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Correlation between FAS single nucleotide polymorphisms and breast carcinoma susceptibility in Asia

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Abstract

Background: FAS cell surface death receptor (FAS) gene has 2 common single nucleotide polymorphisms (SNPs) in its promoter, FAS-1377G > A (rs2234767) and FAS-670A > G (rs1800682). Several studies have investigated the role of these 2 polymorphisms in etiology of breast cancer in Asian population while the outcomes are inconsistent. To derive a more precise assessment of the association between breast cancer susceptibility with FAS gene promoter SNPs, a meta-analysis of published studies was performed.

Material and methods: We systematically searched PubMed, Embase, Web of Science, and the Chinese biomedical database (CBM) for papers published until November 1, 2018. Odds ratio (OR) with 95% confidential interval (95%CI) was conducted to evaluate the associations. Statistical analysis was conducted using Stata13.0 software. A total of 8 studies covering 2564 cases and 2633 controls were included.

Results: The integrated results suggest the following: For the FAS-1377G/A polymorphism, we only found significant associations for allele G vs allele A (OR = 1.100, 95%CI = 1.004–1.206, P = .040). After stratification by ethnicity, a significant association was observed only for the AA+GA vs GG genotype in East Asian populations (OR = 1.177, 95% CI = 1.010–1.371, P = .037). The association was not found in West Asian populations. For the FAS -670A/G polymorphism, no association with cancer risk was found in any comparison model. Sensitivity analysis suggests that the meta-analysis results obtained after excluding any single study were similar to the original ones, suggesting that the meta-analysis results were not significantly affected by any single study.

Conclusion: These results indicated that FAS-1377G/A polymorphism may contribute to the increased breast cancer susceptibility and could be a promising target for cancer risk prediction. Further studies are needed to determine if the *FAS* gene confers a risk of breast cancer in other ethnic groups, such as Africans and Latin Americans.

Abbreviations: 95% CI = 95%confidence interval, CBM = the Chinese biomedical database, FAS = Fas cell surface death receptor, FASLG = FAS ligand, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, SNPs = single nucleotide polymorphisms, TNFR = the tumor necrosis factor receptor.

Keywords: antigens, breast neoplasms, CD95, genetic, meta-analysis, polymorphism

1. Introduction

Breast cancer is the most frequent carcinoma affecting females around the world with around 1 million new patients affected yearly.[1] Among American women, breast cancer patients account for approximately 29% of all newly diagnosed cancer patients.[2] Factors contributing to breast cancer risk include age, hormone levels, lifestyles, environmental factors, genetic factors, and ethnicity.[3,4]

Apoptosis is a process of programmed death of cells that is regulated by genes to manage homeostasis of organisms. Abnormal apoptosis may cause cancers.[5,6] FAS belongs to the

tumor necrosis factor receptor (TNFR) superfamily. The 45-kD molecule binds to FAS ligand (FASLG), activates the apoptotic signaling cascades, and initiates apoptosis by cytotoxic T lymphocytes and natural killer cells.[7] FAS gene consists of 9 exons and 8 introns mapped on the 10q24.1 of human chromosome. The transcriptional mechanism controlling FAS expression is largely unknown, but its gene expression can be regulated by a number of genetic elements located in the 5' upstream region of the gene. The promoter region of the FAS gene encompasses a 2000 bp sequence that consists of basal promoter, enhancer and silencer regions.[8] Two frequently observed polymorphisms were identified in the promoter of this gene. One of them is a G-A transition at nucleotide number -1377 (rs2234767) in the silencer region, and the other is an A-G transition at nucleotide number -670 (rs1800682) in the enhancer site.[9,10] The -1377G/A polymorphism affect the binding site (CACGCCC) of stimulatory protein-1 (Sp1) and The -670A/G polymorphism is located in the consensus sequence of nuclear transcription element GAS binding site (ATTCCAGG/AAA), where transcription factor signal transducer and activator of transcription STAT1 binds.[11,12] Therefore, they can modulate the expression level of FAS and affect the occurrence of breast carcinoma.

Recently, multiple investigations have established associations between -1377G/A or -670A/G with breast carcinoma risk in Asian people.[13–20] However, the conclusions of these reports are inconsistent, with significant regional differences. Zhang et al[14,17,19] found a significant association between FAS -1377G/A and increased breast carcinoma risk, but the association was not found in other studies.[13,15,16,20] Hashemi et al[16,18,20] mentioned that FAS -670G/A gene polymorphism was risk factor, while Dastmalchi et al[13,15,19] found this polymorphism did not affect the risk of breast carcinoma. These inconsistencies may result from small sample sizes and different ethnic backgrounds. As for other single nucleotide polymorphisms (SNPs) in the FAS gene, such as rs2234768 (744A.G), rs2229521 (18272A.G), rs2234978 (22628C.T),[21,22] there are relatively fewer published studies, and the sample size for these SNPs is too small to be included for a meta-analysis.

Meta-analysis can increase the credibility of conclusions by increasing the sample size. It can be used to integrate and analyze results from multiple studies in a systematic, objective, and quantitative manner. Therefore, in this study, we tried to integrate results from case-control investigations on the associations between the 2 frequently observed SNPs in the FAS promoter and the risk of breast carcinoma in Asian populations by meta-analysis to establish a more systematic and accurate relationship between the 2.

2. Material and methods

Since this study is a meta-analysis of previously published studies, the ethical approval and patient consent are not required.

2.1. Materials

We collected worldwide literature on the relationship between FAS gene promoter SNPs and breast cancer susceptibility from Web of Science, Embase, PubMed, and CBM. The publication year and language were not limited so that all case-control investigations on the associations between the SNPs in the FAS gene and the risk of breast carcinoma published before November 2018 were included. The keywords for literature searching were "FAS", "SNPs," and "breast carcinoma (cancer)".

2.2. Inclusion/exclusion criteria

The research subjects were patients diagnosed with breast cancer. The papers reported case-control investigations on the associations between the SNPs in the FAS gene and the risk of breast carcinoma. The frequency distributions of related genotypes were provided or can be calculated. Abstracts, reviews, case reports, repeatedly published literature, incomplete data, and animal experiments were not included.

2.3. Data extraction

The data in each article were extracted separately by 2 researchers. In the event of a disagreement, third-party assistance was provided. The extracted information includes: the first author of the literature, the year and the country of publication, sample sizes of the patients and the healthy controls, the genotype frequencies, and the methods for genotype analysis.

2.4. Statistical analysis

The obtained data was analyzed with Stata 13.0 software. Analyses were performed with two-tailed tests, and $P < .05$ represents a statistically significant value. The genotypes of the control group were subjected to Hardy–Weinberg equilibrium (HWE) tests and $P < .05$ represents a deviation from HWE. OR with 95% CI was used to compare the allele frequency genotype (A vs G), the heterozygous genotype (GA vs GG), the homozygous genotype (AA vs GG), the dominant inheritance genotype (AA+GA vs GG), and the recessive inheritance genotype (AA vs GA/GG) of -1377G/A. The allele frequency (G vs A), the heterozygous genotype (GA vs AA), the homozygous genotype (GG vs AA), the dominant inheritance genotype (GG+GA vs AA), and the recessive inheritance genotype (GG vs GA+AA) of -670A/G were also compared using the same method. Heterogeneity tests (Q tests and I2 tests) were performed on the included literature. If $P < .05$ or $I^2 > 50\%$, random-effect models were used for data integration and analysis. Otherwise, fixed-effect models were used.[23–25] We also divided the patients into subgroups based on their ethnicity for further analysis. In addition, the stability of the results was evaluated through sensitivity analysis. We used the Begg rank correlation method, funnel plots, and the Egger linear regression test to evaluate publication biases in the included literature.

3. Results

3.1. Eligible studies

A total of 35 articles were retrieved after the search from the databases: —29 English articles and 6 Chinese articles. After the titles and abstracts were read, 27 papers—unrelated papers, repeated search results, reviews and abstracts—were excluded. A total of 8 articles[13–20] were eventually included in this study for meta-analysis. The features of the papers involved in this work are listed in Table 1.

3.2. Association between FAS polymorphisms and breast cancer susceptibility

Seven studies[13–17,19,20] covering 2004 patients with breast carcinoma and 2050 unaffected individuals were subjected to meta-analysis. We first assessed the associations between the

Table 1

Characteristics of individual studies included in the meta-analysis.

References	Year	Country	Ethnicity	Control source	Genotyping method	Total size	Genotype distributions		
							Case (n)/control(n)		
Fas-1377G/A							GG	GA	AA
Maryam et al[15]	2015	Iran	West Asian	population	PCR	115/115	35/30	57/58	23/27
WANG et al[17]	2012	China	East Asian	hospital	PCR-RFLP	375/496	138/197	171/246	66/53
Zhang et al[19]	2007	China	East Asian	population	PCR-RFLP	840/839	293/345	418/382	129/112
Tahmasbi fard. et al[14]	2016	Iran	West Asian	population	PCR-RFLP	65/57	18/10	1/15	46/32
Dastmalchi et al[13]	2017	Iran	West Asian	population	Tetra-ARMS-PCR; PCR-RFLP	200/186	120/122	75/57	5/7
Hashemi et al[16]	2013	Iran	West Asian	population	tetra-ARMS-PCR	134/152	20/26	106/115	8/11
Zhou et al[20]	2015	China	East Asian	population	PCR-RFLP	214/204	44/31	123/113	47/60
Fas-670A/G							AA	GA	GG
Maryam et al[15]	2015	Iran	West Asian	population	PCR	115/113	60/54	45/47	10/12
Zhang et al[19]	2007	China	East Asian	population	PCR-RFLP	836/834	320/321	393/390	123/123
Dastmalchi et al[13]	2017	Iran	West Asian	population	Tetra-ARMS-PCR; PCR-RFLP	200/186	84/92	90/70	26/24
Wang et al[18]	2016	China	East Asian	hospital	MassARRAY	560/583	182/226	289/261	89/96
Hashemi et al[16]	2013	Iran	West Asian	population	tetra-ARMS-PCR	134/152	55/63	55/78	24/11
Zhou et al[20]	2015	China	East Asian	population	PCR-RFLP	214/204	49/52	128/135	37/17

6. Tetra-ARMS-PCR = tetra-primeramplification refractory mutation system PCR, PCR = polymerase chain reaction, PCR-RFLP = PCR-restriction fragment length polymorphism.

FAS-1377G/A SNP with the risk of the disease. We compared the 5 genetic models of the SNP and found a statistically significant correlation only between the allele G vs allele A genotype and the incidence of breast carcinoma (OR = 1.100, 95% CI = 1.004–1.206, P = .040). After stratification by ethnicity, different findings were obtained in East Asian and West Asian people. A significant association between the AA + GA vs GG genotype and the incidence of breast carcinoma was observed in East Asian people (OR = 1.177, 95% CI = 1.010–1.371, P = .037), but not in West Asian populations. The detailed results are shown in Tables 2 and 3. Figures 1 and 2 show the corresponding forest plots. A total of 6 studies,[13–15,18–20] including 2063 cases and 2080 controls, were subjected to meta-analysis to examine the associations between the FAS-670A/G SNP and the incidence of breast cancer. We compared the 5 genetic models of the FAS-670A/G SNP and found no association between these genotypes and the incidence of breast carcinoma in any comparison model (Tables 2 and 3). We then divided the patients into subgroups based on their ethnicity and observed no correlation between FAS-670A/G and breast carcinoma

risk in either East Asian populations or West Asian populations.

3.3. Sensitivity analysis

Although the distribution of the -1377 G/A genotype in 2 studies (Hashemi et al[14] and Tahmasbi et al[16]) and the distribution of the -670 A/G genotype in 2 other studies (Hashemi et al[14] and Zhou et al[20]) failed to obey HWE, sensitivity analysis suggested that the meta-analysis results obtained after excluding any single study were similar to the original ones, suggesting the meta-analysis results were not significantly affected by any single study.

3.4. Evaluation of publication bias

We evaluated publication biases in the included studies by funnel plots (Figs. 3 and 4), the Begg rank correlation method and Egger linear regression tests. The only publication bias was found by Egger test in the dominant inheritance model of FAS-1377G/A polymorphism. No other publication bias was found in the remaining genetic models (Table 2).

Table 2

Meta-analysis of FAS polymorphisms and breast cancer susceptibility.

polymorphism	Test of association			Test of heterogeneity			Publication bias	
	OR (95% CI)	P	Model	Q	P	I²(%)	P value (Egger)	P value (Begg)
FAS-1370G/A								
AA vs GG	1.005 (0.699–1.444)	.979	R	13.84	.031	56.7	.130	.881
GA vs GG	1.020 (0.774–1.345)	.887	R	15.51	.017	61.3	.147	.652
AA + GA vs GG	1.141 (0.998–1.304)	.054	F	9.78	.134	38.6	.042	.176
AA vs GA/GG	1.085 (0.784–1.500)	.623	R	14.75	.022	59.3	.709	.652
A vs G	1.100 (1.004–1.206)	.040	F	11.09	.086	45.9	.207	.293
FAS-670A/G								
GG vs AA	1.184 (0.979–1.432)	.082	F	9.11	.105	45.1	.188	.240
GA vs AA	1.106 (0.967–1.265)	.140	F	7.15	.210	30.1	.38	.693
GG + GA vs AA	1.292 (0.955–1.749)	.097	R	22.54	.000	77.8	.573	.385
GG vs GA + AA	1.238 (0.899–1.723)	.206	R	13.28	.021	62.4	.091	.218
G vs A	1.087 (0.995–1.188)	.065	F	5.03	.412	0.6	.573	.452

95% CI = 95%confidence interval, OR = odds ratio.

Table 3

Subgroup analysis of FAS polymorphisms and breast cancer susceptibility.

polymorphism	East Asia				West Asia			
	OR (95% CI)	P	Model	P_h	OR (95% CI)	P	Model	P_h
FAS-1370G/A								
AA vs GG	1.153 (0.664–2.001)	.614	R	.006	0.784 (0.493–1.246)	.302	F	.982
GA vs GG	1.132 (0.964–1.330)	.131	F	.113	0.851 (0.429–1.685)	.643	R	.010-
AA + GA vs GG	1.177 (1.010–1.371)	.037	F	.069	1.028 (0.777–1.359)	.846	F	.287
AA vs GA/GG	1.137 (0.703–1.839)	.601	R	.005	1.013 (0.681–1.508)	.119	F	.948
A vs G	1.068 (0.841–1.355)	.589	R	.012	1.016 (0.841–1.227)	.871	F	.706
FAS-670A/G								
GG vs AA	1.147 (0.927–1.419)	.207	F	.095	1.345 (0.877–2.063)	.174	F	.134
GA vs AA	1.126 (0.967–1.312)	.126	F	.167	1.041 (0.787–1.376)	.780	F	.188
GG + GA vs AA	1.556 (0.932–2.600)	.091	R	.034	1.094 (0.841–1.423)	.504	F	.340
GG vs GA + AA	1.186 (0.801–1.758)	.206	R	.034	1.321 (0.882–1.978)	.177	F	.055
G vs A	1.078 (0.976–1.191)	.139	F	.278	1.123 (0.923–1.367)	.246	F	.311

95% CI = 95%confidence interval, OR = odds ratio, PH = P value of heterogeneity.

4. Discussion

Imbalances between cell proliferation and apoptosis are the basis of carcinogenesis. The *FAS* gene is one of the important factors that regulate apoptosis. Its expression can affect the development of breast cancer. Therefore, we should pay more attention to the FAS SNPs.[26,27] Although many studies worldwide have shown that SNPs in the *FAS* gene could affect breast carcinoma susceptibility, the results are not consistent for many reasons. Therefore, we integrated results from the most-updated case-control investigations on the associations between the SNPs in the *FAS* gene and the risk of breast carcinoma. In Asian populations by meta-analysis to establish more systematic and accurate relationships between the 2.

For FAS-1377G/A, this SNP significantly affect breast carcinoma susceptibility in Asian populations in the allele frequency model (G vs allele A, OR = 1.100, 95% CI = 1.004–

1.206, P = .040), meaning that people who carry FAS-1377A have 10% higher chance of being affected by breast carcinoma than people who carry FAS-1377G. For the FAS-670G/A polymorphism, integrated results suggest that this SNP did not have a statistically significant correlation with the risk of breast carcinoma in Asian populations in any genotype model. These findings are consistent with other studies.[28–30] One possible explanation for these findings is that the FAS-1377G/A polymorphism affects the DNA-binding motif of SP-1 and -1377A disrupts the binding of SP-1, resulting in decreased promoter activity and FAS expression. As a result, FAS-mediated tumor-cell apoptosis is inhibited. Whereas -670A and -670G have equal binding affinity to SP-1, therefore, FAS expression and FAS-mediated tumor apoptosis were not affected by this SNP.

After subgrouping by the subjects' ethnic backgrounds, we observed a significant association between the FAS-1377G/A and
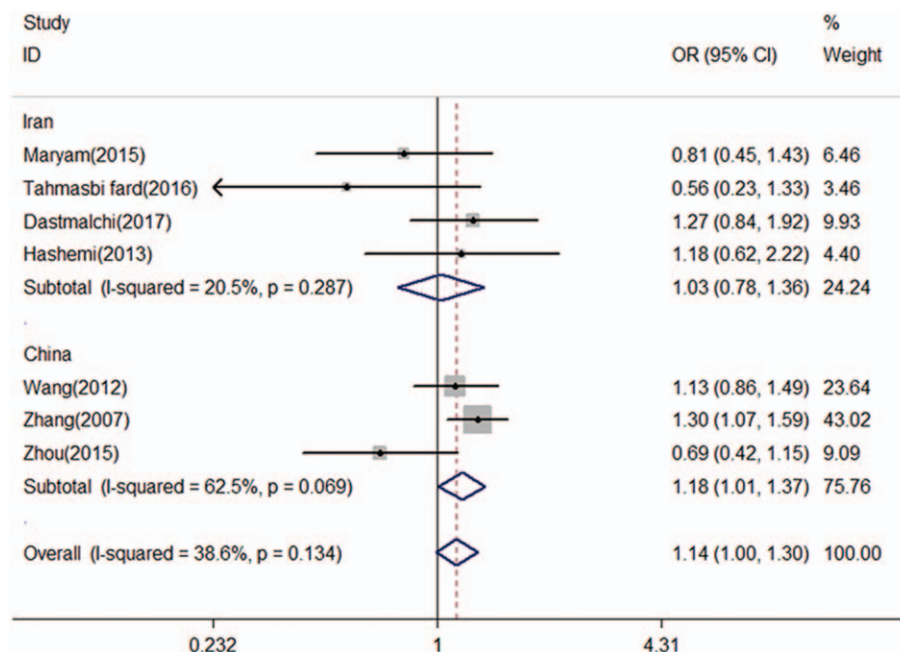

Figure 1. Forest plot of breast cancers risk associated with the FAS-1377G > A polymorphism (GA + AA vs GG).
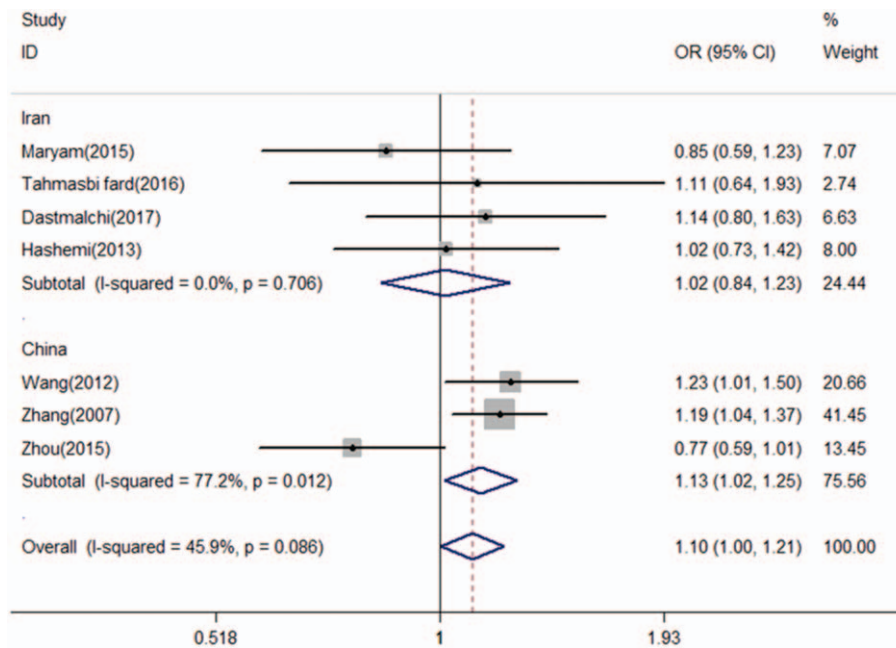
Figure 2. Forest plot of breast cancer risk associated with the FAS-1377G > A polymorphism (Allele A vs. Allele G).

the incidence of breast cancer in East Asian populations but not in West Asian populations. The underlying reasons could be:

1. Different genetic backgrounds or gene-environment interactions may affect the genotype-phenotype correlation.
2. The sample sizes became smaller after stratification, resulting in inaccurate conclusions. Meanwhile, according to our results, the FAS -670A/G does not affect and the risk of breast carcinoma in either East Asian populations or West Asian populations. This result, on the one hand, suggests that the genotype-phenotype correlation may not be affected by ethnic factors. On the other hand, it may also be related to the smaller sample size after stratification. Therefore, we need to include more high-quality studies and expand the sample size for the next study.

It is also necessary to mention the several limitations of this study:

1. This study is a retrospective study; the distribution of the -1377 G/A genotype in 2 included studies and the distribution of the -670 A/G genotype in 2 included studies did not follow HWE. The conclusions may be influenced by recall bias, publication bias, and choice bias. In fact, Egger test showed a publication bias in the dominant inheritance model of FAS-1377G/A polymorphism. Therefore, the findings of this study should be interpreted with caution.
2. The sample sizes were small after stratification; more literature should be included for future meta-analysis.
3. The occurrence of breast cancer may be associated with multiple genes and factors. There may be gene–gene and gene–environment interactions in the development of breast cancer, which we did not address in this study.
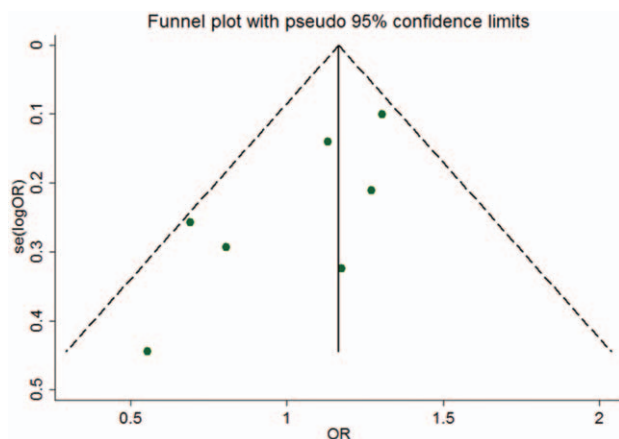

Figure 3. Funnel plot for publication bias test. (FAS-1377G/A: GA + AA vs GG).
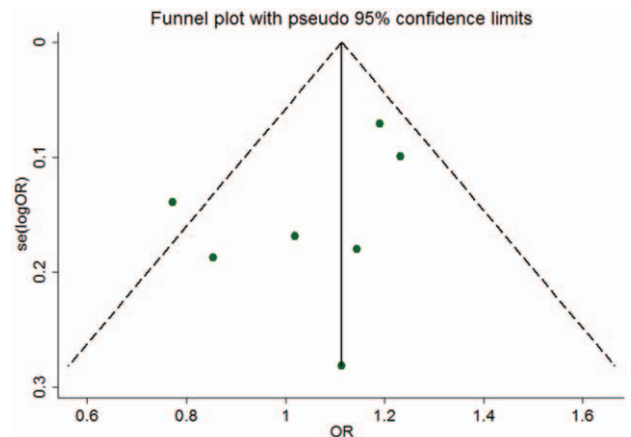

Figure 4. Funnel plot for publication bias test. (FAS-1377G/A: Allele A vs. Allele G).

In summary, meta-analysis based on the existing literature indicates that the -1377G/A SNP of the FAS gene may affect breast cancer susceptibility in Asian populations and that the association is stronger in East Asian populations. However, this study does not find a significant correlation between the FAS-670A/G SNP and the risk of breast carcinoma. Given the limitations of this study, the relationship between this SNP and the risk of breast carcinoma still needs further investigation. Therefore, we need to include more high-quality studies and conduct meta-regression analysis based on multiple factors to draw more reliable conclusions in future studies.

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