© IJHG 2020 Int J Hum Genet, 20(3): 110-119 (2020)
PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330 DOI: 10.31901/24566330.2020/20.03.757

Genetics of Chronic Obstructive Pulmonary Disease- A Literature Review

T. Sangeetha[1*], B. Balamuralikrishnan[2], A. Vijaya Anand[1*] and M. Arun[3]

[1] Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore, Tamil Nadu, India*
E-mail: sangeetha7363@gmail.com / avamiet@yahoo.com
[2]Department of Food Science and Biotechnology, College of Life Science, Sejong University, Seoul 05006, Republic of Korea
[3]EuroEspes Biomedical Research Centre, International Centre of Neuroscience and Genomic Medicine, 15165 Corunna, Spain

KEYWORDS *ADRB2*. Genes. Lung Disorder. Polymorphism. Respiration. *SERPINA1*

ABSTRACT The chronic obstructive pulmonary disease (COPD), a respiratory disease characterized by the limitations in the airflow in the lungs, comprises about 5 percent of global mortality annually. The main objective of the present review is to focus on the genetic etiology of COPD. The literature analysis of the genetics of COPD involves the prediction of the influence of various genes in COPD, such as *SERPINA1, ADRB2, TGFB1, TNF, GSTM1, GSTP1* and *EPHX1*. The literature survey has been carried out by using the standard scientific databases and search engines and the articles of the last twenty years have been collected for the data accumulation. On the elaborate consideration, COPD occurrence has been observed to be highly influenced by the two genes *SERPINA1* and *ADRB2*, rather than the other genetic polymorphisms. The present review might be useful for the easier depiction of significant genes involved in COPD occurrence.

INTRODUCTION

The chronic obstructive pulmonary disease (COPD), which comprises chronic bronchitis and pulmonary emphysema together, is a disease that affect lungs, resulting in breathing difficulties (American Lung Association 2020; Ferri 2016). The obstruction in air passage is due to inflammation in the alveolar sacs, which leads to pulmonary emphysema and whereas, the damages in bronchioles result in chronic bronchitis (Lozano et al. 2012). COPD accounts for the leading cause of mortality rate in the United States, and worldwide according to the survey conducted by the World Health Organisation (WHO) in 2018 and American Lung Association in 2020 (American Lung Association 2020; Duffy and Criner 2019; WHO 2018). COPD has been regarded as the silent killer in most of the developing countries. Approximately 328 million people are affected by COPD and it has been expected to be the foremost leading cause of deaths in the next 15 years (Eisner et al. 2011; Reubi et al. 2016; WHO 2018). COPD accounts for about 5 percent of deaths worldwide and among that 5 percent, approximately 90 percent was found to be in low and middle-income countries (Mathers and Loncar 2006). In India, a study conducted in 2016, showed that the occurrence of COPD has been estimated to be about 55.3 million people and it has been a crude estimation of 8.7 percent out of total deaths in India (Global Burden of Disease Study 2018).

Even though the major etiology of COPD has been associated with environmental factors like tobacco smoking, a genetic basis has also been found to have a prominent association in COPD occurrence (Gupta et al. 2013). Along with the risk factors, COPD also contributes to various problems in human organs, which have been tabulated in briefly in Table 1. Various genes like, *CAT, GSTT1, ADRB2, TGFB1, TNF, GSTM1, GSTP1, EPHX1, SOD3, NFE2L2, KEAP1, OGG1, XRCC1, XRCC3, XRCC4, XRCC5, CDKN1A,* and *p53* has been associated with COPD (Yeo et al. 2018) and few of these genes are considered for the following literature analysis. This review primarily highlights the genetic etiology of COPD and also the related genes, which are critically evaluated.

Objectives

The current literature review has been framed with an ultimate objective of analyzing the role of

[*]Address for correspondence:

Table 1: Major consequences of COPD

Organ affected	*Consequences*	*References*
Heart	Increases the risk for cardio-vascular disease	Crisan et al. 2019; Morgan et al. 2018
Skeletal Muscles	Muscle dysfunctioning	Jaitovich and Barreiro, 2018; Gea et al. 2015
Lungs	Worsens the lung cancer and decreases the rate of survival in lung cancer patients	Parris et al. 2019; Wang et al. 2018; Dai et al. 2019
Bones	Increases the risk for osteoporosis condition	Sarkar et al. 2015
Multiple organs of the body	Increases the risk for metabolic syndrome, which increases risk for cardio-vascular disease, stroke and diabetes	Ballantyne et al. 2008

Source: Author

genetic polymorphism of certain genes like *ADRB2, TGFB1, TNF, GSTM1, GSTP1, EPHX1* in causing the abnormalities in lungs, leading to COPD. The considered genes might be a reason, in which the contribution may be direct or indirect in causing COPD. The possible occurrences of COPD etiology with a genetic basis may pave a novel path in treating the COPD, which is currently not curable in nature. Therefore, the main objectives of this review are to emphasize and discuss the involvement of genetic polymorphisms of seven genes considered in COPD and its evolution.

METHODOLOGY

About, more than 945 articles regarding COPD and the genetic interlink between COPD and the considered genes were analyzed from the authorized scientific databases including PubMed search, Nature, Springer, Elsevier, Wiley, Science, Science Direct. The articles or their abstracts were screened and scrutinized for the appropriate content. The articles were searched by using the keywords, COPD, genetic polymorphism, respective gene names and lung disorders. The research works, which were published for the past twenty years were scrutinized and the analysis was drafted in this literature review.

OBSERVATIONS AND DISCUSSION

Pathophysiology of COPD

The two diseases comprising COPD make the person difficult to respire normally. The alveoli are the parts of the lungs, in which the respiratory gas exchange takes place between the lungs and the bloodstream flowing through the body (Braghiroli et al. 2020; Hogg and Timens 2009). Chronic bronchitis is the clinical condition, in which the alveolar sacs are damaged or destroyed; this state leads to an improper exchange of respiratory gases in the lungs. The bronchioles are branches of the respiratory tract passageway (Kyra and Wright 2016). The bronchioles lead to the small sized-air sacs called alveoli that favor the exchange of the respiratory gases. In the case of pulmonary emphysema, the wall of alveoli gets inflamed and damaged; hence, the to and fro movement of the respiratory gases becomes difficult making the individual struggle for breathing (Hogg and Timens 2009).

Genetics of COPD

The cause of COPD varies with age and genetic makeup of the person. Few studies have suggested that the risk of COPD increase in smokers when compared with the non-smokers of the same age and gender. But, approximately only 20 percent of the smokers are prone to COPD, whereas the remaining 80 percent of the cause lies in the genetic makeup of the person (Yohan 2012; Terzikhan et al. 2016). The genes that have been associated with COPD have been numbered to be more than 86. Among the 86 genes, seven genes were found to be more related to the occurrence of COPD (Yohan 2012). Those seven genes such as Serpin Family A Member 1 (*SERPINA1*), Adrenoceptor beta 2 (*ADRB2*), Transforming Growth Factor Beta 1 (*TGFB1*), Tumor Necrosis Factor (*TNF*), Glutathione S Transferase Mu 1 (*GSTM1*), Glutathione S Transferase Pi 1 (*GSTP1*) and Epoxide Hydrolase 1 (*EPHX1*) are concisely discussed in this review paper.

SERPINA1 Gene

The *SERPINA1* belongs to the serpin family and it encodes for a protein called alpha 1 antitrypsin, which is a serine protease inhibitor. The mutations in the *SERPINA1* gene would result in the abnormally lower ranges of alpha 1 antitrypsin in the circulation. The prominent role of alpha 1 antitrypsin is the protection of the lungs, from protease enzyme, neutrophil elastase, which is secreted during inflammation of the lung tissue (Luisetti and Seersholm 2004; Dickens and Lomas 2011). The lack of alpha 1 antitrypsin due to *SERPINA1* gene mutation makes the lungs more vulnerable to the infection and damage by the body's own protease enzyme, neutrophil elastase. Pulmonary emphysema is the most common clinical condition in the lungs, diagnosed with *SERPINA1* gene mutations and alpha 1 antitrypsin deficiency (Dickens and Lomas 2011; Silverman and Sandhaus 2009).

A novel mutation has been reported by Darren et al. (2012) in the *SERPINA1* gene that modifies the amino acids of alpha 1 antitrypsin protein at T379 by frameshift mutation. A deletion of 49 base pairs results in the failure of alpha 1 antitrypsin synthesis (Darren et al. 2012). Insufficient alpha 1 antitrypsin has been found to be a risk factor genetically, that causes COPD in the earlier ages of 80 percent cases (Lomas and Silverman 2001; Denden et al. 2010). A recent analysis by Deng et al. (2017) has suggested that a mutation in the *SERPINA1* gene, variation at the location rs8004738, has been associated with a higher risk for the development of COPD (Deng et al. 2017). Another study led by Thun et al. (2013), has also supported the evidence of single nucleotide polymorphism in rs8004738 location, which is associated with COPD, but the study also added that alpha 1 antitrypsin levels were not significantly influenced by this specific polymorphism (Thun et al. 2013). Another specific single nucleotide polymorphism at rs112458284 in the *SERPINA1* gene has been found to contribute to COPD origin (Busch et al. 2017).

ADRB2 Gene

A beta-2-adrenergic receptor is a product encoded by the *ADRB2* gene, which belongs to the family of G-protein coupled receptor (Johnson 2006). *ADRB2* is an intronless gene; which means that the whole gene contains exons that can be efficiently used in gene function and evolution analysis (Online Mendelian Inheritance in Man 2019). This receptor presents itself in smooth muscle cells of the respiratory tract; the elevation in the level of expression of the *ADRB2* gene has been found to be highly associated with COPD (Selivanova et al. 2012).

Few studies have suggested that single nucleotide polymorphisms in the *ADRB2* gene like rs1042713 location favor the conversion of amino acid arginine to glycine that contributes to the COPD occurrence (Cao et al. 2009; Wang et al. 2011; Wang et al. 2018). The amino acid glutamine conversion into glutamic acid has been observed in the mutants with rs1042714 polymorphism. The single nucleotide polymorphism in rs1042713 and rs1042714 in the *ADRB2* gene influences the synthesis of the gene, as well as the protein synthesis, get altered. This contributes to the origin of COPD effectively (Ma et al. 2006; Shi et al. 2008; Wang et al. 2012). The functional mutation in the *ADRB2* gene at rs1265477 location has been reported to have a significant association with a higher risk for COPD (Li et al. 2018). The most common mutations in the *ADRB2* gene that has been linked with COPD are heterozygous allele that favors the conversion of glutamine to glutamic acid, glycine to arginine and threonine to isoleucine. Among these three mutants, threonine to isoleucine has a higher contribution towards COPD risk and origin (Thomsen et al. 2011). The specific pathway which contributes to the progression and *ADRB2* association with COPD remains undetermined.

TGFB1 Gene

The *TGFB1* gene encodes transformation growth factor-beta 1 protein that has various important functions in the human body. The functions including, cell division, maturation of cells as well their differentiation process, the movement of cells and the programmed cell death are being regulated and controlled *TGFB1* gene (Ghadami et al. 2000; Vaughn et al. 2000). The *TGFB1* gene is also implicated in inflammatory responses of the immune system (Fujio et al. 2016). A study on mice suggested that the inhibition of expression of the *TGFB1* gene avoids the lung to get inflam-

mation, followed by the prevention of pulmonary edema (Pittet et al. 2001). The emphysema may be caused due to the dormant activation of the *TGFB1* gene that alters macrophage metallo elastase enzyme (Morris et al. 2003).

A significant relationship between the COPD and *TGFB1* gene has been found in the polymorphs at and near three different locations of the *TGFB1* gene such as rs2241712, rs2241718, rs6957 (Celedon et al. 2004). Few studies have suggested that single nucleotide polymorphism at rs1800469 in the *TGFB1* gene is associated with the asthma phenotypes (Celedon et al. 2004; Silverman et al. 2004). Another study by Ito et al. (2008) also added evidence that rs1800469, rs2241712, rs6957 polymorphism in the *TGFB1* gene are associated with severe COPD progression (Ito et al. 2008). A study by Sun et al. (2015) contrastingly suggested that rs1800469, rs2241712 and rs6957 have not been associated with COPD. The polymorphism at rs1982073 in this gene causes proline to leucine transformation that has been found to have a positive correlation with the increased risk of COPD (Sun et al. 2015).

TNF Gene

The *TNF* gene encodes for the protein, tumor necrosis factor-alpha (TNF-α) that involves mainly in the regulation of immune responses. The protein also involves in the regulation of cell differentiation, cell division and programmed cell death (Victor and Gottlieb 2002). Few studies suggested that the increased expression in TNF-α factor showed higher inflammation and pulmonary emphysema occurrence in the mice (Lundblad et al. 2005; Vuillemenot et al. 2004). A study by, Gingo et al. (2008) have suggested that polymorphism in the *TNF* gene at position 308 has increased the susceptibility of individuals to COPD as well as increases the receptiveness of smoking in them (Gingo et al. 2008). A recent study conducted by, Resendiz-Hernandez and his colleagues in 2018, gave the outcome that single nucleotide polymorphisms at the locations in rs1800629 and rs361525 of promoter regions in *TNF* gene elevates the possibility of acquiring COPD (Resendiz-Hernandez et al. 2018).

Another study conducted by Zhan et al. (2010) concluded that TNF-α 308 polymorphism is a considerable factor in increasing the risk for COPD (Zhan et al. 2010). Additionally, the TNF-α factor has been found to increase the susceptibility of smoking habits in individuals (Gingo et al. 2008). Contrastingly, a few studies suggest that the single nucleotide polymorphism of the TNF-α 308 position has no significant association with COPD severity or pulmonary inflammations. Smoking induced COPD and the genetically polymorphic occurrence of COPD have been found to have no significant variation (Patuzzo et al. 2000; Ozdogan et al. 2014). The COPD medications have been included with TNF-α inhibitors, which strongly suggests that TNF-α has a strong relationship with COPD progression even though the genetic basis is still not yet determined (Matera et al. 2010).

GSTM1 Gene

The protein, glutathione S-transferase mu 1 is being encoded by the *GSTM1* gene in humans. The protein encoded by the *GSTM1* gene is one of the soluble proteins that belong to the mammalian glutathione S-transferase family (National Center for Biotechnology Information 2019). The polymorphisms in the *GSTM1* gene have been found to be a higher risk factor in the individuals for the progression of COPD (Cheng et al. 2004; Faramawy et al. 2009). Lakhdar et al. (2010) conducted a study on the null alleles of the *GSTM1* gene and concluded that the variations contributed to COPD (Lakhdar et al. 2010). A study has suggested that the presence of single nucleotide polymorphisms in the *GSTM1* gene was significantly elevated in COPD patients (Shukla et al. 2011). A study by Rabab et al. (2015) supported the previous study by examining the COPD patients for null alleles in the *GSTM1* gene (Rabab et al. 2015).

The liver and the lungs of the human body express the *GSTM1* gene. A study has reported that, among the pulmonary emphysema and lung cancer patients in Europid populations, 50 percent of the patients have been diagnosed with a deletion of the *GSTM1* gene homozygous alleles (Sandford and Silverman 2002). Contrastingly, the *GSTM1* gene polymorphisms have not been found to be associated with COPD, in Korean populations (Yim et al. 2000). The null allele polymorphism in the *GSTM1* gene along with mutations in the *GSTP1* gene contributes to the increased risk of COPD, even though, the *GSTP1*

gene mutation alone did not show significant susceptibility towards COPD (Xue et al. 2012; Ding et al. 2019).

GSTP1 Gene

The *GSTP1* gene encodes an enzyme named as glutathione S-transferase P. The major function of this enzyme is the detoxification process. The kidney and lungs of the human body express the *GSTP1* gene (Tew et al. 2011). Imboden et al. (2007) examined a single nucleotide polymorphism of the *GSTP1* gene leading to isoleucine to valine transformation in COPD patients and suggested that the polymorphisms in the *GSTP1* gene alone do not contribute to COPD, but the *GSTP1* gene variations have been found to be associated with COPD (Imboden et al. 2007). The single nucleotide polymorphism studied at the location of rs1695 in the *GSTP1* gene has shown considerable variations in COPD patients (Thiago et al. 2017). The polymorphic presence in the fifth exon of the *GSTP1* gene has been suggested to influence the pathogenesis of COPD. The transformation of the Ile150Val genotype was found to be highly associated with the occurrence of COPD (Cheng et al. 2004). Another study suggested that Ile105Val homozygous transformation in the *GSTP1* gene may increase the protection against COPD (Sukru Aynacioglu et al. 2003).

A study by Lakhdar et al. (2011) has suggested that the single nucleotide polymorphisms in the *GSTP1* gene have a prominent role in the decline of the functioning of the lungs and the progression of pulmonary emphysema and COPD (Lakhdar et al. 2011). Another study reported that smokers have been associated with polymorphisms in the *GSTP1* gene when compared with non-smokers. Since smoking of tobacco is the major factor influencing COPD, the role of the *GSTP1* gene in COPD is to be found to be determined in smokers. The habit of smoking has observed to have an association in inducing the *GSTP1* gene polymorphisms, which in turn contributes to COPD development (Lakhdar et al. 2011; Tarek et al. 2016).

EPHX1 Gene

The *EPHX1* gene encodes for epoxide hydrolase enzyme, which plays an important function in the epoxide degradation (Vaclavikova et al. 2015). The detoxification of carcinogens released during tobacco smoking is being carried out by the expression of the *EPHX1* gene (Chikako et al. 2006). A study investigated the association between single nucleotide polymorphism at rs1051740, in the *EPHX1* gene and COPD, and the findings have also suggested that polymorphism in rs1051740 increases the risk and susceptibility to COPD (Akparova et al. 2017). Hu et al. (2008) studied the association of various mutants in the *EPHX1* gene with the occurrence and progression of COPD. The study suggested that the heterozygous expression of the *EPHX1* gene at position 139, was beneficial, which protected the lungs against COPD (Hu et al. 2008).

The minimal activity of the *EPHX1* gene results in an elevated possibility of acquiring COPD. Another study suggested that the combination of the *EPHX1* gene mutation along with the *GSTM1* gene mutation decreases the function of the lungs and the respiratory capacity is significantly reduced. These polymorphisms influence the COPD occurrence (Hu et al. 2008; Lakhdar et al. 2011). Further, a contrast report has been given by Lee et al. (2010) as the *EPHX1* gene polymorphism, which reduces the activity of the epoxide hydrolase enzyme are not associated highly with the COPD arise in the individuals, but the effects can be negligible (Lee et al. 2010). The single nucleotide polymorphisms in the sites such as rs1051740 and rs2234922 of the *EPHX1* gene has been observed to be a risk factor for COPD, as the *EPHX1* gene has been found to have a role in protecting the lungs (Vaclavikova et al. 2015).

The particular study has focussed only on the seven genes associated with COPD and the considered seven genes have shown an association with COPD to a particular extent. Among the seven genes, the *SERPINA1* gene directly found to be involved in the COPD disease progression, whereas the shreds of evidence also show that, the *ADRB2* gene is positively associated with COPD. *TGFB1, TNF, GSTM1* and *EPHX1* genes are being less significantly associated with COPD when compared to *SERPINA1* and *ADRB2* genes. The *GSTP1* gene has been suspected to be linked with COPD.

With these available studies, the single nucleotide polymorphisms in these seven genes, *SERPINA1, ADRB2, TGFB1, TNF, GSTM1, GSTP1,*

and *EPHX1* directly or indirectly contribute to the occurrence or progression of COPD. From the above observations, it has been known that, the genetic polymorphisms of *SERPINA1* and *ADRB2* genes contributes to the COPD occurrence, progression and worsening of the condition. Figure 1 depicts the typical mechanisms of the considered seven genes in the human body and their altered pathways, which leads to the disease.

CONCLUSION

With these available studies, the single nucleotide polymorphisms in these seven genes, *SER-*

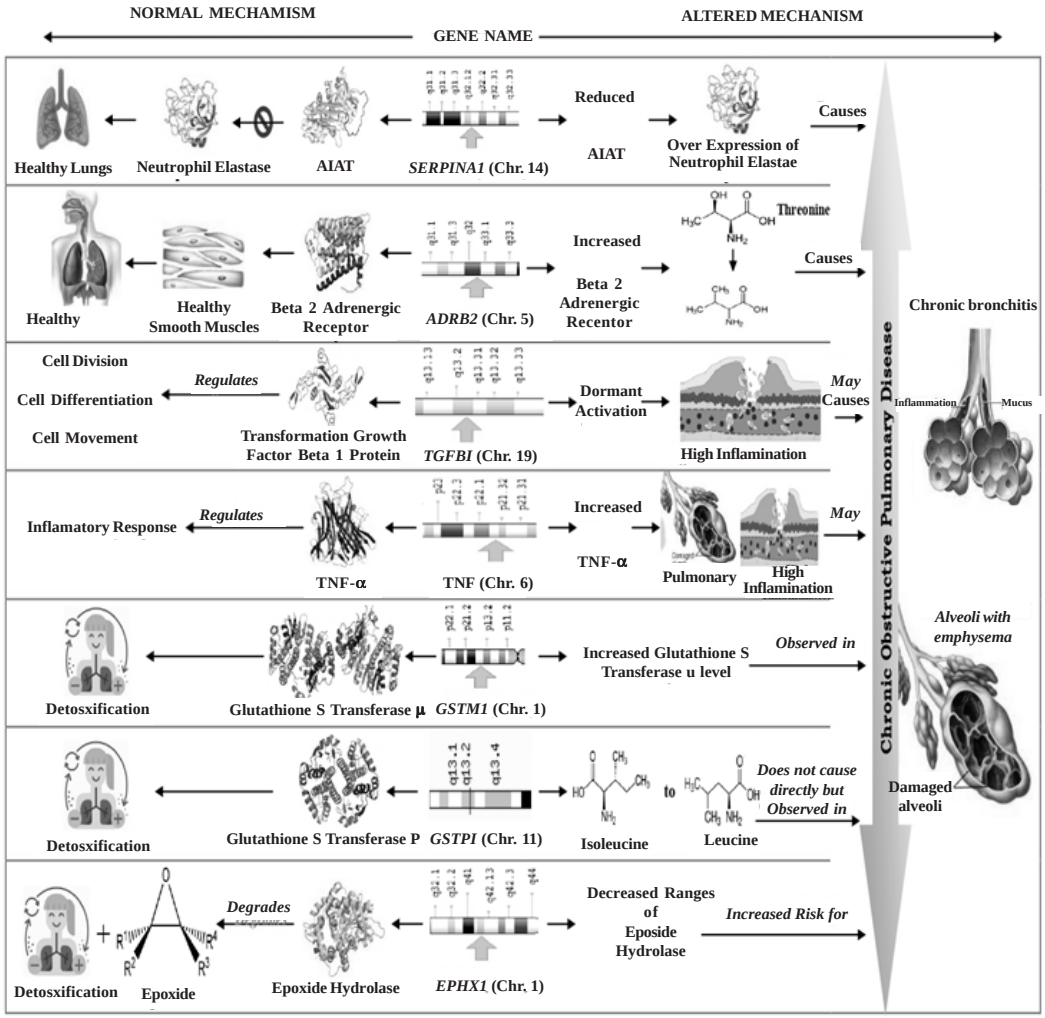

Fig. 1. Schematic representation of the involvement of genes in COPD occurrence
Source: Authors

The genes *SERPINA1, ADRB2, TGFB1, TNF, GSTM1, GSTP1* and *EPHX1* encodes for alpha 1 antitrypsin, beta 2 adrenergic receptor, transformation growth factor beta 1 protein, TNFα, glutathione S transferase μ, glutathione S transferase P, epoxide hydrolase respectively. The alterations in the encoded enzymes result in alterations in the normal functioning of the lungs, resulting in lung disease or increased risk for lung disease.

PINA1, ADRB2, TGFB1, TNF, GSTM1, GSTP1, and *EPHX1* directly or indirectly contribute to the occurrence or progression of COPD (Fig. 1). Among the seven genes considered, based on the available shreds of evidence, it has been depicted that the *SERPINA1* and *ADRB2* genes were highly correlated with the COPD whereas, the other five genes, *TGFB1, TNF, GSTM1, GSTP1,* and *EPHX1* had both positive as well as negative correlations with COPD; but, the positive association was found to be higher, which indicates that the presence of polymorphisms in those genes either directly contributes to COPD or indirectly increases the risk for the disease. Hence, in this literature review, it has been concluded that all the seven genes considered in the study have a significant contribution to increasing the risk and for the occurrence of COPD.

RECOMMENDATIONS

The further studies can be done elaborately on the *SERPINA1* and *ADRB2* genes, which are more significantly correlated with COPD occurrence. The elaborate studies on the presence of the single nucleotide polymorphisms in these two genes along with the analysis of the sequence alterations would lead a pathway for drug development and the treatment of the disease.

ABBREVIATIONS

COPD – Chronic Obstructive Pulmonary Disease;
SERPINA1 – Serpin Family A Member 1;
ADRB2 – Adrenoceptor beta 2;
TGFB1 – Transforming Growth Factor Beta 1;
TNF – Tumor Necrosis Factor;
GSTM1 – Glutathione S Transferase Mu 1;
GSTP1 – Glutathione S Transferase Pi 1;
EPHX1 – Epoxide Hydrolase 1;
TNF-α – tumor necrosis factor

REFERENCES

Akparova A, Abdrakhmanova B, Banerjee N, Bersimbaev R 2017. EPHX1 Y113H polymorphism is associated with increased risk of chronic obstructive pulmonary disease in Kazakhstan population. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* (Internet). *Elsevier BV*, 816-817: 1–6.

American Lung Association. COPD 2020. From <https://www.lung.org/lung-health-diseases/lung-disease-lookup/copd.> (Retrieved on 20 May 2020).

Ballantyne CM, Hoogeveen RC, McNeill AM, Heiss G, Schmidt MI, Duncan BB, Pankow JS 2008. Metabolic syndrome risk for cardiovascular disease and diabetes in the ARIC study. *Int J Obes (Lond)*, S2: S21-24.

Braghiroli A, Braido F, Piraino A, Rogliani P, Santus P, Scichilone N 2020. Day and night control of COPD and role of pharmacotherapy: A review. *Int J Chron Obstruct Pulmon Dis*, 15: 1269-1285.

Busch R, Hobbs BD, Zhou J et al. 2017. Genetic association and risk scores in a chronic obstructive pulmonary disease meta-analysis of 16,707 subjects. *Am J Respir Cell Mol Biol*, 57(1): 35–46.

Cao X, Li QQ, Chen GZ et al. 2009. Polymorphism of IL-4, IL-13, and ADR Beta 2 genes in patients with chronic obstructive pulmonary disease. *Med J Wuhan Univ*, 30(2): 219–223.

Celedon JC 2004. The transforming growth factor- 1 (TGFB1) gene is associated with chronic obstructive pulmonary disease (COPD). *Human Molecular Genetics,* 13(15): 1649–1656.

Cheng SL, Yu CJ, Chen CJ, Yang PC 2004. Genetic polymorphism of epoxide hydrolase and glutathione S-transferase in COPD. *European Respiratory Journal*, 23: 818-824.

Chikako K, Kouichi Y, Koichi T, Yoichi N 2006. EPHX1 polymorphisms and the risk of lung cancer: A HUGE review. *Epidemiology*, 17(1): 89-99.

Crisan L, Wong N, Sin DD, Lee HM 2019. Karma of cardiovascular disease risk factors for prevention and management of major cardiovascular events in the context of acute exacerbations of chronic obstructive pulmonary disease. *Front Cardiovasc Med,* 6: 79.

Dai J, Yang P, Cox A, Jiang G 2017. Lung cancer and chronic obstructive pulmonary disease: From a clinical perspective. *Oncotarget*, 8: 18513-18524.

Darren N. Saunders, Elizabeth A et al. 2012. A novel SERPINA1 mutation causing serum Alpha1-Antitrypsin deficiency. *PLos One*, 7(12): e51762.

Denden S, Khelil AH, Knani J et al. 2010. Alpha-1 antitrypsin gene polymorphism in Chronic Obstructive Pulmonary Disease (COPD). *Genet Mol Biol*, 33(1): 23-26.

Deng X, Yuan CH, Chang D 2017. Interactions between single nucleotide polymorphism of SERPINA1 gene and smoking in association with COPD: A case-control study. *Int J Chron Obstruct Pulmon Dis*, 12: 259-265.

Dickens JA, Lomas DA 2011. Why has it been so difficult to prove the efficacy of alpha-1-antitrypsin replacement therapy? Insights from the study of disease pathogenesis. *Drug Des Devel Ther*, 5: 391-405.

Ding, Z, Wang, K, Li et al. 2019. Association between glutathione S transferase gene M1 and T1 polymorphisms and chronic obstructive pulmonary disease risk: A meta analysis. *Clin Genet*, 95: 53–62.

Duffy SP, Criner GJ 2019. Chronic Obstructive Pulmonary Disease. *Med Clin North Am*, 103(3): 453-461.

Eisner MD, Anthonisen N, Coultas D et al. 2011. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med,* 182: 693-718.

Faramawy MM, Mohammed TO, Hossaini AM et al. 2009. Genetic polymorphism of GSTT1 and GSTM1 and susceptibility to chronic obstructive pulmonary disease (COPD). *J Crit Care*, 24(3): e7-10.

Ferri F 2016. *Ferri's Clinical Advisor*. 1st Edition. Elsevier.

Fujio K, Komai T, Inoue M et al. 2016. Revisiting the regulatory roles of the TGFβ family of cytokines. *Autoimmun Rev*, 15(9): 917-922.

Gea J, Pascual S, Casadevall C, Orozco-Levi M, Barreiro E 2015. Muscle dysfunction in chronic obstructive pulmonary disease: update on causes and biological findings. *J Thorac Dis*, 7: 18-38.

Ghadami M, Makita Y, Yoshida K et al. 2000. Genetic mapping of the Camurati-Engelmann disease locus to chromosome 19q13.1-q13.3. *Am J Hum Genet,* 66(1): 143–147.

Gingo MR, Silveira LJ, Miller YE et al. 2008. Tumour necrosis factor gene polymorphisms are associated with COPD. *European Respiratory Journal*, 31: 1005-1012.

Global Burden of Disease Study – India State-Level Disease Burden Initiative CRD Collaborators 2018. The burden of chronic respiratory diseases and their heterogeneity across the states of India: The Global Burden of Disease Study 1990–2016. *Lancet Glob Health*, 6: e1363–1374.

Gupta D, Agarwal R, Aggarwal AN, Maturu VN, Dhooria S, Prasad KT, Sehgal IS, Yenge LB, Jindal A, Singh N, Ghoshal AG, Khilnani GC, Samaria JK, Gaur SN, Behera D 2013. S.K Jindal for the COPD Guidelines Working Group. Guidelines for diagnosis and management of chronic obstructive pulmonary disease: Joint ICS/NCCP (I) recommendations. *Lung India*, 30: 228-267.

Hogg JC, Timens W 2009. The pathology of chronic obstructive pulmonary disease. *Annu Rev Pathol,* 4: 435-459.

Hu G, Shi Z, Hu J et al. 2008. Association between polymorphisms of microsomal epoxide hydrolase and COPD: Results from meta-analyses. *Respirology*, 13(6): 837–850.

Imboden M, Downs SH, Senn O et al. 2007. Glutathione S-transferase genotypes modify lung function decline in the general population: SAPALDIA cohort study. *Respiratory Research*, 8(1): 2.

Ito M, Hanaoka M, Droma Y et al. 2008. The association of transforming growth factor beta 1 gene polymorphisms with the emphysema phenotype of COPD in Japanese Internal Medicine. *Japanese Society of Internal Medicine*, 47(15): 1387–1394.

Jaitovich A, Barreiro E 2018. Skeletal muscle dysfunction in chronic obstructive pulmonary disease: What we know and can do for our patients. *Am J Respir Crit Care Med*, 198: 175-186.

Jiang Z, Knudsen NH, Wang G, Qiu W, Naing ZZC, Bai Y, Ai X, Lee CH, Zhou X 2017. genetic control of fatty acid β-oxidation in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*, 56(6): 738-748.

Johnson M 2006. Molecular mechanisms of beta(2)-adrenergic receptor function, response, and regulation. *The Journal of Allergy and Clinical Immunology*, 117(1): 18–24, quiz 25.

Kyra B, Wright JL 2016. The pathology of chronic obstructive pulmonary disease progress in the 20th and 21st centuries. *Arch Pathol Lab Med*, 140: 1423–1428.

Lakhdar R, Denden S, Knani J et al. 2011. Combined analysis of EPHX1, GSTP1, GSTM1 and GSTT1 gene polymorphisms in relation to chronic obstructive pulmonary disease risk and lung function impairment. *Dis Markers*, 30(5): 253-263.

Lakhdar R, Denden S, Knani J et al. 2010. Association of GSTM1 and GSTT1 polymorphisms with chronic obstructive pulmonary disease in a Tunisian population. *Biochem Genet*, 48(7-8): 647-657.

Lee J, Nordestgaard BG, Dahl M 2010. EPHX1 polymorphisms, COPD and asthma in 47,000 individuals and in meta-analysis. *European Respiratory Journal* (Internet). *European Respiratory Society (ERS)*, 37(1): 18–25.

Li JX, Fu WP, Zhang J, Zhang XH, Sun C, Dai LM, Zhong L, Yu L, Zhang YP 2018. A functional SNP upstream of the ADRB2 gene is associated with COPD. *Int J Chron Obstruct Pulmon Dis*, 13: 917-925.

Lomas DA, Silverman EK 2001. The genetics of chronic obstructive pulmonary disease. *Respir Res*, 2(1): 20-26.

Lozano R, Naghavi M, Foreman K et al. 2012. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*, 380(9859): 2095-2128.

Luisetti M, Seersholm N 2004. Alpha1-antitrypsin deficiency. 1: epidemiology of alpha1-antitrypsin deficiency. *Thorax*, 59: 164-169.

Lundblad LK, Thompson-Figueroa J, Leclair T et al. 2005. Tumour necrosis factor-a overexpression in lung disease: a single cause behind a complex phenotype. *Am J Respir Crit Care Med*, 171: 1363-1370.

Ma L, Feng DX, Zhang XY et al. 2006. Association between the genetic polymorphisms of β 2-adrenergic receptor and the chronic obstructive pulmonary disease. *Chin J Pract Intern Med*, 26(4): 267–269.

Matera MG, Calzetta L, Cazzola M 2010. TNF-alpha inhibitors in asthma and COPD: We must not throw the baby out with the bath water. *Pulm Pharmacol Ther*, 23(2): 121-128.

Mathers CD, Loncar D 2006. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, 209–224.

Morgan AD, Zakeri R, Quint JK 2018. Defining the relationship between COPD and CVD: what are the implications for clinical practice? *Ther Adv Respir Dis*, 12: 1753465817750524.

Morris DG, Huang X, Kaminski N, Wange et al. 2003. Loss of integrin alpha (v) beta6-mediated TGF-beta activation causes Mmp12-dependent emphysema. *Nature*, 22: 169–173.

National Center for Biotechnology Information, NCBI (Homepage on Internet). GSTM1 glutathione S-transferase mu 1 (Homo sapiens (human)). (Updated 2019 Sep 11; Cited 2020 May 25). From <https://www. ncbi.nlm.nih.gov/gene/2944> (Retrieved on 25 May 2020).

Online Mendelian Inheritance in Man, OMIM (Homepage on Internet). Beta-2-Adrenergic Receptor; ADRB2 (Updated 2017 Nov 27; Edited 2019 May; Cited 2019 Sep 25). From <https://www.omim.org/entry/109690 #references> (Retrieved on 25 April 2020).

Ozdogan N, Tutar N, Demir R et al. 2014. Is TNF-α gene polymorphism related to pulmonary functions and prognosis as determined by FEV1, BMI, COPD exacerbation and hospitalization in patients with smoking-related COPD in a Turkish population? *Revista Portuguesa de Pneumologia - Elsevier BV*, 20(6): 305–310.

Parris BA, O'Farrell HE, Fong KM, Yang IA 2019. Chronic obstructive pulmonary disease (COPD) and lung cancer: Common pathways for pathogenesis. *J Thorac Dis*, 11: S2155-S2172.

Patuzzo C, Gile LS, Zorzetto M et al. 2000. Tumor necrosis factor gene complex in COPD and disseminated bronchiectasis. *Chest Elsevier BV*, 117(5): 1353–1358.

Pittet JF, Griffiths MJ, Geiser T et al. 2001. TGF-beta is a critical mediator of acute lung injury. *J Clin Invest*, 107: 1537-1544.

Rabab AW, Enas SE, Ramadan MB et al. 2015. GSTM1, GSTT1 and EPHX1 gene polymorphisms and susceptibility to COPD in a sample of Egyptian population. *Egyptian Journal of Chest Diseases and Tuberculosis*, 64(4): 829-836.

Resendiz-Hernandez JM, Ambrocio-Ortiz E, Perez-Rubio G et al. 2018. TNF promoter polymorphisms are associated with genetic susceptibility in COPD secondary to tobacco smoking and biomass burning. *Int J Chron Obstruct Pulmon Dis*, 13: 627-637.

Reubi D, Herrick C, Brown T 2016. The politics of noncommunicable diseases in the global South. *Health Place*, 39: 179-187.

Sandford AJ, Silverman EK 2002. Chronic obstructive pulmonary disease c 1: Susceptibility factors for COPD the genotype–environment interaction. *Thorax*, 57: 736–741.

Sarkar M, Bhardwaj R, Madabhavi I, Khatana J 2015. Osteoporosis in chronic obstructive pulmonary disease. *Clin Med Insights Circ Respir Pulm Med*, 9: 5-21.

Selivanova PA, Kulikov ES, Kozina OV et al. 2012. Differential expression of the β2-adrenoreceptor and M3-cholinoreceptor genes in bronchial mucosa of patients with asthma and chronic obstructive pulmonary disease. *Ann Allergy Asthma Immunol*, 108(1): 39-43.

Shi YK, Ma J, Yuan ZJ et al. 2008. Investigation on the relation between polymorphisms of β2 adrenergic receptor and the chronic obstructive pulmonary disease. *Shandong Med J*, 48(13): 9–11.

Shukla RK, Kant S, Bhattacharya S, Mittal B 2011. Association of genetic polymorphism of GSTT1, GSTM1 and GSTM3 in COPD patients in a north Indian population. *COPD,* 8(3): 167–172.

Silverman ES, Palmer LJ, Subramaniam V et al. 2004. The transforming growth factor beta1 promoter polymorphism C-509T is associated with asthma. *Am J Respir Crit Care Med*, 169: 214–219.

Silverman EK, Sandhaus RA 2009. Clinical practice: Alpha1-antitrypsin deficiency. *N Engl J Med*, 360: 2749–2757.

Sukru Aynacioglu A, Muradiye Nacak, Ayten Filiz et al. 2003. Protective role of glutathione S-transferase P1 (GSTP1) Val105Val genotype in patients with bronchial asthma. *J Clin Pharmacol*, 57: 2213–2217.

Sun J, Zhang C, Xu L et al. 2015. The transforming growth factor-β1 (TGF-β1) gene polymorphisms (TGF-β1 T869C and TGF-β1 T29C) and susceptibility to postmenopausal osteoporosis: A meta-analysis. *Medicine (Baltimore)*, 94(4): e461.

Tarek FG, Samy SD, Ibrahim IM et al. 2016. Role of glutathione S-transferase P-1 (GSTP-1) gene polymorphism in COPD patients. *Egyptian Journal of Chest Diseases and Tuberculosis*, 65(4): 739-744.

Terzikhan N, Verhamme KM, Hofman A et al. 2016. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. *Eur J Epidemiol*, 31(8): 785-792.

Tew KD, Manevich Y, Grek C et al. 2011. The role of glutathione S-transferase P in signaling pathways and S-glutathionylation in cancer. *Free Radic Biol Med*, 51(2): 299-313.

Thiago P. Bartholo, Claudia H. Costa, Rogerio R et al. 2017. Glutatione S Tranferase (GSTP1 Polymorphism) and COPD development. *American Journal of Respiratory and Critical Care Medicine*, 195: A2735.

Thomsen M, Nordestgaard BG, Sethi AA et al. 2011. 2-adrenergic receptor polymorphisms, asthma and COPD: Two large population-based studies. *European Respiratory Journal. European Respiratory Society*, 39(3): 558–566.

Thun GA, Imboden M, Ferrarotti I et al. 2013. Causal and synthetic associations of variants in the SERPINA gene cluster with alpha1-antitrypsin serum levels. *PLOS Genetics*, 9(8): e1003585.

Vaclavikova R, Hughes DJ, Soucek P 2015. Microsomal epoxide hydrolase 1 (EPHX1): Gene, structure, function, and role in human disease. *Gene* (Internet). *Elsevier BV*, 571(1): 1–8.

Vaughn SP, Broussard S, Hall CR et al. 2000. Confirmation of the mapping of the Camurati-Englemann locus to 19q13. 2 and refinement to a 3.2-cM region. Genomics, 66(1): 119–121.

Victor FC, Gottlieb AB 2002. TNF-alpha and apoptosis: Implications for the pathogenesis and treatment of psoriasis. *J Drugs Dermatol*, 1(3): 264–75.

Vuillemenot BR, Rodriguez JF, Hoyle GW 2004. Lymphoid tissue and emphysema in the lungs of transgenic mice inducibly expressing tumour necrosis factor-a. *Am J Respir Cell Mol Biol*, 30: 438–448.

Wang C, Yang AL, Li H et al. 2012. Association between the Gln27Glu β2-adrenoceptor polymorphisms and the older-aged chronic obstructive pulmonary disease with hypertension (in Chinese). *J Pract Med*, 28(7): 1100–1103.

Wang W, Xie M, Dou S, Cui L, Zheng C, Xiao W 2018. The link between chronic obstructive pulmonary disease phenotypes and histological subtypes of lung cancer: A case-control study. *Int J Chron Obstruct Pulmon Dis*, 13: 1167-1175.

Wang W, Yu YJ, Qian R et al. 2011. Association between the susceptibility of COPD and IL-13, IL-4, polymorphisms of beta2-adrengic receptor. *J Clin Intern Med*, 28(5): 332–334.

World Health Organization – Global Health Estimates 2016. Disease Burden by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization 2018. From <https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html> (Retrieved on 24 April 2020).

Xue H, Su J, Sun K et al. 2012. Glutathione S-transferase M1and T1 gene polymorphism and COPD risk in smokers: an updatedanalysis. *Mol Biol Rep*, 39: 5033-5042.

Yeo J, Morales DA, Chen T et al. 2018. RNAseq analysis of bronchial epithelial cells to identify COPD-associated genes and SNPs. *BMC Pulm Med*, 18(1): 42.

Yim JJ, Park GY, Lee CT et al. 2000. Genetic susceptibility to chronic obstructive pulmonary disease in Koreans: Combined analysis of polymorphic genotypes for microsomal epoxide hydrolase and glutathione S-transferase M1 and T1. *Thorax*, 55: 121–125.

Yohan Bosse 2012. Updates on the COPD gene list. *Int J Chron Obstruct Pulmon Dis*, 7: 607–631.

Zhan P, Wang J, Wei S-Z et al. 2010. TNF-308 gene polymorphism is associated with COPD risk among Asians: Meta-analysis of data for 6,118 subjects. *Molecular Biology Reports* (Internet). *Springer Science and Business Media LLC*, 38(1): 219–227.

Paper received for publication in April, 2020
Paper accepted for publication in July, 2020