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Most Deleterious Missense Variants of Angiotensin-converting Enzyme 2 Gene have Extremely Low Frequencies and a Little Impact on the Binding Affinity with the SARS-CoV-2 Spike

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Abstract: Angiotensin-converting enzyme 2 (ACE2) is a well-established functional host receptor for the highly devastating ongoing pandemic of coronavirus disease 2019 (COVID-19). This protein provides the entry point through which COVID-19 hooks and infects human cells. A damaged ACE2 could alter the rate of this viral infection. This study was conducted to predict the most deleterious non-synonymous single nucleotide polymorphisms (nsSNPs) on ACE2, assess their frequency among populations, and evaluate their effect on the binding with the SARS-CoV-2 spike. All sequence-based *in silico* tools indicated damaging impacts of V184G, A191P, P235R, P263S, G268C, G377E, Y515C, G466W, and L595V. Structure-based tools showed damaging effects of C141Y, Y158H, G173D, Y207C, I233N, Y252C, Y252N, L291K, M376T, G377E, M383T, N397D, E398K, G405E, L418S, N437H, G448E, W461R, V463D, Y515C, I544N, L570S, L585P, F588S, and N599K. All these risky amino acid alterations were found in extremely low-frequency worldwide. Docking showed few effects of these nsSNPs in altering the binding affinity of ACE2 with SARS-CoV-2 spike. G377E and Y515C showed the highest damaging impacts on the biological activity of ACE2. Though Y515C caused higher affinity than other risky SNPs to bind with spike, no remarkable alteration was observed in this interaction. This entails that the risky SNPs of ACE2 exert low-frequency deleterious impacts on this enzyme without being necessarily involved in the interaction with SARS-CoV-2 spike. To the best of our knowledge, this is the first comprehensive computation that predicted the low effectiveness of altering the ACE2-spike interaction due to the distant positions they occupy away from ACE2-spike interactions.

Keywords: ACE2 gene; computation; COVID-19; missense; SNP; variations.

1. Introduction

It has been postulated that many factors have been associated with both the variation of ACE2 and COVID-19 severity and progression, such as sex [1], age [2], medication [3], and ethnicity [4]. But, the ethnicity of populations is the most controversial element in the severity and progression of infection with COVID-19 [5]. This issue has been given ongoing

importance, but investigations on ethnic inequalities from COVID-19 are still lacking. Many countries with high levels of infectivity have not yet released data on this issue [6].

The Angiotensin-converting enzyme 2 (ACE2) protein is one of the angiotensin-converting enzyme family of dipeptidyl carboxydipeptidases. It plays a crucial role in the pathogenesis of COVID-19, as it provides a route of entry of viral particles, establishing it as a functional receptor for this newly emerged outbreak [7]. This protein is encoded by the *ACE2* gene, which has recently attracted great scientific attention since emerging of the COVID-19 pandemic. Accordingly, one of the current tools that are directed to eliminate the infectivity of the SARS-CoV-2 has been conducted to occupy the active amino acid residues through which the ACE2 interacts with the SARS-CoV-2 spike moiety. The aim of these tools has largely been focused on the ACE2 receptor due to its important role through which the SARS-CoV2 virus particles are interacted before being internalized inside the host cells [8]. Thus, the ACE2 receptor has been considered an important therapeutic target to get rid of the SARS-CoV-2 infection. The *ACE2* gene is positioned on chromosome X, within the Xp22.2 arm. It consists of 19 exons, with an open reading frame encoding 805 amino acids. The mature product of the ACE2 protein has a molecular weight of 110 to 120 KD [9]. It is well-established that ACE2 protein contains an extracellular domain (starting from the first to 740 amino acid residues), a transmembrane region (741 to 768 amino acid residues), and an intracellular tail (769 to 805 amino acid residues) [10]. The binding and entry of SARS-CoV-2 particles into human cells are facilitated by the high-affinity interaction between the receptor-binding domain (RBD) of the viral spike glycoproteins with the ectodomain of ACE2 [11]. This direct interaction between SARS-CoV-2 and ACE2 is thought to be the key essence of the efficient spread of this viral infection among humans [12,13]. Thus, altered binding affinity between SARS-CoV-2 and ACE2 has been proposed to correlate with altered virus transmissibility and severity in patients with COVID19 [14].

Furthermore, genetic polymorphisms within the ACE2 protein have strongly been linked to several disorders associated with this viral infection, such as acute kidney injury [9], cardiovascular disease [15], lung failure [16], hypersensitivity [17], and diabetes [18]. Understanding this protein's functional and structural properties seems to be essential in these aspects. However, the likelihood of disease-causing mutations in complex diseases as pathogenic or neutral remains a monotonous task because of its expensive and time-consuming experiments [19]. Though silent mutations, mutations within introns, and other non-coding sequences have been widely acknowledged to cause alterations in protein expression, function, and conformation [20,21], such mutations do not substitute amino acid sequences. Contrarily, a missense or nonsynonymous single nucleotide polymorphism (nsSNP) causes direct incorporation of an alternative amino acid in the protein structure and is known to be one of the main causes of the possible alterations in mode of action and interactions. Each amino acid substitution has a particular effect on the 3D structure. Accordingly, it is crucial to predict the impact of each one of these amino acid substitutions using state-of-the-art *in silico* tools [15]. Recently, many high throughput innovations have been developed to predict the effects of nsSNPs on protein structure, stability, and interaction by providing a more accurate assessment of deleterious nsSNPs on the targeted proteins [22,23].

Despite the versatile involvement of ACE2 in many crucial biological activities associated with COVID-19 infection [24], no comprehensive study has been conducted to prioritize the most damaging nsSNPs of this highly important protein using computational tools. Taking these data into consideration, an inclusive prediction of the impact of nsSNPs on