Chapter 7

Genetics of Allergic Asthma and Current Perspectives on Therapeutic Management

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Additional information is available at the end of the chapter

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Abstract

Globally, more than 300 million people are asthmatics and this number has been estimated to become 400 million by 2025. Asthma is a chronic inflammatory condition, which, although has no cure, is treatable in most patients. The most common structural alterations in asthmatic airways include thickening of the epithelial and sub epithelial layers, increased airway smooth muscle mass, and angiogenesis. Several genetically controlled factors greatly influence the predisposition and severity of allergic asthma. Twin studies have attributed as much as 75% of asthma susceptibility to heredity. Particularly, genome-wide association studies (GWASs) have discovered several asthma and/or atopy susceptibility genes. Current treatment protocols for managing asthma involve the use of corticosteroids and β-agonists. Over the last 40 years, there has been a marked development-targeted therapy for asthma, such as anti-leukotrienes, anti-immunoglobulin (Ig)E, anti-tumor necrosis factor (TNF)-α, and anti-interleukins (ILs) (Th2 cytokines). To identify novel targets and to develop newer drug generations, better understanding of asthma molecular pathophysiology is required. Furthermore, the pharmacogenetic studies, focusing on better understanding of beneficial or/and adverse effects to anti-asthma drugs, will also facilitate the development of more effective and targeted treatments in specific subpopulations of patients suffering from asthma.

Keywords: asthma, asthma therapies, genetics, pharmacogenetics

1. Introduction

Asthma is an inflammatory chronic condition that has reached globally epidemic levels. Although no cure exists, symptoms are treatable in most patients [1]. Statistically, the number

of asthmatic cases has been on the rise over the past 10 years and affecting up to 10% of adults and 20% of children worldwide [2]. Globally, more than 300 million people are asthmatics, and this estimate is predicted to become 400 million by 2025 [3]. The worldwide economic burden caused by asthma is predicted to be more than that of both acquired immunod eficiency syndrome (AIDS) and tuberculosis combined together. For example, in the United States of America, the annual asthma care costs exceed US$6 billion [4]. Moreover, these numbers are due to the fact that more than 50% of asthmatic cases are poorly controlled by medication, since the response to treatments varies considerably among patients despite having similar clinical features [3, 5]. Asthma is characterized by altered and distinct clinical changes in the lung airways obstructing the flow of air into the lungs. The most prominent airway remodeling features include epithelial and subepithelial layer thickening, increased airway smooth muscle (ASM) mass, and angiogenesis [6]. Different classes of asthma therapies address one or more of the phenotypes of asthma; however, the heterogeneous nature of the disease prevents homogeneous clinical outcomes in response to the current treatment guidelines [7].

In the past two decades, the field of human genetics has evolved due to the advancements in the human genome project and high-throughput sequencing technologies [8, 9]. Currently, the advances in genetic, pharmacodynamic, and pharmacokinetic studies, analyzing responsiveness of patients to various therapies, may eventually allow to prescribe personalized treatment and to shift asthma therapies from classical standards, using mostly corticosteroids and β-adrenergic agonists, to a highly tailored approach [10]. Future genetic profiles of the population would form the basis of tomorrow's treatments in order to potentiate the required therapeutic benefits, and to diminish any possible adverse effect risks. Overall, there remains a great need for comprehensive drug research, paralleled with high-throughput genetic profiling, in order to treat asthma in a personalized or stratified manner [11].

2. Genetic control of airway hyperresponsiveness, atopy, and allergic asthma

The heritable nature of asthma has been demonstrated through various types of studies over the past decades. Family and twin studies indicate that 60–70% of asthma cases are due to genetic factors. Moreover, it has been proven that the concordance of asthma is greater among monozygotic twins rather than among dizygotic ones. Adoption studies have shown greater disease prevalence within biological relatives of the affected people compared to the adopted family [12].

Higher prevalence of allergic disease phenotypes is observed among relatives of atopic individuals compared to nonatopic individuals. Overall, the heritability estimates remain in between the range of 30–66% for airway hyperresponsiveness, 35–95% for asthma, and 35–84% for total serum IgE levels [13]. It is clear that both the inter-genetic individual differences and the degree of allergen exposure contribute to these variations in heritability. Heritability of asthma is linked to both disease susceptibility and severity. While the main concern of asthma genetic studies has been on disease susceptibility, increasing evidence shows that many genetic variants are important in asthma progression and severity as well [14]. Lung

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function tests in asthma showed that genes in the T-helper lymphocyte 1 (Th1) pathway affect asthma severity; meanwhile, T-helper lymphocyte 2 (Th2) pathway genes relate to susceptibility [14]. Based on these hypotheses, genes associated with asthma susceptibility differ from those related to asthma severity; hence, it is important to define both groups distinctly.

By knowing the genetic signature associated with allergic asthma, geneticists can help to better understand the molecular mechanism of this disease, and the shared and distinct pathways among other allergic diseases. Moreover, the genetic signature of asthma-associated genes with altered expression during the peak of asthmatic episodes may help predict the severity and response to therapy. Unfavorable response might be identified and, consequently, more targeted and personalized treatments can be considered for this complex trait. The human genome project and the ongoing advancements in sequencing technologies, both, resulted in more successful gene discovery over the last years, even in diseases as complexed as asthma. Since then, dozens of susceptibility genes were identified through a large variety of methods and rationales. *ADAM33* is the first asthma susceptibility gene to be discovered through positional cloning [15]. ADAM33 (also known as Disintegrin and metalloproteinase domain-containing protein 33) is a membrane-bound metalloproteinase enzyme that has been involved in several cellular interactions involving cell-cell and cell-matrix events [16]. Variants in this gene have been correlated to asthma susceptibility and bronchial hyperresponsiveness, but not atopy. Due to its clinical significance, *ADAM33* studies were conducted among 33 different asthmatic population samples all over the world. Additionally, numerous studies have suggested that altered *ADAM33* DNA methylation patterns could result in diversely unbalanced biological effects in the airways [17]. Studies focused on candidate genes have examined a number of genes involved in asthma and highlighted more than 100 interesting genetic spots; however, the role of those loci in asthma susceptibility remains largely unexplored [18].

Genome-wide association studies (GWASs) extensively investigate the unknown genetic bases of many intricate disorders including asthma [19,20]. In the first reported GWAS study for asthma susceptibility, Moffatt et al. [21] identified the 17q21 locus, containing several genes, for example, *ORMDL3* and *GSDMB* as being associated with childhood asthma. Importance of this region was later on replicated in numerous subsequent studies [22–24]. Expression levels of the gene *ORMDL3* are differentially regulated by distinct haplotypes in this region. This gene encodes protein acting as an inhibitor of sphingolipid biosynthesis and in general Orm family proteins were shown to be implicated in the control of sphingolipid homeostasis [25]. Dysregulated sphingolipid formation in the respiratory tract instigates airway hyperreactivity [26] although exact molecular steps are still not known. The results of these studies suggested that the mechanisms of asthma development are linked with genetically determined abnormalities in some patients resulting in their inability to control balance between oxidative and anti-oxidative reactions. The mechanisms of asthma development are linked with genetically determined abnormalities in the functioning of antioxidant defense enzymes. These alterations seem to be accompanied by a systemic imbalance between oxidative and anti-oxidative reactions with the shift of the redox state toward increased free radical production, oxidation of proteins and phospholipids, and eventually to their selective degradation.

To increase the power of detection of modest alleles due to the large sample size, the results of individual GWAS need to be gathered into a meta-analysis. The scientific literature recognizes two meta-analyses of asthma GWAS. One was done by the GABRIEL Consortium [27] of the European investigators, and the other was conducted by the EVE Consortium of the US investigators [22]. While the EVE meta-analysis included diverse subjects from different ethnic background, US and Mexico population backgrounds, the GABRIEL meta-analysis included only European subjects. Overall, these two thorough meta-analyses present a comprehensive overview of the genetic associations for asthma. Some associations are shared among different populations; by contrast, others are specific to one race. Grouping GWAS in this way increases the power of genetic detection, contrasts different ethnic groups' genotypes, and highlights the worldwide populations' genetic patterns. Overall independent GWASs have identified large number of candidate loci that deserve further testing. Replication studies help to prioritize which genes deserve further study, based on their identification in multiple populations.

Additionally, more loci were identified to be associated with asthma; these include interleukin (IL)-33 (on 9p24), *HLA-DR/DQ* (on 6p21), *IL1RL1/IL18R1* (on 2q12), *TSLP* (on 5q22), and *IL13* (on 5q31) [22,27,28]. Collectively with *ORMDL3/GSDMB* (on 17q21), these are the most remarkable and consistent loci, which are identified for asthma. Since Moffatt et al. had published the first GWAS results for asthma, identifying *ORMDL3* as a candidate gene, numerous other studies have been conducted investigating an array of phenotypes which are observed in allergic diseases. In particular, FCER1A, RAD50, and STAT6 have been associated with total serum IgE levels [29].

3. Environmental factors contributing to asthma

Parallel to genetic factors, environmental factors are also involved in the development and progression of asthma (**Figure 1**). The exposure to some environmental factors was shown to contribute not only to asthma but also to other related respiratory disorders, for example, emphysema development. By contrast, there are also some other environmental factors that seem to be solely linked to the development of asthma but not to other inflammatory or/and respiratory disorders [30]. Various studies assessed the risk factors of asthma and found evidence that allergen exposure, respiratory tract infections, gastroesophageal reflux disease (GERD), and physical and psychosocial stress might represent individual risk factors. It is important to keep in mind that some other environmental factors are protective, such as maternal diet, breastfeeding, and farming conditions [31].

Allergen exposure is the major factor impacting sensitization and constitutes the most common cause of asthmatic exacerbations in adults and children. A wide variety of inhaled allergens may trigger asthma symptoms, for example, house dust mite [32], pollens [33], cockroaches [34], and animal fur [35]. Respiratory tract infections have been implicated in asthma occurrence and exacerbation as well. Examples include infection with viruses [36,37], *Mycoplasma* [38], and *Chlamydia species* [39]. Based on the conclusions from the Japanese study, which

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included 3085 patients, the change in weather followed by smoking was identified as two leading asthma-exacerbating factors [40]. Although (passive) smoking is a predominant contributing factor for the development of asthma [41], one occupational study [42] has shown that nonsmokers might also develop asthma due to occupational air pollutant exposure.

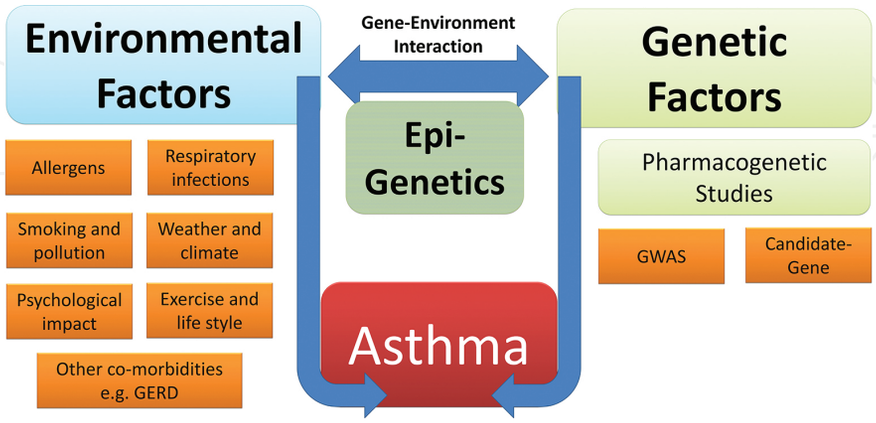

Figure 1. Environmental stress, in conjunction with genetic factors, both contribute to the development of asthma exacerbations.

Additionally, a correlation has been observed between the presence of asthma and gastroesophageal reflux-induced disease, with reports showing one-third of asthmatic patients also diagnosed with GERD [43,44]. Although the coexistence of GERD in asthmatic patients did not affect asthma severity, the airway resistance was significantly higher in asthmatic patients with GERD [45]. Some other psychosocial factors such as parental stress during childhood [46] and the socioeconomic status [47] are reported to influence allergic inflammation severity. It is estimated that psychopathology is six times more common among asthmatics, and accordingly it correlates more closely with the asthmatic quality of life, rather than with lung physiological functions [48,49]. In both directions, psychopathology is supposed to precipitate asthma or vice versa; psychopathology may develop as a consequence of asthma [50].

4. Asthma pathophysiology

Scientists tried to uncover alterations related to asthma since a long time ago. One of the oldest publications that discussed asthma pathophysiology was in 1873 [51]. Later on, in 1886, F.H. Bosworth concluded a possible relation between asthma and hay fever [52]. Clearly, it is well known that asthmatic patients suffer from reversible airway obstruction resulting from an allergen exposure, consequently releasing multiple broncoconstricting mediators that stimulate airway muscles to contract. Furthermore, airways narrow results from past and current mucus and edema occlusion [53]. The chronic inflammation and associated repair of lung airways leads to structural changes, referred to as "*airway remodeling*." Airway remodeling (**Figure 2**) usually involves lung epithelial layer injury and includes features such as subepithelial thickening, airway smooth muscle hyperplasia, and angiogenesis [6].

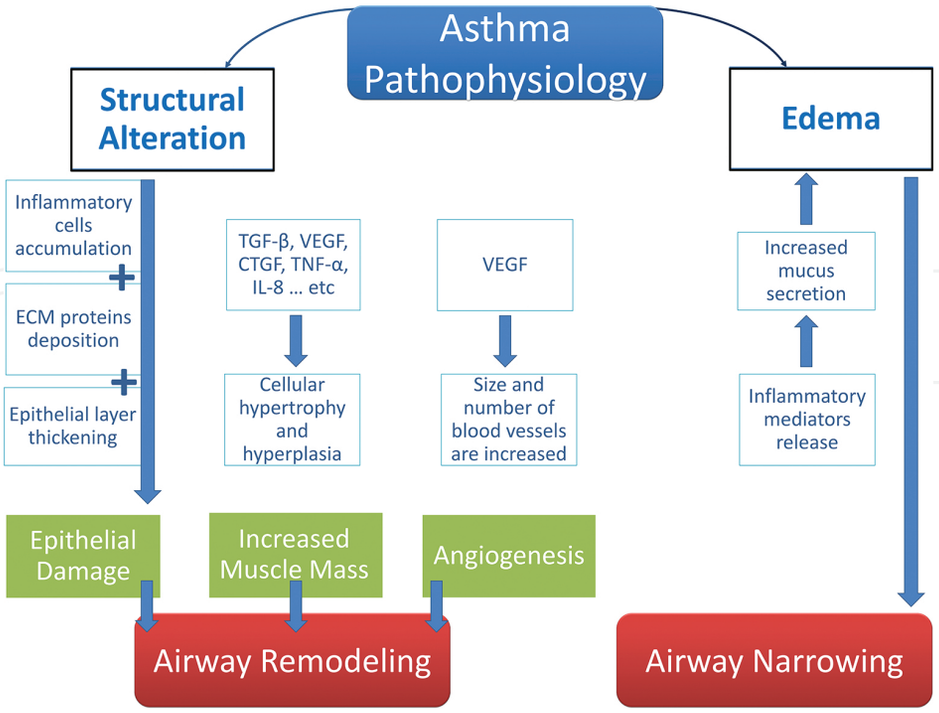

Figure 2. Schematic representation of the major events underlying asthma pathophysiology.

Asthma and COPD (chronic obstructive pulmonary disease) are now considered to be discrete respiratory disorders. Although both share several similar underlying mechanisms, driving airway obstruction in COPD, and hyperresponsiveness in asthma, core molecular pathology remains to be mostly different for both [54]. Pauwels et al. [55] defined COPD as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of lungs to noxious particles and gases." One important reason of asthma and COPD overlap is the effect of aging. Asthma-COPD overlap syndrome (ACOS) is a medically recognized coexisting syndrome of both asthma and COPD [56]. Some other health conditions may occur more frequently in asthmatic patients. Rhinosinusitis [57], obstructive sleep apnea [58], or GERD [59] are the most common documented comorbidities. Substantially, they can contribute to the same pathophysiological process, which is already triggered by allergic response or alter asthma phenotype detrimentally. The impact of these diseases on asthma is variable and still not fully clear [60].

5. Structural alterations in asthmatic airway walls

5.1. Epithelial/subepithelial layer thickening

Epithelial changes are not unique to asthma, they are also observed, in more or less of similar manner, in lungs of smokers and cancer patients [61]. Epithelial layer damage in asthma

includes loss of ciliated cell layer, shedding of the epithelium, goblet cell hyperplasia and growth factors, cytokine and chemokine upregulation [62].

One important feature of asthma, which has been routinely used as an asthma severity index, is the thickening of the subepithelial airways layer. The epithelial and subepithelial layer thickening is caused by the overdeposition of extracellular matrix (ECM) proteins [63]. Roche et al. observed that intensive layers of collagen sedimentation contribute to the thickened subepithelial basement membrane. Through immunohistochemistry, they have shown that the commonly involved collagen types are collagen I, III and V, and fibronectin [64]. Additionally, the cells that are responsible for ECM protein production are myofibroblasts and fibroblasts, as both are embedded in the sophisticated ECM which they secrete [65]. Meanwhile, some inflammatory cells, for example, T cells, mast cells, and eosinophils also accumulate in the submucosal layer [66]. Moreover, transforming growth factor-β (TGF-β), and some similar growth factors, is usually secreted by the lung epithelial cells echoing any ongoing lung injury, and consequently directly impress the matrix proteins' production by fibroblasts/myofibroblasts. By increasing the airway rigidity, however, Holgate et al. suggested that the airway thickening due to the ECM proteins precipitation may in fact have a remodeling protective effect via postponing long-term bronchoconstriction events [62]. Collectively, the ECM proteins, the lung structural cells (i.e., epithelial cells and fibroblasts), and the immune system inflammatory cells, all interact together and control the overall airway remodeling and fibrosis [67].

5.2. Hyperproliferation of airway smooth muscle mass

Hyperproliferation of airway smooth muscle mass is a common event in asthma and has been suggested to be implicated in its pathophysiology. Hyperplasia and hypertrophy of the ASM in the bronchial airways of asthmatics can be observed by three-dimensional (3D) morphometric studies [68]. Airways smooth muscle layer is estimated to be increased by 25–55% in nonfatal asthma and up to 50–200% in fatal asthma [69]. Meanwhile, in response to some growth factors like TGF-β, vascular endothelial growth factor (VEGF), and connective tissue growth factor (CTGF), ASM cells actively participate in the remodeling process through the process of ECM synthesis [70]. ASM cells also express cellular adhesion molecules (CAMs), receptors for cytokines (e.g., tumor necrosis factor-α), Toll-like receptors, and chemokines (eotaxin, macrophage inflammatory protein 1α, and interleukin 8) presenting multiple mechanisms for the inflammatory and remodeling process [71]. Additionally, one characteristic event of the airway remodeling is the ASM cells migration toward the epithelium [72]. Since ASM cells are crucial in asthma, Zuyderduyn et al. suggested that these cells should be targeted, rather than targeting inflammation or dealing with the symptoms [73].

5.3. Angiogenesis

Accumulating evidences indicate that there is an abnormal elevation in the size and number of blood vessels, as well as microvessels vascular leakage within the bronchial tissue in remodeled airways [74]. It is assumed that VEGF strongly affects airways remodeling via its

angiogenic effects, but the exact molecular mechanism linking the increase in the VEGF expression to remodeling of the airways has not been fully understood [75].

Correlation between angiogenesis and asthma severity has also been documented. Dense vascularity occurs in severe asthmatics, followed by moderate, and then finally mild asthmatics, who experience less angiogenesis events [76]. This pattern was also observed in fatal asthmatics compared with nonfatal asthmatics [77]. While current asthma therapeutics is not directly targeting vascular remodeling, recent trials investigate some anti-angiogenic therapies as a new approach for asthma. Yuksel et al. showed that Bevucizamab, which significantly neutralizes VEGF, results in a reduced thickening of lung epithelium, a reduced ASM, and a reduced basement membrane thickness compared with untreated ovalbumin (OVA)-challenged mice [78].

6. Therapies for asthma

Modern treatments for asthma have been tested and used since the early twentieth century [79]. However, the oldest documented drug for asthma dates back to ancient Egypt. Kyphi, an incense mixture drink, was used inside the temples by the priests as a multipurpose lung medicament. There was more than one recipe for Kyphi; each may include as many as 10 herbs [80]. Following this, about 4000 years ago, Atropa Belladonna alkaloids, also called "deadly nightshade" because of their poisonous properties ("Natural Medicinal Herbs"), were derived from the leaves of thorn-apple plant and smoked by the Indians as cough suppressant [82]. Till today, natural and synthesized entities related to the tropane alkaloids class are still widely used. This includes anticholinergics (e.g., natural atropine, hyoscyamine (the levo-isomer of atropine), acopolamine, and the synthetic Ipratropium Bromide and stimulants (e.g., cocaine and hydroxytropacocaine) [83]. In 1872, one of the first papers published on asthma states that rubbing the chest of asthmatics with chloroform liniment can resolve airway constriction [84]. Adrenergic stimulants were in use for asthma over 100 years ago. In 1901, the adrenaline isolated from sheep and oxen adrenal glands was used to treat asthma [85]. The first documented publication of adrenaline as a bronchodilator therapy for asthma was written in 1903 by James Burnett, a physician in Edinburgh [86]. One year later in 1904, adrenaline was synthesized in the laboratories of Friedrich Stolz and Henry Drysdale Dakin, independently [87].

As suggested by the Global Initiative for Asthma (GINA) [88], a five-level step-down approach is widely recognized among the medical practitioners (**Figure 3**). The GINA approach assigns two types of drug classes for managing asthma:

- *Relievers* (bronchodilators) cause immediate dilatation effects on the airways obstruction, mainly by acting on lung's smooth muscle.
- *Controllers* (preventers) provide long-term control of symptoms, mainly by suppressing the underlying disease process.

Legend:
SABA: Short acting beta agonists, ICS: Inhaled corticosteroids (arrow down = low dose, arrow up = high dose), LABA: Long acting beta agoints, LTRA: Leukotriene receptor antagonists, MX: Methylxanthines, OCS: Oral corticosteroids, OZ: Omalizumab

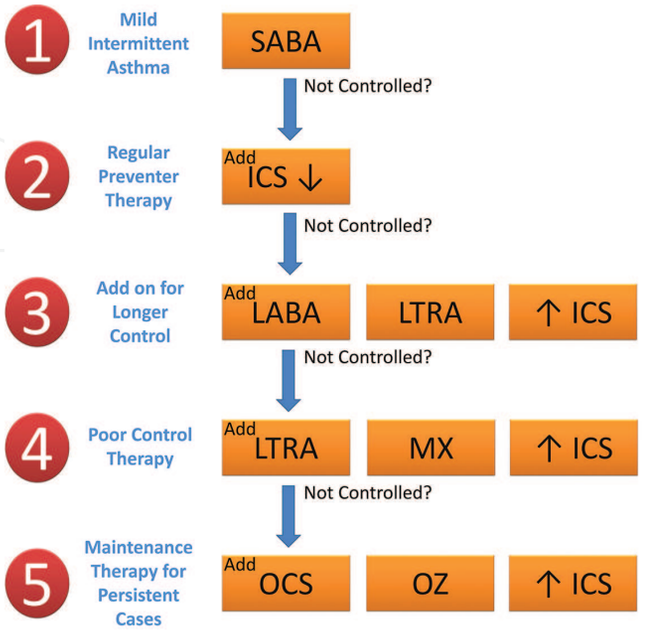

Figure 3. Stepwise approach for controlling asthma symptoms and minimizing future morbidity.

β2-agonists and anticholinergics are considered to be bronchodilator relievers. Asthma controllers include corticosteroids, anti-leukotrienes, and anti-IgE. Theophylline is casually classified as both a bronchodilator and a reliever. The following book section will briefly discuss each therapeutic class.

6.1. Corticosteroids

Nowadays, most popular protocols for managing asthma involve the use of corticosteroids and β-agonists [1]. Anti-inflammatory corticosteroids, which are one of most trusted treatments for asthma, were introduced in mid-twentieth century [79]. The principle mode of action of corticosteroids in asthma is through their direct anti-inflammatory effect in different white blood cells including T cells, mast cells, and eosinophils. Among leukocytes, corticosteroids suppress chemotaxis and adhesion, and prevent inflammatory cytokines recruitment [89]. *In vitro*, corticosteroids reduce human ASM proliferation directly [90] by stimulating p21 gene expression [91], an important regulator of cell cycle progression. Moreover, corticosteroids improve vast majority of vascular remodeling aspects in asthma, reducing angiogenesis, excess blood flow, and vascular leakage [92]. This is mainly mediated by decreasing VEGF activity within the airway wall cells [93].

Various studies describe contradicting effects of corticosteroids on the lung epithelial abnormalities in asthmatics. Dorscheid et al. [94] reported that Dexamethasone treatment resulted

in increased epithelial apoptosis and shedding. Similar results were obtained when treating guinea pigs with Budesonide, which did not improve the tracheal epithelium [95]. By contrast, some *in vivo* studies showed that inhaled corticosteroid (ICS) treatment resulted in improvement of epithelial damage in severe asthmatics [96,97].

ICS has been used around for the past couple of decades. Its idea dates back to the nineteenth century when the hand-held glass bulb nebulizer was used; however, pressurized metered-dose inhaler (pMDI) came to the clinic in 1956. After seeing his daughter's suffering while using the hand-held nebulizer, George Maison, a medical consultant at 3M Pharmaceuticals, had advocated the use of pMDI. In 1959, George Maison and Irvine Porush were awarded a patent on the first pMDI [98].

6.2 β-adrenergic agonists

Long-acting β-agonists (LABAs), for example, Formoterol [99] and Salmeterol [100], offer a longer period of bronchodilation compared to the short-acting beta agonists (SABAs), for example, Salbutamol [101] and Terbutaline [102]. LABAs persist in the airway tissues for long periods due to their lipophilic nature and they provide a good umbrella of asthma bronchodilation and control, particularly at night [99,100]. However, until recently, the medical literature lacked supporting studies reporting the positive effect of β_2 agonists on the chronic airway remodeling [103]. Addition of a β-agonist to the corticosteroid therapy allows a "steroid-sparing" effect, that is, maintains asthma control using lower doses of corticosteroids [104]. LABAs are not used as monotherapies anymore and they must be used in combination with ICS [105], because there have been cases of severe exacerbations and death when LABAs are administrated solely.

6.3. Antimuscarinic agents

Inhaled antimuscarinic agents, also known as inhaled anticholinergics, are considered another alternative bronchodilator group to β-agonists. The bronchodilation effect is functionally mediated via muscarinic receptor subtypes M1, M2, and M3, although five muscarinic receptors have been revealed in the lungs M1, M2, M3, M4, and M5 [106]. It is widely known that parasympathetic stimulation via the vagus nerve leads to immediate smooth muscle contraction and mucus secretion in the airways [107]. It is also suggested that M receptors interact with β2-adrenergic receptors (ADRB2) on the airways smooth muscle, leading to a reduced bronchodilator response of the β-agonists [108]. For years, in both adults and children, short-acting antimuscarinic agents use, for example, Ipratropium [109], has been limited to acute asthma management, in addition to inhaled SABA [110, 111]. Long-acting antimuscarinic agents, for example, Tiotropium [112], appear to have more benefits in difficult-to-control asthma. Adding Tiotropium to the standard asthma therapy significantly reduces asthma symptoms and highly increases the clinical outcomes [113, 114].

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6.4. Targeted therapies

Over the last 40 years, there has been a marked increase in the development of targeted treatments for asthma—anti-leukotrienes, anti-IgE, anti-interleukins, and anti-TNF-α [115]. Obviously, as more of the biological basis of asthma is uncovered, more effective targeted asthma treatments might be developed. The list of most recently published clinical trials covering the period from 1 January 2013 to 1 January 2016, as well as the list of currently ongoing registered clinical trials that has started since 2013 for the new asthma medications are summarized in **Tables 1** and **2**, respectively.

Clinical Trial Identifier	Publication Title	Phase	Drugs	Outcome	Responsible Party	Reference
NCT01147744	Efficacy, safety, and tolerability of GSK2190915, a 5-lipoxygenase-activating protein inhibitor, in adults and adolescents with persistent asthma: a randomized dose-ranging study.	Phase 2	GSK2190915 (5-lipoxygenase-activating protein inhibitor)	GSK2190915 30-mg efficacy was demonstrated in day-time symptom scores and day-time SABA use, compared with placebo. No additional improvement on efficacy was gained by administration of greater doses than 30 mg. GSK2190915 was well tolerated.	GlaxoSmithKline	[1]
NCT00411814	A phase 1, randomized, placebo-controlled, dose-escalation study of an anti-IL-13 monoclonal antibody in healthy subjects and mild asthmatics.	Phase 1	GSK679586 (anti-IL-13)	GSK679586 showed dose-dependent pharmacological activity in the lungs of mild intermittent asthmatic patients. GSK679586 could be a potential therapeutic candidate for treatment of asthma.	GlaxoSmithKline	[2]
NCT00659659)	Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia.	Phase 1	Benralizumab (Anti-IL-5)	Single-dose I.V. and multiple-dose S.C. of benralizumab reduced eosinophil counts in airway mucosa/submucosa and sputum and decreases eosinophil counts in bone	MedImmune LLC	[3]

Clinical Trial Identifier	Publication Title	Phase	Drugs	Outcome	Responsible Party	Reference
				marrow and peripheral blood in asthmatic patients.		
NCT01007149	A proof-of-concept, randomized, controlled trial of omalizumab in patients with severe, difficult-to-control, nonatopic asthma.	Phase 3	Omalizumab (anti-IgE)	Omalizumab may have a therapeutic potential for treatment of severe nonatopic asthma.	Novartis Pharmaceuticals	[4]
NCT00971035	Dose-ranging study of lebrikizumab in asthmatic patients not receiving inhaled steroids.	Phase 2	Lebrikizumab (anti-IL-13)	Blocking IL-13 alone was insufficient to improve lung function in asthmatic patients.	Genentech, Inc.	[5]
NCT00873860	A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma.	Phase 2	Tralokinumab (anti-IL-13)	Safety profile of tralokinumab was acceptable with no serious adverse effects. Although tralokinumab treatment was associated with improved lung function, no improvement in asthma control questionnaire score was observed.	MedImm une LLC	[6]
NCT01018186	Safety and tolerability of the novel inhaled corticosteroid fluticasone furoate in combination with the β2-agonist vilanterol administered once daily for 52 weeks in patients ≥12 years old with asthma: a randomized trial.	Phase 3	Fluticasone furoate (ICS) + Vilanterol (LABA)	Fluticasone furoate/ Vilanterol (100/25 μg or 200/25 μg) administered once daily over 52 weeks was well tolerated by asthmatic patients aged ≥12 years. The overall safety profile of Fluticasone furoate/ Vilanterol did not reveal any serious adverse effects.	GlaxoSmithKline	[7]
NCT00393952	Efficacy and safety of fluticasone/ formoterol combination	Phase 3	Fluticasone propionate (ICS)	Fluticasone/formoterol combination therapy was an efficient alternative treatment option for	SkyePharma AG	[8]

Clinical Trial Identifier	Publication Title	Phase	Drugs	Outcome	Responsible Party	Reference
	therapy in patients with moderate-to-severe asthma.		Formoterol fumarate (LABA)	moderate-to-severe asthmatic patients.		
NCT01691521	Mepolizumab treatment in patients with severe eosinophilic asthma.	Phase 3	Mepolizumab (anti-IL-5)	Administration of mepolizumab (I.V. or S.C.) significantly reduced asthma exacerbations and is associated with improvements in markers of asthma control.	GlaxoSmithKline	[9]
NCT00500539	Immunogenicity and safety of omalizumab in pre-filled syringes in patients with allergic (IgE-mediated) asthma.	Phase 3	Omalizumab (anti-IgE)	Pre-filled syringe of omalizumab was not associated with immunogenicity.	Novartis Pharmaceuticals	[10]
NCT00781443	The effects of lebrikizumab in patients with mild asthma following whole lung allergen challenge.	Phase 2	Lebrikizumab (anti-IL-13)	Lebrikizumab reduced the late asthmatic response in subjects with mild asthma.	Genentech, Inc.	[11]
NCT01181895	Comparison of vilanterol, a novel long-acting beta-2 agonist, with placebo and a Salmeterol reference arm in asthma uncontrolled by inhaled corticosteroids.	Phase 3	Vilanterol (LABA)	The study failed to show a therapeutic difference between vilanterol and placebo for the primary end point. The magnitude of placebo effect may be due to increased compliance with anti-inflammatory therapy regimen during the treatment period.	GlaxoSmithKline	[12]

Clinical Trial Identifier	Publication Title	Phase	Drugs	Outcome	Responsible Party	Reference
NCT01233284	Tiotropium Respimat® in asthma: a double-blind, randomized, dose-ranging study in adult patients with moderate asthma.	Phase 2	Tiotropium (LAMA)	Administration of tiotropium Respimat® (Once-daily) add-on to medium-dose ICS improves lung function in symptomatic patients with moderate asthma, and the largest improvement was with a dose of 5 μg.	Boehringer Ingelheim	[13]
NCT00983658	OX40L blockade and allergen-induced airway responses in subjects with mild asthma.	Phase 2	huMAb OX40L (anti-OX40L)	Anti-OX40L MAb decreased serum total IgE and airway eosinophils at 16 weeks post dosing, but there was no effect on allergen-induced airway responses. This may be due to the treatment duration or dose of antibody was insufficient to have an effect on the airway responses.	Genentech, Inc.	[14]
NCT00768079	A randomized trial of benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, after acute asthma.	Phase 2	Benralizumab (Anti-IL-5)	A dose of benralizumab—when added to usual care—reduced the rate and severity of asthma exacerbations experienced over 12 weeks by subjects who presented to the emergency department with acute asthma.	MedImmune LLC	[15]
NCT01369017	IL-1 receptor antagonist reduces endotoxin-induced airway inflammation in healthy volunteers.	Phase 1	Anakinra (Anti-IL-1)	Anakinra effectively reduced airway neutrophilic inflammation with no serious adverse	University of North Carolina, Chapel Hill	[16]

Clinical Trial Identifier	Publication Title	Phase	Drugs	Outcome	Responsible Party	Reference
				reactions in a model of inhaled lipopolysaccharide challenge. Anakinra is a potential therapeutic candidate for treatment of asthma.		

Abbreviations: **IL**: Interleukin; **IgE**: Immunoglobulin E; **TNF-α**: Tumor necrosis factor – α; **PDE**: Phosphodiesterase enzyme; **ICS**: Inhaled corticosteroids; **OCS**: Oral corticosteroids; **SABA**: Short-acting β-agonists; **LABA**: Long-acting β-agonists; **LAMA**; Long-acting muscarinic antagonists.

Table 1. Summary of recent published clinical trials for new drugs used in the treatment of asthma (from 1 January 2013 to 1 January 2016).

Clinical Trial Identifier	Title	Phase	Drugs	Start Date	Purpose	Study Type	Recruitment Status	Responsible Party
NCT01907763	Phase III study to assess the efficacy and safety of SOTB07 in asthma patients	Phase 3	Placebo SOTB07	Jan 2013	Assessment of the efficacy and safety of SOTB07 in asthma patients.	Interventional	Recruiting	SK Chemicals Co.,Ltd.
NCT02388997	Treatment with Omalizumab to improve the asthmatic response to an experimental infection with rhinovirus	Phase 2	Omalizumab (anti-IgE) Rhinovirus (strain 16)	Feb 2013	Determination of whether anti-IgE therapy will lead to decline in inflammatory biomarkers prior to virus inoculation, and thus reduce the severity of clinical manifestations after an experimental human RV challenge.	Interventional	Recruiting	University of Virginia
NCT01902290	Study of efficacy and safety of Brodalumab compared	Phase 2	Placebo Brodalumab (Anti-IL-17)	May 2013	Determination of the safety and efficacy of Brodalumab (AMG 827).	Interventional	Recruiting	Amgen

Clinical Trial Identifier	Title	Phase	Drugs	Start Date	Purpose	Study Type	Recruitment Status	Responsible Party
	with placebo in inadequately controlled asthma subjects with high bronchodilator reversibility							
NCT01836471	A study to assess the effect of QAW039 in nonatopic asthmatic patients	Phase 2	Placebo QAW039 ICS	May 2013	Assessment of the clinical effect of QAW039 in nonatopic asthmatics taking low-dose ICS as background therapy.	Interventional	Recruiting	Novartis Pharmaceuticals
NCT01955512	Effect of Clopidogrel on allergen challenge in asthma	Phase 2	Placebo Clopidogrel (platelets P2Y12 receptor blocker)	May 2013	Determination if the drug Clopidogrel reduces inflammation following breathing in house dust mite in people with mild asthma.	Interventional	Recruiting	University of Southampton
NCT01705964	Intramuscular epinephrine as an adjunctive treatment for severe pediatric asthma exacerbation	Phase 4	Epinephrine (IM)	Jun 2013	Determination if IM epinephrine is an effective adjunct to inhaled β_2-agonists for children with severe asthma exacerbation.	Interventional	Recruiting	University of Louisville
NCT01868061	A study of Lebrikizumab in patients with uncontrolled asthma on inhaled corticosteroids and a second controller medication	Phase 3	Placebo Lebrikizumab (anti-IL-13)	Jul 2013	Evaluation of the efficacy and safety of Lebrikizumab in patients with uncontrolled asthma despite daily administration of ICS therapy and at least 1-s controller medication.	Interventional	Recruiting	Hoffmann-La Roche
NCT01867125	A study of Lebrikizumab in patients with uncontrolled asthma who are on inhaled	Phase 3	Placebo Lebrikizumab (anti-IL-13)	Jul 2013	Evaluation of the efficacy and safety of Lebriki zumab in patients with	Interventional	Recruiting	Hoffmann-La Roche

Clinical Trial Identifier	Title	Phase	Drugs	Start Date	Purpose	Study Type	Recruitment Status	Responsible Party
	corticosteroids and a second controller medication				uncontrolled asthma despite daily treatment with ICS therapy and at least 1-s controller medication.			
NCT01841281	L-arginine in severe asthma patients grouped by exhaled nitric oxide levels	Phase 2	Placebo L-Arginine (Nitric oxide precursor)	Aug 2013	Identification of the benefit from supplemental L-arginine therapy in adult severe asthma cohort.	Interventional	Recruiting	University of California, Davis
NCT01912872	Study to assess the efficacy and safety of Omalizumab treatment on ICS reduction for severe IgE-mediated asthma (MEXIC)	Phase 4	Omalizumab (anti-IgE) Budesonide Formoterol (LABA)	Nov 2013	Assessment of the efficacy and safety of Omalizumab treatment during 12 months to reduce the use of ICS in pediatric and adult patients with severe IgE-mediated asthma inadequately controlled with high doses of corticosteroids.	Interventional	Recruiting	Novartis Pharmaceuticals
NCT02041221	Pharmacology study of Sun Pharma Advanced Research Company Limited's S0597	Phase 1 Phase 2	Placebo S0597	Jan 2014	Evaluation of safety, tolerability, pharmacokinetics, and pharmacodynamics of S0597 by oral inhalation.	Interventional	Not yet recruiting	Sun Pharma Advanced Research Company Limited
NCT02049294	Study of the prednisone-sparing effect of Xolair (Omalizumab) in patients with Prednisone-dependent asthma with	Phase 2 Phase 3	Omalizumab (anti-IgE) Placebo Normal Saline	Mar 2014	Investigation whether addition of Omalizumab enables a reduction in the dose of prednisone in patients with asthma	Interventional	Recruiting	McMaster University

Clinical Trial Identifier	Title	Phase	Drugs	Start Date	Purpose	Study Type	Recruitment Status	Responsible Party
	eosinophilic bronchitis				and eosinophilic bronchitis.			
NCT01987492	A study of Lebrikizumab In patients with severe asthma who depend on oral corticosteroids	Phase 2	Placebo Lebrikizumab (anti-IL-13)	Mar 2014	Evaluation of the efficacy of Lebrikizumab compared with placebo as measured by the ability of patients to achieve lower daily doses of OCS in patients with severe corticosteroid-dependent asthma.	Interventional	Recruiting	Hoffmann-La Roche
NCT02075008	Long-term safety study of QGE031 in patients with allergic asthma who completed study CQGE031 B2201	Phase 2	QGE031	Mar 2014	Assessment of long-term safety of QGE031 during 12 months of treatment in asthma patients who completed study CQGE031B2201.	Interventional	Recruiting	Novartis Pharmaceuticals
NCT02075255	Efficacy and safety study of Benralizumab to reduce OCS use in patients with uncontrolled asthma on high-dose inhaled corticosteroid plus LABA and chronic OCS therapy	Phase 3	Placebo Benralizumab (anti-IL-5)	Apr 2014	This trial is to confirm if Benralizumab can reduce OCS dependence (after dose optimization) in patients who are uncontrolled on high-dose ICS-LABA, and chronically dependent on OCS as part of their regular asthma controller regimen.	Interventional	Recruiting	AstraZeneca
NCT02135692	A Phase 3a, repeat dose, open-label, long-term safety study of Mepolizumab in asthmatic subjects	Phase 3	Mepolizumab (anti-IL-5) Standard of Care	May 2014	Collection of clinical data for long-term use and further assessment of efficacy in patients	Interventional	Recruiting	GlaxoSmithKline

Clinical Trial Identifier	Title	Phase	Drugs	Start Date	Purpose	Study Type	Recruitment Status	Responsible Party
					with loss of asthma control.			
NCT02126865	Multiple rising oral doses of BI 1060469 in healthy subjects and mild asthma patients	Phase 1	Placebo BI 1060469	May 2014	Investigation of the safety and tolerability of repeated rising doses of BI 1060469 in healthy male and female subjects and in asthmatic male and female patients.	Interventional	Recruiting	Boehringer Ingelheim
NCT02161757	A Phase 3 study to evaluate the efficacy and safety of Tralokinumab in adults and adolescents with uncontrolled asthma (STRATOS1)	Phase 3	Placebo Tralokinumab (Anti-IL-13)	Jun 2014	Evaluation of the efficacy and safety of Tralokinumab in adults and adolescents with asthma inadequately controlled on ICS plus long-acting β_2-agonist.	Interventional	Recruiting	AstraZeneca
NCT02104674	A study evaluating the efficacy and safety of Lebrikizumab in adult patients with mild to moderate asthma	Phase 3	Placebo Lebrikizumab (anti-IL-13) Montelukast	Jun 2014	Assessment of the efficacy and safety of Lebrikizumab in adult patients with mild to moderate asthma treated with SABA therapy alone.	Interventional	Recruiting	Hoffmann-La Roche
NCT02066298	Steroids In eosinophil-negative asthma (SIENA)	Phase 3	Placebo Mometasone Tiotropium (LAMA)	Jul 2014	Determination if patients who are persistently non-eosinophilic differ in their benefit from inhaled corticosteroid treatment compared to patients who are not persistently non-eosinophilic.	Interventional	Recruiting	Milton S. Hershey Medical Center
NCT020	A study	Phase 2	Placebo	Nov 2014	Evaluation	Interve	Recr	Hoffmann-

Clinical Trial Identifier	Title	Phase	Drugs	Start Date	Purpose	Study Type	Recruitment Status	Responsible Party
99656	evaluating the effects of Lebrikizumab on airway eosinophilic inflammation in patients with uncontrolled asthma		Lebrikizumab (anti-IL-13)		of the effects of Lebrikizumab on airway eosinophilic inflammation in patients with uncontrolled asthma on inhaled corticosteroids and a second controller medication.	ntional	uiting	La Roche
NCT02258542	A safety extension study to evaluate the safety and tolerability of Benralizumab (MEDI-563) in asthmatic adults and adolescents on inhaled corticosteroid plus LABA (BORA)	Phase 3	Benralizumab (anti-IL-5)	Nov 2014	Characterization of safety profile of Benralizumab administration in asthma patients who have completed one of the three predecessor studies: D3250C00017, D3250C00018, or D3250C00020.	Interventional	Recruiting	AstraZeneca
NCT02296411	Efficacy of LAMA added to ICS in treatment of asthma (ELITRA)	Phase 2	Placebo CHF 5259 Glycopyrrolate bromide (LAMA)	Nov 2014	Evaluation of the safety and superiority of the glycopyrrolate bromide (CHF 5259 pMDI) versus placebo on top of QVAR® pMDI, in terms of lung functions parameters.	Interventional	Recruiting	Chiesi Farmaceutici S.p.A.
NCT02293265	Cross-sectional study for identification and description of severe asthma patients	Phase 3	Mepolizumab (anti-IL-5) Omalizumab (anti-IgE) Reslizumab (anti-IL-5)	Dec 2014	The potential overlap of patients eligible for treatment with Mepolizumab, Omalizumab and/or Reslizumab will be estimated.	Interventional	Recruiting	GlaxoSmithKline
NCT02281318	Efficacy and safety	Phase 3	Placebo Mepolizumab	Dec 2014	Evaluation of the	Interventional	Recruiting	GlaxoSmithKline

Clinical Trial Identifier	Title	Phase	Drugs	Start Date	Purpose	Study Type	Recruitment Status	Responsible Party
	study of Mepolizumab adjunctive therapy in participants with severe eosinophilic asthma on markers of asthma control		(anti-IL-5) Standard of Care		efficacy and safety of Mepolizumab adjunctive therapy in participants with severe eosinophilic asthma on markers of asthma control.			
NCT02322775	Study to evaluate the efficacy and safety of Benralizumab in adult patients with mild to moderate persistent asthma	Phase 3	Placebo Benralizumab (anti-IL-5)	Feb 2015	Confirmation of the safety and clinical benefit of Benralizumab administration in asthma patients with mild to moderate persistent asthma.	Interventional	Recruiting	AstraZeneca
NCT02382510	Multiple ascending dose study of TRN-157 in stable mild and moderate asthmatics	Phase 2	Placebo TRN-157 Tiotropium (LAMA)	Feb 2015	Determination of the safety and bronchodilator activity of TRN-157 in approximately 54 mild and moderate asthmatics.	Interventional	Recruiting	Theron Pharmaceuticals, Inc.
NCT02315131	Study in healthy volunteers and COPD patients to evaluate the efficacy and safety of inhaled TV46017	Phase 1	Placebo TV46017	Mar 2015	Assessment of the safety profile and duration of bronchodilation of a single dose of inhaled TV46017.	Interventional	Not yet recruiting	Teva Branded Pharmaceutical Products, R&D Inc.
NCT02124226	Low-dose Methotrexate for reduction GINA 5 medications in chronic severe asthma	Phase 3	Placebo Methotrexate	Apr 2015	Investigation of the role of an add-on immunological modifier in patients with chronic severe asthma.	Interventional	Not yet recruiting	Universita degli Studi di Catania
NCT02377427	Pharmaco kinetics and pharmaco dynamics of Mepolizumab administered subcutaneously in children	Phase 2	Mepolizumab (anti-IL-5)	Apr 2015	Assessment of the pharmacokinetics and pharmacodynamics of Mepolizumab in children aged 6–11 years with severe	Interventional	Not yet recruiting	GlaxoSmithKline

Clinical Trial Identifier	Title	Phase	Drugs	Start Date	Purpose	Study Type	Recruitment Status	Responsible Party
					eosinophilic asthma.			
NCT02336425	Efficacy and safety of QGE031 compared with placebo in patients aged 18–75 years with asthma	Phase 2	Placebo QGE031	Apr 2015	The study will assess the safety and efficacy of different dose levels of QGE031 in asthma patients.	Interventional	Not yet recruiting	Novartis Pharmaceuticals
NCT02427165	Comparison of RPL554 With placebo and Salbutamol in asthmatic patients	Phase 2	Placebo RPL554 (PDE-3/4 inhibitor) Salbutamol	Apr 2015	Assessment of the effects of RPL554 compared with Salbutamol and placebo in patients with chronic asthma.	Interventional	Not yet recruiting	Verona Pharma plc
NCT02422121	Effect of RNS60 on the late-phase asthmatic response to allergen challenge	Phase 2	Placebo RNS60 Budesonide	May 2015	Evaluation of the effects of multiple doses of inhaled RNS60 and Budesonide on the late-phase asthmatic response to allergen challenge in patients with mild asthma.	Interventional	Not yet recruiting	Revalesio Corporation
NCT02571660	Efficacy of vitamin D on the clinical management of pediatric patients with asthma	Phase 3	Vitamin D (Low- and high-supplementation doses)	Oct 2015	Evaluation of vitamin D supplementation on exacerbation and clinical control of asthma.	Interventional	Not yet recruiting	Hospital General Naval de Alta Especialidad - Escuela Medico Naval

Abbreviations denote: **IL**: Interleukin; **IgE**: Immunoglobulin E; **PDE**: Phosphodiesterase enzyme; **ICS**: Inhaled corticosteroids; **OCS**: Oral corticosteroids; **SABA**: Short-acting β-agonists; **LABA**: Long-acting β-agonists; **LAMA**; Long-acting muscarinic antagonists.

Table 2. Summary of recent ongoing clinical trials for new drugs used in the treatment of asthma (started in the past 3 years).

6.4.1. Anti-leukotrienes

Leukotrienes are lipid eicosanoids with a wide range of biological activities. They are derived from arachidonic acid through the enzymatic action of 5-lipooxygenase, and play a crucial role

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in asthma inflammatory pathogenesis, and in other allergic diseases such as allergic rhinitis, rhinosinusitis, atopic dermatitis, and urticaria [116]. Leukotrienes class includes three main types: cysteinyl leukotrienes (CysLTs), LTB4, and LTG4. LTG4 is the metabolite of LTE4 in which the cysteinyl moiety has been oxidized to an α-keto-acid [117]. Since, very little is known about the LTG4-putative leukotriene, most clinical research studies focus on CysLTs and LTB4. CysLTs are strong bronchoconstrictors that powerfully affect airway remodeling, whereas LTB4 is a strong chemoattractant for most leukocyte subsets [118]. Over the last 20 years, since leukotriene antagonists were introduced to the clinic for asthma management, Montelukast [119, 120] and Zafirlukast [121] are the most frequently used drugs in this class.

6.4.2. Anti-IgE

At the moment, Omalizumab, which is the only approved targeted monoclonal antibody against IgE, is used to treat allergic asthma in clinical practice. It can significantly decrease serum IgE levels (up to 99%) within 2 h following subcutaneous administration, and diminish serum, sputum, and tissue eosinophilia [122]. Recently, Omalizumab has also been reported to have steroid-sparing effect, reducing the rate of asthma exacerbations up to 50%, and hence improving the quality of life [123]. However, nearly 45% of patients treated with Omalizumab had adverse reaction at the local injection site, which is considered the most commonly observed adverse event for Omalizumab. Some other minor upper respiratory tract infections and sinusitis have also been reported as well. Patients treated with Omalizumab display a very low (0.09%) frequency of anaphylaxis reaction. Importantly, there are no data reporting any correlation between cancer and Omalizumab treatment [124].

6.4.3. Anti-ILs

Three interleukin pathways are of physiological importance for asthma: IL-5, IL-9, and IL-4/IL-13 pathways. IL-5 is pivotal for both eosinophil differentiation and maturation in the bone marrow. Subsequently, it controls eosinophil mobilization, activation, and survival [125]. Hence, antagonizing IL-5 has been proposed to be beneficial for asthma therapy, particularly for predominantly eosinophilic asthma. A number of anti-IL-5 and anti-IL-5 receptor monoclonal antibodies are in the process of development for allergic diseases: Reslizumab [126], Mepolizumab [127], and Benralizumab [128]. IL-9 is one of the T-helper 2 (Th2) pro-inflammatory cytokines that promote mast cell proliferation and T-cell growth [129]. In mouse models, IL-9 causes several common features of chronic asthma: excessive mucus production, eosinophilic airway inflammation, smooth-muscle cell hyperplasia, and aryl hydrocarbon receptor (AHR) [130]. Currently, a phase IIb clinical trial evaluates the efficacy and safety of subcutaneous Medi-528, a humanized IgG1 anti-IL-9 mAb, in adults with uncontrolled asthma (NCT00968669). Activated mast cells, eosinophils, basophils, and dendritic cells secrete IL-4 and IL-13. IL-4 and IL-13 both play an important role in asthma mainly by enhancing IgE production. They also control mast cells' growth and development, eosinophil recruitment, and AHR [131]. The first trial aimed at antagonizing the IL-4 used a soluble recombinant human IL-4 receptor antagonist (IL-4RA), altrakincept, which blocked the binding of IL-4 to

its cellular receptors [132]. Several humanized IL-13-neutralizing antibodies have entered asthma phase I/II clinical trials—anrukinzumab [133], QAX576 [134], and CAT354 [135].

6.4.4. Anti-TNF-α

TNF-α, a cytokine produced by Th1 cells and macrophages, has diverse biological functions. TNF-α shows crucial, and previously extensively documented, role in Crohn's disease, rheumatoid arthritis, and psoriasis pathogenesis. The association between TNF-α increase and these disease progressions had inspired studies aiming to extend anti-TNF-α therapies also for the treatment of severe asthma and COPD [136]. Infliximab and Golimumab, two anti-TNF-α mAbs, and Etanercept, a decoy soluble TNF-α receptor, are both able to biologically neutralize TNF-α cytokine, and blunt the immune response, thereby abolishing TNF-α effects in asthma [137].

7. Pharmacogenetics of asthma

The US Food and Drug Administration definition for pharmacogenomics is "the study of variations in DNA and RNA characteristics as related to drug response" [138]. "*Pharmacogenomics*" differs from "*Pharmacogenetics*" in that the former is concerned with the whole genome, its components, and regulators, while the latter is focused only on the DNA sequences of individual gene. Thus, in sense, pharmacogenetics is thought to be a subset of pharmacogenomics [139].

Because it is a complex trait, the drug response to asthma is diversely heterogeneous even among patients with apparently similar clinical profiles [7]. It is estimated that up to 50% difference in therapeutic response has been attributed to genetic variations between individuals [140]. Although several possible mechanisms have been postulated, genetic variants affect the pharmacogenetic response to drugs in two different ways:

1. *Pharmacodynamic genetic variations* are variations in which the receptor binding the drug ligand or another member of the drug target pathway is altered resulting in different drug effect. Most of the current pharmacogenetic research fall into this mechanistic category. Populations are stratified into responders and nonresponders, and then analyzed for DNA polymorphisms, which distinguish these two groups apart.
2. *Pharmacokinetic genetic variations* are related to altered uptake, distribution, and/or metabolism of the administered drug. Fewer examples fall in this category; however, the most common research subfield here is the area of investigating drug-catabolizing or -excreting enzymes. An important example here is the cytochrome *P450* (CYP450) family, a widely recognized metabolizing enzyme with several variable pharmacogenetic patterns.

Single nucleotide polymorphism, SNP, denoted by a reference sequence (rs) number, represents a class of polymorphism that is derived from a one-base point mutation in which a single nucleotide is substituted with another one. SNPs may be located in the gene regulatory

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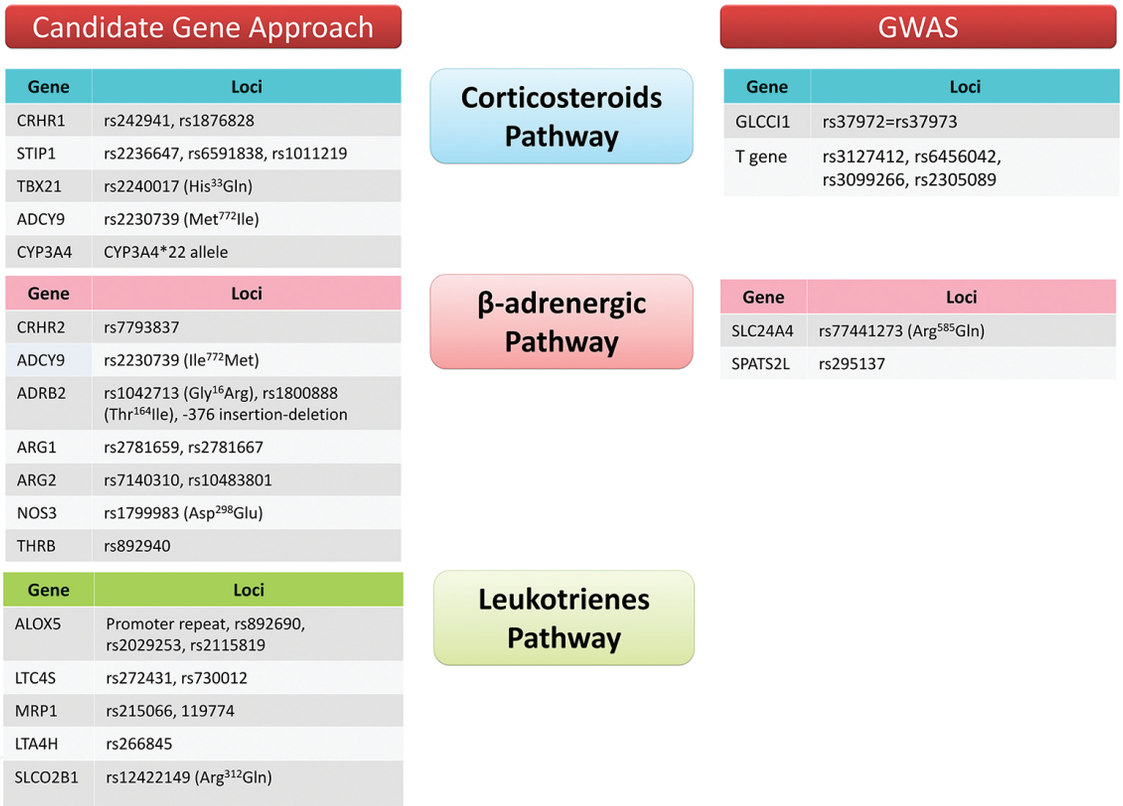
or coding regions, and so it may affect the gene expression in more than one way; however, in majority of cases, most discovered SNPs do not change the gene function in a significant manner [141]. Consequently, it is essential to investigate whether the DNA sequence variances would actually cause significant functional impacts (i.e., resulting in an altered observed biology), or is a linkage disequilibrium marker of another DNA variant, which is the real cause of the response variability, or is generally nonsignificant. Because of its strong importance, since 15 years, catalogs of SNPs have started to outline the most common genetic polymorphisms among different population groups [141, 142], and this process has attracted more attention during the last couple of years [143].



Gene	Loci
CRHR1	rs242941, rs1876828
STIP1	rs2236647, rs6591838, rs1011219
TBX21	rs2240017 (His^{33}Gln)
ADCY9	rs2230739 (Met^{772}Ile)
CYP3A4	CYP3A4*22 allele

Gene	Loci
GLCCI1	rs37972=rs37973
T gene	rs3127412, rs6456042, rs3099266, rs2305089

Gene	Loci
CRHR2	rs7793837
ADCY9	rs2230739 (Ile^{772}Met)
ADRB2	rs1042713 (Gly^{16}Arg), rs1800888 (Thr^{164}Ile), -376 insertion-deletion
ARG1	rs2781659, rs2781667
ARG2	rs7140310, rs10483801
NOS3	rs1799983 (Asp^{298}Glu)
THRB	rs892940

Gene	Loci
SLC24A4	rs77441273 (Arg^{585}Gln)
SPATS2L	rs295137

Gene	Loci
ALOX5	Promoter repeat, rs892690, rs2029253, rs2115819
LTC4S	rs272431, rs730012
MRP1	rs215066, 119774
LTA4H	rs266845
SLCO2B1	rs12422149 (Arg^{312}Gln)

Figure 4. Pharmacogenetically significant genes with relevance to corticosteroids, β-adrenergic, and leukotriene biological pathways. Left side: Candidate gene approach studies, Right side: GWAS (Genome Wide association studies).

All genes contain huge number of SNPs and copy-number variations (CNVs). CNVs are another form of structural variations, which account for 13% of the human genome bulkiness, and manifest as kilo-to-mega bases of deletions or duplications [144]. Conjointly, it is challenging to outline which polymorphism is influencing the treatment response and which are not relevant. Two major approaches declaiming this challenge have been practiced so far: candidate gene approach and GWAS. As it combines transcriptomic, proteomic and metabolomic profiling traits, a third approach, the integrative system biology approach, had led to a more comprehensive pharmacogenetic view [3]. To differentiate, candidate gene approach is based on a prior evidence according to the knowledge of the drug pharmacody-

namics or/and pharmacokinetics, by contrast, GWAS methodology identifies new associations with the null hypothesis being that no associations exist. GWAS picks the variations which are associated with observable phenotypes by scanning SNP markers that tag, via linkage disequilibrium, the complete human genome. GWAS and integrative system biology approaches are modern tools contributing to the recent advancements of genotyping and statistical technologies.

Current pharmacogenetic studies of the corticosteroids, β-adrenergic, and leukotriene pathways are mostly candidate gene studies, with some GWAS, however, altogether have identified several genetic loci in strong association with therapeutic responsiveness to asthma. **Figure 4** summarizes the pharmacogenetically significant genes with relevance to the corticosteroids, β-adrenergic, and leukotriene biological pathways.

7.1. Corticosteroid pathway pharmacogenetics

In cytosol, the glucocorticoids bind to their corresponding glucocorticoid receptor, forming a hetero-complex that is activated by ligand binding, and translocate into the nucleus. In the nucleus, this complex binds to the glucocorticoid response elements in some target genes' promoter region resulting in their expression regulation. The core role of glucocorticoids is mediated via activating the transcription of anti-inflammatory genes, and suppressing the transcription of pro-inflammatory genes [145, 146]. The glucocorticoid pharmacogenetic studies formerly focused on candidate gene approach. Those candidate genes covered functions related to the corticosteroid biosynthetic pathway, the hetero-complex receptor formation, and the related chaperone proteins.

Corticotrophin-releasing hormone *(CRHR1)*, stress-inducible protein 1 *(STIP1), TBX21, CYP3A4, GLCCI1*, T gene, and *FBXL7* are the most up-to-date potential pharmacogenetic biomarker targets for predicting patients' response to ICS [147]. Studies of the corticotrophin-releasing hormone gene are considered to be as one of the oldest and remarkable footsteps in asthma pharmacogenetics. CRHR1 protein, also known as CRF1, is the primary receptor controlling the adrenocorticotropic hormone release; hence, it plays a pleiotropic and vital role in steroid actions. A candidate gene study of *CRHR1* in 1117 asthmatics administrating ICS therapy, from three clinical cohorts, revealed two SNPs (rs242941 and rs1876828) associated with different response in lung functions [148]. Tantisira et al. [148] found that *CRHR1* gene variation was frequently related to augmented therapy response in each of the three studied cohorts. Since 2004, *CRHR1* gene studies opened the doors for all other corticosteroid pharmacogenetics and the possible future therapeutic outcomes.

STIP1 or *HOP* (abbreviated for Hsp70-Hsp90-Organizing Protein) gene mainly functions to reversibly link Hsp70 and Hsp90 together as a co-chaperone [149]. *STIP1* pharmacogenetic studies in one adult cohort revealed three SNPs (rs2236647, rs6591838, and rs1011219) within this heat shock-organizing protein and related to improved lung response during ICS therapy [150]. *STIP1* rs2236647 variant analysis in healthy and asthmatic children showed that this SNP could serve as an asthma marker for choosing the population who receives corticosteroid therapy[151]; however, further replication studies should be held to confirm those results.

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One significant aspect of pharmacogenomics is that it investigates the interactions with genes of other pathways. *TBX21* gene is one good example for observing the ICS response outside the glucocorticoid pathway. *TBX21* is one of the conserved genes of a family sharing a common DNA-binding domain; the T-box encodes T-box transcription factor TBx21 protein. Tbx21 protein is a Th1 (T-helper1) transcription factor, which regulates one of the Th1 cytokine expression, interferon-gamma (IFNG). In 2004, a nonsynonymous SNP rs2240017 ($His^{33}Glu$) in the *TBX21* gene was linked to improvements in bronchial hyperresponsiveness or "broncho-protection" in response to ICS in individuals participating in the Child Asthma Management Program (CAMP) cohort [152]. This finding was also observed in an independent Korean cohort in 2009 [153]. Thus, *TBx21* may be an important determinant pharmacogenetic candidate gene for predicting asthmatics' response to inhaled corticosteroid therapies.

In 2005, another example demonstrated the glucocorticoid pathway interactions with one other pathway. *ADCY9*, adenylyl cyclase type 9, gene encodes a membrane-bound enzyme in the β2-adrenergic receptor pathway, which catalyzes the production of cyclic adenosine monophosphate (AMP) from adenosine triphosphate (ATP). This candidate gene contains a pharmacogenetic nonsynonymous SNP, $Met^{772}Ile$, which was correlated to enhanced Salbutamol (SABA) bronchodilator effects only in patients treated with ICS [154]. An independent Korean cohort replicated the trial, using Formoterol (LABA) treatment in combination with ICS, and confirmed those results [155].

Cytochromes P450s belong to a heme cofactor-containing superfamily of metabolizing enzyme proteins that potentially control the metabolism of drug (i.e., pharmacokinetics), and consequently treatment response in many diseases. For asthma, *CYP3A4*, *CYP3A5*, and *CYP3A7* candidate genes have been studied among a retrospective analysis of 413 asthmatic children treated with the ICS Fluticasone propionate [156]. The three candidate CYPs of all subjects were genotyped for nine SNPs. Results showed that asthmatics with the *CYP3A4*22* allele demonstrated a significant symptom control compared with those lacking that allele. This study included a small number of participants (n = 20), so further large-scale replication is required.

Tantisira et al. [157] conducted the first pharmacogenetic GWAS for ICS treatment in asthma and identified an SNP (rs37972) in the promoter of the glucocorticoid-induced transcript-1 gene (*GLCCI1*), which significantly associates with lung functions. Replicated in four independent populations (935 persons in total), this candidate SNP was linked to substantial decrements in the response to the ICS in asthmatics. The wild-type allele homozygotes (CC) showed greater forced expiratory volume in 1 s (FEV1) in response to the ICS compared with those identified with the homozygote variant allele (TT). Another functionally correlated SNP (rs37973) in the promoter of the same gene was further validated within *in vitro* studies [157]. Results showed declined luciferase reporter activity in cells with the minor allele. *GLCCI1* GWAS outlines that drug response to asthma treatment is subjected to wide inter-individual variation, and GWAS would uncover more novel pharmacogenetic associations in the future. Tantisira et al. conducted a second GWAS among 418 asthmatics randomized to ICS treatment from the Childhood Asthma Research and Education (CARE), Asthma Clinical Research Network (ACRN), and CAMP trial cohorts. The *T-gene* (encoding the Brachyury transcription

factor protein) compromised two SNPs (rs3127412 and rs6456042) that were associated, out of the successfully genotyped 47 SNPs, with altered lung function response to ICS [158].

7.2. β-adrenergic receptor pathway pharmacogenetics

β2-adrenergic receptor gene remains to be the most studied pharmacogenetic loci among the beta-agonist pathways. *ADRB2* gene has several polymorphic variants that were discovered in multi-ethnic genetic asthma cohorts [159, 160]. ADRB2 protein is a cell membrane-spanning receptor that binds epinephrine, but not norepinephrine, unlike the other adrenergic receptors, and consequently mediates both smooth muscle relaxation and bronchodilation [161, 162]. Early ADRB2 studies showed that $Gly^{16}Arg$, a prevalent coding variant of the amino acid at position 16 of ADRB2, is associated with altered bronchodilator response to SABAs [163].

The BARGE (Beta-Agonist Response by Genotype) study [164], held by the National Heart, Lung and Blood Institute Asthma Clinical Network, was one of the first genotype "stratified" pharmacogenetic studies for asthma. In this study, only $Gly^{16}Arg$ homozygotes for ADRB2 were included (i.e., Arg/Arg and Gly/Gly). Participants were randomly receiving either intermittent or regular albuterol, and then crossed over to receive the alternative treatment dose. For statistical stratification, this study ensured that the Arg^{16} homozygotes, who are less frequent, were appropriately randomly distributed to both SABA intermittent and regular protocols. Compared to Gly^{16} homozygotes, the BARGE study showed that the Arg^{16} homozygotes were good responders only to acute intermittent SABAs rather than to long-term regular treatments, a finding that does not coincide with the current clinical asthma treatment guidelines [165] which recommend SABA as for on-demand intermittent usage. Since the 16th amino acid of ADRB2 controls regular response to albuterol, bronchodilator medications other than SABAs would be more appropriate for Arg/Arg asthmatics.

Collectively, the BARGE study [164], along with some other pharmacogenetic studies [163, 166–168] of $Gly^{16}Arg$ and SABAs' exposure, provided insights for further studies [169–171] on LABAs. In contrast to SABAs, a large cohort [169] of 2250 asthmatics, randomly assigned to formoterol plus budesonide, demonstrated no pharmacogenetic action due to *ADRB2* variation on therapeutic response. Furthermore, a multicenter trial [170] showed that asthmatics with both Arg/Arg and Gly/Gly genetic signatures had improved airway functions, if they received combination treatment with Salmeterol and ICS, when compared with ICS therapy alone. Similarly, the results of another prospective trial cohort [171] of 544 subjects, also randomized by genotyping, demonstrated no evidence of any pharmacogenetic action due to *ADRB2* variation in response to Salmeterol. Together, these findings, confirmed among several asthma populations, suggest that in contrast to SABAs, asthmatics can still be treated with LABAs plus ICS irrespective of their genotyping status.

Genetic variants' occurrences among different ethnic groups are quantified by their percentage of allele frequencies. Usually, frequent and common variants have only little or modest impacts on disease susceptibility and, subsequently, therapeutic response. On the other hand, as the variant is characterized to be rare or more "private," its effect size on disease progression and therapeutic response dramatically increases [172]. Early *in vitro* studies had investigated a rare polymorphism of *ADRB2* within the fourth transmembrane domain, the $Thr^{164}Ile$ variant. For

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the Ile^{164} genotype, results showed significant lowering in Gs-protein signaling and different SABA- and LABA-binding affinities [173, 174]. While the Thr^{164}Ile polymorphism is pointed out to be a rare coding variant (i.e., <5%), population studies showed that this variant is more common in non-Hispanic white populations [159, 160], a finding that requires further pharmacogenetic investigation in different and larger populations. To replicate results, a study of two large Copenhagen population cohorts [175], with more than 55,000 participants, was held to investigate the relation of Thr^{164}Ile variation and lung responses. Among the general population, the Copenhagen study reported that the Thr^{164} genotype was associated with decreased FEV1, diminished lung function, and increased the overall COPD risk.

In addition to ADRB2 Gly^{16}Arg and Thr^{164}Ile variants, the (-376 In-Del) polymorphism was extensively studied as another significant pharmacogenetic *ADRB2* variant. Presented primarily among African Americans and Puerto Ricans [159, 160], the 24-bp promoter insertion at −376, related to the start codon, is associated with asthma-related hospitalization in asthmatics treated with LABA [160]. Altogether, these variants, being unique to different populations, highlight the increasing need of personalized-based treatments.

Adenylyl cyclase type 9, encoded in humans by *ADCY9* gene, is a membrane-bound enzyme that catalyzes the formation of cyclic AMP from ATP. ADCY9 is a widely abundant adenylyl cyclase, and it is stimulated via beta-adrenergic receptor activation [176]. Ile^{772}Met is a coding variant of *ADCY9* gene that has been associated with both acute FEV1 bronchodilation in response to SABAs [154] and long-term FEV1 response for LABAs [155]. CRHR2 (which is more commonly known as CRF2) is a type-2 G protein-coupled protein receptor for the corticotropin-releasing hormone [177]. Out of the 28 studied SNPs in *CRHR2*, five SNPs were significantly correlated with acute bronchodilator response in one, or frequently more than one, cohort. Among those, variant rs7793837 was associated with altered SABA response in all three cohorts of the *CRHR2* study containing 607, 427, and 152 participants, respectively [178].

Different variants of *ARG1* (Arginase 1) and *ARG2* (Arginase 2) show altered acute response to SABAs, while the endothelial nitric oxide synthase (*NOS3*) shows altered acute response to LABAs. NO (nitric oxide), an endogenous vasorelaxing bronchodilator, is generated by the action of NOS3 on L-arginine. Since ARG1 and ARG2 are metabolizing L-arginine, so it is expected that the entire three genes, *ARG1*, *ARG2*, and *NOS3*, might be implicated in asthma pharmacogenetics. Combined association evidence, surviving Bonferroni correction for multiple testing from the CAMP four asthma cohorts [179], points to SNP rs2781659 in *ARG1*. C-allele homozygotes for SNP rs2781667 in arginase 1 showed significantly less response to the inhaled corticosteroid treatments [180]. Arginase-2 variants rs17249437 and rs3742879 correlated with increased airway obstruction and airway hyperresponsiveness, and lower reversibility of airway constriction following treatment with beta-2 agonists [180]. A small candidate gene study [181] of *NOS3* had revealed one possible variant (Asp^{298}Glu) correlated with lung function response to ICS/LABA combined treatment; however, this result still needs to be replicated in larger cohorts. *THRB* [182], *SLC24A4* [183], *SLC22A15* [183], *SPATS2L* [184], and SNPs (rs892940, rs77441273, rs1281748/rs1281743, and rs295137, respectively) show promising loci for further pharmacogenetic investigations.

7.3. Leukotriene pathway pharmacogenetics

Relative to the corticosteroid and β-adrenergic pathways, the cysteinyl leukotriene pathway pharmacogenetic studies are generally fewer and have smaller sample sizes. The oldest of these studies [185], held in 1999, had investigated the tandem repeat polymorphism in *ALOX5* promoter. Among 114 asthmatics, it has been shown that the *ALOX5* promoter repeat is associated with altered lung functions in response to a 5-LO inhibitor [185]. It has been shown in children that those who had more or less than five repeats (3, 4, and 6) of the *ALOX5* promoter-binding motif experienced increased urinary leukotriene E4 (the terminal cysteinyl leukotriene metabolite) concentrations and reduced FEV1 baseline than the wild-type genotype with five repeats [186]. Further pharmacogenetic studies revealed that the *ALOX5* promoter polymorphism, along with the *ALOX5* SNPs rs892690, rs2029253, and rs2115819, influences leukotriene pathway antagonist therapy [187–190]. Moreover, variants of *LTC4S*, encoding Leukotriene C4 synthase, and *MRP1* (or *ABCC1*), encoding multidrug resistance-associated protein 1, have been linked to lung function response while treatment with Zileuton and Montelukast [189, 190].

$Arg^{312}Gln$, rs12422149, which is a coding variant in *SLCO2B1* (solute carrier organic anion transporter family member 2B1 gene), has been related to symptom control during Montelukast therapy. This fact was due to the interindividual variability of carrier-mediated Montelukast transport in the intestines, and consequently its plasma levels [191]. By contrast, two other studies, probably due to their small sample sizes, were unable to replicate similar *SLCO2B1* pharmacokinetic effects [192, 193]. Overall, larger replicate cohorts, for the leukotriene pathway identified loci, are still needed.

8. Current and future challenges facing asthma pharmacogenetics

As demonstrated above, there has been fundamental progress in the field of asthma pharmacogenetics; however, these efforts have not yet been introduced into clinical practice to guide physician. There are several reasons that account for this gap. Most important is the limited number of asthma pharmacogenetics-focused GWAS, which would compare common candidate gene methodology that would allow combining all patients from small cohorts studied. Small sample sizes prevent any expansion of the pharmacogenetic research of asthma, which needs a large number of subjects for statistical significance. Along with limited cohort size, study defects due to poor ancestry structuring and stratification substantially result in replication inconsistencies. Furthermore, genes interact together in networks; therefore, simply attributing phenotypic variation to individual genes is not appropriate. Epigenetics studies investigate the changes in gene activities, which are heritable to the subsequent generations, but are independent of any DNA sequence alterations [194, 195]. Epigenetic tuning of the genes associated with asthma has a significant impact on determining the drug response. Several mechanisms, related to epigenetics, are currently being investigated for both biomarker tagging and therapeutic innovation intervention [196]. Moreover, epigenetic changes have the ability to override the genetic effects of time, environment, tissue specificity,

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and other conditions such as age and gender of a patient, nutrition and hygiene, and intestinal microflora, which all highly influence the drug response in addition to the genetic factors. The collective impact of all combination of these factors requires the application of complicated algorithm that could take into consideration each of these factors and their interplay. The prospective genetic profile of an asthmatic should compromise a set of common and rare variants, on ancestral basis, which will be predictive of the pattern of his/her therapeutic responsiveness to different treatment options. The current human variant catalog continues to grow in an exponential manner because of the lower costs associated with whole genomic sequencing. Despite the steep decline in sequencing costs, the technology of sequencing, in terms of speed and quality, enormously increases. The future pharmacogenetic profile would also predict any possible adverse response associated with the chosen line of treatment. Genetic biomarkers are needed to warn the physician about any potential adverse side effects which can be life threatening. It is very important for typical genetic profiling to also consider gene-gene and gene-environment interactions. Gene-gene interactions are predominately crucial in the framework of combination therapies, for example, ICS and β-adrenergic agonists. Interactions between the surrounding environment and the patients' genes are assumed to be an additional element, because environmental stress, apart from the genetic makeup, contributes to the development of asthma exacerbations. Future pharmacogenetic directions need to cover also the pharmacokinetic side of the patient profile. Altered drug absorption, metabolism, distribution, or excretion extensively influence drug dosing and even drug selection. All in all, the complete asthma pharmacogenetic catalog has many aspects to cover, before being introduced into the clinical practice.

9. Conclusion

Asthma is a complex respiratory and immune disease. Inadequate (or exaggerated) ability of genetically predisposed individuals to control inflammation, induced by innate and environmental factors, results in asthma. Further, studies using allergic asthma and atopy models enable to better understand several interacting gene products and variable responsiveness of asthmatic subjects to current therapies. Eventually, thorough investigation of the complexity of asthma might lead to successful designing of personalized therapies for patients suffering from allergic asthma.

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