Chapter 13
Personalized Medicine

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Introduction

Personalized medicine or precision medicine aims to use a subject's characteristics to design an individualized treatment plan. Personalized medicine is based on the premise that biomarkers (e.g., genetic variants) can be used to predict disease risk or response to medications, in order to prevent or treat a disease in a given individual.

Genetic and "omics" studies of respiratory diseases, both published and ongoing, will lead the way to predictive profiles for precision medicine. This chapter will focus on asthma and chronic obstructive pulmonary disease (COPD), not only because of their public health importance (see Chap. 10) but also because of the strength of the evidence to support personalized medicine to prevent and treat these common airway diseases.

The frequency and severity of asthma and COPD differ among racial and ethnic groups in the USA (see Chaps. 2 and 10). In this chapter, we discuss the basis for the variable population structure and genetic diversity of modern human genomes from different racial and ethnic groups. We will summarize how such diversity has impacted genetic studies, and how studies in diverse populations have led to the identification of susceptibility loci for respiratory diseases and response to treatment. Finally, we highlight how future genetics and "omics" research in diverse populations should lead to identification of biomarkers for personalized medicine, which would help eliminate existing respiratory health disparities.

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Genetic Studies in Ethnically Diverse Populations

According the US Census Bureau, the non-Hispanic White population will peak in 2012, and then slowly decrease in size from 2024 to 2060. In contrast, Hispanic and Asian populations will grow over the next four decades, making non-whites surpass non-Hispanic whites as the majority of the US population by 2060 [1].

The diverse genomes of modern racial or ethnic groups in the USA (see Chap. 2) largely resulted from racial admixture during the European colonization of the Americas over the past 500 years. Thus, African Americans and Hispanics (e.g., Puerto Ricans and Mexican Americans) have varying proportions of European, Native American, and African ancestries. On average, African Americans and Puerto Ricans have a greater proportion of African ancestry but a lower proportion of Native American ancestry than Mexican Americans. However, ancestral proportions can vary between members of an ethnic group [2, 3].

Because of human origins in Africa, subjects of sub-Saharan African descent have had a greater number of recombination events over many generations, resulting in greater genetic diversity and fewer co-inherited polymorphisms within genomic regions (i.e., shorter regions of linkage disequilibrium [LD], Fig. 13.1). In contrast, Europeans had loss of genetic diversity during a "bottleneck" as the first modern humans migrated to Europe from sub-Saharan Africa ~40,000 years ago, resulting in high correlation or co-inheritance of polymorphisms within genomic regions (i.e., greater LD, Fig. 13.1) [4]. Because European ancestry leads to lower genetic diversity but greater LD than African ancestry, fewer markers need to be genotyped to "tag" genetic variants in populations of mostly European descent (i.e., European Americans or non-Hispanic whites) than in those of mostly African descent (i.e., African Americans). For the same reasons, rare variants (allele frequency <0.05) are more frequently found in African Americans than in European Americans [4, 5].

High-throughput genotyping allows for the analysis of millions of single nucleotide polymorphisms (SNPs), which have been used in genetic association studies of airway diseases. Such studies have targeted biologically plausible candidate genes or the whole genome (genome-wide association studies or GWAS), most often—but not exclusively—in populations of European descent. More recently, next-generation DNA sequencing has expanded the catalogue of human genetic diversity, facilitating studies of ethnically diverse populations. We will next highlight salient findings from genetic studies of asthma and COPD.

Genetic Studies of Asthma

Early family-based genome-wide linkage studies failed to identify susceptibility genes for asthma or related phenotypes, yet demonstrated that asthma is caused by multiple genes [6–17]. More than 100 genes have been examined for association with asthma, based on biologic plausibility ("functional candidate genes") or location in

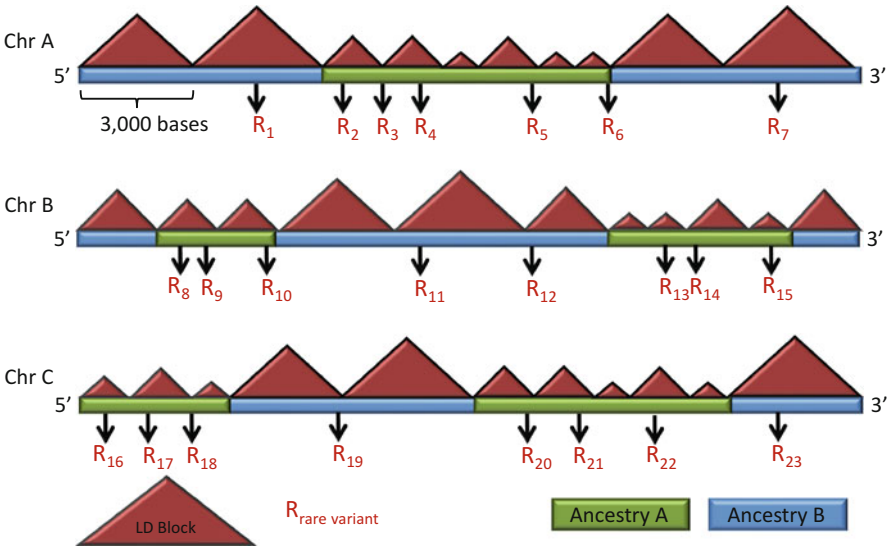

Fig. 13.1 Consequences of ancestral admixture on genetic diversity. The recent admixture of an ancient ancestry (such as African ancestry or ancestry A, highlighted in *green*) with a more recent ancestry (such as European ancestry or ancestry B, highlighted in *blue*) affects genetic diversity in chromosomal (Chr.) regions throughout the genome. The more ancient ancestry (A) has had a greater number of recombination events over more generations, resulting in greater genetic diversity with fewer co-inherited genetic variants in genomic regions, highlighted with the *red triangles* signifying shorter regions of linkage disequilibrium (LD). In comparison, ancestry B resulted from a recent loss of genetic diversity or "bottleneck," leading to gene variants that are highly co-inherited or correlated over longer genomic regions through LD (highlighted with *larger red triangles*). The more ancient ancestry A has also had more time for rare variants to occur (*red* "R") and has a higher frequency of rare variants compared to ancestry B

genomic regions linked to asthma or related phenotypes in family-based studies ("positional candidate genes") [18, 19]. Such studies were largely based on genotyping common SNPs (i.e., allelic frequency ≥0.05) in the genes of interest, which were then tested for association with asthma. Using this candidate-gene approach, the most highly replicated genes for asthma in subjects of European descent were in biologic pathways related to lung development (*ADAM33*), Th2 inflammation (*IL4, IL13, IL4R*), innate immunity (*HLA-DRB1, HLA-DQB1, CD14*), and cellular inflammation (*TNF, FCER1B, DPP10*) [18–28]. Consistent with findings for many candidate genes, *ADAM33* was associated with asthma or related phenotypes in African Americans and New Mexico Hispanics [29], but not in Puerto Ricans or Mexicans [30]. The inconsistent findings for most candidate-gene association studies of asthma could often be due to false positive results from chance or population stratification (confounding by population substructure). Alternatively, nonreplication across ethnic groups may have been due to limited statistical power because of small sample size or ethnic-specific genetic effects (due to differing allelic frequencies (Table 13.1 [31–34]) or gene-by-environment interactions) [29, 35].

Table 13.1 Allele frequencies of asthma risk loci in different racial and ethnic groups

Asthma risk loci		Associated							
Gene names	Gene ID	SNP	CEU	YRI	ASW	MEX	CHB	JPT	References
Interleukin-6 receptor	*IL6R*	rs4129267	0.35	0.07	0.15	0.52	0.39	0.36	[39]
Pyrin and HIN domain family member 1	*PYHIN1*	rs1102000	0.00	0.35	NA	NA	0	0	[42]
Interleukin-1 receptor	*IL1RL1*	rs1420101	0.35	0.32	0.43	0.27	0.39	0.46	[37, 44]
Interleukin-18 receptor	*IL18R1*	rs3771166	0.41	0.72	0.65	0.28	0.13	0.18	[37]
Dipeptidyl peptidase-10	*DPP10*	rs1435879	0.10	0.03	0.04	0.19	0.31	0.30	[42]
GRB2-associated binding protein 1	*GAB1*	rs1397527	0.45	0.84	0.74	NA	0.31	0.30	[31]
Ubiquitin specific peptidase 38	*USP38*	rs7686660	0.21	0.47	0.44	0.52	0.74	0.72	[31]
cAMP-specific phosphodiesterase 4D	*PDE4D*	rs1588265	0.36	0.16	0.22	0.22	0.70	0.73	[43]
WD repeat domain 36	*WDR36*	rs2416257	0.14	0.14	0.10	0.06	0.07	0.04	[45]
Thymic stromal lymphopoietin	*TSLP*	rs1837253	0.28	0.34	0.29	0.30	0.62	0.66	[31, 37, 42, 44]
RAD50 homolog	*RAD50*	rs2244012	0.20	0.73	0.51	0.18	0.19	0.19	[28]
Interleukin-13	*IL13*	rs1295686	0.22	0.73	0.59	0.48	0.34	0.30	[28, 50]
α-1B-adrenergic receptor	*ADRA1B*	rs10515807	0.16	0.03	NA	NA	0.32	0.34	[48]
TNFAIP3 interacting protein 1	*TNIP1*	rs1422673	0.19	0.43	0.37	0.47	0.56	0.51	[50]
Psoriasis susceptibility 1 candidate 1	*PSORS1C1*	rs3094663	0.27	0.24	0.36	0.28	0.31	0.35	[44]
Human leukocyte antigen complex DQB1	*HLA-DQB1*	rs9273349	0.42	0.48	0.47	0.23	0.39	0.44	[28, 37, 44]
Human leukocyte antigen complex DRA	*HLA-DRA*	rs2395185	0.43	0.19	0.20	0.35	0.37	0.39	[50]
Interleukin-33	*IL33*	rs1342326	0.17	0.35	0.32	0.15	0.00	0.00	[37, 42, 44]
GATA Binding Protein 3	*GATA3*	rs10508372	0.04	0.22	0.21	0.35	0.59	0.56	[31]
Ikaros Family Zinc Finger 4	*IKZF4*	rs1701704	0.32	0.07	0.15	0.21	0.23	0.22	[31]
SMAD Family Member 3	*SMAD3*	rs744910	0.45	0.68	0.67	0.54	0.58	0.56	[37]
RAR-Related Orphan Receptor A	*RORA*	rs11071559	0.15	0.56	0.43	0.11	0.14	0.23	[37]
ORM1-Like 3	*ORMDL3*	rs7216389	0.49	0.88	0.70	0.60	0.66	0.72	[36–38, 40–43]
Gasdermin-like B	*GSDMB*	rs2305480	0.47	0.05	0.25	0.40	0.33	0.28	[37, 41, 44, 50]

Asthma risk loci		Associated							
Gene names	Gene ID	SNP	CEU	YRI	ASW	MEX	CHB	JPT	References
Ikaros family Zinc finger 3	*IKZF3*	rs907092	0.49	0.07	0.28	0.39	0.33	0.34	[44]
Prion-related protein	*PRNP*	rs6052761	0.10	0.35	0.39	0.17	0	0.03	[48]
Interleukin-2 receptor, β subunit	*IL2RB*	rs2284033	0.42	0.39	0.45	0.32	0.65	0.58	[37]

Asthma risk loci were among the first identified and denoted by reference sequence number (rs) [28, 31, 36–45, 48, 50]
Minor or less common, variant allele frequencies are based on data from the International HapMap Project Genome Browser release 28, phases 1–3 [32]
Abbreviations from each group are as follows: *CEU* Utah residents with ancestry from northern and western Europe, *YRI* individuals from Yoruba in Ibadan, Nigeria, *ASW* African Americans from the southwest United States, *MEX* Mexican Americans from Los Angeles, CA, *CHB* Han Chinese from Beijing, China, *JPT* Japanese from Tokyo, Japan [33]
Adapted from Ortega VE et al. *Curr Opin Allergy Clin Immunol* 2014;14(5):381–9 [34]

The first GWAS of asthma susceptibility (conducted in Europeans) identified a novel locus on chromosome 17q21 (containing *ORMDL3* and *GSDMB*), which has been well replicated across multiple racial or ethnic groups [36–44]. *ORMDL3* encodes a transmembrane protein anchored to the endoplasmic reticulum, but its role (or that of *GSDMB*) in asthma is unclear. Subsequent GWAS have identified additional asthma-susceptibility loci, notably including genes (*IL33*, *IL1RL1*, and *TSLP*) conferring susceptibility to asthma in ethnically diverse North American populations (non-Hispanic whites, African Americans, Afro-Caribbeans, Puerto Ricans, and Mexicans) [28, 37, 42, 45]. Many of these genes are involved in pathways related to epithelial integrity and adaptive immune responses, suggesting that they promote T_H2-mediated airway inflammation through altered production of cytokines (i.e., *TSLP* and *IL33*) and/or damage of the airway epithelium.

The first GWAS conducted primarily in subjects of African descent identified the genes for the α-1B-adrenergic receptor (*ADRA1B*) and prion-related protein (*PRNP*) as novel asthma-susceptibility loci, while also replicating findings for *DPP10* from an earlier study of Europeans [11, 18, 46–48]. A multiethnic GWAS in North America (see above) also identified a gene (*PYHIN1)* that appears to only confer susceptibility to asthma in subjects of African descent [42].

Severe asthma (characterized by baseline airflow obstruction, uncontrolled symptoms, or frequent exacerbations despite adequate treatment) occurs more frequently among African Americans and Puerto Ricans [49]. Emerging evidence suggests that genes that influence asthma severity differ from those that determine asthma susceptibility [50, 51]. Identifying such loci should thus help to discover mechanisms underlying interethnic differences in asthma severity [52–55].

Lung function is an indicator of asthma severity. SNPs in the gene encoding the hedgehog-interacting protein (*HHIP*) are associated with reduced lung function in African American and non-Hispanic whites with asthma in the Severe Asthma Research Program (SARP) [56]. Moreover, variants in *HHIP* and genes previously associated with lung function in the general population (*FAM13A* and *PTCH1*) had additive effects on lung function and asthma severity in non-Hispanic whites and African Americans with asthma (Fig. 13.2a, b) [3, 56, 57].

SNPs from whole-genome genotyping can be used to estimate whole-genome or global genetic ancestry [58]. As reviewed in Chap. 2, global African genetic ancestry has been associated with an increased risk of asthma, lower FEV_1, and lower FVC in African Americans and Puerto Ricans [3, 57, 59–61]. Conversely, global Native American ancestry has been associated with reduced risk of asthma but higher FEV_1 and FVC in Latinos [60]. Of interest, global African ancestry has also been shown to be associated with severe asthma exacerbations in African American males, further suggesting a role for genetic or environmental risk factors correlated with African ancestry on asthma severity [62].

Admixture mapping (AM) is a whole-genome scanning approach that can be used to identify susceptibility loci for complex diseases in racially admixed populations. AM tests for association between local ancestry at each SNP locus and phenotype, under the assumption of significant differences in both disease prevalence and allelic variation between ancestral groups for a population of interest

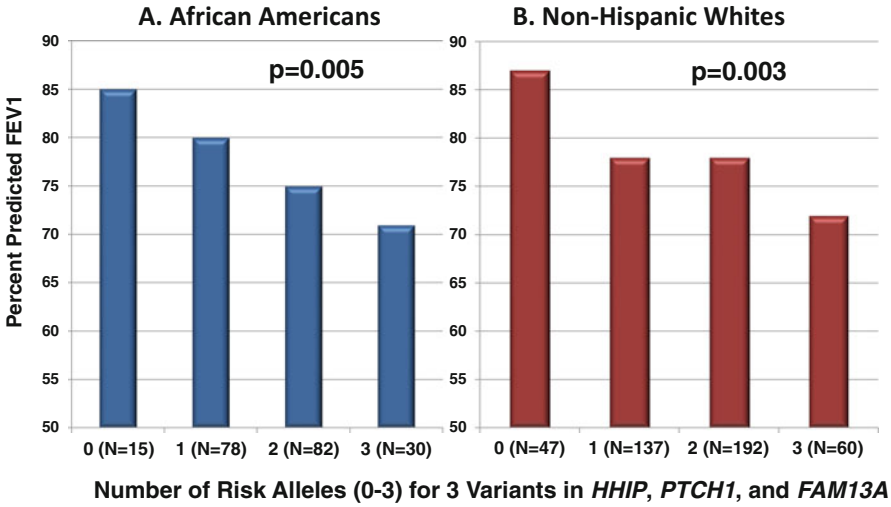

Fig. 13.2 (**a**, **b**): Additive genetic effects of major lung function loci from the general population. An additive effect of risk variants from GWAS of lung function measures in the general population on lung function was shown in 1441 asthma subjects from three asthma cohorts. An increase in the number of risk alleles for SNPs in *HHIP*, *PTCH1*, and *FAM13A* resulted in a significant stepwise decrease in FEV1, FVC, and FEV1/FVC in both non-Hispanic Whites and African Americans. Data for FEV1 is shown for (**a**) African Americans and (**b**) non-Hispanic Whites. Adapted from Li X et al. *J Allergy Clin Immunol* 2011;127(6):1457–65 [56]

(see Chap. 2) [63, 64]. An AM study identified an AM peak for asthma in African Americans on chromosome 6q14, which contained an SNP surrounded by a European ancestral background. This finding was replicated in Puerto Ricans, and an interaction between a susceptibility locus and local genetic ancestry was shown in both African Americans and Puerto Ricans [65]. In another study, six AM peaks containing known asthma risk loci and a novel locus in the *LYN* gene were identified in Puerto Ricans and Mexicans [66, 67]. More recently, AM was combined with allelic association testing to identify a potential asthma-susceptibility locus (*PSORS1C1*) in Latinos [44]. Like genome-wide linkage studies, AM has limited resolution, thus requiring subsequent fine-mapping studies, replication in external cohorts, and functional studies to confidently identify disease-susceptibility variants.

Failure to replicate findings from studies of non-Hispanic whites in minority populations (or vice versa) may be explained by differing allelic frequencies among ancestral populations (Table 13.1), insufficient genomic coverage in populations of African descent, small sample size, or true ethnic-specific effects. Current evidence suggests that most asthma-susceptibility loci identified to date are "cosmopolitan" (affecting all racial/ethnic groups), but that a few such loci may be "ethnic-specific" (affecting one or a few ethnic groups). Pending additional work, however, no ethnic-specific asthma-susceptibility variant has been confidently identified to date.

Genetic Studies of COPD

COPD is a multifactorial disease, caused by the interaction between genetic variants and environmental risk factors such as tobacco smoke [68–72]. Candidate-gene association studies, largely conducted in non-Hispanic whites, have identified a small number of potential COPD-susceptibility loci in inflammatory (*TGFB1*), protease-anti-protease (*ADAM33*, *MMP12*), and oxidant-antioxidant (*GSTM1*, *GSTP1*) gene pathways, some of which (e.g., *MMP12*) have been confirmed in subsequent genome-wide scans [72–78].

Airflow obstruction and lung function decline are key intermediate phenotypes of COPD. GWASs in non-Hispanic whites have identified susceptibility genes for lung function (*GSTO2* and *IL6R*) [79] and airflow obstruction (seven loci, including *HHIP*) [80–82]. Subsequent studies confirmed a role of *HHIP* in COPD susceptibility and showed an association with airflow obstruction in asthma [56, 83–86]. Evidence from murine models suggests that *HHIP* variants alter lung development and baseline respiratory reserve, ultimately increasing the risk of lung function decline and COPD [87–89]. Subsequent meta-analyses of GWASs have identified additional susceptibility loci for lung function in genes which regulate inflammation (*HTR4, THS4D*), lung development (*ADAM19*, *GPR126*), the antioxidant pathway (*GSTCD*), and tissue remodeling (*ADAM19*, *HTR4, THSD4, AGER*, *TNS1*). Of interest, alleles in these genes have differing frequencies across racial or ethnic groups (Table 13.2 [90]) [81, 82, 91, 92]. Cumulative risk scores combining risk SNPs from lung function genes (including *HHIP*, *TNS1*, *GSTCD*, *HTR4*, *AGER*, and *THSD4*) have been shown to be associated with a stepwise decrement in FEV1 and FEV1/FVC, both in non-Hispanic whites and African Americans with asthma, and in non-Hispanic whites from a general population cohort (Fig. 13.2a, b) [56, 85].

Although global African ancestry has been shown to be inversely associated with FEV_1 and FVC in African Americans and Latinos (see Chap. 2), there has been no GWAS of lung function in these populations. An admixture-based genetic study of Mestizo individuals and Native Mexicans demonstrated a strong correlation between Native American ancestry and geographic location within Mexico, resulting in ancestral clusters and ancestry-specific principal components. An analysis of ancestry-specific principal components in Mexicans and Mexican Americans then demonstrated that increased regional variation in Native American ancestry was positively associated with lung function [93]. Native American ancestry was also shown to be positively associated with lung function in a Costa Rican cohort of adolescents and adults with and without COPD [94], as well as in a study of Hispanic adults from New Mexico [95]. In the latter study, Native American ancestry was also inversely associated with lung function decline and COPD [95].

To date, GWASs of COPD have been conducted mostly in subjects of European descent. The first such GWAS identified susceptibility SNPs for COPD chromosome 15q25, a genomic region encompassing genes encoding the α-nicotinic acetylcholine receptors (*CHRNA3/5*) and a gene in the antioxidant pathway (*IREB2*) [86, 96–98].

Table 13.2 Allele frequencies of loci from major lung function genes from general population GWAS by biologic pathway

Lung function genes by pathway	Gene ID	SNP	Phenotype	CEU	YRI	ASW	MEX	CHB	JPT	References
Inflammatory pathway										
Interleukin-6 receptor	*IL6R*	rs4129267	FEF25-75 %	0.35	0.07	0.15	0.52	0.39	0.36	[79]
Transforming growth factor-β2	*TGFB2*	rs993925	FEV1, FEV1/FVC	0.42	0.3	NA	NA	0.42	0.48	[92]
Histone deacetylase-4	*HDAC4*	rs12477314	FEV1, FEV1/FVC	0.13	0	NA	NA	0.28	0.26	[92]
Thrombospondin Type 1 domain containing-4	*THSD4*	rs12899618	FEV1/FVC	0.11	0.09	0.1	0.05	0.11	0.04	[81, 82]
Tensin-1	*TNS1*	rs2571445	FEV1	0.39	0.14	0.24	0.35	0.42	0.45	[81, 82]
5-hydroxytryptamine receptor-4	*HTR4*	rs6889822	FEV1, FEV1/FVC	0.36	0.15	0.2	0.56	0.67	0.6	[81, 82]
Proteolytic pathway										
A Disintegrin and metalloprotease-19	*ADAM19*	rs2277027	FEV1, FEV1/FVC	0.32	0.64	0.62	0.43	0.14	0.16	[81]
Matrix metallopeptidase-15	*MMP15*	rs12447804	FEV1, FEV1/FVC	0.23	0.01	0.11	0.45	0.41	0.34	[92]
Advanced glycosylation end product receptor	*AGER*	rs2070600	FEV1/FVC	0.06	0.01	0.02	NA	0.24	0.13	[81, 82]
Oxidative stress and antioxidant pathway										
Glutathione S-transferase omega-1 subunit	*GSTO2*	rs156697	FEV1, FVC	0.38	0.83	0.69	0.22	0.27	0.29	[79]
Family with sequence similarity 13, member A	*FAM13A*	rs2869967	FEV1/FVC	0.41	0.71	0.65	0.45	0.49	0.59	[81]
C-terminal domain-containing glutathione S-transferase	*GSTCD*	rs17331332	FEV1, FVC	0.06	0	0.01	0.06	0	0.01	[81, 91]
Cell division cycle 123 homolog	*CDC123*	rs7068966	FEV1, FEV1/FVC	0.46	0.13	0.3	0.57	0.29	0.5	[92]
WW domain-containing oxidoreductase	*WWOX*	rs1079572	FVC	0.42	0.43	NA	NA	0.46	0.37	[91]
Lung development pathway										
Hedgehog-interacting protein	*HHIP*	rs13147758	FEV1, FEV1/FVC	0.38	0.02	0.1	0.33	0.31	0.32	[81, 82]
Patched 1 receptor for hedgehog proteins	*PTCH1*	rs16909898	FVC, FEV1/FVC	0.13	0.12	0.11	0.03	0.07	0.1	[81, 91]

(continued)

Table 13.2 (continued)

Lung function genes by pathway	Gene ID	SNP	Phenotype	CEU	YRI	ASW	MEX	CHB	JPT	References
G Protein-coupled receptor 126	*GPR126*	rs3817928	FEV1, FEV1/FVC	0.2	0.21	0.15	0.1	0.08	0.1	[81]
Retinoic acid receptor β	*RARB*	rs1529672	FEV1, FEV1/FVC	0.14	0.27	0.14	0.26	0.42	0.32	[92]
Craniofacial development protein 1	*CFDP1*	rs2865531	FEV1, FEV1/FVC	0.47	0.69	NA	NA	0.44	0.48	[92]
Bone morphogenetic protein-6	*BMP6*	rs6923462	FVC	0.13	0.31	0.24	0.11	0	0	[91]
EGF-containing Fibulin-like extracellular matrix protein-1	*EFEMP1*	rs1430193	FVC	0.42	0.79	NA	NA	0.91	0.86	[91]
PR domain-containing-11	*PRDM11*	rs2863171	FVC	0.16	0.38	0.34	0.09	0	0	[91]
Hydroxysteroid (17-beta) dehydrogenase-12	*HSD17B12*	rs4237643	FVC	0.25	0.39	NA	NA	0.13	0.13	[91]

These gene loci have been identified through GWAS of lung function measures in the general population
Allele frequencies are provided for each ethnic group and ancestral population based on the International HapMap Project Genome Browser release 28, phases 1–3 [32]
ASW African Americans from the southwest United States, *CEU* Utah residents with ancestry from northern and western Europe, *CHB* Han Chinese from Beijing, China, *JPT* Japanese from Tokyo, Japan, *MEX* Mexican Americans from Los Angeles, CA, *YRI* Individuals from Yoruba in Ibadan, Nigeria [33]
Adapted from Ortega VE et al. *Curr Allergy Asthma Rep* 2015;15(4):516 [90]

A second GWAS identified susceptibility SNPs for COPD in *FAM13A,* a gene previously associated with lung function [81, 99]. A subsequent (and larger) GWAS identified a COPD-susceptibility locus containing *CYP2A6*, a key enzyme for nicotine metabolism in the nicotine dependence pathway [100]. The first GWAS to include both non-Hispanic whites and African Americans confirmed risk loci for COPD in *CHRNA3*, *FAM13A*, and *HHIP,* while also identifying a novel locus in *RIN3* (distantly adjacent to *SERPINA1,* which encodes α-1 antitrypsin, the strongest known genetic risk factor for COPD) [101]. A subsequent genome-wide admixture mapping in African Americans identified a novel locus for airflow obstruction (*FAM19A2*) [102]. The first GWAS of COPD in Hispanics (a meta-analysis of three cohorts in Costa Rica, the US Multi-ethnic Study of Atherosclerosis, and New Mexico) identified potential novel COPD-susceptibility loci (adjacent to *KLHL7/NUPL2*, and *DLG2*) and confirmed *FAM13A* as a locus for COPD in Hispanics [103].

Consistent with results in asthma, ancestry influences lung function and COPD in racially admixed populations. Moreover, most COPD-susceptibility loci appear to be "cosmopolitan," but a few may be truly ethnic-specific. Thus, inclusion of large cohorts of minorities in COPD studies may yield novel insights into the role of ancestry and genetics in ethnic differences in the prevalence and severity of COPD.

Pharmacogenetic Studies of Respiratory Diseases

Pharmacologic responses have been shown to have both interindividual variability and significant heritability [104, 105]. Pharmacogenetic studies, which analyze gene-by-drug interactions on clinical outcomes, have been highly successful in identifying targeted therapies in cystic fibrosis. Most pharmacogenetic studies in pulmonary medicine have been conducted in subjects with asthma [106, 107] and have included mostly non-Hispanic whites. However, pharmacogenetic studies of response to inhaled β_2-adrenergic receptor agonists (inhaled β_2-agonists) have included racial and ethnic minorities with asthma.

Inhaled β_2-agonists include short-acting β_2-agonists (SABA, used most often as rescue therapy) and long-acting β_2-agonists (LABA, often used in combination with an inhaled corticosteroid (ICS) for chronic treatment). Findings from surveillance studies and meta-analyses suggest that LABA increase the risk of life-threatening asthma exacerbations and asthma-related deaths when administered as a monotherapy without ICS therapy [108–110]. The largest and most cited of these surveillance studies included 26,355 subjects (4685 African American), who were randomized to salmeterol or placebo with "usual therapy." An interval analysis of that trial (SMART) demonstrated increased risk of asthma or respiratory-related life-threatening exacerbations and death among African Americans randomized to salmeterol [109]. Although limited by lack of a requirement for ICS in all study subjects, such findings formed the basis for a LABA safety controversy, leading to two advisory panel meetings by the US Food and Drug Administration (FDA),

public health advisories, and a boxed warning for all inhalers containing LABA [111]. This controversy, further fueled by findings contradicting those from SMART [112–115], is now being evaluated in an international FDA-mandated LABA safety study of over 40,000 asthmatics [111, 116].

Results from recent clinical trials suggest that African Americans with asthma have a reduced response to LABA-containing combination therapies compared to non-Hispanic Whites and Hispanics [117, 118]. In a study of adults with asthma, African Americans were less likely to respond to LABA than non-Hispanic Whites [117]. Similarly, Puerto Ricans with asthma have been shown to have a lower response to SABA than Mexicans, a finding that could be explained by ethnic-specific differences in genetic variants or response to psychosocial stress [119, 120].

Pharmacogenetic studies of response to inhaled β_2-agonists have focused on the gene encoding the β_2-adrenergic receptor (*ADRB2*), the pharmacologic target for β_2-agonists. Although the most extensively studied *ADRB2* variant is a coding SNP which substitutes a glycine for an arginine in amino acid position 16 ($Gly^{16}Arg$), up to 49 SNPs have been identified through DNA sequencing in multiethnic populations, including rare variants [121, 122]. In vitro studies have shown that beta agonist stimulation results in enhanced downregulation of the β_2-adrenergic receptor with the Gly^{16} allele compared to Arg^{16} [123, 124]. In vitro studies of the rare *ADRB2* variant, $Thr^{164}Ile$, show that this variant causes a marked decrease in receptor ligand binding and coupling to G_s protein in response to different SABAs and LABAs, and impaired salmeterol binding to its receptor "exosite" [125, 126].

Early association studies of *ADRB2* in non-Hispanic whites consistently demonstrated that Arg^{16} homozygotes show greater response to SABA than Gly^{16} homozygotes, a finding confirmed in some ethnic groups (i.e., Puerto Ricans) but not in others (i.e., Mexican Americans) [127, 128]. An SNP in a pathway-related gene (*GSNOR*, encoding S-nitroso-glutathione reductase) has been shown to alter the genetic effect of $Gly^{16}Arg$ on response to SABA in Puerto Ricans but not in Mexican Americans, and thus this gene-gene interaction requires further replication [129].

Two pharmacogenetic studies using data from previous clinical trials (which randomized non-Hispanic whites with asthma to long-term treatment with SABA) demonstrated that *ADRB2* Arg^{16} homozygotes were more likely to have a decline in lung function during SABA treatment than *ADRB2* Gly^{16} homozygotes [130, 131]. The genetic effects of the $Gly^{16}Arg$ locus were confirmed in a genotype-stratified, cross-over pharmacogenetic study, the Beta Agonist Response by Genotype (BARGE) trial. In that trial, 37 Arg^{16} homozygotes and 41 Gly^{16} homozygotes were randomized to regular albuterol or placebo for 16 weeks, with ipratropium provided as a rescue inhaler to minimize β_2-agonist use. Whereas Gly^{16} homozygotes had improved lung function and symptom control during regular albuterol therapy, Arg^{16} homozygotes had no change in lung function and a loss of symptom control during regular albuterol therapy [132].

In the BARGE trial, the proportion of Arg^{16} homozygotes was higher in African Americans (22 %) than in non-Hispanic whites (17 %) (see *ADRB2* in Fig. 13.3) [132]. This is likely because Gly^{16} is the ancestral allele of $Gly^{16}Arg$, and chromosomes from ancient African ancestors have had more generations to distribute the

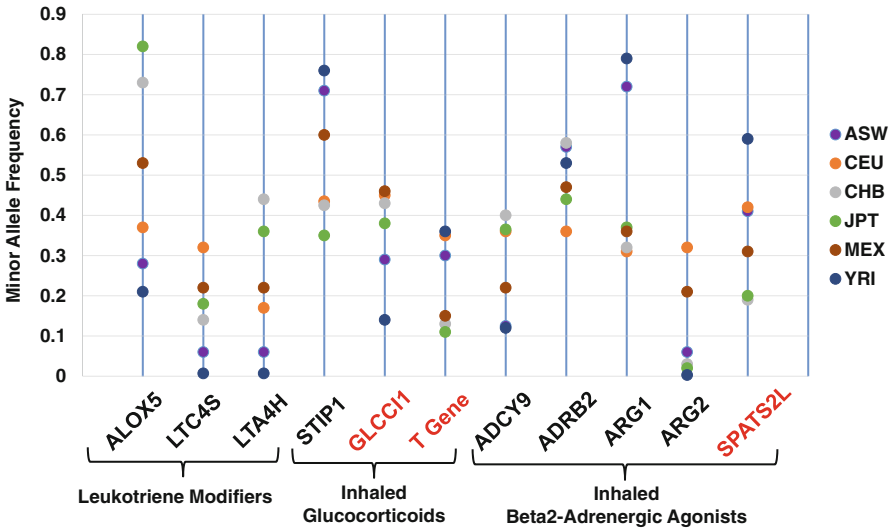

Fig. 13.3 Allele frequencies of different pharmacogenetic loci by race or ethnic group. These pharmacogenetic loci have been identified through candidate-gene studies and GWAS in asthma clinical trials [141, 143–153]. Loci with SNPs identified through GWAS are highlighted in *red*. Allele frequencies are provided for each ethnic group and ancestral population based on the International HapMap Project Genome Browser release 28, phases 1–3 [32]. *ASW* African Americans from the southwest United States, *CEU* Utah residents with ancestry from northern and western Europe, *CHB* Han Chinese from Beijing, China, *JPT* Japanese from Tokyo, Japan, *MEX* Mexican Americans from Los Angeles, CA, *YRI* Individuals from Yoruba in Ibadan, Nigeria [33]

more recent Arg^{16} variant than chromosomes from a European ancestor [133]. The frequency of the Arg^{16} allele is thus higher in African Americans and Puerto Ricans than in non-Hispanic Whites [122], potentially explaining ethnic differences in response to β_2-agonists. However, findings from genotype-stratified clinical trials have largely failed to show an effect of the Arg^{16} allele on response to LABA, with or without concurrent therapy with ICS [134–138]. $Gly^{16}Arg$ (which has a frequency between 40 % and 60 % in different ethnic groups [*ADRB2,* Fig. 13.3]) should not be used to stratify patients for LABA treatment. Rare genetic variants with strong effects could explain the severe adverse effects found in <1 % of the LABA-treated subjects in SMART, but this is highly speculative [109].

Sequencing of *ADRB2* in different ethnic groups has identified $Thr^{164}Ile$, a rare *ADRB2* variant primarily found in non-Hispanic Whites, and a rare 25 base-pair insertion variant at nucleotide position −376 relative to the start codon in the *ADRB2* promoter (−376 In-Del) in African Americans and Puerto Ricans [121, 122, 139]. In a recent study, these rare variants were both associated with asthma-related hospitalizations, asthma-related urgent outpatient visits, and regular use of systemic corticosteroids among non-Hispanic whites and African Americans with asthma treated with LABA (Fig. 13.4a, b) [122]. In another study, an analysis combining results from AM and a GWAS showed an association between rare variants in two solute carrier genes (*SLC24A4* and *SLC22A15*) and response to SABA in Puerto Ricans and Mexican

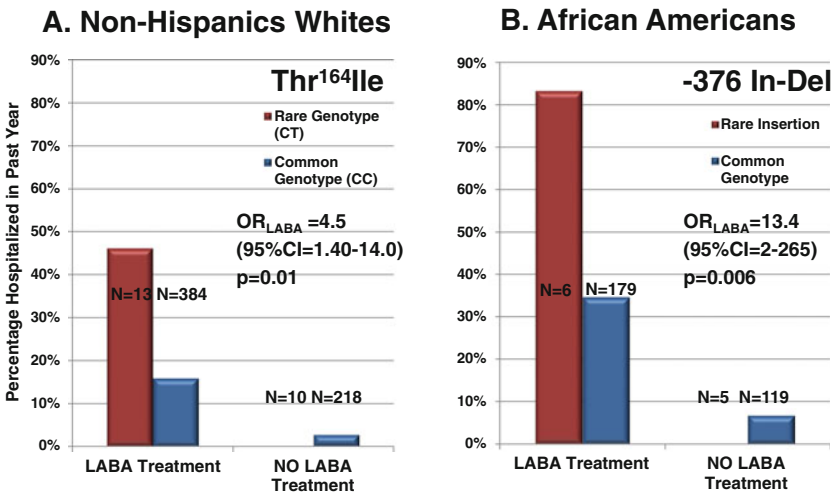

Fig. 13.4 (**a**, **b**): Rare *ADRB2* variants and asthma-related hospitalization with long-acting beta agonist treatment. Two rare ADRB2 variants, Thr^{164}Ile and a 25 base-pair promoter insertion-deletion (−376 In-Del), are shown with odds ratio (OR) for hospitalization in those treated with a long-acting beta agonist (LABA). Reproduced from Ortega VE et al. *Lancet Respir Med* 2014;2(3):204–13 [122]

American with asthma [140]. In that study, rare variants in two genes previously associated with response to SABA in non-Hispanic whites, *ADCY9* and *CRHR2*, were shown to be associated with response to SABA in Latinos [140–142].

Large candidate-gene and GWAS of the pharmacogenetics of asthma have been mostly conducted in non-Hispanic whites. Such studies identified loci for therapeutic responsiveness to SABA, ICS, and leukotriene modifiers, each of which shows varying allele frequencies among different racial and ethnic groups (Fig. 13.3) [141, 143–153]. More recently, large-scale whole-genome sequencing studies have found rare ethnic-specific variants in populations of African descent [5], suggesting that rare variants (such as those in *ADRB2* and solute carrier genes) could be biomarkers for personalized treatment approaches in racial or ethnic minorities (e.g., avoiding inhaled LABA in nonresponders or in subjects likely to experience severe adverse effects).

Future Directions

Whereas most susceptibility alleles for respiratory diseases (or response to treatment for such diseases) are "cosmopolitan," a small but non-negligible proportion of such susceptibility alleles are likely to be ethnic-specific (particularly rare variants). Moreover, differences in environmental and behavioral exposures across racial or ethnic groups are likely to affect gene expression through gene-by-environment interactions or epigenetic mechanisms that remain largely unexplored as potential contributors to respiratory health disparities.

A potential short-term implication of the studies summarized above (including studies of African ancestry and lung function summarized in Chap. 2) is that global ancestry (determined by genetic markers) could replace self-reported race or ethnicity when developing predicted (or reference) values for lung function. For instance, traditional race-based calculations of reference values for lung function can misclassify disease severity in up to 5 % of African Americans with asthma, as African Americans have different proportions of African ancestry [3].

In the medium to long term, predicted values of lung function could be personalized on the basis of whole-genome profiling, as all rare and common susceptibility genes for lung function (and other determinants, see below) become known as a result of large-scale studies of multiethnic populations. Similarly, such studies should lead to the identification of both common and rare (e.g., ethnic-specific) variants associated with response to, or severe adverse effects from specific therapies for pulmonary, critical care, and sleep disorders. In fact, ongoing whole-exome and whole-genome sequencing projects such as the NHLBI GO Exome Sequencing Program, the 1000 Human Genomes Project, and the Consortium on Asthma in African Ancestry Populations (CAAPA) have identified, and will continue to identify, common and rare genetic variation for future genetic studies in racial and ethnic minorities [5, 154].

The path to personalized medicine for all members of society requires enrollment of sufficiently large numbers of subjects from racial or ethnic minorities in studies of gene-by-environment interactions and "omics" (genetics, epigenetics, transcriptomics, proteomics, and metabolomics) of respiratory diseases, as such integrated approaches are more likely to yield novel insights into disease pathogenesis or pharmacogenetics than traditional genetic studies. Such inclusive and diverse studies should lead to personalized medicine for all people, a key step toward eliminating respiratory health disparities and achieving respiratory health equality in the USA.

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References

1. U.S. Census Bureau. U.S. Census Bureau projections show a slower growing, older, more diverse nation a half century from now 2012 [updated December 12, 2012; cited 2014 December 4, 2014]. https://www.census.gov/newsroom/releases/archives/population/cb12-243.html.
2. Choudhry S, Burchard EG, Borrell LN, Tang H, Gomez I, Naqvi M, et al. Ancestry-environment interactions and asthma risk among Puerto Ricans. Am J Respir Crit Care Med. 2006;174(10):1088–93.
3. Kumar R, Seibold MA, Aldrich MC, Williams LK, Reiner AP, Colangelo L, et al. Genetic ancestry in lung-function predictions. N Engl J Med. 2010;363(4):321–30.
4. Marth G, Schuler G, Yeh R, Davenport R, Agarwala R, Church D, et al. Sequence variations in the public human genome data reflect a bottlenecked population history. Proc Natl Acad Sci U S A. 2003;100(1):376–81.

5. Consortium GP, Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, et al. An integrated map of genetic variation from 1,092 human genomes. Nature. 2012;491(7422): 56–65.
6. Barnes KC, Neely JD, Duffy DL, Freidhoff LR, Breazeale DR, Schou C, et al. Linkage of asthma and total serum IgE concentration to markers on chromosome 12q: evidence from Afro-Caribbean and Caucasian populations. Genomics. 1996;37(1):41–50.
7. Postma DS, Bleecker ER, Amelung PJ, Holroyd KJ, Xu J, Panhuysen CI, et al. Genetic susceptibility to asthma—bronchial hyperresponsiveness coinherited with a major gene for atopy. N Engl J Med. 1995;333(14):894–900.
8. Meyers DA, Postma DS, Panhuysen CI, Xu J, Amelung PJ, Levitt RC, et al. Evidence for a locus regulating total serum IgE levels mapping to chromosome 5. Genomics. 1994;23(2): 464–70.
9. Cookson WO, Sharp PA, Faux JA, Hopkin JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. Lancet. 1989;1(8650):1292–5.
10. Young RP, Sharp PA, Lynch JR, Faux JA, Lathrop GM, Cookson WO, et al. Confirmation of genetic linkage between atopic IgE responses and chromosome 11q13. J Med Genet. 1992;29(4):236–8.
11. Daniels SE, Bhattacharrya S, James A, Leaves NI, Young A, Hill MR, et al. A genome-wide search for quantitative trait loci underlying asthma. Nature. 1996;383(6597):247–50.
12. Laitinen T, Daly MJ, Rioux JD, Kauppi P, Laprise C, Petays T, et al. A susceptibility locus for asthma-related traits on chromosome 7 revealed by genome-wide scan in a founder population. Nat Genet. 2001;28(1):87–91.
13. Xu J, Postma DS, Howard TD, Koppelman GH, Zheng SL, Stine OC, et al. Major genes regulating total serum immunoglobulin E levels in families with asthma. Am J Hum Genet. 2000;67(5):1163–73.
14. Young RP, Dekker JW, Wordsworth BP, Schou C, Pile KD, Matthiesen F, et al. HLA-DR and HLA-DP genotypes and immunoglobulin E responses to common major allergens. Clin Exp Allergy. 1994;24(5):431–9.
15. A genome-wide search for asthma susceptibility loci in ethnically diverse populations. The Collaborative Study on the Genetics of Asthma (CSGA). Nat Genet. 1997;15(4):389–92.
16. Ober C, Cox NJ, Abney M, Di Rienzo A, Lander ES, Changyaleket B, et al. Genome-wide search for asthma susceptibility loci in a founder population. The Collaborative Study on the Genetics of Asthma. Hum Mol Genet. 1998;7(9):1393–8.
17. Ober C, Tsalenko A, Parry R, Cox NJ. A second-generation genomewide screen for asthma-susceptibility alleles in a founder population. Am J Hum Genet. 2000;67(5):1154–62.
18. Allen M, Heinzmann A, Noguchi E, Abecasis G, Broxholme J, Ponting CP, et al. Positional cloning of a novel gene influencing asthma from chromosome 2q14. Nat Genet. 2003;35(3): 258–63.
19. Van Eerdewegh P, Little RD, Dupuis J, Del Mastro RG, Falls K, Simon J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature. 2002; 418(6896):426–30.
20. Basehore MJ, Howard TD, Lange LA, Moore WC, Hawkins GA, Marshik PL, et al. A comprehensive evaluation of IL4 variants in ethnically diverse populations: association of total serum IgE levels and asthma in white subjects. J Allergy Clin Immunol. 2004;114(1):80–7.
21. Castro-Giner F, Kogevinas M, Machler M, de Cid R, Van Steen K, Imboden M, et al. TNFA -308G>A in two international population-based cohorts and risk of asthma. Eur Respir J. 2008;32(2):350–61.
22. Nicolae D, Cox NJ, Lester LA, Schneider D, Tan Z, Billstrand C, et al. Fine mapping and positional candidate studies identify HLA-G as an asthma susceptibility gene on chromosome 6p21. Am J Hum Genet. 2005;76(2):349–57.
23. Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. Genes Immun. 2006;7(2):95–100.
24. Chagani T, Pare PD, Zhu S, Weir TD, Bai TR, Behbehani NA, et al. Prevalence of tumor necrosis factor-alpha and angiotensin converting enzyme polymorphisms in mild/moderate and fatal/near-fatal asthma. Am J Respir Crit Care Med. 1999;160(1):278–82.

25. Li YF, Gauderman WJ, Avol E, Dubeau L, Gilliland FD. Associations of tumor necrosis factor G-308A with childhood asthma and wheezing. Am J Respir Crit Care Med. 2006;173(9):970–6.
26. Moffatt MF, Cookson WO. Tumour necrosis factor haplotypes and asthma. Hum Mol Genet. 1997;6(4):551–4.
27. Green SL, Gaillard MC, Song E, Dewar JB, Halkas A. Polymorphisms of the beta chain of the high-affinity immunoglobulin E receptor (Fcepsilon RI-beta) in South African black and white asthmatic and nonasthmatic individuals. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1487–92.
28. Li X, Howard TD, Zheng SL, Haselkorn T, Peters SP, Meyers DA, et al. Genome-wide association study of asthma identifies RAD50-IL13 and HLA-DR/DQ regions. J Allergy Clin Immunol. 2010;125(2):328–35.e11.
29. Howard TD, Postma DS, Jongepier H, Moore WC, Koppelman GH, Zheng SL, et al. Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations. J Allergy Clin Immunol. 2003;112(4):717–22.
30. Lind DL, Choudhry S, Ung N, Ziv E, Avila PC, Salari K, et al. ADAM33 is not associated with asthma in Puerto Rican or Mexican populations. Am J Respir Crit Care Med. 2003;168(11):1312–6.
31. Hirota T, Takahashi A, Kubo M, Tsunoda T, Tomita K, Doi S, et al. Genome-wide association study identifies three new susceptibility loci for adult asthma in the Japanese population. Nat Genet. 2011;43(9):893–6.
32. The International HapMap Consortium. HapMap Genome Browser release #28 (Phases 1, 2 & 3—merged genotypes & frequencies) 2014 [December, 5, 2014]. http://hapmap.ncbi.nlm.nih.gov/cgi-perl/gbrowse/hapmap28_B36/.
33. International HapMap Consortium. The International HapMap Project. Nature. 2003;426(6968):789–96.
34. Ortega VE, Meyers DA. Implications of population structure and ancestry on asthma genetic studies. Curr Opin Allergy Clin Immunol. 2014;14(5):381–9.
35. Haller G, Torgerson DG, Ober C, Thompson EE. Sequencing the IL4 locus in African Americans implicates rare noncoding variants in asthma susceptibility. J Allergy Clin Immunol. 2009;124(6):1204–9.e9.
36. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007;448(7152):470–3.
37. Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med. 2010;363(13):1211–21.
38. Ferreira MA, McRae AF, Medland SE, Nyholt DR, Gordon SD, Wright MJ, et al. Association between ORMDL3, IL1RL1 and a deletion on chromosome 17q21 with asthma risk in Australia. Eur J Hum Genet. 2011;19(4):458–64.
39. Ferreira MA, Matheson MC, Duffy DL, Marks GB, Hui J, Le Souef P, et al. Identification of IL6R and chromosome 11q13.5 as risk loci for asthma. Lancet. 2011;378(9795):1006–14.
40. Hancock DB, Romieu I, Shi M, Sienra-Monge JJ, Wu H, Chiu GY, et al. Genome-wide association study implicates chromosome 9q21.31 as a susceptibility locus for asthma in Mexican children. PLoS Genet. 2009;5(8):e1000623.
41. Fang Q, Zhao H, Wang A, Gong Y, Liu Q. Association of genetic variants in chromosome 17q21 and adult-onset asthma in a Chinese Han population. BMC Med Genet. 2011;12:133.
42. Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, et al. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. Nat Genet. 2011;43(9):887–92.
43. Himes BE, Hunninghake GM, Baurley JW, Rafaels NM, Sleiman P, Strachan DP, et al. Genome-wide association analysis identifies PDE4D as an asthma-susceptibility gene. Am J Hum Genet. 2009;84(5):581–93.

44. Galanter JM, Gignoux CR, Torgerson DG, Roth LA, Eng C, Oh SS, et al. Genome-wide association study and admixture mapping identify different asthma-associated loci in Latinos: the Genes-environments & Admixture in Latino Americans study. J Allergy Clin Immunol. 2014;134(2): 295–305.
45. Gudbjartsson DF, Bjornsdottir US, Halapi E, Helgadottir A, Sulem P, Jonsdottir GM, et al. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. Nat Genet. 2009;41(3):342–7.
46. Wjst M, Fischer G, Immervoll T, Jung M, Saar K, Rueschendorf F, et al. A genome-wide search for linkage to asthma. German Asthma Genetics Group. Genomics. 1999;58(1):1–8.
47. Koppelman GH, Stine OC, Xu J, Howard TD, Zheng SL, Kauffman HF, et al. Genome-wide search for atopy susceptibility genes in Dutch families with asthma. J Allergy Clin Immunol. 2002;109(3):498–506.
48. Mathias RA, Grant AV, Rafaels N, Hand T, Gao L, Vergara C, et al. A genome-wide association study on African-ancestry populations for asthma. J Allergy Clin Immunol. 2010;125(2):336–46.e4.
49. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. Am J Respir Crit Care Med. 2000;162(6):2341–51.
50. Li X, Ampleford EJ, Howard TD, Moore WC, Torgerson DG, Li H, et al. Genome-wide association studies of asthma indicate opposite immunopathogenesis direction from autoimmune diseases. J Allergy Clin Immunol. 2012;130(4):861–8.e7.
51. Li X, Hawkins GA, Ampleford EJ, Moore WC, Li H, Hastie AT, et al. Genome-wide association study identifies TH1 pathway genes associated with lung function in asthmatic patients. J Allergy Clin Immunol. 2013;132(2):313–20.e15.
52. Burchard EG, Avila PC, Nazario S, Casal J, Torres A, Rodriguez-Santana JR, et al. Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. Am J Respir Crit Care Med. 2004;169(3):386–92.
53. Wenzel SE, Busse WW, National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Severe asthma: lessons from the Severe Asthma Research Program. J Allergy Clin Immunol. 2007;119(1):14–21; quiz 2–3.
54. Rose D, Mannino DM, Leaderer BP. Asthma prevalence among US adults, 1998–2000: role of Puerto Rican ethnicity and behavioral and geographic factors. Am J Public Health. 2006;96(5):880–8.
55. Homa DM, Mannino DM, Lara M. Asthma mortality in U.S. Hispanics of Mexican, Puerto Rican, and Cuban heritage, 1990–1995. Am J Respir Crit Care Med. 2000;161(2 Pt 1): 504–9.
56. Li X, Howard TD, Moore WC, Ampleford EJ, Li H, Busse WW, et al. Importance of hedgehog interacting protein and other lung function genes in asthma. J Allergy Clin Immunol. 2011;127(6):1457–65.
57. Brehm JM, Acosta-Perez E, Klei L, Roeder K, Barmada MM, Boutaoui N, et al. African ancestry and lung function in Puerto Rican children. J Allergy Clin Immunol. 2012;129(6): 1484–90.e6.
58. Alexander DH, Novembre J, Lange K. Fast model-based estimation of ancestry in unrelated individuals. Genome Res. 2009;19(9):1655–64.
59. Flores C, Ma SF, Pino-Yanes M, Wade MS, Perez-Mendez L, Kittles RA, et al. African ancestry is associated with asthma risk in African Americans. PLoS One. 2012;7(1):e26807.
60. Pino-Yanes M, Thakur N, Gignoux CR, Galanter JM, Roth LA, Eng C, et al. Genetic ancestry influences asthma susceptibility and lung function among Latinos. J Allergy Clin Immunol. 2015;135(1):228–35.
61. Menezes AM, Wehrmeister FC, Hartwig FP, Perez-Padilla R, Gigante DP, Barros FC, et al. African ancestry, lung function and the effect of genetics. Eur Respir J. 2015;45(6):1582–9.
62. Rumpel JA, Ahmedani BK, Peterson EL, Wells KE, Yang M, Levin AM, et al. Genetic ancestry and its association with asthma exacerbations among African American subjects with asthma. J Allergy Clin Immunol. 2012;130(6):1302–6.

63. Montana G, Pritchard JK. Statistical tests for admixture mapping with case-control and cases-only data. Am J Hum Genet. 2004;75(5):771–89.
64. Patterson N, Hattangadi N, Lane B, Lohmueller KE, Hafler DA, Oksenberg JR, et al. Methods for high-density admixture mapping of disease genes. Am J Hum Genet. 2004;74(5):979–1000.
65. Torgerson DG, Capurso D, Ampleford EJ, Li X, Moore WC, Gignoux CR, et al. Genome-wide ancestry association testing identifies a common European variant on 6q14.1 as a risk factor for asthma in African American subjects. J Allergy Clin Immunol. 2012;130(3):622–9.e9.
66. Beavitt SJ, Harder KW, Kemp JM, Jones J, Quilici C, Casagranda F, et al. Lyn-deficient mice develop severe, persistent asthma: Lyn is a critical negative regulator of Th2 immunity. J Immunol. 2005;175(3):1867–75.
67. Torgerson DG, Gignoux CR, Galanter JM, Drake KA, Roth LA, Eng C, et al. Case-control admixture mapping in Latino populations enriches for known asthma-associated genes. J Allergy Clin Immunol. 2012;130(1):76–82.e12.
68. Silverman EK, Mosley JD, Palmer LJ, Barth M, Senter JM, Brown A, et al. Genome-wide linkage analysis of severe, early-onset chronic obstructive pulmonary disease: airflow obstruction and chronic bronchitis phenotypes. Hum Mol Genet. 2002;11(6):623–32.
69. Silverman EK, Palmer LJ, Mosley JD, Barth M, Senter JM, Brown A, et al. Genomewide linkage analysis of quantitative spirometric phenotypes in severe early-onset chronic obstructive pulmonary disease. Am J Hum Genet. 2002;70(5):1229–39.
70. Malhotra A, Peiffer AP, Ryujin DT, Elsner T, Kanner RE, Leppert MF, et al. Further evidence for the role of genes on chromosome 2 and chromosome 5 in the inheritance of pulmonary function. Am J Respir Crit Care Med. 2003;168(5):556–61.
71. Ober C, Abney M, McPeek MS. The genetic dissection of complex traits in a founder population. Am J Hum Genet. 2001;69(5):1068–79.
72. Celedon JC, Lange C, Raby BA, Litonjua AA, Palmer LJ, DeMeo DL, et al. The transforming growth factor-beta1 (TGFB1) gene is associated with chronic obstructive pulmonary disease (COPD). Hum Mol Genet. 2004;13(15):1649–56.
73. Ito M, Hanaoka M, Droma Y, Hatayama O, Sato E, Katsuyama Y, et al. The association of transforming growth factor beta 1 gene polymorphisms with the emphysema phenotype of COPD in Japanese. Intern Med. 2008;47(15):1387–94.
74. Sadeghnejad A, Ohar JA, Zheng SL, Sterling DA, Hawkins GA, Meyers DA, et al. Adam33 polymorphisms are associated with COPD and lung function in long-term tobacco smokers. Respir Res. 2009;10:21.
75. van Diemen CC, Postma DS, Vonk JM, Bruinenberg M, Nolte IM, Boezen HM. Decorin and TGF-beta1 polymorphisms and development of COPD in a general population. Respir Res. 2006;7:89.
76. van Diemen CC, Postma DS, Vonk JM, Bruinenberg M, Schouten JP, Boezen HM. A disintegrin and metalloprotease 33 polymorphisms and lung function decline in the general population. Am J Respir Crit Care Med. 2005;172(3):329–33.
77. Wu L, Chau J, Young RP, Pokorny V, Mills GD, Hopkins R, et al. Transforming growth factor-beta1 genotype and susceptibility to chronic obstructive pulmonary disease. Thorax. 2004;59(2):126–9.
78. Hunninghake GM, Cho MH, Tesfaigzi Y, Soto-Quiros ME, Avila L, Lasky-Su J, et al. MMP12, lung function, and COPD in high-risk populations. N Engl J Med. 2009;361(27):2599–608.
79. Wilk JB, Walter RE, Laramie JM, Gottlieb DJ, O'Connor GT. Framingham Heart Study genome-wide association: results for pulmonary function measures. BMC Med Genet. 2007;8 Suppl 1:S8.
80. Wilk JB, Chen TH, Gottlieb DJ, Walter RE, Nagle MW, Brandler BJ, et al. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. PLoS Genet. 2009;5(3):e1000429.
81. Hancock DB, Eijgelsheim M, Wilk JB, Gharib SA, Loehr LR, Marciante KD, et al. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet. 2010;42(1):45–52.

82. Repapi E, Sayers I, Wain LV, Burton PR, Johnson T, Obeidat M, et al. Genome-wide association study identifies five loci associated with lung function. Nat Genet. 2010;42(1):36–44.
83. Van Durme YM, Eijgelsheim M, Joos GF, Hofman A, Uitterlinden AG, Brusselle GG, et al. Hedgehog-interacting protein is a COPD susceptibility gene: the Rotterdam Study. Eur Respir J. 2010;36(1):89–95.
84. Zhou X, Baron RM, Hardin M, Cho MH, Zielinski J, Hawrylkiewicz I, et al. Identification of a chronic obstructive pulmonary disease genetic determinant that regulates HHIP. Hum Mol Genet. 2012;21(6):1325–35.
85. Soler Artigas M, Wain LV, Repapi E, Obeidat M, Sayers I, Burton PR, et al. Effect of five genetic variants associated with lung function on the risk of chronic obstructive lung disease, and their joint effects on lung function. Am J Respir Crit Care Med. 2011;184(7):786–95.
86. Pillai SG, Ge D, Zhu G, Kong X, Shianna KV, Need AC, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. PLoS Genet. 2009;5(3):e1000421.
87. Mailleux AA, Kelly R, Veltmaat JM, De Langhe SP, Zaffran S, Thiery JP, et al. Fgf10 expression identifies parabronchial smooth muscle cell progenitors and is required for their entry into the smooth muscle cell lineage. Development. 2005;132(9):2157–66.
88. Chuang PT, Kawcak T, McMahon AP. Feedback control of mammalian Hedgehog signaling by the Hedgehog-binding protein, Hip1, modulates Fgf signaling during branching morphogenesis of the lung. Genes Dev. 2003;17(3):342–7.
89. Shi W, Chen F, Cardoso WV. Mechanisms of lung development: contribution to adult lung disease and relevance to chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2009;6(7):558–63.
90. Ortega VE, Kumar R. The effect of ancestry and genetic variation on lung function predictions: what is "normal" lung function in diverse human populations? Curr Allergy Asthma Rep. 2015;15(4):516.
91. Loth DW, Artigas MS, Gharib SA, Wain LV, Franceschini N, Koch B, et al. Genome-wide association analysis identifies six new loci associated with forced vital capacity. Nat Genet. 2014;46(7):669–77.
92. Soler Artigas M, Loth DW, Wain LV, Gharib SA, Obeidat M, Tang W, et al. Genome-wide association and large-scale follow up identifies 16 new loci influencing lung function. Nat Genet. 2011;43(11):1082–90.
93. Moreno-Estrada A, Gignoux CR, Fernandez-Lopez JC, Zakharia F, Sikora M, Contreras AV, et al. Human genetics. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science. 2014;344(6189):1280–5.
94. Chen W, Brehm JM, Boutaoui N, Soto-Quiros M, Avila L, Celli BR, et al. Native American ancestry, lung function, and COPD in Costa Ricans. Chest. 2014;145(4):704–10.
95. Bruse S, Sood A, Petersen H, Liu Y, Leng S, Celedon JC, et al. New Mexican Hispanic smokers have lower odds of chronic obstructive pulmonary disease and less decline in lung function than non-Hispanic whites. Am J Respir Crit Care Med. 2011;184(11):1254–60.
96. DeMeo DL, Mariani T, Bhattacharya S, Srisuma S, Lange C, Litonjua A, et al. Integration of genomic and genetic approaches implicates IREB2 as a COPD susceptibility gene. Am J Hum Genet. 2009;85(4):493–502.
97. Berrettini W. Nicotine addiction. Am J Psychiatry. 2008;165(9):1089–92.
98. Saccone SF, Hinrichs AL, Saccone NL, Chase GA, Konvicka K, Madden PA, et al. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. Hum Mol Genet. 2007;16(1):36–49.
99. Cho MH, Boutaoui N, Klanderman BJ, Sylvia JS, Ziniti JP, Hersh CP, et al. Variants in FAM13A are associated with chronic obstructive pulmonary disease. Nat Genet. 2010;42(3):200–2.
100. Cho MH, Castaldi PJ, Wan ES, Siedlinski M, Hersh CP, Demeo DL, et al. A genome-wide association study of COPD identifies a susceptibility locus on chromosome 19q13. Hum Mol Genet. 2012;21(4):947–57.
101. Cho MH, McDonald ML, Zhou X, Mattheisen M, Castaldi PJ, Hersh CP, et al. Risk loci for chronic obstructive pulmonary disease: a genome-wide association study and meta-analysis. Lancet Respir Med. 2014;2(3):214–25.

102. Parker MM, Foreman MG, Abel HJ, Mathias RA, Hetmanski JB, Crapo JD, et al. Admixture mapping identifies a quantitative trait locus associated with FEV1/FVC in the COPDGene Study. Genet Epidemiol. 2014;38(7):652–9.
103. Chen W, Brehm JM, Manichaikul A, Cho MH, Boutaoui N, Yan Q, et al. A genome-wide association study of chronic obstructive pulmonary disease in Hispanics. Ann Am Thorac Soc. 2015;12(3):340–8.
104. Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. Br Med Bull. 2000;56(4):1054–70.
105. Kalow W, Tang BK, Endrenyi L. Hypothesis: comparisons of inter- and intra-individual variations can substitute for twin studies in drug research. Pharmacogenetics. 1998;8(4):283–9.
106. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011; 365(18):1663–72.
107. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. N Engl J Med. 2015;373(3):220–31.
108. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ. 1993;306(6884):1034–7.
109. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129(1):15–26.
110. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. Ann Intern Med. 2006;144(12):904–12.
111. Administration USFaD. FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists (LABAs) 2011 [updated 04/15/2011; cited 2012 July 10]. http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm.
112. Peters SP, Prenner BM, Mezzanotte WS, Martin P, O'Brien CD. Long-term safety and asthma control with budesonide/formoterol versus budesonide pressurized metered-dose inhaler in asthma patients. Allergy Asthma Proc. 2008;29(5):499–516.
113. Sears MR, Ottosson A, Radner F, Suissa S. Long-acting beta-agonists: a review of formoterol safety data from asthma clinical trials. Eur Respir J. 2009;33(1):21–32.
114. Anderson HR, Ayres JG, Sturdy PM, Bland JM, Butland BK, Peckitt C, et al. Bronchodilator treatment and deaths from asthma: case-control study. BMJ. 2005;330(7483):117.
115. Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. Cochrane Database Syst Rev. 2005;4:CD005535.
116. Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. N Engl J Med. 2011;364(26):2473–5.
117. Wechsler ME, Castro M, Lehman E, Chinchilli VM, Sutherland ER, Denlinger L, et al. Impact of race on asthma treatment failures in the asthma clinical research network. Am J Respir Crit Care Med. 2011;184(11):1247–53.
118. Lemanske Jr RF, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med. 2010;362(11):975–85.
119. Naqvi M, Thyne S, Choudhry S, Tsai HJ, Navarro D, Castro RA, et al. Ethnic-specific differences in bronchodilator responsiveness among African Americans, Puerto Ricans, and Mexicans with asthma. J Asthma. 2007;44(8):639–48.
120. Brehm JM, Ramratnam SK, Tse SM, Croteau-Chonka DC, Pino-Yanes M, Rosas-Salazar C, et al. Stress and bronchodilator response in children with asthma. Am J Respir Crit Care Med. 2015;192(1):47–56.
121. Hawkins GA, Tantisira K, Meyers DA, Ampleford EJ, Moore WC, Klanderman B, et al. Sequence, haplotype, and association analysis of ADRbeta2 in a multiethnic asthma case-control study. Am J Respir Crit Care Med. 2006;174(10):1101–9.

122. Ortega VE, Hawkins GA, Moore WC, Hastie AT, Ampleford EJ, Busse WW, et al. Effect of rare variants in ADRB2 on risk of severe exacerbations and symptom control during longacting beta agonist treatment in a multiethnic asthma population: a genetic study. Lancet Respir Med. 2014;2(3):204–13.
123. Green SA, Turki J, Bejarano P, Hall IP, Liggett SB. Influence of beta 2-adrenergic receptor genotypes on signal transduction in human airway smooth muscle cells. Am J Respir Cell Mol Biol. 1995;13(1):25–33.
124. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry. 1994;33(32):9414–9.
125. Green SA, Cole G, Jacinto M, Innis M, Liggett SB. A polymorphism of the human beta 2-adrenergic receptor within the fourth transmembrane domain alters ligand binding and functional properties of the receptor. J Biol Chem. 1993;268(31):23116–21.
126. Green SA, Rathz DA, Schuster AJ, Liggett SB. The Ile164 beta(2)-adrenoceptor polymorphism alters salmeterol exosite binding and conventional agonist coupling to G(s). Eur J Pharmacol. 2001;421(3):141–7.
127. Choudhry S, Ung N, Avila PC, Ziv E, Nazario S, Casal J, et al. Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. Am J Respir Crit Care Med. 2005;171(6):563–70.
128. Lima JJ, Thomason DB, Mohamed MH, Eberle LV, Self TH, Johnson JA. Impact of genetic polymorphisms of the beta2-adrenergic receptor on albuterol bronchodilator pharmacodynamics. Clin Pharmacol Ther. 1999;65(5):519–25.
129. Choudhry S, Que LG, Yang Z, Liu L, Eng C, Kim SO, et al. GSNO reductase and beta2-adrenergic receptor gene-gene interaction: bronchodilator responsiveness to albuterol. Pharmacogenet Genomics. 2010;20(6):351–8.
130. Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI. Asthma exacerbations during long term beta agonist use: influence of beta(2) adrenoceptor polymorphism. Thorax. 2000;55(9):762–7.
131. Israel E, Drazen JM, Liggett SB, Boushey HA, Cherniack RM, Chinchilli VM, et al. The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. Am J Respir Crit Care Med. 2000;162(1):75–80.
132. Israel E, Chinchilli VM, Ford JG, Boushey HA, Cherniack R, Craig TJ, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet. 2004;364(9444):1505–12.
133. Meyer LR, Zweig AS, Hinrichs AS, Karolchik D, Kuhn RM, Wong M, et al. The UCSC Genome Browser database: extensions and updates 2013. Nucleic Acids Res. 2013;41(D1): D64–9.
134. Wechsler ME, Kunselman SJ, Chinchilli VM, Bleecker E, Boushey HA, Calhoun WJ, et al. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet. 2009;374(9703):1754–64.
135. Bleecker ER, Nelson HS, Kraft M, Corren J, Meyers DA, Yancey SW, et al. Beta2-receptor polymorphisms in patients receiving salmeterol with or without fluticasone propionate. Am J Respir Crit Care Med. 2010;181(7):676–87.
136. Lee DK, Currie GP, Hall IP, Lima JJ, Lipworth BJ. The arginine-16 beta2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. Br J Clin Pharmacol. 2004;57(1):68–75.
137. Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to longacting beta2-agonist therapy: a pharmacogenetic analysis of two randomised studies. Lancet. 2007;370(9605):2118–25.
138. Bleecker ER, Yancey SW, Baitinger LA, Edwards LD, Klotsman M, Anderson WH, et al. Salmeterol response is not affected by beta2-adrenergic receptor genotype in subjects with persistent asthma. J Allergy Clin Immunol. 2006;118(4):809–16.

139. Drysdale CM, McGraw DW, Stack CB, Stephens JC, Judson RS, Nandabalan K, et al. Complex promoter and coding region beta 2-adrenergic receptor haplotypes alter receptor expression and predict in vivo responsiveness. Proc Natl Acad Sci U S A. 2000;97(19):10483–8.
140. Drake KA, Torgerson DG, Gignoux CR, Galanter JM, Roth LA, Huntsman S, et al. A genome-wide association study of bronchodilator response in Latinos implicates rare variants. J Allergy Clin Immunol. 2014;133(2):370–8.
141. Tantisira KG, Small KM, Litonjua AA, Weiss ST, Liggett SB. Molecular properties and pharmacogenetics of a polymorphism of adenylyl cyclase type 9 in asthma: interaction between beta-agonist and corticosteroid pathways. Hum Mol Genet. 2005;14(12):1671–7.
142. Poon AH, Tantisira KG, Litonjua AA, Lazarus R, Xu J, Lasky-Su J, et al. Association of corticotropin-releasing hormone receptor-2 genetic variants with acute bronchodilator response in asthma. Pharmacogenet Genomics. 2008;18(5):373–82.
143. Telleria JJ, Blanco-Quiros A, Varillas D, Armentia A, Fernandez-Carvajal I, Jesus Alonso M, et al. ALOX5 promoter genotype and response to montelukast in moderate persistent asthma. Respir Med. 2008;102(6):857–61.
144. Klotsman M, York TP, Pillai SG, Vargas-Irwin C, Sharma SS, van den Oord EJ, et al. Pharmacogenetics of the 5-lipoxygenase biosynthetic pathway and variable clinical response to montelukast. Pharmacogenet Genomics. 2007;17(3):189–96.
145. Lima JJ, Zhang S, Grant A, Shao L, Tantisira KG, Allayee H, et al. Influence of leukotriene pathway polymorphisms on response to montelukast in asthma. Am J Respir Crit Care Med. 2006;173(4):379–85.
146. Tantisira KG, Lima J, Sylvia J, Klanderman B, Weiss ST. 5-lipoxygenase pharmacogenetics in asthma: overlap with Cys-leukotriene receptor antagonist loci. Pharmacogenet Genomics. 2009;19(3):244–7.
147. Litonjua AA, Lasky-Su J, Schneiter K, Tantisira KG, Lazarus R, Klanderman B, et al. ARG1 is a novel bronchodilator response gene: screening and replication in four asthma cohorts. Am J Respir Crit Care Med. 2008;178(7):688–94.
148. Vonk JM, Postma DS, Maarsingh H, Bruinenberg M, Koppelman GH, Meurs H. Arginase 1 and arginase 2 variations associate with asthma, asthma severity and beta2 agonist and steroid response. Pharmacogenet Genomics. 2010;20(3):179–86.
149. Duan QL, Gaume BR, Hawkins GA, Himes BE, Bleecker ER, Klanderman B, et al. Regulatory haplotypes in ARG1 are associated with altered bronchodilator response. Am J Respir Crit Care Med. 2011;183(4):449–54.
150. Himes BE, Jiang X, Hu R, Wu AC, Lasky-Su JA, Klanderman BJ, et al. Genome-wide association analysis in asthma subjects identifies SPATS2L as a novel bronchodilator response gene. PLoS Genet. 2012;8(7):e1002824.
151. Tantisira KG, Damask A, Szefler SJ, Schuemann B, Markezich A, Su J, et al. Genome-wide association identifies the T gene as a novel asthma pharmacogenetic locus. Am J Respir Crit Care Med. 2012;185(12):1286–91.
152. Tantisira KG, Lasky-Su J, Harada M, Murphy A, Litonjua AA, Himes BE, et al. Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma. N Engl J Med. 2011;365(13):1173–83.
153. Hawkins GA, Lazarus R, Smith RS, Tantisira KG, Meyers DA, Peters SP, et al. 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(6):1376–83.e7.
154. Exome Variant Server, NHLBI Exome Sequencing Project (ESP) Seattle, WA. http://evs.gs.washington.edu/EVS/. [cited 2012 06/11/2012].