Allergy, Asthma &
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Lessons Learned From GWAS of Asthma

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ABSTRACT

Asthma is a common complex disease of the airways. Genome-wide association studies (GWASs) of asthma have identified many risk alleles and loci that have been replicated in worldwide populations. Although the risk alleles identified by GWAS have small effects and explain only a small portion of prevalence, the discovery of asthma loci can provide an understanding of its genetic architecture and the molecular pathways involved in disease pathogenesis. These discoveries can translate into advances in clinical care by identifying therapeutic targets, preventive strategies and ultimately approaches for personalized medicine. In this review, we summarize results from GWAS of asthma from the past 10 years and the insights gleaned from these discoveries.

Keywords: Asthma; genome-wide association study

INTRODUCTION

Asthma is a heterogeneous and genetically complex respiratory disease.[1] Approaches for gene discovery in asthma were initially candidate gene association studies, followed by family-based genome-wide linkage analyses and, most recently, genome-wide association studies (GWASs).[2,3] For the last decade, GWASs of asthma have dominated, providing bias-free discovery of novel risk loci.[4]

The first GWAS of asthma was reported in 2007.[5] As of July 10, 2018 there were 72 papers written in English on asthma or asthma-related traits reported in the GWAS catalog (https://www.ebi.ac.uk/gwas/). Among these 72 papers, 24 are GWASs of asthmatic subjects and controls, including 7 meta-analyses of asthma GWASs (**Table 1**); 5 are GWASs of asthma sub-phenotypes such as severe asthma or asthma exacerbations; 13 are GWASs of asthma-related traits such as bronchodilator response (BDR), airway hyperresponsiveness (AHR) and total serum immunoglobulin E (IgE) levels; 15 are GWASs of asthma combined with other diseases, such as allergic rhinitis, or factors such as smoking interaction or age of onset; 2 are GWASs of occupational asthma; 2 are GWASs of aspirin-exacerbated respiratory disease (AERD); and 11 are GWASs of asthma pharmacologic responses.

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Table 1. Characteristics of GWASs of asthma

Year	Author	Discovery stage				Replication stage				Combined analysis	Reference
		Ethnicity	Sample size	Childhood onset asthma only	No. of genome-wide significant loci*	Ethnicity	Sample size	Childhood onset asthma only	No. of replicated loci in genome-wide significant loci	No. of genome-wide significant loci in combined analysis	
2007	Moffatt MF	European	994 cases and 1,243 controls	Yes	1	European	5,621 subjects	Yes	1	NA	5
2009	Hancock DB	Latino	492 trios	Yes	0	Hispanic	177 trios	Yes	NA	NA	76
2009	Himes BE	European	359 cases and 846 controls	Yes	0	Multi-ethnic	24,155 subjects	Yes	NA	NA	39
2010	Sleiman PM	European	793 cases and 1,988 controls	Yes	2	European, African American	6,175 subjects	Yes	1†	2‡	77
2010	Himes BE	European	359 cases, 846 controls, and 403 trios	Yes	0	Multi-ethnic	8,550 subjects and 583 trios	No	NA	NA	78
2010	Mathias RA	African American	498 cases and 500 controls	No	0	African Caribbean, African American	6,134 subjects	No	NA	0	79
2010	DeWan AT	Multi-ethnic	66 cases and 42 controls	Yes	0	European, Hispanic	12,337 subjects	No	NA	0	80
2011	Ferreira MA	European	986 cases and 1,846 controls	No	0	European	604 subjects	No	NA	NA	81
2011	Ferreira MA	European	12,475 cases and 19,967 controls	No	8§	European	25,358 subjects	No	NA	2	82
2011	Noguchi E	Asian	938 cases and 2,376 controls	Yes	2	Asian	3,106 subjects	Yes	2	2‡	83
2011	Hirota T	Asian	1,532 cases and 3,304 controls	No	1	Asian	30,247 subjects	No	0	5‖	84
2012	Lasky-Su J	European	1,238 cases and 2,617 controls	No	2¶	European	11,199 subjects	No	NA	1**	85
2012	Li X	European	813 cases and 1,564 controls	No	0	Multi-ethnic	41,400 subjects	No	NA	NA	86
2014	Galanter JM	Latino	1,893 cases and 1,881 controls	Yes	1	Multi-ethnic	12,560 subjects	No	NA	NA	87
2016	White MJ	African American	812 cases and 415 controls	Yes	1	NA	NA	NA	NA	NA	88
2016	Nieuwenhuis MA	European	920 cases and 980 controls	No	0	Multi-ethnic	11,656 subjects	No	NA	1	89
2016	Barreto-Luis A	European	380 cases and 552 controls	No	0	European	2,352 subjects	No	NA	0	90
2010	Moffatt MF††	European	10,365 cases and 16,110 controls	No	7‡	NA	NA	NA	NA	NA	16
2011	Torgerson DG§§	Multi-ethnic	5,416 cases and 7,144 controls	No	4‖	Multi-ethnic	12,649 subjects	No	3¶¶	3¶¶	19
2012	Ramasamy A***	European	1,716 cases and 16,888 controls	No	0	European	15,286 subjects	No	NA	2	91
2016	Pickrell JK	European	28,399 cases and 128,843 controls	No	27	NA	NA	NA	NA	NA	21
2017	Yan Q	Latino	2,144 cases and 2,893 controls	No	1	NA	NA	NA	NA	NA	92
2017	Almoguera B	European, African	5,309 cases and 16,335 controls	No	2	NA	NA	NA	NA	NA	34
2018	Demenais F†††	Multi-ethnic	23,948 cases and 118,538 controls	No	18	NA	NA	NA	NA	NA	14

References are sorted by year. "Mixed" in childhood onset asthma denotes the unknown proportion of childhood onset asthma.

NA, not applicable; GWAS, genome-wide association study; GABRIEL, Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community; SNP, single nucleotide polymorphism.

*Specifications of the discovery stage genome-wide significant *P* value definitions are in **Supplementary Table S1**; †Replication data were shown in only the non-17q12-21 region; ‡Both loci are also genome-wide significant in the discovery GWAS; §One loci from the results of the Australian GWAS only and seven loci from the results of the Australian GWAS and GABRIEL; ‖Genome-wide significant *P* value of the replication stage was less than 5.0 × 10⁻⁸; ¶From the adult asthma combined analysis; **From the adult asthma GWAS results only; ††Meta-Analysis includes GWAS from reference 5; ‡‡Loci including SNPs showing genome-wide significant association with asthma in at least one group using fixed models; §§Meta-Analysis includes GWAS from references 19,39,76,77,79; ‖‖Loci including SNPs showing genome-wide significant association with asthma in at least one ethnic group; ¶¶Replication and combined analysis were done in selected 15 loci; ***Meta-Analysis includes GWAS from reference s19,39,83,85; †††Meta-Analysis includes GWAS from references 5,19,79,82,83,85,90.

In this review, we summarize the results of the 42 GWASs of asthma, asthma sub-phenotypes (*e.g.*, severe asthma, asthma exacerbation) and asthma-related traits (*e.g.*, BDR, AHR, total serum IgE) that are registered in the GWAS catalog. We discuss the challenges posed by GWASs of complex diseases and strategies to overcome these challenges. Other aspects of asthma genetics, such as gene-environment interactions,[6-8] occupational asthma,[9] AERD[10,11] or pharmacogenetics[12,13] are reviewed elsewhere.

GWAS OF ASTHMA

Table 1 summarizes the study populations, sample sizes, and results of the 17 GWASs and 7 meta-analyses of asthma. Additional information on characteristics of the study populations is included in **Supplementary Table S1**.

Eight GWASs and 6 meta-analyses reported one or more association with genome-wide significance in the discovery population. Two additional GWASs reported genome-wide significance in a combined — discovery and replication — sample. These 16 studies together described 35 loci that were significant in at least 1 study (**Tables 2** and **3**, **Supplementary Tables S2** and **S3**). Sixteen of the 35 loci showed nominal significance when replicated in other GWASs, and 14 of those 16 loci showed genome-wide significant associations in at least 2 papers. Taken together, 5 GWASs and 5 meta-analyses of asthma identified genome-wide significant single nucleotide polymorphisms (SNPs) ($P < 5 \times 10^{-8}$) at the 17q12-21 (*ORMDL3*, *GSDMB*), making this the most widely replicated asthma loci. The 6p21 (HLA region), 2q12

Table 2. Asthma susceptibility loci meeting criteria for genome-wide significance in either discovery or combined stage in each GWAS

Year	Author	Region	Reported genes	Lead SNP	Location (Bp)	RAF in controls	*P* value	OR	95% CI	Stage	Replication *P* value	Reference
2007	Moffatt MF*	17q21	*ORMDL3*	rs7216389	39913696	NA	1.00.E-10	NA	NA	Discovery	7.94.E-04	5
2010	Sleiman PM	1q31	*DENND1B*	rs2786098	197356778	0.78	8.55.E-09	1.59	1.28–1.61	Discovery	6.47.E-04	77
		17q21	*ORMDL3/GSDMB*	rs4795400	39910767	NA	2.08.E-08	1.28	NA	Discovery	NA	
2011	Ferreira MA†‡	1q21	*IL6R*	rs4129267	154453788	0.40	2.30.E-08	1.09	1.06–1.12	Combined	3.30.E-03	82
		2q12	*IL1RL1*	rs3771166	102369762	0.61	7.90.E-15	1.16	1.11–0.20	Discovery	NA	
		5q22	*WDR36*	rs1043828	111128310	0.35	1.10.E-08	1.11	1.07–1.15	Discovery	NA	
		5q31	*RAD50*	rs6871536	132634182	0.19	2.40.E-09	1.14	1.09–1.19	Discovery	NA	
		9p24	*IL33*	rs1342326	6190076	0.16	3.50.E-14	1.20	1.14–1.26	Discovery	NA	
		11q13	*C11orf30/LRRC32*	rs7130588	76559639	0.36	1.80.E-08	1.09	1.06–1.13	Combined	3.28.E-02	
		15q22	*RORA*	rs11071559	60777789	0.86	3.80.E-09	1.18	1.11–1.23	Discovery	NA	
		15q22	*SMAD3*	rs744910	67154447	0.49	2.70.E-09	1.11	1.07–1.15	Discovery	NA	
		17q21	*ORMDL3*	rs8079416	39936460	0.44	2.40.E-22	1.19	1.15–1.23	Discovery	NA	
		22q12	*IL2RB*	rs2284033	37137994	0.57	5.00.E-10	1.12	1.09–1.16	Discovery	NA	
2011	Noguchi E§	6p21	*HLA-DPB1*	rs987870	33075103	0.14	7.50.E-09	1.51	1.31–1.74	Discovery	1.20.E-02	83
		8q24	*SLC30A8*	rs3019885	117013406	0.31	1.30.E-14	1.55	1.39–1.73	Discovery	8.70.E-03	
2011	Hirota T	4q31	*USP38*	rs7686660	143082006	0.27	1.87.E-12	1.16	1.11–1.21	Combined	3.33.E-09	84
		5q22	*TSLP*	rs1837253	111066174	0.35	1.24.E-16	1.17	1.13–1.22	Combined	1.02.E-12	
		6p21	*PBX2/NOTCH4/C6orf10/ BTNL2/HLA-DRA/HLA-DQB1/HLA-DQA2/HLA-DOA*	rs404860	32216568	0.50	4.07.E-23	1.21	1.16–1.25	Combined	6.42.E-18	
		10p14	-	rs10508372	8930055	0.43	1.79.E-15	1.16	1.12–1.21	Combined	1.31.E-11	
		12q13	*CDK2/IKZF4*	rs1701704	56018703	0.18	2.33.E-13	1.19	1.14–1.25	Combined	7.22.E-09	
2012	Lasky-Su J	5p15	*FLJ25076*	rs272474	6462225	NA	3.78.E-08	NA	NA	Discovery	NA	85
		6p21	*HLA-DQA1*	rs9272346	32636595	NA	2.20.E-08	NA	NA	Combined	6.70.E-03	
		14q13	*AKAP6*	rs17441370	32775658	NA	1.37.E-11	NA	NA	Discovery	NA	
2014	Galanter JM	17q12	*IKZF3*	rs907092	39766006	0.70	5.70.E-13	1.49	1.33–1.64	Discovery	NA	87
2016	White MJ	10p12	*PTCHD3*	rs660498	27452030	0.46	2.20.E-07	1.62	1.35–1.95	Discovery	NA	88

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Table 2. (Continued) Asthma susceptibility loci meeting criteria for genome-wide significance in either discovery or combined stage in each GWAS

Year	Author	Region	Reported genes	Lead SNP	Location (Bp)	RAF in controls	P value	OR	95% CI	Stage	Replication P value	Reference
2016	Nieuwenhuis MA	17q21	IKZF3/ZPBP2/GSDMB/ORMDL3	rs2290400	39909987	NA	2.55.E-20	1.31	NA	Combined	6.78.E-17	89
Meta-analysis												
2010	Moffatt MF[‖]	2q12	IL1RL2/IL1RL1/IL18R1/IL18RAP	rs3771166	102369762	0.62	3.40.E-09	1.15	1.10–1.20	Discovery	NA	16
		6p21	CCHCR1/HLA-DQB1	rs9273349	32658092	0.58	7.00.E-14	1.18	1.13–1.24	Discovery	NA	
		9p24	RANBP6/IL33	rs1342326	6190076	0.16	9.20.E-10	1.20	1.13–1.28	Discovery	NA	
		15q22	SMAD3	rs744910	67154447	0.49	3.90.E-09	1.12	1.09–1.16	Discovery	NA	
		17q12	STARD3/TCAP/PGAP3/ERBB2/IKZF3/ZPBP2	rs9303277	39820216	0.51	1.62.E-16	0.82	0.79–0.86	Discovery	NA	
		17q21	GSDMB/ORMDL3	rs2305480	39905943	0.55	9.60.E-08	1.18	1.11–1.23	Discovery	NA	
		17q21	GSDMA/PSMD3/MED24	rs3894194	39965740	0.45	4.60.E-09	1.17	1.11–1.23	Discovery	NA	
		22q12	IL2RB	rs2284033	37137994	0.56	1.20.E-08	1.12	1.08–1.16	Discovery	NA	
2011	Torgerson DG	2q12	IL1RL1	rs3771180	102337157	0.86	1.50.E-15	1.20	1.11–1.29	Combined	5.30.E-07	19
		3q27	RTP2	rs2017908	187699930	0.13	4.42.E-09[¶]	1.63	1.43–1.82	Discovery	8.80.E-01	
		5q22	TSLP	rs1837253	111066174	0.74	1.00.E-14	1.19	1.12–1.27	Combined	1.60.E-06	
		9p24	IL33	rs2381416	6193455	0.70	1.70.E-12	1.18	1.08–1.28	Combined	1.30.E-06	
		17q21	GSDMB	rs11078927	39908152	0.55	2.20.E-16	1.27	1.20–1.34	Combined	1.50.E-08	
2012	Ramasamy A	2q12	IL1RL1/IL18R1	rs13408661	102338622	0.84	1.00.E-09	1.23	1.15–1.31	Combined	3.20.E-05	91
		6p21	BTNL2/HLA-DRA	rs9268516	32411712	0.24	1.00.E-08	1.15	1.10–1.21	Combined	1.00.E-03	
2016	Pickrell JK	1q23	ADAMTS4	rs4233366	161189357	NA	4.80.E-15	1.09	1.07–1.11	Discovery	NA	21
		1q24	CD247	rs1723018	167464183	NA	1.40.E-08	0.95	0.93–0.96	Discovery	NA	
		1q25	TNFSF4	rs6691738	173182897	NA	2.90.E-08	0.94	0.92–0.96	Discovery	NA	
		1q32	ADORA1	rs6683383	203131376	NA	1.10.E-08	1.06	1.04–1.08	Discovery	NA	
		1p36	PEX14	rs662064	10497194	NA	3.20.E-08	0.94	0.92–0.96	Discovery	NA	
		2q12	IL1RL1	rs202011557	102297183	NA	5.10.E-31	0.84	0.82–0.87	Discovery	NA	
		2p25	-	rs13412757	8317950	NA	1.30.E-08	1.06	1.04–1.08	Discovery	NA	
		2q37	D2HGDH	rs34290285	241759225	NA	1.80.E-15	1.11	1.08–1.14	Discovery	NA	
		3q28	LPP	rs73196739	188684683	NA	6.50.E-09	0.92	0.90–0.95	Discovery	NA	
		4p14	TLR1	rs5743618	38797027	NA	3.90.E-11	1.08	1.06–1.11	Discovery	NA	
		5q22	TSLP	rs1837253	111066174	NA	3.30.E-31	0.88	0.86–0.90	Discovery	NA	
		5q31	RAD50	rs2244012	132565533	NA	2.10.E-16	1.10	1.08–1.13	Discovery	NA	
		5q31	NDFIP1	rs200634877	142150197	NA	2.50.E-08	0.94	0.92–0.96	Discovery	NA	
		6q15	BACH2	rs58521088	90275479	NA	7.10.E-11	0.93	0.92–0.95	Discovery	NA	
		6p21	HLA-DQA1	rs3104367	32635710	NA	1.00.E-40	0.87	0.86–0.89	Discovery	NA	
		6p21	HLA-C/MICA	rs2428494	31354420	NA	1.40.E-16	0.92	0.90–0.94	Discovery	NA	
		7q22	CDHR3	rs6959584	106035809	NA	2.00.E-08	1.09	1.06–1.12	Discovery	NA	
		8q21	-	rs10957978	80372904	NA	1.10.E-11	0.93	0.92–0.95	Discovery	NA	
		9p24	IL33	rs144829310	3208030	NA	1.30.E-31	1.17	1.14–1.20	Discovery	NA	
		10p14	-	rs12413578	9007290	NA	8.10.E-12	0.89	0.86–0.92	Discovery	NA	
		11q13	C11orf30/LRRC32	rs7936323	76582714	NA	1.40.E-16	0.92	0.91–0.94	Discovery	NA	
		12q13	STAT6	rs3001426	57115272	NA	1.40.E-10	0.94	0.92–0.96	Discovery	NA	
		14q24	RAD51B	rs3784099	68283210	NA	1.60.E-08	0.94	0.92–0.96	Discovery	NA	
		15q22	-	rs10519068	60776505	NA	3.80.E-11	1.10	1.07–1.13	Discovery	NA	
		15q22	SMAD3	rs56375023	67156025	NA	2.40.E-21	0.90	0.88–0.92	Discovery	NA	
		16p13	CLEC16A	rs7203459	11136846	NA	3.50.E-15	1.09	1.07–1.12	Discovery	NA	
		17q12	ZPBP2	rs11655198	39869916	NA	1.00.E-63	0.85	0.83–0.86	Discovery	NA	
2017	Yan Q	17q12	IKZF3	rs907092	39766006	0.68	1.16.E-12	1.41	NA	Discovery	NA	92
2017	Almoguera B	6p21	GRM4	rs1776883	34188667	0.47	5.29.E-09	1.25	1.19–1.31	Discovery	NA	34
		9p21	EQTN	rs72721168	27308290	0.96	7.02.E-10	1.83	1.28–2.37	Discovery	NA	
2018	Demenais F[**]	2q12	IL1RL1	rs1420101	102341256	0.37	3.9.E-21	1.12	1.09–1.15	Discovery	NA	14
		5q22	SLC25A46	rs10455025	111069301	0.34	9.4.E-26	1.15	1.12–1.18	Discovery	NA	
		5q31	IL13	rs20541	111069301	0.79	5.0.E-16	0.89	0.87–0.92	Discovery	NA	
		5q31	NDFIP1	rs7705042	142112854	0.63	7.9.E-9	1.09	1.06–1.12	Discovery	NA	
		6p21	HLA-DRB1	rs9272346	32636595	0.56	5.7.E-24	1.16	1.12–1.19	Discovery	NA	
		6p21	MICB	rs2855812	31504943	0.23	8.9.E-12	1.1	1.07–1.13	Discovery	NA	
		6p22	GPX5	rs1233578	28744470	0.13	5.9.E-7	1.09	1.05–1.12	Discovery	NA	
		6q15	BACH2	rs2325291	90276967	0.33	2.2.E-12	0.91	0.89–0.94	Discovery	NA	

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Table 2. (Continued) Asthma susceptibility loci meeting criteria for genome-wide significance in either discovery or combined stage in each GWAS

Year	Author	Region	Reported genes	Lead SNP	Location (Bp)	RAF in controls	*P* value	OR	95% CI	Stage	Replication *P* value	Reference
		8q21	*TPD52*	rs12543811	80366650	0.66	1.1.E-10	0.92	0.90–0.95	Discovery	NA	
		9p24	*RANBP6*	rs992969	6209697	0.75	7.2.E-20	0.86	0.83–0.88	Discovery	NA	
		10p14	*GATA3*	rs2589561	9004682	0.82	3.5.E-9	0.91	0.88–0.94	Discovery	NA	
		11q13	*EMSY*	rs7927894	76590272	0.37	2.2.E-14	1.1	1.08–1.13	Discovery	NA	
		12q13	*STAT6*	rs167769	57109992	0.4	3.9.E-9	1.08	1.05–1.11	Discovery	NA	
		15q22	*RORA*	rs11071558	60777222	0.14	1.3.E-9	0.89	0.86–0.92	Discovery	NA	
		15q22	*SMAD3*	rs2033784	67157322	0.3	7.4.E-15	1.1	1.08–1.13	Discovery	NA	
		16p13	*CLEC16A*	rs17806299	11106123	0.2	2.7.E-10	0.91	0.88–0.94	Discovery	NA	
		17q12	*ERBB2*	rs2952156	39720582	0.7	2.2.E-30	0.87	0.84–0.89	Discovery	NA	
		17q21	*ZNF652*	rs17637472	49384071	0.39	6.6.E-9	1.08	1.05–1.11	Discovery	NA	

The most significant SNPs at each locus are shown and ordered by genomic location in each reference. Base pair positions (bp) correspond to *GRCh38/hg38* genome assembly.

SNP, single nucleotide polymorphism; RAF, risk allele frequency; OR, odds ratio; CI, confidence interval; FDR, false discovery rate; GWAS, genome-wide association study; GABRIEL, Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community.

*With the exception of the 17q12-21 locus, none of the markers below 5% FDR, after controlling for stratification, were within 1 Mb of each other; †Discovery GWAS was the meta-analysis of results from the Australian GWAS and GABRIEL; ‡RAF was from the Australian GWAS only; §RAF was from the discovery GWAS only; ‖*P* value of random effects; ¶*P* vaule from the Latino GWAS only; **RAF was allele effect frequency from the European GWAS only.

(*IL1RL1/IL18R1*), 5q22 (*TSLP*) and 9p24 (*IL33*) loci showed the next 4 most genome-wide significant associations (**Figure, Table 3**).

A recent meta-analysis of 23,948 asthma cases and 118,538 controls from the Trans-National Asthma Genetic Consortium (TAGC) revealed 18 loci that met the criteria of genome-wide significance,[14] including nine previously known asthma loci, 2 loci previously reported for asthma plus hay fever, 2 previously associated with asthma in ancestry-specific populations and 5 new asthma susceptible loci. The latter included loci at 5q31.3, 6p22.1, 6q15, 12q13.3 and 17q21.33. Nearly all of the lead SNPs at the new loci were located in noncoding regions, and some were expression quantitative trait loci (eQTL) for genes such as *NDFIP1* (chromosome 5q31.3), *ZSCAN12* and *ZSCAN31* (6p22.1), *BACH2* (6q15), *STAT6* (12q13.3) and *GNGT2* (17q21.33). An enrichment in enhancer marks, especially in immune cells, was found at the associated loci, suggesting that the associated SNPs, or SNPs in linkage disequilibrium (LD) with the associated SNPs, play a role in the regulation of the immune processes.

Since the first GWAS of asthma that identified variants at the 17q21 locus and the correlation of those variants with expression of *ORMDL3*,[5] this region has been the most frequently studied and replicated locus. This region harbors a dense haploblock of SNPs that overlap at least 4 genes: *IKZF3*, *ZPBP2*, *GSDMB and ORMDL3*. The locus has since been extended to include regions flanking this core region, implicating *PGAP3* and *ERBB2* at the proximal end and *GSDMA* at the distal end as potentially representing independent asthma loci.[15] Nineteen asthma GWASs overall reported associations with SNPs at the extended 17q12-21 locus (**Table 3**). Moffatt *et al.*[16] carried out a subgroup analysis of childhood-onset asthma and reported the association of this region specific to childhood-onset asthma, but had few later-onset asthma individuals to separately analyze that subgroup in their consortium-based meta-analysis of asthma GWASs. The TAGC meta-analysis of asthma GWAS also showed that the 17q12-21 locus centered on *ORMDL3/GSDMB* was specific to early-onset asthma, while that SNPs at the *PGAP3/ERBB2* loci were not.[14] They also suggested that the asthma-associated signals near the *PGAP3/ERBB2* and *ORMDL3/GSDMB* blocks may affect asthma risk through the expression of different genes in different tissues.[14,15] Of note, the effects of genotype at this locus on asthma risk and protection have been reported to be modified by early-life exposures including environmental tobacco smoking[17] and rhinovirus (RV)-associated wheezing in the first 3 years of life.[18] Despite its

Table 3. Locus-level replications in subsequent GWAS

Reported genes	Region	The initial report			Genome-wide significant replication, reference	Nominal replication, reference
		Strongest SNP	P value	Reference		
STARD3/TCAP/PGAP3/ERBB2/IKZF3/ZPBP2/ GSDMB/ORMDL3/GSDMA/ZNF652/PSMD3/MED24	17q12-21	rs7216389	1.00.E-10	5	14,16,19,21,77, 82,87,89,92	34,39,78,81,83, 85,86,90,91
CCHCR1/PBX2/NOTCH4/C6orf10/BTNL2/GRM4/ HLA region/MICB/MICA	6p21	rs9273349	7.00.E-14	16	14,21,34,83-85,91	19,82,86-89,92
IL1RL2/IL1RL1/IL18R1/IL18RAP	2q12	rs3771166	3.40.E-09	16	14,19,21,82,91	34,81,84-87,90,92
TSLP/WDR36/SLC25A46	5q22	rs1043828	1.10.E-08	82	14,19,21,84	34,85-87,90,92
IL33/RANBP6	9p24	rs1342326	9.20.E-10	16	14,19,21,82	19,34,84-87,89-91
SMAD3/RORA	15q22	rs744910	3.90.E-09	16	14,21,82	19,83,84,91,92
RAD50/IL13/NDFIP1	5q31	rs6871536	2.40.E-09	82	14,21	19,34,83,84,90
C11orf30/LRRC32/EMSY	11q13	rs7130588	1.80.E-08	82	14,21	90
IKZF4/CDK2/STAT6	12q13	rs1701704	2.33.E-13	84	14,21	90
IL2RB	22q12	rs2284033	1.20.E-08	16	82	83,84,87,89,92
BACH2	6q15	rs58521088	7.10.E-11	21	14	NA
TPD52	8q21	rs12543811	1.10.E-10	21	14	NA
GATA3	10p14	rs2589561	3.50.E-09	84	14	NA
CLEC16A	16p13	rs17806299	3.50.E-15	21	14	NA
DENND1B	1q31	rs2786098	8.55.E-09	77	NA	84
SLC30A8	8q24	rs3019885	5.00.E-13	83	NA	88
PEX14	1p36	rs662064	3.20.E-08	21	NA	NA
IL6R	1q21	rs4129267	2.30.E-08	82	NA	NA
ADAMTS4	1q23	rs4233366	4.80.E-15	21	NA	NA
CD247	1q24	rs1723018	1.40.E-08	21	NA	NA
TNFSF4	1q25	rs6691738	2.90.E-08	21	NA	NA
ADORA1	1q32	rs6683383	1.10.E-08	21	NA	NA
-	2p25	rs13412757	1.30.E-08	21	NA	NA
D2HGDH	2q37	rs34290285	1.80.E-15	21	NA	NA
RTP2	3q27	rs2017908	4.42.E-09	19	NA	NA
LPP	3q28	rs73196739	6.50.E-09	21	NA	NA
TLR1	4p14	rs5743618	3.90.E-11	21	NA	NA
USP38	4q31	rs7686660	1.87.E-12	84	NA	NA
FLJ25076	5p15	rs272474	3.78.E-08	85	NA	NA
GPX5	6p22	rs1233578	5.90.E-07	14	NA	NA
CDHR3	7q22	rs6959584	2.00.E-08	21	NA	NA
EQTN	9p21	rs72721168	7.02.E-10	34	NA	NA
PTCHD3	10p12	rs660498	2.20.E-07	88	NA	NA
AKAP6	14q13	rs17441370	1.37.E-11	85	NA	NA
RAD51B	14q24	rs3784099	1.60.E-08	21	NA	NA

The table is sorted by the most number of repeatedly replicated loci. There were no replication data of previously reported GWAS in references 5,76,79,80. Nominal replication signifies the SNPs at each locus with replication P value less than 0.05 when there were replication data of previously reported GWASs. GWAS, genome-wide association study; SNP, single nucleotide polymorphism.

strong and consistent association with asthma, there has been little evidence of association at this locus in African ancestry populations,[14,19] possibly owing to the breakdown of LD on African-derived chromosome.[15] Taken together, SNPs in this locus are robustly associated with childhood-onset asthma in European, Asian and Latino individuals. Stein et al.[15] recently reviewed studies of the 17q12-21 locus that showed the asthma-associated 17q12-21 SNPs are eQTLs for the GSDMA, ORMDL3, GSDMB and PGAP3 in immune cells and/or lung cells. However, the role of 17q12-21 genes in asthma pathogenesis is still unknown. An overview of functional studies of genes at the 17q12-21 locus was reviewed recently by Das et al.[20]

Among the approximately half of the published GWAS of asthma that did not identify any genome-wide significant associations in their discovery stage, most had sample sizes < 2,000 subjects (**Table 1**) suggesting that larger sample sizes (≥10,000) are needed to identify asthma associated loci. For example, the TAGC meta-analysis showed that pooling data from ethnically diverse populations including 23,948 asthma cases and 118,538 controls,[14] and a

Figure. Word cloud consisting of asthma risk genes from asthma GWASs (see **Table 2** for references). Genes at genome-wide significant loci were selected based on the nearest gene. Word weight was assigned based on the number of times these genes were at loci that met the criteria for genome-wide significance. Word cloud was made using R package 'wordcloud' version 2.5. Figure drawn by H. Jang.
GWAS, genome-wide association study.

23andMe GWAS in 28,399 European ancestry cases and 128,843 controls[21] each detected new asthma loci. Although very large studies increase clinical heterogeneity, many true asthma loci can be detected in very large samples.

GWAS OF ASTHMA SUB-PHENOTYPES AND INTERACTIONS

GWASs of asthma sub-phenotypes reduce heterogeneity and can lead to the identification of new asthma risk loci, even in smaller samples, due to increased power in studies of extreme or more homogeneous phenotypes. These studies may unveil genetic factors that are 'masked' in very large GWAS of more heterogeneous cases. For example, this is best illustrated by a GWAS of early childhood asthma with acute exacerbations leading to hospitalization and emergency department visit by Bønnelykke et al.[22] The CDHR3 at 7q22.3 was identified in this study as a new susceptibility gene; this locus was later shown to be genome-wide significant in the 23andMe GWAS in European ancestry individuals,[21] but not in the TAGC meta-analysis of ethnically diverse individuals.[14] Importantly though, subsequent studies showed that CDHR3 functions as a receptor for Rhinovirus C (RV-C),[23] and that the CDHR3 asthma risk allele was associated specifically with RV-C-related respiratory illnesses in the first 3 years of life.[24] This "exacerbation GWAS" also confirmed previously reported asthma loci at genome-wide significance — GSDMB at 17q21, IL33 at 9p24, RAD50 at 5q31 and IL1RL1 at 2q12 loci, but with larger effect sizes despite the smaller sample size (**Table 2**), demonstrating that careful phenotyping and reduced clinical heterogeneity can reveal both novel asthma loci and larger effects of associated loci in smaller sample sizes than typically required for GWAS.

Another GWAS of exacerbations in 2 pediatric cohorts reported a novel asthma locus at the 10q21.3 (CTNNA3) that was genome-wide significant.[25] A meta-analysis of GWASs that included both physician-diagnosed asthma and hay fever compared to controls with neither

asthma nor hay fever revealed 2 novel susceptible loci: *ZBTB10* at 8q21.13 and *CLEC16A* at 16p13.13.[26] A GWAS of asthma with reduced exposure to tobacco smoke identified a locus that included the gene, *HAS2* at 8q24.13, as a susceptibility locus,[27] and another GWAS of active adult-onset nonallergic asthma added novel loci to asthma susceptible genes, *CD200* at 3q13.2 and *GRIK2* at 6q16.3, compared to inactive and mild nonallergic asthma.[28] A GWAS that investigated the age of onset of childhood asthma, revealed loci on 3p26 and 11q24 that were associated with early-onset asthma and potentially to more severe disease.[29] These GWASs of asthma defined by the presence or absence of other conditions identify novel loci, but most still require replication and functional characterizations.

Another approach to disentangle the complexity of asthma phenotypes and account for potential heterogeneity of risk factors have been genome-wide interaction studies (GWISs). A GWIS of genotype-by-sex interactions revealed a male-specific asthma risk locus, which includes *IRF1* at 5q31.1, in European ancestry individuals, and a female-specific asthma risk locus, which included *RAP1GAP1* at 1p36.12, in Latino individuals.[30] The SNPs at these 2 loci showed only nominally significant associations with asthma in an independent GWAS, but emerged as sex-specific asthma risk loci when the effects of both genotype and sex as an interaction were taken into account. Another GWIS of farm-related exposures on asthma and atopy risk did not show any significant associations with either novel or previously reported asthma loci, likely due to low statistical power.[31] Although this is a promising approach to identify loci that may confer risk only in the presence of specific exposures (*i.e.*, gene-environment interactions), it is challenging to conduct these studies in the very large samples because exposures histories are rarely available in those samples.[8]

Finally, gene discovery in smaller samples may be possible using validated phenotyping algorithms that mine electronic medical records (EMRs). This approach has recently been developed as a tool for genomic research by the Electronic Medical Records and Genomics (eMERGE) network.[32,33] A GWAS of asthma in 5,309 cases and 16,335 controls recruited from eMERGE network identified novel loci of 6p21.31 (*GRM4*) and 9p21.2 (*EQTN*),[34] although these associations need further replication and functional characterization. Within EMRs, longitudinal phenotype data and immense amounts of secondary phenotype data, such as laboratory findings and drug responses, can be collected. These data can be analyzed along with genetic data to determine whether loci are specific to asthma or shared with other allergic phenotypes, or how these relationships change over time. Rapid adoption of EMRs and EMR data standardization across hospitals will make available extensive phenotype data on many diseases and, combined with patient genotyping, expedite the identification of shared and unique genetic signatures for asthma endotypes as well as all common diseases.

GWAS OF ASTHMA-RELATED TRAITS

GWASs have been reported for asthma-related traits such as BDR, AHR, blood eosinophils, total serum IgE levels and allergic sensitization. The general assumptions of these studies are that it may be easier to find genes influencing components of asthma because they are less heterogeneous than asthma *per se*, and those same genes may also contribute to asthma risk and potentially provide more direct pharmacologic targets.

A GWAS of BDR — defined as the percentage change in FEV1 after administration of a short-acting β_2-adrenergic receptor agonist — identified rare variants (frequency, <5%)

near the solute carrier (SLC) genes with genome-wide significance in 1,782 Latino asthmatic children.[35] Another GWAS of BDR revealed genome-wide significant variants near the *ASB3* gene at 2p16 in a combined analysis of 1,164 multi-ethnic individuals with asthma.[36] A GWAS of AHR severity — defined as the natural log of the dosage of methacholine causing a 20% drop in FEV1 — in 994 non-Hispanic white asthmatic subjects did not identify any genome-wide significant genes,[37] while another GWAS of AHR severity in 650 European adult asthmatics revealed SNPs at the *PDE4D* gene at 5q11 at genome-wide significance,[38] which is a previously reported asthma gene.[39] Overall however, the BDR and AHR genes identified in GWAS with relatively small sample sizes lack replication. In contrast, a large GWAS of blood eosinophils,[40] pleotropic multifunctional leukocytes that are involved in the pathogenesis of inflammatory diseases including asthma, in 21,510 European subjects (comprised of a discovery, n = 9,392, and replication, n = 12,118, sample) reported SNPs near the *IL1RL1* at 2q12, *IKZF2* at 2q34, *GATA2* at 3q21.3, *IL5* at 5q31.1 and *SH2B3* at 12q24.12 genes with genome-wide significance. Among them, a variant at *IL1RL1* was also associated with asthma in 10 different populations included in this study. *IL1RL1* has been reported as an asthma gene through multiple GWAS of asthma (**Tables 2** and **3**). This finding requires further functional characterization if its relationship to eosinophils, asthma, and especially eosinophilic asthma, and its potential as a therapeutic target.

The first GWAS of total serum IgE levels, which is a strongly heritable trait,[41,42] did not show any genome-wide significant associations in the discovery population of 1,530 individuals of European ancestry. However, by combining the GWAS results with 4 independent replication cohorts, the investigators showed that functional variants near the gene encoding *FCER1A* at 1q23.2 and at the *RAD50-IL13* locus at 5q31 were associated with total serum IgE levels at genome-wide significant thresholds in a combined analysis in of 11,299 individuals of European ancestry.[43] The Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community (GABRIEL) consortium identified SNPs near *HLA-DRB1* at 6p21 as an IgE-associated locus that was independent of associations of this locus with asthma, and confirmed the previously reported associations between total serum IgE levels and SNPs near the *FCER1A*, *RAD50-IL13* and *STAT6* loci, at genome-wide significant level.[16] Three more GWAS of total serum IgE levels revealed loci near the HLA region reaching genome-wide significance;[44-46] the EVE consortium confirmed that these associations were shared among diverse ethnic groups.[47] A GWAS of total serum IgE levels in 3,334 Latinos and a following admixture mapping in 454 Latinos, 1,564 European Americans and 3,187 African Americans revealed a locus near the *ZNF365* gene at 10q21, but this finding still lacks replication.[45] Furthermore, a meta-analysis of GWASs of allergic sensitization in 15,845 individuals of European ancestry and replication in 16,034 individuals of European ancestry identified 10 genome-wide significant loci in or near *TLR6* at 4p14, *C11orf30* at 11q13, *STAT6* at 12q13, *SLC25A46* at 5q22, *HLA-DQB1* at 6p21, *IL1RL1* at 2q12, *LPP* at 3q28, *MYC* at 8q24, *IL2* at 4q27 and *HLA-B* at 6p21.[48] A recent GWAS of allergic disease in 360,838 individuals considered individuals with asthma, hay fever and/or eczema.[49] They identified 136 genome-wide significant risk variants at 99 independent loci, most of which had similar effects on the individual diseases, reflecting etiologic pathways that are common to all 3 diseases. However, this did not explicitly test for independent effects of the associated loci among individuals with only one of the three diseases. The shared loci were predicted to influence the function of immune cells and their target genes suggested opportunities for genomics-guided drug repositioning.

FUNCTIONAL STUDIES OF ASSOCIATED SNPS FROM EXISTING GWAS

A limitation of GWAS is that it identifies SNPs but does not provide information on the genes that the associated SNPs influence or on the causal SNP(s) among all SNPs in strong LD. As a result, nearly all GWASs report the nearest gene(s) as potential asthma candidate genes. However, not all SNPs impact the function or expression of the nearest gene, even when the SNP is within the gene itself. For example, among disease-associated variants that are eQTLs, the target gene will differ from the nearest gene 34% of the time.[50] On the other hand, SNPs that are eQTLs are more likely to be among significant GWAS SNPs compared to SNPs that are not eQTLs,[51] and combining eQTL mapping with GWAS can link GWAS-associated variants with the gene(s) they regulate, particularly if studies are performed in disease-relevant tissues.[15] For example, Li et al.[52] performed cis-eQTL studies in human bronchial epithelial cells (BECs) and cells from bronchial alveolar lavage (BAL) using SNPs near 34 putative asthma genes at 23 loci from previous GWASs. SNPs at 9 of the 23 loci were associated with the expression of nine genes in either BEC or BAL: IL1RL1 (but not IL18R1) at 2q12, TSLP (but not WDR36) at 5q22, HLA-DQB1 at 6p21, CDHR3 at 7q22, ZBTB10 at 8q21, IL33 at 9p24, C11orf30 (but not LRRC32) at 11q13, DEXI (but not CLEC16A) at 16p13, and GSDMB (but not ORMDL3) at 17q21. There are likely to be additional cis-eQTLs at asthma-associated SNPs at some of these loci in other tissues or by considering more SNPs or genes at each locus.

Ferreira et al.[53] used a gene-based association test that integrated published asthma GWAS and eQTL mapping studies to identify SNPs that are eQTLs and the genes they are associating with. They used 16 published eQTL studies in 12 cell types or tissues potentially relevant to asthma: whole blood, lymphoblastoid cell lines, peripheral blood mononuclear cells, monocytes, B cells, T cells, neutrophils, spleen, lung, small airways, fibroblasts, skin. They suggested that asthma risk was associated with the expression of genes related to nucleotide synthesis (B4GALT3 at 1q23.3 and USMG5 at 10q24.33) and nucleotide-dependent cell activation (P2RY13 and P2RY14 at 3q25.1), and referred to these genes as putative novel asthma risk genes. They applied this method to their recent large GWAS of allergic disease,[49] and identified additional significant and reproducible gene-based associations with 19 genes at 11 loci that were missed by single-variant analyses reported in the previous GWASs.[54] Among these were nine genes with known functions relevant to allergic disease: FOSL2 at 2p23, VPRBP at 3p21, IPCEF1 at 6q25, PRR5L at 11p13, NCF4 at 22q12, and APOBR, IL27, ATXN2L and LAT at 16p11. These putative novel associations still need further replication. Luo et al.[55] combined asthma GWAS results and publicly available eQTL data from human epithelial cells from small and large airways. They demonstrated that asthma GWAS hits were enriched as airway epithelial eQTLs and genes regulated by asthma GWAS loci in epithelium were enriched in immune response pathways. Li et al.,[52] Ferreria et al.,[53] and Luo et al.[55] linked asthma-associated SNPs to genes they regulate, potentially elucidating molecular mechanisms for their associations with asthma.[53,55] A great boon to this type of approaches is the Genotype-Tissue Expression (GTEx) consortium, which has made available eQTL data for 44 human tissues that can be used to identify genes and pathways affected by human disease-associated variation.[56]

GWAS OF ASTHMA OR ASTHMA-RELATED TRAITS IN THE KOREAN POPULATION

In 2008, the first GWAS of an asthma phenotype in 347 Korean subjects (84 cases and 263 controls) was published for toluene diisocyanate (TDI)-induced asthma, an occupation-

associated form of asthma.[57] Since then, GWASs of asthma in Korea focused on 80,[58] 100,[59] 117[60] and 179[61] subjects with AERD, which is characterized by the development of bronchoconstriction in asthmatic patients after ingestion of non-steroidal anti-inflammatory drugs including aspirin. However, no genome-wide significant loci were reported in these GWASs, likely due to small sample sizes.

A GWAS of total serum IgE levels was reported in 877 Korean asthmatic patients without any genome-wide significant hits,[62] but a GWAS of asthma in the Korean population has not yet been published. Performing GWASs of asthma in Korean children and adults is called for in the near future in order to identify the major genetic susceptibilities that maybe unique to this population.

ISSUES AND CHALLENGES IN GWAS OF ASTHMA

Despite their power for identifying asthma risk loci, there are many limitations of GWASs. In particular, GWASs identify mostly common variants which tend to have small effect sizes. As a result, GWAS-discovered variants are largely common (MAF > 10%) and account for a small proportion of both the population prevalence and the genetic component of asthma (*i.e.,* the heritability).[63-65] These results in limited predictive power of these variants.[66,67] Although rare and low-frequency variants have potentially larger phenotypic effects, they have not explained a significant fraction of the 'missingness' of asthma heritability thus far.[68] Recently, in a whole-genome sequencing study, Smith *et al.*[69] found a rare loss of function mutation in *IL33* that was associated with both lower blood eosinophils in 103,104 European subjects and reduced risk of asthma in 6,465 European asthmatic subjects and 302,977 controls. This study suggests that rare variants with large effect sizes are segregating in the population. While it is unlikely that such rare variants will account for significant proportions of the population risk for asthma, they can identify new pharmacologic targets and therefore serve a very important function.

Another limitation of GWAS is the statistical approach that tests for association with each of potentially tens of millions of SNPs. As a result, adjustments for multiple testing, typically using a Bonferroni corrected P value of $<5 \times 10^{-8}$ to control the false positive rate, require very large sample sizes (potentially >100,000) to identify loci with modest effect sizes. This stringent significance threshold will miss many true associations, particularly with SNPs involved in gene-gene and gene-environment interactions or those that are associated with specific asthma endotypes or sub-phenotypes. These variants have been referred to as 'mid-hanging fruit' in GWAS,[7] and differentiating true from false associations among variants with small P values (*e.g.*, $<10^{-4}$) that do not meet genome-wide significance thresholds in GWASs remains a major challenge.

Another limitation has been that most GWAS and large meta-analyses of asthma and related traits are in subjects of European ancestry. Thus, most inferences about the genetic architecture of asthma is based on observations in this one continental population, whereas much less is known about Asian, African and admixed populations. Because populations vary with respect to allele frequencies, patterns of LD, and effect sizes of variants that underlie disease risk,[70-72] inferences based on Europeans may have limited utility in other groups. For example, next-generation sequencing studies revealed differences in allele frequencies and haplotype structures at the 17q12-21 asthma-locus between Chinese and other ethnic groups.[73] However, half of the 24 asthma GWAS are only in Europeans (**Table 1**), and those studies are in

general the largest GWAS to date. Moreover, until recently, commercial genotyping arrays were based on European allele frequencies and LD patterns. As a result, GWAS in non-European populations likely missed variants specific to those populations. This also impacts the selection of tag SNPs in replication studies in non-European populations. These issues have recently been addressed by the development of ethnic-specific and pan-ethnic genotyping arrays and publicly available genome sequences that allow for ethnic-specific imputation of genome-wide SNPs.[74] For the first time, GWAS in Asian, Latino and African populations can be performed with excellent SNP coverage. It is crucial to study populations of diverse ethnic backgrounds for identifying shared and unique genetic predictors of asthma and for capturing more global patterns of genetic risk and gene-environment interaction effects on asthma risk.

CONCLUSIONS

Asthma pathogenesis is complex, resulting from heterogeneous genetic and environmental factors that jointly give rise to extensive phenotypic heterogeneity among asthmatics. Age at time of exposure to environmental risk factors and the persistence of these exposures during the lifespan may be critical modifiers of genotype-specific risk. These considerations are rarely, if ever, accounted for in GWAS. Nonetheless, the identification of susceptibility variants has already provided mechanistic insights into asthma pathogenesis, suggesting that asthma risk variants play a role in the regulation of immune cell functions.[14] GWAS findings, considered together with deep learning approaches that can incorporate longitudinal EMR data,[75] have the potential to more fully elucidate the genetic architecture of asthma. Such insights can be translated into advances in clinical care through identifying therapeutic targets and preventive approaches and ultimately personalized medicine.[67]

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIALS

Supplementary Table S1
Characteristics of the study populations of GWAS of asthma

Click here to view

Supplementary Table S2
Asthma susceptibility SNPs that met criteria for genome-wide significance in either discovery or combined stage in each GWAS

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Supplementary Table S3
Asthma susceptibility SNPs that met criteria for genome-wide significance in meta-analyses

Click here to view

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