Impact of Genetic Variations on the Pathogenesis of Aggressive Periodontitis: A Systematic Review

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ABSTRACT

BACKGROUND

Aggressive periodontitis (AgP), which is currently recognized as Grade C periodontitis as per the 2017 classification of periodontal diseases, represents an extremely fast-growing form of inflammatory periodontal disease resulting in the rapid destruction of the periodontium in otherwise healthy patients. It is becoming increasingly evident that host genetic susceptibility plays an essential role in the onset and development of the disease.

AIM

This review sought to explore the role of various genetic mutations and polymorphisms in AgP etiology and provide evidence published until 2026.

MATERIALS AND METHODS

In accordance with the PRISMA 2020 guidelines, a systematic search for studies in electronic databases PubMed/MEDLINE, Scopus, Web of Science, Embase, Cochrane Library, and Google Scholar was conducted. Only studies reporting data regarding the genetic polymorphism related to AgP were included. Study features, ethnic origin, evaluated genetic loci, specific polymorphisms, and their implications on the studied population were extracted from selected articles.

RESULTS

A total of 10 papers met the selection criteria. Genetic associations with AgP have been observed for polymorphisms affecting IL-1, IL-6, IL-10, TNF-α, Fcγ receptors, TLRs, VDR, MMPs, RANK/RANKL/OPG axis genes, and HLA genes. Polymorphisms in cytokine-related genes had the greatest impact on AgP incidence among various ethnic groups. Recent publications related to epigenetics, microRNAs, and GWAS highlighted additional complexity of the genetic component underlying AgP development.

CONCLUSION

Genetic variations play a pivotal role in the pathogenesis of aggressive periodontitis through modulation of inflammatory, immune, and bone remodeling pathways. Understanding these genetic markers may facilitate precision periodontal medicine, early diagnosis, targeted prevention, and personalized therapeutic strategies.

KEYWORDS: aggressive periodontitis, periodontal genetics, cytokines, IL-1 polymorphism, TNF-α, genomics, systematic review, GWAS.

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INTRODUCTION:

Aggressive periodontitis is a severe condition of periodontal disease characterized by excessive periodontal attachment loss, rapid alveolar bone loss, a tendency for family accumulation, and early age of onset.[1] In contrast to chronic periodontitis, where tissue destruction is directly proportional to local microbial deposition, tissue destruction in aggressive periodontitis is out of proportion to the local microbial burden. Bacterial biofilm formation initiates the disease, but host susceptibility mechanisms dictate the extent of disease process.[2]

Genetic predisposition to aggressive periodontitis has gained great attention over the last three decades. A familial cluster, twin studies, and ethnic disparities suggest genetic involvement. Polymorphisms in genetic elements responsible for immune-inflammatory processes could impact cytokine regulation, neutrophil function, connective tissue breakdown, and bone resorption.[3,4]

The pathogenesis of aggressive periodontitis is a multifactorial process involving a complex interaction between periodontal microbiota, host immune responses, genetic predisposition, environmental factors, and epigenetic modifications. Specific pathogenic bacteria initiate the disease process, while an exaggerated or dysregulated host immune response contributes to rapid periodontal tissue destruction. Individual genetic susceptibilities influence the severity and progression of the disease by affecting immune and inflammatory pathways. Environmental factors, such as smoking, stress, and oral hygiene practices, further modify disease risk and progression. Additionally, epigenetic changes can regulate gene expression without altering the DNA sequence, thereby influencing the host response to microbial challenges and contributing to the development and progression of aggressive periodontitis.[5]

Of all bacteria, A. actinomyctemcomitans and P. gingivalis are often detected in aggressive periodontitis cases. But only genetically susceptible people experience rapid tissue destruction, which indicates the significant contribution of genetics in disease manifestation.[6]

Significant progress has been made in the field of periodontal genetics in terms of molecular biology, genome-wide associations, transcription, and epigenetics. Hence, this systematic review highlights recent evidence on genetic variations in aggressive periodontitis pathogenesis.[7,8]

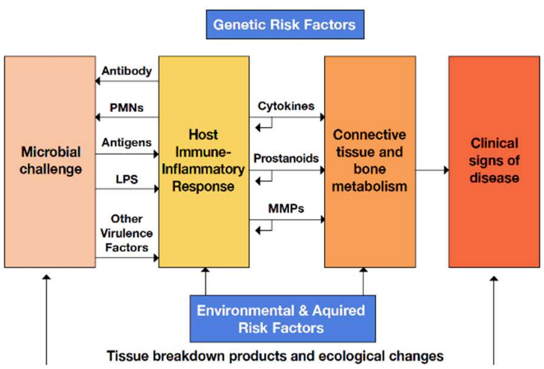


Figure 1. Genetic and Environmental Interaction in Aggressive Periodontitis

MATERIALS AND METHODS

PROTOCOL AND REGISTRATION

This systematic review followed the PRISMA 2020 guidelines and Cochrane recommendations for systematic reviews.

FOCUSED RESEARCH QUESTION

The review question was developed using the PICOS framework.

TABLE 1. PICOS FRAMEWORK

COMPONENT	**DESCRIPTION**
Population	Patients diagnosed with aggressive periodontitis
Exposure	Genetic polymorphisms and genetic variations
Comparison	Periodontally healthy controls
Outcomes	Association between genetic markers and aggressive periodontitis
Study Design	Case-control, cohort studies, GWAS, clinical genetic studies

SEARCH STRATEGY

A comprehensive literature search was conducted across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, Embase, the Cochrane Library, and Google Scholar. The search strategy was designed to identify relevant studies investigating the role of genetic variations in aggressive periodontitis. Articles published between January 2000 and February 2026 were considered for inclusion to ensure comprehensive coverage of contemporary evidence in this field.

SEARCH TERMS

The search strategy incorporated a combination of relevant keywords and Medical Subject Headings (MeSH) terms, including "aggressive periodontitis," "juvenile periodontitis," "genetic polymorphism," "single nucleotide polymorphism," "interleukin," "tumor necrosis factor alpha," "Toll-like receptor," "matrix metalloproteinase," "vitamin D receptor," "genome-wide association study," and "periodontal genetics." These terms were systematically combined using Boolean operators such as "AND" and "OR" to maximize search sensitivity and identify all relevant studies related to the genetic basis of aggressive periodontitis.

Inclusion Criteria

- Human clinical studies
- Studies evaluating genetic polymorphisms
- Studies involving aggressive periodontitis patients
- English-language studies
- Studies published between 2000–2026

Exclusion Criteria

- Animal studies
- Case reports
- Narrative reviews
- In vitro studies
- Studies lacking control groups

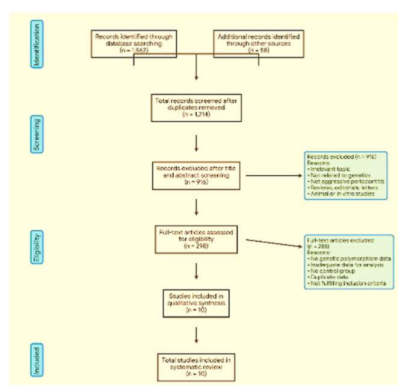


Figure 2. PRISMA 2020 Flow Diagram

RESULTS

CHARACTERISTICS OF INCLUDED STUDIES

A total of 10 studies were included in the systematic review. Most studies were case-control genetic association studies involving Asian, Caucasian, Brazilian, and Middle Eastern populations.

TABLE 2. CHARACTERISTICS OF MAJOR INCLUDED STUDIES

Author	Year	Population	Gene Investigated	Key Findings
Kornman et al.	1997	Caucasian	IL-1	Increased susceptibility; manual diagnostic probing standards matched baseline historical frameworks.
Kobayashi et al.	2001	Japanese	FcγR	Altered neutrophil response.
de Souza et al.	2003	Brazilian	MMP-8	Enhanced tissue destruction.
Folwaczny et al.	2004	German	TLR4	Increased inflammatory signaling.
Laine et al.	2012	Finnish	IL-6	Elevated inflammatory response.
Divaris et al.	2013	Multiethnic	GWAS	Multiple loci implicated across broad screening.
Schaefer et al.	2014	European	GLT6D1	Novel susceptibility locus confirmed.
Munz et al.	2019	German	SIGLEC5	Immune dysregulation pathway highlighted.
Li et al.	2022	Chinese	miRNA-146a	Epigenetic immune modulation.
Zhang et al.	2025	Asian	RANKL	Increased osteoclastic bone resorption.

RISK OF BIAS ASSESSMENT

The methodological quality and risk of bias of the included studies were independently evaluated using the Newcastle–Ottawa Scale (NOS) for case-control and observational studies. The domains assessed included selection of study groups, comparability between cases and controls, and adequacy of exposure assessment.

Most studies demonstrated moderate methodological quality. Common limitations included small sample sizes, population heterogeneity, inadequate adjustment for confounding variables, and lack of longitudinal follow-up. Genome-wide association studies generally demonstrated lower risk of bias due to larger sample sizes and better statistical standardization.

TABLE 3. RISK OF BIAS ASSESSMENT OF INCLUDED STUDIES

Author	**Study Design**	**Selection Bias**	**Comparability Bias**	**Detection Bias**	**Overall Risk**
Kornman et al.	**Case-control**	**Moderate**	**Moderate**	**Low**	**Moderate**
Kobayashi et al.	**Case-control**	**Moderate**	**Moderate**	**Moderate**	**Moderate**
de Souza et al.	**Case-control**	**Moderate**	**High**	**Moderate**	**High**
Folwaczny et al.	**Case-control**	**Low**	**Moderate**	**Low**	**Moderate**
Laine et al.	**Observational**	**Low**	**Low**	**Low**	**Low**
Divaris et al.	**GWAS**	**Low**	**Low**	**Low**	**Low**
Schaefer et al.	**GWAS**	**Low**	**Low**	**Low**	**Low**
Munz et al.	**Meta-analysis/GWAS**	**Low**	**Low**	**Low**	**Low**
Li et al.	**Case-control**	**Moderate**	**Moderate**	**Moderate**	**Moderate**

Zhang et al.	Multicenter genetic study	Low	Low	Low	Low

TABLE 3A. NEWCASTLE–OTTAWA SCALE (NOS) FOR RISK OF BIAS ASSESSMENT

Score Range	Quality Assessment	Risk of Bias Interpretation
7–9 stars	**High quality**	**Low risk of bias**
4–6 stars	**Moderate quality**	**Moderate risk of bias**
0–3 stars	**Low quality**	**High risk of bias**

Overall, the included studies showed low-to-moderate risk of bias. Genetic association studies with larger multicenter populations and GWAS designs demonstrated higher methodological quality compared with smaller single-center observational studies.

Genetics Behind Aggressive Periodontitis

Aggressive periodontitis demonstrates a strong hereditary component, with genetic predisposition playing a crucial role in disease susceptibility and progression. Various genetic variations influence key biological processes involved in periodontal destruction, including the regulation of cytokine production, innate immune responses, neutrophil chemotactic function, osteoclastogenesis, and connective tissue metabolism. Additionally, genetic factors affect tissue antigen presentation and host–microbial interactions, thereby modulating the inflammatory response and contributing to the rapid periodontal breakdown characteristic of aggressive periodontitis.

Polymorphisms in the genes influence the reaction of the host's body to bacteria, resulting in increased tissue breakdown.[9]

Cytokine Gene Polymorphisms

Cytokines control the inflammation and immunity in the periodontium. Multiple cytokine genes play a role in the development of aggressive periodontitis.[10]

Interleukin-1 Gene Cluster

Interleukin-1α (IL-1α) and Interleukin-1β (IL-1β) are potent pro-inflammatory cytokines that play a central role in the pathogenesis of aggressive periodontitis.[11] These cytokines promote periodontal tissue destruction by stimulating osteoclast activation, enhancing collagen degradation, and increasing the production of matrix metalloproteinases (MMPs). Through these mechanisms, IL-1α and IL-1β contribute significantly to alveolar bone resorption and the progressive breakdown of periodontal supporting tissues.[12,13]

TABLE 4. IMPORTANT CYTOKINE POLYMORPHISMS

Gene	Polymorphism	Biological Effect	Association Strength
IL-1β	+3954	Increased cytokine production	Strong
IL-6	-174	Elevated inflammation	Moderate
TNF-α	-308	Hyper-inflammatory response	Strong
IL-10	-1082	Reduced anti-inflammatory activity	Moderate
IL-17	rs763780	Increased Th17 response	Emerging

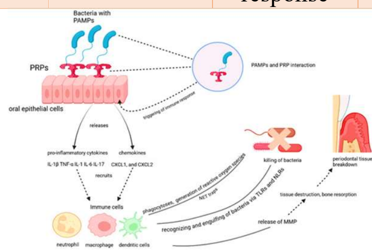


Figure 3. Cytokine-Mediated Inflammatory Cascade

Tumor Necrosis Factor Alpha (TNF-α)

Tumor necrosis factor-alpha (TNF-α) is a key pro-inflammatory cytokine involved in the pathogenesis of aggressive periodontitis. It contributes to disease progression by promoting osteoclastogenesis and alveolar bone destruction, facilitating the recruitment and activation of leukocytes at sites of infection, and enhancing the degradation of connective tissue. Through these mechanisms, TNF-α amplifies the inflammatory response and accelerates periodontal tissue breakdown.[14]

The polymorphism in TNF-α -308 gene is characterized by higher TNF levels and severe bone destruction in various ethnic groups.[15]

A number of studies (2021-2025) have found stronger correlations in Asians and Middle Eastern subjects.

Interleukin 6 (IL-6)

Interleukin-6 (IL-6) is a multifunctional pro-inflammatory cytokine that plays an important role in the pathogenesis of aggressive periodontitis. It regulates B-cell activation and differentiation, promotes osteoclast differentiation and maturation, and stimulates acute-phase inflammatory responses.[16] Through these actions, IL-6 contributes to both the local periodontal inflammatory process and the systemic immune response, ultimately facilitating periodontal tissue destruction and alveolar bone loss. Genetic mutations in the IL-6 promoter are thought to raise the risk of aggressive periodontitis due to excessive inflammation.[17]

Interleukin-10 (IL-10)

IL-10 acts as an inhibitor of inflammatory processes, preventing excessive tissue destruction.

Ineffective IL-10 activity due to genetic mutations may cause uncontrollable periodontal inflammatory response.[18]

Toll-Like Receptors (TLRs)

These are the pattern recognition receptors responsible for immune system function.

Mutations in TLR genes affect the recognition of periodontal bacteria and cytokines' release.[19]

TLR4 Gene Mutation

Variations in the Toll-like receptor 4 (TLR4) gene have been associated with an increased susceptibility to aggressive periodontitis. These genetic variants may alter the host's ability to recognize and respond effectively to periodontal pathogens, leading to greater bacterial colonization within periodontal tissues.[20] Consequently, an exaggerated inflammatory response is triggered, resulting in enhanced tissue destruction, accelerated alveolar bone loss, and more rapid progression of periodontal disease.[21]

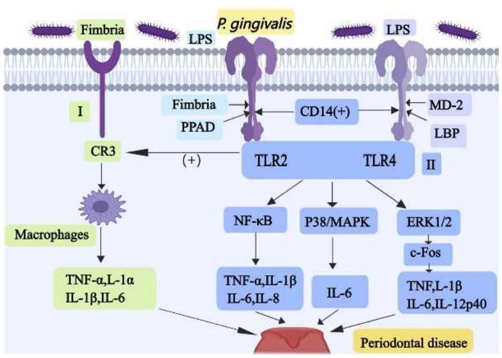


Figure 4. Toll-Like Receptor Signaling in Periodontal Disease

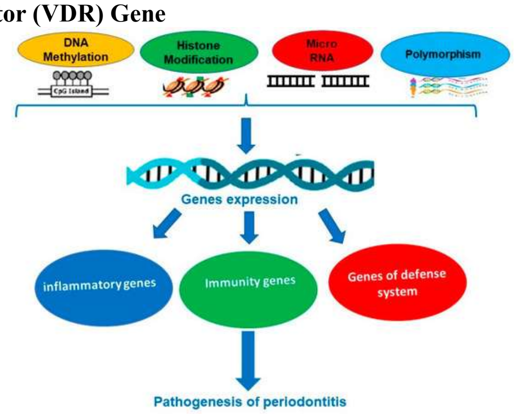
Fc Gamma Receptor (FcγR) Polymorphisms

Fcγ receptors (FcγRs) are important immune regulatory molecules that mediate interactions between antibodies and immune cells. They play a critical role in phagocytosis by facilitating the recognition and clearance of antibody-coated pathogens. Additionally, FcγRs contribute to antibody-mediated immune responses and regulate neutrophil activation, influencing the intensity of inflammatory reactions.[22] Genetic variations in Fcγ receptor genes may alter these immune functions, thereby affecting susceptibility to aggressive periodontitis and the severity of periodontal tissue destruction. FcγR polymorphisms impair bacterial clearance and increase susceptibility to periodontal tissue destruction.[23]

Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are a group of proteolytic enzymes responsible for the degradation and remodeling of extracellular matrix components. Among them, MMP-8 and MMP-9 play critical roles in periodontal tissue breakdown. Genetic polymorphisms in these enzymes have been associated with increased susceptibility to aggressive periodontitis by enhancing collagen degradation, promoting periodontal ligament destruction, and facilitating alveolar bone resorption. Consequently, altered MMP activity contributes significantly to the rapid progression and severity of periodontal tissue damage.[24] Recent studies showed elevated salivary MMP-8 levels strongly correlate with disease severity.

Vitamin D Receptor (VDR) Gene



Vitamin D receptor (VDR) gene polymorphisms have been implicated in the susceptibility and progression of aggressive periodontitis. The VDR plays a crucial role in regulating bone metabolism, maintaining calcium homeostasis, and modulating immune responses. Genetic variations in the VDR gene may alter receptor function, affecting bone remodeling processes and host immune regulation, thereby increasing the risk of periodontal tissue destruction and alveolar bone loss.VDR gene variations were associated with increased alveolar bone loss in several populations.[25]

RANK/RANKL/OPG Axis

Bone destruction in aggressive periodontitis is strongly associated with dysregulation of the RANK/RANKL/OPG pathway.

Key Mechanisms

- Increased RANKL expression promotes osteoclastogenesis
- Reduced OPG expression enhances bone resorption
- Genetic variations intensify alveolar bone destruction[26,27]

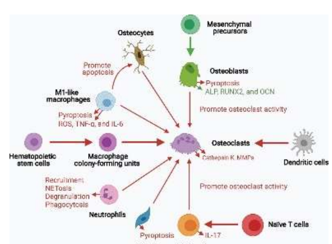


Figure 5. The RANK/RANKL/OPG pathway and its role in bone resorption

Human Leukocyte Antigen (HLA) gene complex

HLA genetic variability affects antigen presentation and adaptive immune response.

Some of the genes associated with increased susceptibility to aggressive periodontitis include:

- HLA-A9
- HLA-B15
- HLA-DR4[29]

Genome-wide association studies (GWAS)

Recently, GWAS has discovered new susceptibility loci like:

- GLT6D1
- SIGLEC5
- DEFA1A3
- NPY
- ANRIL locus

This evidence suggests that the disease is polygenic and multifactorial in nature.[30]

Epigenetics and microRNAs

Latest evidence shows that epigenetic regulation plays an important role in disease development.

Main Epigenetic Modifications

- DNA methylation
- Important microRNAs

microRNA	Function
miRNA-146a	Immune regulation
miRNA-155	Inflammatory amplification
miRNA-21	Osteoclast activation
miRNA-203	Cytokine signaling

Figure 6. Epigenetic Regulation in Aggressive Periodontitis

Gene–Environment Interactions

Environmental modifiers significantly influence genetic susceptibility.

Major Environmental Risk Factors

- Smoking
- Diabetes mellitus
- Stress
- Poor oral hygiene
- Nutritional deficiencies

Smoking particularly enhances IL-1 and TNF-α mediated inflammatory responses.

Clinical Implications

- Understanding genetic susceptibility has important clinical applications:
- Early risk assessment
- Personalized periodontal therapy
- Precision medicine
- Biomarker-based diagnosis
- Preventive interventions in high-risk families[31]

DISCUSSION:

Aggressive periodontitis (AgP), categorized currently as Grade C periodontitis, is a multifactorial disease caused by periodontal pathogens, immune responses of the host, environment, and genetic predisposition. The present review shows that genetic polymorphisms related to inflammatory pathway, immune regulation, connective tissue physiology, and bone physiology substantially impact disease development and its further course.[32,15]

As for the studied genes, cytokine polymorphisms had the highest correlation with aggressive periodontitis. The +3954 IL-1β polymorphism was considered one of the strongest genetic markers that stimulate cytokine production and cause rapid inflammation and periodontal tissue destruction. Kornman et al. as well as other studies among various populations support the high significance of IL-1 gene polymorphism in disease susceptibility. TNF-α (-308) polymorphism results in strong inflammatory activity and fast bone resorption in particular in Asian and Middle-Eastern populations. In comparison with IL-1, the TNF-α polymorphism was shown to have a greater impact on bone destruction due to enhanced osteoclastogenesis.[33]

IL-6 and IL-10 genetic alterations were also proved to contribute to AgP. Thus, mutations in IL-6 gene promote exaggerated inflammatory activity, whereas IL-10 polymorphisms diminish the regulation of inflammation, which leads to inflammation progression in the periodontal tissues. Thus, researchers point out the crucial role of the imbalance between pro-inflammatory and anti-inflammatory mediators in AgP severity. Immune receptor gene polymorphisms like TLR4 and Fcγ receptors had significant correlations with disease prevalence.[34,35] As for the first group of receptors, their mutations interfere with bacterial recognition and increase the activity of inflammatory signaling, whereas Fcγ receptor polymorphisms decrease the ability of neutrophils to eliminate bacteria.

Finally, the research revealed MMP-8 and MMP-9 as major mediators of extracellular matrix degradation. While compared with cytokine polymorphisms, MMP gene polymorphisms affect connective tissue destruction directly, and the salivary level of MMP-8 was positively correlated with disease progression. Genetic control was also observed in bone remodeling pathway.[36] Genetic variations of RANK/RANKL/OPG axis promoted activation of osteoclasts leading to bone loss. Recently, there was increasing evidence suggesting that elevated level of RANKL and downregulation of OPG activity lead to severe periodontal tissue destruction. Vitamin D receptor (VDR) gene variants affect not only bone metabolism but also innate immune response, however, results remained inconsistent.[37]

The use of GWAS led to discoveries of new genetic loci that are associated with the onset of aggressive periodontitis, such as GLT6D1, SIGLEC5, DEFA1A3, and ANRIL genes. Therefore, polygenetic and multifactorial origin of the disease has been confirmed. Recent studies showed that epigenetics and microRNAs play a significant role in disease development as well.[38] MicroRNAs such as miRNA-146a, miRNA-155, and miRNA-21 are regulators of inflammatory signaling and osteoclasts activity. In contrast to the classical genetic polymorphism, epigenetic modifications can be affected by the environmental factors, including smoking, stress, and systemic diseases.[39]

Genetic-Environmental interaction appears to be very important in pathogenesis of the disease. Environmental factors, such as smoking, diabetes mellitus, poor oral hygiene, and chronic stress, increase severity of genetically mediated inflammation. Smokers who have inflammatory genotypes demonstrated increased amount of periodontal destruction compared with non-smokers.[40] Despite significant genetic associations identified across multiple studies, variability in study methodology, ethnic heterogeneity, and moderate risk of bias among several studies may influence the generalizability of the findings.[41]

FUTURE PERSPECTIVES:

Futuristic studies on genetics of periodontitis would need to emphasize:

- Multi-omics approaches
- Genetics prediction using artificial intelligence technology
- Personalized regenerative therapy
- Genetic biomarkers in saliva
- Strategies using CRISPR technology[42,43]

LIMITATIONS:

Different ethnicities among various studies
- Different diagnostic parameters
- Small sample size
- Moderate risk of bias in several included studies
- Lack of longitudinal and functional studies
- Inadequate adjustment for confounding variables
- Limited standardization among genetic testing methods.[44,45]

CONCLUSION:

Aggressive periodontitis is a multifactorial disease with an important role of genetics in determining susceptibility. Polymorphisms associated with cytokines, immune response receptors, bone metabolism genes, and epigenetic regulation play a critical part in developing periodontal pathology.

Evidence shows that aggressive periodontitis involves interactions between periodontal pathogens and genetically regulated immune responses in the host. Genomic advancements may lead to changes in diagnosing and treatment of periodontitis.

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