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TISSUE-SPECIFIC REGULATORY EFFECTS OF FGB GENE (rs1800790) IN COVID-19

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The aim of research *– to investigate the transcriptional impact of the FGB gene promoter variant rs1800790 through expression quantitative trait loci analysis to elucidate its potential regulatory role in COVID-19 pathophysiology.*
Material and methods. *Genotyping of the FGB locus (rs1800790) was performed in 72 patients with moderate and severe COVID-19 and in 48 patients with mild disease. The inclusion criterion in the study was a laboratory-confirmed (using polymerase chain reaction) diagnosis of COVID-19. Laboratory examination, treatment and diagnosis of COVID-19, taking into account the severity of the course, were carried out in accordance with the current Protocol "Provision of medical care for the treatment of coronavirus disease (COVID-19)" (Orders of the Ministry of Health of Ukraine dated 02.04.2020 No. 762 as amended on 20.09.2021 No. 1979) with amendments and supplements (Order of the Ministry of Health of Ukraine dated 17.05.2023 No. 913) and recommendations of WHO, CDC and global standards for the diagnosis, treatment and prevention of COVID-19. Genomic DNA was extracted from peripheral blood leukocytes and allelic discrimination of the target SNP was performed by real-time polymerase chain reaction (RT-PCR). The tissue-specific transcriptional effects of the FGB rs1800790 variant were further assessed by eQTL analysis based on publicly available QTLbase data. The research was carried out in compliance with the main provisions of the Law of Ukraine No. 2801-XII "Fundamentals of the Legislation of Ukraine on Health Care", ICH GCP (1996-2016), the Declaration of Helsinki of the World Medical Association on Ethical Principles of Scientific Medical Research Involving Human Subjects (1964-2013), the Council of Europe Convention on Human Rights and Biomedicine (dated 04.04.1997), Order of the Ministry of Health of Ukraine No. 690 dated 23.09.2009 (as amended by Order of the Ministry of Health of Ukraine No. 523 dated 12.07.2012). Approval was obtained from the Bioethics Commission of the Bukovinian State Medical University (Protocol No. 2 dated 16.10.2025). Written informed consent was obtained from all participants before inclusion in the study. All statistical analyses were performed in accordance with current standards of biomedical research using Statistica 13.0 software (StatSoft Inc., USA; license number JPZ804I382130ARCN10-J). The χ^2 (Pearson test) was used to assess differences in genotype frequency distributions. The significance of differences between independent samples with approximately normal distributions was assessed using the Student's t-test, while for data with non-normal distributions the Wilcoxon-Mann-Whitney U-test was used. Statistical significance was considered at a p value of < 0.05.*
Results. *The mapping identified 25 eQTLs exhibiting cis-regulatory effects, whereas no trans-regulatory associations were detected. The most statistically significant transcriptional effects of the FGB rs1800790 variant on loci located on chromosome 4. The functional A allele demonstrated the strongest positive association with FGG gene expression in the adrenal glands, while slightly lower, but still significant upregulation, was observed in pulmonary tissue. In contrast, the G allele was associated with moderately enhanced expression in lymphocytes. Furthermore, the FGB rs1800790 A allele displayed a positive regulatory interaction with the LRAT gene in atrial appendage tissue and iPSCs.*
Conclusions. *The observed upregulation of FGG and LRAT in pulmonary and hepatic tissues, coupled with differential expression patterns in lymphocytes and gastrointestinal organs, highlights the multifaceted role of FGB in modulating coagulation, inflammation, and endothelial integrity.*

Key words: *COVID-19, expression quantitative trait loci (eQTL), polymorphism, gene, FGB (rs1800790).*

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ТКАНИННОСПЕЦИФІЧНІ РЕГУЛЯТОРНІ ЕФЕКТИ ГЕНА FGB (rs1800790) ПРИ COVID-19

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Мета дослідження *– вивчити транскрипційний вплив поліморфного варіанта*

Ключові слова: *COVID-19, локуси кількісних ознак експресії (eQTL), поліморфізм, ген, FGB (rs1800790).*

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промоторної ділянки гена FGB rs1800790 за допомогою аналізу локусів кількісних ознак експресії з метою з'ясування його потенційної регуляторної ролі у патофізіології COVID-19.

Матеріал і методи. *Генотипування локусу FGB (rs1800790) проведено у 72-х пацієнтів із середньо-тяжким і тяжким перебігом COVID-19 та у 48 пацієнтів із легким перебігом захворювання. Критерієм включення у дослідження був підтверджений лабораторно (за допомогою полімеразної ланцюгової реакції) діагноз: COVID-19. Лабораторне обстеження, лікування та встановлення діагнозу COVID-19 з урахуванням тяжкості перебігу здійснювали відповідно до діючого Протоколу "Надання медичної допомоги для лікування коронавірусної хвороби (COVID-19)" (наказами МОЗ України від 02.04.2020 року №762 в редакції від 20.09.2021 року №1979) зі змінами і доповненнями (наказ МОЗ України від 17.05.2023 № 913) та рекомендацій ВООЗ, CDC та світових стандартів із діагностики, лікування та профілактики COVID-19. Геномну ДНК екстрагували з лейкоцитів периферичної крові, а алельну дискримінацію цільового SNP виконували методом полімеразної ланцюгової реакції в реальному часі (RT-PCR). Тканиноспецифічні транскрипційні ефекти варіанта FGB rs1800790 надалі оцінювали за допомогою аналізу eQTL на основі загальнодоступних даних бази QTLbase. Дослідження виконували з дотриманням основних положень Закону України № 2801-XII «Основи законодавства України про охорону здоров'я», ICH GCP (1996-2016 рр.), Гельсінської декларації Всесвітньої медичної асоціації про етичні принципи проведення наукових медичних досліджень за участю людини (1964-2013 рр.), Конвенції Ради Європи про права людини та біомедицину (від 04.04.1997 р.), наказу МОЗ України № 690 від 23.09.2009 р. (зі змінами, внесеними згідно з Наказом Міністерства охорони здоров'я України № 523 від 12.07.2012 р.). Отримано схвалення Комісії з питань біоетики Буковинського державного медичного університету (протокол № 2 від 16.10.2025 р.). Письмова інформована згода отримана від усіх учасників перед включенням до дослідження. Усі статистичні аналізи проводили відповідно до сучасних стандартів біомедичних досліджень із використанням програмного забезпечення Statistica 13.0 (StatSoft Inc., США; ліцензія № JPZ804I382130ARCN10-J). Для оцінки відмінностей у розподілі частоти генотипів використовували χ^2 (тест Пірсона). Значимість відмінностей між незалежними вибірками з приблизно нормальним розподілом оцінювали за допомогою t-тесту Стьюдента, тоді як для даних із ненормальним розподілом застосовували U-тест Вілкоксона-Манна-Вітні. Статистичну значущість приймали за значенням $p < 0,05$.*

Результати. *Картування виявило 25 eQTL, що демонструють цис-регуляторні ефекти, тоді як транс-регуляторних асоціацій виявлено не було. Найбільш статистично значущі транскрипційні ефекти варіанта FGB rs1800790 виявлені на локусах, розташованих на хромосомі 4. Функціональний алель A продемонстрував найсильнішу позитивну асоціацію з експресією гена FGG у надниркових залозах, тоді як дещо нижчу, але все ще значно підвищену регуляцію спостерігали в легеневій тканині. Навпаки, алель G пов'язаний із помірно посиленою експресією в лімфоцитах. Крім того, алель A гена FGB rs1800790 продемонстрував позитивну регуляторну взаємодію з геном LRAT у тканині вушка передсердя та iPSC.*

Висновки. *Виявлене підвищення експресії FGG та LRAT у легеневій і печінковій тканинах, а також диференційовані патерни експресії у лімфоцитах і тканинах шлунково-кишкового тракту засвідчують про багатогранну роль гена FGB у регуляції коагуляції, запалення та ендотеліальної цілісності.*

Introduction

The appearance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the end of 2019 triggered a worldwide pandemic of respiratory infection, clinically recognized as coronavirus disease 2019 (COVID-19) [1]. Understanding the molecular determinants of this disease has become increasingly important, particularly because COVID-19 represents a complex, multifactorial disorder involving intricate host-pathogen interactions. In such diseases, deciphering the global architecture of gene expression provides a critical foundation for uncovering the biological mechanisms that drive disease progression and individual variability in clinical outcomes. Expression quantitative trait loci (eQTLs) are genetic variants that influence transcriptional regulation in a tissue- or cell-specific context. Integrating genome-wide association study (GWAS) findings with eQTL data has proven to be a powerful strategy for functionally characterizing disease-linked loci and clarifying the molecular networks underlying host immune responses to infection [2].

Among the genetic factors implicated in COVID-19 pathogenesis, particular attention has been drawn to the FGB gene, which encodes the β-chain of fibrinogen. This gene plays an essential role in coagulation and inflammatory signaling-two processes that are

profoundly dysregulated in severe COVID-19. Altered FGB expression may underlie the thrombotic complications frequently observed in critically ill patients, while the promoter variant rs1800790 has consistently been associated with interindividual differences in circulating fibrinogen concentrations and heightened cardiovascular risk [3]. Nevertheless, population studies examining FGB polymorphisms have produced inconsistent results, implying that their clinical impact is shaped by a complex interplay of genetic, environmental, and regulatory influences. Despite these associations, systematic analyses exploring the tissue-specific transcriptional consequences of FGB polymorphisms through eQTL mapping remain limited. In particular, the cis-regulatory role of rs1800790 across diverse tissues has not yet been thoroughly characterized. Bridging this gap in knowledge could provide important insights into the molecular basis of COVID-19-related coagulopathy and further elucidate the interconnected pathways linking inflammation, thrombosis, and host genetic susceptibility.

The study aims

To investigate the transcriptional impact of the FGB gene promoter variant rs1800790 through expression quantitative trait loci (eQTL) analysis to elucidate its potential regulatory role in COVID-19 pathophysiology.

Research materials and methods

Clinical and Demographic Characteristics of Patients. The cohort study encompassed a total of 257 individuals diagnosed with COVID-19, including 197 patients presenting with a moderate-to-severe disease course and 60 individuals with mild infection. Diagnostic evaluation, laboratory testing, and treatment adhered to the Ukrainian Ministry of Health protocols on COVID-19 management [4], as well as WHO, CDC, and international standards for COVID-19 diagnosis, treatment, and prevention [5]. The inclusion criterion for the study was a laboratory-confirmed (by polymerase chain reaction) diagnosis of COVID-19 [6]. The study adhered to international ethical and bioethical principles in compliance with the ICH-GCP standards, the Declaration of Helsinki (1964, with subsequent amendments), the Council of Europe's Convention on Human Rights and Biomedicine (1997), and the current legislation of Ukraine. The study protocol was reviewed and approved by the Bioethics Committee of Bukovinian State Medical University (Protocol No. 2, 16October 2025). Written informed consent was obtained from all participants prior to inclusion in the study.

The conducted study is one of the stages of the implementation of the initiative research project of the Department of Family Medicine on the topic: "Improvement of diagnostics and prediction of hypertensive-mediated damage to individual target organs and symptom control in conditions of comorbid pathology, taking into account clinical-metabolic and molecular-genetic predictors" (2024-2028), state registration number: 0124U002524.

Identification of Genetic Polymorphisms. Genotyping of the FGB (rs1800790) loci was performed in 72 patients with moderate-to-severe COVID-19 (study group) and 48 patients with mild disease (control group). Genomic DNA was extracted from peripheral blood leukocytes using the Thermo Scientific™ GeneJET™ Whole Blood Genomic DNA Purification Mini Kit, following the manufacturer's instructions. In brief, 200 μL of whole blood from each participant was lysed with proteinase K and a proprietary lysis buffer, followed by sequential washing and elution of purified DNA. Allelic discrimination of the target SNPs was conducted by real-time polymerase chain reaction (RT-PCR) using the CFX96™ Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., USA). Genotyping assays employed specific TaqMan™ SNP Genotyping Kits in combination with TaqMan® Genotyping Master Mix (Cat. No. 4371355), in accordance with the Applied Biosystems protocol. The Master Mix contained AmpliTaq Gold® DNA polymerase, dNTPs, ROX™ reference dye, and optimized reaction buffers. Allele-specific TaqMan® probes, labeled with reporter dyes (VIC® for allele 1 and 6-FAM™ for allele 2) at the 5′ end and a non-fluorescent quencher (NFQ) at the 3′ end, were used for fluorescence-based detection. Each 10 μL reaction mixture contained genomic DNA, primers, probes, and Master Mix reagents. The thermal cycling conditions were as follows: initial denaturation at 95 °C for 10 min; 49 cycles of denaturation at 95 °C for 15 s and annealing/extension at 60 °C for 70 s; followed by a final melting-curve analysis. Allelic calls were determined by relative fluorescence unit (RFU) analysis using CFX Manager™ software. Genotype verification was performed through melting-curve analysis within the CFX96™ Real-Time PCR Basic module. Tissue-specific transcriptional effects of the FGB rs1800790 variant were subsequently evaluated through expression quantitative trait loci (eQTL) analysis using publicly accessible data from the QTLbase database.

Statistical Analysis. All statistical analyses were performed in accordance with contemporary biomedical research standards using Statistica 13.0 software (StatSoft Inc., USA; license No. JPZ804I382130ARCN10-J). The χ^2 (Pearson) test was employed to assess differences in genotype frequency distributions. The significance of differences between independent samples with approximately normal distributions was evaluated using Student's t-test, whereas the Wilcoxon–Mann–Whitney U test was applied for non-normally distributed data. Statistical significance was accepted at $p < 0.05$.

Results and their discussion

Tissue-dependent transcriptional activity of the FGB gene carrying the rs1800790 variant was characterized using expression quantitative trait loci (eQTL) data from the publicly accessible QTLbase platform. According to this analysis, the highest abundance of FGB transcripts occurred in liver and lung tissues, with male samples exhibiting particularly prominent expression levels (TPM = 3993). In comparison, expression in the renal cortex and spleen was substantially lower (TPM = 2–4), while only minimal transcript levels were identified in visceral adipose depots, the brain, and whole blood. In all other evaluated tissues, FGB expression was negligible (Fig. 1).

Expression quantitative trait loci (eQTL) analysis was performed across a ±10 megabase (Mb) genomic interval

surrounding the transcription start site of the FGB gene that harbors the rs1800790 variant. The assessment encompassed both cis- and trans-regulatory elements to delineate the full range of regulatory influences acting on this locus. In total, 25 eQTLs with cis-regulatory activity were identified, whereas no trans-acting effects were observed. These cis-driven interactions spanned 12 different tissues and involved regulatory connections with eight distinct genes, as depicted in Fig. 2.

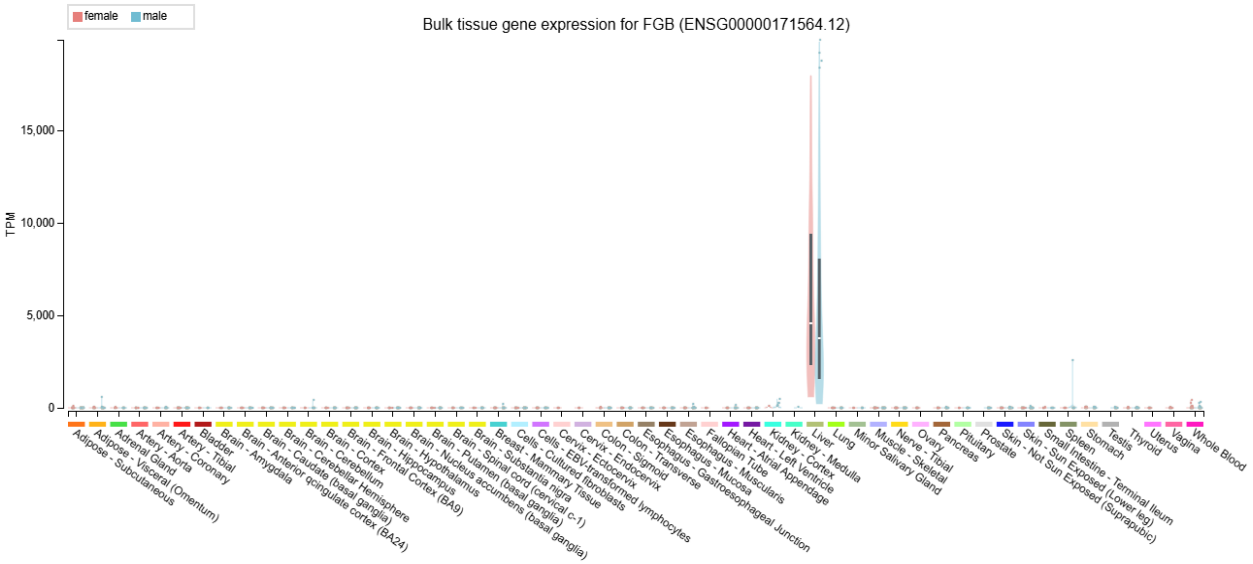

Fig. 1. Tissue- and organ-specific eQTL expression of the FGB gene (rs1800790)

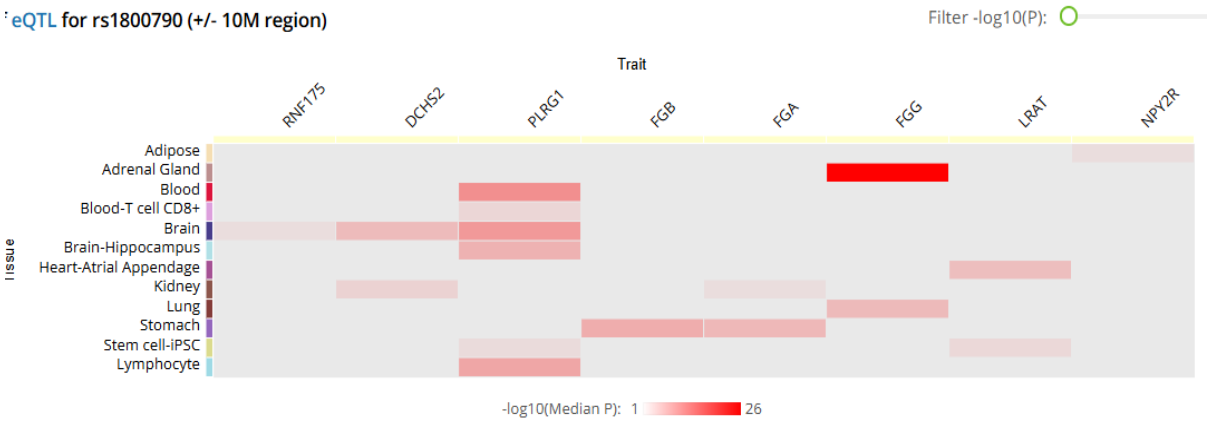

Fig. 2. Heatmap of cis-regulatory expression quantitative trait loci (eQTLs) within a ±10 Mb region surrounding dbSNP: rs1800790 of the FGB gene across tissues and organs (chr4:155483708, hg19). The color intensity of each cell represents the median $-\log_{10}$(P) value of the corresponding eQTL

The most statistically robust transcriptional influences of the FGB rs1800790 polymorphism on chromosome 4 loci are presented in Table 1. The A allele exhibited the strongest positive regulatory association with FGG gene expression in adrenal tissue (β = 0.9295–0.9843; p = 3.050e-13–4.290e-38), with slightly weaker—but still highly significant—upregulation observed in lung tissue (β = 0.2330–0.3235; p = 2.850e-5–3.610e-6). A more modest elevation in transcription was detected for PLRG1 in the hippocampus and in induced pluripotent stem cells (iPSCs) (β = 0.0606–0.1124; p = 9.770e-4–1.190e-6).

In contrast, the G allele showed a moderate enhancing effect on gene expression in lymphocytes (β = 0.3248; p = 5.600e-8). Additionally, the A allele displayed a positive regulatory interaction with LRAT in atrial appendage tissue and iPSCs (β = 0.2346–0.3235; p = 0.0206–2.790e-5). Several suppressive regulatory patterns were also identified. These included reduced expression of PLRG1 in $CD8^+$ T cells (β = –2.4580; p = 0.0140), decreased expression of FGB (Chr4:155484108–155492238) in gastric tissue (β = –0.2319 to –0.3743; p = 6.790e-6–1.430e-8), and downregulation of DCHS2 in renal tissue (β = –0.4894; p = 0.0056).

The rs1800790 substitution, situated within the promoter region of the FGB gene, has previously been shown to alter transcriptional output and modulate circulating fibrinogen concentrations [7]. Elevated levels of fibrinogen are known to drive hypercoagulability, impair endothelial function, and amplify systemic inflammatory responses—core pathological features frequently reported in individuals with severe SARS-CoV-2 infection [8]. Findings from our tissue-resolved eQTL analysis strengthen the evidence that rs1800790 plays a regulatory role in modulating gene expression within the lungs and liver, two organs that are central to the clinical course of COVID-19. Our results indicate

Table 1

Expression quantitative trait loci (eQTLs) of the FGB gene (dbSNP: rs1800790) across human tissues and organs

Gene affected by expression regulation	Tissue, Organ	Effective interacting allele	Effect size β	SE	P
DCHS2	Brain	-	-	-	1,420e-5
	Kidney	-	-0,4894	0,1726	0,0056
PLRG1	Blood	G	-0,0222	0,0034	1,230e-10
	$CD8^+$ T cells	A	-2,4580	0,9613	0,0140
	Brain - Hippocampus	A	0,0606	0,0122	1,190e-6
	Stem Cells -iPSCs	-	0,1124	0,0341	9,770e-4
	Lymphocytes	G	0,3248	0,0598	5,600e-8
FGB (Chr4:155484108-155492238)	Stomach	A	- 0,2319-/- 0,3743/	0,0498-0,0810	$6,790e^{-6}$-$1,430e^{-8}$
FGG	Adrenal Gland	A	0,9295-0,9843	0,0595-0,0970	$3,050e^{-13}$-$4,290e^{-38}$
	Lung	A	0,2330-0,3235	0,0497-0,0575	$2,850e^{-5}$-$3,610e^{-6}$
LRAT	Heart – Atrial Appendage	A	0,3235	0,0760	2,790e-5
	Stem Cells -iPSCs	-	0,2346	0,1013	0,0206

Notes. SE - standard error

that the A allele is associated with increased expression of FGG and LRAT, whereas the G allele corresponds to heightened transcription in lymphocytes, suggesting that this polymorphism exerts regulatory effects extending beyond hepatic fibrinogen production. These observations align with earlier studies implicating promoter variants of FGB in shaping transcriptional activity in pulmonary and hepatic tissues. In addition, the reduced expression of FGB observed in gastrointestinal tissues points to a nuanced, tissue-dependent regulatory architecture that may influence inflammatory pathways and coagulation signaling [19]. Collectively, these findings support the concept that rs1800790 contributes to the genetic predisposition underlying thromboinflammatory manifestations of COVID-19. By integrating genotyping data, epidemiological findings, and eQTL-based functional analyses, our study provides a multidimensional framework for understanding SNP-driven regulation across human tissues. Within this context, the rs1800790-associated increase in FGG expression in lung tissue may facilitate localized fibrin accumulation and microvascular obstruction, while systemic alterations in fibrinogen synthesis could modulate overall susceptibility to COVID-19-associated coagulopathy and thromboinflammatory complications.

Conclusions

The observed upregulation of FGG and LRAT in pulmonary and hepatic tissues, coupled with differential expression patterns in lymphocytes and gastrointestinal organs, highlights the multifaceted role of FGB in modulating coagulation, inflammation, and endothelial integrity. The predominance of the G allele—particularly in carriers of the GG genotype—among patients with moderate-to-severe COVID-19 suggests a potential genetic predisposition to hypercoagulability and severe disease outcomes. The present study provides compelling evidence that the FGB rs1800790 polymorphism exerts tissue-specific regulatory effects that may contribute to the thromboinflammatory phenotype observed in severe COVID-19. Integrating epidemiological data, genetic profiling, and eQTL analysis allowed for a comprehensive interpretation of how this promoter variant influences gene transcription across multiple tissues.

Prospects for further research

Future investigations should focus on validating these findings in larger, ethnically diverse cohorts to strengthen the generalizability of FGB rs1800790 associations with COVID-19 outcomes.

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