Title: **Does apolipoprotein E genotype predict COVID-19 severity?**

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A challenge facing the medical community caring for coronavirus disease 2019 (COVID-19) patients is predicting who will eventually progress to severe illness and even death, which is usually from acute respiratory distress syndrome (ARDS) [1]. A major driving force for the development of ARDS is a cytokine storm, which is an uncontrolled release of pro-inflammatory cytokines and chemokines by immune effector cells in response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. Risk factors associated with subsequent death include older age, hypertension, diabetes, ischemic heart disease, obesity and chronic lung disease; however, sometimes there are no obvious risk factors [3]. We hypothesize that the apolipoprotein E4 (apoE4) genotype may predict the propensity to manifest rapid and severe illness with COVID-19.

Although ApoE has been classically associated with lipoprotein metabolism and atherosclerosis, it is also associated with the risk the susceptibility to viral, bacterial and parasitic infections [4]. Notably, apoE exists in three isoforms (apoE2, apoE3, apoE4) giving rise to three homozygous and three heterozygous phenotypes; in the general population, the three alleles differ in frequency (ε2: 5-10%, ε3: 65-70%, ε4: 15-20%) [4]. Interestingly, individuals of African decent may have twice the frequency of the ε4 allele (30-40%) compared to individuals of European and Asian decent [5]. It has been shown that possessing one or two copies of apoE4, versus two copies of apoE3, is associated with an augmented *in vivo* innate immune response to an intravenous lipopolysaccharide challenge, as manifested by higher hyperthermia and cytokine levels [6]. An example of the modulation of viral infections by apoE, is that the apoE4 isoform has been shown to increase HIV-1 cell entry *in vitro*, and possessing two copies of apoE4 results in a more rapid HIV disease progression [7]. Of interest, apoE4 has also been associated with some of the comorbid risk factors associated with severe COVID-19, such as atherosclerosis and hypertension [4,8].

It is also noteworthy that apoE is expressed by many cell types in the lung, including macrophages and both type I and type II alveolar epithelial cells [9]; while the functional receptor for SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2), is highly expressed on type II alveolar cells [10]. Moreover, the local pulmonary apoE concentration acts as a danger signal in asthmatics, which activates the inflammasome and subsequently interleukin (IL)-1β production by macrophages [9].

Therefore, it is possible that having one or two copies of apoE4 predisposes one to be at high risk to progress to severe illness from SARS-CoV-2, by virtue of a sequence of robust innate immune response, followed by cytokine storm, and resulting ARDS. Furthermore, apoE polymorphism may explain in part why African-Americans appear to be disproportionally affected with severe illness from COVID-19, in addition to other well known socioeconomic inequalities and risk factors. The apoE genotype is easily obtained by buccal swab analysis or blood test, and investigators should determine if having a copy of apoE4 does indeed predict more severe COVID-19 and death. If so, this group could be targeted more aggressively from the outset of the disease.

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