative resection with a 5-year survival rate lower than 30%. Therefore, preoperative chemotherapy, an important adjuvant treatment improving prognosis after surgery, has obtained more attention [5].

FOLFOX regimen is the most commonly used chemotherapy regimen for advanced esophageal squamous cell carcinoma. It is composed of 5-FU, L-OHP and CF. The effective rate of FOLFOX regimen is approximately 48.5%, with varied responses from different patients [6]. Its efficacy has been related to sensitivity of cancer cells to platinum drugs [7, 8]. Nicotinamide phosphoribosyl transferase (NAMPT) was first identified as pre-B-cell colony enhancing factor (PBEF). NAMPT genes are located on chromosome 7q22, spanning 34.7 kb, having 11 exons and 10 introns, and producing cDNA of 2,357 kb translated into a 491-amino acid and 52-kDa protein that stimulates early B-cell formation [9, 10]. Fibroblast factor receptor 4 (FFR4) is a kind of transmembrane tyrosine kinase receptor from the fibroblast growth factor receptor family. It can initial PLC, Ras, and several other signal transduction pathways to transfer extracellular signaling into cells by binding with fibroblast growth factor, thus, getting involved in embryonic development, angiogenesis, wound healing, tissue differentiation and repair, and other important physiological processes. It has already become a promising target of cancer treatment [11, 12].

**Table 1.** Demographic clinical characteristics of patients

| Variables | n (%) |
|---|---|
| Gender | |
| Male | 41 (53.9) |
| Female | 35 (46.1) |
| Age | |
| ≤55 | 30 (39.5) |
| >55 | 46 (60.5) |
| Smoking | |
| Yes | 33 (43.4) |
| No | 43 (56.6) |
| Alcohol | |
| Yes | 53 (69.8) |
| No | 23 (30.2) |
| Tumor site | |
| Upper | 10 (13.2) |
| Medium | 55 (72.4) |
| Lower | 11 (14.4) |
| TNM staging | |
| 0-II | 37 (48.7) |
| III-IV | 39 (51.3) |
| Depth of invasion | |
| T1 | 14 (18.4) |
| T2 | 15 (19.7) |
| T3 | 26 (34.2) |
| T4 | 21 (27.7) |
| Lymph node metastasis | |
| Negative | 54 (71.1) |
| Positive | 22 (28.9) |
| Tissue differentiation | |
| Well/moderate differentiation | 63 (82.9) |
| Poor differentiation | 13 (17.1) |

In recent years, studies have found that NAMPT and fibroblast factor receptor 4 (FFR4) gene polymorphisms are closely correlated to sensitivity of advanced non-small-cell lung cancer cells to platinum drugs [4]. Therefore, this present study investigated correlation between SNP of NAMPT and FFR4 and chemotherapy outcomes and prognosis of FOLFOX regimen in advanced esophageal squamous cell carcinoma.

## Patients and methods

### *Patients*

This study was approved by the Ethics Committee of our hospital. A total of 106 patients with advanced esophageal squamous cell carcinoma, undergoing treatment from January 2008 to December 2012, were collected. Finally, 76 patients were recruited. Inclusion criteria: patients were diagnosed with advanced esophageal squamous cell carcinoma by CT scan; patients had completed chemotherapy and surgical treatment. Exclusion criteria: patients having insufficiencies in the liver, kidneys, and other organs; patients that did not provide informed content. All patients underwent routine blood tests and liver and kidney function tests before chemotherapy.

**Table 2.** Proportion of NAMPT and FFR4 genotypes and corresponding CR\PR\SD\PD conditions

| Genotype | n (%) | CR | PR | SD | PD |
|---|---|---|---|---|---|
| NAMPT | | | | | |
| A\A | 57 (75.0) | 14 | 16 | 10 | 17 |
| A\G | 17 (22.4) | 1 | 2 | 3 | 6 |
| G\G | 2 (2.6) | 1 | 0 | 1 | 1 |
| FFR4 | | | | | |
| C\C | 38 (50.0) | 2 | 2 | 13 | 21 |
| C\T | 31 (40.8) | 1 | 2 | 10 | 18 |
| T\T | 7 (9.2) | 0 | 1 | 2 | 4 |

Note: NAMPT, nicotinamide phosphoribosyl transferase; FFR4, fibroblast factor receptor 4.

### *Chemotherapy regimen*

All patients were treated with FOLFOX regimen. Each cycle included L-OHP (Jiangsu Hengrui Pharmaceutical Co., Ltd.) 85 mg/m$^2$, d1, leucovorin (CF, Jiangsu Hengrui Pharmaceutical Co., Ltd.) 300 mg, d1~d2, 5-FU (Tianjin Jin Yao Amino Acid pharmaceutical company) and 400 mg/m$^2$, intravenous infusion, d1~d2, 5-FU 600 mg/m$^2$, with continuous micro-pump for 2 days every 2 weeks. All patients completed 4 to 6 cycles and then underwent CT scan to evaluate clinical efficacy.

### *Specimen collection and experimental methods*

*Primary instruments and reagents:* DNA Extraction Kit was purchased from Beijing Seduo Biotechnology Co., Ltd (Beijing, China). RCP reagents, restriction enzymes, and DNA maker were purchased from Yu Bao Bioengineering (Dalian) Co., Ltd (Dalian, Liaoning Province, China).

**Table 3.** Correlation between NAMPT and FFR4 SNPs and mPFS in patients with advanced esophageal squamous cell carcinoma

| Genotype | mPFS (95% CI), months | HR | 95% CI | *P* value |
|---|---|---|---|---|
| NAMPT | | | | |
| A\A | 6.77 (5.34-7.77) | R | N/A | 0.344 (A\A vs A\G for mPFS) |
| A\G | 6.92 (5.77-8.34) | 0.95 | 0.77-1.15 | 0.005 (A\G vs G\G for mPFS) |
| G\G | 1.97 (0.55-3.23) | 2.37 | 1.15-3.75 | 0.015 (G\G vs A\A for mPFS) |
| FFR4 | | | | |
| C\C | 6.01 (4.45-7.55) | R | N/A | 0.645 (C\C vs C\T for mPFS) |
| C\T | 6.12 (5.55-7.45) | 0.95 | 0.77-1.17 | 0.205 (C\T vs T\T for mPFS) |
| T\T | 5.57 (2.67-7.05) | 1.25 | 0.82-1.89 | 0.292 (T\T vs C\C for mPFS) |

Note: NAMPT, nicotinamide phosphoribosyl transferase; FFR4, fibroblast factor receptor 4. HR: Hazard ratio; mPFS: Median progression-free survival; R: Reference category; N\A: Not applicable.

**Table 4.** Correlation between NAMPT and FFR4 and disease control rates for patients with advanced esophageal squamous cell carcinoma

| Genotype | DCR (n, %) | $X^2$ | *P* value |
|---|---|---|---|
| NAMPT | | 0.534 | 0.767 |
| A/A | 40/57 (70.2) | | |
| A/G | 11/17 (64.7) | | |
| G/G | 1/2 (50.0) | | |
| FFR4 | | 0.911 | 0.456 |
| C/C | 17/38 (44.7) | | |
| C/T | 13/31 (41.9) | | |
| T/T | 3/7 (42.9) | | |

Note: DCR, Disease control rate; NAMPT, nicotinamide phosphoribosyl transferase; FFR4, fibroblast factor receptor 4.

**Table 5.** Correlation between NAMPT and FFR4 and objective response rates for patients with advanced esophageal squamous cell carcinoma

| Genotype | ORR (n, %) | $X^2$ | *P* value |
|---|---|---|---|
| NAMPT | | 0.456 | 0.339 |
| A/A | 30/57 (52.6) | | |
| A/G | 8/17 (47.1) | | |
| G/G | 1/2 (50.0) | | |
| FFR4 | | 0.564 | 0.449 |
| C/C | 4/38 (10.5) | | |
| C/T | 3/31 (9.7) | | |
| T/T | 1/7 (14.3) | | |

Note: OPR, Objective response rate; NAMPT, nicotinamide phosphoribosyl transferase; FFR4, fibroblast factor receptor 4.

*Specimen collection and experimental methods:* Two mL of peripheral venous blood were collected from patients before chemotherapy. After sodium citrate anticoagulation treatment, blood samples were stored in -20°C refrigerator. Restriction fragment length polymorphism-polymerase chain reaction (RFLP-PCR) technique was used to detect single nucleotide polymorphisms of the targeted genes. After extracting DNA from blood samples, the polymerase chain reaction (PCR) technique was used to amplify nicotinamide phosphoribosyl transferase (NAMPT) and fibroblast factor receptor 4 (FFR4) genes. Sizes of PCR products were 751 and 436 bp, respectively. PCR total reaction system was 50 μL, including DNA template 10 μL, upstream primer 1 μL, downstream primer 1 μL, 1X dNTP 4 μL, 1X Taq enzyme 0.25 μL, 1X PCR Buffer 5 μL, and $H_2O$ 28.75 μL. PCR reaction conditions included pre-denaturation at 94°C for 3 minutes, 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 30 seconds, with 38 cycles in total. Then, extension at 72°C for 10 minutes. Next, 10 μL of PCR product was taken and restriction endonucleases Sty I and Pst I were used to digest for 2 and 5 hours.

Analysis with 1.5% agarose gel electrophoresis was used to perform genotyping. Sty I was used to identify PCR product containing NAMPT alleles, containing two restriction sites. After cleavage, C/C (wild type) resulted in two fragments with the sizes of 507 and 244 bp, respectively. C/T (heterozygous mutant type) resulted in four fragments with sizes of 507, 474, 244 and 33 bp, respectively. T/T (homozygous mutant type) resulted in three fragments with sizes of 474, 244 and 33 bp, respectively. Pst I was used to identify PCR product containing FFR4 alleles. A/A (wild type) resulted in two fragments with sizes of 290 and 146 bp. A/G (heterozygous mutant type) resulted in four fragments with sizes of 290, 227, 146 and 63 bp. G/G (homozygous mutant type) resulted in

**Table 6.** Cox proportional hazards regression analysis of mPFS for patients with advanced esophageal squamous cell carcinoma

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* value | HR | 95% CI | *P* value |
| NAMPT | | | | | | |
| A\A | 1.099 | 0.465-1.457 | 0.567 | 1.145 | 0.455-1.456 | 0.153 |
| A\G | 0.845 | 0.745-1.155 | 0.633 | 0.967 | 0.745-1.167 | 0.655 |
| G\G | 1.457 | 1.045-1.999 | 0.020 | 1.458 | 1.045-2.056 | 0.017 |
| FFR4 | | | | | | |
| C\C | 1.019 | 0.888-1.184 | 0.059 | 1.077 | 0.990-1.155 | 0.088 |
| C\T | 0.599 | 0.395-1.045 | 0.756 | 0.894 | 0.434-1.567 | 0.655 |
| T\T | 0.856 | 0.505-1.455 | 0.631 | 0.456 | 0.705-1.455 | 0.630 |

Note: NAMPT, nicotinamide phosphoribosyl transferase; FFR4, fibroblast factor receptor 4.

three fragments with sizes of 227, 146 and 63 bp.

Primer used for NAMPT was as follows: upstream 5'-CTGTTGGTGGGTGCCCGTTATCTGTTGGTCT-3'; downstream 5'-TAATATCGGGGCTCACCCTGCAGCACTTCCT-3'. Primer used for FFR4 was as follows: upstream 5'-GCCCGCTCTGGATTATACG-3'; downstream 5'-CTATCATCTCCTGGCCCCC-3'.

*Clinical efficacy evaluation:* Clinical efficacy evaluation was based on RESIST 1.1 solid tumor standards including total remission (CR), partial relief (PR), stability of disease (SD), and progress of disease (PD). Indicators including progression-free survival (PFS), disease control rate (DCR), and objective response rate (ORR) were recorded via follow up with outpatient, twice a year for five years. DCR was defined as CR + PR + SD; ORR was defined as CR + PR. Adverse events were evaluated with Common Toxicity Criteria System, CTC 3.0 Toxicity Criteria.

*Statistical analysis*

Data were analyzed by SPSS 19.0. Count data are expressed as numbers and percentages. Comparison between groups was performed with Chi-square test. Comparison of NAMPT and FFR4 SNPs and mPFS was performed by Mann-Whitney rank sum test while correlation between NAMPT and FFR4 genotypes and clinical efficacy was analyzed by Chi-square test. Related factors influencing patient mPFS was analyzed by Cox regression analysis. P<0.05 was considered to indicate statistical significance.

## Results

*Basic data analysis*

Among all enrolled patients, there were 41 males and 35 females with a median age of 57 years (29-76 years). Clinical characteristics of all patients are shown in **Table 1**.

The proportion of NAMPT and FFR4 genotypes and corresponding CR\PR\SD\PD conditions are listed in **Table 2**. NAMPT genotype frequencies among all patients included 57 cases (75.0%) A/A, 17 cases (22.4%) A/G, and 2 cases (2.6%) G/G. FFR4 genotype frequencies among all patients included 38 cases (50.0%) C/C, 31 cases (40.8%) C/T, and 7 cases (9.2%) T/T.

*Correlation between NAMPT and FFR4 genotypes and mPFS*

As shown in **Table 3**, regarding correlation between NAMPT genotypes and mPFS, differences of mPFS among A/G and G/G and G/G and A/A were statistically significant (P= 0.005, A/G versus G/G for mPFS; P=0.344 A/G versus A/A for mPFS; P=0.015, G/G versus A/A for mPFS); For correlation between FFR4 genotypes and mPFS, there were no statistically significant differences regarding mPFS between C/C and C/T, C/T and T/T, and T/T and C/C (P=0.645, 0.205 and 0.292, respectively).

*Correlation between NAMPT and FFR4 genotypes and clinical efficacy*

As shown in **Tables 4** and **5**, there was no statistical significance between the genotypes and DCR and ORR (all P>0.05).

*Univariate and multivariate regression analysis*

As shown in **Table 6**, results showed that NAMPT A/A and A/G and FFR4 C/C, C/T, and T T were not predictive factors for mPFS. However, NAMPT G/G was an independent risk factor for mPFS demonstrated by both univariate and multivariate regression analysis (P=0.020, P= 0.017, respectively).

**Table 7.** Correlation of NAMPT and FFR4 genotypes with adverse events in patients with advanced esophageal squamous cell carcinoma

| AEs | Genotypes | III or IV\total (n) | Percentage | $X^2$ | *P*-value |
|---|---|---|---|---|---|
| Leukopenia | NAMPT | | | 2.134 | 0.567 |
| | A\A | 3\57 | 5.26 | | |
| | A\G | 2\17 | 11.76 | | |
| | G\G | 0\2 | 0.00 | | |
| | FFR4 | | | 2.199 | 0.565 |
| | C\C | 7\38 | 18.42 | | |
| | C\T | 5\31 | 16.13 | | |
| | T\T | 1\7 | 14.29 | | |
| Anemia | NAMPT | | | 2.349 | 0.393 |
| | A\A | 1\57 | 1.75 | | |
| | A\G | 1\17 | 5.88 | | |
| | G\G | 0\2 | 0.00 | | |
| | FFR4 | | | 2.349 | 0.677 |
| | C\C | 6\38 | 15.79 | | |
| | C\T | 4\31 | 12.90 | | |
| | T\T | 2\7 | 11.76 | | |
| Thrombocytopenia | NAMPT | | | 9.349 | 0.020 |
| | A\A | 31\57 | 54.39 | | |
| | A\G | 3\17 | 17.65 | | |
| | G\G | 0\2 | 0.00 | | |
| | FFR4 | | | 7.221 | 0.025 |
| | C\C | 8\38 | 21.05 | | |
| | C\T | 6\31 | 19.35 | | |
| | T\T | 4\7 | 57.14 | | |
| Nausea and vomiting | NAMPT | | | 6.199 | 0.023 |
| | A\A | 27\57 | 47.37 | | |
| | A\G | 3\17 | 17.65 | | |
| | G\G | 0\2 | 0.00 | | |
| | FFR4 | | | 7.122 | 0.017 |
| | C\C | 7\38 | 18.42 | | |
| | C\T | 5\31 | 16.13 | | |
| | T\T | 5\7 | 71.43 | | |
| Liver damage | NAMPT | | | 2.459 | 0.448 |
| | A\A | 3\57 | 5.26 | | |
| | A\G | 1\17 | 5.88 | | |
| | G\G | 0\2 | 0.00 | | |
| | FFR4 | | | 2.449 | 0.567 |
| | C\C | 19\38 | 50.00 | | |
| | C\T | 15\31 | 48.39 | | |
| | T\T | 3\7 | 42.56 | | |
| Peripheral neuritis | NAMPT | | | 2.339 | 0.339 |
| | A\A | 32\57 | 56.14 | | |
| | A\G | 7\17 | 41.18 | | |
| | G\G | 1\2 | 50.00 | | |
| | FFR4 | | | 2.495 | 0.945 |
| | C\C | 7\38 | 18.42 | | |
| | C\T | 7\31 | 22.58 | | |
| | T\T | 2\7 | 28.57 | | |

Note: NAMPT, nicotinamide phosphoribosyl transferase; FFR4, fibroblast factor receptor 4.

*Adverse events*

As shown in **Table 7**, severe adverse events, especially thrombocytopenia, nausea, and vomiting, were significantly associated with NAMPT genotype A/A and FFR4 genotype T/T.

## Discussion

Previous studies have proven that SNP is correlated with cancer treatment efficiency [13, 14]. For example, Gan et al. studied a total of 289 patients with colorectal cancer receiving 5-FU combined with oxaliplatin. The results showed that patients carrying XPD751 mutant genotypes were 0.55 times more likely to die than those who carrying the wild-type [15]. They believed that XPD751 SNP can be used as a predictive indicator for clinical efficacy of FOLFOX. In this present study, correlation between NAMPT and FFR4 SNPs and preoperative chemotherapy efficacy for patients with esophageal squamous cell carcinoma was investigated.

In the present study, median PFSs for patients with A/A, A/G and G/G genotypes were 6.77, 6.92 and 1.97 months, respectively. The differences were statistically significant, consistent with one previous study [16]. Zhang et al. reported that genetic polymorphisms of NAMPT related with susceptibility to esophageal squamous cell carcinoma [17]. Therefore, NAMPT SNP may be a prognostic indicator for patients with

advanced esophageal squamous cell carcinoma receiving FOLFOX regimen.

Current results regarding correlation between FFR4 and chemosensitivity are conflicting. Some studies have suggested that FFR4 and chemosensitivity are correlated. For example, Koole et al. found that overexpressed FGFR4 protein was 64% and 41% of oropharyngeal squamous cell carcinoma (OSCC) and 41% of oral squamous cell carcinoma (OPSCC). Gene amplification of FGFR4 was 0.47% and 0.42%, of OSCC and OPSC, while protein expression, gene copy numbers, and genotypes of FGFR4 were not related to overall survival or response to radiotherapy in OSCC or OPSCC [18].

The present study demonstrated that for patients carrying A/A, the DCR was 70.2% and ORR was 52.6%. For patients carrying A/G, the DCR was 64.7% and ORR was 47.1%. For patients carrying G/G, the DCR was 50.0% and ORR was 50.0%. For patients carrying C/C, the DCR was 44.7% and ORR was 10.5%. For patients carrying C/T, the DCR was 41.9% and ORR was 9.7%. For patients carrying T/T, the DCR was 42.9% and ORR was 14.3%. There were no statistically significant differences in DCR and ORR between NAMPT and FFR genotypes, suggesting that NAMPT and FFR4 polymorphisms and chemotherapy clinical efficacy for patients with advanced esophageal squamous cell carcinoma may not be relevant, consistent with the results from Liu et al. [14, 19].

Multivariate analysis results showed that only NAMPT G/G was correlated with mPFS. Therefore, carrying NAMPT G/G is predictive indicator of prognosis for patients with advanced esophageal squamous cell carcinoma. Patients carrying NAMPT G/G may be less sensitive to FOLFOX regimen. In addition, the present study found that patients carrying NAMPT A/A and FFR4 T/T had more severe thrombocytopenia and nausea and vomiting. All of these findings prove that NAMPT and FFR4 SNPs, along with their expression levels, have potential value in the evaluation of treatment effects and prognosis in patients with advanced esophageal squamous cell carcinoma.

Nevertheless, there were some limitations to this study. There were a limited number of cases and this was a retrospective study. Therefore, prospective studies with larger sample sizes are needed to verify the results and further explore the mechanisms.

In conclusion, SNP of NAMPT may be associated with chemosensitivity to FOLFOX regimen in patients with esophageal squamous cell carcinoma. This may be a promising predictor of prognosis for patients with advanced esophageal squamous cell carcinoma.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Changhua Wang, Department of CT-MRI, Tengzhou City Central People's Hospital Affiliated to Jining Medical College, No.181 Xingtan Road, Tengzhou 277500, Shandong Province, China. Tel: +86-0632-5531603; Fax: +86-0632-5531603; E-mail: wangchanghua128@163.com

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