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MECHANISTIC INSIGHTS INTO TISSUE-SPECIFIC REGULATION OF NOS3 GENE (rs2070744) IN COVID-19

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Aim*. To investigate the tissue-specific transcriptional effects of the NOS3 promoter variant rs2070744 through eQTL analysis to elucidate its potential regulatory role in endothelial function and its contribution to COVID-19 pathophysiology.*

Material and methods. *Genotyping of the NOS3 gene (rs2070744) locus was performed in 72 patients with moderate-to-severe COVID-19 and 48 patients with a mild course of the disease. Genomic DNA was extracted from peripheral blood leukocytes, and allelic discrimination of the target SNP was conducted using RT-PCR. Tissue-specific transcriptional effects of the NOS3 gene (rs2070744) variant were subsequently eQTL analysis based on publicly available data from the QTLbase database.*

Results. *A total of 82 eQTLs were detected, all of which represented cis-acting regulatory variants spanning thirteen tissues and organs. The NOS3 rs2070744 variant demonstrated transcriptional interactions with 27 genes, with regulatory effects largely driven by the T allele. This allele was primarily linked to reduced expression of several genes, including KCNH2 in the cerebellum and central nervous system, AOC1 in the left ventricular myocardium, WDR86 in induced pluripotent stem cells (iPSCs), and ASB10 in renal tissue. In contrast, the T allele also exhibited transcription-enhancing effects, promoting increased expression of AOC1, ASIC3, GIMAP2, and TMEM176A in adipose tissue, as well as CHPF2 and TMUB1 in iPSCs, dendritic cells, and the kidney.*

Conclusions. *The NOS3 rs2070744 polymorphism exhibits pronounced tissue-specific regulatory activity, with the functional T allele influencing the expression of a broad range of genes. Collectively, these transcriptional effects suggest that this variant may act as a modifier of endothelial and immune function, potentially shaping COVID-19 severity and progression.*

МЕХАНІСТИЧНІ АСПЕКТИ ТКАНИННОСПЕЦИФІЧНОЇ РЕГУЛЯЦІЇ ГЕНА NOS3 (RS2070744) ПРИ COVID-19

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Ключові слова: *COVID-19, NOS3 (rs2070744), ген, локуси кількісних ознак експресії (eQTL), поліморфізм.*

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Мета дослідження *– вивчити тканинноспецифічні транскрипційні ефекти промоторного варіанта NOS3 rs2070744 за допомогою аналізу eQTL для з'ясування його потенційної регуляторної ролі у функціонуванні ендотелію та внеску в патофізіологію COVID-19.*

Матеріал і методи. *Генотипування локусу NOS3 (rs2070744) виконано в 72 пацієнтів із середньотяжким і тяжким перебігом COVID-19 та 48 пацієнтів із легким перебігом захворювання. Геномну ДНК виділяли з лейкоцитів периферичної крові, а алельну дискримінацію цільового SNP проводили методом RT-PCR. Тканинноспецифічні транскрипційні ефекти варіанта NOS3 rs2070744 надалі оцінювали шляхом аналізу eQTL на основі загальнодоступних даних бази QTLbase.*

Результати. *Усього ідентифіковано 82 eQTL, з яких усі класифіковані як цис-регуляторні варіанти, що охоплювали 13 тканин та органів. Варіант NOS3 rs2070744 продемонстрував транскрипційні взаємодії з 27 генами, причому регуляторні ефекти переважно опосередковувалися Т-алелем. Цей алель був здебільшого пов'язаний зі зниженням експресії низки генів, зокрема KCNH2 у мозочку та центральній нервовій системі, AOC1 - у міокарді лівого шлуночка, WDR86 - в індукованих плюрипотентних стовбурових клітинах (iPSC) та ASB10 - у нирковій тканині. Водночас Т-алель виявляв і активувальні транскрипційні ефекти, сприяючи підвищенню*

експресії AOC1, ASIC3, GIMAP2 та TMEM176A у жировій тканині, а також CHPF2 та TMUB1 в iPSC, дендритних клітинах і нирках.

Висновки. *Поліморфізм NOS3 rs2070744 демонструє виражену тканинноспецифічну регуляторну активність, при цьому функціональний Т-алель впливає на експресію широкого спектра генів. Сукупність виявлених транскрипційних ефектів свідчить про те, що цей варіант може виступати модифікатором ендотеліальної та імунної функції, потенційно визначаючи тяжкість перебігу COVID-19 та особливості його прогресування.*

Introduction. Endothelial nitric oxide (NO) functions as a physiological vasodilator and a potent inhibitor of platelet aggregation, and is widely recognized as a crucial component of the body's innate antiviral defense system [1]. The replication of numerous RNA and DNA viruses – including SARS-CoV-2 – is effectively suppressed by NO. This suppression may occur indirectly through reduced viral replication and protein synthesis within host cells, mediated by the direct inactivation or post-translational modification of viral replicative enzymes [2].

Insufficient production of NO derived from endothelial nitric oxide synthase (eNOS) represents a fundamental mechanism underlying endothelial dysfunction, which can compromise vascular integrity and contribute to microvascular damage [3]. Given the pivotal role of eNOS in the autonomous cellular defense against SARS-CoV-2, genetic polymorphisms within the eNOS-encoding gene (NOS3) may directly influence the severity and clinical course of COVID-19. The NOS3 gene is highly polymorphic, and several of its variants have functional consequences. Among them, the promoter single nucleotide polymorphism g.−786T>C (rs2070744) is of particular interest, as it has been shown to modulate NOS3 expression and alter nitric oxide bioavailability, potentially affecting vascular tone, inflammatory signaling, and antiviral resistance [4] .

Tissue-specific immunopathology occurs in COVID-19, implicating a significant component of the immune-mediated, virus-independent immunopathologic process as a primary mechanism in severe disease. Advances in large-scale transcriptomic technologies have revolutionized the ability to chart genome-wide transcriptional activity, offering comprehensive insights into the mechanisms of gene regulation underlying complex human diseases [5]. These high-resolution datasets not only expose coordinated patterns of gene co-expression but also pinpoint critical hub genes that occupy central nodes within disease-related regulatory networks, thereby elucidating hierarchical and functional interdependencies among molecular pathways [6]. In the context of COVID-19, several genomic loci have been associated with susceptibility and clinical severity; however, the precise transcriptional consequences of many of these variants remain largely unresolved [7]. This gap underscores the importance of comprehensive, integrative functional-genomic approaches aimed at bridging the relationship between genetic variation and its downstream impact on gene expression.

This study aims to investigate the tissue-specific transcriptional effects of the NOS3 promoter variant rs2070744 through eQTL analysis to elucidate its potential regulatory role in endothelial function and its contribution to COVID-19 pathophysiology.

Research material 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 [8], as well as WHO, CDC, and international standards for COVID-19 diagnosis, treatment, and prevention [9]. The inclusion and exclusion criteria applied in this study were previously detailed in our earlier publication [10]. 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, October 2025). Written informed consent was obtained from all participants prior to inclusion in the study.

Identification of Genetic Polymorphisms. Genotyping of the NOS3 (rs2070744) loci was performed in 72 patients with moderate-to-severe COVID-19 and 48 patients with mild disease. 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. The transcriptional pattern of the NOS3 gene containing the rs2070744 single-nucleotide polymorphism (SNP) was analyzed across a broad spectrum of human tissues based on expression quantitative trait loci (eQTL) data derived from the publicly available QTLbase repository. The most pronounced expression of NOS3 (dbSNP: rs2070744) was identified in the spleen, where the median transcript abundance reached 77.45 transcripts per million (TPM). In comparison, transcript levels were over four times lower in visceral and subcutaneous adipose tissues, the mammary gland, uterus, fallopian tubes, and tibial nerve, with median TPM values ranging between 19.27 and 14.66. Expression was approximately sixfold lower in the renal medulla, coronary artery, endocervix, and lung tissue (TPM = 14.59–13.21). In all other tissues investigated, NOS3 expression was negligible, with TPM values not exceeding 10 (Fig. 1).

Expression quantitative trait loci (eQTL) analysis for the rs2070744 polymorphism was performed to detect both cis- and trans-regulatory variants within a ±10 megabase (Mb) region surrounding the transcription start site of the NOS3 gene. The intensity of regulatory associations exhibited an inverse relationship with genomic distance from the affected locus, suggesting that the variant primarily functions through local (cis) mechanisms. Overall, 82 eQTLs were identified for rs2070744, all classified as cis-acting loci (cis-eQTLs) and distributed across 13 different tissues and organs. These regulatory connections involved 27 distinct genes, with the T allele emerging as the functional variant responsible for significant modulation of transcriptional activity (Fig. 2).

The NOS3 locus (dbSNP: rs2070744) exhibited transcriptional associations with 27 genes mediated by the functional T allele, which primarily resulted in gene expression suppression (Table 2). The most prominent downregulatory effects were observed for KCNH2 within the cerebellum and central nervous system ($\beta = -0.1504$ to -0.3704; $p \leq 1.690e\text{-}5$–$1.940e\text{-}16$), AOC1 in the left ventricular myocardium ($\beta = -0.2804$; $p = 3.540e\text{-}5$), WDR86 in induced pluripotent stem cells (iPSCs) ($\beta = -0.1079$ to -0.1264; $p = 0.0021$–0.011), ASB10 in renal tissue ($\beta = -0.2548$; $p = 0.0142$), and ATG9B in the uterus ($\beta = -0.3313$; $p = 0.0341$).

Conversely, NOS3 rs2070744 through the same T allele was linked to increased transcriptional activation of several genes. These included AOC1, ASIC3, GIMAP2, and TMEM176A in adipose tissue ($\beta = 0.1519$–0.2578; $p = 0.0211$–$5.970e\text{-}5$); CHPF2 and TMUB1 in iPSCs, dendritic cells, and kidneys ($\beta = 0.1637$–2.3281; $p = 0.0188$–0.0019); as well as CDK5 in whole blood ($\beta = 1.9603$; $p = 0.05$).

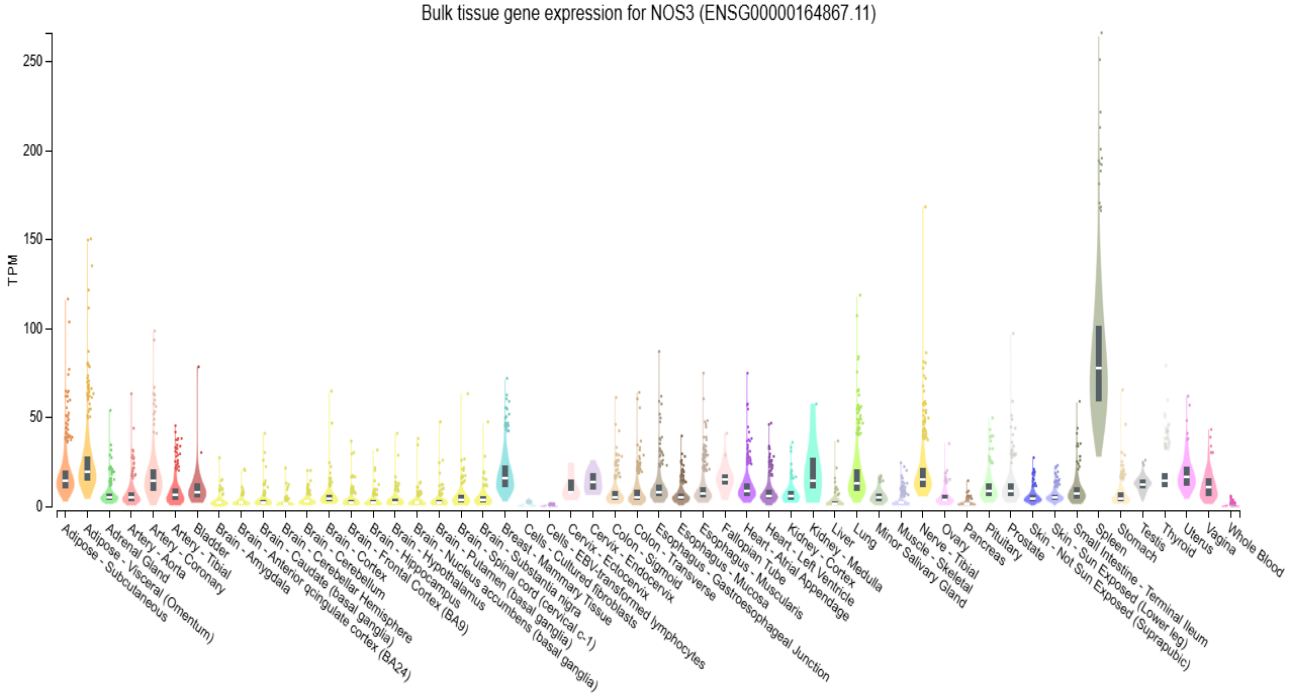

Fig. 1. Distribution of NOS3 rs2070744 eQTL expression across human tissues

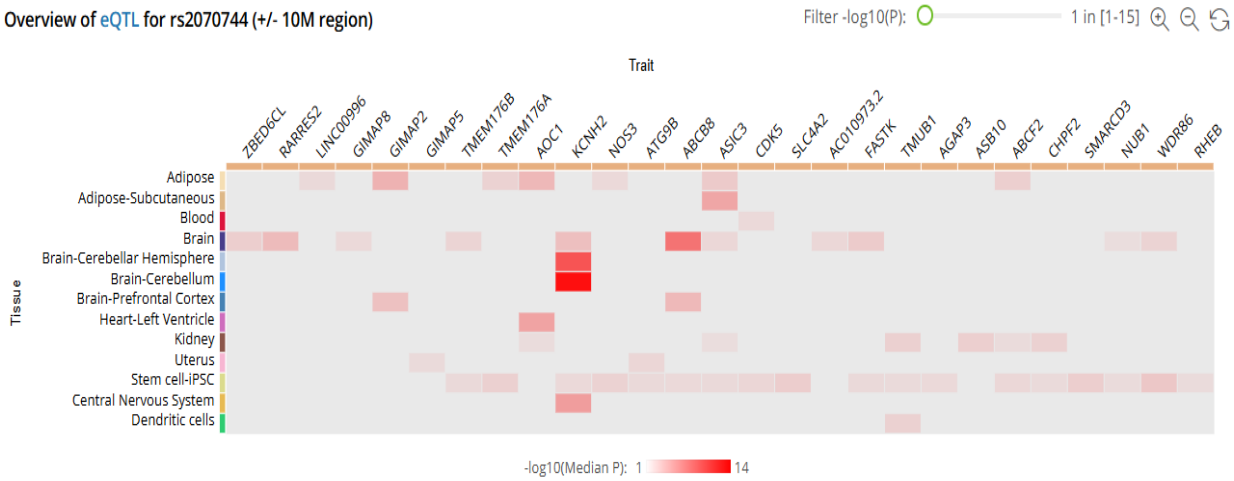

Fig. 2. Visualization of NOS3 (rs2070744) cis-eQTLs mapped within a ±10 Mb genomic interval, showing 82 regulatory relationships across 13 tissues and 27 genes (chr7:150690079, hg19).

Table 1

Top statistically significant eQTL associations of the NOS3 gene (dbSNP: rs2070744) identified across human tissues

Gene affected by expression regulation	Tissue	Effective interacting allele	Effect size β	SE	P
KCNH2	Brain-Cerebellum	T	-0,3704	0,0405	1,940e-16
	Central Nervous System (CNS)	T	-0,1504	0,0346	1,690e-5
	Stem cells -iPSC	T	0,0981	0,0351	0,0052
AOC1	Heart – Left Ventricle	T	-0,2804	0,0668	3,540e-5
	Adipose Tissue	T	0,2439	0,0706	6,050e-4
ASIC3	Adipose - Subcutaneous	T	0,1519	0,0375	5,970e-5
	Adipose Tissue	T	0,1913	0,0710	0,0073
GIMAP2	Adipose Tissue	T	0,2578	0,0705	2,850e-4
	Brain - Prefrontal Cortex	T	0,1433	0,0462	0,0021
CHPF2	Stem cells - iPSC	-	0,1637	0,0527	0,0019
	Kidney	-	0,1964	0,0826	0,0188
SLC4A2	Brain - Prefrontal Cortex	T	0,1219	0,0394	0,0020
WDR86	Stem cells -iPSC	-	-0,1079-/-0,1264/	0,0351	0,0021-0,011
TMUB1	Stem cells -iPSC	T	0,0903	0,0342	0,0082
	Kidney	-	0,3513	0,1438	0,0164
	Dendritic Cells	T	2,3281	0,9644	0,0199
ASB10	Kidney	T	-0,2548	0,1026	0,0142
ATG9B	Uterus	T	-0,3313	0,1552	0,0341
TMEM176A	Adipose Tissue	T	0,1646	0,0711	0,0211
CDK5	Blood	T	1,9603	0,9733	0,0500

Notes. SE - standard error.

Although genome-wide association studies (GWAS) have identified numerous genetic loci associated with susceptibility to both immune and infectious disorders, the underlying causal variants and corresponding effector genes responsible for these associations remain poorly characterized. Mapping colocalized cis-expression quantitative trait loci (cis-eQTLs) provides an effective means of prioritizing regulatory variants that are likely to exert functional influence on gene expression. Nevertheless, existing reference datasets of immune-related cis-eQTLs are still fragmentary, as many regulatory effects are highly context-specific and demonstrate marked dependence on particular tissues or cellular environments [11].

The NOS3 gene encodes the endothelial isoform of nitric oxide synthase (eNOS), a central enzyme regulating vascular tone, platelet reactivity, leukocyte–endothelium interactions, and inflammatory balance through the generation of nitric oxide (NO) [12]. The rs2070744 variant is positioned within the promoter region of NOS3 and involves a T→C nucleotide substitution known to diminish promoter efficiency and suppress eNOS expression, particularly in individuals carrying the C allele [13]. In the present analysis, eQTL profiling demonstrated that rs2070744 exerts a widespread transcriptional influence, encompassing both suppressive and activating effects on multiple target genes across cardiovascular, immune, and adipose tissues. The functional T allele

displayed notable cis-regulatory potential, particularly in the spleen, adipose tissue, and vascular endothelium. Repression of KCNH2 and ATG9B expression, alongside enhanced transcription of AOC1, GIMAP2, and TMEM176A, points to a complex pattern of downstream modulation, suggesting that this variant contributes indirectly to vascular and immune dysregulation.

Endothelial dysfunction has been recognized as a defining feature of severe COVID-19, with substantial evidence linking SARS-CoV-2 infection to endothelialitis, microvascular inflammation, and prothrombotic abnormalities [14]. Genetic variants that downregulate NOS3 transcription or attenuate eNOS activity – such as rs2070744 – may exacerbate these alterations by limiting NO availability, impairing vasodilatory capacity, and fostering leukocyte adhesion to the endothelium. This interpretation is supported by previous findings associating the C allele with a higher incidence of hypertension, thrombosis, and cardiovascular pathology [15]. Accordingly, while rs2070744 may not directly influence susceptibility to SARS-CoV-2 infection, its tissue-specific eQTL effects appear to modify the course of disease progression through disturbed endothelial-immune signaling and inflammatory imbalance.

Conclusions. This study revealed that the NOS3 promoter variant rs2070744 exerts tissue-specific transcriptional regulatory effects across multiple organs. eQTL mapping demonstrated 82 significant cis-acting interactions involving 27 genes, with the functional T allele predominantly associated with transcriptional repression. The observed modulation of endothelial- and vascular-related genes supports the hypothesis that NOS3 rs2070744 contributes to endothelial dysfunction and altered nitric oxide bioavailability, processes closely linked to the vascular and inflammatory complications of COVID-19. These findings highlight the potential of NOS3 rs2070744 as a molecular marker of endothelial vulnerability in SARS-CoV-2 infection.

Prospects for further research. Future studies should focus on the correlation of NOS3 genotypes with endothelial biomarkers and disease outcomes, which may help establish genotype-based strategies for risk prediction and personalized therapy in COVID-19 and other endothelial-associated diseases.

Conflict of interest. The authors declare no conflict of interest.

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