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Association of the CTLA-4 1722TC polymorphism and systemic lupus erythematosus: a systematic review and meta analysis

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Abstract

Background: Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is an important negative regulator of T-cell responses. The -1722TC polymorphism of the CTLA-4 gene may be associated with systemic lupus erythematosus (SLE) risk, but related results from previous studies have been inconsistent. We carried out a meta-analysis to assess this association more precisely.

Methods: A systematic search through PubMed, Science Direct, and OVID, Iran doc, Iranmedex and SID (Scientific Information Database) databases was performed with the last search updated on December 30, 2011. The odds of ratio (OR) and its 95% confidence interval (95%CI) were used to assess the strength of the association. We evaluated both fixed and random effect models, depending on the presence of between-study heterogeneity. The analyses were conducted using STATA software, version 11.0.

Results: A total of 9 independent studies on the CTLA-4 gene -1722TC polymorphism and SLE, including 1422 cases and 1417 controls were used in this meta-analysis. In the present meta-analysis, we found a significant association between -1722TC polymorphism and SLE risk in the overall analysis (TT versus TC/CC: OR=1.18, 95%CI 0.84-1.66, p= 0.32; TT/TC versus CC: OR = 2.06, 95%CI 1.07–3.99, p= 0.03; TT versus CC: OR = 2.32, 95%CI 1.62–3.32, p< 0.001; TC versus CC: OR = 1.99, 95%CI 1.42–2.78, p<0.001; TT versus TC: OR = 1.2, 95%CI 0.86–1.66, p= 0.28; T versus C: OR = 1.22, 95%CI 0.91–1.64, p= 0.16). In the subgroup analysis by ethnicity, -1722TC polymorphism was significantly associated with SLE risk in Asian population.

Conclusion: This meta-analysis suggests a significant association between -1722TC polymorphism and SLE susceptibility. Large-scale and well-designed case-control studies are necessary to validate the risk identified in the present meta-analysis.

Keywords: Systemic lupus erythematosus (SLE), 1722TC polymorphism, CTLA-4, Meta-analysis.

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Introduction

Systemic lupus erythematosus (SLE) is a complex inflammatory disease characterized by autoantibody production (1). The disease is more common in women but could be found in different racial and ethnic

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groups. It is more frequently reported in individuals in the second, third or fourth decades of life (2). The etiology of the disease is unknown but is thought to be caused by both genetic and environmental factors (3). The expression of CTLA-4 is increased in patients with active SLE (4). Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) is an important negative regulator of T-cell responses, and its dysregulation has the potential to affect the pathogenesis of SLE by altered activation of T cells to self-antigens (1) in multiple organs including kidneys, heart, lung, joints and immune system (5). CTLA-4 polymorphisms have been confirmed to be associated with several autoimmune disease such as, Graves' disease, type I diabetes, celiac disease, autoimmune thyroid disease, rheumatoid arthritis and multiple sclerosis and SLE (6). A polymorphism is located at position -1722 in the promoter region. Several studies have been performed on association between -1722TC polymorphism and SLE but results were inconsistent (7-11). Meta-analysis is a good approach to categorize the results from different studies by producing a single estimate of the major effect with enhanced precision. Meta-analysis is an appropriate way to increase sample size and avoid from random error. The aim of this study was to investigate the association of -1722TC polymorphism with SLE risk by conducting a meta-analysis from all eligible case-control studies published until December 2011.

Methods

Literature Search Strategy

We searched through PubMed, Science Direct, OVID, Iran doc, Iranmedex and SID (Scientific Information Database) for all articles in English published until December 30, 2011, on the association between -1722TC polymorphism and SLE risk. The search was confined to studies conducted on human subjects, using the following query, "Systemic Lupus Erythematosus [mh]" or "Systemic Lupus Erythematosus [tiab]" or "SLE" or "CTLA-4" or "CTLA4" or " 1722TC" or "1722TC polymorphism" and "(Systemic Lupus Erythematosus [mh] OR Systemic Lupus Erythematosus [tiab]) AND (CTLA-4 OR CTLA4)". The reference lists of major textbooks, reviews and included articles were studied for other potentially eligible studies. We did not consider unpublished reports.

Inclusion and exclusion criteria

The studies focused on the association between the CTLA-4 gene 1722TC polymorphism and the susceptibility of SLE with case-control design. Review articles, case reports, editorials, conference abstracts and letters were therefore excluded. When there were multiple publications from a single project, only the largest study was included. When a study reported the results on different ethnicities, they treated as separate studies in stratified analysis. When a study included subjects of different countries, the related data was extracted separately.

Data extraction

Two of the authors extracted data according to a standard protocol independently. Disagreement was resolved by discussion between the two authors, if they could not reach a consensus, however, a third author was consulted. The information extracted from the literature included the name of the first author, year of publication, study region, race, total sample size, number of genotypes and alleles in both case and control groups.

Statistical analysis

We predicted the contribution of the -1722TC polymorphism of CTLA-4 gene to susceptibility of SLE by adopting the review manager software version 4.2 developed by the Cochrane collaboration. The strength of the association was measured by the odds of ratio (OR) and 95% confidence interval (CI). Hardy-Weinberg equilibrium (HWE) was assessed for the control group of each study using the goodness-of-fit test. Heterogeneity assumption was assessed by the Chi-square-based Q test and was

Table 1. Characteristics of the individual studies of CTLA-4 polymorphism with SLE

study	population	Ethnicity	Sample size Case	Control	Detection method	Source of control	Findings
Hudson et al (2002)	Korean	Asian	130	200	PCR-RFLP	Population-based	Genotype and allele distribution (p<0.05)
Aguilar et al (2003)	Spanish	Caucasian	276	194	PCR-RFLP	Population-based	Not significant
Fernandez et al (2004)	Spanish	Caucasian	214	235	PCR-RFLP	Population-based	C allele distribution (p<0.05)
An-ping et al (2004)	Chinese	Asian	103	110	PCR-RFLP	Population-based	TC and CC genotype distribution (p<0.05)
Parks et al (2004)	USA	African-American	144	72	PCR-RFLP	Population-based	Not significant
Parks et al (2004)	USA	Caucasian	85	202	PCR-RFLP	Population-based	Not significant
Takeuchi et al (2007)	Japanese	Asian	61	104	PCR-RFLP	Not available	Not significant
Chua et al (2010)	Malaysian	Asian	130	130	PCR-RFLP	Population-based	Not significant
Khalaf et al (2011)	Chinese	Asian	279	170	PCR-RFLP	Population-based	Genotype and allele distribution (P<0.05)

regarded to be statistically significant at p< 0.1. The random-effects model (using the Der Simonian and Laird method) was used when the test of heterogeneity was significant; otherwise, the fixed-effects model (using the Mantel-Haenszel method) was applied. The potential publication bias, was evaluated by Egger's linear regression and was regarded to be statistically significant at p<0.05. The analyses were conducted using STATA software, version 11.0.

Results

Although 659 articles were retrieved according to our key words, nine articles were eligible for this meta-analysis on the association between CTLA-4 gene 1722TC polymorphism and SLE susceptibility (figure 1) (7-14). Fernandes et al had only reported allele frequency and no information

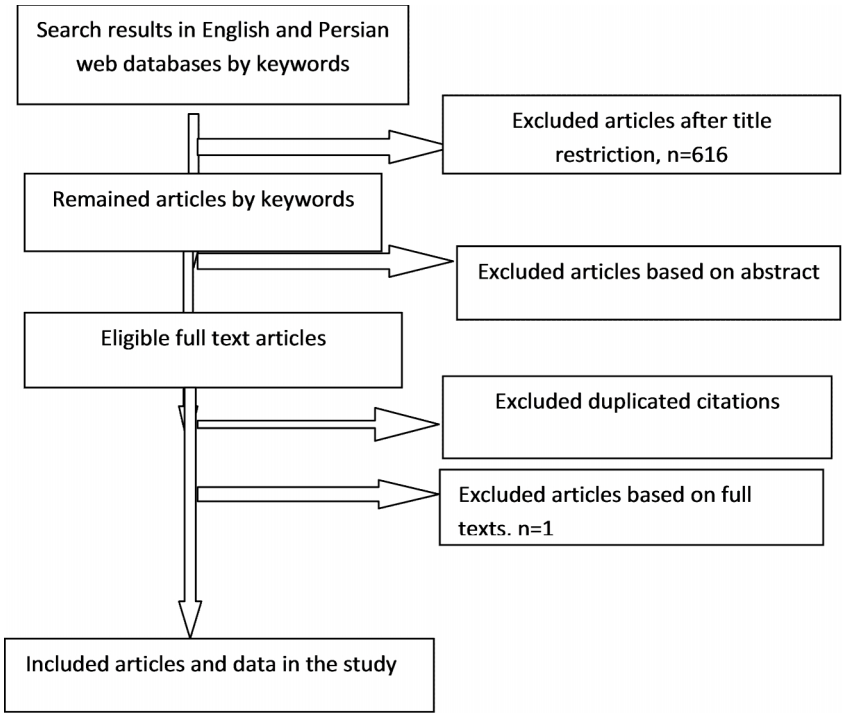

Fig. 1. Flow diagram of the studies selection process

on the genotype of the studied patients. Park's study was comprised of two independent case-control studies, and thus was treated as two separate estimates (9). As a final point, we surveyed nine studies consisting of a total of 1422 SLE cases and 1417 controls. The genotype distributions among the controls of all studies were consistent with HWE. From among these studies, five were conducted on the Asian population, three on the Caucasians and one on the African-Americans (Table1).

Quantitative synthesis

The main results of this meta-analysis and the heterogeneity test in whole population and ethnicity subgroups are shown in Table 2. As it presents, a significant association was found between 1722TC polymorphism and increased SLE risk in the whole population (TT/TC vs. CC: OR=2.06, 95%CI 1.07–3.99, p= 0.03 (Figure 2); TT vs. CC: OR=2.32, 95%CI 1.62–3.32, p<0.001 (Fig. 3); TCvs. CC: OR=1.99, 95%CI 1.42_2.78, p<0.001 (Fig. 4)). Stratified analysis indicated that the frequency of TT/TC versus CC (OR= 2.37, 95%CI 1.12–5.02, p= 0.02), TT versus CC (OR= 2.35, 95%CI 1.37–4.03, p= 0.002), TC versus CC (OR= 2.06, 95%CI 1.46–2.91, p<0.001) and T versus C (OR= 1.49, 95%CI 1.14–1.96, p=0.003) was significantly higher in Asian SLE patients than the controls. The meta-analysis included 1 study in African-American population but there was no significant difference between SLE and control in any genotype and allele in this subgroup (Table 2).

Table 2. Meta-analyses of 1722TC polymorphism in the CTLA-4 gene in overall and ethnicity subgroup analysis

Polymorphic sites	Population	No. of studies	Sample size Case	Control	Test of association OR	95% CI	p	Test of heterogeneity Model	I2	p
TT versus TC/CC	All	8	1208	1182	1.18	0.84-1.66	0.32	Random	67	0.003
	Asian	5	703	714	1.27	0.80-2.04	0.30	Random	73.2	0.005
	Caucasian	2	361	396	0.85	0.42-1.72	0.67	Random	68	0.077
	African-American	1	144	72	1.55	0.83-2.89	0.16	--------	-----	-------
TT/TC versus *CC*	All	8	1208	1182	2.06	1.07-3.99	0.03	Random	69.4	0.002
	Asian	5	703	714	2.37	1.12-5.02	0.02	Random	80	0.001
	Caucasian	2	361	396	0.79	0.17-3.63	0.77	Fixed	1	0.627
	African-American	1	144	72	2.01	0.12-32.67	0.62	--------	-----	------- ---
TT versus CC	All	8	677	729	2.32	1.62-3.32	<0.001	Fixed	34.3	0.154
	Asian	5	277	352	2.35	1.37-4.03	0.002	Random	50.9	0.087
	Caucasian	2	290	328	0.76	0.16-3.46	0.72	Fixed	1	0.578
	African-American	1	110	49	2.27	0.14-37.06	0.56	--------	-----	-------
TC versus CC	All	8	498	606	1.99	1.42-2.78	<0.001	Fixed	16.5	0.30
	Asian	5	356	511	2.06	1.46-2.91	<0.001	Fixed	48	0.11
	Caucasian	2	73	71	1.07	0.22-5.16	0.93	Fixed	1	0.89
	African-American	1	69	24	1.47	0.08-24.84	0.78	--------	-----	-------
TT versus TC	All	8	1047	982	1.20	0.86-1.66	0.28	Random	62.6	0.009
	Asian	5	511	565	1.29	0.82-2.04	0.26	Random	68.7	0.010
	Caucasian	2	359	393	0.86	0.43-1.73	0.68	Random	65.8	0.087
	African-American	1	177	24	1.53	0.82-2.88	0.18	--------	-----	-------
T versus C	All	9	2650	2834	1.22	0.91-1.64	0.16	Random	77.3	<0.001
	Asian	5	1144	1428	1.49	1.14-1.96	0.003	Random	62.6	0.003
	Caucasian	3	1150	1262	0.80	0.41-1.54	0.51	Random	81.2	0.005
	African-American	1	356	144	1.47	0.84-2.56	0.17	--------	----	-------

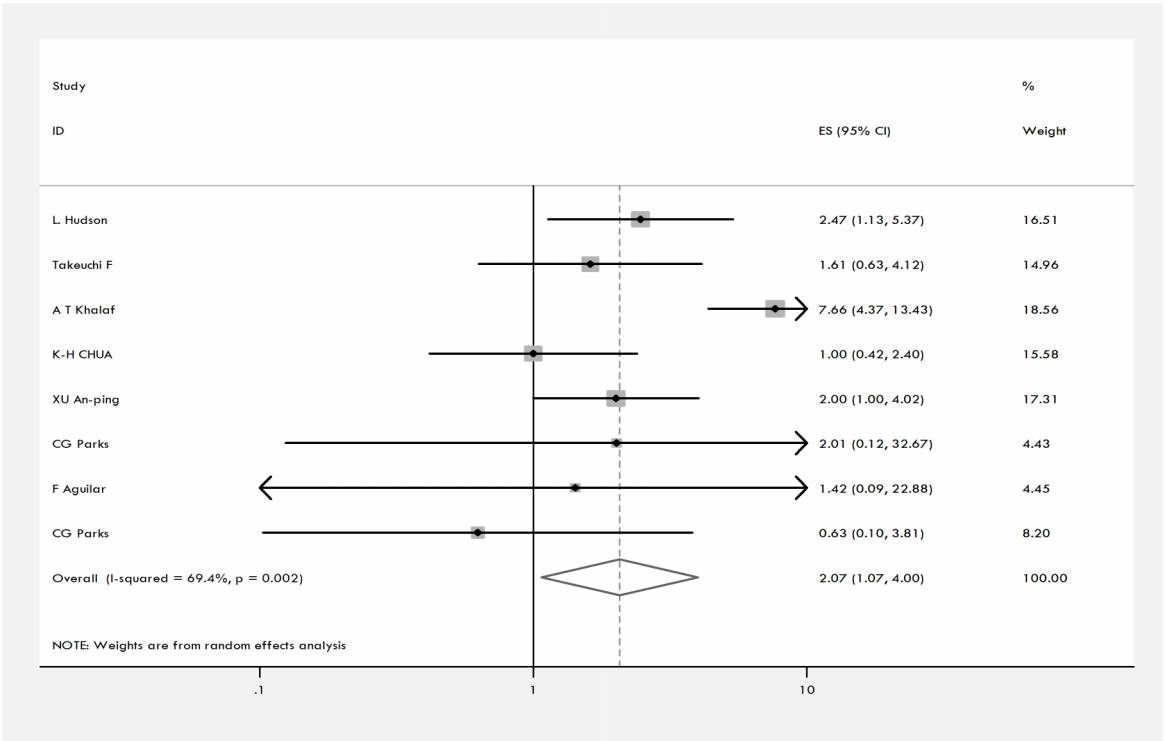

Fig. 2. Odds ratio and 95% CI of individual studies and pooled data for the association of the CTLA-4 1722TC polymorphism and SLE comparing TT/TC genotypes with CC genotype in overall population using random effect model meta-analysis. OR: Odds of ratios.

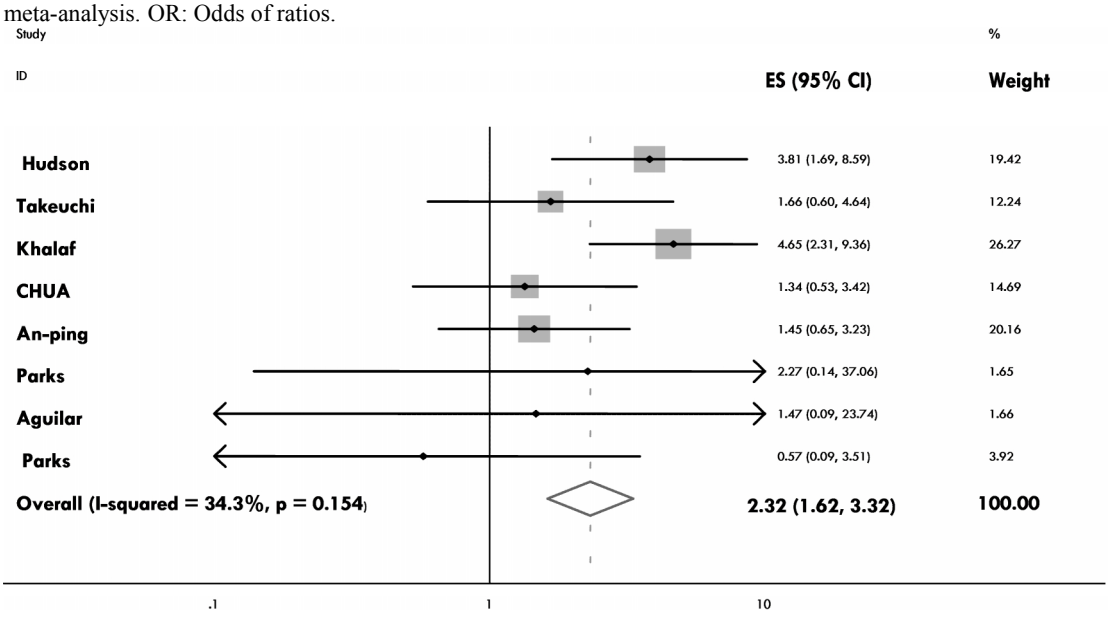

Fig. 3. Odds of ratios and 95% CI of individual studies and pooled data for the association of the CTLA-4 1722TC polymorphism and SLE comparing TT genotype with CC genotype in overall population using fixed effect model meta-analysis. OR: Odds of ratios.

Publication bias

The Egger test showed no publication bias either TT vs. TC/CC: ap= -5.89, p= 0.17; TT/TC vs. CC: ap=-1.99, p= 0.18.; TT vs. CC: ap=-1.27, p= 0.27; TC vs. CC: ap= -1.17, p= 0.22; TT vs. TC: a = -5.84, p= 0.12; T vs. C: ap= -6.50, p= 0.06, respectively.

Discussion

Genetic inheritance is an important risk factor for SLE. Several studies have reported that many different environmental factors act together to place genetically pre-

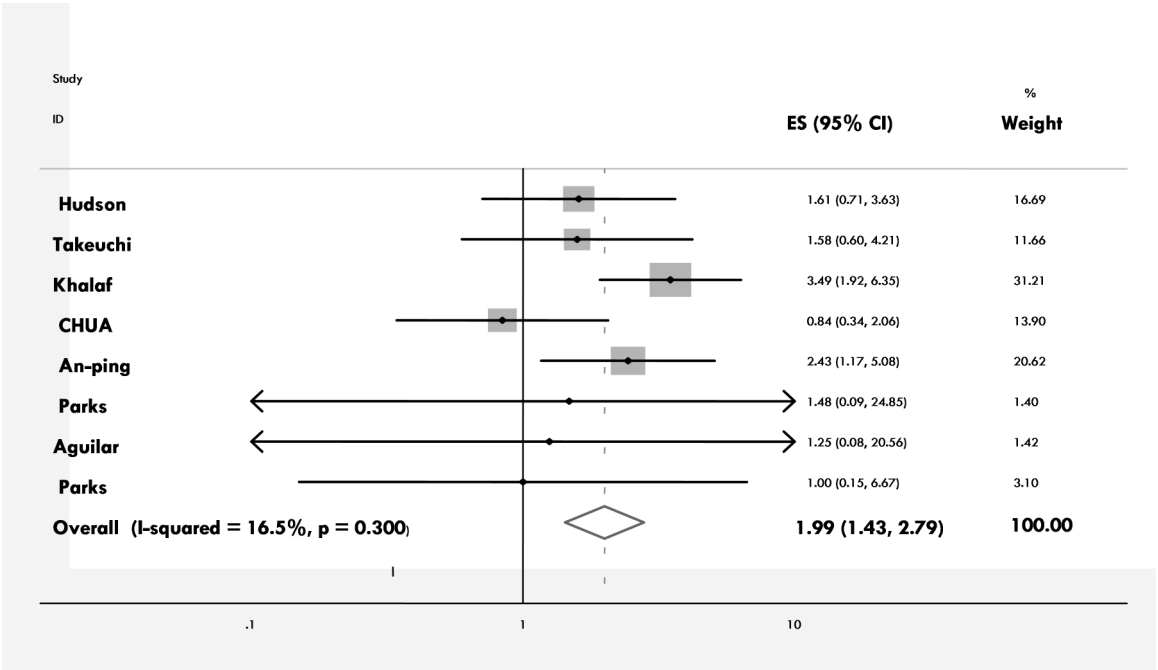

Fig. 4. Odds of ratios and 95% CI of individual studies and pooled data for the association of the CTLA-4 1722TC polymorphism and SLE comparing TC genotype with CC genotype in overall population using fixed effect model metaanalysis . OR: Odds of ratios.

disposed individuals at a higher risk of SLE (15). Cytotoxic T lymphocyte associated antigen 4 (CTLA-4) plays a key role in the regulation of T-cell stimulation and inhibits T-cell activation (16) .Reduced expression or function of CTLA-4 contributes to the pathogenesis of autoimmune diseases. Consequently, CTLA-4 polymorphisms could be associated with several autoimmune disorders including rheumatoid arthritis (17), cancer (18), diabetes mellitus (19) and SLE. Furthermore, reported in various studies there are several polymorphisms for CTLA-4 gene like 49AG in exon 1, 1661AG, 318CT in promoter region (9, 20-21).

Numerous studies have investigated the association between 1722TC polymorphism of CTLA-4 gene and SLE; their results, however, are controversial (9-14). Alternatively, meta-analysis can overcome some problems caused by a single study, such as small sample size, low test power and selection bias.

The present meta-analysis of nine published studies was conducted on 1422 SLE cases and 1417 controls. The results suggested that TC and TT genotypes of 1722TC polymorphism might be related to an increased risk of SLE in the overall population. The ethnicity can strongly influence the distribution of CTLA-4 gene polymorphisms. In the Asian patients, TT, TC genotype and T allele were more frequently linked with the higher susceptibility to SLE compared with C allele and CC genotype. This comes while we failed to find any significant association between 1722TC polymorphism and SLE among the Caucasian and African-American population. There are many other factors such as age, gender, age at onset, disease severity, family history, having consanguineous parents, consumption of certain drugs, and smoking as well as the influence of other genes like tumor necrosis factor (TNF), interleukins, Fc gamma receptors (FcγRs), and major histocompatibility complex genes (MHC) that may explain why a single polymorphism acts differently in dissimilar ethnic groups. Our result was not consistent with a previous meta-analysis conducted by Lee et al (22). This is most probably because the previous meta-analysis had a relatively small sample size and had assessed only three studies (9, 11-12). The main limita-

tions of the current meta-analysis are as follows: firstly, meta-analysis is a retrospective research that is subject to methodological limitations. Secondly, the results should be interpreted with caution because of obvious heterogeneity in some comparisons. Thirdly, the number of studies included in the meta-analysis was small and finally, subjects have been picked with different methods that this diversity could effect on results.

Conclusion

The result of our study demonstrated a statistically significant association between CTLA-4 1722TC polymorphism and increased SLE susceptibility in the overall population and especially in the Asians population. Larger well-designed case-control studies in different ethnic groups are needed to approve the association between CTLA-4 1722TC polymorphism and increased SLE susceptibility.

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