Respiratory medicine – genetic base for allergy and asthma

Aristea Binia[a,b], Michael Kabesch[a,c]

[a] Department of Pediatric Pneumology, Allergy and Neonatology, Hannover Medical School, Hannover, Germany

[b] Nestle Research Centre, Bioanalytical Science Department, Lausanne, Switzerland

[c] Department of Pediatric Pneumology and Allergy, KUNO Children's University Clinic, Regensburg, Germany

Summary

Allergy and asthma are complex diseases influenced by many genes and molecular mechanisms. Recently a number of genome-wide association studies (GWAS) have investigated asthma- and allergy-related phenotypes. Results suggest the existence of sub phenotypes of asthma and document a need to better define the disease. Genetics may also help to identify groups of patients susceptible for specific forms of treatment and those at risk for adverse effects of therapy. Thus, genetics may represent a key tool to achieve individualised medicine in asthma and allergy in the future.

Key words: genetics; asthma; allergy; respiratory medicine

Introduction

Asthma and allergy are complex conditions often present in the same family or closely related subjects. Genetic factors undoubtedly contribute to disease susceptibility but the expression of the disease can be modulated by environmental exposures and the interactions between the two. Candidate-gene and linkage studies followed by positional cloning have already provided a large number of susceptibility genes [1]. The last decade has been marked by the publication of more than 20 genome-wide association studies (GWAS) in asthma or allergy phenotypes. GWAS have reported novel and interesting genes but have also confirmed the role of some functionally relevant genes previously described. However, heritability of allergic diseases has not been elucidated completely so far [2].

Abbreviations			
ACRN	Asthma clinical research network	IL1,2,3,4,5,10,13,33	Interleukin 1,2,3,4,5,10,13,33
ADRB2	β_2-adrenoreceptor	IL18R1	Interleukin 18 receptor 1
BCAP	B-cell adaptor for phosphatidylinositol 3-kinase	IL2RB	Interleukin 2 receptor, beta
CAMP	Childhood asthma management programme	LABA	Long acting β_2-adrenoreceptor agonists
CHI3L1	Chitinase 3-like 1	LCR	Locus control region
CRHR1	Corticotropin-releasing hormone receptor 1	MHC	Major histocompatiblity complex
DENND1B	DENN/MADD domain containing 1B protein	MRPL4	Mitochondrial ribosomal protein L4
EDC	Epidermal differentiation complex	NHLBI	National Heart Lung and Blood Institute
FCER1A	High affinity receptor for IgE	NK2R	Neurokinin receptor 2
FCER2	Low affinity receptor for IgE	ORMDL3	ORM1-like 3
FEF_{25-75}	Forced expiratory flow 25% and 75%	PDE4D	Phosphodiesterase 4D, cAMP-specific
FEV_1	Forced expiratory volume in 1 second	PYHIN1	Pyrin and HIN domain family member 1
FLG	Fillagrin	RAD50	DNA repair protein RAD50
FVC	Forced vital capacity	SABAs	Short acting β_2-adrenoreceptor agonists
GATA2	GATA binding protein 2	SH2B3	SH2B adapter protein 3
GLCCI1	Glucocorticoid-induced transcript 1	SNP	Single nucleotide polymorphism
GM-CSF	Granulocyte-macrophage colony-stimulating factor	SPT	Skin prick test
GSDMA,B	Gasdermin A, B	STAT6	Signal transducer and activator of transcription 6
GSTO2	Glutathione S-transferase omega 2	TBX21	T box 21
GWAS	Genome-wide Association Studies	TENOR	The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens
HHIP	Hedgehog-interacting protein	TSLP	Thymic stromal lymphopoietin
HLA	Human leukocyte antigen	V(D)J	Variable, diverse, and joining
ICS	Inhaled corticosteroids		

The purpose of this review is to evaluate how genetic studies have advanced the understanding of asthma and allergy by identifying specific disease-related markers or sub-phenotypes of the diseases. A search for all published GWAS in allergy-related phenotypes was conducted in MEDLINE using "asthma", "allergy", "atopy", "lung function" and "GWAS" as subject headings. The results were compared with the online catalogue of published GWAS from the National Human Genome Research Institute (http://www.genome.gov/) for the Disease/Trait: "asthma", "asthma (childhood onset)", "pulmonary function", "eosinophil counts", "IgE levels", "IgE grass sensitisation", "YKL-40 levels", "atopy" and "atopic dermatitis" (version November 2011). In the second part we evaluate how genetic findings may contribute to pharmacogenetics of asthma and allergies.

Genetic epidemiology of asthma and allergy

Genetics of distinct asthma phenotypes

Asthma is a heterogeneous disease characterised by inflammation of the small airways, bronchial hyper-responsiveness, intermittent airway obstruction, smooth muscle hypertrophy and mucus hypersecretion. Many physiological mechanisms contribute to the disease involving many different cell types [3]. Clinical symptoms differ greatly between patients, suggesting that clinicians are not dealing with a single disease but rather with overlapping conditions of a syndrome [4]. For example atopy, the IgE-mediated response to common allergens in a skin prick test, may be present in many children with asthma but there is a substantial number of patients with non-atopic forms of asthma, where IgE responses to allergens seem not to play a significant role [5].

Descriptive criteria such as age of onset, triggers, frequency and severity of symptoms, as well as response to treatment are often used to classify different sub-phenotypes of asthma. However, these asthma phenotypes are based on the course of the disease and clinical presentation may not reflect distinct disease mechanisms. The discovery of precise markers for specific asthma sub-phenotypes would help greatly in dissecting different entities of the asthma syndrome and would facilitate prevention and treatment of the disease on an individual level.

"Omics" have recently been applied in the quest for such markers in many complex diseases. Genomics is one of the approaches contributing to marker identification. One advantage is that GWAS can systematically interrogate millions of genetic markers across the genome simultaneously and relate them to clinical outcomes or patient characteristics [6] without an *a priori* hypothesis. Powerful GWAS have now been published involving thousands of subjects and testing association with different disease phenotypes [7].

Childhood onset asthma

Childhood onset asthma was investigated in the first published GWAS on asthma in 2007 by the GABRIEL consortium, phase I [8]. A novel locus on chromosome 17q21

was reported to contribute to the susceptibility for early-onset childhood asthma. Associated variants were correlated with mRNA levels of the *ORMDL3* gene indicating a genotype-specific regulation of its expression. Other genes on the 17q21 region, namely *GSDMA* and *GSDMB*, were later found to also be regulated by the same asthma-associated variants, suggesting that more than one gene from 17q21 may contribute to asthma development [9]. The association of the locus with asthma was robustly replicated in studies involving ethnically diverse populations [10–12]. Chromosomal region 17q21 represents an example of the complexity in delineating the functional variants underpinning the genetic associations. The locus is characterised by high linkage disequilibrium complicating the dissection of the true functional variants from the proxy variants. The co-regulation of *ORMDL3* and *GSDMA*/*GSDMB* genes by the same variants complicates the identification of the functional gene (or genes) even more. Extensive fine mapping approaches, including complete re-sequencing of the region followed by standardised functional assays for example, are underway to explain the nature of the 17q21 genetic associations [9].

Initial functional studies suggest that ORMDL3 may be implicated in calcium homeostasis which could induce intracellular mechanisms of inflammation [13]. Other studies propose a role of ORMDL proteins in the regulation of sphingolipid metabolism, a hypothesis which needs to be tested further for its relevance in asthma [14]. The observed association between the SNPs at 17q21 locus and other inflammatory diseases such as inflammatory bowel disease and diabetes could also hint to a more general or basic role of this locus in chronic inflammatory conditions [15, 16].

The GABRIEL consortium investigated different forms of asthma, including childhood onset in phase II published in 2010 [17]. In that study, 8,730 asthmatics and 11,389 controls were included; 6,783 were childhood onset asthmatics. The association of the 17q21 locus with childhood onset asthma remained and additional associations with *HLA-DQA1*, *-DQB1*, *IL33*, *IL1RL1/IL18R1*, *SMAD3*, *IL2RB* and *IL13* were reported, mainly attributable to childhood onset asthma (≤16 years).

In another GWA study, childhood onset asthma was also found to be associated with *DENND1B* (*DENN/MADD domain containing 1B protein*) [18]. The study included asthmatics with the severe form of the disease. However, replication of this signal is sparse in other populations which could indicate that it may be related to a specific yet unidentified sub-phenotype of asthma present in the US discovery cohort. The gene is a plausible candidate for a role in asthma pathogenesis as it seems to encode for a protein interacting with TNFα (Tumour necrosis factor α). As *DENND1B* is expressed by dendritic cells it could very easily play a role in adaptive immune responses [19]. In a second GWAS in a US cohort, the Childhood Asthma Management Program (CAMP) study, a region on chromosome 5q12 was suggested to be associated with childhood asthma, even though the signal did not reach significance in the discovery cohort [20]. Without further fine mapping, the authors concluded that the association signal is related to *PDE4D* (*Phosphodiesterase 4D, cAMP-specific*), a gene harboured in the locus. The encoded protein is involved in

the airway smooth muscle contractility in knockout mice suggesting that it is a potential therapeutic target [21]. In replication cohorts within the same study the finding remained significant in some study populations of European and Hispanic people, but not in populations of African ancestry.

Childhood asthma was associated with the *HLA-DP* locus (*HLA-DPA1* and *HLA-DPB1*) in Japanese and Korean populations [22]. In that study, modest associations were shown for the 17q21 locus containing *ORMDL3/GSDMB/GSDMA* and 5q31 (*IL5/RAD50/IL13*), whereas there were no associations with *PDE4D*, *DENND1B*, *IL18R1*, and *IL2RB*.

Adult onset asthma

The GABRIEL consortium GWAS in phase II included 1,947 adult onset asthmatics. *HLA-DQ* was the only locus presenting strong associations with later onset asthma [17]. A separate analysis of 529 subjects with occupational asthma did not reveal significant results. *HLA-DQ/DR* variants were also associated with "difficult-to-treat" asthma in TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) GWAS [23]. The study investigated asthmatic adults though it did not provide any information regarding the age of onset of the disease.

GWAS in Asian populations also confirmed genetic heterogeneity between children and adults. The largest GWAS so far published on an Asian population identified the most significant associations between adult asthma and the major histocompatibility complex region (MHC) [24]. The effects were independent of the *HLA-DQ* associations found in the GABRIEL Consortium GWAS [17].

Atopy and asthma

It is a common belief that the development of IgE-mediated atopy is a precursor for the later development of asthma, a theory also propagated as the atopic march. However, it seems that genetic susceptibility influencing IgE synthesis differs greatly from the susceptibility to developed asthma. Thus, one may speculate that IgE and asthma, while linked to each other, are not linearly related. The idea that asthma just develops on the basis of atopy seems to be too simple in the light of genetic data.

The first GWAS on IgE serum levels identified functional variants on chromosome 1q23 which includes *FCER1A* (*High affinity receptor for IgE*) gene, variants within the 5q31 locus, and the 12q13 locus encoding the transcription factor *STAT6* [25]. Both FCER1A and STAT6 are functionally involved in IgE regulation, the first being part of the high affinity IgE receptor complex and the second being the intracellular signal from IL4 necessary to induce IgE switching. Both have been extensively studied in atopy and asthma genetics [26, 27]. The 5q31 locus was identified to encompass variants also associated with severe asthma in the TENOR GWAS [23]. The overlapping association of 5q31 locus in IgE [25] and severe asthma [23] could imply that it is involved in atopic asthma. The 5q31 region contains many cytokines genes such as *IL3*, *IL4*, *IL5*, *IL13* and *GM-CSF,* and the *RAD50* gene (*DNA repair protein RAD50*) a less obvious candidate for IgE reg-

ulation. The *RAD50* gene contains a locus control region (LCR) which could also regulate the transcription of *IL4* and *IL13* genes [28]. However, RAD50 may itself participate in V(D)J (variable, diverse and joining) and class-switch recombination based on its role in DNA repair and re-ligation [29].

In the GABRIEL consortium study, only *HLA-DRB1* was significantly associated with serum IgE levels [17]. These results confirm that genetic determinants of IgE and asthma do not overlap in the populations included in the study. While it is still unclear whether IgE is a secondary event in the development of an asthmatic phenotype, it is obvious that atopic and non-atopic asthma are two diverse entities in terms of genetic susceptibility.

Skin prick test (SPT) and allergen-specific IgE levels have also been analysed for genetic susceptibility signals in a recent GWAS but no consistent patterns of associations were found [30]. In another study performed mainly in adult populations, grass sensitisation was associated with the *HLA-DRB4* locus [31]. Taken together, one could hypothesise that genetic determinants for atopy-phenotypes and specific sensitisation differ.

Intermediate phenotypes of asthma

Studying asthma by disease-onset phenotype, severity or atopic status has been the preferred method in GWAS. There are nevertheless studies using intermediate or asthma-related phenotypes in GWAS resulting in statistically strong and plausible outcomes (table 1).

Eosinophilia and asthma

Eosinophils are important in asthma-related inflammatory responses and high eosinophil counts are a prominent feature of severe asthma [32]. In addition, studies have shown that corticosteroids are more efficient in eosinophilic asthma [33]. An Icelandic study found *IL1RL1* variants to be associated with higher blood eosinophil counts and to also confer susceptibility to atopic asthma [34]. The replication included nine European populations and one from East Asia. Interestingly, *IL1RL1/IL18R1* on 2q12 was also associated with childhood asthma in the GABRIEL Consortium [17] and seems to associate with other inflammatory conditions such as Crohn's disease [35] and atopic dermatitis [36]. This could imply that the *IL1* receptor gene cluster on 2q12 also contributes to common mechanisms in inflammatory diseases. In the same GWAS, *GATA2* (*GATA binding protein 2*), *IL5* and *SH2B3* (*SH2B adapter protein 3*) were linked to eosinophil counts but not to asthma. All these genes are encoding for proteins expressed in blood cells involved in hematopoietic cell maturation, T cell activation and eosinophil activation, making their role in eosinophilia plausible.

Chitinases and asthma

Serum YKL-40 levels may represent a biomarker for asthma and disease severity [37]. YKL-40 serum levels were increased in asthmatics and in those with bronchial hyper-responsiveness compared to controls. A study by Ober *et al.* used GWA to study genetic involvement in the regulation of YKL-40 levels and found an association between a promoter SNP in *CHI3L1* (*Chitinase 3-like 1*)

and YKL-40 levels [38]. *CHI3L1* variations were also associated with bronchial hyper-responsiveness and lung function but not atopic state. Despite the compelling role of chitinases in the pathogenesis of asthma [39], *CHI3L1* associations with asthma could not yet be replicated in subsequent studies [40].

Pulmonary function

Reduced pulmonary function is not specific for asthma but plays a role in many obstructive pulmonary diseases. Pulmonary function is a heritable trait depicting the physiological capacity of the lungs [41] and can be viewed as an intermediate and easily measurable phenotype related to asthma. GWAS were conducted in healthy individuals to interrogate the heritability of lung function, and spirometry measurements were tested for genetic associations [42–46]. Variants in the putative genes *GSTO2* (*Glutathione S-transferase omega 2*) on chromosome 10 and *IL6R* (*Interleukin 6 receptor*) on chromosome 1 showed significant associations with FEV_1, FVC and $FEF_{25–75}$, respectively [42]. Thus, *IL6R* SNPs are associated with both asthma and lung function [42, 47]. *HHIP* (*Hedgehog-interacting protein*) was also identified as a lung function susceptibility locus in a number of well-powered studies [43–46]. HHIP is part of the hedgehog signalling pathway and may play

a role in embryonic lung development [48]. However, the reproducible and plausible association of *HHIP* with lung function was independent of the asthmatic phenotype [43]. Therefore, association of genes with lung function measurements and asthma may identify lung specific mechanisms in asthma development in contrast to general inflammatory mechanisms (such as eosinophilia) that also play a role in asthma development.

Ethnic diversity in GWAS results with asthma

Most GWAS have been conducted in populations of European ancestry (tables 1, 2). However, genetic associations with asthma differ significantly between European, African and Asian populations. The 17q21 signal is a good example of this diversity in disease heritability [49, 50]. Association between asthma and 17q21 was well replicated in Europeans and Hispanic populations but not in populations of African ancestry where *PYHIN1* (encoding Pyrin and HIN domain family member 1) was identified as a specific risk locus exclusive for this ethnic group. Interestingly, variants in *DENND1B* showed opposite directions of association with asthma in European and African populations [18]. *DENND1B* is currently the only asthma candidate gene found to be associated with the disease in both European and African populations.

Table 1: GWAS findings in intermediate asthma phenotypes.			
Phenotype	**Genetic locus**	**Chromosome**	**Population***
YKL-40 levels	*CHI3L1*	1q32	European [38]
Bronchial hyper-responsiveness			
Blood eosinophil counts	SH2B3	12q24	European [34]
	GATA2	3q21	
	IL1RL1	2q12	
	IL5	5q31	
	IKZF2	2q34	
	WDR36	5q22	
	MHC	6p21	
	IL33	9p24	
	MYB	6p22	
Total serum IgE	FCER1A	1q23	European [25]
	RAD50	5q31	
	STAT6	12q13	
Specific IgE levels (HDM, cat fur, mixed grass)	C11orf30/LRRC32	11q13	European [31]
	FNDC3A	13q14	European [30]
Lung function (FEV_1 and FVC)	GSTO2	10q25	European [42]
Lung function ($FEF_{25–75}$)	IL6R	1q21	
Lung function (FEV_1 and FEV_1/FVC)	HHIP	4q31	European [44]
	GSTCD	4q24	
	AGER	6p21	
	THSD4	15q23	
	TNS1	2q35	
	HTR4	5q32	
	DAAM2	6p21	
	HHIP	4q31	European [45]
	AGER/PPT2	6p21	
	HTR4	5q32	
	ADAM19	5q33	
	GPR126	6q24	
	FAM13A	4q22	
	PTCH1	9q22	
* The term populations refers to the ethnicity of the original study.			

Susceptibility for atopic dermatitis and allergic rhinitis in relation to asthma

Together with asthma, atopic dermatitis and allergic rhinitis belong to the group of atopic diseases [51, 52]. These diseases often occur in the same family and thus, a shared genetic susceptibility was suspected for a long time.

Atopic dermatitis often coexists or even precedes asthma. In atopic dermatitis a major gene driving the disease was identified before the GWAS era. The *fillagrin* (*FLG*) gene is located in the epidermal differentiation complex (EDC) on chromosome 1q21. It was first associated with *ichthyosis vulgaris* (common dry skin), before the relationship with atopic eczema was discovered [53]. In cross sectional studies it was shown that *FLG* accounts for approximately 15% of atopic dermatitis patients in European populations [54]. If and how fillagrin deficiency may influence other atopic phenotypes is still a matter of debate [55].

A GWAS on atopic dermatitis showed significant associations with the 11q35.5 locus (table 2) [56]. The region includes the *C11orf30* gene which encodes for the nuclear protein EMSY involved in DNA repair [56]. In that GWAS, modest associations were also detected for the EDC, apart from *FLG* within the region suggesting that other variants in the EDC also contribute to atopic dermatitis. A recent GWAS study in Han Chinese confirmed *FLG* as a genetic susceptibility locus also in that population. It also uncovered novel susceptibility loci [57]. Ethnic heterogeneity in genetic variants across populations was observed for *FLG* [58]; however, functional relevant variants in the gene were always associated with atopic dermatitis, independent of ethnicity.

Allergic rhinitis is another expression of an allergic disease with a familial aggregation. A GWAS conducted for allergic rhinitis in a population of Chinese origin showed significant associations with *MRPL4* (*mitochondrial ribosomal protein L4*) on chromosome 19p13.2 and *BCAP* (*B-cell adaptor for phosphatidylinositol 3-kinase*) on 10q24.1, in both discovery and replication panels [59]. A suggestive association was detected for the previously atopy-related locus *HLA-DQB1/HLA-DRB1* [17]. In a meta-analysis of four European populations, variants within the 11q13 locus were associated with allergic rhinitis and grass sensitisation [31]. Harbouring variants in *C11orf30* and *LRRC32*, the locus showed association with atopic dermatitis [56] and atopic asthma [47], respectively. In addition, the previously identified atopic dermatitis susceptibility locus *TMEM232/SLC25A46* was also significantly associated with allergic rhinitis [31]. Further suggestive associations were found for SNPs in the *TSLP* (*Thymic stromal lymphopoietin*) gene.

Not surprisingly, GWAS reflect the genetic heterogeneity underlying allergic diseases. Although a few shared genetic loci exist among some allergic or asthmatic phenotypes, it is evident that each of these phenotypes has distinctive genetic determinants (fig. 1).

Pharmacogenetics in asthma

Current asthma treatments are based on inhaled corticosteroids (ICS), long and short acting β_2-adrenoreceptor agonists (LABAs and SABAs) as well as leukotriene antagonists. In the vast majority of patients symptoms are well-controlled with these conventional asthma therapies. However, approximately 20% of patients are not responsive to ICS, a phenotype often called "difficult to treat" or severe asthma [60, 61]. It is this form of asthma which shows an increased risk for exacerbations, hospitalisation and death.

Thus, there is a need for markers characterising patients who (1) benefit from a particular treatment and (2) exclude those at risk for side effects. Identification of responders and non-responders to certain (expensive) medications may also reduce costs for the treatment of severe asthma [62]. Pharmacogenetic studies show that genetic variation can determine and modify an individual's response to drugs. In asthma, most pharmacogenetic studies retrospectively in-
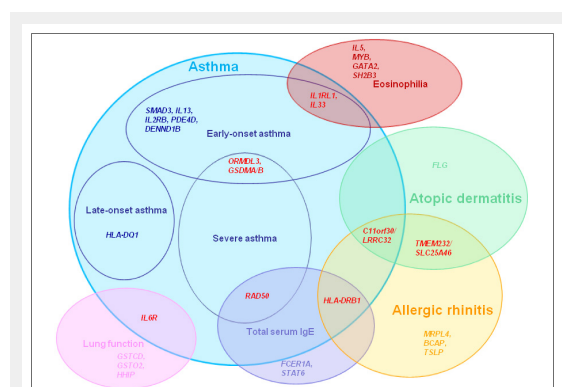

Figure 1

Major susceptibility loci for allergic diseases as identified by GWAS (Venn approach diagram). Genetic loci associated with different subphenotypes are shown in red.

Table 2: GWAS findings in allergic diseases other than asthma.

Phenotype	Genetic locus	Chromosome	Population*
Atopic dermatitis	*C11orf30*	11q13	European [56]
	FLG	1q21	European [56], Asian [57]
	TMEM232/SLC25A46	5q22	Asian [57]
	TNFRSF6B/ZGPAT	20q13	
Allergic rhinitis	*MRPL4*	19p13	Asian [59]
	BCAP	10q24	
	HLA-DQB1/HLA-DRB1	6p21	
	TMEM232/SLC25A46	5q22	European [31]
	TSLP	13q31	
	C11orf30/LRRC32	11q13	
*The term populations refers to the ethnicity of the original study.			

vestigated effects of medication on changes in FEV$_1$ or asthma exacerbations in relation to genetic variation in a specific candidate gene (or a candidate pathway), potentially involved in treatment-associated mechanisms. Here, we firstly discuss pharmacogenetic studies related to polymorphisms in the β$_2$-adrenoreceptor (*ADRB2*) important in SABA and LABA treatment. Then, we describe studies dealing with severe or "difficult to treat" asthma and finally we discuss the potential role of pharmacogenetics in treatment with biologicals, a new group of asthma medication only recently introduced to clinical practice.

The β$_2$-adrenoreceptor

Short and long acting β$_2$-adrenoreceptor agonists (SABAs and LABAs) are the most commonly prescribed reliever drugs in asthma, ameliorating bronchoconstriction and leading to long-term symptom control [63]. The primary target of β$_2$-adrenoreceptor agonists is the β$_2$-adrenoreceptor located on the surface of airway smooth muscle cells. The *ADRB2* gene, coding for this receptor, is a highly polymorphic locus with common and rare SNPs in exonic and regulatory regions of the gene. These SNPs are associated with asthma phenotypes and response to treatment [64].

When clinical and epidemiological studies reported that some patients were experiencing life-threatening symptoms and death following the use of β$_2$-adrenoreceptor agonists [65–67], the need to have a better understanding of individual differences to treatment responses became essential. Three polymorphisms leading to amino acid changes in the receptor, Arg16Gly, Gln27Glu and the rare Thr164Ile, have been the focus of *ADRB2* pharmacogenetic studies on SABA and LABA effects.

The Arg16Gly polymorphism is very common in Europeans; approximately 40% of the population carries an Arg16 allele. Patients with the Arg16Arg variation were more responsive to SABA treatment with albuterol [68]. However, Arg16Arg carriers had a reduced response compared to Gly16Gly carriers when albuterol was used regularly [69]. In case of severe asthma exacerbations, children with Gly16Gly showed a better response to albuterol [70]. It was speculated that these differences in response to SABA may be modified by further polymorphisms in the gene such as Gln27Glu [71].

To date it is unclear if the Arg16Gly genotype could be used to predict which patients will respond well to LABA treatment in combination with ICS and which are at increased risk for serious adverse effects. An initial retrospective study by the National Heart Lung and Blood Institute (NHLBI) Asthma Clinical Research Network (ACRN) suggested that patients with Arg16Arg showed a decline in lung function following combined LABA and ICS treatment [72]. The findings of a British cohort study consisting of children under regular use of salmeterol and children not taking salmeterol supported the idea that Arg16Arg carriers have a higher asthma exacerbation risk compared to Gly16Gly carriers [73]. Extending their cohort population, the authors investigated the risk of asthma exacerbations related to Arg16Gly polymorphism in young asthmatics under regular and "on demand" use of albuterol [74]. The increasing exacerbation risk effect of Arg16 was still evident in patients under regular use of SABAs or

LABAs. The results emphasise that carriers of Arg16 are at increased risk for exacerbation when either SABAs or LABAs are used as a regular reliever. Later studies consisting of asthmatic adults under combined LABA and ICS treatment showed no pharmacogenetic effect of Arg16Gly [75, 76]. Indeed comparative meta-analysis suggested that children have an augmented risk for adverse effects compared to adults but these differences (potentially due to small sample size in childhood studies) did not reach statistical significance [77].

Gln27Glu is in high linkage disequilibrium with Arg16Gly [78] and thus, Arg16Arg is predominantly combined with Gln27Gln. As a result Gln27Glu could be considered to act as a co-modifier of Arg16Gly effects. The combination of the two polymorphisms seems to affect the binding of the ligand to the ADRB2 receptor and the downstream signal transduction [79–81]. Similarly, Thr164Ile may potentially influence the binding of β$_2$-adrenoreceptor agonists. Despite its low frequency (<3% in European populations), the position of Thr164Ile polymorphism in one of the transmembrane domains suggests that it may affect ADRB2 function [80, 82] in a small fraction of the population carrying the polymorphisms and taking SABA or LABA.

Existing pharmacogenetic studies on *ADRB2* have provided initial evidence that genetic factors could be important in patients treated for asthma. However, due to study design, it is difficult to distinguish if *ADRB2* polymorphisms increase the risk for exacerbation *per se*, or if these effects are truly due to pharmacogenetic interaction with SABA and LABA. In prospective pharmacogenetic studies a comparison needs to be made between carriers of different *ADRB2* genotypes and use of either β$_2$-adrenoreceptor agonists or anticholinergics.

The corticosteroid pathway

Inhaled corticosteroids (ICS) represent the main and most effective anti-inflammatory controller treatment in asthma improving bronchial hyper-responsiveness and lung function while reducing asthma exacerbations [63, 83]. Corticosteroid function in asthma is not fully understood. In part, it may act on intracellular glucocorticoid receptors. Corticosteroids can inhibit the expression of pro-inflammatory molecules such as IL5 and IL6 while promoting the expression of regulatory cytokines such as IL10 [84, 85]. Furthermore, corticosteroids are potent regulators of histone acetylation, having significant epigenetic effects [86]. Asthmatic patients do not always respond to ICS and in severe asthma high doses of inhaled or even oral corticosteroids are often administered in an attempt to control symptoms [60, 87].

Three separate candidate gene studies conducted in the CAMP population suggested pharmacogenetic effects of variants in *CRHR1* (*Corticotropin-releasing hormone receptor 1*) [88], *TBX21* (*T box 21*) [89] and *FCER2* (*Low affinity receptor for IgE*) [90] in relation to ICS treatment. *CRHR1* variants significantly influenced lung function in patients receiving ICS [88]. However, the result could not be replicated in a following study [91]. In a second study in the same population, a rare SNP leading to an amino acid change in the Th1 cells induction transcription factor T-bet, modulated the effect of ICS treatment on bronchial

hyperresponsiveness [89]. In an independent study of mild to moderate Asian asthmatics receiving ICS, asthma control was more easily achieved in patients carrying the wild type alleles of *TBX21* H33Q and *NK2R* (*Neurokinin receptor 2*) G231E polymorphism [92]. As NK2 receptors can mediate bronchoconstriction it was plausible that this genetic variant was associated with increased FEV_1% in the same study [92].

Again in the CAMP study, the T2206C polymorphism in the *FCER2* gene was associated with severe exacerbations and increased IgE levels in severe asthmatic children receiving ICS but not in those not receiving medication [90]. *FCER2* gene encodes for the low affinity receptor for IgE, CD23. CD23 is a major regulator in allergic asthma and could be implicated in persistently elevated IgE levels seen in some asthmatics under ICS [93]. The effect was present in patients from European and African ancestry in the CAMP study. An independent study confirmed that the T2206C variant is a genetic marker for severe exacerbations in children with severe asthma despite increased use of ICS [94].

A recent GWAS aimed to examine pharmacogenetic effects in children on ICS (budesonide) [95]. The study found a number of suggestive hits in a small discovery cohort associated with improvement of lung function measurements after ICS treatment. After replication in additional small patient groups, further investigations focused on one of these polymorphisms located near *GLCCI1* (*Glucocorticoid-induced transcript 1* gene) [96]. Preliminary molecular studies suggest that polymorphism rs37973 may indeed influence gene function. The authors suggest that this SNP may be a marker for ICS response but further, independent replications and proper functional assessments are necessary before drawing conclusions.

Biological therapies for allergic diseases

The fact that there are asthma patients who do not respond well to current standard therapy leads to the development of novel drugs addressing specific immune-mechanisms thought to be important in asthma. A biological therapy which has already entered clinical practice is omalizumab, a humanised IgE monoclonal antibody used in both severe to moderate allergic asthma and allergic rhinitis [97, 98]. Treatment with omalizumab resulted in reduction of asthma exacerbations, hospitalisations and use of inhaled corticosteroids as well as improved lung function in a number of studies [99–101]. Serious adverse effects, in particular anaphylactic episodes, have been reported [102]. At present, a series of steps are recommended to be taken by the physicians to avoid anaphylactic reactions [103]. Considering the potential specificity of the action, potential side effects and the considerable cost of treatment, it is surprising how little effort has been made for proper matching of patients to this therapy.

Genetics could be one of the tools used for matching; others will be immunological and clinical profiling. Most likely, a combination of these approaches will be successful [104, 105]. Considering treatment costs of biologicals, matching is necessary and cost effective. It will increase acceptance of these expensive treatments with patients and the public. One obvious factor to be considered should be the T2206C polymorphism in the *FCER2* gene [90]. According to recent data, patients with elevated IgE and exacerbations induced by infections may also profit from omalizumab therapy [100].

Other biological therapies are mepolizumab, an anti-IL5 monoclonal antibody; the IL4 variant pitrakinra; and lebrikizumab, a humanised monoclonal antibody against IL13. Clinical trials including patients non-responsive to inhaled or oral corticosteroids and eosinophilic severe asthma showed that anti-IL5 can provide an effective treatment by acting on airway thickening and improving the disease exacerbations [106, 107]. Randomised, double-blind, placebo-controlled clinical trials on anti-IL13 and the IL4 variant resulted in the reduction of therapy-related adverse effects and significant improvement of lung function [108, 109]. In these studies, specific subphenotypes of asthma had been selected for clinical trials based on rather simple selection criteria. It is conceivable that subgroups of patients characterised by an aggravation of genetic variants in the IL4/IL13 pathway would be an even better target population for pitrakinra and lebrikizumab therapies [110].

So far, there are no pharmacogenetic studies published relating to biological treatments. However treatments in severe or "difficult to treat" asthmatics would be facilitated by the identification of molecular markers which could convincingly identify responders and those at increased risk for side effects. In these settings, pharmacogenetic information can be of great clinical importance.

Conclusion

When using genetics it becomes clear that asthma may not be just one disease but many. Different mechanisms may lead to different sub phenotypes, some of which are not sufficiently controlled with current therapy. Thus, genetic studies can contribute to the understanding of the disease and, in a second step, may improve diagnosis and therapy. Modern genetic tools such as GWAS and whole genome sequencing are now feasible in clinical studies and should be applied in pharmacological trials. The ultimate goal would be to apply a personalised approach in respiratory medicine, to which genetics can contribute. This would increase the efficacy and safety of treatment and reduce side effects.

Correspondence: Michael Kabesch, MD, KUNO Children's Hospital Regensburg, Department of Pediatric Pneumology and Allergy, Campus St. Hedwig, Steinmetzstr. 1–3, DE-93049 Regensburg, Germany, kabesch.michael[at]barmherzige-regensburg.de

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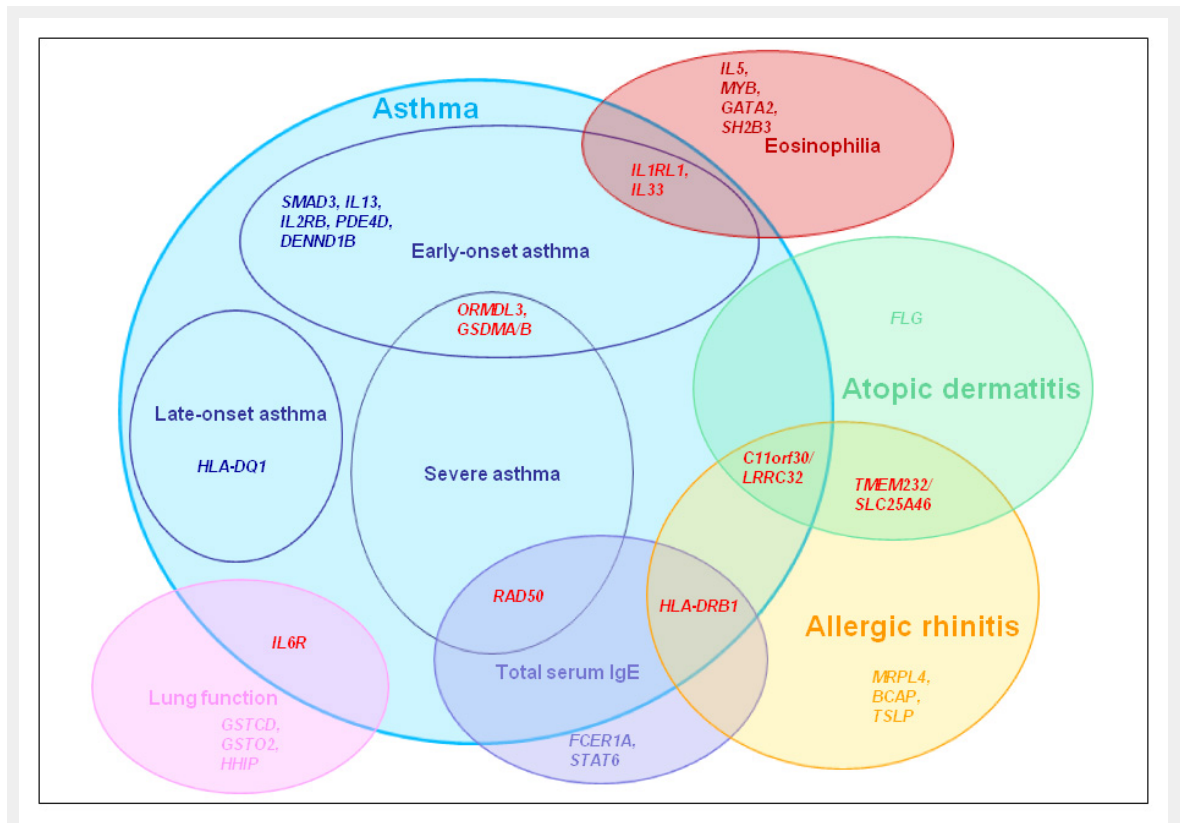
Figures (large format)

Figure 1

Major susceptibility loci for allergic diseases as identified by GWAS (Venn approach diagram). Genetic loci associated with different subphenotypes are shown in red.