Title:	Systematic review and meta-analysis of human genetic variants contributing to COVID-19 susceptibility and severity Author links open overlay panel
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Abstract:	The COVID-19 pandemic has spawned global health crisis of unprecedented magnitude, claiming millions of lives and pushing healthcare systems in many countries to the brink. Among several factors that contribute to an increased risk of COVID-19 and progression to exacerbated manifestations, host genetic landscape is increasingly being recognized as a critical determinant of susceptibility/resistance to infection and a prognosticator of clinical outcomes in infected individuals. Recently, several case-control association studies investigated the influence of human gene variants on COVID-19 susceptibility and severity to identify the culpable mutations. However, a comprehensive synthesis of the recent advances in COVID-19 host genetics research was lacking, and the inconsistent findings of the association studies required reliable evaluation of the strength of association with greater statistical power. In this study, we embarked on a systematic search of all possible reports of genetic association with COVID-19 till April 07, 2022, and performed meta-analyses of all the genetic polymorphisms that were examined in at least three studies. After identifying a total of 84 studies that investigated the association of 130 polymorphisms in 61 genes, we performed meta-analyses of all the eligible studies. Seven genetic polymorphisms involving 15,550 cases and 444,007 controls were explored for association with COVID-19 susceptibility, of which, ACE1 I/D rs4646994/rs1799752, APOE rs429358, CCR5 rs333, and IFITM3 rs12252 showed increased risk of infection. Meta-analyses of 11 gene variants involving 6702 patients with severe COVID-19 and 8640 infected individuals with non-severe manifestations revealed statistically significant association of ACE2 rs2285666, ACE2 rs2106809, ACE2 rs2074192, AGTR1 rs5186, and TNFA rs1800629 with COVID-19 severity. Overall, our study presents a synthesis of evidence on all the genetic determinants implicated in COVID-19 to date, and provides evidence of correlation between the above polymorphisms with COVID-19 susceptibility and severity.
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