Review/Metaanalysis

Genetic Polymorphism of the Angiotensin-Converting Enzyme in Bronchial Asthma

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Abstract.

Background: Bronchial asthma (BA) is among the most prevalent chronic inflammatory disorders of the lung airways, and it has become clear that a combination of genetic predisposition and environmental factors plays a critical role in its pathogenesis. ***Objective:*** The correlation of the angiotensin-converting enzyme (ACE) insertion/deletion polymorphism and other factors with risk for bronchial asthma development was assessed. ***Materials and Methods:*** Online literature search was conducted to identify the most relevant studies. ***Results and Discussion*:** The ACE insertion/deletion (I/D) gene polymorphism, correlating with cellular and circulating ACE concentration, may play a critical role in BA pathogenesis and has been a focus of numerous epidemiologic studies; however, the results are currently inconclusive. The contradictions in the literature between research groups on the role of ACE alleles and genotypes can be explained by genetic variation and multifactorial causes of BA. ***Conclusion:*** This literature review demonstrates that the ACE I/D polymorphism might be related to the risk of bronchial asthma and can become a useful tool in designing effective treatment approaches.

Keywords: bronchial asthma; genetic factors; ACE gene polymorphism

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Introduction

Bronchial asthma (BA) is among the most common chronic inflammatory disorders of the bronchial airways, which gradually results in increased contractibility of the surrounding smooth muscles and deterioration of pulmonary function[1,2,3]. The US Center of Disease Control and Prevention estimates that 235 million people worldwide currently suffer from BA, including 6 million children[1].

The World Health Organization (WHO) performed the largest epidemiologic survey to date evaluating BA prevalence in adults, which covered 70 countries[4]. The data analysis assessed the prevalence of self-reported doctor diagnosed asthma, clinical/treated asthma, and wheezing, with the global prevalence rates estimated at 4.3, 4.5, and 8.6%, respectively. Corresponding numbers in Ukraine were 2.77, 2.90, and 11.13%, respectively. However, a recent report by Ukrainian authorities found that the prevalence of "doctor diagnosed asthma" was 12.5 per 1000 persons, and the prevalence of "wheezing

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symptoms" - 74.4 per 1000 in Ukraine, suggesting that the WHO's survey likely underreported BA at least in Ukraine[5]. An international, multicentered, cross-sectional study of childhood asthma found a relatively low prevalence of BA in Ukrainian children aged 7–13, which also suggests underdiagnosis of BA in Ukraine, especially in rural areas[6]. The numbers for Ukraine were as follows: BA diagnosis (rural vs urban: 1.4 %, vs. 2.1 %); spastic bronchitis (rural vs urban: 7.5 % vs 6.5 %;); chest wheeze in the last year (rural vs urban: 11.5 % vs 13.0 %); and the ratio of current wheeze: BA diagnosis (rural: 17.3:1 vs urban: 7.3:1).

BA negatively affects patients' quality of life, their families, and the community by contributing to work and school days loss, frequent emergency visits and hospitalizations, and increase in mortality[1, 5]. Globally, BA is currently ranked 16th among the leading causes of years lived with disability and 28th among the leading causes of disease burden, as calculated by disability-adjusted life years (DALYs). In 2013, the WHO estimated that 25 billion DALYs are lost every year because of asthma[7]; of this, 5.2 billion DALYs are lost within the EU alone. The total annual monetary loss due to BA in Europe is estimated to be €17.7 billion[8].

Though BA prevalence is higher in high income countries, most asthma-related mortality occurs in low and middle income countries, possibly due to health care quality. For the past 40 years, the prevalence of BA in developing countries has been increasing steadily by 50% per decade and now accounts to as many as 250,000 deaths each year[1]. Rapid urbanization in developing countries, among other reasons, may be behind the increasing prevalence of BA, since it contributes to air pollution, declined sports activities, overpopulation, and decreased stress resistance. According to Nugmanova et al., over 80% of all BA-related deaths now take place in low and lower-middle income countries, where BA is often misdiagnosed and undertreated[5].

During COVID-19 pandemic, when the outcomes and long-term consequences of an infection considerably vary between individuals[9, 10], BA as a heterogeneous clinical syndrome that includes airway inflammation, bronchial hyperresponsiveness, and variable expiratory airfow limitation can be accounted as comorbidity which may worsen the outcomes of COVID-19 infection and increase the risks of admission to intensive care unit[11]. Recently, few studies suggested possible non-harmful effects of BA on the clinical outcomes of COVID-19[12, 13]. Allergic, antibacterial, and antiviral responses include two different arms in the immune system, which are reciprocally operating, involving an extensive regulatory immunity network. It is possible, as in other viral infections, that a predominance of type 2 cytokines might lessen the accumulation of proinflammatory cytokines in the pathogenesis of COVID-19. Moreover, controlled allergen exposures and respiratory allergy are associated with significant reductions in the expression of angiotensin-converting enzyme 2 (ACE2) receptor, which is the entry receptor for SARS-CoV-2. Type I interferons can upregulate ACE2 expression, and the deficient interferon responses in BA patients may reduce the SARS-CoV-2 invasion by limiting the ACE2 expression on the target cells [14].

Although the exact etiology of BA stays uncertain, it became evident that a combination of genetic predisposition and environmental exposures are involved in its pathogenesis[15-20]. Genetic factors contributing to BA appear as a result of complex patterns in haplotype combinations of polymorphic genes. Variation in different groups of genes may influence the development of atopic sensibilization, while other genetic changes contribute as the disorder progresses. As of today, more than 50 different genes have been associated with the development and progression of BA[21, 22]. Chromosomal regions carrying BA susceptibility genes include 6p22.3-p21.1 (bronchial hyperactivity), 5q11.2-q14.3 and 6pter-p22.3 (total IgE levels), 3p22.1-q22.1, and 17p12-q24.3 (positive skin test). Identification of BA susceptibility genes contributing to asthma pathogenesis and treatment response is the first step towards the development of personalized medicine [23, 24]. To summarize, researching BA-linked gene polymorphisms can help to clarify heterogeneity of the disease and estimate its severity[25], which in turn will aid in developing an appropriate treatment corresponding to the patient's unique asthma pathogenesis.

Objective: to analyze the published data on the genetic preconditions of bronchial asthma and the possible role of ACE gene polymorphism in its development.

Research Methods

We searched PubMed and Google scholar databases for publications including the following keywords: Bronchial Asthma Patients, Genetic Factors, ACE Gene Polymorphism, Randomized Controlled or Clinical Trials, Systematic Reviews; a total of 45 papers were retrieved and analyzed.

Results and Discussion

Genes controlling the pathogenesis of BA are generally categorized as major genes and modifier genes, and their interaction defines asthma clinical features. Modifier genes usually predispose to the development of corresponding diseases and include detoxification system genes, membrane receptors genes, as well as trigger genes, which act as shunts in the cascade of vital biochemical reactions[26].

Among the numerous genes involved in the pathogenesis of BA, Smirnova et al.[27] discern the following five groups: 1) Genes encoding antigen recognition factors and humoral immune response, such as interleukin genes (IL4, IL5, IL9, IL13), mast cell growth factor (MGF), genes of the main histocompatibility complex (HLAB, HLADR), , and α-subunit of antigenic T-receptor (TCRA); 2) Genes encoding for inflammation mediators, chemokines and intercellular adhesion molecules, including leukotriene-C4 synthase (LTC4S), 38 platelet activating factor acetyl hydrolase (PAFAH), nitric oxide synthase (NOS1, NOS2, NOS3), arachidonate-5-lipoxygenase (ALOX5), histamine releasing factor (HRF) and others; 3) Genes encoding for the receptors binding to external ligand molecules on target cells, such as α-chain of the IL4 receptor (IL4RA), α-chain of the IL5 receptor (IL5RA), glucocorticoid receptor (GRL), β2-adrenergic receptor (ADRB2), β-chain of high-affinity immunoglobulin E receptor (FCER1B), and serotonin receptor (HTR2A); 4) Genes encoding intracellular signaling molecules and transcription factors including JAK family tyrosine kinase 1 (JAK1) and tyrosine kinase (JAK3), signal transducer and transcription activator 6 (STAT6), β-subunit of nuclear transcription factor Y (NFYB), and nuclear factor κB subunit 1 (NFKB1); 5) Other genes, such as xenobiotic biotransformation genes NAT2, CYP1A, GSTT1, GSTM1.

A 2008 review by Vercelli suggested a useful classification of BA susceptibility factors[28]: a) triggers of the immune response (CD14, IL10, STAT3, MHC class II molecules); b) regulators of the T helper 2 (Th2) differentiation (IL12B, IL4, IL13, STAT6, IL4RA); c) factors associated with epithelial organization and function (CCL5, FLG, SPINK5, GSDML); and d) factors linked to lung function, airway remodeling and BA severity (ADRB2, ADAM33, DPP10, PHF11).

Since BA is a multi-complex chronic disorder characterized by inflammation of airway mucosa, which is influenced by a number cytokines, it has been suggested that clinical symptoms in BA reflect an imbalance in pro- and anti-inflammatory cytokine levels. It was found that the largest segment of publications consists of research on the relationship between cytokine polymorphism and BA. However, while some research groups demonstrate positive association of certain cytokine polymorphisms with BA, others report contradictory data. For instance, Trajkov et al. examined the association of 22 cytokine gene polymorphisms in the Macedonian population with BA2[9] and found protective cytokine polymorphisms for seven cytokine genotypes (IL4 -1098/G:T, TNFα -238/G:G, IL2 -330/G:T, IL4 -590/C:T, IFNγ utr5644/A:T, IL1β +3962/C:T, IL10 -1082/A:G), six cytokine diplotypes, four cytokine haplotypes, and four cytokine alleles. Du et al. examined the associations between the single-nucleotide polymorphisms (SNPs) of IL17, including rs763780 (7488A/G), rs2275913 (–197G/A), and rs8193036 (–737C/T), and asthma susceptibility in an Asian population and demonstrated that IL17 rs763780, rs2275913, and rs8193036 SNPs might be associated with asthma susceptibility, and G/A genotype in rs2275913 and TT genotype in rs8193036 of IL-17 may contribute to the increased risk of asthma in Asians[30].

Berenguer et al. showed that IL4-590*CT/TT genotypes were associated with a 2.2-fold increased asthma risk (2.4-fold for persistent asthma and 4-fold for moderate-severe asthma), while IL4-590*T allele was linked to a 2-fold risk for asthma (2.2-fold for persistent asthma and 3.4-fold for moderate-severe asthma), compared to individuals carrying other IL4-590 C/T genotypes or alleles[31].

Tumor necrosis factor α (TNFα) is a potent pro-inflammatory cytokine that mediates the airway inflammatory response in atopic asthma cases. Recent

meta-analysis showed that the TNFα-308 G/A polymorphism is associated with an increased risk of asthma in adults and children, in Asians, but not in Caucasians; and in atopic population, but not in non-atopic population[32].

Ali and Settin studied the associations of TNFα-308G/A, IL6-174G/C, IL-10 1082G/A and IL-Ra VNTR polymorphisms with chronic asthma susceptibility in adult Egyptian patients[33]. The researchers found significantly higher frequency of the genotypic polymorphisms IL10-1082 AG + GG (dominant mode), TNFα-308 GA + AA (dominant mode) and IL1RA VNTR heterozygous genotype A1A2 in BA cases compared to controls. The frequency difference in other genotypes, such as IL6-174 C/C + G/C vs. G/G (dominant mode), was not significant.

Forkhead box (FOX) family of transcription factors have key roles in immunoregulation and homeostasis. FOXO3a is involved in suppressing inflammatory cytokine production by dendritic cells and initiation of TGF1 dependent pathway in monocytes[34-36]. A study by Barkund et al. showed that FOXO3a SNP (rs13217795) is associated with asthma incidence in an Indian population, possibly because it contributes to the hyperactivity of T cells, neutrophils, and mast cells, increased production of pro-inflammatory cytokines, and down-regulation of anti-inflammatory cytokines[37]. Additionally to the significant association of FOXO3a with BA, a gender based stratification revealed the association of a mutant T allele with an increased asthma risk in females of the Indian population.

Airway obstruction, characteristic to BA, results in impaired air movement, which not only requires additional physical effort during respiration, but also induces remodeling mechanisms of the bronchopulmonary system3[8]. An important role in this process is played by matrix metalloproteinases (MMPs), involved in the metabolism of proteins of the intercellular matrix. As cytokine proteinases, they affect the morphogenesis, resorption, migration, adhesion and proliferation of various cells and tissues[39].

A study by Lebedenko et al. found higher frequency of homozygous C/C MMP20 gene variant with 320A>C polymorphism, heterozygous MMP20 gene variant Val275Ala and heterozygous MMP9 gene variant with -8202A>G polymorphism in patients with BA[38]. However, the frequencies of these alleles and genotypes were not significantly different in the affected children while comparing to the healthy group. Notably, the patients who had both GG genotype of the MMP9 -8202A>G allele and homozygous C-allele of the 320A>C allele of the MMP20 gene, suffered from a more severe course of the disease associated with polyvalent sensitization and increased levels of total blood IgE.

The beta-2 adrenergic receptor gene (ADRB2) was shown to have clear association with the course of asthma. It encodes β-2 adrenergic receptors, has nine identified polymorphisms, and is located on chromosome 5 q31-q32. Four of those polymorphisms have potential clinical effects on the response to β-2 adrenoreceptor agonist therapy in asthmatic patients[40,41]. Arg16Gly and Glu27Gln ADRB2 polymorphisms are associated with increased risk of severe asthma development [21]. Moreover, patients which are homozygous for these gene variants rapidly lose sensitivity to β2-adrenoceptor agonists resulting in required treatment with hormonal drugs[42].

Glutathione S-transferase gene family encodes for enzymes which are involved in antioxidant protection and cell and tissue resistance to toxic substances and lipid peroxidation products[43]. The impact of their polymorphisms on asthma is well studied[21]. A study by Sardaryan found that allelic polymorphism of glutathione S-transferase T1 (GSTT1) and glutathione-S-transferase M1 (GSTM1) genes, namely the GSTT1– / GSTM1– genotypes, caused a 5-fold increase in the risk for asthma development[26].

The angiotensin-converting enzyme (ACE) insertion/deletion (I/D) gene polymorphism, correlating with circulating and cellular ACE concentrations, may also play a major role in BA pathogenesis and has been a focus of numerous epidemiological studies; however, so far the results are currently inconclusive.

ACE is an endopeptidase consisting of two catalytic domains; this enzyme is expressed by endothelial, epithelial, neuronal cells and exists both in a membrane-bound form (ACE) and a soluble form (sACE)[44]. A soluble ACE form is produced through exposure to a zinc metalloprotease (referred to as "ACE secretase"), which cleaves the mature membrane-bound ACE in the juxtamembrane extracellular domain to release the large extracellular

part of the enzyme[45]. ACE is involved in renin-angiotensin system, since it catalyzes the synthesis of a vasoconstrictor angiotensin II from its non-vasoactive precursor, angiotensin I[46]. Angiotensin II is a powerful vasopressor, which regulates blood pressure and fluid and electrolyte balance, mainly by mediating biosynthesis of aldosterone[47]. Almost all body organs possess their own local paracrine renin-angiotensin system producing organ-specific effects[48].

ACE expressed in lungs plays a significant role in BA pathogenesis[49], since ACE mediates proliferation of smooth vascular muscle cells, which affects aggregation and adhesion of platelets and monocytes[50] and can lead to excessive bronchiectasis[51].

Since ACE converts angiotensin I into angiotensin II, it can feasibly contribute to asthma etiology by interaction with bronchial muscles. In addition to converting angiotensin I to angiotensin II, ACE is also a kininase enzyme (kininase II, peptidyl-dipeptidase A; EC 3.4.15.1) that reduces concentrations of several inflammatory mediators such as bradykinin, substance P, and neurokinin A[52-56]. These substances are considered to play considerable roles in the pathogenesis of BA, especially in neurogenic inflammation. Bradykinin causes enhanced vascular permeability, bronchoconstriction, leads to mucosal edema, and increases the production of mucus by direct effects or stimulating release of neuropeptides, such as tachykinins from C-fibers. Asthmatic patients were reported to show bronchial hyper-reactivity to bradykinin, compared to healthy subjects. Tachykinins are inducers of airway smooth muscle constriction, bronchial edema, extravasation of plasma, and mucus hyper-secretion, acting as important mediators of neurogenic inflammation[57,60]. In turn, ACE inhibition is associated with inhibition of kinase II activity, leading to substantial accumulation of kinins, substance P and prostaglandins in the airways. This stimulates afferent impulses in the vagus nerve, which causes bronchial hyper-reactivity and airway inflammation in patients with BA, resulting in cough and bronchospasm[52,58].

The ACE gene is located on the q23 locus of chromosome 17. Individual variability in the plasma ACE levels is associated with a presence [insertion (I)] or absence [deletion (D)] of a 250-bp region located in the intron 16 of the ACE gene, which is known as the ACE I/D polymorphism [54]. Since the polymorphism is located in an intron region, it does not affect ACE structure, but the polymorphism accounts for 47% of the total phenotypic variance in serum ACE levels. There are three genotypes of ACE I/D polymorphism: deletion homozygote, D/D; insertion homozygote, I/I; and heterozygote, D/I. The serum ACE concentration with the D/D genotype is about double that of the I/I type; D/I genotype exhibits intermediate serum ACE level[53].

A meta-analysis of the relevant studies estimated the risk of asthma and ACE I/D polymorphism[59]. The meta-analysis involved 11,897 subjects and showed that human subjects with the D/D genotype had increased asthma risk compared to those with the I/I genotype or ID/II. Stratified analyses by ethnicity (Europeans and Asians) and age (adults and children) produced statistically similar results regarding two genetic models. As for the subgroup analysis by the source of controls, the D/D genotype was associated with a significantly higher asthma risk among population-based controls, but not hospital-based controls. ACE D/D genotype had significantly higher occurrence in atopic asthmatic patients, compared to healthy control subjects; patients with D/D genotype had 6.8 fold higher risk for atopic asthma development than those with non-D/D genotype[60].

Similar results were obtained in a study on distribution of ACE genotypes in asthma patients in France[61], as well as on the prevalence of ACE gene genotypes among Czech asthma patients[62]. Comparable findings were reported by Lee et al.[49] and Nakahama et al.[63] Another meta-analysis confirmed the effect of ACE I/D polymorphism on the risk of asthma, indicating that the D/D homozygote carriers had a 59% increased risk of asthma, when compared with the I/I homozygote and D/I heterozygote[64]. A Ukrainian study showed that the relative risk (RR) of developing asthma was 2.67 for patients with the ACE D/D genotype; 0.46 for the ACE D/I genotype and 0.69 for the ACE I/I genotype, suggesting a possible protective role of the I allele[65]. The authors point out that individuals carrying ACE D/D genotype predominate (54.2%) among bronchial asthma patients. This is also supported by a study indicating that children with the D/D genotype are in the group of high risk for asthma development[51]. A study by Gao et al. found a higher prevalence of

the ACE D/D genotype in BA patients with bronchial hyperreactivity; such patients had lower FEV1 and FEV1/FVC compared to non-D/D genotype patients[66]. The ACE D/D genotype is also associated with severe disease progression[67].

A genetic analysis study by Jung et al. investigated the association of the ACE gene polymorphism with clinical phenotype based on differentiation syndrome (a deficiency syndrome group (DSG) and an excess syndrome group (ESG) according to their symptomatic classification) of bronchial asthma in Korean patients[54]. No significant differences in pulmonary function were noted between DSGA and ESGA patients. The genotypic frequency of ACE I/D polymorphism was found to differ slightly between DSGA and ESGA. However, there were no significant differences in allelic frequency between DSGA and ESGA. Interestingly, the allelic and genotypic frequencies of the ACE I/D polymorphism in female patients differed significantly between DSGA and ESGA comparing to male patients.

On the other hand, a study by Cortez et al. shows a higher prevalence of ACE I/I genotype among patients with asthma; the authors conclude that ACE I/D gene polymorphism is a controversial risk factor for asthma severity[68]. The study did not find significant differences in the frequencies of genotypes between atopics and non-atopics; men and women; controlled and uncontrolled asthma; and between different age groups.

Similarly, Saba et al. investigated the role of ACE I/D polymorphism (rs4646994) in asthma development in a study which involved 854 Pakistani subjects, including 333 asthma patients and 521 ethnically matched controls[69]. Homozygous insertion genotype II and insertion allele (I) was significantly more frequent in BA patients than in healthy controls. The D/I genotype and the D allele were associated with protection from the disease.

Finally, some studies failed to establish any associations of ACE gene polymorphisms with asthma. For instance, ACE gene polymorphism is not significantly associated with BA or with its severity among Egyptian adults[70]. The frequencies of the D/D, D/I and I/I genotypes were 46.7%, 40%, and 13.3%, respectively, among asthmatic patients, and 33.3%, 40%, and 26.7%, respectively, among the controls, and no significant differences in ACE genotype distribution was observed between asthmatic cases and controls. Genotype distribution did not differ according to the timing of onset or severity of asthma, total serum IgE levels, SPT positivity, or number of positive SPT reactions. Furthermore, ACE polymorphism was not significantly different between asthmatic patients without any associated atopic disease and those with an associated atopic disease.

Similarly, the ACE genotype frequencies also do not significantly differ between the patients with asthma and healthy controls in several studies conducted in Turkey[71,72]. A number of studies on the possible links between the ACE gene polymorphism and the risk of developing asthma in Japanese and American populations have also found no associations[49,63,73].

For instance, a study by Tomita et al. did not find any association of the ACE gene polymorphism with BA in Japanese population[53]. Of the 142 healthy controls, 57 had the I/I genotype, 69 the D/I type and 16 the DD type. The I allele/D allele (I/D) ratio was 0.6441/0.356. As for 71 patients with asthma, 25 were type I/I, 37 were D/I and nine were D/D. The I/D ratio was 0.6131/0.387. The observed genotype distributions were in agreement with the Hardy-Weinberg expectations. No significant differences in genotype distribution or the allele frequencies were observed between the healthy subjects and asthmatic patients.

Similarly, no significant differences were found in either the ACE genotype or allele frequencies between asthmatic patients and control subjects with Iranian Azeri-Turkish origin, in female cases versus female controls, and male cases versus male controls[74]. A systematic review by Alizadeh-Navaei et al. indicated that none ACE genotype was more susceptible to asthma in Iranian population[75].

To summarize, the literature review gives some insights to the conclusion that not a single factor alone contributes to the development and progression of BA, as contribution of ACE I/D polymorphism may be controversial and depends on other factors, both genetic and environmental. For example, a specific single nucleotide polymorphism in the CD14 region contributes to asthma development only after exposure to endotoxin at a certain level, which may come from several environmental sources[76]. Though the overall conclusion is that DD genotype of ACE I/D

polymorphism is associated with increased risks for BA, it is important to understand that a combination of factors, both genetic and environmental, triggers BA development and determines its progression. The found and analyzed data may indicate that investigated genetic factor is minor and BA development and progression may heavily depend on other genetic predispositions and environmental risks, as well as geographical location.

Conclusion

This review provides some evidence that the specific ACE I/D polymorphism may be associated with asthma risk. The difference in the literature on the role of ACE alleles and genotypes can be explained by minor influence of the investigated genetic component and contributions of other genetic variations, as well as other environmental factors, considering multifactorial causes of BA. The ACE I/D polymorphism may contribute to an important molecular mechanisms of asthma development if other pieces of puzzle are known, and may become a useful tool in risk assessment and in designing effective treatment approaches; however, it requires further investigation.

Authors' Contribution:

Idea owner of this study: Marushchak M., Krynytska I.

Study design: Marushchak M., Krynytska I.

Data gathering: Marushchak M., Krynytska I., Koval M.

Writing and submitting manuscript: Marushchak M., Krynytska I., Koval M.

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