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Original Article

Association between Fas/FasL polymorphism and susceptibility to leukemia: a meta-analysis

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Abstract: The polymorphisms in Fas/FasL system were proposed to be associated with susceptibility to leukemia, but recent studies reported controversial findings. Hence, we performed a meta-analysis to assess the association between Fas gene polymorphisms and susceptibility to leukemia. We carried out a literature search in PubMed, Embase, Web of Science and CNKI databases for studies on the associations between Fas/FasL gene polymorphisms and susceptibility to leukemia. The associations were assessed by odds ratio (OR) together with its 95% confidence intervals (CIs). 7 literatures and 14 studies with a total of 8787 subjects were eventually included into our meta-analysis. Overall, there was no association between Fas/FasL polymorphisms and susceptibility to leukemia. In subgroup analysis by ethnicity, there was also no association between Fas/FasL polymorphisms and susceptibility to leukemia in Asians and Caucasians. In addition, there was also a significant association between Fas-1377G/A polymorphism and susceptibility to leukemia in ALL patients, the A allele seemed to be a protective factor in ALL risk. In summary, more studies with large sample size are needed to provide further evidence for association between Fas/FasL polymorphisms and susceptibility to leukemia.

Keywords: Leukemia, polymorphism, meta-analysis

Introduction

Leukemia is one of the most common malignant tumors, which make up 30.4% of all hematological malignancies and are one of the most common hematological malignancies according to the information collected by (SEER) Cancer Statistics Review 1975-2006. The change of apoptosis induced by gene mutation could result in leukemia [1, 2]. Fas also known as CD95/TNFSF6/APO-1 belongs to the subgroup of the tumor necrosis factor receptor (TNF-R) family and is one of the important molecules contributed to apoptosis pathway. The human Fas gene located on chromosome 10q 24.1 [3], which contains nine exons and eight introns [4]. Fas-induced apoptosis in the control of the immune system and its critical function as a guardian against autoimmune disease and certain lymphoid malignancies [5]. And the Fas could cooperate with Fas ligand (FasL) to trigger programmed cell death [6]. Previous studies have reported two functional single nucleotide polymorphisms (SNPs) in the promoter region of Fas gene [7, 8] and one single nucleotide polymorphism in FasL gene. One of these polymorphisms is A to G substitution at position -670 in the enhancer region which changes the activators of transcription 1 (STAT1) transcription factor-binding site of Fas gene. The other polymorphism is G to A base change at position -1377 situated between two putative silencer regions which alters SP-1 transcription factor-binding site [8, 9]. In addition, the change of T to C base at position-844 of FasL gene also has been suggested to alter the expression of FasL gene [10]. In current studies, the association between Fas/FasL gene polymorphisms and susceptibility to cancers including lung cancer [11], gastric cancer [12], breast cancer [13], cervical cancer [14], prostate cancer [15] and leukemia [8] has been showed. Currently, there are many case-control studies published to evaluate the association between Fas gene polymorphisms between susceptibility to leukemia, but these studies reported controversial findings [8, 10, 16, 17]. In addition, there were several meta-analyses on association between Fas/FasL polymorphisms and cancer risk recently [18-20]. How-

ever, these meta-analyses did not include the studies on leukemia completely and there is no meta-analysis on association between Fas/FasL polymorphisms and leukemia risk. So, we performed a meta-analysis to assess the association between Fas/FasL polymorphisms and susceptibility to leukemia.

Methods

Search strategy

We carried out a literature search in PubMed, Embase, Web of Science and CNKI databases for studies on the associations between Fas/FasL polymorphisms and susceptibility to leukemia. The search strategy was based on the combination of following key words ("Fas", "FasL", "CD95", "TNFSF6", "APO-1", "rs2234767", "rs1800682" or "rs763110") and ("polymorphism(s)", "variants", "genotype") and ("leukemia" or "leukaemia" or "leucocythaemia"). There was no language limitation. The last search was updated on April 2014. All searched studies were retrieved, and their references were also checked for other relevant publications. If more than one cancer type was reported in one study, the data for each type was extracted separately. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

Inclusion criteria

The following criteria were used for the inclusion of eligible articles for our meta-analysis: (1) Studies that assessed the association between the Fas/FasL polymorphisms and risk of leukemia; (2) Studies with a case-control study design; (3) Studies with detailed genotype frequencies for cases and controls or studies provided sufficient data to calculate genotype frequencies; (4) Genetic testing method is reasonable. The exclusion criteria were as follows: (1) Studies without control population; (2) Studies without available genotype frequency for the Fas or FasL polymorphisms; (3) Studies that contained overlapping data; (4) Studies not in Hardy-Weinberg equilibrium (HWE).

Data extraction

Two investigators independently extracted data using a standardized extract form. Disagreement was solved by discussion between the two investigators. If these two investigators could not reach a consensus, another investigator was consulted to resolve the dispute. The following information was extracted from each publication: the first author, year of publication, country of origin, ethnicity of participants and genotyping methods, total number of cases and controls, and source of controls, whether or not the genotype distributions among controls were in accordance with Hardy-Weinberg equilibrium (HWE). Ethnicity of participants was categorized as Caucasians, Asians and South Latinas. The leukemia types were further categorized as acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelocytic leukemia (AML), chronic myeloid leukemia (CML) and other leukemia types.

Statistical analysis

The pooled OR and its 95% CI were used to assess the strength of the associations. The significance of the pooled OR was determined by Z test, and a *P* value of less than 0.05 was considered significant. We examined the associations between Fas polymorphisms and susceptibility to leukemia under four different models including the allele model, the dominant model, the recessive model and the homozygous model. The heterogeneity between the studies was assessed by the χ^2 test-based Q statistic method [21] and I^2 statistic which provides values between 0 and 100% with a greater degree of heterogeneity (I^2 = 0-25%: no heterogeneity; I^2 = 25-50%: moderate heterogeneity; I^2 = 50-75%: large heterogeneity; I^2 = 75-100%: extreme heterogeneity) [22]. A *P* value of < 0.10 and I^2 > 50% indicated evidence of significant heterogeneity. The combined OR was calculated by the fixed-effects model (Mantel-Haenszel) [23] in the absence of heterogeneity; otherwise, the random-effects model (the DerSimonian and Laird method) [24] was used to calculate the pooled OR. The departure of the SNP from expected frequencies under HWE was assessed in controls using the Pearson χ^2 test (P < 0.05 was considered significant). Subgroup analysis by ethnicity was further performed. Sensitivity analysis was performed to assess influence of each study on our pooled results. Publication bias was observed with the funnel plot using the standard error of logOR (An asymmetric plot and suggests a possible publication bias) and Egger's test (P < 0.05 was considered representative of statistically significant publication bias) [25]. All the statistical tests were performed with Stata 12.0.

Table 1. Characteristics of studies on the association between Fas/FasL polymorphisms and leukemia risk

Study	Ethnicity	Countries	Type of cases	Type of controls	Sample size Case/Control	Genotype frequencies Case/Control			Allele frequencies Case/Control		HWE
Fas-670A/G (rs1800682)						AA	AG	GG	A	G	
Valibeigi, 2013	Caucasian	Iran	ALL	PB	142/117	44/47	77/57	21/13	165/151	119/83	0.487
Prajitha, 2013	Asian	India	CML	PB	290/300	90/83	147/155	53/62	327/321	253/279	0.506
Tong, 2012	Asian	China	ALL	PB	361/519	157/198	159/255	45/66	473/651	249/387	0.249
Kim, 2010	Asian	Korea	AML	PB	592/858	168/251	307/421	117/186	643/923	541/793	0.704
Farre, 2008	Latinas	Brazil	ATL	HB	31/60	12/10	8/31	11/29	32/51	30/89	0.714
Sibley, 2003	Caucasian	UK	AML	PB	454/934	129/280	228/449	97/205	486/1009	422/859	0.324
Fas-1377G/A (rs2234767)						GG	GA	AA	G	A	
Valibeigi, 2013	Caucasian	Iran	ALL	PB	142/117	117/94	21/17	4/6	255/205	29/29	0.487
Prajitha, 2013	Asian	India	CML	PB	290/300	176/190	106/100	8/10	458/480	122/120	0.506
Tong, 2012	Asian	China	ALL	PB	361/519	177/212	139/225	45/82	493/649	229/389	0.249
Kim, 2010	Asian	Korea	AML	PB	592/858	195/286	303/427	94/145	693/999	491/717	0.704
Rollinson, 2004	Caucasian	England	AML	PB	482/838	NA	NA	NA	752/1525	212/151	NA
Sibley, 2003	Caucasian	UK	AML	PB	471/931	319/726	136/186	16/19	774/1638	168/224	0.324
FasL-844T/C (rs763110)						TT	TC	CC	T	C	
Tong, 2012	Asian	China	ALL	PB	361/519	192/132	107/276	62/111	491/540	231/498	0.249
Kim, 2010	Asian	Korea	AML	PB	592/858	52/75	236/321	302/462	340/471	840/1245	0.704

PB, population based; NA, not available; HWE, Hardy-Weinberg Equilibrium.

Table 2. Meta-analysis of the association between Fas/FasL polymorphisms and susceptibility to leukemia

Study groups	OR (95% CI), I^2 (%)							
	Recessive model		Homozygous model		Dominant model		Allele model	
Fas-670A/G	GG vs AG/AA		GG vs AA		GG/AG vs AA		G vs A	
Overall (6)	0.94 (0.80, 1.09)	0.0	0.93 (0.78, 1.11)	28.7	1.01 (0.89, 1.14)	47.4	0.96 (0.89, 1.05)	38.6
Caucasian (2)	1.01 (0.78, 1.30)	0.0	1.10 (0.82, 1.48)	27.5	1.15 (0.92, 1.43)	20.9	1.06 (0.92, 1.23)	37.4
Asian (3)	0.90 (0.74, 1.09)	0.0	0.88 (0.71, 1.10)	0.0	0.92 (0.78, 1.07)	13.4	0.93 (0.84, 1.04)	0.0
AML (2)	0.93 (0.77, 1.12)	0.0	0.98 (0.79, 1.22)	0.0	1.06 (0.90, 1.25)	0.0	1.00 (0.90, 1.11)	0.0
ALL (3)	1.06 (0.75, 1.51)	0.0	1.12 (0.58, 2.17)	55.2	1.05 (0.57, 1.93)	77.4	1.05 (0.72, 1.53)	71.9
Fas-1377G/A	AA vs GA/GG		AA vs GG		AA/GA vs GG		A vs G	
Overall (6)	0.91 (0.74, 1.12)	13.8	0.89 (0.71, 1.12)	48.2	1.06 (0.77, 1.45)	81.8	1.21 (0.82, 1.81)	94.4
Caucasian (3)	0.99 (0.76, 1.27)	42.4	1.10 (0.62, 1.96)	55.0	1.20 (0.79, 1.80)	80.3	1.41 (0.82, 2.42)	95.3%
Asian (3)	0.78 (0.54, 1.11)	0.0	0.69 (0.47, 1.00)	0.0	0.89 (0.57, 1.37)	75.7	0.89 (0.66, 1.22)	69.1
AML (3)	1.15 (0.66, 2.03)	61.0	1.26 (0.64, 2.48)	70.3	1.31 (0.80, 2.14)	88.7	1.64 (0.88, 3.04)	96.7
ALL (2)	0.75 (0.51, 1.09)	0.0	0.64 (0.43, 0.96)	0.0	0.74 (0.58, 0.95)	0.0	0.78 (0.64, 0.94)	0.0
FasL-844T/C	CC vs TC/TT		CC vs TT		CC/TC vs TT		C vs T	
Overall (2)	0.86 (0.72, 1.03)	0.0	0.60 (0.25, 1.45)	90.6	0.54 (0.17, 1.75)	96.0	0.69 (0.38, 1.25)	95.3

The results that are in bold type show statistical significance. OR, odds ratio; CI, confidence interval.

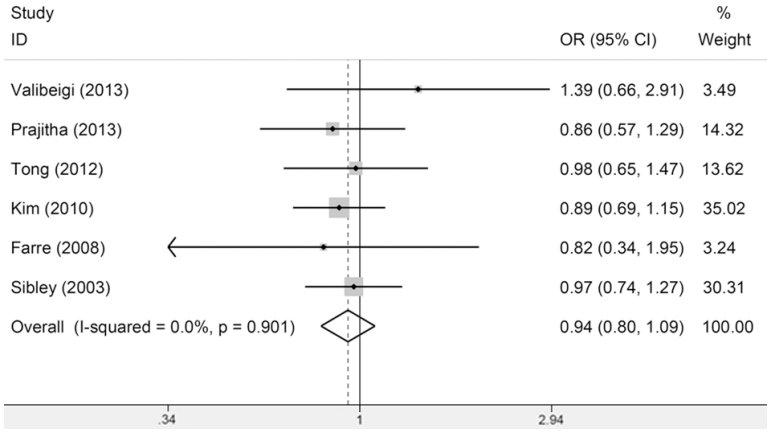

Figure 1. Meta-Analysis of association between Fas-670 polymorphism and susceptibility to leukemia (GG vs AG/AA).

Results

Study characteristics

According to the inclusion criteria defined for the studies available for this meta-analysis, 7 publications with a total of 14 studies were finally included into the meta-analysis [8, 10, 16, 17, 26-28]. There were 6 studies with a total of 1870 cases and 2788 controls on the association between Fas-670A/G polymorphism and susceptibility to leukemia [8, 10, 16, 17, 26, 27]. And there were 6 studies with a total of 2338 cases and 3563 controls on the association between Fas-1377G/A polymorphism and susceptibility to leukemia [8, 10, 16, 17, 27, 28]. In addition, there were 2 studies with a total of 953 cases and 1377 controls on association between FasL-844T/C polymorphism and susceptibility to leukemia. The alleles within control groups of all studies are in Hardy-Weinberg equilibrium, one study only provides the frequency of alleles [28]. The summary characteristics of studies are listed in **Table 1**.

The summary results of the meta-analysis on the association between Fas/FasL polymorphisms and susceptibility to leukemia are shown in **Table 2**. Overall, there was no association between Fas-670A/G polymorphism and susceptibility to leukemia (G vs A: OR = 0.94, 95% CI = 0.80-1.09; GG vs AA: OR = 0.93, 95% CI = 0.78-1.11; GG/AG vs AA: OR = 1.01, 95% CI = 0.89-1.14; GG vs AG/AA: OR = 0.96, 95% CI = 0.89-1.05). In addition, there was also no association between Fas-1377G/A or FasL-844T/C polymorphisms and susceptibility to leukemia (AA vs GA/GG: OR = 0.91, 95% CI = 0.74-1.12; AA vs GG: OR = 0.89, 95% CI = 0.71-1.12; AA/GA vs GG: OR = 1.06, 95% CI = 0.77-1.45; A vs G: OR = 1.21, 95% CI = 0.82-1.81; CC vs TC/TT: OR = 0.86,

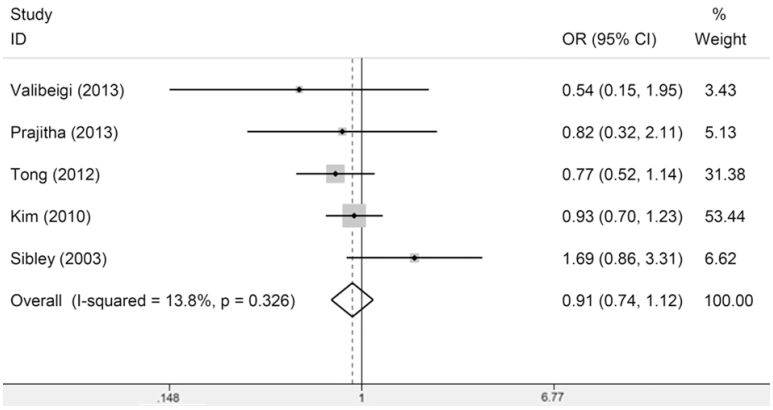

Figure 2. Meta-Analysis of association between Fas-1377 polymorphism and susceptibility to leukemia (AA vs GA/GG).

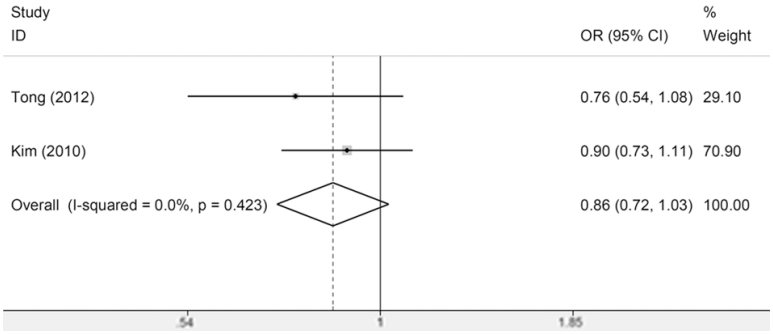

Figure 3. Meta-Analysis of association between FasL-844 polymorphism and susceptibility to leukemia (CC vs TC/TT).

95% CI = 0.72-1.03; CC vs TT: OR = 0.60, 95% CI = 0.25-1.45; CC/TC vs TT: OR = 0.54, 95% CI = 0.17-1.75; C vs T: OR = 0.69, 95% CI = 0.38, 1.25). Subgroup analysis by ethnicity suggested that there was no association between Fas/FasL polymorphisms and leukemia risk under all four genetic models in Asians or Caucasians (**Table 2**). In the subgroup analysis by leukemia type, we observed that Fas-1377G/A polymorphism was associated with leukemia risk in ALL patients under all models except the recessive model (**Table 2**).

Sensitivity analysis

To examine the stability and reliability of our meta-analysis results, we performed sensitivity analysis by sequentially removing the single studies one at time. In this meta-analysis, the results of sensitivity analysis showed that no single study influenced the recalculated ORs and 95% CIs quantitatively, suggesting robustness and reliability of our results.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures in the analyses of FAS-670A/G and FAS-1377G/A polymorphisms. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (**Figure 4**). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not show any evidence of publication bias (All $P > 0.05$, **Table 3**). The publication bias cannot be analyzed in the analysis of Fas-844T/C polymorphism due to the limit of study number.

Discussion

Leukemia risks were affected by various environmental and genetic factors. Genetic polymorphisms in Fas/FasL gene were also proposed to be associated with susceptibility to leukemia, but recent studies reported controversial findings. We performed a meta-analysis to assess the association between Fas/FasL polymorphisms and susceptibility to leukemia. Our meta-analysis is the first meta-analysis on the association between Fas/FasL polymorphisms and leukemia risk. However, the findings from the overall analyses did not support the associations of Fas/FasL polymorphisms with leukemia (**Table 2**).

In the meta-analysis for the association between Fas-670A/G and leukemia risk, no association was observed under all models (**Figure 1**) and there was also no significant heterogeneity. From the subgroup analysis by leukemia type, we found that the between-study heterogeneity was significant among ALL subgroup under all models except the recessive model, suggesting that the studies in ALL and leukemia type might be the source of heterogeneity (**Table 2**). In the meta-analysis for the association between Fas-1377G/A and leuke-

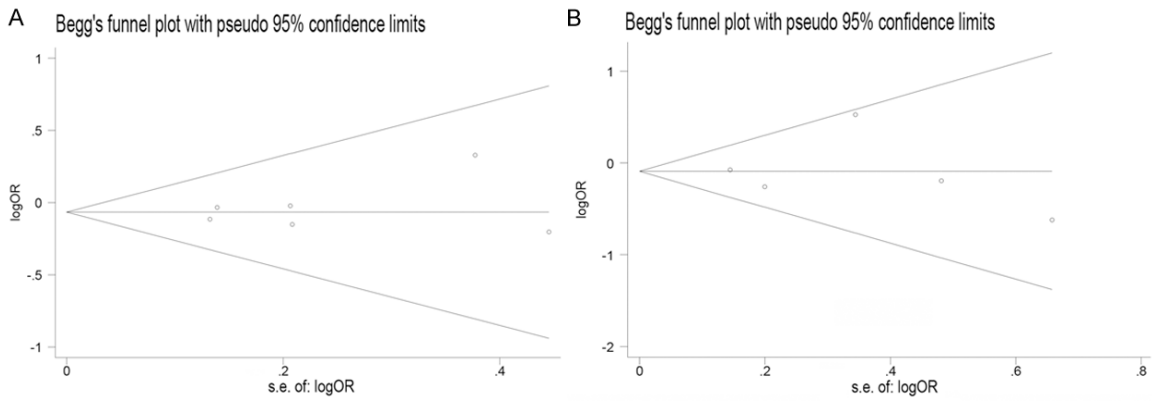

Figure 4. Funnel plots between Fas polymorphisms and leukemia risk. A. GG vs AG/AA (Fas-670); B. AA vs GA/GG (CC vs TC/TT).

mia risk, no association was observed (**Figure 2**) and there was significant heterogeneity in allele model (A vs G) and dominant model (GA/AA vs GG) and there was no significant heterogeneity in the recessive model (AA vs GA/GG) and the homozygous model (AA vs GG). From the subgroup analysis by ethnicity, we found that the between-study heterogeneity in Asians and Caucasians was still significant, suggesting that the ethnicities might be the source of heterogeneity (**Table 2**). However, from the subgroup analysis by leukemia type, we observed significant association in ALL subgroup and no heterogeneity was observed in ALL subgroup. These results suggested A allele of Fas-1377G/A may be a protective factor to ALL risk (**Table 2**). As for the FasL-844T/C polymorphism, only two studies meet the Inclusion criteria and no significant association was observed (**Figure 3**). Thus more studies on FasL-844T/C polymorphism were required in the future.

There were some limitations of our meta-analysis. First, there was heterogeneity among studies and the heterogeneity was significant under several models. The heterogeneity was still existed in some subgroups under several models and the heterogeneity (**Table 2**). So, we could not conclude whether the heterogeneity came from ethnicity or leukemia type in subgroups (ALL in Fas-670A/G polymorphism; Caucasians or AML in Fas-1377G/A polymorphism).Second, studies on the association between Fas polymorphisms and cancer risk mainly focus on solid tumor. The number of studies on hematological malignancy was limited. So the case group and control group were fewer in number, which could increase the likelihood of type I and type II errors. Only 2 studies assessed association between FasL-844T/C polymorphism and leukemia risk were included. Third, although no obvious publication bias was detected by funnel plot or Egger's test. Fourth, in the subgroup analyses by ethnicity, most studies were from Caucasians and no studies among Africans, suggesting the inapplicability of our results for these populations. Fifth, several risk factors are related to hematological malignancies, such as age, sex, family history, environmental factors, cancer stage, viral and bacterial infections, toxic chemistry, smoking status, and so on. Our meta-analysis didn't discuss these information due to lack of original information. Sixth, leukemia contains different types while our meta-analysis mainly included AML and ALL. Seventh, our meta-analysis was limited to language; the included published studies were all in English. In spite of these limitations, our meta-analysis had several advantages. First, the quality of the case-control studies included in our meta-analysis was satisfactory and met our inclusion criteria. Second, we did not detect any publication bias, suggesting that the whole pooled result was unbiased. Third, our study is the first meta-analysis assesses the Fas/FasL polymorphisms and leukemia risk

This meta-analysis suggests that there was no association between Fas/FasL polymorphisms and susceptibility to leukemia except the association between Fas-1377G/A polymorphism and ALL risk. The A allele of Fas-1377G/A was suggested as a protective factor in ALL risk. However, further studies with large sample size

Table 3. Egger's test for publication bias

Variables	Models	P	95% CI
Fas-670A/G			
	GG vs AG/AA	0.510	(-1.31, 2.22)
	GG vs AA	0.537	(-4.70, 2.86)
	GG/AG vs AA	0.206	(-1.79, 6.04)
	G vs A	0.527	(-5.12, 3.07)
Fas-1377G/A			
	AA vs GA/GG	0.991	(-3.69, 3.72)
	AA vs GG	0.926	(-4.94, 5.26)
	AA/GA vs GG	0.767	(-14.50, 11.83)
	A vs G	0.851	(-15.54, 17.95)

are needed to further assess the association between Fas/FasL and susceptibility to leukemia, especially on FasL-844T/C polymorphism.

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Disclosure of conflict of interest

None.

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