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Pharmacogenomic Evidence and Factors Influencing Treatment Response in Asthma and COPD

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous respiratory diseases in which treatment response varies substantially among individuals. Pharmacogenomics investigates how genetic variation may contribute to differences in drug efficacy and clinical outcomes. This narrative mini-review summarizes evidence on pharmacogenetic and pharmacogenomic associations with responses to commonly used respiratory medications in asthma and COPD, distinguishes candidate-gene findings from genome-wide and genotype-stratified trial evidence, examines limitations affecting clinical translation, and discusses research priorities. In asthma, the best-studied associations involve inhaled corticosteroids (ICS; GLCCI1, CRHR1, FCER2), β2-agonists (ADRB2), and leukotriene modifiers. A genome-wide study identified GLCCI1 rs37972 as associated with ICS response, and a systematic review found the most consistent candidate-gene evidence for FCER2 rs28364072, yet replication has been limited overall and even replicated variants explain only a small fraction of response variability. Two prospective genotype-stratified trials of ADRB2 Arg16Gly gave different clinical signals depending on the treatment regimen. In COPD, research is less developed, and a meta-analysis found no consistent association between the examined ADRB2 variants and β2-agonist response. Differences in populations, phenotypes, treatment regimens, and outcome definitions further limit comparisons. Although pharmacogenomics may eventually contribute to precision respiratory medicine, routine treatment decisions are not currently guided by most candidate pharmacogenomic markers in asthma or COPD. Larger and ancestrally diverse studies, independent replication, standardized response outcomes, and prospective evaluation of clinical utility are needed before broader implementation.

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1. Introduction

Asthma and COPD are heterogeneous chronic respiratory disorders associated with respiratory symptoms and variable airflow limitation. Although inhaled corticosteroids (ICS), β2-agonists, and muscarinic antagonists are used in the management of these diseases according to clinical indication, their roles differ between asthma and COPD. Leukotriene modifiers are used mainly in asthma and are not standard routine therapy for COPD. Even among patients with apparently similar clinical characteristics, responses to the same medication may differ. This variability reflects many factors, including adherence, inhaler technique, environmental exposures, smoking history, disease phenotype, inflammatory pathways, and comorbidities. Genetic background is a further contributor and is the focus of this review (1, 2).

Strictly, pharmacogenetics refers to the study of individual, usually candidate, variants, whereas pharmacogenomics refers to genome-wide approaches. Because respiratory research draws on both, this review uses "pharmacogenomics" as an umbrella term and states the study design where it matters. By identifying variants associated with response differences, this research may help explain some interindividual variability and inform individualized treatment strategies. In respiratory medicine, studies have primarily examined genetic determinants of bronchodilator responsiveness and corticosteroid efficacy, as well as responses to leukotriene modifiers in asthma. However, many reported associations have not been consistently replicated across independent populations, and association alone does not establish predictive performance or clinical usefulness (3, 4). Interpreting this literature requires attention to study design. Candidate-gene studies test a small number of biologically plausible variants and are prone to false-positive findings from small samples, multiple testing, and population stratification. In a landmark review of association studies of disease susceptibility, only 6 of 166 associations studied three or more times were consistently replicated (5), and pharmacogenetic candidate-gene studies share the same design vulnerabilities. Genome-wide association studies (GWAS) apply stringent significance thresholds and replication, but they need sample sizes that pharmacogenomic cohorts rarely reach. Genotype-stratified randomized trials provide the most direct test of clinical relevance but are scarce. Genetic effects may also vary by age, ancestry, and environmental exposure (6). A statistically significant genetic association therefore does not by itself demonstrate that genotype-guided prescribing improves patient outcomes.

This narrative mini-review draws on published literature, including relevant systematic reviews and meta-analyses, as well as selected primary studies reporting genetic associations, genome-wide findings, and genotype-stratified clinical trials. The literature was selected non-systematically based on its relevance to pharmacogenomic responses to inhaled corticosteroids, β2-agonists, and leukotriene modifiers in asthma, and to bronchodilators and inhaled corticosteroids in COPD. The review focuses on the reproducibility of reported associations, the clinical relevance of treatment-response outcomes, and the evidence required for clinical implementation. It was not designed or conducted as a systematic review and does not aim to provide an exhaustive assessment of all available studies. **Figure 1** summarizes the pharmacogenomic evidence discussed in this review, highlighting the principal drug classes and candidate genes investigated in asthma and COPD, factors influencing treatment response, and key considerations for clinical translation.

2. Pharmacogenomics of Asthma

Asthma is a heterogeneous respiratory disease characterized by variable airflow limitation, airway inflammation, and substantial differences in treatment response. Pharmacogenomic research has examined genes involved in glucocorticoid signaling, IgE-mediated inflammation, β2-adrenergic receptor function, and leukotriene biosynthesis and transport. The most frequently studied candidates are GLCCI1, CRHR1, and FCER2 for ICS; ADRB2 for β2-agonists; and ALOX5, LTC4S, and LTA4H for leukotriene modifiers (3, 7). Table 1 summarizes the principal findings. The strength and reproducibility of the evidence vary by gene, variant, population, and outcome, and the findings remain investigational: they do not currently support routine genotype-based selection of asthma medication.

2.1. Inhaled Corticosteroids

ICS are central to asthma management, but the magnitude of clinical benefit varies among patients. GLCCI1 was identified through a genome-wide approach, CRHR1 encodes the corticotropin-releasing hormone receptor 1, and FCER2 encodes CD23, the low-affinity receptor for immunoglobulin E (3).

The best-known finding is the genome-wide study by Tantisira et al., which identified rs37972 in GLCCI1 (in complete linkage disequilibrium with rs37973) as asso-

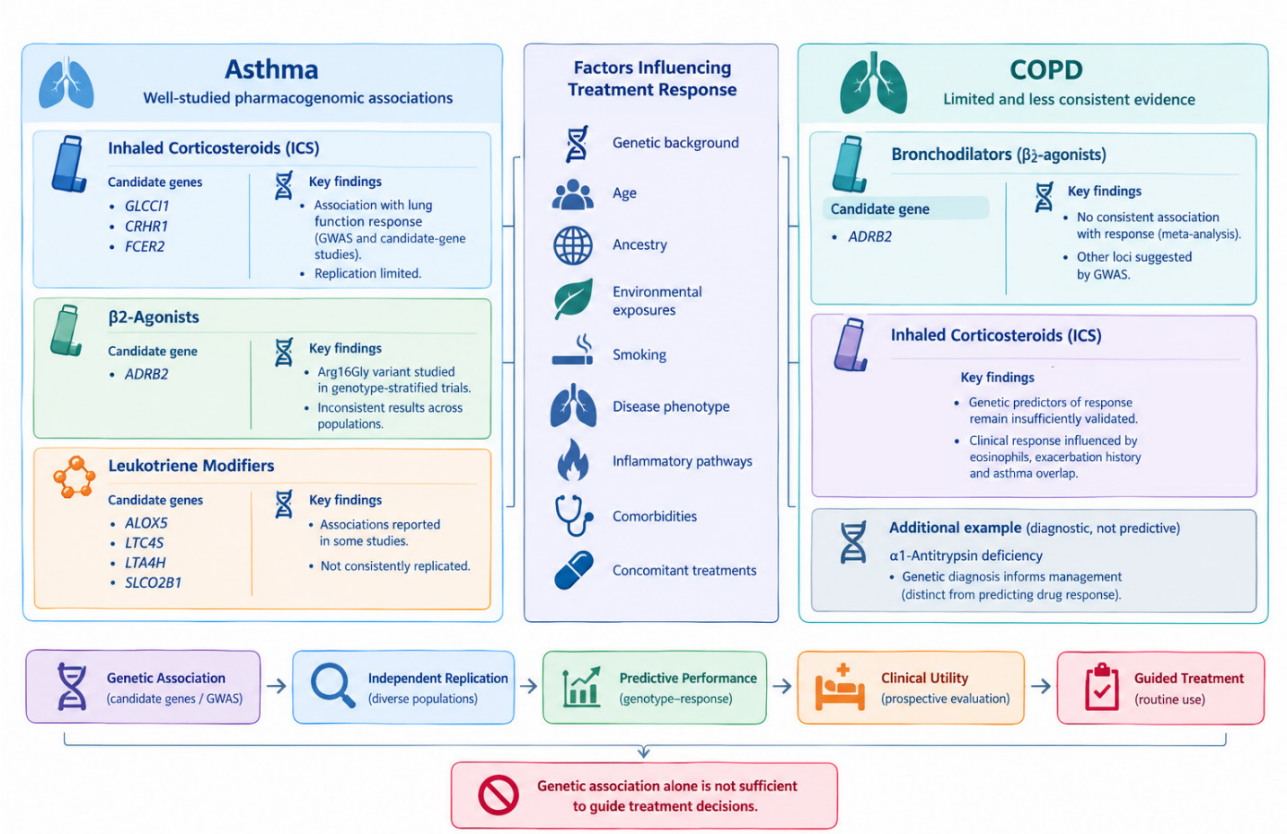


Figure 1. *Overview of pharmacogenomic evidence and clinical translation in asthma and COPD. The figure summarizes the principal drug classes and candidate genes investigated in asthma and COPD, key findings and limitations of the available evidence, and genetic and non-genetic factors that may influence treatment response. It also illustrates the steps required to translate genetic associations into clinical practice, including independent replication, validation of predictive performance, and prospective evaluation of clinical utility. The examples shown represent investigated associations and should not be interpreted as validated biomarkers for routine prescribing.*

ciated with the FEV1 response to ICS. The association was replicated in four independent populations totaling 935 participants; patients with the unfavorable genotype had a significantly higher risk of poor response (odds ratio 2.36, 95% CI 1.27–4.41), and the genotype accounted for about 6.6% of overall response variability (8). This also illustrates a general point: even a replicated genome-wide signal explains only a small fraction of response variability, which limits prediction for individual patients. Replication has nonetheless been limited: in an earlier systematic review, none of the four ICS GWAS reported similar results and none of the candidate-gene SNPs was identified in a GWAS (3). By 2019, seven GWAS of ICS response had been published, and the authors concluded that none of the genetic markers had reached clinical practice (7).

In a systematic review of 59 publications on ICS and leukotriene modifiers (33 on ICS, including four GWAS), the most consistent candidate-gene evidence concerned FCER2 rs28364072, which was associated with poor ICS response across outcome types, with the largest effect for exacerbation risk (hazard ratio 3.95, 95% CI 1.64–9.51) (3). In children from the CAMP trial, the minor allele of CRHR1 rs242941 was associated with a poorer lung-function response to ICS. Outcome definition matters. In the same CAMP cohort (311 children), predictors of recurrent exacerbations (prior exacerbations, younger age, higher IgE) differed from predictors of poor lung-function response, and the two outcomes were not associated with each other ($p = 0.72$) (9). An association with lung-function change therefore cannot be assumed to predict symptom control or exacerbation reduction. Differences in age, ancestry, treatment duration, baseline severity, concomitant therapy, and outcome definitions may further contribute to inconsistent findings. Accordingly, these markers are not sufficiently validated to guide routine ICS selection (3, 7).

2.2. β2-Agonists

ADRB2 encodes the β2-adrenergic receptor, which mediates an important component of β2-agonist-induced airway smooth-muscle relaxation. ADRB2 is one of the

most studied genes for bronchodilator response (1), and the Arg16Gly variant has been tested for associations with clinical outcomes during β2-agonist treatment. Two prospective, genotype-stratified randomized trials from the NHLBI Asthma Clinical Research Network tested the Arg16Gly question directly, with different results by regimen. In the BARGE trial of regularly scheduled albuterol, patients with the Arg/Arg genotype had lower morning peak expiratory flow during albuterol than during placebo (−10 L/min, 95% CI −19 to −2), whereas Gly/Gly patients improved (+14 L/min, 95% CI 3 to 25), a genotype-attributable difference of −24 L/min (95% CI −37 to −12) (10). In the LARGE trial, adding salmeterol to ICS improved morning peak flow in both Arg/Arg (n = 42) and Gly/Gly (n = 45) participants with no difference in improvement by genotype, and the authors concluded that long-acting β2-agonist plus moderate-dose ICS should be continued irrespective of Arg16 genotype; a genotype difference in methacholine responsiveness and a post hoc observation in African American participants were flagged for further investigation (11). Genome-wide data suggest that bronchodilator response has a polygenic and ancestry-specific architecture. In a GWAS of 1,782 Latino children with asthma (replication n = 531), seven variants reached genome-wide significance, all with frequencies below 5%, with an excess of signals near solute carrier genes (12). Evidence that a gene has a plausible biological role should be distinguished from a reproducible pharmacogenetic association and from demonstrated clinical utility. Bronchodilator responsiveness is likely influenced by multiple genetic and non-genetic factors rather than by a single variant. At present, the evidence is insufficient to recommend routine ADRB2 testing to guide β2-agonist prescribing in asthma.

2.3. Leukotriene Modifiers

Genetic variation in leukotriene biosynthesis, signaling, and transport pathways may contribute to differences in response to leukotriene modifiers. Investigated genes include ALOX5, LTC4S, LTA4H, and SLCO2B1 (13). The 2017 systematic review identified 26 publications on leukotriene modifiers, including two GWAS, and found no consistent reports for candidate-gene studies (3). A later systematic review and meta-analysis (31 studies, 8,084 participants) again found the two GWAS to show different results, none of the candidate-gene SNPs identified in the GWAS, and inconsistent conclusions for the most widely studied variants; in the pooled analysis, LTC4S −444A/C was not significant overall, although subgroup findings suggested a possible influence in patients taking non-selective CysLT receptor antagonists or taking leukotriene modifiers without ICS (13). The available evidence is therefore insufficient to establish a clinically validated genetic algorithm for selecting leukotriene modifiers. Safety is an additional consideration: in March 2020, the U.S. Food and Drug Administration (FDA) required a boxed warning about serious neuropsychiatric side effects associated with montelukast and recommended restricting its use for allergic rhinitis to patients who do not respond adequately to, or cannot tolerate, alternative treatments (14). Genetic predictors of these adverse reactions have not been established in the literature reviewed here.

3. Pharmacogenomics of COPD

Compared with asthma, pharmacogenomic research in COPD is less developed. Studies have mainly examined genetic variation in relation to bronchodilator responsiveness and ICS response; a recent narrative review identified 25 such studies (37,022 individuals) (6). COPD heterogeneity can confound pharmacogenomic studies if disease subtypes are not addressed in the study design (15). ADRB2 has been investigated in relation to β2-agonist response; however, a systematic review and meta-analysis did not find a consistent association between the examined ADRB2 variants and therapeutic response to inhaled β2-agonists in COPD (4). This finding applies to the variants and outcomes assessed and does not exclude a role for other genetic factors. A recent expert review concluded that there is insufficient evidence for clinical implementation of COPD pharmacogenomics (15). For ICS, a genome-based study reported variants associated with the effect of ICS on long-term lung-function decline, which the authors interpreted as offering insight into the biology of steroid responsiveness rather than as ready clinical predictors (16). Clinical factors such as exacerbation history, blood eosinophil count, and coexisting asthma features inform ICS decisions, but they are clinical and biomarker predictors, not germline pharmacogenomic markers. Any genetic marker would need to show incremental value over these readily available predictors. Two monogenic examples place these findings in context. Alpha-1 antitrypsin deficiency (SERPINA1) defines a genotype-based COPD subgroup with a genotype-selected therapy: this has been described as the only fully developed application of COPD pharmacogenomics (15). In the RAPID randomized trial, intravenous augmentation with alpha-1 proteinase inhibitor slowed the loss of CT lung density

at total lung capacity compared with placebo (−1.45 vs −2.19 g/L per year, p = 0.03), although the combined total lung capacity and functional residual capacity analysis was not significant (17). In cystic fibrosis, the CFTR potentiator ivacaftor improved percent predicted FEV1 by 10.6 percentage points compared with placebo in patients carrying the G551D mutation (18). These cases show that genotype-directed therapy can succeed in respiratory disease when a single causal variant defines both the disease and the drug target. They do not demonstrate that common variants predict differential drug response in polygenic diseases such as asthma and COPD, where effects are likely to be small and multifactorial.

Table 1. Selected pharmacogenomic evidence in asthma and COPD.

Gene / variant	Drug (disease)	Key evidence	Interpretation	Reference
GLCCI1 rs37972 (in LD with rs37973)	ICS (asthma)	GWAS with replication in four populations (n = 935); poor-response OR 2.36 (95% CI 1.27–4.41); about 6.6% of response variability.	Replicated in the discovery report (four cohorts); other ICS GWAS did not report similar signals; not yet validated for prescribing.	(3, 7, 8)
FCER2 rs28364072	ICS (asthma)	Most consistent candidate-gene signal in a systematic review of 59 publications; exacerbation HR 3.95 (95% CI 1.64–9.51).	Informative signal; clinical utility not established.	(3, 7)
CRHR1 rs242941	ICS (asthma)	Minor allele associated with poorer lung-function response in CAMP children (n = 311).	Outcome-dependent; clinical utility not established.	(3, 7, 9)
ADRB2 Arg16Gly	Regular albuterol (asthma)	BARGE: genotype-attributable difference in morning PEF of −24 L/min (95% CI −37 to −12), Arg/Arg vs Gly/Gly.	Regimen-specific; not seen with LABA + ICS in LARGE.	(10, 11)
ADRB2 Arg16Gly	LABA + ICS (asthma)	LARGE: no genotype difference in PEF improvement (Arg/Arg n = 42; Gly/Gly n = 45); methacholine and African American post hoc signals flagged.	Authors advised no genotype-based change in therapy; subgroup signals need study.	(11)
Multiple loci, rare variants (SLC genes)	Albuterol, BDR (asthma, Latino children)	GWAS n = 1,782, replication n = 531; seven genome-wide significant variants, all MAF < 5%.	Ancestry-specific; needs replication in other populations	(12)
ALOX5, *LTC4S*, *LTA4H*, *SLCO2B1*	Leukotriene modifiers (asthma)	26 publications incl. two GWAS with differing results; later review of 31 studies: inconsistent conclusions, *LTC4S* −444A/C not significant overall.	Inconsistent across studies.	(3, 13)
ADRB2 variants	β2-agonists (COPD)	Meta-analysis: no consistent association with treatment response.	Inconclusive for the variants examined	(4)
Variants associated with ICS effect on lung-function decline	ICS (COPD)	Genome-based study; interpreted as insight into steroid-response biology.	Insufficient evidence for clinical implementation.	(15, 16)

Entries summarize the studies cited in the text; effect sizes and interpretations are those reported by the cited authors. The absence of clinical implementation does not mean these findings lack scientific value: they inform biology and generate testable hypotheses, but current evidence is insufficient to guide routine prescribing. ICS, inhaled corticosteroids; LABA, long-acting β2-agonist; BDR, bronchodilator response; MAF, minor allele frequency.

4. Clinical Challenges and Future Perspectives

Several challenges limit clinical implementation. First, many associations have not been replicated in independent populations, and candidate-gene designs are vulnerable to false positives (3, 8). Second, effect sizes are modest: the replicated GLCCI1 signal accounts for about 6.6% of ICS response variability (8). Third, studies use different response outcomes, including lung function, symptom control, exacerbation frequency, and medication requirements; these are related but not equivalent, and they can have different genetic and clinical predictors (9). Fourth, ancestry matters: a GWAS in Latino children identified rare-variant signals (12), the LARGE trial flagged a possible genotype effect in African American participants (11), and a review of albuterol pharmacogenetics highlights the need for additional studies in minority populations. Finally, genetic effects may be modified by age and by environmental exposures (1). Prospective evaluation is feasible but uncommon. BARGE and LARGE show that genotype-stratified trials can resolve whether a candidate variant matters clinically, and that the answer can depend on the treatment regimen (10, 11). Within the literature reviewed here, comparable prospective trials for ICS and leukotriene-modifier markers are lacking. Future studies should prioritize larger and more diverse cohorts, prespecified and standardized response outcomes, independent replication, and prospective comparison of genotype-guided strategies with usual care. Polygenic scores and multi-omic data (for example, transcriptomic and epigenetic) may capture more variance than single variants, but such models require external validation, assessment of calibration and generalizability, and demonstration of incremental benefit over clinical predictors and established biomarkers. Implementation would also require evidence of cost-effectiveness, assay availability and turnaround, integration into clinical decision support, and equitable access across populations. Ultimately, adoption should depend on evidence that testing changes clinical decisions and improves meaningful patient outcomes.

A recent review of genetic determinants in acute respiratory failure and acute respiratory distress syndrome likewise notes that clinical translation of pharmacogenomic findings remains limited (19). However, these conditions and care settings differ from chronic asthma and COPD, so this literature provides broader context rather than validation of markers for either disease.

5. Conclusion

Pharmacogenomics offers a potential framework for understanding some interindividual variability in asthma and COPD treatment. A small number of signals have been replicated (for example, GLCCI1 rs37972 and FCER2 rs28364072 for ICS response in asthma), but they explain limited variability, depend on the outcome definition, and have not been shown to improve patient outcomes when used to guide therapy. Genotype-stratified trials of ADRB2 gave regimen-specific results, and the COPD evidence is sparse and largely unvalidated. Most pharmacogenomic markers are therefore not ready to guide routine treatment decisions in either disease. Larger and more diverse studies, independent validation, standardized response outcomes, and prospective trials comparing genotype-guided care with usual care are needed to determine whether genetic information can improve clinically meaningful outcomes.

6. Declrations

Ethical Approval and Consent to Participate

Not applicable.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to institutional and patient privacy restrictions but are available from the corresponding author on reasonable request.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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Author's Contributions

Investigation, Visualization, writing original draft: MF, NGH, MAB, SHA. Conceptualization, project administration, validation, review and editing: NK, HH. All authors read and approved the final version of the manuscript.

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Artificial Intelligence Statement

The authors used an artificial intelligence (AI)-assisted language tools to improve the readability and language of the manuscript, as well as to format the tables and generate the illustrative figure. All scientific content, study design, data collection, data analysis, interpretation of the findings, and final editorial decisions were performed entirely by the authors. The authors have reviewed and approved the final manuscript and accept full responsibility for their accuracy and integrity.

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