doi 10.18699/bgrs2024-4.1-13

HSPA8 gene polymorphisms and the risk of severe COVID-19

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Key words: heat shock; severe COVID-19; rs1461496; rs1136141

Motivation and Aim: COVID-19, caused by the novel coronavirus SARS-CoV-2, has varying degrees of severity, from mild or asymptomatic cases to critical symptoms such as respiratory failure and multiple organ dysfunction. Heat shock proteins (HSPs) are induced by cellular stressors such as inflammation and infection and are involved in cellular homeostasis and immune responses. HSPs have the ability to protect cells and tissues from the harmful effects of inflammation, and HSP70 may have a protective effect on the immune system by promoting antigen processing and presentation. HSPA8, a member of the heat shock protein 70 (HSP70) family, has been implicated in various stages of the viral life cycle, including attachment [1, 2], internalization [3], and replication [4]. The aim of our study was to evaluate the impact of polymorphic variants rs1461496 and rs1136141 *HSPA8*, member of the HSP70 family, on the severity of COVID-19 in the population of Central Russia.

Methods and Algorithms: The study included 1,152 unrelated individuals from Central Russia, including 199 patients with COVID-19 hospitalized in the intensive care units of Kursk hospitals, and 905 patients in the control group with a mild form of COVID-19 that did not require hospitalization. Genotyping of *HSPA8* SNPs was carried out using real-time PCR. A log-additive regression model was used to assess associations. Functional annotation of SNPs was performed using a range of bioinformatics resources.

Results: Our study identified that the rs1461496 *HSPA8* increased the risk of severe COVID-19 in patients aged 68 and older (risk allele A, OR = 1.61, 95 % CI 1.06–2.44, p = 0.024), while also decreasing the time to the onset of clot growth in the overall group (Tlag, minutes, P = 0.02). This SNP regulates the expression via cis-eQTL effects of *CRTAM*, that was found to be down-regulated in COVID-19 patients. *CRTAM* plays a role in the activation and differentiation of several T-cell subsets, including NK cells [5]. Moreover, analysis of transcription factors (TF) binding to SNP, revealed that the risk allele A rs1461496 *HSPA8* is implicated in various pathological pathways crucial for COVID-19, such as positive regulation of viral transcription by the host, lymphocyte differentiation, and the canonical Wnt signaling pathway, which can lead to a cytokine storm [6]. In contrast, the protective allele G rs1461496 *HSPA8* creates DNA binding sites for TFs involved in biological processes that may positively impact COVID-19 outcomes. These processes include the positive regulation of nitric oxide (NO) biosynthesis, regulation of transforming growth factor beta (TGF-β) signaling and production, and response to hypoxia. Firstly, NO operates in COVID-19 through four mechanisms: regulating blood flow, initiating anti-inflammatory responses, promoting

anti-coagulation effects, and exerting antiviral properties [7], thus indicating the protective effect of this SNP. Secondly, TGF-β influences immune cell development, differentiation, tolerance induction, and homeostasis. A study found that serum levels of TGF-β positively correlated with improved outcomes in COVID-19 patients [8].

Additionally, we identified that rs1136141 *HSPA8* increased the risk of a severe COVID-19 course in patients under 68 years old (risk allele A, OR = 1.55, 95 % CI 1.06–2.28, p = 0.03). Data from the Lung Knowledge Portal also associate rs1136141 *HSPA8* with reduced forced expired volume in 1 second (FEV1), forced vital capacity (FVC), and peak expiratory flow. Furthermore, the risk allele A rs1136141 *HSPA8*, through TF binding, is involved in leukocyte differentiation and hippo signaling, inhibition of which significantly reduces SARS-CoV-2 replication [9]. Conversely, the protective allele G rs1136141 *HSPA8* positively regulates CD8-positive, alpha-beta T cell differentiation, negatively regulates leukocyte cell-cell adhesion, and is involved in response to cAMP, which can prevent antibody-mediated coagulopathy in COVID-19 [10]. Moreover, rs1136141 *HSPA8* (p = 0.007) and rs10892958 *HSPA8* (p = 0.007) were associated with lower ground-glass opacity upon admission to the ICU, and these same SNPs, rs1136141 *HSPA8* (p = 0.025) and rs10892958 *HSPA8* (p = 0.015), showed associations with reduced ground-glass opacity upon discharge from the ICU.

Conclusion: Thus, our study represents the first investigation into the associations of *HSPA8* SNPs rs1461496 and rs1136141 with severe COVID-19 within the Caucasian population of Central Russia. We conducted a comprehensive analysis of the impact of *HSPA8* loci on the clinical manifestation of the disease, thrombodynamic parameters, and the modifying effects of age on the risk of severe COVID-19, providing novel insights into the genetic factors underlying disease severity in this population.

Funding: The study is supported by Kursk State Medical University.

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