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Asthma 2020 3

The genetics of asthma and the promise of genomics-guided drug target discovery

Zaid W El-Husseini, Reinoud Gosens, Frank Dekker, Gerard H Koppelman

Asthma is an inflammatory airway disease that is estimated to affect 339 million people globally. The symptoms of about 5–10% of patients with asthma are not adequately controlled with current therapy, and little success has been achieved in developing drugs that target the underlying mechanisms of asthma rather than suppressing symptoms. Over the past 3 years, well powered genetic studies of asthma have increased the number of independent asthma-associated genetic loci to 128. In this Series paper, we describe the immense progress in asthma genetics over the past 13 years and link asthma genetic variants to possible drug targets. Further studies are needed to establish the functional significance of gene variants associated with asthma in subgroups of patients and to describe the biological networks within which they function. The genomics-guided discovery of plausible drug targets for asthma could pave the way for the repurposing of existing drugs for asthma and the development of new treatments.

Introduction

Asthma is a heterogeneous, inflammatory airway disease that is associated with remodelling of the airways. Patients with asthma have symptoms such as shortness of breath and wheezing, due to airway obstruction and airway hyper-responsiveness.¹ Asthma is the leading chronic disease of childhood,² but is also common in the adult population.³ This prevalent disease affects 339 million people worldwide and the total is expected to reach 400 million by 2025.^{4,5} The rising prevalence and associated burden of asthma^{4,5} add weight to the importance of understanding the underlying disease mechanisms and finding novel treatments. Current asthma therapy, which is based mainly on inhaled corticosteroids and bronchodilators, suppresses symptoms rather than changing the natural history of the disease, and is not sufficient to control symptoms in 5–10% of patients.⁶ Asthma is considered to be a complex disease because of its polygenic nature; the environment also plays a part in triggering the disease. The combination of and possible interaction between multiple environmental factors and the genetic makeup of individuals makes asthma a truly multifactorial disease.⁷ Twin studies suggest that the heritability of asthma can be as high as 60–70%,⁸ which implies that understanding the genetic basis of asthma might unravel many disease-causing mechanisms.

In the past 30 years, interest in gaining a better understanding of the genetic risk factors for asthma has increased. These risk factors are largely single base-pair variations, known as single-nucleotide polymorphisms (SNPs), which are genetic variants with an allele frequency of more than 1% in the population, occurring on average in one in every 300 nucleotides.⁹ In 2002, an array technique was introduced that enabled genotyping of hundreds of thousands of SNPs in one experiment, so-called genome-wide genotyping.¹⁰ Selection of SNPs on these arrays took advantage of increasing insight into the genetic architecture of human populations, revealing

the correlation of SNPs that are in close vicinity to each other. This approach made genome-wide association studies (GWASs) possible in large groups of people with and without asthma.^{11,12} Sample sizes went up from more than 1000 cases and controls, to tens of thousands, and in the most recent GWAS hundreds of thousands of participants.¹³ These GWASs have included large populations and rigorous assessments of multiple testing and replication, and have accelerated the acquisition of knowledge about the genetic basis of asthma.

In the past 3 years, collaborative studies with large sample sizes have increased our understanding of the

Key messages

- Asthma is a multifactorial disease caused by both genetic and environmental factors
- Identification of genetic factors that increase the risk of asthma can provide insight into disease-causing mechanisms and, ultimately, novel targets for asthma therapeutics
- A review of genome-wide association studies allowed the identification of 128 independent single-nucleotide polymorphisms that are associated with asthma (97 reported in the past 3 years)
- Functional interpretation of these polymorphisms enabled the proposal of 161 possible drug targets for asthma
- Of these 161 possible drug targets, 16 are already targeted by existing asthma drugs
- Identified genes that encode cell-surface receptors, which are classical drug targets, include *IL7R*, *CCR7*, *IL2RB*, *GPR183*, and *ITGB8*
- The concept of genomics-based drug repositioning should be explored in future studies; proposed therapies for asthma include olamkicept, which targets the IL-6 trans-signalling pathway, and the NOD2 activator inarigivir soproxil, which targets innate immunity

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This is the third in a *Series* of three papers about reducing the burden of asthma (paper 1 appears in *The Lancet*)

For the *Asthma 2020 Series* see www.thelancet.com/series/asthma-2020

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Panel: Methods

The asthma single-nucleotide polymorphisms (SNPs) identified in this Series paper were independently associated with asthma at a genome-wide significance threshold of $p < 5 \times 10^{-8}$ in populations of European ancestry, with a linkage disequilibrium $r^2 < 0.05$ between associated SNPs. The method is described by Vicente and colleagues.²¹ We added additional SNPs reported between Oct 30, 2017, and April 4, 2019. In more recent studies, which used the 1000 Genomes Project reference panel (1000G) for imputation, a more stringent significance threshold of $p < 3 \times 10^{-8}$ was used for genome-wide significance.

The independence of the SNPs identified was tested using LD Matrix on LDLink for European populations, with a cutoff of $r^2 < 0.05$.²⁶ When two SNPs were found to be in high linkage disequilibrium, the most significant SNP was selected. All the information about the base pair, reference allele, alternative allele, and alternative allele frequency of the top SNPs was acquired using SNP-Nexus and Ensembl gene/protein consequence. European population data from the 1000 Genomes Project filters were applied and GRCh37 (hg19) was used as the reference genome.

Target genes were found linking asthma SNPs to expression quantitative trait locus (eQTL) databases and databases describing amino acid changes. First, eQTLs that were mentioned in 2017 and 2019 by Ferreira and colleagues^{19,24} were added. Second, the same annotation strategy as described by Vicente and colleagues²¹ was applied ($p < 2.3 \times 10^{-9}$). The eQTL data files were downloaded from GTEx,²⁷ Blood eQTL browser,²⁸ and NESDA-NTR catalog.²⁹ In the GTEx download, we selected lung, spleen, lymphocytes, fibroblasts, whole blood, skin exposed to sun, and skin not exposed to sun as described previously by Vicente and colleagues.²¹ We interrogated all SNPs in linkage disequilibrium with our top asthma SNPs ($r^2 > 0.8$) in the European population, which were selected by LDLink (appendix 1 sheet 9). For possible coding variation, all SNPs in linkage disequilibrium with our top SNPs were applied to SNP-Nexus, RefSeq, Ensembl, and UCSC genome browser were selected to predict the consequences. Sift and Polyphen were used to predict the effect of non-synonymous coding SNPs on protein function.

For LDLink see <https://ldlink.nci.nih.gov/>

For SNP-Nexus see <https://www.snp-nexus.org/v4/>

For GTEx see <https://www.gtexportal.org/home/>

For the Blood eQTL browser see <https://genenetwork.nl/bloodeqtlbrowser/>

For the NESDA-NTR catalog see <https://eqtl.onderzoek.io/>

See Online for appendix 1

genetic basis of asthma at an unprecedented pace. In this Series paper, we describe the current state of the art in asthma genetics. We provide an update of genetic findings from GWASs and—using expression quantitative trait locus (eQTL) mapping and coding variation—we link asthma-associated SNPs to possible drug targets. On the basis of our analysis, we propose novel drug targets and consider the possibility of genomics-based drug repositioning for the treatment of asthma.¹⁴ Finally, we discuss the limitations of GWAS and eQTL analyses and outline future directions for the field.

GWASs in asthma

The first GWAS of asthma was published in 2007 by Moffatt and colleagues.¹⁵ This study reported that genetic variation at chromosome 17q12–21 is associated with childhood asthma. Asthma-associated SNPs in this locus were related to levels of mRNA expression of *ORMDL3* in lymphoblastic cell lines using eQTL mapping, which associates SNPs with gene expression. Subsequent investigations also linked SNPs at this locus to *GSDMA*, *GSDMB*, *CRKRS*, *ZBPB2*, and *IKZF2* expression in whole blood cells and lung tissue.^{16–18} The 17q12–21 locus was associated with childhood-onset asthma but not adult-onset asthma, as was later confirmed by other

studies.^{19,20} This association illustrates that genetic risk factors might be particularly important for subgroups of patients with asthma. These findings also showed the use of eQTL mapping to link disease SNPs to target genes.

In 2017, Vicente and colleagues²¹ summarised all findings from GWASs of asthma that had been published between 2007 and 2016. In total, 119 asthma-associated genetic variants were reported, although many of these variants were not independent. Genetic variants that occur closely together on the genome can be correlated in populations, a dependency that is termed linkage disequilibrium. It is therefore possible that closely correlated SNPs in a given locus all associate with asthma, yet reflect only one independent signal. On the basis of an analysis of the independence of SNPs (linkage disequilibrium correlation [r^2] cutoff < 0.05), a list of 31 top SNPs (independent SNPs with low linkage disequilibrium and highest significance) was generated.²¹ In the past 3 years, five well powered GWASs of asthma have been published (appendix 1 sheet 1).^{19,22–25} We therefore extended the list of Vicente and colleagues by adding all published results from Oct 30, 2017, to April 4, 2019, using the same methodology (panel), leading to an updated list of 128 independent asthma-associated SNPs (figure 1; appendix 1 sheet 2). Notably, asthma GWASs have been done mainly in populations of European descent, with a very small number of studies analysing other ethnic groups. Studies of populations of non-European descent are urgently needed. Having identified asthma-associated SNPs, the next challenge is to link them to potential target genes to better understand how these SNPs might cause asthma.

Linking GWAS SNPs to target genes

Approximately 88% of the disease-associated variants acquired from GWASs reside in non-coding regions.³⁰ eQTL analysis is able to identify genetic variation that is involved in gene expression within a particular tissue or cell type. An SNP within a gene or in close vicinity (within 1 Mbp) of the gene that is associated with gene expression is called a cis-eQTL. We annotated the top 128 asthma-associated SNPs (panel) using published cis-eQTL datasets from the blood, lungs, spleen, lymphocytes, fibroblasts, and skin, as described previously.²¹ Consequently, 161 target genes were significantly related to the top asthma SNPs in one or more studies (appendix 1 sheet 3), with 154 unique target genes and seven genes overlapping. We observed that 30 top asthma SNPs were linked to multiple gene transcripts, which might be because one SNP functionally regulates multiple genes, or that SNPs that are in high linkage disequilibrium with the asthma-associated SNP are eQTLs for other genes. Moreover, we observed that publicly available eQTL data are absent for many asthma-associated cells and tissues, such as type 2 innate lymphoid cells, eosinophils, or airway smooth muscle cells, limiting interpretation of eQTL signals.

Coding mutations can cause changes in protein function through altering the amino acid sequence. Such mutations could alter mRNA splicing, which can lead to a truncated protein, or alter codons to give different amino acids.^{31,32} Amino acid changes can affect the protein shape, subcellular localisation, and function or binding properties, and potentially protein concentrations by affecting protein degradation. We therefore also linked the 128 top asthma-associated SNPs to coding changes (panel) and identified 35 coding variants. Of these variants, 18 were non-synonymous (appendix 1 sheet 4), and two different variants were found in two genes, toll-like receptor 1 (*TLR1*) and regulator of telomere elongation helicase 1 (*RTEL1*). In total, 16 genes were considered as target genes on the basis of protein coding variants. For three of these coding changes, functional studies have been done. Basnet and colleagues³³ studied the effect of cadherin-related protein 3 (*CDHR3*) SNP (rs6967330), associated with severe childhood asthma. Risk allele A (adenine) was found to be associated with higher *CDHR3* protein expression and increased rhinovirus C binding and replication in epithelial cells compared with the protective allele G (guanine). Another study, by Lundtoft and colleagues,³⁴ investigated *IL7R* SNP (rs6897932). In this case, the risk allele (C [cytosine]) was associated with higher soluble IL-7 receptor α chain (IL-7R α) serum concentrations compared with the protective allele (T [thymine]). Finally, two studies investigated the *IL6R* SNP (rs2228145), which induces the IL-6 trans-signalling pathway by increasing soluble IL-6 receptor (IL-6R) concentrations.^{35,36}

On the basis of these analyses, we generated a list of 161 asthma target genes from both the eQTL genes (154 genes) and genes with non-synonymous mutations (16 genes; appendix 1 sheet 5). Nine target genes were implicated by both eQTL and protein coding variants by different SNPs within that gene (*IL6R*, *RTEL1*, *HLA-DQA1*, *ZBPB2*) or by SNPs that lead to coding changes but also had eQTL effects (*IL7R*, *GSDMB*, *NOD2*, *TESPA1*, *TLR1*).

Asthma-associated gene networks

GWASs can be used to identify biological networks underlying complex diseases. We hypothesised that the asthma target genes do not act in isolation, but might cluster in networks that are biologically relevant for disease development (figure 2). Identification of these networks might point to new opportunities for downstream intervention. This pathway blocking approach is often used in cancer therapeutics, as one type of cancer can be due to different genetic mutations in different patients, yet can be treated by blocking a common downstream pathway. Examples of pathways or networks that are implicated by GWASs in asthma are the IL-33–IL-1RL1 receptor pathway, leading to eosinophilia,³⁷ and the T-helper-2 (Th2) cytokine IL-5 and

Figure 1: Top SNPs associated with asthma in GWASs of populations of European descent between 2007 and 2019

Some of the SNPs were labelled as well known asthma genes on the basis of their physical location. GWAS=genome-wide association study. SNP=single-nucleotide polymorphism.

IL-4RA receptor, leading to eosinophilia and type 2 inflammation or viral response (*CDHR3*, *ORMDL3*).^{33,38} Therefore, we submitted our list of 161 asthma target genes to several pathway analysis tools, such as Reactome, Integrating Network Objects with Hierarchies Pathway Database (INOH), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Wikipathways, implemented in the programme Drug Research Advisor, which was accessed on June 18, 2019. 47 pathways were found with gene enrichment, with between three and eight genes in each pathway (appendix 1 sheet 6). We observed a dominance of immune pathways, strongly driven by MHC II, and cytokines and their receptors (IL-33, IL-1RL1, IL-6R, IL-2). Prominent examples are IL-2 and IL-4 signalling, as well as Th2 pathways, T-cell-to-B-cell interaction pathways, as well as adenosine A1 receptor signalling pathways. We also found evidence for IL-16 signalling, CXC3-B signalling, and CCL19-mediated and CCL21-mediated chemotaxis. Notably, 71 (44%) of 161 asthma target genes were not annotated to any pathway. Examples include *GSDMB*, *WDR36*, *ADAMTS4*, and *PEX14*, which indicates that the current biological interpretation of asthma target genes is limited by the absence of functional evidence.

Target discovery and drug repositioning

Drug development takes about 13–15 years, from drug design to market approval, and costs more than US\$2 billion on average.³⁹ After entering the first clinical phase, new molecules have a 10% chance of being approved by regulatory agencies and reaching the market.⁴⁰ For a drug to be effective, it needs to be targeted to a protein involved in the causal pathway of the disease or to a physiological repressor of such a causal pathway. After drug target validation, drug development is still a time-consuming process, including toxicology studies,

shown that drugs targeting proteins implicated by genetic studies have about twice the success rate of reaching the market (from phase 1 to approval) than drugs developed for targets without genetic evidence.⁴¹ Although no examples of genomics-based target discovery exist in the respiratory field, an example from the lipid field might illustrate its potential: proprotein convertase subtilisin/kexin type 9 (PCSK9) is a target linked to cardiovascular disease on the basis of genetic studies. Previously, it was reported that nonsense mutations that cause loss of function in *PCSK9* are associated with lower plasma concentrations of LDL.⁴³ Another common SNP in *PCSK9* was reported to be associated with LDL cholesterol based on a GWAS.⁴⁴ Two monoclonal antibodies were launched to inhibit PCSK9, evolocumab and alirocumab, which lowered LDL cholesterol concentrations in clinical trials by 60% and 40%, respectively.^{45,46} Genetics can also be used to help to predict target side-effects, such as individuals that have so-called protective genetic variants. For example, those who have a rare genetic variant (rs146597587-C) in *IL33* have a lower risk of asthma development, and lower circulating blood eosinophils. This rare variant is related to less production of the IL-33 protein and reduced binding to its receptor.⁴⁷ Individuals with this rare allele do not appear to be at risk for other diseases, which suggests that it is safe to reduce IL-33 concentrations or partly block IL-33 function. However, genomics cannot predict off-target effects.

We filtered our list of 161 target genes (appendix 1 sheet 5) by crosschecking this list with a drug target list from Drug Research Advisor—Target Druggability. This database, developed by Clarivate Analytics, combines genetic data, proteomic data, and drug intelligence data to generate specific information about each target, such as drug availability, drug status, specific pathways, and target novelty for a specific condition. This comprehensive database is up-to-date, but not a free service, and addresses specific targets rather than implicated pathways. First, we excluded *HLA* and non-coding genes, which resulted in 142 protein coding genes, and found that 16 (11%) of the 142 targets had previously been targeted for asthma, including *TNF* and *IL4R* (appendix 1 sheet 7). We split the 142 potentially novel targets into two categories. First, for drug target discovery, targets for which drugs are in phase 1 clinical development or earlier were selected. Second, for drug repositioning, targets for which drugs are under development in phase 2 clinical trials or higher phases of clinical development were selected (figure 3).

The genes filtered using the Drug Research Advisor database left us with 120 targets to be considered for drug target discovery, of which four are not novel to asthma development (appendix 1 sheet 7). We filtered the genes further using the druggable genome list presented in the Drug Gene Interaction Database to

Figure 3: Target-filtering steps using Drug Research Advisor

This flowchart shows target filtration for asthma by drug target discovery and drug repositioning.

yield 32 druggable targets.⁴⁸ The druggable genome concept was presented by Hopkins and Groom in 2002.⁴⁹ The druggable genome represents those genes that encode proteins with the potential of being targeted by small-molecule therapeutic agents. The druggable genome list has been updated three times since its initial publication.^{50–52} From the list of 32 targets generated as such, we excluded ten targets that were reported previously to end up with 22 novel targets (table 1).²¹ These 22 targets were grouped into seven classes (enzyme, cell-surface receptor, carrier, ion channel, structural protein, transcription factor, and other). Cell-surface receptors make interesting drug candidates, as they can easily be activated by agonists or antagonised by competitive antagonists or ligand-directed or receptor-directed antibodies. Accordingly, we chose to highlight here the target genes that encode receptors: *IL7R*, *CCR7*, *IL2RB*, *ITGB8*, and *GPR183*.

IL-7Rα, encoded by the *IL7R* gene, is expressed most abundantly in T cells, but also in a variety of other cells such as dendritic cells, natural killer (NK) cells, and pre-B cells.⁵³ *IL-7Rα* binds to IL-7 or thymic stromal lymphopoietin and then transduces their signals through the formation of a heterodimeric complex with the common γ chain (*IL-2R γ*) for IL-7 and cytokine receptor-like factor 2 (*CRLF2*) for thymic stromal lymphopoietin. The cytoplasmic tail of *IL-7Rα* directly associates with JAK1, which initiates intracellular signalling together with *IL-2R γ* to activate JAK3, whereas in a complex with *CRLF2*, JAK1 and JAK2 are activated (appendix 2 p 1).⁵⁴ These interactions can activate at least three downstream pathways: JAK–STAT,⁵⁵ PI3K–Akt–mTOR,⁵⁶ and MEK–ERK,⁵⁷ which might have a regulatory role in type 2 inflammation, as mice treated with an antibody against *IL-7Rα* showed improved lung function and reduced eosinophilic inflammation, associated with reduced

See Online for appendix 2

	Protein target	Class of protein	Highest phase of development	Drugs at highest phase
SLC22A4	Solute carrier family 22 member 4	Carrier	No drug	..
SLC25A46	Solute carrier family 25 member 46	Carrier	No drug	..
SLC44A4	Solute carrier family 44 member 4	Carrier	Phase 1	ONCR-177
CHIT1	Chitinase 1	Enzyme	Phase 1	OATD-01
ENDOG	Endonuclease G	Enzyme	No drug	..
ERMP1	Endoplasmic reticulum metalloproteinase 1	Enzyme	No drug	..
HSD17B8	Hydroxysteroid 17- β dehydrogenase 8	Enzyme	No drug	..
PHOSPHO1	Phosphoethanolamine/phosphocholine phosphatase 1	Enzyme	Biological testing	862572, ML-086, 862569
SIK2	Salt-inducible kinase 2	Enzyme	Investigational new drug filed	ARN-3261
SPPL3	Signal peptide peptidase-like 3	Enzyme	No drug	..
SUOX	Sulfite oxidase	Enzyme	No drug	..
TRIM27	Tripartite motif-containing 27	Enzyme	No drug	..
ITPR3	Inositol 1,4,5-trisphosphate receptor type 3	Ion channel	Preclinical	2-APB
C4A	Complement C4A (Rodgers blood group)	Other protein	No drug	..
CHI3L1	Chitinase-3-like 1	Other protein	Preclinical	G-721-0282, 1055440, 1054419, 1021662, mja-miR-35
CCR7	C-C motif chemokine receptor 7	Receptor	Preclinical	CAP-100, CCX-662
GPR183	G protein-coupled receptor 183	Receptor	Biological testing	SAE-1, SAE-14
IL2RB	Interleukin-2 receptor subunit β	Receptor	Preclinical	IOV-3001, MDNA-209, MDNA-19, H-9
ITGB8	Integrin subunit β -8	Receptor	No drug	..
IL7R	Interleukin-7 receptor	Receptor	Phase 1	GSK-2618960, OSE-127
EFEMP2	EGF-containing fibulin extracellular matrix protein 2	Structural protein	No drug	..
PA2G4	Proliferation-associated 2G4	Transcription factor	No drug	..

This table lists novel potential drug targets for asthma. Targets with genetic support were filtered based on the phase of the drug targeting them and other criteria.

Table 1: Novel druggable targets in asthma

specific IgE and Th2 cytokines, in response to house dust mite exposure.⁵⁸ The *IL7R* non-synonymous SNP (rs6897932) is associated with asthma. This SNP is located in exon 6, which affects the extracellular domain of the protein by alternative splicing exon 6 in *IL7R*.⁵⁹ Furthermore, eQTL analysis showed that the coding SNP (rs6897932), risk allele (C), is also associated with higher transcript abundance than the T allele in whole blood. Moreover, one of the ligands for this receptor (ie, thymic stromal lymphopoietin) is an asthma gene. eQTL analysis shows that the risk allele (G) of *TSLP* SNP (rs10073816) is associated with higher *TSLP* gene expression in whole blood. IL-7R is targeted by 16 drugs, with one drug being assigned for asthma in preclinical studies. However, for *TSLP* and *CRLF2*, there are 14 drugs assigned for asthma, with one drug, tezepelumab, in phase 3 clinical trials for patients with uncontrolled asthma.⁶⁰

C-C motif chemokine receptor 7 (*CCR7*), encoded by *CCR7*, was previously named EB11. *CCR7* is a member of the G protein-coupled receptor superfamily, and acts as a receptor for the chemokines CCL21 and CCL19. This receptor is expressed in immune cells such as B cells, dendritic cells, and T cells. *CCR7* is involved in the regulation of many aspects of the immune response,

since it has an important role in the homing of T cells and dendritic cells to the lymph nodes.⁶¹ When interacting with CCL19, *CCR7* can activate either direct G protein signalling or β -arrestin signalling, which leads to internalisation of the receptor. However, when binding to CCL21, it appears to display G protein signalling only.⁶¹ As such, *CCR7* appears to have a crucial role in the exiting of T cells from the lung to the draining lymph nodes.⁶² According to eQTL analysis, the risk allele of *CCR7* SNP (rs7226035) is upregulated in patients with asthma in lymphoblastoid cell lines. There are 18 drugs targeting *CCR7*, all novel to asthma; the highest phase of investigation is preclinical studies for glioblastoma multiforme and lymphocytic leukaemia.

Interleukin-2 receptor subunit β (*IL-2R β*), encoded by the *IL2RB* gene, is expressed mainly on immune cells such as CD4+ and CD8+ T cells, NK cells, and B cells.⁶³ *IL-2R β* is part of the IL-2 receptor protein complex. The IL-2R subtypes can assemble in different ways to yield low-affinity, medium-affinity, or high-affinity complexes for its ligand, IL-2. The low-affinity IL-2 receptor is composed of the *IL-2R β* subunit alone, the medium-affinity form is composed of *IL-2R β* and *IL-2R γ* subunits, and the high-affinity form is composed of the three

subunits IL-2R α , IL-2R β , and IL-2R γ .⁶⁴ The interaction between IL-2R and its ligand activates three major pathways: RAS–MEK–MAPK, PI3K–AKT–mTOR, and JAK–STAT.⁶⁵ IL-2R α can also bind to IL-15 together with IL-2R γ to activate the same downstream pathways.⁶³ Mice with IL-2R α deficiency have severe autoimmunity and reduced CD8⁺ cell function; they also have spontaneous activation of T cells, which can result in more B-cell differentiation and thus a high concentration of immunoglobulin and autoantibodies.⁶⁶ This finding shows the important role of IL-2R α in keeping the T-cell activation system under control, maintaining homeostasis, and preventing autoimmunity. Several studies reported a significant association between asthma and the *IL2RB* SNP (rs2284033).^{67–69} According to the eQTL analysis, the SNP risk allele (G) is associated with higher *IL2RB* gene expression in whole blood and skin. There are three drugs in preclinical development for this target. Moreover, *IL2RA* is also one of the targets generated by eQTL analysis. The risk allele of *IL2RA* is associated with its upregulation. A drug targeting IL-2R α , daclizumab, already exists and reached clinical phase 2.⁷⁰ However, it was withdrawn in 2018 because of reports of inflammatory encephalitis and meningoencephalitis.⁷¹

G protein-coupled receptor 183 (GPR183), also known as EBI2, is encoded by *GPR183*. This gene is highly expressed in B lymphocytes, lymphoid tissue such as the spleen and lymph nodes, and lung tissue.^{72,73} The receptor can function in different ways. First, it acts as a receptor to oxysterols (eg, 7- α ,25-OHC).⁷⁴ Oxysterols are chemotactic agents that direct the migration of the immune cells expressing GPR183. Therefore, this receptor has an important role in immune cell migration and in the adaptive immune response.⁷⁵ It can also form a heterodimer receptor complex with CXCR5 and modulate its interaction with CXCL13.⁷⁵ The heterodimer receptor complex has a higher binding affinity for CXCL13 than for CXCR5 alone, and efficacy in cells expressing both receptors.⁷⁵ This interaction has an important role in B cell migration to lymphoid follicles and generation of an antibody response. *GPR183* SNP (rs9517642) is in high linkage disequilibrium ($r^2=0.95$) with one of the top SNPs (rs1319132) associated with asthma. The risk allele of the SNP (A; the top SNP risk allele is C=A in this SNP) is associated with lower gene expression ($\beta -0.796$) in blood. There are two drugs in preclinical studies for this target. Both drugs are GPR183 antagonists and are being tested as a treatment for neuropathic pain.⁷⁶

Integrin subunit β -8 (ITG β -8) is a protein encoded by *ITGB8*. This subunit associates with integrin subunit α -V to form a heterodimer receptor complex called integrin α v β 8, which is expressed on airway epithelial cells and fibroblasts.⁷⁷ Integrin α v β 8 has a high affinity for the latency-associated peptide, which has a non-covalent association with transforming growth factor- β 1 (TGF- β 1) and TGF- β 3; α v β 8 is therefore considered to be an

essential mediator for TGF- β activation.⁷⁸ TGF- β has a role in the homeostasis of immune cells and airway remodelling in asthma.^{79,80} TGF- β signalling has a dual function: it can be proinflammatory in airway epithelial cells through its role in the development of T-helper-17 cells, or anti-inflammatory through the induction of regulatory T cells (Tregs).⁸¹ Integrin α v β 8-mediated activation of TGF- β can also affect dendritic cell trafficking and migration to the lymph nodes.⁸¹ Functional experiments done in mice without α v β 8 show that this complex is required for dendritic cell-mediated Treg induction in colonic tissue.⁸² Another study indicated that *ITGB8*^{-/-} mice have elevated pulmonary inflammation at baseline.⁸³ According to our analysis, *ITGB8* has a nonsense mutation (rs2230398) resulting in premature termination in exon 6 that is in high linkage disequilibrium ($r^2=0.89$) with one of the top SNPs (rs6461503) associated with asthma. Unfortunately, there are no publications on this mutation and also no drugs for this target.

Drug repositioning

The concept of drug repositioning refers to the identification of a drug either on the market or under development for a certain condition, with the aim of repurposing it for another condition. This approach increases drug development efficiency and lowers cost and time as the safety profile has been established already.⁸⁴ Of 142 asthma target genes, 22 were annotated as targets with drugs that are either currently available or in clinical studies of phase 2 or higher. We continued with these 22 targets, of which 12 were not novel to asthma development (appendix 1 sheet 7) and selected the ten targets that are novel for asthma (figure 3). Drugs for three of these targets have already been launched (tucidinostat and vorinostat for *HDAC3*, sarilumab and tocilizumab for *IL6R*, and norfloxacin for *SLC22A5*), one is in a phase 3 clinical trial (*APOA2*), five are in phase 2 clinical trials (drugs targeting *ERBB3*, *NOD2*, *TLR6*, *LTA*, *PSMB9*), and one is in a clinical trial combining phase 1 and 2 (a drug targeting *EP300*; table 2; appendix 1 sheet 8). We subsequently verified whether the drug antagonises the direction of effect of the asthma risk allele. When a risk allele upregulates a gene product, the drug should block or downregulate this gene product. Here, an important assumption is that increased amounts of mRNA relate to increases in protein concentration. Of note, for 13 of the coding SNPs, it was not possible to predict the direction of function (appendix 1 sheet 4). We highlight two prominent targets, *IL6R* and *NOD2*.

IL-6R α is a receptor encoded by *IL6R*. This receptor is strongly expressed on the surface of immune cells such as neutrophils and macrophages.⁸⁵ IL-6 pathway activation occurs upon interaction of the ligand IL-6 with the receptor IL-6R α in combination with gp130 to form a hexameric complex (appendix 2 p 2).⁸⁶ IL-6 can activate two signalling pathways, the IL-6 classic signalling pathway (IL-6 cis-signalling pathway) or the IL-6

	Protein target	Molecular mechanism	Condition	Phase of development
Olamkicept	IL-6R	Anti-soluble IL-6R α	Ulcerative colitis	Phase 2
Inarigivir soproxil	NOD2	NOD2 activator	Chronic hepatitis B infection	Phase 2*
Norfloxacin	SLC22A5	SLC22A5 inhibitor	Infection, bacterial infection	Launched
Pelacarsen	APOA	APOA expression inhibitor	Cardiovascular disorders	Phase 3
ISIS-494372	APOA	APOA expression inhibitor	Atherosclerosis	Phase 2
KZR-616	PSMB9	PSMB9 inhibitor	Autoimmune haemolytic anaemia	Phase 2
CCS-1477	EP300	P300 inhibitors	Cancer, prostate cancer	Phase 1–2
Tucidinostat	HDAC3	HDAC3 inhibitor	Peripheral T-cell lymphoma	Launched
Vorinostat	HDAC3	HDAC3 inhibitor	Cutaneous T-cell lymphoma	Launched
Fimepinostat mesylate	HDAC3	HDAC3 inhibitor	Cancer, thyroid cancer	Phase 2
Domatinostat tosylate	HDAC3	HDAC3 inhibitor	Digestive-gastrointestinal cancer	Phase 2
CG-745	HDAC3	HDAC3 inhibitor	Myelodysplasia	Phase 1–2
Tinostamustine	HDAC3	HDAC3 inhibitor	Multiple myeloma	Phase 1–2
Nanatinostat	HDAC3	HDAC3 inhibitor	Lymphoma	Phase 1–2
Sarilumab	IL-6R	Anti-IL-6R α	Rheumatoid arthritis	Launched
Tocilizumab	IL-6R	Anti-IL-6R α	Castleman's disease, rheumatoid arthritis	Launched
Satralizumab	IL-6R	Anti-IL-6R α	Neuromyelitis optica	Registered
Levilimab	IL-6R	Anti-IL-6R α	Rheumatoid arthritis	Phase 3
Vobarilizumab	IL-6R	Anti-IL-6R α	Rheumatoid arthritis	Phase 2
Zenocutuzumab	ERBB3	Anti-HER3	Cancer, breast cancer	Phase 2
Duligotuzumab	ERBB3	Anti-HER3	Colorectal cancer therapy	Phase 2
Patritumab	ERBB3	Anti-HER3	Cancer, breast cancer	Phase 2
PUL-042	TLR6	TLR6 agonist	Rhinovirus, COVID-19	Phase 2
Pateclizumab	LTA	Anti-LTA	Rheumatoid arthritis	Phase 2

This table shows drugs that could potentially be repurposed for asthma. The first seven drugs in the list have the potential to antagonise the direction of effect of the asthma risk allele. *Discontinued because of serious adverse events.

Table 2: Proposed drugs for repositioning in asthma

trans-signalling pathway. The cis-signalling pathway is activated in cells that can express IL-6R α , whereas cells that cannot express IL-6R α can use the trans-signalling pathway. In the trans-signalling pathway, IL-6 interacts with soluble IL-6R α and gp130, which is expressed in all cells.⁸⁷ Soluble IL-6R α is produced by alternative splicing or cleaved from the membrane by ADAM10 or ADAM17.^{88,89} The IL-6 trans-signalling pathway is considered to be pro-inflammatory, whereas the IL-6 cis-signalling pathway, which supports Tregs, is anti-inflammatory.⁹⁰ In our data, one of the top SNPs associated with asthma (rs4129267) is in high linkage disequilibrium with a non-synonymous SNP (rs2228145), which maps to the cleavage site of IL-6R. The SNP risk allele for asthma (C) is associated with higher soluble IL-6R concentrations in serum, which increases IL-6 trans-signalling and therefore leads to more inflammation.^{91,92} Previous efforts attempted to target the IL-6 pathway through binding of IL-6 with antibodies (eg, siltuximab for Castleman's disease), targeting IL-6R α with antibodies (eg, sarilumab for rheumatoid arthritis), or targeting the downstream pathway such as JAK or STAT3 (eg, tofacitinib, C188-9).^{93–96} All these methods blocked both classic signalling and trans-signalling pathways. Selective inhibition of IL-6 trans-signalling through soluble IL-6R binding might have

anti-inflammatory effects, which was made possible with the introduction of olamkicept, a soluble gp130 fusion protein positioned for the treatment of infertility and ulcerative colitis in phase 2 clinical trials. Theoretically, this drug is able to selectively inhibit the IL-6 trans-signalling pathway and might have the potential to benefit patients with asthma—in particular, those with transcriptional evidence of epithelial activation of the IL-6 trans-signalling pathway. Recently, it was shown that these patients do not overlap with patients with severe asthma with a type 2-high gene expression signature.⁹⁷ IL-6 is not a novel target for asthma, and drugs targeted at IL-6 had side-effects (eg, sirukumab).⁹⁸ However, by modifying this pathway in a more specific way through modulation of IL-6 trans-signalling only, the efficacy and side-effect profile might be more beneficial.

NOD2, encoded by the *NOD2* gene, can sense bacterial peptidoglycan in the host cytosol to stimulate another level of microbial surveillance that is often associated with pathogen invasion.⁹⁹ It has been suggested that NOD2 expression is most abundant in inflammatory cells. However, in the lung, NOD2 expression and function has also been reported in airway smooth muscle,^{100,101} airway epithelial cells, and eosinophils.¹⁰² NOD2 is able to activate the nuclear factor κ B family after

the detection of peptidoglycan fragments,¹⁰³ and play a part in the production of proinflammatory cytokines and antimicrobial peptides.^{104,105} In mice, NOD2 ligands induce a rapid activation of alarmin signals such as IL-25 and thymic stromal lymphopoietin, and promote Th2-type inflammation.¹⁰⁶ NOD2 is also required for antimicrobial and antiviral defence, making prediction of functional outcomes of NOD2 modulation in asthma less clear. NOD2 mutations have been linked to sarcoidosis, Blau syndrome, and inflammatory bowel disease.^{107,108} The NOD2 asthma SNP (rs2066844) T allele is associated with reduced expression in whole blood, which might imply that activation of this pathway is beneficial. Therefore, repositioning of inarigivir soproxil, a NOD2-activating drug in phase 2 clinical studies for chronic hepatitis B infection, might be considered for the treatment of asthma, or to prevent asthma exacerbations by boosting antiviral immunity. However, as a note of caution, in January, 2020, inarigivir soproxil was discontinued after phase 2 trials because of adverse events (one patient death, currently under investigation).¹⁰⁹

Conclusions and future directions

Although the combination of GWASs and eQTL analyses can lead to a better understanding of disease aetiology, such analyses have limitations. First, individual SNP effects, and not their potential interactions, are addressed. Second, it can be difficult to pinpoint causal SNPs due to linkage disequilibrium, which might extend over more than one gene. Therefore, eQTL studies in populations with low linkage disequilibrium, such as the African American population, are warranted to identify causal genes. This approach was recently shown in an airway epithelial eQTL analysis of the 17q12–21 locus, which provided evidence for gasdermin B (*GSDMB*) as the causal asthma gene in this locus.¹¹⁰ In our analysis, we tried to reduce the number of false-positive findings by using a stringent genome-wide significance threshold of $p < 5 \times 10^{-8}$. This threshold might have resulted in missing true-positive risk alleles that have low allele frequency. Our eQTL analysis also had its drawbacks. Since there are almost no eQTL studies in cell types related to asthma, eQTL analysis in whole blood was represented abundantly in the results we reviewed. Blood eQTL might not illustrate what happens in lung cells; however, it gives an indication of the SNP–gene relationship.

The use of genetic approaches in the development of targeted therapy might pave the way for precision medicine approaches in three different scenarios. First, genetic testing could identify those with a risk genotype that is related to a target for a drug on the market. Individuals at genetic risk might respond better to such a drug than those who do not have the risk genotype. This approach could be successful if a substantial proportion of the disease is due to this risk allele. Whereas it is known that asthma genetic variations explain a very small proportion of asthma at the population level, it is

not known how important these variants and their interactions might be at the individual level; intervention studies are needed to address this question. Second, an asthma risk allele might also link to a biomarker, such as a cytokine or a soluble receptor, that could be used as a marker to select potential responders. For example, an asthma risk variant in the gene encoding the IL-33 receptor *IL1RL1* is associated with lower concentrations of the soluble receptor protein IL1RL1-a in lung and serum.¹¹¹ This finding could indicate that individuals with low concentrations of IL1RL1-a respond to anti-IL-33–IL1RL1 treatments, a possibility that should be further studied. Third, genetic studies of subgroups of patients with asthma might reveal gene variants important for that subgroup, such as patients with childhood-onset asthma,^{19,20} eosinophilic asthma,¹¹² or moderate-to-severe asthma.²⁵ In this phenotype-driven approach, drugs targeted at genes specific for these phenotypes might be efficacious in these patient subgroups.

Many factors, beyond genetics, might ultimately determine treatment response. This variation in inter-individual and intra-individual treatment response might be due to different factors, such as time-specific and tissue-specific epigenetic effects,¹¹³ the predominant immune-inflammatory pathway, the contribution of remodelled tissue, as well as local effects and concentrations of the drug at the target site.¹¹⁴ Moreover, environmental factors such as smoking, allergen exposure, nutrition, or microbial factors could potentially interact with genetic factors to contribute to the clinical features and clinical course of asthma and the response to treatment.¹¹⁴

Although many novel asthma target genes have been identified in the past few years, an important question remains: how can the medical and scientific field use these insights to develop novel drugs or repurpose existing drugs for asthma? Recent progress in the identification of asthma genetic variation points to many interesting drug targets, including classical surface receptors. Moreover, using genomics-based drug repositioning, existing drugs such as olamkicept and inarigivir soproxil could be repurposed and tested in patients with asthma. However, data for the functional annotation of many asthma genes are still missing, as many genetic variants have no known function, and eQTL mapping in many cell types relevant to asthma has not been reported to date. Validation of a proposed link between an asthma SNP and gene expression is needed, by the identification of relevant cell types that express the gene and validation of mRNA expression at the protein level. Airway wall single-cell sequencing data that includes single-cell eQTL and protein QTL analysis could improve the annotation of these SNPs. Whereas this Series paper focused on a general asthma phenotype, genes might also be identified for a subset of patients with asthma, such as those with childhood-onset asthma or recurrent exacerbations.^{19,115} Novel drugs developed or repurposed on the basis of such findings might be applied first in these patients,

Search strategy and selection criteria

Studies included in this Series paper were identified through searches of PubMed for articles published from Feb 1, 2017, to June 12, 2020, by use of the search terms “asthma”, “genetics”, “gene”, “genome wide association”, “drug repositioning”, and “drug repurposing”. We also checked the GWAS Catalog using “asthma” as a keyword. Articles resulting from these searches and relevant references cited in these articles were reviewed. Drug targets were identified with Drug Research Advisor. Potential druggable targets were prioritised using the druggable genome list presented in the Drug Gene Interaction Database. Prioritised drug targets were reviewed using additional PubMed searches in April, 2020, using the drug target name, gene, and “asthma” as keywords, without applying time restrictions. Only articles published in English were included.

For the GWAS Catalog see <https://www.ebi.ac.uk/gwas/>

For the Drug Gene Interaction Database see www.dgidb.org

contributing to a more personalised approach in asthma. Our review and analysis was limited by the dominance of studies in populations of European descent, and more studies in populations of other ethnicities are urgently needed. Finally, for many asthma genes, associated pathways are missing because the emergence of functional evidence is lagging behind gene discovery. Multi-disciplinary research that integrates genetic findings, functional evidence, and therapeutic intervention might offer a way to move forward in developing much-needed asthma therapies.

Contributors

ZWE-H, RG, and GHK conceived this review. ZWE-H and GHK did the literature and database search. ZWE-H, RG, and GHK drafted the review. ZWE-H, RG, FD, and GHK provided intellectual input, and contributed to and approved the final version of this Series paper.

Declaration of interests

RG reports grants from Marie Skłodowska-Curie, during the conduct of this study; and grants from Aquilo, Boehringer Ingelheim, and Novartis, outside of the submitted work. GHK reports grants from Marie Skłodowska-Curie and GlaxoSmithKline, during the conduct of the study; and grants from TEVA Nederland, Lung Foundation of the Netherlands, VERTEX, UBBO EMMIUS foundation, and TETRI Foundation, outside of the submitted work. GHK has participated in advisory board meetings for GlaxoSmithKline and PURE-IMS (money paid to institution). ZWE-H and FD declare no competing interests.

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