



PATHWAYS OF SEVERE COVID-19: OVERLAPPING GENETIC MARKERS BETWEEN OBESITY AND THE SARS-COV-2 DISEASE.

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Introduction: Throughout the public health emergency caused by SARS-CoV-2, Covid-19 has presented very different manifestations among the population. Although most infected individuals are asymptomatic or develop mild flu-like symptoms, about 20% develop severe symptoms, with impairment of vital functions. This heterogeneity in response to the virus is a multifactorial phenotype and there is evidence that the genetics of the host is important for the infection and clinical course of the disease. The literature has consistently associated the underlying condition of host obesity with the most severe forms of Covid-19, although the mechanisms leading to such an outcome are still poorly understood. Considering this fact and that the pathophysiology of both severe Covid-19 and obesity have in common a context of an exacerbated inflammatory response, these diseases may have shared genetic pathways.

Objective: This study aimed to investigate the potential common genetic mechanisms between obesity and Covid-19 severity. **Methods:** We use data based on summary statistics from a published genome-wide association study of Nature Genetics that identified obesity loci (5,530 obese cases, 8,318 non-obese controls, n = 13,848), and GWAS summary statistics from The COVID-19 Host Genetics Release 6 (14,480 hospitalized Covid-19 cases, 73,191 non-hospitalized Covid-19 controls, n = 87,671) to perform a gene-based cross-trait metanalysis in MAGMA v.1.10 software. Subsequently, we conducted an enrichment analysis in FUMA GWAS platform using the 15 most strongly associated genes in the meta-analysis. **Results:** The loci 3p21.31 and 21q22.1, consistently associated with susceptibility to critical illness in Covid-19, were confirmed in our study, and new associations of *PCDH1*, *LTF*, *DNAJC27*, *SS18*, and *PSMA8* genes were found. In the enrichment analysis, it is possible to observe that there is a high expression of *PCDH1*, *DNAJC27*, and *SS18* genes both in adipose

tissue and in the lung, and of LTF in the lung, offering a biological hypothesis consistent with the findings of the meta-analysis. Unlike the others, PSMA8 has a high expression only in the testes. Considering that Covid-19 severity has been consistently associated with males in many epidemiological studies, this finding may be an important insight for further studies on this genetic marker. **Conclusions:** The relationship between the *PCDH1*, *LTF*, *DNAJC27*, *SS18*, and *PSMA8* genes, obesity, and hospitalized Covid-19 is an interesting target for studies to better understand the pathophysiological mechanisms involved in these two important conditions. Comorbidity between obesity and severe Covid-19 may be mediated by common genetic factors that play an important role in the critical illness pathways.

Keywords: Covid-19; obesity; genomic.