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ELF5 SNPs and the risk of severe COVID-19 in Russian population

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Motivation and Aim: COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), presents a spectrum of clinical manifestations, ranging from asymptomatic to severe organ failure. The variation in symptom severity poses a significant challenge for clinicians, underscoring the need to decipher the underlying factors contributing to disease severity. Addressing this complexity necessitates the identification of environmental and genetic risk factors. The aim of our study was to evaluate the impact of the polymorphic variants of *ELF5* gene rs7949972 and rs61882275, established by previously conducted GWAS, on the severity of COVID-19 in the population of Central Russia.

Methods and Algorithms: The study included 798 unrelated individuals from Central Russia, including 199 patients with COVID-19 hospitalized in the intensive care units of Kursk hospitals, and 599 control group patients with a mild form of COVID-19. Genotyping of rs7949972 and rs61882275 *ELF5* was carried out using real-time PCR according to a method developed in the laboratory of genomic research of the Research Institute for Genetic and Molecular Epidemiology. The thrombodynamics test was performed using the laboratory diagnostic system "Thrombodynamics Recorder TD-2". A log-additive regression model was used to assess associations. Bioinformatics resources were used to analyze the functional effects of SNPs.

Results: We determined that rs7949972 *ELF5* had a protective effect only in COVID-19 patients with a BMI < 30 (protective allele T, OR = 0.67, 95 % CI = 0.47–0.95, P = 0.02, P_{bonf} = 0.04). In this subgroup, we observed that allele T rs7949972 *ELF5* reduced the clot size at 30 min after coagulation activation (CS, μm, P = 0.02) and stationary spatial clot growth rates (Vst, μm/minutes, P = 0.02), and allele A rs61882275 *ELF5* was found to increase time of appearance of spontaneous clots (Tsp, P = 0.003).

ELF5, a member of the Ets transcription factor family, has been extensively investigated in breast cancer studies [1, 2]. Recent findings have underscored its relevance in COVID-19, revealing upregulation of key host factors (Ace2 and Tmprss4) in Elf5-overexpressing AT2 cells [3]. Moreover, ELF5, via cis-eQTL effects, modulates the expression of CAT, an antioxidant enzyme, in whole blood and the tibial artery, with elevated levels observed in COVID-19 patients [4]. Analysis of the impact of the risk allele C rs7949972 ELF5 on TFs binding sites suggests a potential role in exacerbating COVID-19 severity by positively regulating CD8-positive, alpha-beta T cell differentiation, negatively regulating CD4-positive, alpha-beta T cell differentiation, and

contributing to the defense response to viruses. Additionally, protective allele T rs7949972 is associated with improved lung function parameters, such as forced vital capacity (FVC), forced expired volume in 1 second (FEV1), FEV1 to FVC ratio, and peak expiratory flow, as evidenced by data from the Lung Knowledge Portal.

Conclusion: In the present study, we replicated associations of the SNP rs7949972 *ELF5* with severe COVID-19 within the Caucasian population of Central Russia, and determined BMI as modifier of the risk. We were the first to establish the impact of *ELF5* loci on thrombodynamic parameters such as CS, Vst and Tsp.

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References

1. Chakrabarti R., Hwang J., Andres Blanco M. et al. Elf5 inhibits the epithelial–mesenchymal transition in mammary gland development and breast cancer metastasis by transcriptionally repressing Snail2. *Nat Cell Biol.* 2012;14(11):1212-1222. doi 10.1038/ncb2607
2. Kalyuga M., Gallego-Ortega D., Lee H.J. et al. ELF5 suppresses estrogen sensitivity and underpins the acquisition of antiestrogen resistance in luminal breast cancer. *PLoS Biol.* 2012;10(12):e1001461. doi 10.1371/journal.pbio.1001461
3. Pietzner M., Chua R.L., Wheeler E. et al. ELF5 is a potential respiratory epithelial cell-specific risk gene for severe COVID-19. *Nat Commun.* 2022;13(1):4484. doi 10.1038/s41467-022-31999-6
4. Martín-Fernández M., Aller R., Heredia-Rodríguez M. et al. Lipid peroxidation as a hallmark of severity in COVID-19 patients. *Redox Biol.* 2021;48:102181. doi 10.1016/j.redox.2021.102181