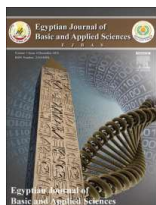


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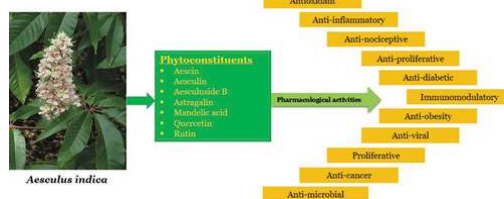
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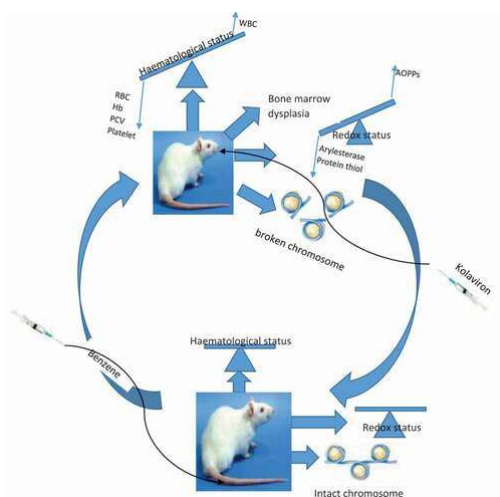
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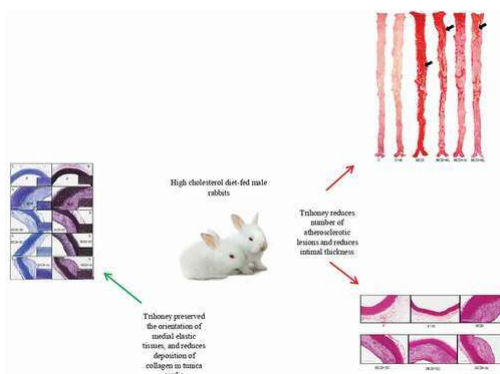
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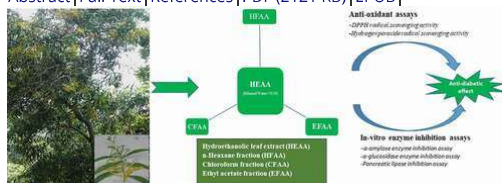
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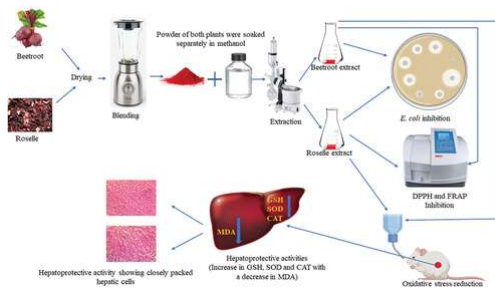
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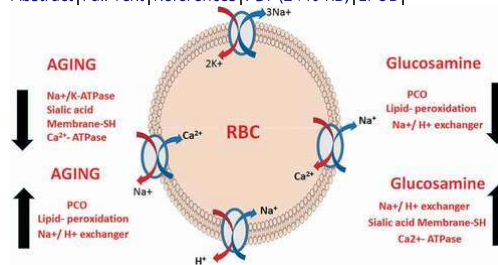
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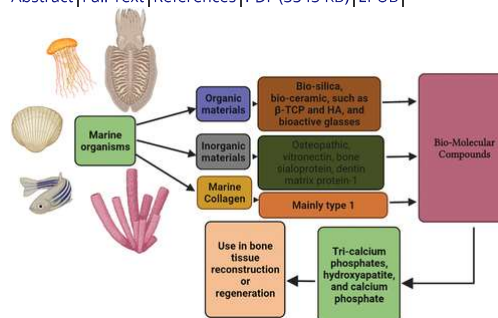
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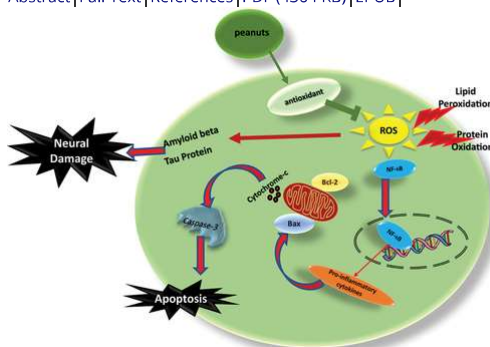
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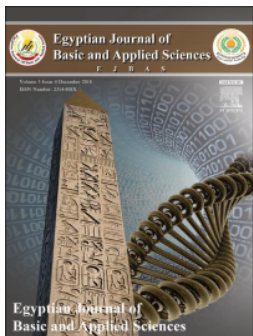


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ABSTRACT

COVID-19-related morbidity and mortality are significantly increased with increasing age and the presence of co-existing health conditions, such as cancer and cardiovascular disease. While most infected people recover, even very young and otherwise healthy patients may unpredictably succumb to this disease. COVID-19 is highly susceptible to Angiotensin-converting enzyme 2 (ACE2) and Transmembrane protease-serine 2 (TMPRSS2) polymorphisms altering the angiotensinogen-ACE2 interactions, such as *p. Arg514Gly* and its prevalence. The article describes the role of understanding the genetic basis of COVID-19 and its susceptibility to human genes.

KEYWORDS

Genetics; susceptibility; COVID-19; ACE2; TMPRSS2

Introduction

Human genetics is the empirical study of human variability inherited from birth [1]. Genes affect human traits, behavior, health, and diseases [2]. Several of the fundamental processes of evolutionary change are mediated through genetic variation [3]. There are three causes of genetic variation: sex, gene flow, and mutations. Sex may introduce new gene combinations by shuffling genes from male and female species into a population [4].

The interchange of genes between populations is known as gene flow, and it is a significant source of genetic variation [2]. While a single mutation can have considerable, specific evolutionary scenarios necessitate many mutations. Polymorphisms are genetic variants that affect more than 1% of the population [2]. Polymorphisms are responsible for many typical differences between people, like the color of the eyes, hair color, and blood types. Though various polymorphisms may

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not adversely affect an individual's health, some may increase the risk of developing other disorders [5].

Numerous diseases, if not all, are caused by genetics and the proteins encoded by them [6]. Genes dictate how efficiently meals and chemicals are metabolized, how pollutants are detoxified, and how vigorously illnesses are resisted [6]. Genetic illnesses can be classified into three broad categories: single-gene disorders, multifactorial disorders, and chromosomal disorders [6].

Changes in single-gene DNA sequences, referred to as mutations, are responsible for hundreds of diseases. A gene can mutate in various ways, altering the protein output and rendering it incapable of performing its regular function. The most common type of gene mutation occurs when a single DNA nucleotide is altered or 'misspelled' [7]. Numerous mutations result from the loss (deletion) or gain (duplication or insertion) of single or multiple bases [6]. Multifactorial diseases are caused by a complex interaction of genetic, behavioral, and environmental variables. Spina Bifida, heart disease, and diabetes are all examples of these illnesses. While multifactorial conditions tend to run in families, specific mutations such as cancer can be acquired throughout a person's lifespan [7]. Genes are involved in environmental and behavioral regulation. Changes in behavior or environment, such as food, exercise, exposure to toxic substances, or drug use, can all affect genetic features [7].

Understanding how Coronavirus Disease 2019 (COVID-19) evolved involves critical measures and investigations. Researchers working on coronaviruses in 2007 revealed a reservoir of SARS-CoV-like viruses in bats [5]. SARS, MERS, and COVID-19 are part of a vast range of bat coronaviruses that have spread globally, and that many of these viruses are functionally pre-adapted for human emergence [8].

At the end of 2019, Wuhan city, a developing economic hub in China, saw an outbreak of a novel coronavirus that claimed over 1,800

lives and infected over 70,000 people within the first 50 days of the epidemic [9]. This virus was identified as a β -group coronavirus [9]. Chinese researchers have named the novel virus Wuhan coronavirus or the 2019 novel coronavirus (2019-nCoV). The International Committee on Taxonomy of Virus (ICTV) labeled SARS-CoV-2 and COVID-19 as the disease [10].

Morbidity and mortality associated with COVID-19 increased significantly with increasing age and co-existing health conditions, such as cancer and cardiovascular disease [11,12]. While most infected persons recover, mainly young and healthy patients may succumb suddenly to this disease [13]. These findings raise the intriguing question of how much genetic susceptibility can account for variance in COVID-19 disease severity.

Given the wide variety of clinical manifestations and problems associated with COVID-19, discovering risk variables that could predict the disease's severity would improve the fate of infected patients. In this regard, advanced age, smoking, hypertension, diabetes mellitus, heart disease, chronic lung disease, and cancer have all been linked to the severity and fatality of COVID-19 [14,15].

Nonetheless, far less is known about the genetic underpinnings of COVID-19 risk, both in terms of infection susceptibility and the severity of infection-related complications. However, a strong association between blood type, COVID-19 diagnosis, as well as a gene-rich locus on chromosome 3p21.31 and severity was reported [16].

Understanding genetic variation

When the DNA sequences of people within a group vary, genetic variation occurs [17]. Both the germ and somatic cells exhibit variation. A germ cell comprises both egg and sperm, whereas somatic cells are made up of all other types of cells. Most of the variation happens because of mutation and recombination [18].

Only germ cell variation is transferable and can be passed down from generation to generation, resulting in evolution and, more crucially, population dynamics [12]. Evolution is dependent on the genetic variation being passed down from generation to generation. Genetic variation enables living organisms to be distinct. The variety in facial shape, skin color, eye color, and hair color, among other characteristics, is caused by genetic variation [11]. Genetic diversity contributes to disease/infection susceptibility and how individuals respond to medications and treatments [11].

The effect of different genetic variants among other populations occurs due to genetic drift [19]. Genetic drift occurs in diverse peoples, where there is the infrequent occurrence of alleles that face a chance of being lost. Once it starts, genetic drift will continue until the involved alleles are either lost by a population or are the only alleles present at a present or particular gene locus within a population [19]. Both possibilities decrease the genetic diversity of a person. Genetic drift can result in the loss of rare alleles and can reduce the size of the genetic pool. It also causes a new population to genetically district from its original population, which has led to the hypothesis that genetic drift plays a role in the evolution of more recent species [19].

Genetic basis of COVID-19 infection

Infection with SARS-CoV-2 depends on the host cell factors angiotensin-converting enzyme 2 (ACE2) for cell entry and the host transmembrane serine protease TMPRSS2 for SARS-CoV-2 spike protein (S) priming [20]. ACE2 located on the X-chromosome catalyses the conversion of angiotensin II to angiotensin [21], which functions as a vasodilator and affects the cardiovascular system significantly [22]. TMPRSS2 is a critical gene in prostate cancer because a related translocation promotes the family of oncogene expression in a significant proportion of tumors [23]. The single-cell RNA sequencing was used to explore the

distribution of ACE2 mRNA, and both ACE2 and TMPRSS2 mRNA are likely to influence the SARS-CoV-2 tissue's tropism [24].

Genetic profile of COVID-19 patients

The genetic profile of COVID-19 patients would enable researchers to repurpose medications existing since time immemorial for COVID-19-specific therapeutic approaches while also expediting the creation of innovative and effective antiviral drugs [25]. Patients prone to acute pneumonia are easier to treat when their susceptibility is understood, and their response to medication treatment is continuously monitored [25]. Large-scale genetic screening to identify populations vulnerable to COVID-19 may well be possible by describing the two opposing enzyme processes that occur when the coronavirus enters the body [25].

One aspect that leads to infection is the virus's ability to penetrate cells. On the other hand, the other mechanism defends the body by preventing the virus from infecting its target cells. They stated that genetic differences between individuals alter the strength of these infections and defense mechanisms, with some people inheriting genes that predispose them to infection and others inheriting genes that boost the body's defense mechanism [26]. If a genetic risk score is constructed using the data from the genetic databases analyzed by the researchers, then groups at risk of severe COVID-19 can be identified by specific genetic profiles [27].

Age-related susceptibility of COVID-19

Different physiological systems deteriorate markedly with age, indicating a depletion of coping capacity [28]. Individuals over the age of 60 have been observed to have poorer health outcomes, with mortality rates exceeding 50%. Physical retrogression, disability, and poor health outcomes are critical clinical characteristics of aging [28].

The increased susceptibility may be due to changes in the tissue's physical qualities and immune-senescence, the aging of the immune system. This is because when SARS-CoV-2 gets inside the lung, it attaches and initiates infection. The lung relies on mechanical defenses such as coughing, mucus, and epithelium to build a barrier and mucociliary clearance to clear aspirated or inhaled materials such as pathogenic microorganisms [12,29].

In contrast, it is well established that age contributes to declining levels of these coordinated responses that prevent the deposit and spread of hazardous chemicals and pathogens [10]. As a consequence of persistent viral infections, a decreasing diversity of memory T cells may develop over time due to the monoclonal growth of T cells [10]. If T-cells are exposed to emerging threats such as SARS-CoV-2, immunological exhaustion is one of the problems resulting from reducing the T-cell variety [10,30].

Children are less likely to have thrombosis because of coagulation, unbalance, inherited, or acquired thrombophilia, so there is a low prevalence among them [13]. The more rare disseminated intravascular coagulation (DIC) and microthromboembolic events or cardiac injury in the more severe elderly patients may be partly explained by this fact, strongly substantiating heparin-based anticoagulant treatments in selected severe cases [9,13,29,31]. The severity of COVID-19 increases with advancing age in male and female sexes, possibly due to deregulated immune responses, differences in sex hormones at older ages, or a significant imbalance in coagulation and fibrinolysis with advancing age [28].

Sex-related genetic susceptibility in COVID-19 patients

Not only has the COVID-19 pandemic had tremendous health and economic consequences for multiple countries/regions worldwide, but the disease has also affected various racial/ethnic subpopulations. Extensive genetic studies in

geographically varied populations have revealed significant genetic variation in protein-coding areas, with allele frequencies differing significantly [32]. Past epidemiological data corroborate developing conclusions, demonstrating a sizable, sex-dependent disparity in disease infection and outcome for SARS-CoV-2 disease (COVID-19), as well as for prior SARS [29]. Male-to-female disparities in incidence and death rates were also distinct to early SARS. On the other hand, infants and children have milder symptoms and a better prognosis, regardless of gender, and have a mildly enhanced pro-inflammatory cytokine storm during the early phase of the illness [29].

Meanwhile, the severity of COVID-19 worsens with increasing age in both sexes, possibly due to a dysregulated immune response, a dwindling difference in sex hormones with age, or a significant imbalance in the coagulation/fibrinolytic system and endothelial dysfunction with aging [5,20]. Due to the location of the ACE2 gene on the X-chromosome, the gender-related susceptibility hypothesis may apply, leaving females as likely heterozygotes [33]. Man has a higher conversion rate due to over-expression of ACE2 [33].

However, gonadectomy did not affect male mice's disease outcome, whereas ovariectomy or estrogen receptor antagonists resulted in higher mortality in females following SARS-CoV infection [22,26]. This research supports the notion that females have far stronger innate and adaptive immune responses and are significantly more resistant to viral infections than males. The difference in the copy number of X-linked genes involved in the immune response, the presence of genes associated with disease susceptibility between males and females may explain any other sex advantage [1,6].

In terms of sex hormones, testosterone suppresses innate immune responses. In contrast, estrogens have an immune-suppressive effect at high concentrations and an immune-stimulant effect at low concentrations, with

peculiar functions such as preventing virus replication in selected tissues such as human nasal epithelial cells [29].

Male and female COVID-19 patients have remarkably different incidence and mortality rates, and the disease is connected with preexisting conditions such as cancer and cardiovascular disorders, particularly those with hypertension receiving antihypertensive drugs [26]. ACE2 polymorphisms were more likely to be associated with cardiovascular and pulmonary conditions by altering the angiotensinogen-ACE2 interactions, such as *p.Arg514Gly* in the African/African-American population [2].

The unique but common variants in TMPRSS2 may explain differential genetic susceptibility to COVID19 and risk factors such as cancer and the high-risk group of male patients [29,32]. TMPRSS2 enzyme activity is essential for coronavirus spread and pathogenesis in the infected host [34]. TMPRSS2 polymorphisms in the general population (*rs2070788*, *rs7364083*, *rs9974589*), and especially in sex-related perspective (*rs8134378*), play a vital role in assisting protein priming by attaching the virus to the target cell [35]. COVID-19 genetic polymorphisms ACE and TMPRSS2 combine to further the virus and cellular membrane, occurring when TMPRSS2 cleaves the (S) protein [35].

In SARS-CoV-2, males tend to experience protein fusion more often than females because SARS-CoV-2 men are more susceptible to viruses, while women generally have more excellent immunity to them [36]. A SARS-CoV uses the SARS-CoV reception ACE2 for entry and TMPRSS2 for S protein priming. TMPRSS2 is highly expressed in men's prostates, and its expression is regulated by the androgen receptor [36].

Additionally, estrogens boost the expression of ADAM17 and ADAM10, two putative shedders responsible for numerous ectodomain cleavages in atherosclerosis, implying a protective role for females against cardiovascular events. This mechanism may account for the observed COVID-19 sex discrepancy [29].

Russo et al. [37] reported that low levels of androgens might adequately maintain TMPRSS2 manifestation in women.

COVID-19 susceptibility with ACE2 isoform

Previously, ACE2 encoded five transcripts and a single 805-amino-acid protein. An isoform of ACE2 with a shorter amino acid sequence was recently discovered. Short ACE2 is expressed in the airway epithelium, the primary site of SARS-CoV-2 infection; it is significantly upregulated in response to interferon stimulation and rhinovirus (RV) infection, but not in response to SARS-CoV-2 infection, and it is regulated differently in asthmatic patients. This short isoform lacks SARS-CoV-2 spike glycoprotein high-affinity binding sites, and altogether, short ACE2 may influence host susceptibility to SARS-CoV-2 infection [38].

Yan et al. [28] simulated the structure of the short isoform of ACE2 based on its full-length system determined by cryo-Electron Microscopy (PDB 6M18) better to understand the putative functions of this minor isoform. This demonstrates the extent to which the SARS-CoV-2 binding area in short ACE2 has been lost, with numerous residues previously proven to be critical for viral binding being absent from the short ACE2 sequence. Short ACE2, in particular, lacks two complete areas that interact with the SARS-CoV-2 spike glycoprotein (*aa 30–41* and *aa 82–84*) [28]. This later region is substituted by the N-terminal sequence of short ACE2, which is predicted to create a disordered/helical secondary structure via PEP-fold, compared to the beta-sheet found in long ACE2, altering the third binding interface to Spike. However, short ACE2 preserves the sequences required for ADAM17, TMPRSS11D, and TMPRSS2 cleavage, indicating that it can act as a substrate for these proteases [38].

Interestingly, the ACE2 residue required for substrate selectivity toward Angiotensin II (*Arg514*) is absent from short of ACE2, implying

that it lacks catalytic activity. Altogether, this analysis indicates that short ACE is not capable of high-affinity binding to SARS-CoV-2 spike protein. Still, it may be a substrate for host proteases acting on long ACE2 during viral entry. It can be speculated from the above results that specific individuals could have 100% COVID-19 immunity if they have 100% short ACE2.

Conclusion

Understanding the role of the COVID-19 susceptibility genetic base at the cellular level can help develop vaccines and formulate control measures. The development of vaccines and formulation of control measures for COVID-19 can be from genome sequencing. The sequencing of genomes can identify genetic factors that contribute to immunity or vaccine success and patterns related to the virulence of a disease. Ideally, this information will lead to vaccines with more precise targets, which elicit better immune responses. Comparing the genome sequences of infectious and noninfectious viruses may also explain why certain viruses cause disease. The use of genome manipulation can facilitate the development of attenuated strains or other methods for delivering the desired antigens to stimulate an immune response. On the other hand, an analysis of host diversity and possibly the host's genetic makeup can help identify the optimal immune response. Extensive viral detection and characterization of SARS-CoV-2 can help identify genetic differences and formulate vaccines and antiviral drugs in different world regions.

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Ethical statements

This article does not contain any studies with human participants or animal use.

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