

SYSTEMATIC REVIEW

C3953T genetic variation in interleukin 1 β and idiopathic male infertility: a systematic review and meta-analysis

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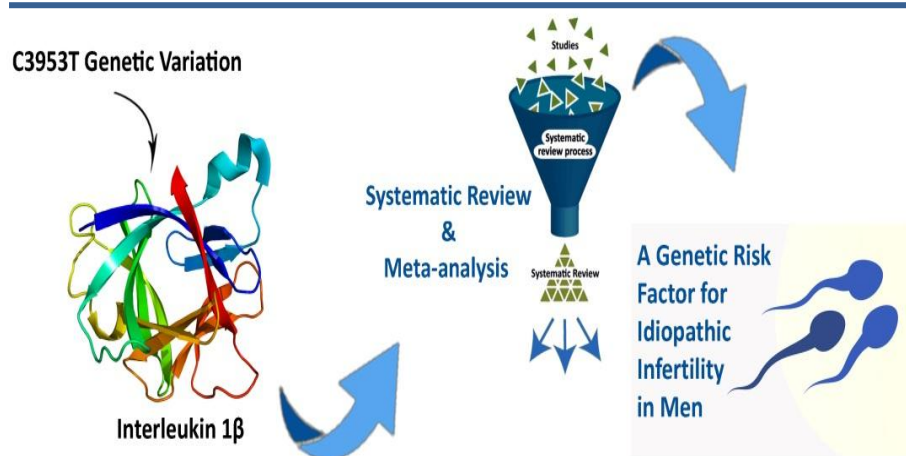
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Highlights

- Cytokines may play an important role in the male reproductive system, and alterations in their structure and function may increase the risk of male infertility.
- Interleukin-1-beta may affect sperm function by influencing oxidative stress.
- The C3953T polymorphism in interleukin-1-beta may be a genetic risk factor for male infertility.

Graphical Abstract



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Abstract

According to the World Health Organization, infertility means that a couple will not have children after 12 months of unprotected sex. Half of all cases of infertility are due to male factors. Environmental and genetic factors play a role in idiopathic infertility in men. Genetic polymorphisms in cytokine family genes may be an important risk factor for male infertility. This study aimed to investigate the association of C3953T polymorphism in the interleukin-1-beta gene with male infertility through a meta-analysis approach. For this study, an electronic search was conducted in reputable databases such as PubMed, Google Scholar, and Science Direct. Finally, three eligible studies were included in our meta-analysis. The results of the meta-analysis showed that C3953T polymorphism was associated with male infertility in allelic model (OR= 1.2143, 95% CI= 1.0057; 1.4662, p= 0.0433) and homozygous codominant model (OR= 3.0292, 95% CI= 1.5681; 5.8519, p= 0.00097). Another study also showed that there was no publication bias in our study and a sensitivity analysis showed that the exclusion of one study could not have a significant effect on the pooled ORs. Based on these results, the C3953T polymorphism may be a genetic risk factor for idiopathic infertility in men. However, due to the limited number of studies in this meta-analysis, further studies with higher sample sizes and different races are needed to obtain more accurate results.

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Introduction

Infertility is defined as the inability to reproduce after one year of intercourse without using any method of prevention. According to the World Health Organization, 10-15% of couples are in this group, of which 40% of infertility factors are related to male factors and 40% are related to female factors. In the remaining 20%, both sexes are involved (1). However, 50-70% of the causes of infertility remain unknown, of which genetic factors account for 30% (2). There are many factors involved in male infertility, one of which is a chronic or acute inflammation of the genital system, which leads to oxidative stress. An imbalance between prooxidative and antioxidant substances has caused functional and metabolic disorders of male germ cells, which may be the main cause of some kinds of infertility (3). Infectious factors and local tissue destruction result in the infiltration of leukocytes into the site of inflammation and stimulate the secretion of large amounts of biological substances such as proteases and inflammatory cytokines (4). Cytokines are paracrine-autocrine growth factors that are secreted by a wide range of cells in the male reproductive system, even in the absence of genital infections, and exert effects on estradiogenesis, spermatogenesis, and sperm function (5).

Spermatogenesis is an active procedure involving mitotic and meiosis divisions, and adult sperm formation. Establishing epithelium homeostasis in the seminiferous tubule requires a balance between cell proliferation and programmed cell death. A change in the balance between these two processes can lead to testicular diseases such as fertility disorders and testicular cancer (6). Homeostasis in testis needs a special immune status in the gonad of males. The immune system, with the help of proinflammatory cytokines, promotes cell growth and differentiation while allowing a normal inflammatory response against pathogens (7).

Most spermatogenesis occurs in a specific microenvironment, somewhere behind the blood-testicular barrier. The blood-testicular barrier is a physical barrier between the blood and the seminiferous tubules that is created by the connection of Sertoli cells near the basal membrane of the seminiferous tubules (8). Cytokines mediate the interaction between Sertoli and germ cells and are essential to facilitate the movement of germ cells along the tubular epithelium and their differentiation. The main source of cytokines in the testis is macrophages, but they are also produced by Leydig and Sertoli cells (9). Cytokines such as interleukin 1, 2, 6, 18, TNF α , and soluble receptors such as SRIL2 and 6 are the cytokines involved in spermatogenesis that affect sperm parameters (10). If the function of chemokines is disrupted, it could result in male infertility by affecting the spermatogenic functions (Figure 1).

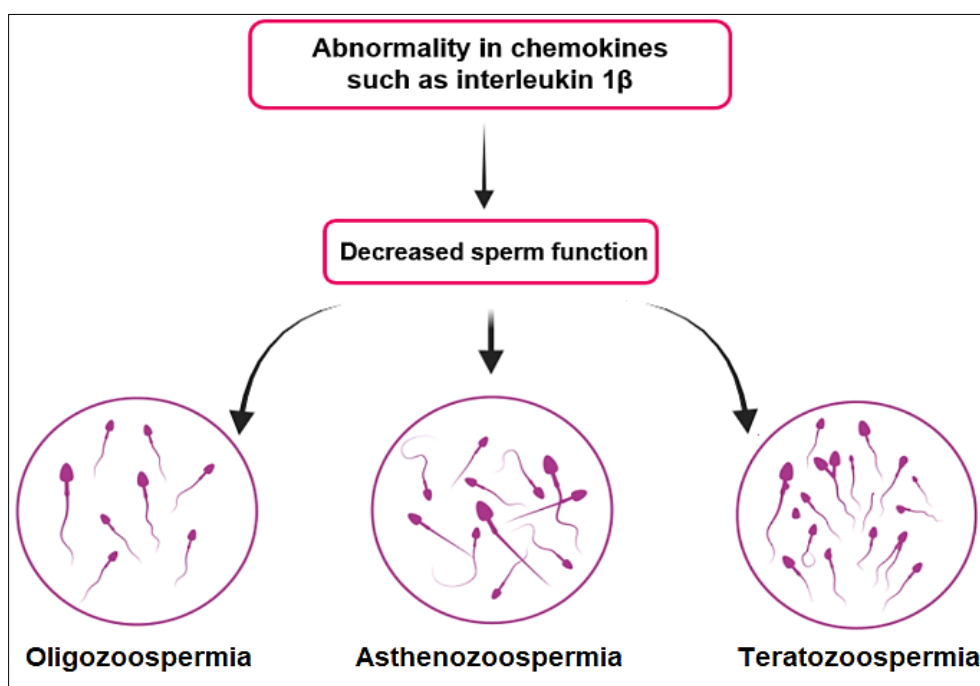


Figure 1. Disrupted sperm function by chemokines abnormalities. The defects in chemokines function could lead to sperm count, motility, and morphology.

The interleukin-1 family includes several members, including IL-1 α , IL-1 β , and IL-1RA, which modulate the expression of proteins involved in proliferation, cell survival, and angiogenesis for spermatogenesis. Interleukin-1 is expressed continuously under normal homeostasis in the testes and creates a unique microenvironment for the transformation of diploid gametogenic cells into haploid spermatozoa, the production of which increases during inflammation and infection (11). Common polymorphisms in the genes of pro-inflammatory and anti-inflammatory cytokines can affect its production and function in response to pathogens and may be a risk factor for infertility in men (12). Polymorphisms mean differences in DNA sequences that are very diverse in human populations. One of them is SNP or single nucleotide polymorphism (13). Studies by Bentz et al., 2007, Jaiswal et al., 2013, and Zamani-Badi et al., 2019, showed that the C3953T SNP in the IL-1 β gene is associated with infertility in men (14-16). Since there is no meta-analysis, in this case, this study aimed to examine the relation between the above polymorphism and male infertility with a meta-analysis approach.

Material and methods

Search approach and selection criteria

We performed a computer-based electronic search of Google Scholar, PubMed, and science direct without any language restriction up to July 2021. The words used in the electronic search were as follows: "interleukin 1 β " or "IL1 β ", "mutation" or "polymorphism" or "variation", "infertility" or "male infertility". Also, we checked the citations of all possible qualified articles which our electronic research discovered. The inclusion criteria for the meta-analysis were as follows: 1) human studies; 2) studies investigating the association between IL-1 β C3953T variation and risk of male infertility; 3) studies with the design of case-control; 4) adequate data to calculate odds ratio (OR), and 95% confidence interval (CI). Review articles, letters, meta-analyses and the same publications were excluded from our study.

Data extraction procedure

Based on the mentioned inclusion and exclusion principles, the two authors independently extracted the information in order to certify the correctness of extracted data. For contradictory assessments, an agreement was achieved by a discussion. The information including first author name, publication date, country, Hardy-Weinberg equilibrium (HWE) in control group, and genotype frequencies were collected from all eligible studies (Table 1). In the studies in which there was no *p*-value of HWE in the text, it was calculated.

Table 1. Characteristics of included studies in the meta-analysis.

Country	Genotype frequencies						<i>P</i> _{HWE} in control groups	Genotyping method	Author. Year
	Fertile			Infertile					
	CC	TC	TT	CC	TC	TT			
Germany	72	53	2	248	156	31	0.025	PCR-RFLP	Bentz et al., 2007
India	151	76	3	151	61	10	0.052	PCR-RFLP	Jaiswal et al., 2013
Iran	141	81	8	106	86	15	0.377	PCR-RFLP	Zamani-Badi et al., 2019

Statistical analysis

The relation between IL-1 β C3953T genetic variation and the risk of male infertility was assessed by pooled ORs and 95% CI. Deviation from HWE for control groups was evaluated by a Chi-squared test and a *p*-value less than 0.05 was considered as a significant value. In this meta-analysis, heterogeneity among studies was measured by the *I*² in both random (the Mantel-Haenszel method) and fixed-effects model (the DerSimonian and Laird method). Also, to evaluate the stability of the results, sensitivity examination was done by removing

one article at a time. As publication bias was usually concerned in the meta-analysis, an assessment of which was performed with Egger's test and funnel plot. The statistical analysis was conducted by MetaGenyo software (Meta-Analysis of Genetic Association Studies).

Results and Discussion

Studies and populations characteristics

By electronic search and manual evaluation recognized 12 potentially relevant papers and six of them were selected for review of full-text based on details of title and abstract. Three studies were removed because they contained other polymorphisms, meta-analysis, or review. Lastly, three published papers were included in our meta-analysis (14-16). These papers included 866 infertile and 587 fertile reporting the association between IL-1 β C3953T gene variation and male infertility risk. Two of these studies were from the Caucasian population while one of them was from the Asian population. Three papers had enough information to achieve the frequency of C and T alleles in both fertile and infertile groups. The frequency of genotype in the control group of one of these papers was not consistent with HWE. The characteristics of each selected study are detailed in Table 1.

Quantitative analysis

The genetic association results are summarized in Table 2. Our data revealed that the T allele of IL-1 β C3953T gene variation was associated with increased risk of male infertility in allelic (T vs. C: OR= 1.2143, 95%CI= 1.0057; 1.4662, p = 0.043) and homozygous codominant (TT vs. CC: OR= 3.0292, 95% CI= 1.5681; 5.8519, p = 0.00097) models (Figure 2). But we did not observe any significant association between the mentioned polymorphism and risk of male infertility in the heterozygous codominant model (TC vs. CC: OR= 0.9924, 95% CI= 0.6966; 1.4139, p = 0.9664). Heterogeneity analysis showed that there are no true heterogeneities among studies in three allelic, homozygous codominant, and heterozygous codominant models (Table 2).

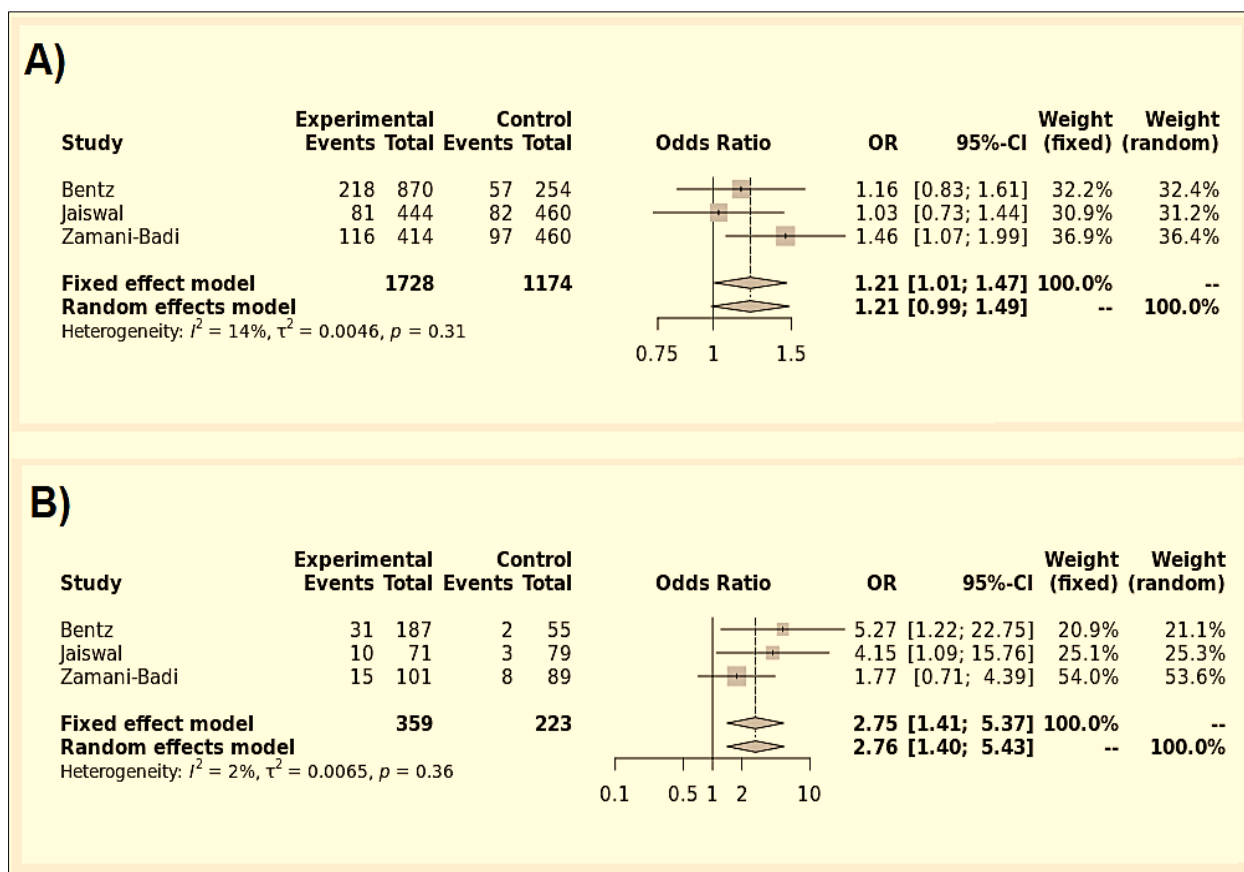


Figure 2. Forest plot. Meta-analysis showed that the IL-1 β C3953T polymorphism is associated with male infertility in allelic (A) and homozygous codominant (B) models.

Table 2. Results of meta-analysis.

Hereditary model	Analysis model	OR (95% CI)	P-value	tau ²	Q(df=2)	PH	I ²	P Egger
T vs. C	Random effect	1.2123 [0.9891; 1.4859]	0.063	0.00	2.33	0.31	0.14	0.0651
	Fixed effect	1.2143 [1.0057; 1.4662]	0.043	0.00	2.33	0.31	0.14	0.0651
TT vs. CC	Random effect	3.0292 [1.5681; 5.8519]	0.00097	0.00	0.49	0.78	0.00	0.0724
	Fixed effect	3.0292 [1.5681; 5.8519]	0.00097	0.00	0.49	0.78	0.00	0.0724
TC vs. CC	Random effect	0.9924 [0.6966; 1.4139]	0.9664	0.06	4.64	0.10	0.57	0.1487
	Fixed effect	0.9965 [0.7899; 1.2570]	0.97615	0.06	4.64	0.10	0.57	0.1487

OR, odds ratio; CI, confidence interval; PH, *P*-values for heterogeneity; df: degrees of freedom; PH, *P*-value for heterogeneity.

Publication bias and sensitivity analysis

As shown in Table 2, neither funnel plot nor Egger's test showed true publication bias in allelic ($P_{\text{Egger}}=0.0651$), homozygous codominant ($P_{\text{Egger}}=0.0724$), and heterozygous codominant ($P_{\text{Egger}}=0.1487$) models. The form of the funnel plot was observed symmetrical (Figure 3). We analyzed sensitivity for statistically significant outcomes. For the association of the IL-1 β C3953T genetic variation and male infertility susceptibility, the found the significant result was not substantially changed after successively removing each study.

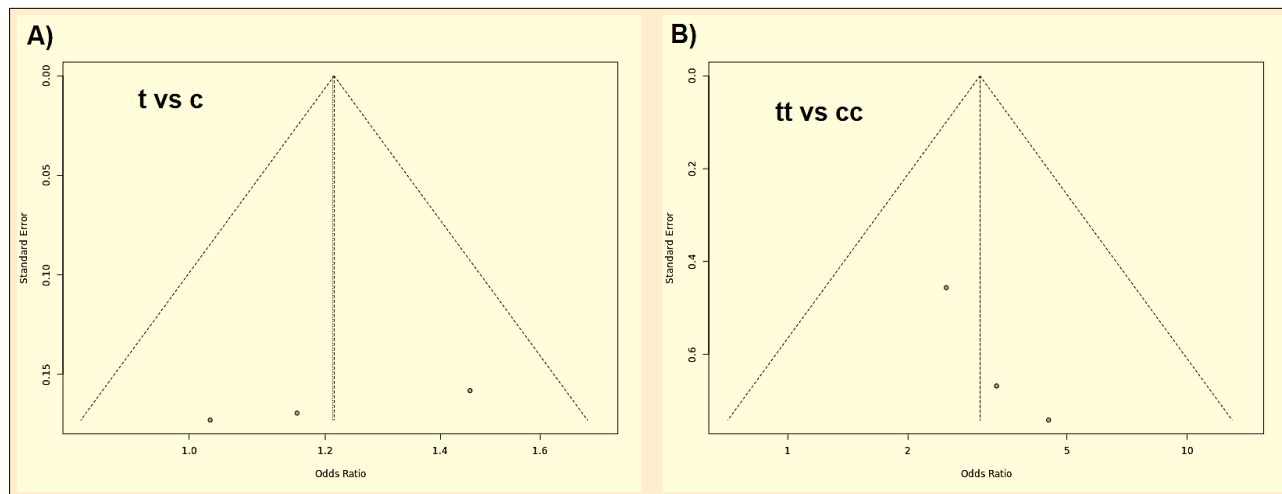


Figure 3. Funnel plot. Meta-analysis showed no publication bias for the relationship between IL-1 β C3953T SNP with male infertility in allelic (A) and homozygous codominant (B) models.

Infertility occurs in 10 to 15% of couples worldwide and about half of the causes of infertility are in men. With the advancement of molecular biology, many of the genes involved in infertility have been identified (17). Defects in genes involved in spermatogenesis can cause infertility. The cytokine family is very broad and there are also many polymorphisms in the structure of interleukin genes. Polymorphism in cytokine genes has been shown to play an important role in male infertility. One of the polymorphic genes of the cytokine family is interleukin-1-beta, which has many polymorphisms. Some studies have shown that the C3953T polymorphism in the interleukin-1-beta gene can increase the risk of idiopathic infertility in men (14-16). These studies have examined limited populations with low sample sizes.

In order to achieve more accurate results, in this study, we investigated the association between the above polymorphism and male infertility using a meta-analysis approach. The results of this study showed that C3953T polymorphism in the interleukin-1-beta gene is associated with an increased risk of idiopathic infertility. The mutant allele of this polymorphism could be a potential biomarker for male infertility. This study also showed that there is no significant publication bias in the study. In addition, sensitivity analysis showed that the eliminating of an article could not have a significant effect on the overall OR. Therefore, the results of this study can be reliable. Of course, the number of studies included in the article is very low, and to achieve more accurate results, different studies should be done in different populations of different races.

In the gonadal environment, there is a unique immune system that, by helping to balance cell proliferation and apoptosis, induces homeostasis in the epithelium of the seminiferous tubules. The presence of an immune system in the male gonad is essential for normal spermatogenesis. Semen plasma contains immunomodulatory factors, including cytokines (18). Cytokines are proteins that are naturally present in the gonads of men. They provide the necessary immunity for germ cells in the male gonad, affect spermatozoa, and are essential for regulating the reproductive system. They also lead to germ cell differentiation, affect testicular cell function, and prevent the overproduction of reactive oxygen species by modulating pre-oxidative and antioxidant reactions. Therefore, any disorder in immune factor genes can have a detrimental effect on spermatogenesis (5). The interleukin-1 family plays an important role in balancing and regulating spermatogenesis, as well as in cell survival and proliferation. This family has several members, including IL-1 α , IL-1 β , and IL-1RA. IL-1 α and IL-1 β act as agonists and IL-1RA acts as antagonists and is a natural anti-inflammatory factor. The genes of the interleukin family are polymorphic and there is at least one common SNP in each gene (19). Alteration of IL-1 β with TNF α leads to decreased sperm motility and asthenozoospermia phenotype. This change is caused by the lipid peroxidation of the sperm membrane and the production of large amounts of ROS.

Increasing the amount of ROS leads to the destruction of sperm DNA and thus reduces its motility. In addition, increased ROS can cause an oligospermia phenotype (16). Oxidative stress destroys cells by chemical changes such as oxidizing proteins or DNA and lipid peroxidation. DNA damage can cause mutations, while protein breakdown reduces protein and inhibits enzymes. Lipid peroxidation in sperm reduces the fluidity of the cell membrane and reduces the cellular mechanisms required for fertilization. Previous studies have shown that patients with high levels of ROS have sperm with multiple gene mutations. Oxidative stress may lead to point mutations, deletions, frameshift mutations, and other chromosomal abnormalities. ROS also reduces sperm count with sperm apoptosis and results in oligospermia phenotype (20, 21).

Single nucleotide polymorphisms based on their position on the gene can alter the structure and function of cytokine genes. If genetic variants are located upstream of the gene, they can alter gene expression by acting on the promoter of genes. If the polymorphisms are in the intron, they can affect RNA function or affect the splicing process. If the polymorphisms are on the exon region, they can change the structure and function of the protein, if the exon mutations are non-synonymous. However, if genetic variants are downstream of the gene, they can affect the regulation of gene expression (22). A study by Zamani-Badi et al., 2019 showed that the C3953T polymorphism of the interleukin-1-beta gene as a synonymous exon polymorphism could alter RNA structure and the splicing process (16). Therefore, the pathological effects of the above polymorphism may result from these molecular changes. However, animal and in vitro studies are needed to determine the exact function of the C3953T polymorphism on the structure of the interleukin-1-beta gene (23).

Conclusion

Male infertility can be influenced by inflammatory factors and cytokine genes. Many cytokines are involved in the functioning of the male reproductive system, one of the most important of which is interleukin-1-beta. This interleukin is a polymorphic gene that has many SNPs on it. One of the common polymorphisms of this gene is C3953T polymorphism, which is a synonymous exon variety. Results of our meta-analysis revealed that this polymorphism could be a molecular risk factor for idiopathic male infertility. However, this meta-analysis

was performed on three studies, the number of these studies is very limited and to achieve more accurate results, studies with large sample sizes and in different populations are needed. Of course, access to the original data of articles including age, clinical and demographic factors can produce more reliable results in a meta-analysis.

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