Association of COVID-19 with genotyping ApoEe4 and APOBEC3B.

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Abstract

The novel Coronavirus disease 2019 (COVID-19), with no doubt is currently overwhelming the health care system capacity worldwide. Genetic implementation and practice may provide a ground for future studies on the role of human genetics in modulating the susceptibility to COVID-19 infection, disease severity and outcome. We will, briefly, overview and present the available scientific data, about ApoEe4 and APOBEC3B genotyping, and whether if they are associated with the pathogenesis of COVID-19 up to the current day. The novel coronavirus SARS-CoV-2 uses the ACE2 (Angiotensin Converting Enzyme 2) receptor for cell entry. ACE2 is highly expressed in type II alveolar cells in the lungs, where also ApoE is one of the highly co-expressed genes. ApoE was shown to be associated with susceptibility risk to viral, bacterial and parasitic infections.

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ApoE

ApoE exists in three isoforms (apoE2, apoE3, apoE4), giving rise to three homozygous and three heterozygous phenotypes, where, in the general population the three alleles differ in frequency (e2: 5%-10%, e3: 65%-70%, e4: 15%-20%). Furthermore, African American are presented with as twice as the frequency of the e4 allele (30%-40%), when compared to individuals from either European or Asian populations. Also, it has been found that possessing one or two copies of apoE4, versus two copies of apoE3 is related to an augmented in vivo innate immune response to an intravenous lipopolysaccharide challenge, which is then manifested by higher hyperthermia and cytokine levels [1-6].

The modulatory effect of ApoE can be illustrated in the increased HIV-1 cell entry in vitro, which is mainly related to ApoE4 isoform. The possession of two copies of apoE4 is causing in turn a more rapid progression of HIV disease [7].

In addition to the fact that apoE4 has been associated with some comorbid risk factors associated with severe COVID-19, such as atherosclerosis and hypertension, ApoE e4e4 genotype was also associated with increased risks of COVID-19 test positivity (OR=2.24, 95% CI: 1.72 to 2.93, $p=3.24 \times 10^{-9}$) and with mortality with positive test-confirmed COVID-19 cases (OR=4.29, 95% CI: 2.38 to 7.72, $p=1.22 \times 10^{-6}$), compared to e3e3s [4,6].

These findings demonstrate that advanced chronological age or even the comorbidities that are commonly seen in aging, are not acting as the only risk factors for COVID-19 mortality [7]. Actually, the presence of ApoE e4e4 genotype can independelty increases the risks of severe COVID-19 infection, this apart from the pre-existing dementia, cardiovascular disease, or type-2 diabetes, [8]. ApoE e4 not only affects lipoprotein function and subsequent cardio-metabolic diseases, but also has the ability to moderate macrophage pro-inflammatory and anti-inflammatory phenotypes [9].

Therefore, it is possible that having one or two copies of apoE4 acts as a predisposing factor for higher risk for progressing to severe illness from SARS-CoV-2. It may happen by the virtue of a sequence of robust innate immune response, followed by cytokine storm, and resulting acute respiratory distress syndrome [9]. Furthermore, the presence of apoE polymorphism may explain why African-Americans appear to be disproportionally affected with severe illness from COVID-19, far from the other well-known socioeconomic inequalities and other risk factors.

ApoE genotyping can be easily obtained via Buccal swab analysis or blood test. Investigators should determine if more severe COVID-19 and death are related to having a copy of apoE4, if so, this group could then be targeted more aggressively from the outset of the disease [10].

APOBEC3

APOBEC3 enzymes in eukaryotic cells are considered to be part of the integral cell defense system [11]. The APOBEC is a family of enzymes primarily work on DNA, and can also target RNA viral genomes, thus, they're having RNA editing capability that may help contributing to the innate defense system against various RNA viruses. They might have a direct impact on the genomic signature of RNA viruses [12].

Cytidinedeaminase APOBEC3B is one of the innate immunity genes which have an insertion/deletion polymorphism. In fact, APOBEC3 locus is involved in widespread editing of viral genomes and also limit the replication and infectivity of not only hepatitis B and human immunodeficiency viruses, but also to coronaviruses [13].

Wide range of the APOBEC3B insertion/deletion frequencies are reported across global populations, including India, with fixation of the "insertion allele" in Africa. The geographic distribution of the protective allele in India presents a true striking overlay with low-incidence COVID- 19 regions. On the other hand, It was shown that one of the consequences of APOBEC3B allele deletion is the facilitation of Alu insertion in the ACE1 (angiotensin converting enzyme 1) gene, and thus resulting in lower expression and reduced plasma levels of ACE [13].

Conclusion

As a conclusion, the aforementioned data clarify the higher prevalence and mortality of COVID-19 in individuals with genotype ApoEe4. Thus, early screening and correct management are of high importance for such individuals. Besides, the editing genetic activity of APOBEC3B; the innate immunity gene, can lead to a protective allele that may show lower incidence of COVID-19.

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