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Analysis of the interaction of ACE2, TMPRSS2 genes and their polymorphisms with the SARS-CoV-2 virus

Host genes act as a factor related to susceptibility and resistance to viral infections. The article provides a description of modern scientific studies devoted to the study of the role of the ACE2, TMPRSS2 genes, and their single-nucleotide polymorphisms in infection with the SARS-CoV-2 virus. SNPs of the ACE2 gene, TMPRSS2 can affect the penetration of SARS-CoV-2 into the cell. In addition, the study of these polymorphisms will determine the predisposition of an individual to the disease COVID–19, or the nature of its course. Based on the literature sources, the role of angiotensin-converting enzyme 2 and transmembrane proteases in the participation of the SARS-CoV-2 virus penetration process with the body cells is noted. Other functions that ACE2 and TMPRSS2 receptors perform in the human body are also described. The characteristics of two genes and their fairly well-known polymorphisms are given. The tissues and organs in which genes are expressed are marked. Information on the frequency of alleles of genetic variants of genes in different populations is shown. In addition to describing the relationship of gene polymorphisms with the disease caused by SARS-CoV-2, information is provided on the association of these genetic variations with diseases of the blood vascular system and oncological diseases.

Keywords: ACE2, TMPRSS2, genes, SARS-CoV-2, COVID-19, single nucleotide polymorphisms, receptors.

Introduction

In December 2019, a new highly pathogenic SARS-CoV-2 caused an outbreak in Wuhan, Hubei Province, China [1], which quickly spread across China, and soon around the world, causing a pandemic. At the moment, the virus is rapidly mutating, spreading around the world and poses a serious threat to the health of the global population.

Phylogenetic analysis of the coronavirus genome has shown that SARS-CoV-2 belongs to the genus *Betacoronavirus*, which includes coronaviruses associated with SARS-CoV and MERS-CoV. Scientists have found that the SARS-CoV-2 sequences are almost identical and 79.6 % identical to the SARS-CoV sequence, as well as 96 % identical on the level of the entire genome to the bat coronavirus [2].

Currently, it has become obvious that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2), encoded by the ACE2 gene, acting as a SARS-CoV-2 receptor for S (spike) protein, through which the virus can attach to host cells [3–5]. Consequently, it can be assumed that the high risk of infection and severe course of the COVID–19 disease depends on an increase in the number of ACE2 receptors.

SARS-CoV-2 has many S-proteins that perform the function of binding the virus to the organism's cell. According to Fang Li's research, "During virus entry, S1 binds to a receptor on the host cell surface for viral attachment, and S2 fuses the host and viral membranes, allowing viral genomes to enter host cells" [6]. Primarily, S-proteins bind to cellular receptors ACE2, whose main function is to bind the hormone angiotensin. After being attached to the cell membrane to introduce the virus genome into the cell, the S-protein undergoes a small transformation using the body's enzymes, transmembrane proteases TMPRSS2. It is proteases that cut and activate it, opening a fragment of a protein that triggers the fusion of the virus and cell shells [4].

ACE2 is a membrane protein that is involved in the normalization of blood pressure, the key constituent of the renin-angiotensin system (RAS). ACE2 participates in transferring certain amino acids, regulates the permeability of blood vessels [7]. The receptor is related to the mechanism of development of such diseases as heart failure, myocardial infarction, hypertension, lung diseases, diabetes mellitus, and intestinal dysbacteriosis [8].

The signification of ACE2 and TMPRSS2 genes, as well as their polymorphisms

TMPRSS2 gene (PP9284; PRSS10) — transmembrane serine protease 2 — encodes a protein of the same name from the family of serine proteases [9].

The TMPRSS2 gene encodes a protein that is present in all possible targets of SARS-CoV-2 infection, including respiratory epithelial cells, heart endothelium, microvascular endothelial cells, kidneys, and digestive tract [10].

According to the HUGO Gene Nomenclature Committee (HGNC), the "ACE2 gene is located on chromosome Xp22 and contains 22 exons and 112,671 bases" [11]. ACE2 mutations are related to cardiovascular disease, in addition to acute pulmonary insufficiency, phlogotic colitis [12, 13].

The ACE2 gene is expressed in the small intestine, kidneys, heart, thyroid gland, lungs, adipose tissue, colon, liver, bladder, blood, spleen, bone and brain, blood vessels and muscles [3]. In addition, ACE2 expression was detected in epithelial cells of the oral and nasal mucosa [14, 15].

The penetration of the virus and further infection depend on the complex interaction between several host components encoded by genes involved in controlling the penetration of the virus, as well as the presence of proteins and immune responses to neutralize the virus. In addition to the components of the host's immune response, the resistance of the virus and the heaviness of the incidence are affected by such a factor as the presence of concomitant or chronic diseases [16]. Mortality from COVID–19 is especially increasing in the category of elderly people and people with concomitant diseases (diabetes mellitus, diseases of the cardiovascular system, etc.) [17]. For example, among people who have been found to have COVID–19 suffering from hypertension and type 1 or type 2 diabetes mellitus, it was identified that the expression of ACE2 is significantly increased due to treatment with ACE inhibitors [18]. Therefore, increased expression of the ACE2 gene will favor SARS-CoV-2 infection and enhance the possibility of a heavy degree of disease development. However, the harm of taking ACE inhibitors has not yet been proven, and if they are refused, the risk of complications of these concomitant diseases is possible.

One of the significant factors determining the severity and susceptibility of coronavirus infection is the genetic differences between individuals. Such genetic variations are single-nucleotide polymorphisms (SNPs), which can suggest the disease progression. Exploring of ACE2 gene SNPs within different populations opens up the possibility to prove that variants of the ACE2 gene can be complicit in the control of susceptibility to COVID-19 disease. For example, in studies on the effects of various variants of the ACE2 gene, its polymorphisms associated with hypertension were found [19–21]. Another study revealed a high correlation between the frequency of rs2285666 polymorphism (the most studied) and the frequency of COVID–19 cases between rs2285666 frequency and mortality rates [22]. The research data conducted in Italy showed that the polymorphisms rs35803318 and rs2285666 have a significant difference in the frequency distribution among the Italian cohort in relation to other populations of the world [23]. rs2285666 has the following alleles C> A / C> G / C> T. According to the allele frequency data presented in the Database of Single-nucleotide Polymorphisms (dbSNP), the frequency of the allele C prevails among different populations [24]. The two-allele polymorphism rs35803318 C> T is dominated by the C allele, rs35803318 occupies the position of chrX: 15564086, is a synonymous variant of the ACE2 gene, i.e. does not change the amino acid chain in the protein [25].

The enhanced intensity of COVID–19 in males was presumably associated with ACE2 gene polymorphisms and expression levels. Simultaneously, typically ACE2 gene expression tended to be more intense in men compared to women [26, 27], although other studies showed ambiguous results [28, 29]. The high level of ACE2 gene expression in men can be explained by the fact that X chromosome carries this gene, i.e. men carry and express only one variant of ACE2. A group of scientists explains this as follows: "... females will typically express those variations in a mosaic distribution determined by early X-inactivation event" [30]. Consequently, when men have one variant of the ACE2 gene that is more suitable for SARS-CoV-2, that variant will be expressed in all cells. For a better understanding of the influence of gender on susceptibility to the virus and the course of the illness, studies should include an analysis of the ACE2 gene polymorphisms, taking into account gender specificity.

Serine protease TMPRSS2 is the second host protein (after ACE2) that affects the facilitation of SARS-CoV-2 binding to cells, but to date, it has received much less attention in genetic studies.

It has been presupposed that someone may have a genetic predisposition to SARS-CoV-2 infection, and of distinctive research interest are variants of the TMPRSS2 gene involved in the penetration of the virus into cells. Variants of this gene can regulate the risk of infection and severe disease, making some people more vulnerable than others [31, 32].

Scientists analyzed the allele frequencies of two non-synonymous variants rs12329760 and rs75603675 of the TMPRSS2 gene, found a significant relationship between the frequency of COVID-19 deaths and the allele frequencies of two SNPs. The obtained data demonstrate that East Asians have higher frequencies of the rs12329760 allele than Europeans and suggested that this may provide resistance to SARS-CoV-2 [33].

A study conducted by Italian scientists identified ars35074065 that was simultaneously related to intensified TMPRSS2 gene expression, however diminished expression of the interferon-inducible MX1 gene in lung tissue [34]. That is, people with this SNP may have an elevated sensitivity to SARS-CoV-2 as a consequence of increased expression of the TMPRSS2 gene on the cell cover and simultaneous weakening of the cellular antiviral response.

Researchers from Iran discovered 11,184 SNPs of the TMPRSS2 gene; found out that 21 of them have an impact on the structure and function of the gene. Besides, we obtained data on the frequency of the SNPs allele in different populations and in the world as a whole. For example, in all the above populations, the SNP rs12329760 is dominated by the C allele [35].

Another study showed plentiful SNPs of TMPRSS2 in the Italian cohort, which were all predicatively associated with higher levels of gene expression [28]. It follows from this that the separation of the detected variants as positive and negative is untimely until supplementary research can be done to confirm their biology.

Furthermore, the scientists found no distinction in gene expression between males and females in non-sex-specific organs [28, 34].

The TMPRSS2 gene is activated by androgen hormones in prostate cancer cells and is a clinical marker of this disease. As already mentioned above, the mortality rate and the number of severe cases of COVID-19 is especially increasing in the category of elderly people and people with concomitant diseases [17].

Conclusions

In general, the ACE2 gene is one of the genetic factors that affects the resistance and receptiveness to COVID–19 disease, and the genetic variants within this gene can be key in determining the susceptibility, severity and outcome of the disease. However, there is still no accurate and complete evidence that ACE2 gene polymorphisms affect the receptiveness and stability to SARS-CoV-2 infection, and have a close relationship with the intensity of COVID-19 in the context of concomitant diseases of the host, gender, age, and different populations.

This also applies to the TMPRSS2 gene, since there is currently no information about the influence of TMPRSS2 gene polymorphisms on the susceptibility, resistance and severity of the disease, as well as in terms of populations, age and gender.

Identification of polymorphisms of genes encoding virus-binding receptors, in particular the TMPRSS2 gene, will open up opportunities for the development of personalized treatment.

Moreover, there is insufficient data on the evolution of polymorphisms that are related to susceptibility to SARS-CoV-2, their origin and frequency changes.

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ACE2, TMPRSS2 гендерінің және олардың полиморфизмдерінің SARS-CoV-2 вирусымен өзара әрекеттесуін талдау

Ағзаның гендері вирустық инфекцияларға сезімталдық пен төзімділікке байланысты фактор ретінде әрекет ететіні белгілі. Мақалада SARS-CoV-2 вирусын жұқтырудағы ACE2, TMPRSS2 гендерінің және олардың бірнуклеотидті полиморфизмдерінің рөлін зерттеуге арналған заманауи ғылыми зерттеулердің сипаттамасы ұсынылған. ACE2, TMPRSS2 генінің SNP SARS-CoV-2 жасушаға енуіне әсер етуі мүмкін. Сонымен қатар, олар адамның COVID-19 ауруына бейімділігін немесе оның ағымының сипатын анықтауға мүмкіндік береді. Әдеби дереккөздерге сүйене отырып, ангиотензин түрлендіретін фермент 2 және трансмембраналық протеазалардың SARS-CoV-2 вирусының дене жасушаларына ену процесіне қатысудағы рөлі атап өтілді. ACE2 және TMPRSS2 рецепторлары адам ағзасында орындайтын басқа да функциялар сипатталған. Екі генге және олардың кеңінен танымал полиморфизмдеріне сипаттама берілген. Бұл гендердің генетикалық ақпаратты жүзеге асыратын тіндер мен мүшелері көрсетілген. Әр түрлі популяциялардағы гендердің генетикалық нұсқаларының аллельдерінің жиілігі туралы ақпарат айтылған. Гендердің полиморфизмдерінің SARS-CoV-2 туындаған аурумен байланысын сипаттаумен қатар, бұл генетикалық вариациялардың қан айналымы жүйесінің және онкологиялық ауруларымен байланысы туралы ақпарат келтірілген.

Кілт сөздер: SARS-CoV-2, COVID-19, ACE2, TMPRSS2, гендер, бірнуклеотидті полиморфизмдер, SNP, рецепторлар.

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Анализ взаимодействия генов ACE2, TMPRSS2 и их полиморфизмов с вирусом SARS–CoV–2

Общеизвестно, что гены хозяина выступают в качестве фактора, имеющего отношение к восприимчивости и устойчивости к вирусным инфекциям. В статье представлено описание современных научных исследований, посвященных изучению роли генов ACE2, TMPRSS2 и их однонуклеотидных полиморфизмов в инфицировании вирусом SARS–CoV–2. SNPs гена ACE2, TMPRSS2, которые могут влиять на проникновение SARS–CoV–2 в клетку. Кроме того, исследование этих полиморфизмов позволит определить предрасположенность индивидуума к заболеванию COVID–19 либо характер его течения. На основании анализа литературных источников отмечена роль ангиотензин превращающего фермента 2 и трансмембранных протеаз в участии процесса проникновения вируса SARS–CoV–2 с клетками организма. Также описаны другие функции, которые рецепторы ACE2 и TMPRSS2 выполняют в организме человека. Дана характеристика двух генов и их довольно широко известных полиморфизмов. Отмечены ткани и органы, в которых экспрессируются гены. Показана информация о частоте аллелей генетических вариантов генов в разных популяциях. Помимо того, что описывается связь полиморфизмов генов с заболеванием, вызванным SARS–CoV–2, приводится информация об отношении этих генетических вариаций с заболеваниями кровеносной системы и онкологическими болезнями.

Ключевые слова: SARS–CoV–2, COVID–19, ACE2, TMPRSS2, гены, однонуклеотидный полиморфизм, SNP, рецепторы.

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