The Genetics of Asthma

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Abstract. Asthma is a chronic inflammatory disease characterized by airway obstruction and hyper-responsiveness. It is a complex disorder influenced by genetic and environmental factors, which contribute to the clinical manifestations of asthma. Asthma may affect the lower respiratory tract, causing epithelial damage, mucus hyper-secretion, edema, bronchospasm, and airway remodeling. Genetic studies have uncovered single nucleotide polymorphisms (SNPs) associated with asthma. However, knowledge of the functional impact of these SNPs is lacking. Several genes associated with asthma have been well characterized on a functional level: *ORMDL3, S1PR1, PHF11, F3*, and *ADAM33*. Epigenetic modifications, which include DNA methylation, histone modification, and miRNA, affect transcriptional activity in multiple genetic pathways associated with the development of asthma. The aim of this paper is to describe the pathophysiology, etiology, genetics, and epigenetics of asthma and the factors contributing to its development.

Keywords: asthma, genetics, epigenetics

1 Introduction

Asthma is a chronic inflammatory disease characterized by airway obstruction and hyperresponsiveness. The condition runs in families; therefore, children of asthmatic parents are at an increased risk of developing asthma [1,2]. It has been documented that approximately 300 million people of all ages and ethnicities suffer from asthma worldwide. Episodes of asthma happen recurrently and can involve wheezing, coughing, tightness of the chest, and shortness of breath. These episodes are caused by airway obstruction and may be reversed spontaneously or with treatment [3,4].

Asthma is a complex disorder influenced by genetic and environmental factors, both of which modulate the clinical expression of asthma. Genetic factors play a key role and determine whether the person is susceptible to the disease. Multiple genes have been known to cause asthma: each gene contributes a small amount to the overall pathology, and genes interact with each other and with the environment to determine the phenotype. The frequency and duration of environmental exposures might complicate the disease [5].

As asthma is a complex disease, so it does not follow the simple Mendelian pattern so it is not caused by a single mutation of the disease just like the monogenic disease, which is the autosomal dominant or the autosomal recessive. Complex disease or polygenic disease needs multiple factors to be contributed to make the disease happens [2].

The degree of genetic relatedness to an affected family member influences the risk of asthma in a person. If a person in the family is severely affected or affected at an early age, the risk will also be higher in the person's relatives. In children with asthmatic parents, the risk of asthma occurrence is 25% when one parent is affected and 50% when both parents have asthma. The risk of asthma in a dizygotic twin with an affected twin is lower than that in monozygotic twins. However, the risk of asthma in a monozygotic twin when the other twin is affected is not 100% but 75%, due to the effects of environmental circumstances that interact with the person's genetic background [2].

The prevalence of asthma is higher in children than in adults and higher in females than in males [6]. Male children have a higher risk of asthma than female children, whereas the prevalence of asthma in adults is higher in females than in males [4]. Geographic and racial differences in asthma occurrence also exist. This indicates that environmental factors interact with genes to determine the risk of asthma [2].

Studies have identified genetic variants associated with asthma risk; however, single nucleotide polymorphisms (SNPs) alone could not explain the inheritance patterns of asthma. Therefore, studies on gene-environment interactions were carried out, and it was observed that air pollutants, cigarette smoke, allergens, and exposure to bacterial and viral agents during the prenatal and postnatal periods contributed to asthma development [7].

2 Asthma

The Global Strategy for Asthma Management and Prevention (Batemen *et al.* 2008) defines asthma as a chronic inflammatory disorder of the airways involving many cells and cellular elements. Chronic inflammation in asthma is associated with airway hyper-responsiveness, which leads to recurrent episodes of coughing, breathlessness, wheezing, and chest tightness. These episodes are due to obstruction of the airway within the lung, which can be reversible with treatment or spontaneous [8].

Asthma is associated with atopy, but factors unrelated to atopy can also influence the disease [8]. Atopic asthma commonly starts in adolescence or even in childhood. It is related to allergens, which trigger the immune system of the body. This type of asthma is commonly associated with a history of allergy in the family. The asthma itself occurs as a response to allergens, for example, tree and grass pollen, pet dander, and dust mites [8].

2.1 Risk Factors of Asthma

A study identified the risk factors contributing to asthma development in childhood [9]. Genetic susceptibility alone is not sufficient to cause asthma. Environmental

factors interact with genetic predisposition to trigger the disease. Factors that influence asthma development in predisposed individuals include air pollution, allergens, and tobacco smoking [4].

2.2 Pathophysiology of Asthma

Asthma is a disorder involving airway obstruction and airflow restriction. The release of mediators and metabolic products from inflammatory cells, caused by allergenic and non-allergenic stimuli, may induce bronchoconstriction [6]. Asthma affects the lower respiratory tract, such as the bronchi, bronchioles, and trachea. Bronchoconstriction and abnormal airway narrowing are caused by damage to the airway epithelium, edema, bronchospasm, mucus overproduction, and damage to the airway musculature [8].

These airway changes may become permanent and may also increase hyper-responsiveness and obstruction, decreasing the response to treatment. This is called "airway remodeling"; the extent of airway remodeling is an indicator of the severity of asthma as well as being a clinical manifestation of the disease [6].

Asthma is classified as atopic, non-atopic or a combination of both, based on the presence of immunoglobulin E (Ig-E) antibodies to environmental antigens, such us pollen, dander, and mites, and to microbiologic antigens, such as bacteria and viruses. An immunologic response suggests an acquired cause of asthma, whereas the absence of an immunologic response suggests an innate cause [6,8].

Both allergic (atopic) and non-allergic (non-atopic) asthma are characterized by infiltration of the airways by T-helper cells. The T-helper cells produces cytokines, for example, interleukin (IL)-13, IL-4, and IL-5, stimulating basophil, eosinophil, mast cell, and leukocyte migration to the airways. These cells cause bronchospasms, mucous production, edema, and an exaggerated inflammatory response [6].

Mast cells produce cytokines, which cause hyper-responsiveness of the smooth muscle of the airway, recruitment of eosinophils, and synthesis of IgE. Another mast cell product is proteases, which destroy the airway epithelium and contribute to airway modeling. TNF-α, which is also released by mast cells, potentially causes bronchoconstriction. The persistent activation of mast cells may lead to the symptoms of chronic asthma via the constant release of inflammatory mediators and cytokines and inflammation of the airway. If this happens over a long period, it may contribute to airway remodeling [6].

In most forms of allergic asthma, eosinophils are the most common effector cells found in the airways. Granules in the eosinophils release inflammatory mediators, including eosinophil cationic protein, major basic protein, and eosinophil peroxidase, which are highly bronchoconstrictive. Eosinophil cationic protein will induce mucous hypersecretion, and histamine will be released from mast cells. Another product of eosinophils, leukotrienes, is also bronchoconstrictive and causes thick mucus secretion, which may obstruct the airway. Moreover, it will enhance vascular permeability and cause edema [6].

2.3 The Genetics of Asthma

Asthma is a complex disease that does not result from a single gene mutation. Rather, the genetics of asthma depends on variation in single nucleotide polymorphisms (SNPs) and the functional impacts of their related phenotypes [2,10]. A number of studies have investigated the association of SNPs with asthma [10].

2.4 Genetic Studies of Asthma

The types of studies that have been widely used to identify asthma-related genes are linkage studies, association studies, and genome-wide association studies (GWAS), each with their own advantages and disadvantages. Candidate gene association studies are usually case-control studies in which the researcher searches for a marker allele, the SNP. This type of study can also find the haplotypes or allele combinations in a particular disease and compare it with those in the control groups. Other approaches that can be used are cohort and cross-sectional studies. These studies search for additional markers of the diseases in individuals with certain genotypes at the haplotype or marker locus [11].

Genes selected for these studies functional candidates or those positioned is near to the candidate. Candidate gene association studies are commonly used and select genes based on their function and involvement in pathogenesis. The next strategy requires some knowledge of the gene's haplotype structure and the ability to select the associated SNPs that occur in common haplotypes. Therefore, such studies can be biased toward immune-related genes. Another limitation of this type of study is that it cannot be used to discover novel genes or pathways [11].

Another approach that has been used is the GWAS. In this type of study, researchers search the entire genome without any prior knowledge of the location of genes that contribute to the disease. In contrast to candidate gene studies, GWAS can be used to discover new genes and pathways to the pathogenesis of the disease. The weakness of this type of study is the need for a large number of tests and a very large sample size to obtain statistical significance. Moreover, it does not always explain the association between variants or loci and disease pathogenesis [11]. The advantages of this study are that it has good power to detect risk variants with small effect sizes, it does not require the participation of families, and has high resolution. The candidate gene approach can be extended to obtain markers that tag all common variation in the genome [11].

A second type of genome-wide study is the genome-wide linkage study. This type of study requires a large sample and the availability of a family with at least two affected members. In linkage studies, the loci associated with the disease cosegregate with the disease in families [11].

2.5 Genes Associated with Asthma

The interaction between genetics and genomics with environmental exposure at different times during the course of a person's life causes asthma susceptibility and severity. Genes associated with susceptibility interact with environmental risk factors, causing early, mild, or intermittent asthma. Then, other genes which interact with additional environmental exposure or epigenetic factors will lead to disease progression. In severe asthma, there is a variation in the clinical pattern, which

shows individual genetic profiles combined with environmental exposures that initiate persistent bronchial inflammation and tissue injury. This condition will lead to pathophysiological abnormalities and airway wall remodeling [12].

Moffat and colleagues in 2007 were the first to identify a novel locus on 17q21 containing the *ORMDL3* and *GSDMB* genes through GWAS. This locus is the most consistently identified locus associated with asthma in subsequent GWAS. This study revealed that GWAS has the potential to uncover novel susceptibility genes and to identify previously unknown biological processes involved in asthma susceptibility. Other loci which have been identified by GWAS are *IL33* on chromosome 9p24, *HLA-DR* and *HLA-DQ* genes on chromosomes 6p21, *IL1RL1* and *IL18R1* on chromosomes 2q12, *WDR36* and *TSLP* on chromosome 5q22, and *IL13* on chromosome 5q31[12].

Genetic variants are often assumed to contribute equally to disease susceptibility. However, some genomic regions are unique to each group of loci. However, due to inconsistent findings in different populations, these variants cannot be identified as causative. If the SNPs are located in functional regions and are more evolutionary conserved, the minor allele of the SNPs will be rarer [10].

The protein code might be changed on the level of translation, structure, stability, and transcription, depending on the location of the gene variation. The SNPs identified by GWAS were likely to be in 5-kilobase-pair (kbp) promoter regions and at non-synonymous sites, unlike SNPs which are selected randomly from genotyping arrays. Alterations in mRNA expression influence the modes of action of the disease variants [10].

The SNPs associated with asthma whose functional effects or impact have been well characterized will be discussed here. The genes known to be functionally associated with the pathophysiology of asthma are *ORMDL3*, *GSDMB*, *S1PR1*, and *PHF11* [10].

The genes *ORM1-like3* (*ORMDL3*) and gasdermin are associated with childhood asthma, and they are located at 17q21.1. The gene product of *ORMDL3*, ORM1-like protein 3, is a transmembrane protein located in the endoplasmic reticulum. The reduction of the Ca2+ level in the endoplasmic reticulum is caused by overexpression of this gene in HEK293 and Jurkat T-cell lines. Overexpression of this gene will also upregulate the expression of immunoglobulin heavy chain-binding protein or BIP and early growth response factor 1 (EGR1) and enhance the phosphorylation of eukaryotic initiation factor. All of these mechanisms are pathway in the unfolded-protein response (UPR) [10]. The SNP in this gene, which is associated with childhood asthma, is rs7216389. In white blood cells, other SNPs in this region have been associated with *ORMDL3* mRNA expression and that of *GSDMB*, which is located nearby [10].

Modulation of the expression *ORMDL3* and its neighboring genes is the result of interactions with SNP rs12936231 (C>G), in which the G allele binds more strongly to CCCTC-binding factor (CTCF) proteins compared with the C allele. This polymorphism causes CTCF to be involved in nucleosome repositioning and chromatin looping. It can be said that *ORMDL3* gene expression is the result of initiation of these binding interactions [10].

The exact role of *ORMDL3* in the pathogenesis of asthma is still unknown, but its role in asthma is believed to be via participation in the UPR. This pathway may activate c-Jun N-terminal kinase and B cells (NF-kB), which are activated by the nuclear factor kappa-light-chain enhancer, and therefore will trigger inflammation [10].

The *sphingosine-1-phosphate receptor 1* or *S1PR1* gene is located on chromosome 1p21. This gene is expressed in the pulmonary vessels and lungs, and it encodes the protein sphingosine-1-phosphate receptor1 [10]. The *S1PR1* gene was cloned and sequenced and found to be associated with different SNPs. Some of the SNPs reside in introns, and others, such as rs2038366 (G>T) and rs3753194 (T>C), are in the promoter region. It has been confirmed that alteration of the nucleotide bases at these sites results in a biological change [10].

The *in vivo* mechanism by which these SNPs influence the pathophysiology of asthma is still unclear, but the protein product of the *S1PR1* gene was confirmed as an important factor in asthma development. Other proteins that are important factors in asthma interact with S1PR1, and it is responsible for airway remodeling, vascular permeability, and hyper-responsiveness regulation [10].

Other manifestations of asthma related to the *S1PR1* gene occur via alterations in airway vascular permeability and angiogenesis. Overexpression of this gene has also been known to increase sputum production caused by vascular endothelial growth factor. Upregulation of SIPRI may thus lead to vasodilatation and angiogenesis via activation of nitric oxide synthase 3 (NOS3) [10].

The *PHD finger 11* gene (*PHF11*) is located on chromosome 13q14.1 and encodes the protein plant homeodomain (PHD) finger protein 11. The SNP rs1046295 (G>A) was confirmed to have functional effects in asthma. A study showed that the minor allele A had stronger binding affinity for octamer-binding transcription factors than the minor allele G in a human B-cell line. Allele A was found to be overexpressed in T-helper type 1 (Th1) cells [10].

The PHF11 gene isoform that lacks exon II in SNP rs1046295 results in a malfunctioning transcript in T-helper 1 cells. This interaction, however, will not affect splicing straightaway because of its location in the 3′-UTR [10].

There are several effects of PHF on gene expression. The first is reduction of NF-kB import to the nucleus in activated cells. The second is reduction of transcription of the Th1 cytokine interferon-γ, CD28 co-receptors in T cells, and IL-2. Lastly, PHF11 expression reduction leads to a reduction in T cell number, resulting in an increased risk of low-serum IgE asthma in the presence of the atopy-associated G-allele. The NF-kB-mediated T-helper 1 response may be suppressed, thus reducing T-cell viability [10].

A disintegrin and metalloprotease 33 gene (*ADAM33*) was the first identified asthma susceptibility gene. It is located on chromosome 20p13. *ADAM33* has 22 exons and a domain structure consisting of a metalloprotease domain, a prodomain, a disintegrin domain, a cysteine-rich domain (with epidermal growth factor (EGF)-like motif), transmembrane and cytoplasmic domains, a signal sequence, and protease activity. These domains impart different functions of *ADAM33*, which are cell-cell adhesion, cell-cell and cell-matrix interactions, and cell migration. The ADAM protein family constitutes many kinds of cell-surface proteins, including receptors,

cytokines, and growth factors [13]. A study by Awasthi found an association of the *ADAM 33* SNPs T2, T1, and S1 with asthma.

2.6 Epigenetics of Asthma

Asthma is a chronic inflammatory disease of the airways; as such, inflammatory and immunologic factors play major roles in its natural history and etiology. The immune response can be modulated by many environmental exposures, such as endotoxins, and those that impart oxidative stress in airways, such as tobacco smoke and air pollution; all of these will increase the risk of asthma. So, it can be said that environmental factors are the first signals to initiate of the mechanism of epigenetics [14,15].

The most widely studied epigenetic mechanisms are DNA methylation, histone modification, and miRNA or small noncoding mRNA. These mechanisms affect transcriptional activity in many genetic pathways in relation to asthma development. Epigenetic markers may alter DNA or chromatin structure via changes in histone proteins. These alterations may remain and be inherited as an epigenetic profile. Concurrently, gene polymorphisms can generate variation in the methylation pattern at quantitative loci. For example, replacement of GA dinucleotide sequences with CG may generate potential methylation sites [14,15].

Epigenetics has a major impact on the development of asthma and other related lung diseases. The process of the cellular activity is commonly the same with other lung diseases, and modification of gene expression may occur in different cell types as a result of environmental exposure. Below is the schematic view of the role of epigenetics in asthma pathogenesis [14].

2.7 DNA Methylation

DNA methylation is the covalent addition of a methyl group to a cytosine residue (5-methylcytosine) located next to a guanine residue in the DNA sequence. DNA methylation occurs at CpG sites in C-G-rich regions. Clusters of CpGs located next to gene promoters are called CpG islands. CpG islands are located in the promoter regions and first exons of many genes. This region is the location of the transcriptional start site, and is thus a target for modulation of gene expression [15].

DNA methyl transferases add methyl groups to the cytosine bases in CpG dinucleotides. Most CpG islands are methylated, but single CpGs are not. DNA methylation may affect the transcription of the gene straightaway. It works by blocking transcription factor binding and by indirectly binding methyl-CpG-binding domain proteins. Other proteins may bind to this region, for example, histone deacetylases, which increase chromosome condensation, preventing transcription [14].

Gene silencing, which is often associated with the promoter region of specific genes, is the result of DNA hypermethylation; however, intragenic DNA methylation is correlated with the transcriptional level of CD19+ B lymphocytes in humans [15].

Perera and colleagues were the only group to conduct a study about the relationship between asthma and gene-specific DNA methylation. They found that polycyclic aromatic hydrocarbons, which are found in the diet, air pollution, and tobacco smoke, were associated with DNA methylation levels at CpG sites in white blood cells of the umbilical cords of asthmatic patients [15].

Many studies have confirmed that diet, maternal smoking, microbial exposure, air pollution during pregnancy, maternal allergy, and low birth weight modulate DNA methylation. These environmental exposures influence DNA methylation preferentially over other epigenetic alterations [15].

2.8 Histone Modification

The histones proteins pack tightly with the DNA to establish chromatin structure. Post-translational modification of core histone tails is a particularly important epigenetic modification affecting gene transcription. Histone acetylation, for example, at lysine residues, is catalyzed by histone acetyltransferase or HATs and is important in the regulation of gene expression. Histone hyperacetylation favors gene expression, whereas deacetylation by histone deacetylases or HDACs causes gene silencing. The imbalance of HATs and HDACs will cause inappropriate gene expression and thus lead to disease development (e.g., cancers and asthma) [14,15].

Histone tail acetylation itself is often caused by loose chromatin structure. This modification will amplify the accessibility of transcription factor binding sites and gene expression activation. When the chromatin structure is unwound, HATs can act to increase histone acetylation. Moreover, when transcriptional activation occurs, the action of HDACs will remove acetyl groups, leading to transcriptional silencing and chromatin condensation [15].

HDACs affect T lymphocyte regulation and development, which contribute to the pathophysiology of asthma. HDAC inhibition may result in atopic airway inflammation, whereas in a study using a mouse model, conditional deletion of HDAC in T cells caused eosinophil recruitment to the lungs, hypersecretion of mucus, inflammation of the lung parenchyma, and increased airway resistance. In addition, Th2 cytokines (IL-13 and IL-4) were increased in HDAC-deficient T helper 2 cells [15].

In a study on rats, exposure to cigarette smoke resulted in a significant reduction of HDAC2 expression in the lungs. This supports the evidence presented by a study that documented associations between exposure to asthma-risk-inducing environmental agents and histone modification [15].

2.9 miRNA

microRNAs (miRNAs) are short (19–25 nucleotides), non-coding single-stranded RNA (ssRNAs) that regulate gene expression by binding to specific sequences. This will target the mRNA for degradation, ultimately preventing protein translation [14].

mRNA destabilization and translational inhibition will cause most miRNAs to repress gene expression. Polymerase II transcribes miRNA genes and will generate a hairpin loop of primary miRNA (pri-miRNA). The product of transcription is spliced, capped at the 5′-end and polyadenylated. In order to produce a precursor miRNA, the pri-miRNA should be cleaved by the RNase III endonuclease Drosha and the dsRNA-binding protein DGCR8/Pasha. Subsequently, Exportin-5 will help to transport pre-miRNA into the cytoplasm, where it is cleaved by the RNase III endonuclease Dicer to produce miRNA [15].

Pathophysiological aspects of asthma such airway inflammation, airway hyperresponsiveness, and immunity involve many miRNAs. miRNA genes and DNA sequence variations including the pri-and pre-miRNA influence miRNA function. A study found that an asthma susceptibility gene (HLA-G) and its SNPs (+3142C/G SNP (rs1063320) in the HLA-G 3′-UTR) affect the occurrence of maternal asthma, which may increase the risk of asthma in the offspring. HLA-G expression is affected by binding of miR-148a, miR-148b, and miR-152 to the mRNA [15].

3 Conclusion

Asthma is a complex disorder influenced by genetic and environmental factors. Genetic factors play a key role in the development of asthma and determine whether a person is susceptible to the disease. [5] Many factors increase the risk of asthma development; these include age, sex, prenatal factors, viruses, microorganisms, diet, smoking, air pollution, house dust mites, occupational exposure, pets, endotoxins, and many more [9].

Asthma is a chronic disorder which involves airway obstruction and causes airflow limitation. The mediators and metabolic products released from inflammatory cells upon stimulation by external factors may induce bronchoconstriction. Asthma may cause epithelial damage, mucus hypersecretion, edema, bronchospasm, and airway remodeling [4,6].

Many studies have been conducted to identify the genetics of asthma; these have found a number of SNPs associated with asthma. However, further studies are required on the functional impact of these SNPs. Some SNPs have been shown to have a role in asthma pathogenesis. Some of these are rs12936231 in the *ORMDL3* gene, rs2038366 and rs3753194 in the promoter region of *S1PR1,* and a rs1046295 at the 3′-end of *PHF11* [10].

Allele-specific binding affinity of SNP variants to CCCTC-binding factor mediates the effects of rs12936231 in the *ORMDL3* gene, which are the result of differential interaction between nucleosomes and active chromatin, whereas rs2038366 and rs3753194 in the promoter region of S1PR1 may contribute to the asthma phenotype via transcriptional regulation. Another mechanism is transcriptional regulation and splicing of the gene, which is altered by variation at rs1046295 at the 3'-end of PHF11 [10].

Asthma is a complex disease influenced by genetic and environmental factors. Transcriptional activity in multiple genetic pathways associated with the development of asthma is affected by epigenetic modifications, which are DNA methylation, histone modification, and miRNA. Numerous studies have found an association between environmental exposures in asthma etiology and epigenetic alterations such as air pollution, maternal smoking, diet, and many more [15].

References

1. Maslan J, Mims JW. What is asthma? Pathophysiology, demographics, and health care costs. Otolaryngol Clin North Am. 2014;47(1):13-22.
2. Thomsen SF. Genetics of asthma: an introduction for the clinician. Eur Respir J. 2015;2(1): 24643.

3. Moheimani F, Hsu AC, Reid AT, Williams T, Kicic A, Stick SM, Hansbro PM, Wark PA, Knight DA. The genetic and epigenetic landscapes of the epithelium in asthma. Respir Res. 2016;17(1):119.
4. Lynn BSJ, Kushto-reese K. Understanding asthma pathophysiology, diagnosis, and management. Am Nurse Today. 2015:49-51.
5. Halapi E, Bjornsdottir US. Overview on the current status of asthma genetics. Clin Respir J. 2009;3(1):2-7.
6. Nowak R, Tokarski G. Pulmonary system, Asthma. In: Rosen's Emergency Medicine. 2013:941-6.
7. Lee JU, Kim JD, Park CS. Gene-environment interactions in asthma: genetic and epigenetic effects. Yonsei Med J. 2015;56(4):877-86.
8. Kaufman G, Rebecca R, Kaufman G. Asthma: pathophysiology, diagnosis and management. Nurs Stand RCN Publ. 2011.
9. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? The Lancet. 2015;386(9998):1075-85.
10. Poon A, Litonjua AA, Laprise C. Relevance and implication of genetic determinants to asthma pathophysiology. Curr Opin Allergy Clin Immunol. 2011;11(5):407-13.
11. Ober C, Yao TC. The genetics of asthma and allergic disease: a 21st century perspective. Immunol Rev. 2011;242(1):10-30.
12. Meyers DA, Bleecker ER, Holloway JW, Holgate ST. Asthma genetics and personalised medicine. Lancet Respir Med. 2014;2(5):405-15.
13. Awasthi S, Tripathi P, Prasad R, Ganesh S. Association of A Disintegrin And Metalloprotease 33 Gene Polymorphisms and Their Haplotypes with Asthma in The North-Indian Population. Indian J. Med. Sci. 2016;68(1):54-62.
14. Alizadeh Z, Mortaz E, Adcock I, Moin M. Role of Epigenetics in the Pathogenesis of Asthma. Iran J Allergy Asthma Immunol. 2017;16(2):82.
15. Salam MT, Zhang Y, Begum K. Epigenetics and childhood asthma: current evidence and future research directions. Epigenomics. 2012 Aug;4(4):415-29.