Review

The Genetic Factors of the Airway Epithelium Associated with the Pathology of Asthma

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Abstract: Asthma is a chronic disease of the airways characterized by inflammation, tightened muscles, and thickened airway walls leading to symptoms such as shortness of breath, chest tightness, and cough in patients. The increased risk of asthma in children of asthmatic parents supports the existence of genetic factors involved in the pathogenesis of this disease. Genome-wide association studies have discovered several single nucleotide polymorphisms associated with asthma. These polymorphisms occur within several genes and can contribute to different asthma phenotypes, affect disease severity, and clinical response to different therapies. The complexity in the etiology of asthma also results from interactions between environmental and genetic factors. Environmental exposures have been shown to increase the prevalence of asthma in individuals who are genetically susceptible. This review summarizes what is currently known about the genetics of asthma in relation to risk, response to common treatments, and gene-environmental interactions.

Keywords: asthma; genetics; single nucleotide polymorphisms (SNPs); association studies; treatment response; gene-environment interaction

1. Introduction

Asthma is a heterogenous inflammatory disease of the airways characterized by airways hyperresponsiveness, reversible airflow obstruction, and mucus hypersecretion [1]. Poorly controlled asthma may be adversely impacted by several comorbidities including rhinosinusitis, gastro-oesophageal reflux disease (GERD), obstructive sleep apnea (OSA), psychological dysfunction, and chronic infections [2]. Asthma has affected approximately 262 million individuals in 2019 and its prevalence has been increasing worldwide [3]. The incidence of asthma is significantly higher among children and adolescents as these populations are highly exposed to allergens, including air pollution and tobacco smoke, and their immune system is not trained to function properly when triggered by such allergens [3]. It has long been known that asthma is a complex disease with several risk factors involved in its etiology. It was first confirmed by a study in twins that asthma has a hereditary component. In other words, genetic predispositions contribute to the development of asthma and this heritability rates in the adult population of up to 60 percent [4].

The airway epithelial cells are the first barrier against pathogens and environmental insults. Any damage to the epithelium promotes the release of alarmin cytokines, including TSLP, IL-33, and IL-25. These cytokines activate a variety of immune cells and downstream inflammatory pathways. Activated Mast cells and basophils release mediators, including histamine, prostaglandin (PG) D2 and leukotrienes, which contract airway smooth muscle and increase mucus secretion. Drugs targeting these mediators, including SABA, LABA, and anti-leukotrienes, prevent the development of these pathways [5].

Alarmin cytokines also promote the activation of group 2 innate lymphoid cells (ILC2s), the maturation of CD4+ T cells into Th2 cells, and the production of Type 2 cytokines (IL-4, IL-5, IL-13) which promote B cell differentiation and IgE production, the hallmark of allergic inflammation.
IL-5, and IL-13). Type 2 cytokines result in airway eosinophilia, mucus overproduction, bronchial hyperresponsiveness (BHR), and remodeling of the epithelium and subepithelial matrix, which can be suppressed by glucocorticoids [6] (Figure 1).

Figure 1. Pathophysiology of asthma. Alarmin cytokines IL-25, IL-33 and TSLP are released from the airway epithelium in response to external stimuli such as pathogens, allergens, and pollution. These cytokines result in the downstream production of type 2 cytokines (IL-4, IL-5, and IL-13) from Th2 cells and their innate counterpart, ILC2s. The type 2 cytokines induce airway inflammation, FeNO, airway hyperresponsiveness, and remodeling, all inhibited by corticosteroids. The production of histamine and leukotrienes from activated basophils and mast cells promotes bronchoconstriction, which is prevented by antagonists. FeNO = fractional exhaled nitric oxide; LABA = long acting β-agonist; SABA = short-acting β-agonist.

The presence of such genetic factors associated with asthma implies that understanding the genetic basis of this disease might explain many mechanisms affecting the pathology of this disease. In the past decades, there has been an increased interest to obtain a better understanding of the genetic risk factors involved in asthma. The majority of these risk factors are single variations occurring within the DNA, which are known as single-nucleotide polymorphisms [SNPs], and these genetic variants have an allele frequency of more than 1% in the population [7]. With the help of next-generation sequencing technology in recent years, genome-wide association studies (GWASs) have become a novel approach to identify associations between genotypes and phenotypes [8]. The primary methods for studying complex disease-susceptibility genes include GWASs, candidate gene association studies, and genome-wide linkage analyses, which can provide insight into disease-causing mechanisms and, eventually, novel targets for asthma therapeutics.

In this review paper, we summarize the data on the genetic single nucleotide polymorphisms responsible for the susceptibility to asthma, the patients’ responses to treatments in the presence of different genetic factors, and gene-environment interactions involved in the pathobiology of asthma.

2. Genetic Polymorphisms Associated with Asthma Susceptibility and Severity

There are several genes that regulate asthma, and others that contribute to disease risk. Moreover, clinical findings have shown that asthma severity varies among individuals and
may also change over time. Among the susceptibility genes, there are those that are known to significantly increase the risk of asthma. Genetic polymorphisms in genes including alarmin cytokines (TSLP and IL-33) type 2 cytokines (IL-4, IL-13) and other inflammatory-related proteins (HLA, ADAM33), and vitamin D receptor have been shown to enhance, or reduce, the risk and severity of asthma in individuals.

2.1. Thymic Stromal Lymphopoietin (TSLP)

Thymic stromal lymphopoietin (TSLP) is an epithelial-derived cytokine that is produced following exposure to external stimuli such as bacteria, viruses, smoke, and allergens [9]. TSLP drives allergic inflammation through binding to the TSLP receptor on inflammatory cells, including mast cells, dendritic cells, and eosinophils. TSLP expression is increased in patients with asthma compared to healthy controls and correlates with measures of the airway obstruction [10]. An anti-human TSLP monoclonal antibody (AMG157/tezepelumab) that prevents the interaction of TSLP with its receptor was shown to significantly reduce allergen-induced airway responses and airway inflammation in patients with mild allergic asthma [11]. Tezepelumab has been approved for use in severe asthma following clinical trials showing a reduction in asthma exacerbation, improvement in lung function and asthma control, and reduction of blood eosinophils and airway fractionated nitric oxide (FeNO) levels [12].

Genetic studies have shown that TSLP gene variants play a role in the development of asthma and are associated with the risk and severity of this disease, however, the results are inconsistent. A study published by Harada et al. demonstrated that two single nucleotide polymorphisms existing at the promoter region of the TSLP gene (rs3806933 and rs2289276) were positively associated with asthma susceptibility in children and adult asthmatics [13], this positive or direct association can be explained as a higher risk of asthma in individuals carrying these SNPs. The results of this study were expanded by Birben et al. showing that the association with these SNPs is sex-specific with the CC genotype of SNP rs3806933 positively associated with asthma in the male population, while the CC genotype of rs2289276 correlated with higher eosinophil counts in female subjects [14]. While these two studies showed a positive association between the TSLP polymorphisms and asthma, a study conducted by Hunninghake et al. and others contradicted the previous findings by showing that two SNPs in the genomic region of TSLP (rs1837253 and rs2289276) were inversely correlated with asthma and thereby making them less susceptible to developing asthma [15–17]. Moorehead et al. investigated the expression of the SNP rs1837253 in the TSLP gene, and its association with asthma, allergic disease, and eosinophilia [16]. The authors found protective effects in individuals carrying rs1837253, and speculated this may be related to the changes happening in the production of the long isoform of TSLP, which ultimately leads to reduced production of this protein [16].

Overall, more studies are required to discover the functional effects of each polymorphism, which could provide a basis for investigating the clinical effects of anti-TSLP therapies in different TSLP gene variant groups.

2.2. Interleukin-33 (IL-33)

IL-33 is an epithelial-derived alarmin cytokine that plays a significant role in the pathobiology of allergic disease and asthma. IL-33 is secreted by epithelial cells and inflammatory cells in the airways and plays a role in type-2 innate immunity by activation of mast cells, group 2 innate lymphoid cells [ILC2], basophils, eosinophils, and macrophages through the ST2 receptor [18]. IL-33 is one of the earliest cytokines released in response to stimulation with allergens [19], with elevated levels found in the airway secretions of patients with acute asthma, and these elevated levels of IL-33 expression in lung epithelium correlates with asthma severity [20].

GWAS have shown that polymorphisms in the IL-33 gene are associated with asthma susceptibility [21], however the impacts of these polymorphisms are not restricted to the risk of asthma. A study conducted by Wu et al. [22] demonstrated that rs4742170 was associated
with higher FENO levels, and a worse response to ICS treatments, indicating that SNPs may also affect the severity and treatment response in patients. A larger study conducted in Finland, including 521 cases of adult onset asthma and 1016 controls reported a direct association between SNPs rs996029, rs2006682, rs7037276, and adult onset asthma [23]. The same correlation has been demonstrated for the SNPs rs3939286 and rs1342326 [24].

In contrast to SNPs evaluated in the previous studies, a whole genome sequencing project in Iceland found the IL-33 SNP rs146597587 was associated with lower eosinophil counts in children, suggesting expression of this SNP provides protection from developing asthma [25]. The same inverse association between IL-33 SNPs and asthma was reported by Queiroz et al. [26]. The protective or indirect association would suggest a lower risk of developing asthma in those who have these SNPs present in their genome.

2.3. Interleukin-1 Receptor-like 1 (IL1RL1)

IL1RL1, also known as ST2, is a member of the IL-1 family and serves as the receptor for the epithelial-derived IL-33 cytokine. There are 3 different subtypes of ST2 expressed in the lungs; sST2, IL1RL1-b, and IL1RL1-c. sST2 is a soluble form and acts as a decoy receptor preventing the IL-33 from binding to the receptors expressed on immune cells. IL1RL1-b is the main receptor expressed on the surface of immune cells. The binding of IL-33 to IL1RL1-b will activate the MyD88/NFkB pathway, resulting in the downstream activation of cells involved in type2 immune response, thus promoting airway inflammation [27].

In a Chinese population, Zhang et al. reported a significant positive association between two SNPs in the IL1RL1 gene, rs1420102, and rs13431828, with an increased risk of asthma [28]. Another study conducted in a Chinese Han population reported that two SNPs located in the intron of IL1RL1 (rs10208293 and rs13424006) were associated with eosinophilic inflammation and childhood asthma [22]. The functional mechanism of these two SNPs is not fully understood; however, it can be hypothesized that these variants might play a role in regulating the production of the sST2 receptor, which serves as a decoy receptor to reduce free IL-33.

A study performed on the European population by Savenije et al. had shown a positive correlation between two SNPs [rs10513854 and rs9290936] and persistent wheeze in childhood asthma [17]. However, these findings could not be replicated in Wu et al.’s study in a Chinese Han population, and this discrepancy may be related to the small sample size or ethnic group studied. Since the prevalence of mutant genotypes of SNPs is normally low in populations, a small number of subjects may not be sufficient to show any significant differences between patients and the healthy control group. This issue could also explain the lack of any significant associations between IL1RL1 gene variants and asthma in a study of a Puerto Rican population [29].

Moreover, there are different variants in the IL1RL1 gene that have demonstrated protective associations; in a European study reported by Savenije et al., rs11685480 and rs1420102 correlated with lower counts of blood eosinophils, indicating a decreased risk of developing severe asthma. They also showed that these variants impact the serum level of sST2 [30]. The effect of IL1RL1 gene polymorphisms on serum levels has also been reported by Dijk et al. which showed significant associations between rs13431828, rs1420101, rs1921622, and rs10204137 and lower serum sST2 levels. It can be concluded that gene variants can exert their effects by regulating the protein expression [31]. Dijk has also reported that the SNP rs13431828 can promote a more severe phenotype of asthma by increasing the risk of exacerbations and hospitalizations in children [32].

2.4. Interleukin-13 (IL-13)

Interleukin-13 is an inflammatory cytokine produced by type 2 T helper cells and group 2 innate lymphoid cells. The IL-13 gene is located on chromosome 5 and contains four exons and three introns. IL-13 shares similar secondary structures with IL-4, which is also an important cytokine in allergic inflammation, and both IL-13 and IL-4 exert their effects through a shared receptor. The binding of IL-13 to its receptor in the
airway epithelium of asthmatic patients leads to mucus hypersecretion and promotion of bronchial hyperresponsiveness [33].

A genome-wide association study has highlighted the essential role of the SNP rs1295686, located in the intron of the IL-13 gene, in the impairment of total IgE production [34]. The finding of this GWAS study prompted further genetic studies to replicate the results in different ethnic populations, which confirmed and extended the findings of the GWAS study to show an increased risk of asthma among children and adults carrying the SNP rs1295686 in Asian, Caucasian, and middle eastern ethnicities [35–38]. Similarly, rs20541 is significantly associated with a higher risk of asthma and airway hyperresponsiveness [35,39]. It is suggested that the single change in the nucleotide sequence of the IL-13 gene substitutes the arginine amino acid with glutamine, increasing the receptor binding affinity of the secreted cytokine which ultimately increases the downstream inflammatory activity [40]. Imraish et al., however, report a significant reduction in IgE serum levels in asthmatics carrying the minor allele of the rs20541, suggesting an inverse relationship between this SNP and the severity of asthma [41]. The mechanisms by which this SNP affects asthma risk are not clear yet.

2.5. Interleukin-4 (IL-4)

Interleukin-4 (IL-4) is a pivotal cytokine in allergic inflammation with a central role in driving the differentiation of naïve T helper cells into Type 2 helper T cells and in the isotype switching of B cells to IgE antibody production. Production of IL-4 in the asthmatic airway epithelium results in production of chemokines from epithelial cells, increased airway eosinophil numbers, and increased bronchial hyperresponsiveness [42]. The IL-4 gene is located on chromosome 5 in a region that has been reported to be correlated with asthma and other allergic disorders [43].

Among the different single nucleotide polymorphisms discovered in the IL-4 gene, rs2070874, located on the UTR region of the gene, has been shown to be associated with higher serum IgE levels and increased risk of asthma in different ethnic populations [44,45]. Another SNP in the promoter region of the IL-4 gene (rs2243250) has been shown to increase the risk of asthma in children and adults [46,47]. This direct pattern has been replicated by Michael et al. also reporting a direct association for allergic rhinitis in a population of 106 patients with allergic rhinitis [48]. The mechanism by which this polymorphism increases the asthma risk has been explained by Rosenwasser et al. demonstrating an increase in the binding of transcription factors to the promoter region when this SNP is present. It can be concluded that increased transcription factor binding will lead to increased production of IL-4 cytokine and, therefore, upregulation of inflammatory responses [46].

In contrast, the rs2227284 SNP in the IL-4 gene was reported to have an inverse and protective association with asthma by decreasing the risk of asthma in carriers, and furthermore, the protective effect of rs2227284 was more pronounced in carriers with homozygous mutant genotype compared to a heterozygous genotype [47].

2.6. The Human Leukocyte Antigen (HLA)

The airway epithelium is exposed to a large number of inhaled antigens. Human leukocyte antigens (HLA) are a genomic region located on chromosome 6, encoding a large variety of proteins important in the regulation of the immune system. In general, the main role of HLA molecules is to present antigens to CD4+ and CD8+ T lymphocytes, where HLA class I molecules present peptides originating from inside the cells to CD8+ cytotoxic T cells and HLA class II molecules present the antigens that have entered the cells from outside to CD4+ T helper lymphocytes [49].

HLA loci are considered highly polymorphic regions that are linked to susceptibility to immunological disorders, transplantation success, host defense, and atopic diseases such as asthma. Several studies have shown that various HLA alleles are associated with asthma [50]. A large GWAS has identified single nucleotide polymorphisms in the HLA-DQ locus that are highly associated with an increased risk of asthma. SNP rs9272346, located
near the HLA-DQA1 locus, is one of the SNPs shown to have a significant association with both adult and childhood asthma [51]. HLA-DQA1 locus is among the MHC class II loci with the most polymorphisms linked to asthma and allergic disease. Several studies have demonstrated a positive correlation between HLA-DQA1* 0101, DQA1 * 0601, HLA-DQB1 * 0303, DQB1 * 0601, and HLA-DQB1 * 0201 alleles and susceptibility to asthma in diverse ethnic populations [52–55].

2.7. A Disintegrin and Metalloproteinase 33 (ADAM33)

The ADAM33 gene located on chromosome 20 was one of the first genes identified to be associated with asthma. ADAM33 plays several important roles in cell activation, proteolysis, adhesion, fusion, and signaling. It has been shown that the expression of ADAM33 is increased in the epithelium and airway smooth muscles of asthmatics, suggesting a role in the pathogenesis of bronchial hyperresponsiveness and airway remodeling [56]. Studies have shown that ADAM33 levels are higher in asthmatic patients and correlate with serum levels of IL-4 and IL-13, suggesting that its expression is regulated by Th2 cytokines [57].

Taken together, ADAM33 is considered an important element in the promotion of asthmatic response, and therefore, genetic variations throughout its gene may be linked to asthma susceptibility and severity.

A genome-wide evaluation of 460 Caucasian families by identified several polymorphisms within the ADAM33 gene associated with asthma susceptibility [58]. Following the findings of this study, many candidate gene studies were conducted in different populations to replicate the results; however, there were several inconsistent reports, potentially resulting from ethnic differences and smaller sample sizes. There was no association between any of the four ADAM33 SNPs and asthma in the Iranian population [59]. Similarly, a German study did not find any correlations between SNPs of the ADAM33 gene and childhood asthma, despite a large study population [60]. Shen B et al., reported a significant association between SNP rs44707 and severe asthma, as well as rs2787094 with less severe asthma, in an Asian population [61], and similar results were reported in a Thai study in which rs44707 was associated with the high severity group [62]. Furthermore, there was a significant correlation between F+2, rs44707, and V4 variants and the risk of asthma in the Indian population [63]. The same significant association for rs44707 was equally reported by Fedorova et al., who also reported the prevalence of haplotypes rs44707, rs2787095, rs2485700, and rs2280091 was higher in the healthy control compared to the asthmatics suggesting a protective effect against asthma in those carrying this haplotype [64]. In a study consisting of 96 asthmatics and 86 healthy children, Ning et al. reported a significant correlation between SNP rs678881 and increased risk of childhood asthma but no significant differences in the prevalence of rs2280089 and rs2853209 between the two groups [65].

2.8. Vitamin D Receptor (VDR)

Vitamin D is a steroid soluble nutrient predominantly located in the skin with the function of calcium absorption and bone health. It is also reported to have immunomodulatory effects on both innate and adaptive immunity. Vitamin D metabolism in airway epithelium is shown to increase the lung immune response and therefore modulate the production of inflammatory cytokines from these cells [66]. A Cochrane review of vitamin D in asthma found that while there was no effect on lung function or asthma control, oral vitamin D supplementation reduced the risk of severe asthma exacerbations requiring systemic corticosteroids and hospital admission, with no adverse effects reported, suggesting it is a safe and potentially effective intervention [67].

The vitamin D receptor [VDR] gene is located in chromosome 12 near asthma-related genes suggesting that polymorphisms in this gene may be a good indicator of asthma occurrence. GWAS has identified four single nucleotide polymorphisms within the VDR gene that are shown to be related to asthma risk and severity. These SNPs include TaqI [rs731236], Apal [rs7975232], FokI [rs2228570] and BsmI [rs1544410] [68]. Findings from a study conducted in Turkey provide evidence for an association between TaqI and Apal
polymorphisms and asthma susceptibility. These polymorphisms were also shown to be correlated with lower mRNA gene expression of VDR [69]. The significant association between TaqI and asthma susceptibility was also reported by other studies [70–72].

Pillai et al., reported that VDR polymorphisms may affect the severity of asthma, demonstrating that rs7975232, rs2239185, rs2107301, rs1540339, rs3782905, and rs2228570 were significantly associated with lower pre-bronchodilator spirometry and greater reversibility, both indicators of increased risk of asthma severity [73]. Taken together, the polymorphisms within the vitamin D receptor gene play a role in the susceptibility to asthma, and lead to an increased risk of asthma in the carriers.

A summary of the genetic polymorphisms in the alarmin cytokines (TSLP and IL-33), type 2 cytokines (IL-4, IL-13) as well as HLA, ADAM33, and vitamin D receptor are summarized (Table 1, Figure 2).

![Genes 2022, 13, x FOR PEER REVIEW 10 of 26](image)

**Figure 2.** Summary of SNPs associated with asthma. Some SNPs have been reported to have both direct and indirect effects based on the study.
| Gene | Study Design | Race | SNP   | Allele | Association                                                | Ref |
|------|--------------|------|-------|--------|------------------------------------------------------------|-----|
|      |              |      |       |        | TSLP                                                        |     |
|      | Candidate gene study | Caucasian | rs1837253 | C/T   | Inversely correlated with risk of asthma [16]             |     |
|      | Candidate gene study | Middle eastern | rs2289276 | C/T   | Inversely correlated with the risk of asthma              | [17]|
|      | Candidate gene study | Middle eastern | rs2289278 | C/G   | No association                                             |     |
|      | Candidate gene study | Asian | rs3806933 | C/T   | Associated with asthma susceptibility in adult and childhood asthma [13] | |
|      | Candidate gene study | Asian | rs2289276 | C/T   | Associated with lung function [FEV1/FVC]                |     |
|      | Candidate gene study | Asian | rs2289278 | C/G   | Associated with lung function [FEV1/FVC]                |     |
|      | Candidate gene study | Caucasian | rs3806933 | C/T   | Associated with asthma in boys                           | [14]|
|      | Candidate gene study | Caucasian | rs2289276 | C/T   | Associated with higher eosinophil counts in asthmatic girls |     |
|      | Candidate gene study | Caucasian | rs10073816 | G/A   | Associated with lower FEV1 level in asthmatic             |     |
|      | Candidate gene study | Caucasian | rs11466749 | A/G   | The presence of allergic rhinitis in asthmatic children strengthened the association of the rs11466749 genotype with asthma |     |
|      | Candidate gene study | Mixed | rs1837253 | C/T   | Associated with a reduced risk of asthma in males        | [15]|
|      | Candidate gene study | Mixed | rs2289276 | C/T   | Associated with a reduced risk of asthma in females      |     |
|      | Candidate gene study | Asian | rs4742170 | C/T   | Associated with risk of higher FeNO at baseline          |     |
|      | Candidate gene study | Asian | rs2381416 | A/C   | No association                                             | [22]|
|      | Candidate gene study | Asian | rs928413  | A/G   | No association                                             |     |
|      | Candidate gene study | Asian | rs992969  | A/G   | No association                                             |     |
|      | GWAS          | Caucasian | rs146597587 | G/C   | Associated with lower eosinophil count and reduced risk of asthma [25] | |
|      | Candidate gene study | Caucasian | rs1412420 | C/A   | Associated with adult-onset asthma                        | [23]|
|      | Candidate gene study | Caucasian | rs7037276 | G/C   | Associated with adult-onset asthma                        |     |
|      | Candidate gene study | Caucasian | rs996029  | A/T   | Associated with higher risk of asthma                     |     |
|      | Candidate gene study | Middle eastern | rs1342326 | A/C   | Associated with higher risk of asthma                     | [24]|
|      | Candidate gene study | Middle eastern | rs3939286 | G/A   | Associated with higher risk of asthma                     |     |
Table 1. Cont.

| Gene   | Study Design     | Race          | SNP             | Allele | Association                                      | Ref |
|--------|------------------|---------------|------------------|--------|--------------------------------------------------|-----|
|        |                   |               | rs11685480       | G/A    | Associated with lower blood eosinophil count      | [30]|
|        |                   |               | rs1420102        | C/A    |                                                  |     |
|        |                   |               | rs1041973        | C/A    | Associated with decreased risk of developing asthma |     |
| IL1RL1 | Candidate gene study | Caucasian | rs1420102        | C/A    | Associated with lower blood eosinophil count      |     |
|        |                   |               | rs13431828       | T/C    | Associated with increased risk of exacerbation   |     |
|        |                   |               | rs1041973        | A/C    | No association                                   | [32]|
|        |                   | Puerto Rican  | rs1921622        | A/G    | No association                                   | [29]|
|        |                   | Asian         | rs1420102        | C/A    | Associated with higher risk of asthma            | [28]|
|        |                   | Mixed         | rs13431828       | T/C    | Associated with increased risk of exacerbation   |     |
|        |                   |               | rs1946131        | G/A    | No association                                   |     |
|        |                   |               | rs1420101        | G/A    |                                                  |     |
|        |                   |               | rs1921622        | G/A    | Associated with lower serum sST2 levels          |     |
|        |                   |               | rs10204137       | G/A    |                                                  |     |
|        | Candidate gene study | Mixed     | rs1295686        | C/T    | Associated with increased risk of asthma         | [37]|
|        |                   |               | rs20541          | G/A    | Associated with increased risk of asthma         | [41]|
| IL-13  | Candidate gene study | Middle eastern | rs1295686       | C/T    | Associated with increased risk of asthma         |     |
|        |                   |               | rs20541          | G/A    | Associated with increased risk of asthma         | [35]|
|        |                   |               | rs1800925        | G/A    | No association                                   |     |
|        |                   |               | rs762534         | C/A    |                                                  |     |
|        | Candidate gene study | Asian    | rs20541          | G/A    | Associated with AHR                              | [39]|
|        |                   |               | rs2243250        | C/T    | Associated with higher serum IgE levels          | [74]|
| IL-4   | Candidate gene study | Caucasian | rs2227284        | T/G    | Associated with reduced risk of asthma           |     |
|        |                   |               | rs2243250        | T/C    | No association                                   | [47]|
|        |                   | Asian         | rs2070874        | T/C    | No association                                   |     |
|        |                   |               | rs2243290        | A/C    |                                                  |     |
Table 1. Cont.

| Gene | Study Design | Race | SNP    | Allele | Association                                      | Ref  |
|------|--------------|------|--------|--------|--------------------------------------------------|------|
|      |              |      | IL-4   |        |                                                  |      |
|      |              |      |        | rs2243250 | T/C                           | Associated with asthma and allergic rhinitis [48] |
|      |              |      |        | rs2227284 | T/G                           |                                                |      |
|      |              |      |        | rs2070874 | T/C                           | No association                                  |      |
| HLA  | GWAS         | Mixed|        | rs9272346 | A/G                           | Associated with increased risk asthma [51]     |      |
|      |              |      |        | rs2280091 | A/G                           |                                                |      |
|      | Candidate gene study | Middle eastern |        | rs3918396 | G/A                           | No association                                  [59] |
|      |              |      |        | rs2280089 | G/A                           |                                                |      |
|      |              |      |        | rs511898  | C/A                           |                                                |      |
|      | Candidate gene study | Middle eastern |        | rs44707    | G/C                           | Associated with severe asthma                   |      |
|      |              |      |        | rs2280089 | G/A                           | Associated with increased risk asthma           |      |
|      |              |      |        | rs2787094 | G/C                           | Associated with less severe asthma              |      |
| ADAM33| Candidate gene study | Asian |        | rs612709   | G/A                           |                                                |      |
|      |              |      |        | rs511898  | C/A                           | No association                                  [61] |
|      |              |      |        | rs2280091 | A/G                           |                                                |      |
|      |              |      |        | rs528557  | G/C                           |                                                |      |
|      |              |      |        | rs3918396 | G/A                           |                                                |      |
|      | Candidate gene study | South Asian |        | rs528557   | G/C                           | Associated with increased risk asthma [63]     |      |
|      |              |      |        | rs597980   | C/T                           |                                                |      |
|      |              |      |        | rs511898  | C/A                           |                                                |      |
|      |              |      |        | rs44707    | G/C                           |                                                |      |
|      |              |      |        | rs2787094 | G/C                           |                                                |      |
### Table 1. Cont.

| Gene   | Study Design   | Race        | SNP        | Allele | Association                          | Ref |
|--------|----------------|-------------|------------|--------|--------------------------------------|-----|
| ADAM3  | Candidate gene study | Asian      | rs528557   | G/C    | Associated with low severity asthma  | [62]|
|        |                |             | rs598418   | C/T    | Associated with high severity asthma |     |
|        |                |             | rs44707    | G/C    |                                       |     |
|        |                |             | rs2853209  | A/T    | No association                        |     |
|        |                |             | rs597980   | C/T    |                                       |     |
|        |                |             | rs11905233 | G/A    |                                       | [62]|
|        |                |             | rs2787094  | G/C    |                                       |     |
|        |                |             |            |        |                                       |     |
|        | Candidate gene study | Caucasian  | rs2787094  | G/C    | Associated with mild asthma          | [75]|
|        |                |             | rs511898   | G/A    |                                       |     |
|        |                |             | rs3918395  | G/T    |                                       |     |
|        |                |             | rs3918396  | G/A    |                                       |     |
|        |                |             | rs528557   | G/C    |                                       |     |
|        |                |             | rs44707    | G/C    | No association                        | [60]|
|        |                |             | rs597980   | C/T    |                                       |     |
|        |                |             | rs574174   | G/A    |                                       |     |
|        |                |             | rs2280091  | A/G    |                                       |     |
|        |                |             | rs2280090  | C/T    |                                       |     |
|        |                |             | rs2787094  | G/C    |                                       |     |
|        | Candidate gene study | Caucasian  | rs44707    | G/C    | Associated with increased risk of asthma | [64]|
|        |                |             | rs2787095  | G/T    |                                       |     |
|        |                |             | rs2485700  | G/A    | No association                        |     |
|        |                |             | rs2280091  | A/G    |                                       |     |
|        | Candidate gene study | Asian      | rs678881   | G/C    | Associated with increased risk of asthma | [65]|
|        |                |             | rs2280089  | G/A    | No association                        |     |
|        |                |             | rs2853209  | A/T    |                                       |     |
| Gene     | Study Design    | Race            | SNP   | Allele | Association                                      | Ref  |
|----------|-----------------|-----------------|-------|--------|-------------------------------------------------|------|
| VDR      | Candidate gene  | Caucasian       | rs731236 | C/T    | Associated with increased risk of asthma        | [69] |
|          | study           |                 | rs7975232 | A/C    | Associated with reduced mRNA gene expression in |      |
|          |                 |                 |        |        | asthmatic group.                                |      |
|          | Candidate gene  | North African   | rs731236 | C/T    | Associated with increased risk of asthma        | [72] |
|          | study           |                 | rs7975232 | A/C    |                                                  |      |
|          |                 |                 | rs2228570 | T/C    |                                                  |      |
|          |                 |                 | rs1544410 | G/A    |                                                  |      |
|          | Candidate gene  | North African   | rs7975232 | A/C    | No association                                  | [70] |
|          | study           |                 | rs731236 | C/T    | Associated with increased risk of asthma        |      |
|          |                 |                 | rs1544410 | G/A    |                                                  |      |
|          | Candidate gene  | Caucasian       | rs731236 | C/T    | Associated with increased risk of asthma        | [71] |
|          | study           |                 | rs7975232 | A/C    |                                                  |      |
|          |                 |                 | rs1544410 | G/A    |                                                  |      |
|          | Candidate gene  | Caucasian       | rs731236 | C/T    | Associated with increased risk of asthma        | [76] |
|          | study           |                 | rs7975232 | A/C    | No association                                  |      |
|          |                 |                 | rs1544410 | G/A    |                                                  |      |
|          | Candidate gene  | Asian           | rs7975232 | A/C    | Associated with increased risk of asthma        | [77] |
|          | study           |                 | rs2228570 | T/C    |                                                  |      |

Definition of abbreviations: AHR = airway hyperresponsiveness; FeNO: fractionatal exhaled nitric oxide; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; GWAS = genome-wide association studies; IgE = immunoglobulin-E; IL- = interleukin-; mRNA = messenger ribonucleic acid; SNP = single nucleotide polymorphism; TSLP = thymic stromal lymphopoietin; VDR = vitamin D receptor.
3. Genetic Polymorphisms Associated with Asthma Treatment Response

Treatment for asthma is aimed at either bronchoconstriction or airway inflammation components of the disease. Spasmogens such as histamine, cysteinyl leukotrienes, and prostaglandin D2 released from airway mast cells and basophils promote smooth muscle contraction resulting in bronchoconstriction [78], which can be prevented by treatment with β-2 agonists and anti-leukotrienes. Activation of the epithelium and resident inflammatory cells leads to the accumulation of immune cells, including eosinophils, lymphocytes, macrophages, neutrophils, and basophils, which support an inflamed tissue environment and contribute to mucus hypersecretion, airway hyperresponsiveness, and remodeling. Corticosteroids are effective for suppressing airway inflammation and thereby preventing asthma exacerbations [79]. The variable rate of response to asthma therapies across the patient population can be related to genetic differences among individuals.

3.1. Corticosteroids

Corticosteroids are first-line therapy for the management of asthma, both as an inhaled therapy for symptom control and the prevention of exacerbations, and orally and intravenously during acute exacerbations. Corticosteroids are effective in improving asthma symptoms and bronchial hyperresponsiveness through suppression of recruitment and activation of epithelium and inflammatory cells, including but not limited to eosinophils, mast cells, basophils, lymphocytes, and ILC2 cells. However, there is a variable response to inhaled corticosteroid (ICS) therapy in patients with asthma, with some patients not responding despite high doses of therapy, and this variable interindividual response to ICS is highly repeatable, supporting a genetic basis for it [80]. Recent candidate gene studies and genome wide association studies have identified potential phenotypic indicators of response with the hope that clinicians will be able to use this information in guiding patient care and medication use to increase effectiveness and decrease harmful side effects.

Pharmacogenetic studies of the glucocorticoid pathway have identified genetic polymorphisms on biological candidate genes encoding the glucocorticoid biosynthetic pathway, the receptor heterocomplex and chaperone proteins. These studies identified SNPs in the corticotropin-releasing hormone gene (CRHR1), the heat shock organizing protein gene (STIP1), and glucocorticoid receptor gene (NRSC1), which are all associated with increased responsiveness to ICS therapy as measured by increased FEV1 post ICS treatment [81–84]. Genotype analysis of nine different SNPs in the CYP3A gene locus on chromosome 7, encompassing the genes CYP3A4, CYP3A5, and CYP3A7, found a significant improvement in asthma control scores, among patients with a CYP3A4*22 variant T-allele [85]. TBX21 encoding for the transcription factor T-bet, which influences naïve T lymphocytes development, was found to have a nonsynonymous variation coding for replacement of histidine 33 with glutamine (H33Q C>G) which is associated with significant improvement in bronchial hyperresponsiveness and asthma control with ICS treatment [86,87]. Both heterozygous and homozygous variants in the FCER2 gene are associated with increased FEV1 in response to treatment with ICS and are indicators of good responders to ICS [88]. Polymorphisms in both vascular endothelial growth factor (VEGFA) and collagen type II alpha 1 chain (COL2A1), a fibrillar collagen found in cartilage, are significantly associated with improved FEV1 response to ICS and [89].

In addition to candidate gene studies, GWAS studies have identified a promoter SNP in the glucocorticoid-induced transcript-1 gene (GLCCI1) which is associated with a change in lung function during ICS treatment. Unlike other polymorphisms, mutations in both rs37972 and rs37973 were associated with a smaller improvement of lung function in response to ICS compared to those with the wild-type allele [90]. Another GWAS study identified SNPs in the T gene (rs3127412 and rs6456042) which were associated with a twofold to threefold improvement in FEV1 response to ICS therapy in patients homozygous for the wild-type versus mutant alleles [91]. The T gene has not previously been implicated in asthma or corticosteroid pathology. The T gene is a founding member
of an ancient family of genes containing a common protein motif, the T locus [92]. The T locus encodes a product with DNA binding activity which has a role in early vertebrate developmental processes [92].

Recent research has highlighted new candidate gene polymorphisms of interest. Polymorphisms in IL-13 rs20541 locus may correlate with therapeutic efficacy; patients carrying the GG allele were more responsive to ICS therapy than those with the GA or AA allele [93]. Vitamin D has multiple effects on the immune system from modulating T cell proliferation causing a switch from a T helper (Th1) phenotype to a Th2 phenotype by inhibiting the synthesis, secretion and release of Th1 cell anti-inflammatory cytokines (IL-4, IL-10) while inducing Th2 cell pro-inflammatory cytokines (IL-1, TNFα, IFN-γ) [94]. Reduced vitamin D levels are associated with asthma severity [95] and increased airway hypersensitivity requiring increased doses of ICS [96]. Polymorphisms in the vitamin D receptor gene (VDR) FokI showed an association between patients with the TT genotype and T allele carriers and glucocorticoid-resistance [97]. No associations were found in the VDR Apal [97].

The glucocorticoid pathway interacts with other biological pathways which influences the response to ICS monotherapy or when in combination with short-acting β agonists (SABA) or long-acting β agonists (LABA). Adenylyl cyclase type 9 (ADCY9) is an enzyme within the canonical B2-adrenergic receptor pathway responsible for producing the second messenger cyclic AMP (cAMP). A SNP in ADCY9 is associated with a strong bronchodilator response to SABA treatment only when used in combination with ICS [98]. Therefore, gene polymorphisms may assist us in understanding interindividual variability in response to ICSs in asthma, and further our understanding regarding steroid resistance in asthma.

3.2. β-2 Adrenergic Receptor Pathway

β-2 agonists exert their bronchodilator effects via β-2 adrenoceptors (β2-ARs) that are heavily expressed on airway smooth muscle (ASM) cells of the lower respiratory tract. Inhaled β agonist binding to the β2-AR activates a coupling with adenylate cyclase through a trimeric G-protein leading to an increased production of cyclic adenosine monophosphate and protein kinase A resulting in smooth muscle relaxation. Short acting β2-agonists (SABA) are used for the treatment of acute symptoms of bronchospasm, while long acting β2-agonists (LABA) are used in conjunction with ICS to provide long-term asthma control. The most frequently studied gene related response to β-2 agonist treatment response is ADRB2, a small intron-less gene with more than 49 different genetic variants. Early pharmacogenetic studies have demonstrated that patients homozygous for Arg-16 or heterozygous for Arg-16 of the rs1042716 SNP have a greater acute response to SABA bronchodilation compared to Gly-16 [99–102]. Israel et al. studied the effects of polymorphisms at codon 16 [b2-AR-16] and codon 27 (b2-AR-27) of the β2AR in 190 mild asthmatics [103] finding regular SABA use, as opposed to as-needed use, resulted in a decline in peak expiratory flow rate [PEFR] in asthmatics homozygous for ARG-16, while the PEFR in Gly-16 homozygotes remained unchanged. A further study of 78 mild asthmatics enrolled in pairs to match for lung function, found that regular SABA resulted in a significant increase in PEFR Gly-16 homozygotes, while ARG-16 homozygotes had a significant improvement in PEFR during the placebo phase when SABA use was limited, suggesting ARG-16 homozygotes should be treated with other agents such as ipratropium as a reliever, rather than SABA [104]. Early studies of ADRB2 polymorphisms in response to LABA showed that Arg-16 homozygotes experienced a decline in PEFR and a deterioration of symptoms after LABA treatment however two subsequent prospective studies were not able to identify significant differences in PEFR responsiveness to LABA therapy [105,106].

Candidate gene studies of β agonist response have also included genes within ADCY9. The Ile-772 Met variant was associated with acute bronchodilation in response to SABA in ICS-treated asthmatics and increased lung function response to LABA and ICS treatment [98,107]. Five SNPs in CRHR2 have been associated with an acute SABA bronchodilator response in three independent cohorts [108]. Rare variants adjacent to ADCY9 and CRHR2 are
associated with SABA bronchodilator response in a cohort of patients from Puerto Rico and Mexico [109]. SNPs in the genes that encode the enzymes arginase-1 and arginase-2 metabolize L-arginine (ARG1 and ARG2) within the nitric oxide biosynthetic pathway have been associated with an increased response to acute SABA therapy [110,111]. Additionally, the endothelial nitric oxide synthase gene (NOS3) the variant Asp-298 Glu was associated with increased lung function response to LABA and ICS combination therapy [112]. A polymorphism in the thyroid hormone receptor B-gene (rs892940) was associated with bronchodilator response in a childhood population and two adult populations [113].

GWAS performed in non-Hispanic white asthmatics identified a promoter SNP in SPATS2L associated with an acute bronchodilator response to SABA treatment [114]. Another GWAS study showed that SNPs (rs912142) in SPATA13-AS1, an anti-sense RNA that overlaps the gene SPATA13, were associated with increased SABA bronchodilator response [115,116]. Admixture mapping from a GWAS of BDR in a cohort of African Americans with asthma identified SNPs (rs7081864 and rs790336) in the PRKG1 gene which were significantly associated with bronchodilation response to SABA treatment [116,117]. Additionally, admixture mapping identified a novel candidate gene expressed in the lung and bronchial epithelial cells (SLC22A15] with two rare SNPs [rs1281748 and rs1281743] in which individuals carrying the minor allele had enhanced bronchodilation to SABA treatment [109].

3.3. Leukotrienes

Leukotrienes are a family of lipid mediators with a pivotal and integral role in airway tone and inflammation. There are two types of leukotrienes: \( \text{LTB}_4 \) which acts as a potent immune cell chemotactic mediator of inflammation; and the cysteinyl leukotriene group (\( \text{LTC}_4, \text{LTD}_4, \text{LTE}_4 \)) which are capable of causing significant bronchoconstriction. Leukotriene receptor antagonists, including montelukast and zafirlukast, have anti-inflammatory and anti-bronchoconstrictor properties which improve lung function (FEV1, peak flow) and decrease asthma exacerbations however patients show a wide variety of responsiveness. Variances in the genes coding the enzyme 5-lipoxygenase pathway (coded by ALOX5) showed that wild type or heterozygous ALOX5 promoter and additional SNPs have increased bronchodilator response with montelukast compared to the mutant alleles [118,119]. In contrast the mutant variants in \( \text{LTC}_4 \) and MRP1 have been associated with increased lung function response to montelukast and zileuton [120,121]. Additionally, SNPs in gene coding for \( \text{LTA}_4 \) showed that patients heterozygous or homozygous for the mutant G allele were at greater risk of having exacerbations while on montelukast [122]. Montelukast is a substrate of organic anion transporting OATP2B1 encoded by the SLCO2B1 gene. A coding variant in SLCO2B1 was found to be associated with increased symptom control in a small cohort of patients [123] however larger cohort studies were not able to replicate these results [124,125]. Table 2 and Figure 3 summarize the association between treatment response and gene polymorphisms.
| Gene          | Study Design         | Race                  | SNP               | Allele   | Drug Class | Response Phenotype                                      | Ref  |
|--------------|----------------------|-----------------------|-------------------|----------|------------|--------------------------------------------------------|------|
| CRHR1        | Candidate gene study | Mixed                 | rs242941          | C/A      | ICS        | Variants improves FEV1                                  | [81] |
|              |                      |                       | rs1876828         | C/T      |            |                                                        |      |
| STIP1        | Candidate gene study | Asian/Caucasian       | rs2236647         | C/T      | ICS        | Variants improves FEV1                                  | [82,83]|
|              |                      |                       | rs6591838         | A/G      |            |                                                        |      |
|              |                      |                       | rs1011219         | G/A      |            |                                                        |      |
|              |                      |                       | rs4980524         | A/C      |            |                                                        |      |
| NR3C1        | Candidate gene study | Caucasian             | rs41423247        | G/C      | ICS        | Variants improve FEV1                                  | [84] |
| TBX21        | Candidate gene study | Mixed                 | rs2240017         | C/G      | ICS        | Variant improved airway hyperresponsiveness            | [86,87]|
| GLCCI1       | GWAS                 | Mixed                 | rs37973           | G/T      | ICS        | rs37973 Wild-type allele had improved FEV1 and response to ICS compared to mutant allele | [90] |
|              |                      |                       | rs37972           | A/T      |            |                                                        |      |
| T gene       | GWAS                 | Mixed                 | rs3127412         | A/C      | ICS        | Wild-type allele had improved FEV1 and response to ICS compared to mutant allele | [91] |
|              |                      |                       | rs6456042         | C/A      |            |                                                        |      |
|              |                      |                       | rs3099266         | A/T      |            |                                                        |      |
| ADCY9        | Candidate gene study | Mixed                 | rs2230739         | T/C      | ICS B2 agonist | Variants improved bronchodilator response | [98] |
| CYP3A4       | Candidate gene study | Mixed                 | CYP3A4*22 allele  |          | ICS        | T-allele variants improved asthma control               | [85] |
| FCER2        | Candidate gene study | Mixed                 | rs28364072        | A/G      | ICS        | Variants improve FEV1                                  | [88,126,127]|
| VEGFA        | Candidate gene study | Mixed                 | rs3025039         | C/T      | ICS        | Variants improve FEV1                                  | [89] |
| COL2A1       | Candidate gene study | Mixed                 | rs3809324         | G/T      | ICS        | Variants improve FEV1                                  | [89] |
| IL-13        | Candidate gene study | Mixed                 | rs20541           | C/A      | ICS        | Variants improved FEV1                                  | [93] |
| Vitamin D receptor | Candidate gene study | Middle eastern     | FokI rs228570    | T/C      | ICS        | FokI variants are associated with GC-resistance        | [97] |
|              |                      |                       | Apal Rs795232    | A/C      |            |                                                        |      |
| ADRB2        | Candidate Gene Study | Mixed                 | rs1042716         | G/T      | SABA       | Short-term use: Arg 16 has greater bronchodilation response than Gly 16 Long-term use: no allele effect | [99–102]|
| ADCY9        | Candidate gene study | Mixed                 | rs11959427        | A/C      | SABA       | Acute FEV1 bronchodilation                              | [98] |
| CRHR2        | Candidate Gene Study | Mixed /South American | rs7793837         | A/T      | SABA       | Acute FEV1 bronchodilation                              | [108,109]|

Table 2. Single Nucleotide polymorphisms associated with treatment response.
Table 2. Cont.

| Gene      | Study Design       | Race            | SNP            | Allele   | Drug Class | Response Phenotype                          | Ref     |
|-----------|--------------------|-----------------|----------------|----------|------------|---------------------------------------------|---------|
| ARG1      | Candidate Gene Study | Caucasian       | rs2781659      | A/G      | SABA       | Acute FEV1 bronchodilation                  | [110,111] |
|           |                    |                 | rs2781667      | C/T      |            |                                             |         |
| ARG2      | Candidate Gene Study | Caucasian       | rs7140310      | T/G      | SABA       | Acute FEV1 bronchodilation                  | [111]   |
|           |                    |                 | rs10483801     | C/A      |            |                                             |         |
| THR2      | Candidate Gene Study | Caucasian       | rs892940       | G/A      | SABA       | Acute FEV1 bronchodilation                  | [113]   |
| SPATS2L   | GWAS               | Caucasian       | rs295137       | C/T      | SABA       | Acute FEV1 bronchodilation                  | [114]   |
| SPATA13-AS1 | GWAS               | Mixed/African American | rs912142 | A/G      | SABA       | Acute FEV1 bronchodilation                  | [115,116] |
| SLC22A15  | Admixture mapping  | South American  | rs1281748      | A/G      | SABA       | Acute FEV1 bronchodilation                  | [109]   |
|           |                    |                 | rs1281743      | G/A      |            |                                             |         |
| PRKG1     | Candidate Gene Study | Mixed           | rs7081864      | G/A      | SABA       | Acute FEV1 bronchodilation                  | [116,117] |
| ADRB2     | Candidate Gene Study | Mixed           | rs1042716      | G/T      | LABA       | No allele effect                            | [105,106] |
|           |                    |                 | rs1800888      | C/T      |            |                                             |         |
| ADCY9     | Candidate Gene Study | Asian           | rs2230739      | T/C      | LABA       | Long-term increased FEV1 response           | [107]   |
| NOS3      | Candidate Gene Study | Mixed           | rs1799983      | A/T      | LABA       | Acute FEV1 bronchodilation in Asp 298 Glu   | [112]   |
| ALOX5     | Candidate Gene Study | Mixed           | rs892690       | C/T      | Antileukotriene | Wild type allele increased BDR   | [118,119] |
|           |                    |                 | rs2115819      | G/A      |            |                                             |         |
|           |                    |                 | rs10507391     | C/A      |            |                                             |         |
|           |                    |                 | rs4986832      | G/A      |            |                                             |         |
|           |                    |                 | rs4987105      | C/T      |            |                                             |         |
| LTC4      | Candidate Gene Study | Mixed           | rs272431       | G/T      | Antileukotriene | Mutant allele increased BDR   | [120,121] |
|           |                    |                 | rs730012       | A/C      |            |                                             |         |
| MRP1      | Candidate Gene Study | Mixed           | rs119774       | C/T      | Antileukotriene | Mutant allele increased BDR   | [121]   |
| LTA4      | Candidate Gene Study | Mixed           | rs2660845      | A/G      | Antileukotriene | Wild type allele decreased asthma exacerbations | [122] |
| SLC22B1   | Candidate Gene Study | Mixed           | rs12422149     | G/A      | Antileukotriene | Increased symptom control   | [123]   |

Definition of abbreviations: FEV1 = forced expiratory volume in one second; GC = glucocorticoid; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; SABA = short-acting β-agonist; SNP = single nucleotide polymorphism.
4. Interactions between Genetic Polymorphisms and Environmental Factors

Gene-environment interactions can contribute to the development of asthma when individuals with specific variants of allele genotypes and SNPs are exposed to environmental factors affecting the airway epithelium, such as ambient air pollution, oxidative stress, tobacco smoke, and aeroallergens (Figure 4).

4.1. Air Pollution

Gene-environment interactions between amino acid variants of Glutathione S-transferase Pi (GSTP1) and air pollution have been extensively studied in the past. At the Ile-105 locus, Ile-105 homozygotes in areas of high air pollution have a higher risk of asthma compared to those with any Val-105 allele and who are exposed to low air pollution levels [128]. Various studies indicate a val/val genotype at the ile105val locus may be an indicator of injury from oxidative stress in asthmatic children [129], whereas conflicting evidence supports the hypothesis of the val/val genotype acting as a protective genotype [130].

In discussions of gene-environment interactions, children who carry the minor allele for the GSTP1 SNPs rs1138272 or rs1695 (Ile105Val), plus exposure to NO2 using land use regression and dispersion modelling have greater susceptibility to injury from air pollution in comparison to major allele carriers, and this susceptibility is highest in children with current asthma, ever asthma, and ever wheeze [131,132]. mRNA expression of Toll-like receptor 2 (TLR2) on human airway epithelial cells has been shown to be involved in the response to air pollution particle [or particulate matter] exposure, whereas Toll-like receptor 4 [TLR4] plays a lesser role through its expression on alveolar macrophages [133]. The rs4696480 and rs1898830 SNPs in the TLR2 gene enhance the effect of exposure of particulate matter in asthmatic children from birth to 8 years of age [134]. Similarly, the SNPs rs2770150 TC, rs10759931 GG, rs6478317 GG, and rs1927911 TT of the TLR4 gene modify the effect of exposure to particulate matter in asthmatics, thus making children susceptible to adverse affects of air pollution when carrying select genotypes of these two
genes [134]. Previous studies on TGF-β1 elucidate its role in possible airway inflammation through the release of inflammatory cytokines [135], and in airway remodeling, such as in subepithelial fibrosis [136]. Traffic and tobacco smoke exposure in utero in combination with the TGF-β1 -509TT (rs4803457) genotype increase the risk of asthma [137].

**Figure 4.** Gene-environmental factor interactions related with modified effects, susceptibility, complications, symptoms, or development of asthma, or asthma exacerbations. SNPs with more than one symbol may demonstrate multiple effects, or may differ depending on genotype, allele pairing, or type of allele (variant vs. wild-type, major vs. minor carrier).

### 4.2. Aeroallergens

The combined effect of a genetic predisposition and environmental allergen exposure may influence asthma severity or susceptibility (Figure 3). The FOXP3 gene is expressed on Tregs cells, and T regulatory 1-like cells (Tr1) cells mediate the Th2 immune response to environmental allergens [138]. The T allele of rs2232368 of the FOXP3 gene increases the risk of asthma symptoms and onset of atopy to aeroallergens in females [139]. In aeroallergen exposure as well, asthmatics with the GSTP1 SNPs rs1138272 or rs1695 (Ile105Val) may influence asthma severity or susceptibility (Figure 3). The gene increases the risk of asthma symptoms and onset of atopy to aeroallergens in females [139]. In aeroallergen exposure as well, asthmatics with the GSTP1 SNPs rs1138272 or rs1695 (Ile105Val) may influence asthma severity or susceptibility (Figure 3). The G allele is an important for immunity and has been shown to be upregulated in asthma patients [140]. In asthma carrying the dominant genotype for the rs1741137 SNP (T allele) or the rs2069885 SNP (A allele) there is a 4-fold increase in the risk of asthma [141].

**ORMDL3** polymorphisms found on chromosome 17q21 have been shown to promote asthma, and when overexpressed, ORMDL3 increases Th2 cytokine production, and subsequently increases childhood asthma susceptibility [142]. Household allergens such as domestic furred pets, in combination with rs7216389 SNP homozygous carriers of the ORMDL3 gene, contribute to the significant association of recurrent wheeze in children [143].
The P2RY12 (P2Y12 receptor) mediates LTE4-induced pulmonary inflammation in studies when using Chinese hamster ovary cells transfected with human P2Y12 constructs [144]. The rs8180086, rs3732765, rs10935840, and rs11708767 SNPs of P2RY12, can alter airway hyperresponsiveness in asthmatics exposed to a 1.85 µg/g concentration of house dust mite, whereas the rs7615865 and rs149197 SNPs modified bronchodilator reversibility. HDM exposure at 10 µg/g demonstrated similar results, in where the rs3732765, rs10935840, and rs1170876 SNPs demonstrated altered airway hyperresponsiveness, and the rs10935844 and rs8180086 SNPs alter FVC in an asthmatic cohort, thereby providing evidence for a gene-environment interaction between P2RY12 variants and HDM [145].

4.3. Oxidative Stress

The NFE2L2 gene is responsible for encoding a transcription factor is known for its defensive properties against oxidative injury and inflammatory disorders by upregulating antioxidant and detoxifying phase 2 enzymes [146]. NO2 exposure can increase the risk of an asthma exacerbation in individuals with respiratory infections [147]. In the NFE2L2 gene, the rs2588882 and rs6721961 SNPs have a protective effect during infection-induced exacerbation in asthmatics (IIA). These SNPs demonstrate variability in asthmatics depending on their exposure to different polluted areas [148].

4.4. Smoking

A gene-smoking environmental interaction exists in asthmatic patients who carry the rs1800795 SNP of the IL-6 gene [149]. Although the uncommon rs2234678 SNP of the IL1RN gene is protective against the development of asthma in those without childhood tobacco exposure, those carrying this SNP with childhood environmental tobacco exposure, are at higher risk of early onset asthma [150]. In a UK cohort, maternal smoking during pregnancy in infants with the rs2234678 GG SNP of IL1RN was also identified as a gene-environment interaction that increased the susceptibility to repeated asthma and persistent asthma in children [151]. Table 3 demonstrates the summary of the effects of gene-environment interactions.
**Table 3. Combined effects of gene-environmental interactions.**

| Gene   | Study Design | Race                                      | SNP       | Allele | Association                                                                                                                                                                                                 | Ref             |
|--------|--------------|-------------------------------------------|-----------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| FOXP3  | Candidate gene | Brazilian                                 | rs2233268 | C/T    | Associated with asthma susceptibility and onset of atopy in females.                                                                                                                                          | [139]           |
| TGF-B1 | Candidate gene | Mixed                                     | rs4803457 | C/T    | -500T allele carriers have higher susceptibility to early-onset childhood asthma and increased risk of asthma, asthma, and injury from air pollution compared to major allele carriers.                          | [137]           |
| GSTP1  | Candidate gene | Canadian, Swedish, German, Netherlands (six birth cohorts) | rs1138272 | C/T    | Minor allele carriers with NO2 exposure have higher risk to current asthma, ever asthma, and injury from air pollution compared to major allele carriers.          | [131]           |
|        |              |                                           | rs1695    | A/G*   | Minor allele carriers for both rs1138272 and rs1695 exposed to traffic and NO2 may be at an increased risk of asthma, current asthma, and ever asthma. *A/A genotype has protective properties against complications from household allergens, G allele makes asthmatics more prone to complications | [131,132]       |
| NFE2L2 | Candidate gene | Hungarian                                  | rs258882  | T/G    | Protective effect during infection-induced exacerbation in asthmatics [IIA]                                                                                                                                   | [148]           |
|        |              |                                           | rs6721961 | G/T    |                                                                                                                                                                                                             |                 |
| TLR2   | Candidate gene | Netherlands                                | rs4696480 | T/A    | Modifies effect of exposure of air pollution on asthma from birth to 8 years of age.                                                                                                                        | [134]           |
|        |              |                                           | rs1898830 | A/G    |                                                                                                                                                                                                             |                 |
| TLR4   | Candidate gene | Netherlands                                | rs2770150 | A/G    | Modify the effect of exposure to air pollution on asthma                                                                                                                                                     | [134]           |
|        |              |                                           | rs10759931| G/A    |                                                                                                                                                                                                             |                 |
|        |              |                                           | rs6478317 | A/G    |                                                                                                                                                                                                             |                 |
|        |              |                                           | rs4927911 | C/A    |                                                                                                                                                                                                             |                 |
| ORMDL3 | Candidate gene | Danish, delivered in Copenhagen           | rs7216389 | T/C    | Significant association with risk of recurrent wheeze in homzygous variant allele carriers                                                                                                                                 | [143]           |
| IL9    | GWAS         | Mixed                                     | rs1174137 | C/T    | Significant interactions of the rs1174137, rs2069885, and rs1859430 SNPs with dust mite allergen exposure. Increase in the likelihood of exacerbation for dominant genotype carriers [rs1174137, rs2069885] and with increased dust mite exposure | [141]           |
|        |              |                                           | rs2069885 | G/A    |                                                                                                                                                                                                             |                 |
|        |              |                                           | rs1859430 | G/A    |                                                                                                                                                                                                             |                 |
| P2RY12 | Candidate gene | Mixed                                     | rs8180086 | G/A    | Modified airway hyperresponsiveness values with HDM exposure                                                                                                                                                 | [145]           |
|        |              |                                           | rs3732765 | G/A    |                                                                                                                                                                                                             |                 |
|        |              |                                           | rs10935840| A/G    |                                                                                                                                                                                                             |                 |
|        |              |                                           | rs11708767| G/A    |                                                                                                                                                                                                             |                 |
|        |              |                                           | rs7615865 | A/T    | Modified bronchodilator reversibility with HDM exposure                                                                                                                                                      |                 |
|        |              |                                           | rs1491978 | G/C    |                                                                                                                                                                                                             |                 |
| IL6    |               | Chinese                                    | rs1800795 | G/C    | Gene-smoking environmental interaction increases risk of asthma                                                                                                                                              | [149]           |
| IL1RN  | Candidate gene | Mixed [150] or Caucasian [151]             | rs2234678 | A/G    | Protective properties in the development of asthma in those without childhood environmental tobacco exposure; those with childhood exposure, were at higher risk of early onset asthma. Maternal smoking during pregnancy in infants with the GG genotype had increased susceptibility to repeated asthma and persistent asthma in children | [150,151]      |
5. Conclusions

Asthma is a heterogeneous disease resulting from a complex interplay between genetic and environmental factors. Single nucleotide polymorphisms throughout the genome have diverse impacts on the susceptibility and severity of asthma. While a majority of SNPs affecting asthma lead to increased risk or susceptibility in the carriers, there are specific variants that have a protective effect and decrease the risk when present. The same pattern is also seen in response to drug treatments, where asthmatic patients with specific polymorphisms in their genome demonstrate an improved response to universal asthma medications suggesting that genetic predispositions should be taken into account when prescribing different asthma therapies.

Studying the genetics of asthma advances our understanding of the pathology, diagnosis, and treatment of this complex disease. Discovering new single nucleotide variations in the genetic material of individuals will not only help identify novel biomarkers and phenotypes but also provide us insights to design beneficial and individualized treatments.

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References

1. Quirt, J.; Hildebrand, K.J.; Mazza, J.; Noya, F.; Kim, H. Asthma. Allergy Asthma Clin. Immunol. 2018, 14, 50. [CrossRef] [PubMed]
2. Boulet, L.-P. Influence of comorbid conditions on asthma. Eur. Respir. J. 2009, 33, 897–906. [CrossRef] [PubMed]
3. Dharmage, S.C.; Perret, J.L.; Custovic, A. Epidemiology of Asthma in Children and Adults. Front. Pediatr. 2019, 7, 246. [CrossRef] [PubMed]
4. Thomsen, S.F.; Ulrik, C.S.; Kyvik, K.O.; Ferreira, M.A.R.; Backer, V. Multivariate genetic analysis of atopy phenotypes in a selected sample of twins. Clin. Exp. Allergy 2006, 36, 1382–1390. [CrossRef] [PubMed]
5. Barnes, P.J. Asthma mechanisms. Medicine 2016, 44, 265–270. [CrossRef]
6. Dunican, E.M.; Fahy, J.V. The Role of Type 2 Inflammation in the Pathogenesis of Asthma Exacerbations. Ann. Am. Thorac. Soc. 2015, 12 (Suppl. 2), S144–S149. [CrossRef]
7. Shen, L.X.; Basilion, J.P.; Stanton, V.P., Jr. Single-nucleotide polymorphisms can cause different structural folds of mRNA. Proc. Natl. Acad. Sci. USA 1999, 96, 7871–7876. [CrossRef] [PubMed]
8. Tam, V.; Patel, N.; Turcotte, M.; Bossé, Y.; Paré, G.; Meyre, D. Benefits and limitations of genome-wide association studies. Nat. Rev. Genet. 2019, 20, 467–484. [CrossRef] [PubMed]
9. Demehri, S.; Morimoto, M.; Holtzman, M.J.; Kopan, R. Skin-Derived TSLP Triggers Progression from Epidermal-Barrier Defects to Asthma. PLOS Biol. 2009, 7, e1000067. [CrossRef] [PubMed]
10. Ying, S.; O’Connor, B.; Ratoff, J.; Meng, Q.; Mallett, K.; Cousins, D.; Robinson, D.; Zhang, G.; Zhao, J.; Lee, T.H.; et al. Thymic Stromal Lymphopoietin Expression Is Increased in Asthmatic Airways and Correlates with Expression of Th2-Attracting Chemokines and Disease Severity. J. Immunol. 2005, 174, 8183–8190. [CrossRef] [PubMed]
11. Gauvreau, G.M.; O’Byrne, P.M.; Boulet, L.-P.; Wang, Y.; Cockcroft, D.; Bigler, J.; FitzGerald, J.M.; Boedigheimer, M.; Davis, B.E.; Dias, C.; et al. Effects of an Anti-TSLP Antibody on Allergen-Induced Asthmatic Responses. N. Engl. J. Med. 2014, 370, 2102–2110. [CrossRef] [PubMed]
12. Menzies-Gow, A.; Corren, J.; Bourdin, A.; Chupp, G.; Israel, E.; Wechsler, M.E.; Brightling, C.E.; Griffiths, J.M.; Hellqvist, Å.; Bowen, K.; et al. Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. N. Engl. J. Med. 2021, 384, 1800–1809. [CrossRef] [PubMed]
13. Harada, M.; Hirota, T.; Jodo, A.I.; Hitomi, Y.; Sakashita, M.; Tsunoda, T.; Miyagawa, T.; Doi, S.; Kameda, M.; Fujita, K.; et al. Thymic Stromal Lymphopoietin Gene Promoter Polymorphisms Are Associated with Susceptibility to Bronchial Asthma. Am. J. Respir. Cell Mol. Biol. 2011, 44, 787–793. [CrossRef] [PubMed]
37. Ramphul, K.; Lv, J.; Hua, L.; Liu, Q.; Fang, D.; Ji, R.; Bao, Y. Single nucleotide polymorphism predisposing to asthma in children of Mauritian Indian and Chinese Han ethnicity. *Braz. J. Med. Biol. Res.* 2014, 47, 394–397. [CrossRef] [PubMed]

38. Xu, Y.; Li, J.; Ding, Z.; Li, J.; Li, B.; Yu, Z.; Tan, W. Association between IL-13 +1923C/T polymorphism and asthma risk: A meta-analysis based on 26 case-control studies. *Biosci. Rep.* 2017, 37, BS20160505. [CrossRef]

39. Utsumi, Y.; Miyamoto, T.; Sekimura, K.; Sasaki, N.; Suzuki, N.; Nakamura, Y.; Kobayashi, H.; Yamauchi, K. The effect of single-nucleotide polymorphism in IL-13 on airway hyperresponsiveness in asthmatics. *Eur. Respir. J.* 2012, 40, P1786.

40. Vladich, F.D.; Brazzile, S.M.; Stern, D.; Peck, M.L.; Ghittoni, R.; Vercelli, D. IL-13 R130Q, a common variant associated with allergy and asthma, enhances effector mechanisms essential for human allergic inflammation. *J. Clin. Investig.* 2005, 115, 747–754. [CrossRef]

41. Imraish, A.; Abu-Thiab, T.; Zhihf, M. IL-13 and FOXP3 genes polymorphisms regulate IgE levels in asthmatic patients. *Biomed. Rep.* 2021, 14, 55. [CrossRef] [PubMed]

42. Shi, H.-Z.; Deng, J.-M.; Xu, H.; Neng, Z.-X.; Xiao, C.-Q.; Liu, Z.-M.; Qin, S.-M.; Jiang, H.-X.; Liu, G.-N.; Chen, Y.-Q. Effect of Inhaled Interleukin-4 on Airway Hyperreactivity in Asthmatics. *Am. J. Respir. Crit. Care Med.* 1998, 157, 1818–1821. [CrossRef] [PubMed]

43. Steinke, J.W.; Borish, L. Th2 cytokines and asthma—Interleukin-4: Its role in the pathogenesis of asthma, and targeting it for treatment with interleukin-4 receptor antagonists. *Respir. Rev.* 2001, 6, 60–66. [CrossRef] [PubMed]

44. Basehore, M.J.; Howard, T.D.; Lange, L.A.; Moore, W.C.; Hawkins, G.A.; Marshik, P.L.; Harkins, M.S.; Meyers, D.A.; Bleecker, E.R. A comprehensive evaluation of IL-4 variants in ethnically diverse populations: Association of total serum IgE levels and asthma in white subjects. *J. Allergy Clin. Immunol.* 2004, 114, 80–87. [CrossRef]

45. Suzuki, I.; Hizawa, N.; Yamaguchi, E.; Kawakami, Y. Association between a C+33T polymorphism in the IL-4 promoter region and total serum IgE levels. *Clin. Exp. Allergy* 2000, 30, 1746–1749. [CrossRef]

46. Rosenwasser, L.J.; Borish, L. Promoter polymorphisms predisposing to the development of asthma and atopy. *Clin. Exp. Allergy* 1998, 28 (Suppl. 5), 13–15, discussion 26–18. [CrossRef]

47. Wang, R.-S.; Jin, H.-X.; Shang, S.-Q.; Liu, X.-Y.; Chen, S.-J.; Jin, Z.-B. Associations of IL-2 and IL-4 Expression and Polymorphisms with the Risks of Mycoplasma pneumoniae Infection and Asthma in Children. *Arch. Bronconeumol.* 2015, 51, 571–578. [CrossRef]

48. Micheal, S.; Minhas, K.; Ahmed, A. IL-4 gene polymorphisms and their association with atopic asthma and allergic rhinitis in Pakistani patients. *J. Investigig. Allergy Clin. Immunol.* 2013, 23, 107–111.

49. Terasaki, P.I. *History of HLA: Ten Recollections*.; UCLA Tissue Typing Laboratory Press: Los Angeles, CA, USA, 1990.

50. Svejaard, A.; Platz, P.; Ryder, L.P.; Nielsen, L.S.; Thomsen, M. HL-A and Disease Associations—A Survey. *Transplant Rev.* 1975, 22, 3–43. [CrossRef]

51. Lasky-Su, J.; Himes, B.E.; Raby, B.A.; Klanderman, B.J.; Sylvia, J.S.; Lange, C.; Melen, E.; Martinez, F.D.; Israel, E.; Gauderman, J.; et al. HLA-DQ strikes again: Genome-wide association study further confirms HLA-DQ alleles in the diagnosis of asthma among adults. *Clin. Exp. Allergy* 2012, 42, 1724–1733. [CrossRef] [PubMed]

52. Guo, X.; Ni, P.; Li. Association between asthma and the polymorphism of HLA-DQ genes. *Zhonghua Jie He Hu Xi Za Zhi = Chin. J. Tuberc. Respir. Dis.* 2012, 37, 139–141. [PubMed]

53. Guo, X.; Ni, P.; Li. Association between asthma and the polymorphism of HLA-DQ genes. *Zhonghua Jie He Hu Xi Za Zhi = Chin. J. Tuberc. Respir. Dis.* 2006, 7, 215–220. [PubMed]

54. Munthe-Kaas, P.L. *History of HLA: Ten Recollections*.; UCLA Tissue Typing Laboratory Press: Los Angeles, CA, USA, 1990.

55. Movahedi, M.; Moin, M.; Gharagozlou, M.; Aghamohammadi, A.; Dianat, S.; Moradi, B.; Nicknam, M.H.; Nikbin, B.; Amirzargar, A. Association of HLA class II alleles with childhood asthma and Total IgE levels. *Iran. J. Allergy Asthma Immunol.* 2008, 7, 82–99. [PubMed]

56. Munthe-Kaas, M.C.; Carlsten, K.L.; Carlsten, K.H.; Egeland, T.; Håland, G.; Devulapalli, C.S.; Akselsen, H.; Undlien, D. HLA Dr-Dq haplotypes and the TNFA-308 polymorphism: Associations with asthma and allergy. *Allergy* 2007, 62, 991–998. [CrossRef] [PubMed]

57. Tripathi, P.; Awasthi, S.; Gao, P. ADAM Metalloproteinase Domain 33 (ADAM33): A Promising Target for Asthma. *Mediat. Inflamm.* 2014, 2014, 572025. [CrossRef]

58. Powell, R.M.; Hamilton, L.M.; Holgate, S.T.; Davies, D.E.; Holloway, J.W. ADAM33: A novel therapeutic target for asthma. *Expert Opin. Ther. Targets* 2003, 7, 485–494. [PubMed]

59. Van Eerdewegh, P.; Little, R.D.; Dupuis, J.; Del Mastro, R.G.; Falls, K.; Simon, J.; Torrey, D.; Pandit, S.; McKenny, J.; Braunischweiger, K.; et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 2002, 418, 426–430. [CrossRef]

60. Farjadian, S.; Moghtaderi, M.; Hoseini-Pouya, B.-A.; Ebrahimpour, A.; Nasiri, M. ADAM33 gene polymorphisms in Southwestern Iranian patients with asthma. *Iran J. Basic Med. Sci.* 2018, 21, 813–817. [CrossRef]

61. Schedel, M.; Depner, M.; Schoen, C.; Weiland, S.K.; Vogelberg, C.; Niggemann, B.; Lau, S.; Illig, T.; Klopp, N.; Wahn, U.; et al. The role of polymorphisms in ADAM33, a disintegrin and metalloproteinase 33, in childhood asthma and lung function in two German populations. *Respir. Res.* 2006, 7, 91. [CrossRef]

62. Shen, B.; Lin, R.; Wang, C.-C.; Rei, J.; Sun, Y.; Yang, Y.-L.; Lin, Y.-Y. ADAM33 gene polymorphisms identified to be associated with asthma in a Chinese Li population. *Biomed. Rep.* 2017, 6, 323–328. [CrossRef]
62. Thongngarm, T.; Jameekorntrak, A.; Limwongse, C.; Sangasapavilija, A.; Jirapongsananuruk, O.; Assawamakin, A.; Chaiyaratana, N.; Luangwedchakarn, V.; Thongnoppakhun, W. Association between ADAM33 polymorphisms and asthma in a Thai population. *Asian Pac. J. Allergy Immunol.* 2008, 26, 205–211. [PubMed]

63. Awasthi, S.; Tripathi, P.; Ganesh, S.; Husain, N. Association of ADAM33 gene polymorphisms with asthma in Indian children. *J. Hum. Genet.* 2011, 56, 188–195. [CrossRef] [PubMed]

64. Fedorova, Y.; Karunas, A.; Gimalova, G.; Guryeva, L.; Ramazanova, N.; Levashova, L.; Muhtarova, L.; Murzina, R.; Etkina, E.; Zagidullin, S.; et al. Association of ADAM33 gene polymorphisms with asthma in Volga-Ural region of Russia. *Eur. Respir. J.* 2011, 38, p436.

65. Ning, X.; Zhang, Y.; Wu, H.; Bai, L.; Gong, C.; Wang, Z. Genetic association of ADAM33 polymorphisms with childhood asthma in Chinese Han population: A case-control study. *Medicine* 2019, 98, e17327. [CrossRef] [PubMed]

66. Hanssottir, S.; Monick, M.M.; Hinde, S.L.; Lovan, N.; Look, D.C.; Hunninghake, G.W. Respiratory Epithelial Cells Convert Inactive Vitamin D to Its Active Form: Potential Effects on Host Defense. *J. Immunol.* 2018, 191, 709–7099. [CrossRef]

67. Martineau, A.R.; Cates, C.J.; Urashima, M.; Jensen, M.; Griffiths, A.P.; Nummatov, U.; Sheikh, A.; Griffiths, C.J. Vitamin D for the management of asthma. *Cochrane Database Syst. Rev.* 2016, 2019, CD011511. [CrossRef]

68. Mirzakhani, H.; Al-Garawi, A.A.; Carey, V.J.; Qiu, W.; Litonjua, A.A.; Weiss, S.T. Expression network analysis reveals cord blood vitamin D-associated genes affecting risk of early life wheeze. *Thorax* 2019, 74, 200–202. [CrossRef]

69. Kilic, M.; Ecin, S.; Taskin, E.; Sen, A.; Kara, M. The Vitamin D Receptor Gene Polymorphisms in Asthmatic Children: A Case-Control Study. *Pediatr. Allergy Immunol. Pulmonol.* 2019, 32, 63–69. [CrossRef]

70. Ahmed, A.E.; Hassan, M.H.; Toghan, R.; Rashwan, N.I. Analysis of 25-hydroxy cholecalciferol, immunoglobulin E, and vitamin D receptor single nucleotide polymorphisms (Apa I, Taq I, and Bsm I), among sample of Egyptian children with bronchial asthma: A case-control study. *Pediatr. Pulmonol.* 2020, 55, 1349–1358. [CrossRef]

71. Hutchinson, K.; Kerley, C.P.; Faul, J.; Greally, P.; Coghlan, D.; Louw, M.; Elnazir, B.; Rochev, Y. Vitamin D receptor variants and uncontrolled asthma. *Eur. Ann. Allergy Clin. Immunol.* 2018, 50, 108–116. [CrossRef] [PubMed]

72. Maalmi, H.; Al-Garawi, A.A.; Carey, V.J.; Qiu, W.; Litonjua, A.A.; Weiss, S.T. Expression network analysis reveals cord blood vitamin D-associated genes affecting risk of early life wheeze. *Thorax* 2019, 74, 200–202. [CrossRef]

73. Pillai, D.K.; Iqbal, S.F.; Benton, A.S.; Lerner, J.; Wiles, A.; Foerster, M.; Ozedirne, T.; Holbrook, H.P.; Payne, P.W., Jr.; Kabesch, M.; Schedel, M.; Carr, D.; Woitsch, B.; Fritzsch, C.; Weiland, S.K.; von Mutius, E. IL-4/IL-13 pathway genetics strongly influence serum IgE levels and childhood asthma. *J. Allergy Clin. Immunol.* 2011, 128, 938–946. [CrossRef] [PubMed]

74. Berenguer, A.G.; Fernandes, A.T.; Oliveira, S.; Rodrigues, M.; Ornelas, P.; Romeira, D.; Serrahima, R.; Rosa, A.; Câmara, R. Genetic polymorphisms and asthma: Findings from a case–control study in the Madeira island population. *Biol. Res.* 2014, 47, 40. [CrossRef]

75. Papadopoulou, A.; Kouis, P.; Middleton, N.; Kolokotroni, O.; Karpathios, T.; Nicolaidou, P.; Yallouros, P.K. Association of vitamin D receptor gene polymorphisms and vitamin D levels with asthma and atopy in Cypriot adolescents: A case-control study. *Multidiscip. Respir. Med.* 2015, 10, 26. [CrossRef] [PubMed]

76. Zhang, Y.; Wang, Z.; Ma, T. Associations of Genetic Polymorphisms Relevant to Metabolic Pathway of Vitamin D3 with Development and Prognosis of Childhood Bronchial Asthma. *DNA Cell Biol.* 2017, 36, 682–692. [CrossRef]

77. Bossé, Y. Asthmatic airway hyperresponsiveness: The ants in the tree. *Trends Mol. Med.* 2012, 18, 627–633. [CrossRef] [PubMed]

78. Ducharme, F.M.; Lasserson, T.J.; Cates, C.J. Long-acting beta2-agonists versus anti- leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. *Cochrane Database Syst. Rev.* 2006, 4, Cd003137. [CrossRef]

79. Drazen, J.M.; Silverman, E.K.; Lee, T.H. Heterogeneity of therapeutic responses in asthma. *Br. Med. Bull.* 2000, 56, 1054–1070. [CrossRef] [PubMed]

80. Tantisira, K.G.; Lake, S.; Silverman, E.S.; Palmer, L.; Lazarus, R.; Silverman, E.K.; Liggett, S.B.; Gelfand, E.W.; Rosenwasser, L.J.; Richter, B.; et al. Corticosteroid pharmacogenetics: Association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. *Hum. Mol. Genet.* 2000, 9, 1353–1359. [CrossRef] [PubMed]

81. Huang, J.; Hu, X.; Zheng, X.; Kuan, J.; Liu, C.; Wang, X.; Tang, Y. Effects of STIP1 and GLCCI1 polymorphisms on the risk of childhood asthma and inhaled corticosteroid response in Chinese asthmatic children. *BMC Pulm. Med.* 2020, 20, 303. [CrossRef] [PubMed]

82. Hawkins, G.A.; Lazarus, R.; Smith, R.S.; Tantisira, K.G.; Meyers, D.A.; Peters, S.P.; Weiss, S.T.; Blecker, E.R. The glucocorticoid receptor heterocomplex gene STIP1 is associated with improved lung function in asthmatic subjects treated with inhaled corticosteroids. *J. Allergy Clin. Immunol.* 2009, 123, 1357–1363.e7. [CrossRef]

83. Keskin, O.; Uluca, U.; Birben, E.; Coşkun, Y.; Ozkars, M.Y.; Keskin, M.; Kucukosmanoglu, E.; Kalayci, O. Genetic associations of the response to inhaled corticosteroids in children during an asthma exacerbation. *Pediatr. Allergy Immunol.* 2016, 27, 507–513. [CrossRef] [PubMed]

84. Stockmann, C.; Fassl, B.; Gaedigk, R.; Nkoy, F.;UCHIDA, D.A.; Monson, S.; Reilly, C.A.; Leeder, J.S.; Yost, G.S.; Ward, R.M. Fluticasone Propionate Pharmacogenetics: CYP3A4*22 Polymorphism and Pediatric Asthma Control. *J. Pediatr.* 2013, 162, 1222–1227.e2. [CrossRef]
86. Tantisira, K.G.; Hwang, E.S.; Raby, B.A.; Silverman, E.S.; Lake, S.L.; Richter, B.G.; Peng, S.L.; Drazen, J.M.; Glimcher, L.H.; Weiss, S.T. TBX21: A functional variant predicts improvement in asthma with the use of inhaled corticosteroids. Proc. Natl. Acad. Sci. USA 2004, 101, 18099–18104. [CrossRef]

87. Ye, Y.M.; Lee, H.Y.; Kim, S.-H.; Jee, Y.-K.; Lee, S.K.; Park, H.S. Pharmacogenetic study of the effects of NK2R G231E G>A and TBX21 H33Q C>G polymorphisms on asthma control with inhaled corticosteroid treatment. J. Clin. Pharm. Ther. 2009, 34, 693–701. [CrossRef] [PubMed]

88. Duong-Quy, S.; Le-Thi-Minh, H.; Nguyen-Thi-Bich, H.; Pham-Thu, H.; Thom, V.; Pham-Thi-Hong, N.; Duong-Thi-Ly, H.; Nguyen-Huy, B.; Ngo-Minh, X.; Nguyen-Thi-Dieu, T.; et al. Correlations between exhaled nitric oxide, rs28364072 polymorphism of FCER2 gene, asthma control, and inhaled corticosteroid responsiveness in children with asthma. J. Breath Res. 2020, 15, 016012. [CrossRef]

89. Wan, Z.; Tang, Y.; Song, Q.; Zhang, J.; Xie, W.; He, Y.; Huang, R.; Zheng, X.; Liu, C.; Liu, J. Gene polymorphisms in VEGFA and COL2A1 are associated with response to inhaled corticosteroids in children with asthma. Pharmacogenomics 2019, 20, 947–955. [CrossRef] [PubMed]

90. Tantisira, K.G.; Hwang, E.S.; Raby, B.A.; Silverman, E.S.; Lake, S.L.; Meyers, D.A.; Ambrose, H.J.; Goldman, M. Effect of ADRB2 polymorphisms on response to longacting β2-agonist therapy: A pharmacogenetic analysis of two randomised studies. Lancet 2005, 365, 1342–1349. [CrossRef] [PubMed]

91. Gupta, A.; Sjoukes, A.; Richards, D.; Banya, W.; Hawrylowicz, C.; Bush, A.; Saglani, S. Relationship between serum vitamin D, disease severity, and airway remodeling in children with asthma. J. Clin. Pharm. Ther. 2011, 184, 1342–1349. [CrossRef] [PubMed]

92. Korn, S.; Hübner, M.; Jung, M.; Blettner, M.; Buhl, R. Severe and uncontrolled adult asthma is associated with vitamin D insufficiency and deficiency. Respir. Res. 2013, 14, 25. [CrossRef] [PubMed]

93. Mohamed, N.A.; Abdel-Rehim, A.S. (Eds.) Influence of vitamin D receptor gene FokI and ApaI polymorphisms on glucocorticoid response in patients with asthma. In International Forum of Allergy & Rhinology; Wiley Online Library: Hoboken, NJ, USA, 2020.

94. Tantisira, K.G.; Small, K.M.; Litonjua, A.A.; Weiss, S.T.; Liggett, S.B. Molecular properties and pharmacogenetics of a polymorphism of adenyl cyclase type 9 in asthma: Interaction between β-agonist and corticosteroid pathways. Hum. Mol. Genet. 2005, 14, 1671–1677. [CrossRef] [PubMed]

95. Kotani, Y.; Nishimura, Y.; Maeda, H.; Yokoyama, M. β2-Adrenergic Receptor Polymorphisms Affect Airway Responsiveness to Salbutamol in Asthmatics. J. Asthma 1999, 36, 583–590. [CrossRef]

96. Martinez, F.; Weiss, S.T. Gene as a Novel Asthma Pharmacogenetic Locus. Am. J. Respir. Crit. Care Med. 2011, 184, 1318–1323. [CrossRef] [PubMed]

97. Mohamed, N.A.; Abdel-Rehim, A.S. (Eds.) Influence of vitamin D receptor gene FokI and ApaI polymorphisms on glucocorticoid response in patients with asthma. In International Forum of Allergy & Rhinology; Wiley Online Library: Hoboken, NJ, USA, 2020.

98. Tantisira, K.G.; Small, K.M.; Litonjua, A.A.; Weiss, S.T.; Liggett, S.B. Molecular properties and pharmacogenetics of a polymorphism of adenyl cyclase type 9 in asthma: Interaction between β-agonist and corticosteroid pathways. Hum. Mol. Genet. 2005, 14, 1671–1677. [CrossRef] [PubMed]

99. Kotani, Y.; Nishimura, Y.; Maeda, H.; Yokoyama, M. β2-Adrenergic Receptor Polymorphisms Affect Airway Responsiveness to Salbutamol in Asthmatics. J. Asthma 1999, 36, 583–590. [CrossRef]

100. Martinez, F.D.; Graves, P.E.; Baldini, M.; Solomon, S.; Erickson, R. Association between genetic polymorphisms of the beta2-adrenoceptor and response to albuterol in children with and without a history of wheezing. J. Clin. Invest. 1997, 100, 3184–3188. [CrossRef] [PubMed]

101. Lima, J.J.; Thomason, D.B.; Mohamed, M.H.N.; Eberle, L.V.; Self, T.H.; Johnson, J.A. Impact of genetic polymorphisms of the β2-adrenergic receptor on sharing a conserved protein motif with the T locus. Nat. Genet. 1994, 7, 383–389. [CrossRef]

102. Bollag, R.J.; Siegfried, Z.; Cebras-Thomas, J.A.; Garvey, N.; Davison, E.M.; Silver, L.M. An ancient family of embryonically expressed mouse genes sharing a conserved protein motif with the T locus. J. Clin. Pharmacol. Ther. 2019, 519–525. [CrossRef]

103. Israel, E.; Drazen, J.M.; Liggett, S.B.; Calhoun, W.J.; Ameredes, B.T.; Castro, M.; Craig, T.J.; Denlinger, L. Effect of β2-adrenergic receptor polymorphism on response to longacting β2 agonist in asthma (LARGE trial): A genotype-stratified, randomised, placebo-controlled crossover trial. Lancet 2004, 364, 1505–1512. [CrossRef]

104. Bleecker, E.R.; Postma, D.S.; Lawrance, R.M.; Meyers, D.A.; Ambrose, H.J.; Goldman, M. Effect of ADRB2 polymorphisms on response to longacting β2-agonist therapy: A pharmacogenetic analysis of two randomised studies. Lancet 2007, 370, 2118–2125. [CrossRef]

105. Wechsler, M.E.; Kunselman, S.J.; Chinchilli, V.M.; Bleecker, E.; Boushey, H.A.; Calhoun, W.J.; Ameredes, B.T.; Castro, M.; Craig, T.J.; Denlinger, L. Effect of β2-adrenergic receptor polymorphism on response to longacting β2 agonist in asthma (LARGE trial): A genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet 2009, 374, 1754–1764. [CrossRef] [PubMed]

106. Kim, S.H.; Ye, Y.M.; Lee, H.Y.; Sin, H.J.; Park, H.S.; Ms, H.Y.L. Combined pharmacogenetic effect of ADCY9 and ADRB2 gene polymorphisms on the bronchodilator response to inhaled combination therapy. J. Clin. Pharm. Ther. 2011, 36, 399–405. [CrossRef] [PubMed]
108. Poon, A.H.; Tantisira, K.G.; Litonjua, A.A.; Lazarus, R.; Xu, J.; Lasky-Su, J.; Lima, J.J.; Irvin, C.G.; Hanrahan, J.P.; Lange, C. Association of corticotropin releasing hormone receptor 2 (CRHR2) genetic variants with acute bronchodilator response in asthma. *Pharm. Genom.* 2008, 18, 373. [CrossRef] [PubMed]

109. Drake, K.A.; Torgerson, D.G.; Gignoux, C.R.; Galanter, J.M.; Roth, L.A.; Huntsman, S.; Eng, C.; Oh, S.S.; Yee, S.W.; Lin, L.; et al. A genome-wide association study of bronchodilator response in Latinos implicates rare variants. *J. Allergy Clin. Immunol.* 2014, 133, 370–378.e15. [CrossRef] [PubMed]

110. Litonjua, A.A.; Lasky-Su, J.; Schneiter, K.; Tantisira, K.G.; Lazarus, R.; Klanderman, B.; Lima, J.J.; Irvin, C.G.; Peters, S.P.; Hanrahan, J.P. ARG1 is a novel bronchodilator response gene: Screening and replication in four asthma cohorts. *Am. J. Respir. Crit. Care Med.* 2010, 18, 688–694. [CrossRef] [PubMed]

111. Vonk, J.M.; Postma, D.S.; Maarsingh, H.; Bruinenberg, M.; Koppelman, G.H.; Meurs, H. Arginase 1 and arginase 2 variations associate with asthma, asthma severity and β2 agonist and steroid response. *Pharmacogen. Genom.* 2010, 20, 179–186. [CrossRef]

112. Mougey, E.B.; Feng, H.; Castro, M.; Irvin, C.G.; Lima, J.J. Absorption of montelukast is transporter mediated: A common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. *Pharmacogen. Genom.* 2009, 19, 129–138. [CrossRef] [PubMed]

113. Duan, Q.L.; Du, R.; Lasky-Su, J.; Klanderman, B.J.; Partch, A.B.; Peters, S.P.; Irvin, C.G.; Hanrahan, J.P.; Lima, J.J.; Blake, K.V.; et al. A polymorphism in the thyroid hormone receptor gene is associated with bronchodilator response in asthmatics. *Pharmacogen. J.* 2012, 13, 1363–1372. [CrossRef]

114. Himes, B.E.; Jiang, X.; Hu, R.; Wu, A.C.; Lasky-Su, J.A.; Klanderman, B.J.; Ziniti, J.; Senter-Sylvia, J.; Lima, J.J.; Irvin, C.G.; et al. Genome-Wide Association Analysis in Asthma Subjects Identifies SPATS2L as a Novel Bronchodilator Response Gene. *PLoS Genet.* 2012, 8, e1002524. [CrossRef] [PubMed]

115. Padhukasahasram, B.K.; Yang, J.J.; Levin, A.M.; Yang, M.; Burchard, E.G.; Kumar, R.; Kwok, P.Y.; Seibold, M.A.; Lanfear, D.E.; Williams, L.K. Gene-based association identifies SPATA13-AS1 as a pharmacogenomic predictor of inhaled short-acting β-agonist response in multiple population groups. *Pharmacogen. J.* 2014, 14, 365–371. [CrossRef] [PubMed]

116. Fishe, J.N.; Labilloy, G.; Higley, R.; Casey, D.; Ginn, A.; Baskovich, B.; Blake, K.V. Single Nucleotide Polymorphisms (SNPs) in PRKGI & SPATA13-AS1 are associated with bronchodilator response: A pilot study during acute asthma exacerbations in African American children. *Pharmacogen. Genom.* 2012, 31, 146–154. [CrossRef]

117. Spear, M.L.; Hu, D.; Pino-Yanes, M.; Huntsman, S.; Eng, C.; Levin, A.M.; Ortega, V.E.; White, M.J.; McGarry, M.E.; Thakur, N.; et al. A genome-wide association and admixture mapping study of bronchodilator drug response in African Americans with asthma. *Pharmacogen. J.* 2013, 19, 249–259. [CrossRef]

118. Drazen, J.M.; Yandava, C.N.; Dubé, L.; Szczeczenzuback, N.; Hippensteel, R.; Pillari, A.; Israel, E.; Schork, N.; Silverman, E.S.; Katz, D.A.; et al. Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nat. Genet.* 1999, 22, 168–170. [CrossRef]

119. Telleria, J.J.; Blanco-Quirós, A.; Varillas, D.; Armentia, A.; Fernandez-Carvajal, I.; Alonso, M.J.; Diez, I. ALOX5 promoter genotype and response to montelukast in moderate persistent asthma. *Respir. Med.* 2008, 102, 857–861. [CrossRef]

120. Sampson, A.P.; Siddiqui, S.; Buchanan, D.; Howarth, P.H.; Holgate, S.T.; Holloway, J.W.; Sayers, I. Variant LTC4 synthase allele modifies cysteinyl leukotriene synthesis in eosinophils and predicts clinical response to zafirlukast. *Thorax* 2000, 55, S28–S31. [CrossRef]

121. Tantisira, K.G.; Lima, J.; Sztukiwycz, J.; Klanderman, B.; Weiss, S.T. 5-lipoxygenase pharmacogenetics in asthma: Overlap with CystITRI loci. *Pharmacogen. Genom.* 2009, 19, 244. [CrossRef]

122. Lima, J.J.; Zhang, S.; Grant, A.; Shao, L.; Tantisira, K.G.; Allayee, H.; Wang, J.; Sylvestre, J.; Holbrook, J.; Wise, R.; et al. Influence of Leukotriene Pathway Polymorphisms on Response to Montelukast in Asthma. *Am. J. Respir. Crit. Care Med.* 2006, 173, 379–385. [CrossRef]

123. Mougey, E.B.; Feng, H.; Castro, M.; Irvin, C.G.; Lima, J.J. Absorption of montelukast is transporter mediated: A common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. *Pharmacogen. Genom.* 2009, 19, 129–138. [CrossRef] [PubMed]

124. Kim, K.-A.; Lee, H.-M.; Joo, H.-J.; Park, I.-B.; Park, J.-Y. Effects of polymorphisms of the SLCO2B1 transporter gene on the pharmacokinetics of montelukast in humans. *J. Clin. Pharmacol.* 2013, 53, 1186–1193. [CrossRef]

125. Tapaninen, T.; Karonen, T.; Backman, J.T.; Neuvonen, P.J.; Niemi, M. SLCO2B1 c.935G>A Single Nucleotide Polymorphism Has No Effect on the Pharmacokinetics of Montelukast and Aliskiren. *Pharmacogen. Genom.* 2013, 23, 19–24. [CrossRef] [PubMed]

126. Tapaninen, T.; Karonen, T.; Backman, J.T.; Neuvonen, P.; Jitronjua, A.; Lazarus, R.; Rosenwasser, L.J.; Fuhlbrigge, A.L.; et al. FCER2 T2206C variant associated with chronic symptoms and exacerbations in steroid-treated asthmatic children. *Allergy* 2011, 66, 1546–1552. [CrossRef]

127. Lee, Y.-L.; Lin, Y.-C.; Lee, Y.-C.; Wang, J.-Y.; Hsuie, T.-R.; Guo, Y.L. Glutathione S-transferase P1 gene polymorphism and air pollution as interactive risk factors for childhood asthma. *Clin. Exp. Allergy* 2004, 34, 1707–1713. [CrossRef]
129. Erkan, H.; Birben, E.; Dizdar, E.A.; Keskin, O.; Karaaslan, C.; Soyer, O.U.; Dut, R.; Sackesen, C.; Besler, T.; Kalayci, O. Oxidative stress and genetic and epidemiologic determinants of oxidant injury in childhood asthma. *J. Allergy Clin. Immunol.* 2006, 118, 1097–1104. [CrossRef]

130. Aynacioglu, A.S.; Nacak, M.; Filiz, A.; Ekinci, E.; Roots, I. Protective role of glutathione S-transferase P1 (GSTP1) Val105Val genotype in patients with bronchial asthma. *Br. J. Clin. Pharmacol.* 2003, 57, 213–217. [CrossRef]

131. Becker, S.; Dailey, L.; Soukup, J.M.; Silbajoris, R.; Devlin, R.B. TLR-2 is involved in airway epithelial cell response to air pollution particles. *Toxicol. Appl. Pharmacol.* 2005, 203, 45–52. [CrossRef] [PubMed]

132. Kokturk, N.; Taticioglu, T.; Memis, L.; Akayurek, N.; Akyol, G. Expression of Transforming Growth Factor-β1 in Bronchial Biopsies in Asthma and COPD. *J. Asthma* 2003, 40, 887–893. [CrossRef]

133. Sordillo, J.E.; Kelly, R.; Bunyavanich, S.; McGeachie, M.; Qiu, W.; Croteau-Chonka, D.C.; Soto-Quiros, M.; Avila, L.; Celedón, J.C.; Brehm, J.M.; et al. Genome-wide expression profiles identify potential targets for gene-environment interactions in asthma severity. *J. Allergy Clin. Immunol.* 2015, 136, 885–892.e2. [CrossRef]

134. Paruchuri, S.; Tashimo, H.; Feng, C.; Maekawa, A.; Xing, W.; Jiang, Y.; Kanaoka, Y.; Conley, P.; Boyce, J.A. Leukotriene E4–induced pulmonary inflammation is mediated by the P2Y12 receptor. *J. Exp. Med.* 2010, 210, 229–237. [CrossRef] [PubMed]

135. Linaker, C.H.; Coggon, D.; Holgate, S.T.; Clough, J.; Josephs, L.; Chauhan, A.J.; Inskip, H. Personal exposure to nitrogen dioxide (P2RY12) and lung function in children with asthma. *Thorax* 2012, 67, 1567–1575. [CrossRef]

136. MacNulty, E.A.; Brauer, M.; Molen, E.; Bauer, C.P.; Bauer, M.; Bendel, D.; Bergström, A.; Brunekreef, B.; Chan-Yeung, M.; Klimper, C.; et al. GASTP1 and TNF Gene Variants and Associations between Air Pollution and Incident Childhood Asthma: The Traffic, Asthma and Genetics (TAG) Study. *Environ. Health Perspect.* 2014, 122, 418–424. [CrossRef]

137. Salam, M.T.; Gauderman, W.J.; McConnell, R.; Lin, P.-C.; Gilliland, F.D. Transforming Growth Factor-β and Growth Factor β1 and pre-natal smoke exposure are associated with childhood asthma. *Thorax* 2007, 62, 213–217. [CrossRef]

138. Shao, Y.; Zhang, Y.; Liu, M.; Fernandez-Beros, M.-E.; Qian, M.; Reibman, J. Gene-Environment Interaction between the IL1RN Gene Polymorphisms with Smoking Associated with Susceptibility to Asthma in Chinese Han Adults. *Int. J. Environ. Res. Public Health* 2020, 17, 2036. [CrossRef] [PubMed]

139. Becker, S.; Dailey, L.; Soukup, J.M.; Silbajoris, R.; Devlin, R.B. TLR-2 is involved in airway epithelial cell response to air pollution particles. *Toxicol. Appl. Pharmacol.* 2005, 203, 45–52. [CrossRef] [PubMed]

140. Kerkhof, M.; Postma, D.S.; Brunekreef, B.; Reijmerink, N.E.; Wijga, A.H.; Gehring, U.; Koppelman, G.H. Toll-like receptor 2 and 4 genes influence susceptibility to adverse effects of traffic-related air pollution on childhood asthma. *Thorax* 2010, 65, 690–697. [CrossRef] [PubMed]

141. Paruchuri, S.; Tashimo, H.; Feng, C.; Maekawa, A.; Xing, W.; Jiang, Y.; Kanaoka, Y.; Conley, P.; Boyce, J.A. Leukotriene E4–induced pulmonary inflammation is mediated by the P2Y12 receptor. *J. Exp. Med.* 2010, 210, 229–237. [CrossRef] [PubMed]

142. Kokturk, N.; Taticioglu, T.; Memis, L.; Akayurek, N.; Akyol, G. Expression of Transforming Growth Factor-β1 in Bronchial Biopsies in Asthma and COPD. *J. Asthma* 2003, 40, 887–893. [CrossRef]

143. Sordillo, J.E.; Kelly, R.; Bunyavanich, S.; McGeachie, M.; Qiu, W.; Croteau-Chonka, D.C.; Soto-Quiros, M.; Avila, L.; Celedón, J.C.; Brehm, J.M.; et al. Genome-wide expression profiles identify potential targets for gene-environment interactions in asthma severity. *J. Allergy Clin. Immunol.* 2015, 136, 885–892.e2. [CrossRef]

144. Paruchuri, S.; Tashimo, H.; Feng, C.; Maekawa, A.; Xing, W.; Jiang, Y.; Kanaoka, Y.; Conley, P.; Boyce, J.A. Leukotriene E4–induced pulmonary inflammation is mediated by the P2Y12 receptor. *J. Exp. Med.* 2009, 206, 2543–2555. [CrossRef] [PubMed]

145. MacNulty, E.A.; Brauer, M.; Molen, E.; Bauer, C.P.; Bauer, M.; Bendel, D.; Bergström, A.; Brunekreef, B.; Chan-Yeung, M.; Klimper, C.; et al. GASTP1 and TNF Gene Variants and Associations between Air Pollution and Incident Childhood Asthma: The Traffic, Asthma and Genetics (TAG) Study. *Environ. Health Perspect.* 2014, 122, 418–424. [CrossRef]

146. MacNulty, E.A.; Brauer, M.; Molen, E.; Bauer, C.P.; Bauer, M.; Bendel, D.; Bergström, A.; Brunekreef, B.; Chan-Yeung, M.; Klimper, C.; et al. GASTP1 and TNF Gene Variants and Associations between Air Pollution and Incident Childhood Asthma: The Traffic, Asthma and Genetics (TAG) Study. *Environ. Health Perspect.* 2014, 122, 418–424. [CrossRef]

147. Linaker, C.H.; Coggon, D.; Holgate, S.T.; Clough, J.; Josephs, L.; Chauhan, A.J.; Inskip, H. Personal exposure to nitrogen dioxide (P2RY12) and lung function in children with asthma. *Thorax* 2012, 67, 1567–1575. [CrossRef]

148. Paruchuri, S.; Tashimo, H.; Feng, C.; Maekawa, A.; Xing, W.; Jiang, Y.; Kanaoka, Y.; Conley, P.; Boyce, J.A. Leukotriene E4–induced pulmonary inflammation is mediated by the P2Y12 receptor. *J. Exp. Med.* 2009, 206, 2543–2555. [CrossRef] [PubMed]

149. Du, J.-W.; Xu, Z.-L.; Xu, Q.-X. Interaction of Interleukin 7 Receptor (IL7R) with Susceptibility to Asthma in Chinese Han Adults. *Immunol. Invest.* 2022, 51, 1364–1371. [CrossRef]

150. Shao, Y.; Zhang, Y.; Liu, M.; Fernández-Beros, M.-E.; Qian, M.; Reibman, J. Gene-Environment Interaction between the IL1RN Gene Polymorphisms with Smoking Associated with Susceptibility to Asthma in Chinese Han Adults. *Int. J. Environ. Res. Public Health* 2020, 17, 2036. [CrossRef] [PubMed]

151. Ramadas, R.A.; Sadeghnejad, A.; Karmaw, M.; Arshad, S.H.; Matthews, S.; Huebner, M.; Kim, D.-Y.; Ewart, S.L. Interleukin-1R antagonist gene and pre-natal smoke exposure are associated with asthma and phenotypic manifestations. *J. Allergy Clin. Immunol.* 2007, 129, 502–508. [CrossRef]