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Review

The Impact of *ACE* and *ACE2* Gene Polymorphisms in Pulmonary Diseases Including COVID-19

IPHIGENIA GINTONI[1,2], MARIA ADAMOPOULOU[2,3] and CHRISTOS YAPIJAKIS[1,2,4]

[1]*Unit of Orofacial Genetics, 1st Department of Pediatrics, National Kapodistrian University of Athens, "Hagia Sophia" Children's Hospital, Athens, Greece;*
[2]*Department of Molecular Genetics, Cephalogenetics Center, Athens, Greece;*
[3]*Department of Biomedical Sciences, University of West Attica, Athens, Greece;*
[4]*University Research Institute of Maternal and Child Health and Precision Medicine, National and Kapodistrian University of Athens, Athens, Greece*

Abstract. *Chronic and acute respiratory diseases pose a major problem for public health worldwide due to the high morbidity and mortality rates, while treatment options remain mostly symptomatic. The renin-angiotensin system (RAS) plays an important role in lung tissue, regulating pulmonary circulation and blood pressure, but also contributing to normal pulmonary function and development. Angiotensin-converting enzyme (ACE) and its homologous angiotensin-converting enzyme 2 (ACE2) are considered to be amongst the main RAS regulators and are highly expressed in the pulmonary vascular endothelium. This review discusses the impact of ACE and ACE2 functional gene polymorphisms on seven major pulmonary diseases, in terms of predisposition, course, and outcome, revealing their potential utility as both genetic markers and biomarkers. The discussed conditions include chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PH), asthma, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), lung cancer and pulmonary sarcoidosis (PS), as well as SARS-CoV-2 viral infection and COVID-19 disease.*

Correspondence to: Associate Professor Christos Yapijakis, DMD, MS, Ph.D., "Cephalogenetics" Center, Philaretou 88, Kallithea 17675, Athens, Greece. Tel: +30 2109595772, e-mail: cyapi@med.uoa.gr

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Chronic respiratory diseases (CRDs) have been among the leading causes of morbidity and mortality around the globe for the last two decades (1-3). Their constantly increasing rates of occurrence may vary both between the genders, but also between different regions and socio-economic backgrounds (4). Nevertheless, the common denominator includes the deterioration of patients' quality of life that can often lead to several years of disability. The main CRDs are chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PH), asthma and lung cancer, with COPD alone being the third leading cause of death worldwide, as reported in 2010 (1, 5, 6).

On the other hand, acute lung diseases with an infectional etiology, pose a significant threat not only to lung health but also to human life (7). A recent great example is the 2019 outbreak of the novel coronavirus strain SARS-CoV-2 in China, causing the extremely infectious disease COVID-19, that led to a global pandemic and to millions of deaths, mainly due to severe respiratory complications (8, 9).

So far, therapeutic approaches are mainly symptomatic, while knowledge on the exact pathogenetic mechanisms for complex lung-diseases remains limited. Consequently, prevention is predominantly based on general lifestyle guidelines, whereas the establishment of *a priori* personalized preventive measures, according to an individual's genetic predisposition, is still in its infancy (1, 5). Nevertheless, there are important known genetic markers that may be utilized for their predictive value.

The renin-angiotensin system (RAS), in addition to its great importance for the overall homeostasis of the body, through the regulation of blood pressure and electrolyte balance, has a strong tissue-specific expression in the respiratory tract and functions both autonomously and

interdependently with its circulating equivalent (10). Due to the system's ability to mediate intrapulmonary blood pressure, inflammation, fibrosis, as well as its key role in lung-cell proliferation and apoptosis, inappropriate function of RAS has been widely associated with lung pathology (11, 12). The most targeted RAS catalytic compound in terms of lung disease is the angiotensin converting enzyme (ACE), while its homologous angiotensin-converting enzyme 2 (ACE2) seems to play a counterbalancing role in blood pressure regulation, but has recently acquired widespread recognition due to its involvement in the entry of SARS-CoV-2 into respiratory tract cells (13, 14).

In light of all the above, in this review we present the associations of the functional polymorphism I/D in the *ACE* gene with the predisposition, pathogenesis and progression of six major respiratory diseases as well as the influence of both *ACE* I/D and several DNA polymorphisms in the *ACE2* gene on susceptibility to SARS-CoV-2 infection, as well as on COVID-19 disease course and outcome.

The Renin-angiotensin System (RAS)

The renin-angiotensin system (RAS) is an endocrine cataract, which is mainly responsible for regulating blood pressure, fluid volume, and electrolyte balance. These functions make it necessary for the maintenance of human body homeostasis and overall health. RAS has a systemic impact on the body through blood circulation, but also exists in a tissue-specific form (tRAS), that functions autonomously in every organ system (15). The latter is critical for the development and vascular function of each organ and it also takes place in local fibrotic and inflammatory responses (16, 17).

The RAS cascade starts with the proteolytic conversion of liver-derived angiotensinogen (AGT) to angiotensin I (Ang I) by active plasma renin (18). On the surface of vascular endothelial cells, angiotensin I is then processed and converted into the vasoactive octapeptide angiotensin II (Ang II) by the angiotensin-converting enzyme (ACE), a dipeptidyl carboxypeptidase predominantly found in lung tissue (15). Although it is important for cellular functions and differentiation, Ang II exerts vasoconstrictive, hypoxic, oxidative, hypertrophic, fibrotic, and inflammatory actions, by binding to its type 1 receptor (AT1R) of the G-protein coupled receptor (GPCR) superfamily (19). Thus, the ACE/AngII/AT1R axis of the renin-angiotensin system is involved in the development of various pathologies (19, 20). In 2000, ACE2, an ACE homologue, was discovered (Figure 1), shedding more light on this system, which is responsible for counteracting the adverse effects of angiotensin II through its proteolytic product, angiotensin (1-7) (Ang 1-7) (21-23). ACE2 acts on two substrates of RAS with different affinity. It cleaves angiotensin I to angiotensin (1-9) which is then converted to the heptapeptide Ang 1-7, by the ACE. At the same time and with higher affinity, it directly hydrolyzes angiotensin II to angiotensin (1-7), hence counterbalancing its levels (Figure 2). Angiotensin (1-7), which is the common result of the above two reactions, binds to Mas receptors (MasR) and therefore, activates signaling pathways that lead to vasodilation and inhibition of cell proliferation, but also accounts for strong anti-inflammatory, anti-fibrosing and anti-oxidative effects (13, 24-26).

Hence, with ACE and ACE2 controlling the "ACE/AngII/AT1R" and "ACE2/Ang 1-7/MasR" axis and, therefore, the quantities of the two antagonistic hormones, both enzymes have been considered to be the main endogenous regulators of the renin-angiotensin system (23, 27).

RAS in Lung Disease: The Involvement of ACE and ACE2

RAS has a strong independent presence in lung tissue, contributing to normal pulmonary function and development (10, 12, 28). The most studied RAS catalytic compound in pulmonary disease is the angiotensin converting enzyme (ACE), a matrix metallopeptidase that is mainly expressed in lung tissue and is responsible for the formation of angiotensin II (Ang II), a biologically active peptide-hormone. Ang II accounts for vasoconstrictive, inflammatory, hypoxia-inducing, and oncogenic actions, *via* its main receptor angiotensin II type 1 receptor (AT1R). ACE is considered to be the controller of the ACE/Ang II/AT1R axis and generally a key mediator of RAS (29-31).

Abnormal fluctuations in its levels in the plasma and tissues can lead to pathological phenomena. More specifically, the Insertion/Deletion (I/D) functional polymorphism of the *ACE* gene may result to elevated levels of the enzyme in the plasma, tissues and the intracellular compartment. Homozygosity for the D allele (DD genotype) leads to about twice the concentration and activity of ACE compared to the homozygosity for the normal I allele (II genotype) (32-34). The I/D polymorphism has been strongly associated with many of the most serious and common lung disorders, including COPD, pulmonary hypertension, asthma, acute lung injury, lung cancer, pulmonary sarcoidosis, and it has recently been shown to influence the disease course of COVID-19, as well as the susceptibility to SARS-CoV-2 infection (35-41).

Another important axis of RAS is the ACE2/Ang 1-7/MasR, which offsets the adverse effects of Ang II by counterbalancing its levels and exerting the opposite effects (42-44). The controller of this axis is the angiotensin-converting enzyme 2 (ACE2), a metalloprotease homologous to ACE. ACE2 is responsible for the formation of angiotensin 1-7 (Ang 1-7), a vasodilating, antioxidative and anti-inflammatory peptide-hormone that acts *via* the Mas receptors (MasR) (13, 45, 46). The transmembrane form of ACE2 has recently acquired widespread recognition due to

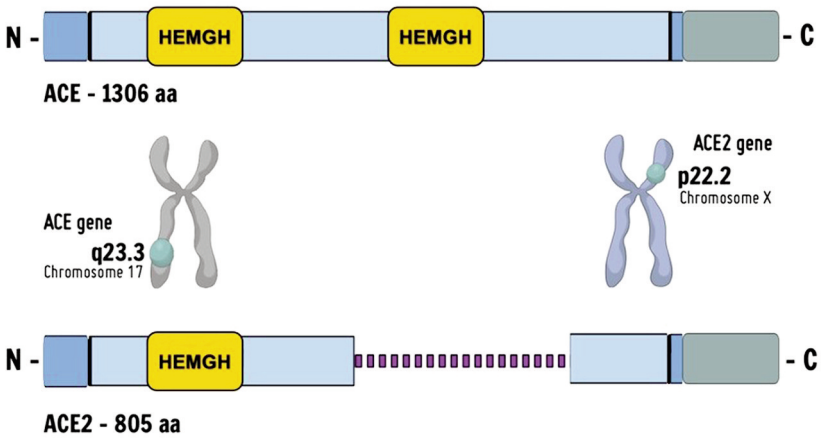

Figure 1. *Representation of the ACE and ACE2 metalloproteases, as well as the location of their genes on chromosomes 17 and X, respectively. Orange indicates the single catalytic domain with the zinc-binding motif (HEMGH) that is common between the two enzymes. HEMG present twice in the amino acid sequence of ACE that cleaves two peptide bonds in the sequence of its substrates angiotensin I (ANG I) and angiotensin 1-9 (ANG 1-9), and only once within the ACE2 sequence, which cleaves one peptide bond on the C-terminus of angiotensin II (ANGII) with high affinity and of its other substrate ANG I with lower affinity.*

its involvement in the entry of SARS-CoV-2 into respiratory tract cells (14) and recently numerous single nucleotide polymorphisms (SNPs) of the *ACE2* gene have been shown to have an impact on both the susceptibility to infection and the outcome of COVID-19 disease (47-50).

Both ACE and ACE2 enzymes are strongly expressed in the pulmonary vascular endothelium. Specifically, the production of 75% of soluble ACE takes place in the endothelial cells of lung capillaries and lung is considered to be the central tissue for ACE-mediated peptide degradation (51, 52). At the same time, lung endothelium is the primary site of the human body in terms of ACE2 concentration and function (26).

Angiotensin II and angiotensin (1-7) receptors are normally expressed in human lungs, indicating the concomitant action of the two opposing RAS axes. In fact, pharmacological inhibition of the ACE/AngII/AT1R axis and the parallel enhancement of ACE2/Ang (1-7)/MasR, are considered therapeutic targets for various serious lung diseases, with particularly encouraging results (12).

Given the system's role in inflammation, fibrosis and cell proliferation, a dysfunctional, poorly regulated RAS has been shown to contribute to the development of major lung diseases such as chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH), asthma, acute lung injury (ALI) and idiopathic pulmonary fibrosis (IPF) (12, 28).

Furthermore, regarding the involvement of the system in pulmonary pathology, the binding of angiotensin II to its type I receptor (AT1R) has been shown to promote the secretion of growth factors favoring cell proliferation, while activating hypoxia-causing protein factors (30, 53). The latter creates active forms of oxygen, resulting in an intense cycle of oxidative stress, a catastrophic condition for the integrity of DNA, as well as for cell and tissue function. The hypoxic, oxidative and hypertrophic environment created by the AngII octapeptide acts favorably on carcinogenesis and the growth of tumors, while providing them with resistance to treatment and increased metastatic potential. Among many types of cancer, RAS has been shown to be highly involved in the pathogenesis of various lung cancer types (29, 30, 54-56).

Adding to the above, RAS seems to be involved in lung disorders of infectious and inflammatory etiology, but also in complications associated with their treatment. In particular, administration of ACE inhibitors leads to up to 47% reduced risk of patients with lung-inflammatory pneumonia, underscoring the pathogenetic role of excessive angiotensin II production. At the same time, in cases of severe disease and possible lung failure where mechanical support is necessary, the levels of both Ang II and its receptor AT1R increase significantly, promoting inflammation that leads to ventilator-induced lung injury (VILI) and posing a critical threat for the patients' health (11).

In terms of viral infection, RAS is significantly implicated in coronavirus infection through the transmembrane form of ACE2, which acts as a gateway to human cells (57). As to most recent coronavirus example of SARS-CoV-2, which causes the respiratory disease COVID-19, ACE2 seems also to protect the lung tissue through the ACE2/Ang 1-7/MasR RAS axis (58).

The importance of the two enzymes in RAS, but also in lung health is undeniable. Thus, it is not surprising that

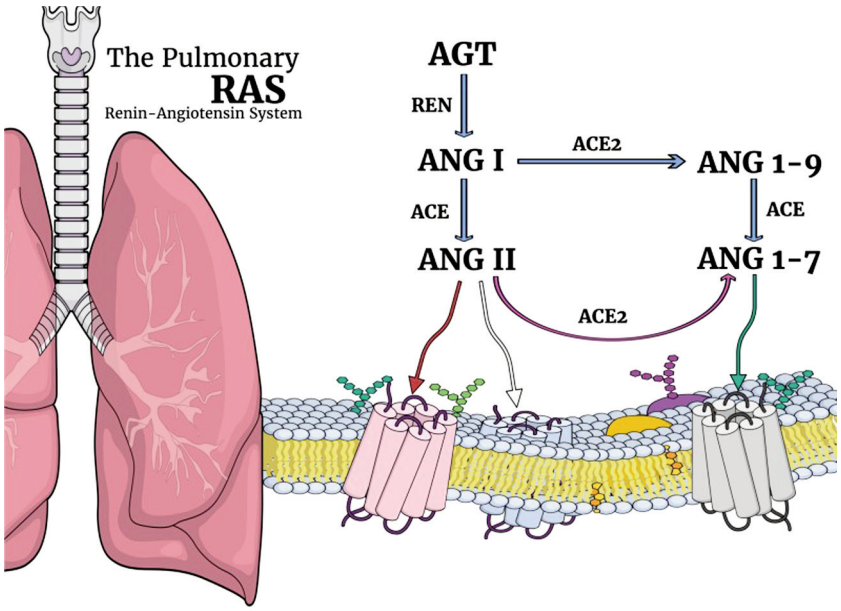

Figure 2. *The renin-angiotensin system (RAS) shows a strong expression in the lung where it functions both independently and in cooperation with its circulating equivalent. The hormonal cascade of RAS starts with the hydrolytic cleavage of the circulating, liver-derived angiotensinogen (AGT) by the protease renin (REN), that results in the formation of the decapeptide angiotensin I (ANG I). ANG I is then cleaved by the matrix metallopeptidase angiotensin-converting enzyme (ACE). The latter results in the formation of the peptide hormone with eight amino acids, angiotensin II (ANG II) the main RAS effector. ANG II by binding to its main receptor AT1R (Angiotensin II Type 1 Receptor) activates several signal transduction pathways and promotes vasoconstriction, as well as hypoxic, oxidative, inflammatory and proliferative events. The above constitute the ACE/ANGII/AT1R axis starting with ACE. The levels and consequently the actions of ANGII are counterbalanced by the activation of the ACE2/ANG1-7/MasR axis that is, respectively, controlled by the angiotensin-converting enzyme 2 (ACE2), an ACE homologue with the exact opposite role. ACE2 cleaves ANGII by hydrolyzing one peptide bond in its C-terminus. The result of this particular reaction is the formation of the heptapeptide hormone angiotensin 1-7 (ANG 1-7), that counterbalances the adverse effects of ANG II. ANG 1-7 gets alternatively proteolysed, also by ACE2, that hydrolyzes its secondary substrate, ANG I, resulting in the production of angiotensin 1-9 molecule that is afterwards cleaved by the ACE into ANG 1-7. ANG 1-7 exerts vasodilative, antioxidant, anti-inflammatory and anti-proliferative effects by binding to the Mas G protein-coupled receptor (MasR).*

abnormal fluctuations in their levels or changes in their functionality can lead to a dysfunctional RAS with pathogenetic dynamics. This is usually a consequence of genetic variability due to the presence of functional polymorphisms or mutations in its key genes (10, 12, 35).

Chronic Obstructive Pulmonary Disease and *ACE* I/D Polymorphism

Chronic obstructive pulmonary disease (COPD) can be described as a heterogeneous set of respiratory disorders that induce bronchoconstriction and airway inflammation with consequent breathing conditions such as emphysema, chronic obstructive bronchitis and respiratory failure (59, 60). Worldwide, COPD poses a great burden to health systems and is considered to be the third leading cause of death (61). The number of patients worldwide is estimated at 300 million, with an approximate 21.3% suffering from disease-related disabilities (62).

Patients with COPD are likely to experience chronic coughing, excessive mucus production, dyspnea, a sensation of tightness in the chest area, as well as frequent respiratory infections (63). Symptoms worsen overtime due to the progressive nature of the disease and can be indicative of its developmental stage and pulmonary function (64, 65). The deterioration of the lung structures that occurs is usually irreversible and so far there is no radical cure. However, symptomatic treatment - mainly focused on bronchodilation- can improve a patient's clinical picture and minimize the need for hospitalization (66).

Decreased oxygen availability (hypoxia) and inflammation are among the disease landmarks and are a common point of reference of renin-angiotensin system disorder. The activation of the system and upcoming phenomena such as oxidative stress and vasoconstriction -mainly caused by angiotensin II- negatively affect the progression of the disease and contribute to the occurrence of parallel cardiovascular complications (67). RAS has not only been reported to affect the disease course,

but is also implicated in COPD pathogenesis (68). The functional I/D polymorphism of the *ACE* gene, that affects ACE plasma and tissue levels, has been broadly studied as to its influence on an individual's susceptibility to develop COPD due to the pathogenetic effects of increased angiotensin II formation in the lung tissue. The available literature is contradictory but several studies have yielded unexpected findings on the association of the polymorphism with the disease. According to a meta-analysis conducted in 2016, that included 2113 patients with chronic obstructive pulmonary disease and 8,796 controls in terms of *ACE* genotype, there is no correlation between a person's genotype for the *ACE* I/D polymorphism and predisposition to the development of the disease (69). The same negative association came from a case-control study in a Turkish population that included 47 COPD patients (70), although another investigation that included a larger sample of the Turkish population showed a significant association between the polymorphism and COPD development (71). In another study that did not show any association between the polymorphism and disease, it appeared that homozygosity for the D allele was associated with lower risk of complications in the course of COPD in male patients (72). In contrast, it has been shown that the same allele can be correlated with endothelial dysfunction in patients with COPD and result in increased capillary permeability due to enhanced ACE activation and Ang II production (73).

In regard to disease course, two studies showed that the presence of allele I seems to reduce the levels of reactive oxygen species (ROS) produced during oxidative stress in COPD (74), while it is strongly associated with stable disease (75). Regarding susceptibility, studies in Asian populations have shown a clear association between the *ACE I/D* polymorphism and an increased risk of developing COPD, presenting the D allele and DD homozygosity as strong molecular markers (35). In fact, when the results of numerous case-control studies were compared between Asian and Caucasian populations, it emerged that the former were predisposed towards COPD pathogenesis by the presence of the D allele and particularly the DD genotype, as opposed to Caucasian populations in which the polymorphism seems to have no significant effect (76, 77).

Finally, a study in a Caucasian population sample alone confirmed the negative correlation, but underscored the relationship between the presence of the D allele and pulmonary arterial pressure (Ppa) in patients with COPD. It appears that the ID and DD genotypes are associated with an increase in mean and systolic pulmonary artery pressure, which follows the pattern of the increase in ACE levels (II<ID<DD) and indirectly influences COPD course (78). The above results are in agreement with those of Ma *et al*., who highlighted the association of the DD genotype with the development of pulmonary hypertension in patients with chronic pulmonary disease (77).

Pulmonary Hypertension and *ACE* I/D Polymorphism

The term "pulmonary hypertension (PH)" applies to five different diseases with the common denominator of elevated mean pulmonary arterial pressure (mPAP), that exceeds 25 mmHg in a resting state (79, 80). PH is a chronic and progressive lung disease that affects approximately 1% of the general population that is associated with an extremely poor prognosis if left untreated (81, 82). A major PH clinical subgroup is pulmonary arterial hypertension (PAH), which is distinct from simple PH due to low pulmonary arterial wedge pressure (PAWP) and elevated vascular resistance (PVR) in the lung circulation (79, 81). PAH progressively results in the destruction of small pulmonary arteries and the survival window from the moment of diagnosis corresponds to a maximum of 5 years, if the appropriate treatment is not provided (83).

RAS is a crucial system for pulmonary artery remodeling and function (84). Thus, it is implicated both in the development and the progression of the disease by regulating cellular proliferation, remodeling of the vascular endothelium and fibrosis that take place in small arteries of the lungs. The ACE/AngII/AT1R axis of the cataract appears to aggravate the pathology through its up-regulation, while the opposing ACE2/Ang1-7/MasR axis represents a promising therapeutic target (12).

Considering the role of RAS in respiratory endothelium, one would expect to see numerous studies regarding the relationship of *ACE* variability and pulmonary hypertension. However, in most of the available literature, this relationship has been explored by treating pulmonary hypertension as part of the clinical picture of other diseases. A typical example is a study that showed a strong association between the DD genotype of the *ACE* I/D polymorphism and increased mean and systolic Ppa rates and the development of pulmonary hypertension in patients with COPD (77, 78). Another investigation that also considered PH as a COPD characteristic examined the genetic interaction between *ACE* I/D and *eNOS* G894T polymorphisms and reported that the *ACE* I allele, when combined with the *eNOS* T allele, promotes the course of the disease by increasing vasodilation and reducing AngII-induced vasoconstriction (85).

Beyond the spectrum of COPD, pulmonary hypertension is also considered to be one of the complications of atrial septal defect (ASD). However, *ACE* I/D polymorphism does not appear to have an impact on the clinical progression of PH/PAH in ASD patients (86).

Considering pulmonary hypertension as an independent condition, the first study to highlight the influence of the I/D polymorphism of the *ACE* gene on its pathogenesis and clinical picture was performed as early as 1995. It turned out that the cardiac output (CO) of patients with the genotypes II and ID was significantly lower compared to those with DD, which in

turn correlated with severe PH development (36). Despite evidence that the D allele is associated with the pathogenesis of pulmonary hypertension due to elevated enzyme levels, the II genotype also appears to be strongly associated with one type of PH. More specifically, homozygosity for the I allele is 3 times more common in individuals with high altitude PH compared to normal controls (87).

In regards to genetic interactions, coexistence of the *ACE* I/D and *AGT* M235T polymorphisms may be associated with persistent PH in neonates suffering from congenital diaphragmatic hernia (88), while the interaction of I/D and the C825T polymorphism of the G-protein β3 subunit (*GNB3*) gene appears to affect the efficacy of pharmacological treatment with PDE-5 inhibitors for PH. More specifically, the presence of the D allele combined with the TT genotype of the *GNB3* C825T polymorphism predisposes patients to accelerated clinical PH worsening compared to patients carrying the II/TT genotypes, in whom the progression of the disease is delayed (89).

Asthma and *ACE* I/D Polymorphism

The term "asthma" represents a spectrum of chronic pulmonary conditions that includes numerous phenotypes with the common hallmark of airway inflammation (90, 91). Globally, asthma is one of the most common diseases affecting around 330 million individuals and 20 million in the United States alone (12, 92). It affects both children and adults of all ages and its pathological etiology lies in an interaction of genetic and environmental factors (93, 94). The disease has been a worldwide concern for the last 25 years, since diagnosed cases have significantly increased (95, 96), but fortunately death rates have been significantly reduced (97). Although pharmacotherapy has made asthma a manageable condition (98), many cases develop severe and persistent asthmatic conditions, which cannot be easily controlled even by inhalation of high doses of corticosteroids (99-101).

Although the exact role of RAS in asthma still remains foggy, the levels of its inflammatory effector angiotensin II appear to be elevated in several cases of acute, severe asthma (102). ACE has been linked to asthma pathogenesis alongside to other pulmonary diseases, while induced activation of its main competitor ACE2 seems to have a protective effect against asthma in animal models (103) and the enhancement of the ACE2/Ang1-7/MasR axis that counteracts Ang II-induced inflammation has been considered as a therapeutic approach (12).

The *ACE* I/D polymorphism has been extensively studied worldwide for its implication in the predisposition to asthma and the severity of the symptoms. The results seem to indicate a consensus in most populations, although there is no shortage of unexpected findings in some countries. Admittedly, the functional D allele of the polymorphism, which increases the levels of the enzyme at the tissue and plasma level, is strongly associated with high asthma predisposition (37, 39, 104-106). In fact, it appears that individuals carrying the D allele in a homozygous state are of approximately 60% higher risk of developing the disease than heterozygous individuals and II genotype carriers (37). As to the impact on the disease's symptomatology, I/D does not seem to affect asthma severity although it appears to be implicated to its pathogenesis (106).

The majority of studies on the positive correlation between the *ACE* I/D variation and asthma pathogenesis come from China, while studies on populations from certain other countries appear to have produced contradicting results. More specifically, case-control studies on population samples from South Korea, Egypt and Japan conclude that this particular *ACE* polymorphism is not associated with asthma development (107-109). A relevant study in Turkey, in which researchers also measured enzyme activity in the participating subjects, did not show significant differences in allele distribution between patients and controls, but the ACE activity was significantly increased in patients with asthma (110). One of the most interesting findings was that of a case-control study in Pakistan which included 330 asthma cases and showed that the I allele was significantly increased in patients with asthma compared to healthy controls and that the D allele appears to have a protective role against asthma pathogenesis (111).

The findings of childhood asthma research, like those of adult asthma, seem to be ambiguous among different countries. Chinese studies demonstrate a positive association between the DD genotype and the elevated susceptibility of children to asthma (112, 113), as well as recurrent wheezing in infancy and early childhood (114). On the contrary, Turkish children do not seem to be affected by their *ACE* I/D genotype in terms of asthma predisposition (115).

Acute Lung Injury, Acute Respiratory Distress Syndrome and *ACE* I/D Polymorphism

Acute lung injury (ALI) and its worse form, acute respiratory distress syndrome (ARDS) consist of a set of pathological lung modifications that occur from pulmonary destructive events, such as pneumonia, sepsis, pulmonary trauma, viral infections and various other situations or diseases (116-118). Such phenomena deteriorate the vascular endothelium and the alveolar epithelium (119) resulting in loss of function of the corresponding cells due to excessive inflammation, hypoxemia and eventually respiratory failure (120, 121). Both ALI and ARDS, due to the severe nature of their manifestations, are characterized by high mortality rates, despite the available treatment options that aim to optimize the diseases' outcome (116, 122).

The imbalance between the ACE/AngII/AT1R and the ACE2/Ang1-7/MasR axes in a dysfunctional RAS may lead to both the pathogenesis and the unfavorable progression of

ALI and ARDS due to elevated concentrations of angiotensin II and insufficient control of its inflammatory and fibrotic actions (12, 118). On the other hand, over-expression of *ACE2* that leads to the elevation of angiotensin 1-7 levels acts against lung injury, and exogenous ACE2 administration seems to improve ALI symptoms in mice models (123).

Acute lung injury, when genetically predisposed, can be a fatal pathological modification for a patient. Thus, the available literature that focuses on the genetic factors that predispose an individual to this complication or shed light on the prognosis of its progression can be of paramount importance. According to the findings of several studies, the I/D polymorphism of the *ACE* gene can be used as a prognostic factor for ALI, but can also be predictive of its outcome, since homozygotes for the functional D allele are prone to higher mortality risk compared to insertion allele (I) carriers (124). Three other studies have reported the correlation of the D allele and especially the DD genotype, with greater mortality rates (38, 125, 126). Two of these underpin that the risk of a fatal ALI/ARDS outcome appears to be increased in individuals of Asian origin (38, 126). In terms of predisposition, a meta-analysis of 22 relevant studies has shown a highly significant association between the Insertion/Deletion polymorphism and the risk for ALI followed by ARDS in Caucasian adults and children (38).

Lung Cancer and *ACE* I/D Polymorphism

Nowadays, lung cancer that arises from lung-tissue cells, is the leading cause of mortality worldwide (127, 128). Lung cancer is a complex, multi-subtype disease, which develops due to the unfortunate interaction of the genome with certain environmental factors (129). The predominant environmental risk factor for lung cancer development has been proved to be the inhalation of tobacco smoke, a practice that increases the risk for disease by 5 to 10 ten times (130). Besides smoking, exposure to certain chemicals, chronic lung conditions, air pollution, family history and lifestyle choices comprise an additional set of risk factors for lung cancer pathogenesis (131, 132).

Despite the leaps and bounds in available therapeutic strategies over the last decade, given that the symptoms present at an advanced stage of the disease, several cases are difficult to treat or even considered incurable. Thus, early diagnosis at an initial stage is the key to ensuring maximum effectiveness of treatment (133-135).

Angiotensin II of the ACE/AngII/AT1R axis bridges RAS with all cancer types, including that of the lung. The binding of the hormone to its type 1 receptor (AT1R) activates certain signal transduction pathways that result in the expression of growth factors and increased cell proliferation and angiogenesis in the tumor microenvironment, but also in hypoxic conditions and oxidative stress due to the formation of ROS. All the above create a "tumor-friendly" environment in lung tissue that promotes the growth of the cancerous mass, increases its metastatic potential and resistance to treatment, mainly in the hypoxic areas of the tumor (29, 30, 53).

The relationship of AngII to cancer is clear through its oncogenic and inflammatory properties that are exerted *via* the ACE/AngII/AT1R axis of RAS. However, most studies regarding the I/D polymorphism of the *ACE* gene that increases the levels of its converting enzyme do not present the expected results. Despite the data indicating that homozygotes for the D allele are approximately twice as likely to develop lung cancer (136), meta-analyses and case-control studies in populations from Europe and Asia have failed to find a significant association between the polymorphic genotypes and lung carcinogenesis (136-141). However, a subgroup analysis in a case-control study in 2012 revealed a significantly high risk for squamous non-small cell lung carcinoma (NSCLC) in Croatians who carry the DD genotypic variant (137). Those findings were partially supported by a study, which demonstrated a 2.29-fold increased risk of NSCLC development in association to the ID genotype (142).

Contrary to all of the above, a Turkish study showed a statistically significant association between the II genotype and lung cancer pathogenesis and suggested its potential role as a possible risk factor (143). The existence of the I allele in an individual's genotype (II or ID) has also been highly correlated with increased risk of nicotine dependence through tobacco smoking in male lung cancer patients who have an approximately 5-fold higher risk compared to DD carriers (144).

SARS-CoV-2 Infection and COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus strain that emerged in the city Wuhan of China in late 2019 and had spread to such extend by March 2020 that the World Health Organization (WHO) declared a state of global pandemic (145, 146). SARS-CoV-2 is an extremely transmissible, single-stranded RNA virus that causes the coronavirus disease 19 (COVID-19) that mostly and severely manifests in the respiratory tract. The clinical picture of COVID-19 ranges from influenza-like symptoms and shortness of breath, to viral pneumonia and complications such as ARDS, respiratory failure and even death of immune-compromised individuals (147-152). The immune system's response to SARS-CoV-2 infection, both locally and systemically, triggers intense inflammatory reactions that can lead to pathological tissue destruction (153). RAS, in addition to its critical role in inflammation, is at the forefront of SARS-CoV-2 infection due to its component ACE2, the transmembrane form of which is responsible for the viral entry in the cells of the human respiratory epithelium (154). Specifically, the spike (S) protein on the virus surface is

responsible for cell-membrane penetration though its interaction with membrane bound ACE2 (147, 155). Furthermore, SARS-CoV-2 infection triggers the system's activation, accompanied by an imbalance between its two main axes, ACE/AngII/AT1R and ACE2/Ang1-7/MasR. Since the S protein of the virus binds to ACE2 with high affinity, it functions as an antagonist for its main substrate, angiotensin II and disrupts the enzyme's normal function. The latter results in the down-regulation of the protective ACE2/Ang1-7/MasR axis and in a pathological ACE/AngII/AT1R up-regulation that exerts vasoconstrictive and inflammatory effects that negatively affect the progression of the disease (156-158).

Given the significance of the two enzymes and their implication in SARS-CoV-2 infection and COVID-19, several studies have shown that *ACE* and *ACE2* genetic variations can influence both disease progression and clinical outcome, but also the susceptibility to the initial infection.

ACE I/D Polymorphism in SARS-CoV-2 Infection and COVID-19

The *ACE I/D* polymorphism, which affects enzyme's levels and consequently the ACE/AngII/AT1R axis' function, also shows many correlations with SARS-CoV-2 infection and appears to influence the outcome of COVID-19 disease. More specifically, the II genotype that is associated with the least ACE plasma levels compared to the ID and DD variants, is the most prevalent genotype among asymptomatic COVID-19 cases. On the contrary, the DD genotype is the predominant genotypic variant among COVID-19 patients who present severe disease symptomatology (159). The DD genotypic frequency has been found to be significantly increased among the elderly, which is the most vulnerable subgroup of the European population and it has also been suggested that it may increase the risk for COVID-19-related mortality (160).

In addition to vulnerable groups, from 2020 to date, it has been repeatedly demonstrated that the D allele can be indicative of both the severity of the disease and the number of deaths nationwide. More specifically, the DD genotype appears to increase SARS-CoV-2 infection susceptibility, as well as COVID-19 severity and mortality. Moreover, DD may be a potential risk factor for intense, possibly fatal complications such as acute pulmonary embolism in SARS-CoV-2-induced pneumonia (41, 161-163). In contrast, the presence of the I allele, either in a homozygous or heterozygous state, appears to be associated with decreased infection and mortality rates, as well with the rates of recovery (164-166). In fact, the frequency of the II genotype is more prevalent in countries with fewer COVID-19 cases and comparatively low related mortality. A typical example of this correlation is that Asians, which show higher II populational genotypic frequency compared to Europeans and Africans, have lower COVID-19-related morbidity and mortality rates (165, 166).

ACE2 Gene Polymorphisms in SARS-CoV-2 Infection and COVID-19

The genetic variability of the *ACE2* gene is currently under investigation in regard to the effect of certain polymorphic alleles on infection, and the course and outcome of COVID-19. The differences in the frequency of certain *ACE2* variants among different populations are possible to be indicative of their epidemiological status (149, 167). The main focus is on functional polymorphisms that affect gene expression, as well as those that impose structural changes in the final protein product. The latter can affect the interactions of ACE with the spike glycoprotein on the surface of the SARS-CoV-2 viral strain (168-170). The genetic variants can affect aspects of COVID-19 either by genetic interactions, or due to certain deleterious alleles (171).

One of the most studied functional polymorphisms of the *ACE2* gene is the rs2285666 or otherwise the G8790A variation. The A polymorphic allele causes up to a 50% increase in gene expression when in homozygosity, in comparison to the G allele (48, 172). Despite certain studies suggesting that increased gene expression increases the risk of infection (173) or that the G8790A polymorphism is not associated with any aspect of COVID-19 (174), a recent study revealed that the GG genotype, which is associated with lower expression levels, is strongly associated with an approximately 2-fold in the risk of viral infection and a 3-fold increased risk for severe disease or even a fatal outcome (175). In contrast, the A allele, which is characterized by enhanced gene expression and enzyme activity, has been associated with decreased risk of infection and COVID-19-related death (47). Examination of the incidence of variants in differed populations indicated that the A allele appears to have a lower incidence in severely affected populations, such as Italians and other Europeans, compared to Asians that appear to have a higher A allele frequency and have presented a better epidemiological picture (48).

Another example of a functional *ACE2* polymorphic variant which decreases its expression is the rs5934250. This polymorphism appears to have an increased frequency in the populations of Europe and Africa. On the other hand, the polymorphisms rs182366225 and rs2097723 that can possibly increase *ACE2* gene expression, are more prevalent in East Asian populations (49). Other polymorphisms associated with an increased predisposition to this viral infection are rs4646114 and rs4646115, which are of high prevalence in the African continent, as opposed to rs536092258 and rs370596467, which provide a favorable response to infection and predominate in South and East Asia (50).

Pulmonary Sarcoidosis and *ACE I/D* Polymorphism

Sarcoidosis is a granulomatous disease of unclear etiology that globally affects individuals in the age range of 20-60 years (176). Although any organ-system in the body can be affected, sarcoidosis mostly occurs in the respiratory system, specifically in the lung tissue (177). Pulmonary sarcoidosis (PS) presents various clinical phenotypes and its severity can range from asymptomatic to fatal, due to disease complications, including respiratory failure (177-178). The diagnosis of pulmonary sarcoidosis is based on the exclusion of other conditions and still remains complicated (179). The non-specific nature of the symptoms often confuses healthcare professionals and leads to misdiagnosis of PS as bronchitis or asthma. Therefore, PS patients are delayed in receiving final diagnosis and appropriate medical care (180-182).

Being a granulomatous condition, it has been shown that ACE is expressed in the epithelium of sarcoidosis granulomas and that soluble ACE concentrations can be indicative of the granuloma load of a PS patient's body, as well as a useful tool to monitor disease course (182, 183). In fact, ACE activity was apparently increased in patients with active sarcoidosis and returned to normal after symptomatic treatment with corticosteroids (184). Fluctuations in ACE levels due to genetic variation can affect a person's susceptibility to PS and could influence the disease course too.

The number of available studies is not large regarding the effect of the *ACE I/D* polymorphism on the susceptibility and the course of the disease. The results seem to be contradictory, although there is significant evidence supporting the possible role of the polymorphism, especially of the D allele, in the proinflammatory stages of the condition (185).

A meta-analysis of 18 studies including 1626 patients concluded that the carriers of the DD genotype have a significantly higher risk for sarcoidosis development, underpinning the role of increased ACE levels in its pathogenesis (40). These results concur with those of an Iranian case-control study that demonstrated the possible use of the ID and DD genotypes as a predictive factor for sarcoidosis development (186). Moreover, a Swedish study reported that the ACE levels appear to be significantly elevated in sarcoidosis patients in comparison with a healthy control group and that the DD genotype presented with higher frequency in patients suffering from auto-immune manifestations of the disease and seems to increase sarcoidosis susceptibility (187).

On the other hand, some studies in Europe present some contradictory findings. More specifically, the I/D polymorphism does not appear to play a role in either the predisposition or the severity and clinical course of sarcoidosis lung disease in UK and Chez populations (188), while the DD and ID variants might be predictive of predisposition but not disease development in Slovenians (189). Finally, a Japanese study reported interesting findings that associate the II genotype with great bronchial responsiveness but also with increased cough in a sarcoidosis patient (190).

Discussion

The renin-angiotensin system has a strong presence in the respiratory system mainly in the lung tissue, regulating pulmonary circulation and blood pressure, as well as lung development and function (10, 12, 28). RAS also plays a role in local inflammatory, oxidative, and fibrotic events and can sometimes contribute into creating a fertile soil for carcinogenesis, due to the adverse effects of the protein hormone angiotensin II, which is formed by the hydrolytic action of the ACE and counterbalanced by ACE2 and its product Ang 1-7 (13, 25, 26, 42, 43, 54).

ACE and ACE2 are considered to be amongst the main RAS regulators and the quantitative imbalance between them may lead to pathological manifestations (23, 27). Moreover, ACE2 acts as gateway for coronavirus strains to enter the cells of the respiratory epithelium, including the novel SARS-CoV-2 that causes the COVID-19 disease (14). Given the importance of the two enzymes for the function of RAS, as well as their bold presence in lung tissue, in this review we focused on the role of functional polymorphisms of the *ACE* and *ACE2* genes in major lung disorders, in terms of predisposition, as well as disease course and outcome. The polymorphisms of interest were the Insertion/Deletion (I/D) variation of the *ACE* gene, where the D allele increases the levels of the enzyme in plasma and tissue, as well as some single nucleotide polymorphisms (SNPs) of *ACE2* gene that also have a functional effect on its expression. We focused on a set of seven main lung diseases including chronic obstructive pulmonary disease (COPD), pulmonary hypertension (PH), asthma, acute lung injury (ALI), lung cancer and pulmonary sarcoidosis (PS) as to the *ACE* I/D polymorphism and SARS-CoV-2 viral infection and COVID-19 disease as to both *ACE* I/D and a number of *ACE2* SNPs.

COPD, one of the predominant mortality causes worldwide, has been extensively studied in relation to RAS system and the *ACE* I/D polymorphism in particular. There is relative heterogeneity in the results of meta-analyses and case-control studies among different populations as to the association of I/D with the risk of developing the disease (69-73). However, it has been repeatedly reported that the presence of the D allele, either in homozygous (DD) or heterozygous (ID) state, can predispose Asian populations to COPD pathogenesis, in contrast to Caucasians who do not appear to be correspondingly affected (76, 77). In addition, the presence of the D variant seems to positively affect COPD progression (74, 75, 78), as well as to be highly associated with the development of PH, as a parallel COPD manifestation (77, 78).

As to PH, the DD genotype is strongly associated with severe PH development (36), while the II genotype has been interestingly correlated with a 3-fold increased risk for high altitude PH (87). Genetic interactions between the *ACE* I/D and other gene variants such as *eNOS* G894T, *AGT* M235T and *GNB3* C825T also seem play a significant role in PH (85, 88, 89), with the *ACE* I/D and *AGT* M235T interaction being associated with occurrence of persistent PH in neonates, in the presence of congenital diaphragmatic hernia (88).

In the field of asthma, a large number of studies, mainly in Chinese, correlates the D allele with its pathogenesis (37, 39, 104-106, 112-114), underpinning the fact that individuals carrying the DD genotype are at up to a 60% higher risk of asthma development (37). On the other hand, studies in South Korea, Egypt, Japan and Turkey agree that *ACE* I/D is not associated with asthma development (107-109, 115), while within the Pakistani population the I allele unexpectedly appears to be a predisposing factor and the D allele a possible protective trait (111).

The I/D polymorphism also appears to be prognostic as to the occurrence and outcome of acute lung injury, with the DD genotype being strongly correlated to ALI-related mortality (38, 124-126), mainly in Asian populations (38, 126), while it increases the risk for ALI, followed by ARDS occurrence in Caucasians (38).

While angiotensin II promotes oncogenic effects, studies in both Europe and Asia on the effect of the *ACE* I/D polymorphism on the pathogenesis of lung cancer show lack of association (136-141). Association between lung cancer risk and the D allele seems to exist for the category of non-small cell carcinoma (NSCC) in Europeans (137, 142). On the contrary, the II genotype has been implicated in the risk of lung carcinogenesis in Turks (143), while the presence of the I allele has been associated with nicotine dependence in male lung cancer patients (144). Interestingly, although the *ACE* DD genotype has been strongly associated with sarcoidosis in general (40), the findings regarding its pulmonary manifestations show enormous heterogeneity between studies between populations of different countries and continents, failing to result in a unanimous or inclusive conclusion (186-190).

Finally, in terms of viral infection and specifically the new coronavirus strain SARS-CoV-2 that causes the COVID-19 disease, the picture is much clearer. As to the *ACE* I/D variation, the II genotype is the most common among asymptomatic cases, whereas the DD genotype has been highly associated with increased COVID-19-related severity and mortality, as well as higher risk of initial infection. In fact, II and DD nationwide genotypic frequencies may be indicative of a country's epidemiological status (41, 159, 160-166).

ACE2 polymorphisms, such as rs2285666, rs182366225, rs2097723, rs536092258 and rs370596467 that increase its expression appear to be associated with a reduced risk of infection and death due to COVID-19, with high frequencies of the corresponding alleles in regions with a relatively better epidemiological picture (47-50). In contrast, *ACE2* polymorphisms such as rs4646114 and rs4646115, as well as the G allele of rs2285666 (G8790A) that corresponds to lower ACE2 levels compared to the A allele, appear to predominate in areas that have been severely affected such as Africa and European countries including Italy (48, 50).

In conclusion, the aggregated findings of this literature research shed some light on the role of polymorphic traits in the genes of the two major RAS mediators, ACE and ACE2, in the predisposition, development and outcome of severe lung diseases affecting millions of individuals worldwide, revealing their potential utility as both genetic markers and biomarkers. Such molecular biomarkers are needed since the majority of lung diseases are complex and difficult to diagnose in early stages, therefore patients do not have timely access to appropriate medical care and consequently the disease progresses silently and tissue damage becomes usually irreversible. The importance of easily diagnosing as well as preventing severe lung diseases became obvious when an infectious disease such as COVID-19 changed the world in a couple of months.

Mounting research findings underline the significance of a normally functioning and balanced RAS, not only for maintaining health and homeostasis but also to ensure the best possible response of the body in case of lung disease. Findings on the involvement of RAS in pathologies outside the cardiovascular spectrum illustrate the fact that research extending beyond obvious target systems may reveal causes of conditions which so far fall into the category of "unclear" etiology and are treated symptomatically. Therefore, the continuation and extension of such studies may be opening new horizons for alternative and more targeted pharmacological research.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Iphigenia Gintoni performed the literature research, prepared the first draft and drew the figures; Maria Adamopoulou performed critical text revision; Christos Yapijakis was responsible for the overall development of the work and the final draft of the manuscript.

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