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REVIEW

Genetic risk factors for the development of allergic disease identified by genome-wide association

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Summary

An increasing proportion of the worldwide population is affected by allergic diseases such as allergic rhinitis (AR), atopic dermatitis (AD) and allergic asthma and improved treatment options are needed particularly for severe, refractory disease. Allergic diseases are complex and development involves both environmental and genetic factors. Although the existence of a genetic component for allergy was first described almost 100 years ago, progress in gene identification has been hindered by lack of high throughput technologies to investigate genetic variation in large numbers of subjects. The development of Genome-Wide Association Studies (GWAS), a hypothesis-free method of interrogating large numbers of common variants spanning the entire genome in disease and non-disease subjects has revolutionised our understanding of the genetics of allergic disease. Susceptibility genes for asthma, AR and AD have now been identified with confidence, suggesting there are common and distinct genetic loci associated with these diseases, providing novel insights into potential disease pathways and mechanisms. Genes involved in both adaptive and innate immune mechanisms have been identified, notably including multiple genes involved in epithelial function/secretion, suggesting that the airway epithelium may be particularly important in asthma. Interestingly, concordance/discordance between the genetic factors driving allergic traits such as IgE levels and disease states such as asthma have further supported the accumulating evidence for heterogeneity in these diseases. While GWAS have been useful and continue to identify novel genes for allergic diseases through increased sample sizes and phenotype refinement, future approaches will integrate analyses of rare variants, epigenetic mechanisms and eQTL approaches, leading to greater insight into the genetic basis of these diseases. Gene identification will improve our understanding of disease mechanisms and generate potential therapeutic opportunities.

Atopic disease and evidence of a familial component

Allergy is a hypersensitive inflammatory immune response to innocuous environmental antigens, mediated by immunoglobulin type E (IgE) antibodies. By definition, this is the underlying cause of all allergic disease, although there is significant heterogeneity between different allergic conditions, such as allergic asthma, atopic dermatitis (AD) (eczema) and seasonal allergic rhinitis (AR) (hay fever). The prevalence of allergic disease has increased globally in the last few decades and more than a third of the UK population are affected by some form of allergy, which is accompanied by significant economic burden [1–5].

All authors contributed equally.

The development of allergic disease is complex and not fully understood, with both environmental and genetic components. Environmental changes are thought to have contributed to the increased incidence of allergy in recent years with evidence for a role for tobacco smoke exposure, respiratory viral infections, use of antibiotics, diet and exposure to allergens to name a few. The first study to identify the heritability of allergy found that 48.4% of a group of 621 sensitised individuals had a family history of sensitisation to common environmental allergens, compared with only 14.5% of the control group of 76 non-sensitised individuals [6]. A few years later, the term atopy was first coined, to mean inherited hypersensitivity [7]. More recent studies in twins provide further evidence for allergy heritability, due to the higher levels of

concordance for allergic phenotypes in monozygotic, compared with dizygotic twins, where atopy heritability is estimated between 50% and 84% [8–10]. Heritability estimates for allergic disease vary, but have been described as high as 95% for asthma, 91% for AR and 84% for AD (reviewed [11]).

Different allergic diseases are related by overlapping aetiology, i.e. elevated IgE, therefore co-morbidity due to a genetic component is logical. However, other factors are important within the disease *per se*, e.g. non-IgE mechanisms in asthma. Initial allergic sensitisation occurs on exposure to an allergen breaching the epithelial barrier, due to disruption or dysfunction, which may have genetic and/or environmental causes (Fig. 1). Specifically, disruption of the epidermal barrier is considered to be the first step in the development of eczema. This cutaneous sensitisation might then become systemic and subsequently give rise to other allergies, such as AR; this phenomenon is referred to as 'atopic march' and contributes to co-morbidity of allergies [12].

In this review, we will provide an overview to the current status of the genetics of asthma, AD and AR including related allergic traits; serum IgE, sensitisation and blood eosinophil counts with a focus to Genome-Wide Association Studies.

Methods for identifying genes associated with complex diseases

Our understanding of the extent and nature of variation in the human genome has significantly improved following the first draft genome sequence in 2001. Recent figures suggest that > 20 million single nucleotide polymorphisms (SNP) or single base pair changes, exist out of a 3-billion-base pair genome. Early methods used to map genes of relevance in allergic disease included linkage analysis (mainly 1980–1990′s) and candidate gene association studies (1970's – present). Reproducibility of linkage and association approaches was disappointing primarily due to inadequate power, subject heterogeneity (different phenotype definition), population stratification and multiple testing without correction. This has generally led to inconsistent results; however, several genes have been identified with confidence, e.g. *DPP10, PCDH1, HLAG, NPSR1, PHF11, PLAUR, ADAM33, IL10, CD14, IL4, IL13, ADRB2, HLA-DRB1, HLA-DQB1, TNFA, FCER1B, INPP4A, STAT6* and *IL4RA* for asthma, e.g. *COL6A5*, *FLG, TLR9, IL13, SPINK5, CMA1, IL4RA* and *RANTES* for AD and *FLG*, *S100A7, HDC, IL13, IL6, TLR7* for AR (reviewed [11, 13, 14]). Of special note is the identification of filaggrin (*FLG*) as a susceptibility gene for AD. Several polymorphisms and loss of function mutations within *FLG*, a gene that can influence the epidermal barrier, cause increased susceptibility to AD [15]. Carriers of specific SNPs of *FLG* can have an approximately three-fold greater chance of developing AD compared to non-carriers. This effect size is particularly large for a complex trait and exemplifies the usefulness of genetics to identify altered biology in disease (reviewed [16]).

Genome-Wide Association Studies in allergic disease

GWAS is the current method of choice for gene identification in complex disorders, which involves

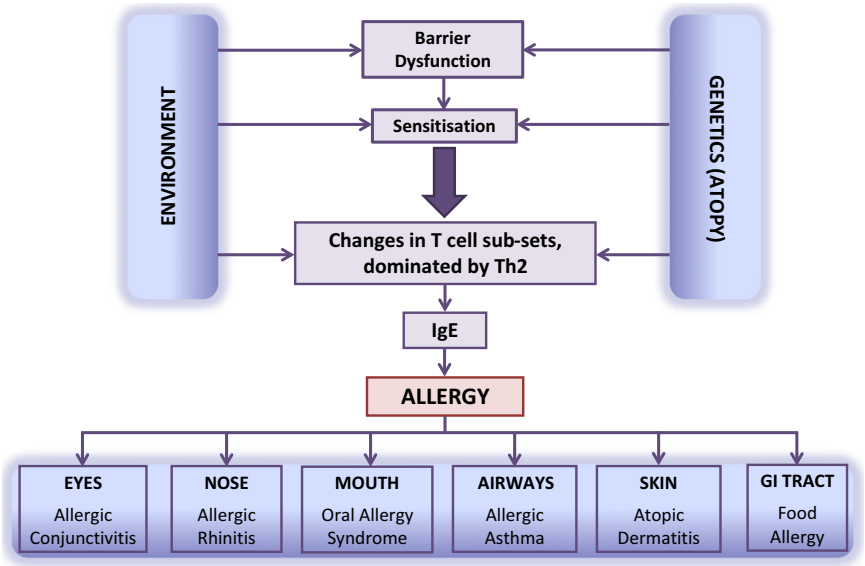

Fig. 1. Development of allergy. Both environmental and genetic factors influence barrier integrity and sensitisation to common environmental allergens. This can lead to a Th2-dominant environment, elevated IgE levels, and allergic phenotypes that affect a variety of organs.

examining association with typically 500 000+ common (> 5% frequency) polymorphisms spanning the entire genome in cases and controls with very stringent statistical thresholds, e.g. $P < 5 \times 10^{-8}$. In the following sections, we provide an overview of current findings of recent GWAS for i) self-reported/doctor-diagnosed asthma, AR and AD and ii) measures of allergic disease including total serum IgE, allergic sensitisation and blood eosinophil counts.

Genetic risk factors associated with self-reported/doctor-diagnosed allergic disease

Asthma, AR and AD are clinically diagnosed as discrete diseases; however, the interrelationship between these diseases has long been recognised. For example, individuals with AR have a 5–6-fold greater risk of developing asthma [17, 18]. Similarly, it is established that there are shared and distinct genetic components to these diseases with correlation estimates at 0.55 for asthma and eczema, at 0.47 for asthma and rhinitis and at 0.62 for eczema and rhinitis [19]. In the following sections, we will outline recent findings from GWAS of these diseases; however, it is important to note that few have taken into account co-morbidities in recruitment strategies.

Asthma

The first GWAS for asthma was completed in 2007 by Moffatt and colleagues, a discovery cohort of 994 patients with childhood onset asthma and 1243 non-asthma controls identified significant association to a locus on chromosome 17q21 [20]. This locus included genes for zona pellucida binding protein 2 (*ZPBP2*), gasdermin B (*GSDMB*) and orm1-like protein 3 (*ORMDL3*). The 17q21 locus has been reproduced as a locus associated with asthma [21], severe asthma [22] and asthma with severe exacerbations [23] in subsequent GWAS. Similarly, SNPs in the 17q21 locus are associated with several clinical measures in multiple asthma cohorts, including lung function, bronchial hyper-responsiveness and disease severity [24, 25]. The identification of the specific gene(s) underlying these effects remains to be resolved; *ZPBP2, GSDMB* and *ORMDL3* have been implicated in gene transcription, cell apoptosis and sphingolipid synthesis, respectively. Recently, a role for *ORMDL3* in eosinophil trafficking and degranulation, mechanisms thought to be important in asthma, has been identified [26]. Similarly, a role for sphingolipid synthesis in determining bronchial reactivity [27] and a role for the endoplasmic reticulum unfolded protein-response pathway as a mechanism by which *ORMDL3* is linked to asthma, have been reported [28]. It is important to note that the effect of *ORMDL3* polymorphisms has been shown to be significantly influenced by the age of onset of asthma, with the effect being particularly important in childhood asthma [20]. This is a relevant point as several asthma phenotype cluster analyses have identified that the age of asthma onset was amongst the strongest factors in discriminating different asthma phenotypes [29–31].

Subsequent GWAS in asthma have now identified around 13 susceptibility loci with confidence in the Caucasian population (Table 1). It is important to note that in the GWAS in asthma and other allergic diseases most single variants confer a very modest odds ratio of 1.1–1.3 to develop disease; however, this has also been observed in other complex disorders. Of note is the largest GWAS for asthma completed to date by the GABRIEL consortium which involved 10 365 cases and 16 110 controls [21]. This study identified association between polymorphisms spanning *IL33, IL1RL1/IL18R1, HLA-DQ, SMAD3, IL2RB*, the 17q21 locus and asthma [21]. These genes represent a novel insight into potential molecular mechanisms underlying asthma, e.g. *HLA* would be anticipated to be important for T-cell-mediated responses, *SMAD3* is a signalling intermediate involved in fibrosis and *IL2RB* for T cell survival. However, the finding that both the interleukin 33 (*IL33*) and interleukin 33 receptor (*IL1RL1* or *ST2*) genes were identified is of relevance as GWAS examining allergic sensitisation and blood eosinophilia have also identified these two loci (Table 2). Subsequent GWAS have replicated the association signal to *IL33* for severe asthma with exacerbation [23] and to *IL1RL1* for asthma [32] and severe asthma [22]. Interestingly, in this recent study of severe asthma with exacerbation, the effect sizes for individual polymorphisms at multiple loci including *IL33* key SNPs were increased with number of hospitalisations per genotype (e.g. OR 1.32, 1.22, 1.47, 1.91 for 2, 3, 4/5 and 6 or more hospitalisations, respectively) [23]. There is accumulating evidence that the IL33/IL1RL1 axis may be of relevance in asthma. IL33 has been shown to be elevated in the airways of asthma patients, particularly in the airway structural cells including the bronchial epithelium [33]. In addition, a soluble form of the ST2 receptor (sST2) has been shown to be elevated during asthma exacerbation [34]. The functional genetics of the *IL1RL1* locus are particularly advanced with key SNPs associated with sST2 levels being identified [35]. These included polymorphisms that altered ST2 amino acid residues which can influence IL33 and sST2 production providing a putative mechanism [35].

Multiple other asthma susceptibility genes have now been identified using GWAS approaches with variable supporting evidence (Table 1). These include genes involved in diverse roles including inflammatory cell function and activation (*IL13, IL6R, DENND1B, LRRC32, IL2RB, IL1RL1*), airway smooth muscle con-

Table 1. Susceptibility genes for asthma, allergic rhinitis and atopic dermatitis recently identified by Genome Wide Association Studies (GWAS)

Gene(s)	Chrs	Association	Potential Function	GWAS
IL6R	1q21	Asthma	Regulatory T-cell function, T-cell differentiation	1
DENND1B	1q31		Memory T-cell functions	2[†]
IL1RL1	2q11		IL-33 receptor-recruitment of inflammatory cells	3–5[‡], 6[†], 11
PDE4D	5q12		Cell signalling, inflammation, ASM function	7
TSLP	5q22*		Activates dendritic cells, Th2 immune responses	3
SLC22A4/RAD50/IL13	5q31		Organic cationic transporter/DNA repair/Th2 cytokine	6[†], 8[‡]
HLA-DRA/DRQ	6p21*		T-cell responses/many additional genes in region	3, 9, 11
CDHR3	7q22		Epithelial polarity, cell–cell contact and differentiation	6[†]
IL33	9p24		Recruitment/activation of inflammatory cells	3, 4, 6[†]
C11orf30/LRRC32	11q13		Regulates gene expression, epithelial barrier/regulatory T-cell function	1
SMAD3	15q22		TGF-β signalling intermediate, fibrosis	3
ORMDL3/GSDMB	17q21		Sphingolipid synthesis/cell apoptosis	3, 5[‡], 6[†], 10[§]
IL2RB	22q12		Binds IL-2/IL-15, lymphoid cell differentiation	2, 3
C11orf30/LRRC32	11q13	Allergic Rhinitis	Regulates gene expression, epithelial barrier/regulatory T-cell function.	12
FLG, LCE3A	1q21*	Atopic Dermatitis	Epidermal differentiation and structure	13, 14, 15, 16 [¶]
IL1RL1, SLC9A4	2q12*		IL-33 receptor/sodium-hydrogen exchanger	15[¶]
IL2-IL21	4q27		T-cell survival/B cell proliferation and IgE production	15[¶]
SLC22A4/RAD50/IL13/KIF3A	5q31*		Organic cationic transporter/DNA repair/Th2 cytokine/cilia protein	14, 15, 16 [¶]
HLA-B (BAT1/TNXB/CREBL1)	6p21		T-cell responses/many additional genes in region	16
PRR5L	11p13		Cellular apoptosis	15[¶]
OVOL1	11q13*		Development and differentiation of epidermal/epithelial tissues	14
C11orf30/LRRC32	11q13*		Regulates gene expression, epithelial barrier/regulatory T-cell function	13, 15[¶], 16
CLEC16A	16p13		Inflammatory cell function (ITAM receptor)	15[¶]
ZNF652	17q21		Transcriptional repressor in epithelial cancers	15[¶]
ADAMTS10/ACTL9	19p13*		Extracellular matrix cleavage/epithelial morphology	14
TNFRSF6B	20q13*		Decoy receptor, immunomodulation of T cells	14, 15[¶]

*Association also observed in the Asian population GWAS (see text).

Genes focused to those meeting conventional genome-wide significance ($P < 5 \times 10^{-8}$) and/or independent replication in the Caucasian population. [†]Childhood severe asthma with exacerbation; [‡]Severe Asthma and [§]Childhood onset asthma. Data taken from; Asthma: 1. [67], 2. [68], 3. [21], 4. [55], 5. [22][‡], 6. [23][†], 7. [69], 8. [70], 9. [71], 10. [20], 11. [32]. Allergic Rhinitis: 12. [37]. Atopic Dermatitis: 13. [41], 14. [42], 15. [46]; [¶]Using Immunochip array, 16. [48].

IL, interleukin; *IL6R*, IL-6 receptor; *DENND1B*, Denn/madd domain-containing 1b; *IL1RL1*, IL-1 receptor like 1; *PDE4D*, phosphodiesterase 4d, cAMP-specific; ASM, airway smooth muscle; *TSLP*, thymic stromal lymphopoietin; Th2, T helper 2; *SLC22A4*, solute carrier family 22 (organic cation/zwitterion transporter), member 4; *RAD50*, *S. cerevisiae, homolog of (DNA repair)*; IL13. IL-13; *HLA-*, Human Leukocyte Antigen, class II; *CDHR3*, cadherin-related family member 3; *IL33*, IL-33; *C11orf30*, chromosome 11 open reading frame 30; *LRRC32*, leucine rich repeat containing 32; *SMAD3*, mothers against decapentaplegic drosophila homolog 3; TGF-β transforming growth factor beta; *ORMDL3*, orm1-like protein 3; *GSDMB*, gasdermin b; *IL2RB*, IL-2 receptor beta; Ig, immunoglobulin; *FLG*, filaggrin; *LCE3A*, late cornified envelope 3A; *SLC9A4*, solute carrier family 9, subfamily A (NHE4, cation proton antiporter 4), member 4; *IL2-IL21*, interleukin 2/21; *KIF3A*, kinesin family member 3A; *PRR5L*, proline rich 5-like; *OVOL1*, ovo-like 1(Drosophila); *CLEC16A*, C-type lectin domain family 16, member A; *ZNF652*, zinc finger protein 652; *ADAMTS10*, ADAM metallopeptidase with thrombospondin type 1 motif, 10; *ACTL9*, actin-like 9; *TNFRSF6B*, tumour necrosis factor receptor superfamily, member 6b, decoy.

traction (*PDE4D*), and cell apoptosis and differentiation (*GSDMB*) again providing a unique insight into potentially altered mechanisms in asthma. Of interest is the large number of genes associated with epithelial cell functions and homeostasis, e.g. *IL33, IL1RL1, C11orf30* and *TSLP* providing further support for the accumulating data suggesting the epithelium is altered in asthma [36]. Further supporting this concept of an altered epithelial barrier in asthma is the recent finding that polymorphisms spanning *CDHR3* are associated with severe asthma with exacerbation [23]. *CDHR3* encodes cadherin-related family member 3, with other family members being involved in epithelial polarity and cell-cell interactions.

Overall, the susceptibility genes identified to date using GWAS are consistent with the hypothesis that asthma is caused by epithelial barrier/function abnormalities and altered innate and adaptive

Table 2. Susceptibility genes for allergic traits recently identified by Genome-Wide Association Studies (GWAS)

Gene(s)	Chrs	Association	Potential Function	GWAS
FCER1A	1q23	Total IgE	Alpha chain of the high affinity IgE receptor	1–3
IL13/RAD50	5q31		Cytokine involved in Ig class switch/DNA repair	1–3
HLA-DRB1	6p21		T-cell responses/many additional genes in region	2
HLA-G	6p21		T-cell responses/many additional genes in region	3
HLA-A	6p21		T-cell responses/many additional genes in region	3
HLA-DQA2	6p21		T-cell responses/many additional genes in region	3
STAT6	12q13		Signal transduction linked to IgE synthesis	1–3
IL4R/IL21R	16p12		IgE regulation via IL4 and IL21	2
TMEM232/SLC25A46/TSLP	5q22	IgE to grass	Tetraspan protein/transporter/activates dendritic cells	4
HLA-DRB4	6p21		T-cell responses/many additional genes in region	4
C11orf30/LRRC32	11q13		Regulates gene expression, epithelial barrier/regulatory T-cell function	4
IL1RL1	2q12	Allergic sensitisation	IL-33 receptor-recruitment of inflammatory cells	5, 6
PLCL1	2q33		Intracellular signalling	6
LPP	3q27		Cell adhesion/motility/transcription	5, 6
TLR1/6/10	4p16		Pathogen recognition and activation of innate immunity	5, 6
IL2/ADAD1	4q27		Lymphocyte activity/RNA binding protein	5, 6
PTGER4	5p13		Receptor for prostaglandin E2, smooth muscle relaxation	6
SLC25A46	5q22		Member solute carrier/transporter protein family	5
WDR36/CAMK4	5q22		Cell cycle progression and gene regulation/T-cell function	6
HLA-DQA1/DQB1	6p21		T-cell responses/many additional genes in region	5, 6
HLA-B/C/MICA	6p21		T-cell responses/many additional genes in region/MHC-related protein	5, 6
MYC-PVT1	8q24		Cell cycle progression and apoptosis/regulates extracellular matrix	5
IL33	9p24		Recruitment/activation of inflammatory cells	6
GATA3	10p14		Th2 transcriptional regulator	6
C11orf30/LRRC32	11q13		Regulates gene expression, epithelial barrier/regulatory T cell function	5
STAT6	12q13		Signal transduction linked to IgE synthesis	5
FOXA1/TTC6	14q21		Embryonic development/affiliated with the lncRNA class	6
SMAD3	15q22		TGF-β signalling intermediate	6
GSDMB	17q12		Cell apoptosis	6
NFATC2	20q13		Gene expression/cellular migration	6
IL1RL1	2q12	Blood eosinophil count	IL-33 receptor-recruitment of inflammatory cells.	7
IKZF2	2q34		Lymphocyte differentiation	7
GATA2	3q21		Transcription factor, inflammatory cell differentiation	7
IL5	5q23		Production and activation of eosinophils	7
SH2B3	12p24		Adaptor protein involved in T-cell function	7

Genes focused to those meeting conventional genome-wide significance ($P < 5 \times 10^{-8}$) and/or independent replication in the Caucasian population. Total IgE: 1. [49]; .2. [21]; 3. [50], IgE to grass: 4. [37]; Allergic sensitisation by allergen-specific IgE/SPT 5. [53] or self-reported cat, house dust-mite and pollen allergies 6. [54], Blood Eosinophil Count: 7. [55].

FCER1A, Fc fragment of IgE, high affinity I, receptor alpha polypeptide; IL, interleukin; *IL13*, IL-13; *RAD50*, *S. cerevisiae, homolog of (DNA repair)*; *HLA*-, Human Leukocyte Antigen, class II; *STAT6*, signal transducer and activator of transcription 6, *IL4R*, IL-4 receptor; *IL21R*, IL-21 receptor; *TMEM232*, transmembrane protein 232; *SLC25A46*, solute carrier family 25, member 46; *TSLP*, thymic stromal lymphopoietin; *C11orf30*, chromosome 11 open reading frame 30; *LRRC32*, leucine rich repeat containing 32; *IL1RL1*, interleukin 1 receptor-like 1; *PLCL1*, phospholipase C-like 1; *LPP*, LIM domain containing preferred translocation partner in lipoma; *TLR1/6/10*, Toll-like receptor 1/6/10; *IL2*, IL-2; *ADAD1*, adenosine deaminase domain containing 1 *PTGER4*, prostaglandin E receptor 4 (subtype EP4); *WDR36*, WD repeat domain 36; *CAMK4*, calcium/calmodulin-dependent protein kinase IV; *MICA*, MHC class I polypeptide-related sequence A; *MYC*, v-myc avian myelocytomatosis viral oncogene homolog; *PVT1*, Pvt1 oncogene (non-protein coding); *IL33*, IL-33; *GATA3*, GATA binding protein 3; *FOXA1*, forkhead box A1; *TTC6*, tetratricopeptide repeat domain 6; *SMAD3*, mothers against decapentaplegic drosophila homolog 3; *GSDMB*, gasdermin b; *NFATC2*, nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 2; *IKZF2*, IKAROS family zinc finger 2 (Helios); *GATA2*, GATA binding protein 2; *IL5*, IL-5; *SH2B3*, SH2B adaptor protein 3.

immune responses. It was reported by the GABRIEL consortium that ~49% of the lifetime risk of asthma could be explained by the loci identified in this study [21].

Allergic rhinitis

In contrast to asthma, there are limited data for GWA approaches in AR in the Caucasian population with

only one study published to date that identified genome-wide significant association [37]. 2.2 million SNPs were evaluated in 3933 self-reported cases of seasonal AR versus 8965 control subjects. Only one locus reached genome-wide significance near chromosome 11 open reading frame 30 (*C11orf30*) and leucine-rich repeat containing 32 (*LRRC32*) at 11q13 [37]. Interestingly, this locus has been previously identified in both asthma and AD GWAS (Table 1). *C11orf30* encodes EMSY, a protein implicated in epithelial cancers [38], potentially via mechanisms involving transcriptional repression [39]. *LRRC32* encodes a T-cell surface receptor that modulates latent TGF-β and is thought to be important for regulatory T-cell functions [40].

Atopic dermatitis

To date, there have been four GWAS for AD in the Caucasian population (Table 1). The first of these used a parallel family-based and case–control design to identify associated SNPs with confidence [41]. This approach identified two genetic loci for AD on chromosomes 1p21 and 11q13. Reassuringly, the chromosome 1 locus encompassed *FLG* previously identified as a major AD susceptibility gene. Interestingly, the chromosome 11 locus encompassed *C11orf30/LRRC32* previously discussed for AR and asthma, suggesting altered epithelial biology may be a feature of AD [41]. Amongst other genes, which gave signals not meeting stringent criteria, was *HRH4* encoding histamine H4 receptor, which is important in pruritis [41]. Subsequent GWAS for AD have used case–control designs. In the largest study to date, Paternoster and colleagues used meta-analyses of 5606 cases and 20 566 controls for discovery and 5419 cases and 19 833 controls for replication to identify five loci with confidence: 1q21 (*FLG*), 5q31 (*KIF3A*), 11q13 (*OVOL1*), 19p13 (*ADAMTS10/ACTL9*) and 20q13 (*TNFRSF6B*) [42]. Again, the *FLG* locus was prominent in these findings and several new loci were identified providing a potentially novel insight into the molecular mechanisms underlying AD. *KIF3A* encodes a component of the kinesin complex involved in assembly of cilia, mice deficient in *kif3a* have thinning of the epidermal layer [43], *OVOL1* encodes an epidermal transcriptional repressor potentially involved in keratinocyte differentiation [44] and *TNFRSF6B* which encodes decoy receptor 3 (DcR3) has multiple functions including inhibiting T-cell chemotaxis [45]. Ellinghaus and colleagues used an Immunochip approach to investigate AD, testing 128 830 SNPs in 2425 cases and 5449 controls, with further replication in multiple diverse ethnic populations [46]. This study identified multiple associated loci; 1q21 (*FLG*), 2q12 (*IL1RL1-SLC9A4*), 4q27 (*IL2-IL21*), 11p13 (*PRR5L*), 11q13 (*C11orf30/LRRC32*), 16p13 (*CLEC16A*), 17q21 (*ZNF652*) and 20q13 (*TNFRSF6B*). These loci show excellent replication for several previously identified loci, e.g. *FLG*, *C11orf30/LRRC32* and potentially identify novel susceptibility genes, e.g. *ZNF652,* which encodes a transcription repressor previously linked to epithelial cancers [47]. Similarly, a recent GWAS for childhood onset AD using 1563 cases and 4054 controls confirmed association with loci on chromosomes 1, 5 and 11 and provided evidence for a susceptibility locus encompassing the *HLA-B* region on chromosome 6p21 (Table 1, [48]). As for asthma, GWAS of AD in the Caucasian population have now identified several loci with replication in three or more studies suggesting that genetic susceptibility involves a combination of altered barrier integrity and altered innate and adaptive immune responses. Recent estimates suggest that ~14.4% heritability of AD can now be explained by currently reported loci.

Genetic risk factors associated with serum IgE, allergic sensitisation and blood eosinophil counts

While studies using disease phenotypes such as asthma or AD have been useful, studies in parallel have aimed to understand genetic regulation of more quantitative measures of allergic disease.

GWAS of serum total IgE levels

The first GWAS for IgE levels was reported by Weidinger and colleagues using a cohort of 1530 asthma subjects and replication in four independent population-based study samples (n = 9769 total subjects) [49]. Significant associations between total IgE levels and loci on chromosomes 1q23, 5q31 and 12q13 were identified [49]. These variants map to the alpha chain of the high-affinity receptor for IgE (*FCER1A* at 1q23) as well as *STAT6* (12q13), two genes involved in IgE binding and signalling, respectively. *RAD50* (5q31) homolog gene was also identified as a potential determinant of IgE levels [49]. A second total IgE GWAS was completed by the GABRIEL consortium, which identified two additional loci on chromosomes 6p21.3 and 16p12, in asthmatic patients and non-asthmatic control subjects, adjacent to the *HLA-DRB1* and *IL4R/IL21R* genes, respectively. This GWAS also confirmed the association of loci on chromosomes 1q23 (*FCER1A*), 5q31 (*IL13/RAD50)* and 12q13 (*STAT6*) with serum IgE levels [21]. Similarly, analyses in the Framingham cohort confirmed these three loci as containing genetic determiants of total IgE and again suggested the HLA region on 6p21 is important [50] (Table 2). Of importance was the association of these *FCER1A* polymorphisms with diseases such as asthma (P = 0.021) and AR (P = 0.015) and with allergic sensitisation defined by skin prick test (P = 0.03) [51].

GWAS of allergic sensitisation

In an attempt to move from total IgE analyses to more allergen-specific IgE approaches, Wan and colleagues completed a GWAS for atopy, defined by elevated-specific IgE levels in 1083 cases and 2770 controls from the British 1958 Birth Cohort [52]. A single SNP in the 13q14 (*FNDC3A*) locus was identified as genome-wide significant with an additional six loci showing suggestive evidence, 8q12, 8q22, 10q26, 11q24, 18q22 and 20p13. These loci were not replicated in additional cases/controls defined by specific IgE or skin prick test suggesting very large numbers would be required to investigate these phenotypes and/or definition of cases using multiple allergens may lead to heterogeneity; analyses of single allergens may be more productive [52]. At around the same time, the first GWAS for a single specific IgE (grass) using 2315 cases and 10 032 control subjects was published, that identified three loci, 5q22 (*TMEM232/SLC25A46/TSLP*), 6q21 (*HLA-DRB4*) and 11q13 (*C11orf30/LRRC32*) [37]. *TMEM232* encodes transmembrane protein 232, a member of the tetraspan proteins, *SLC25A46* encodes a solute carrier protein involved in transport of metabolites, and *TSLP* is involved in dendritic cell activation.

Recently, GWAS of allergic sensitisation, defined by serum levels of specific IgE to individual allergens house dust mite and animal dander, in 5789 atopic individuals and 10 056 controls was reported [53]. This study identified ten loci with replication in 6114 case individuals and 9920 controls [53]. The loci defined by this study have substantially increased the number of genes associated with allergic sensitisation and include *TLR6, C11orf30, STAT6, SLC25A46, HLA-DQB1, IL1RL1, LPP, MYC, IL2* and *HLA-B* [53]. The authors suggest that these ten loci account for a minimum of 25% of IgE-defined allergic sensitisation, making these loci significant contributors to atopic disease. The study also confirmed several previous associations including the relationship between *STAT6* and circulating IgE levels and the *C11orf30* locus (Table 2).

A meta-analysis of genome-wide associations in 53 862 case individuals from the 23andMe, Inc. dataset using self-reported cat, dust-mite and pollen allergies identified a total of sixteen loci of which some were novel; 2q33 (*PLCL1*), 5p13 (*PTGER4*), 5q22 (*WDR36/CAMK4*), 9p24 (*IL33*), 10p14 (*GATA3*), 14q21 (*FOXA1/TTC6*), 15q22 *(SMAD3*), 17q12 (*GSDMB*) and 20q13 (*NFATC2*) for sensitisation [54]. In addition, these data showed a striking overlap with the previous large-scale study of allergic senisitisation at six of these loci (Table 2). However, this GWAS defined case subjects as those with self-reported allergies and therefore is likely to have a significant number of false-positives and to have missed a number of loci due to these confounders [54].

GWAS of blood eosinophil count

A GWAS for blood eosinophil counts used a combined population of 21 510 European subjects to identify five loci, 2q12 (*IL1RL1*), 2q34 (*IKZF2*), 3q21 (*GATA2*), 5q23 (*IL5*) and 12p24 *(SH2B3*), showing overlap with previously identified allergic trait loci as well as disease-specific loci [55].

Overlap in GWAS results of allergic disease: 'the atopic march'

Tables 1 and 2 suggest that allergic diseases and traits share a large number of genetic susceptibility loci (Fig. 2). Of note, the IL33/IL1RL1 axis appears to be particularly important for asthma, AD, allergic sensitisation and blood eosinophil counts, suggesting this pathway may represent an underlying mechanism and therapeutic opportunity. Similarly, the *C11orf30/LRRC32* locus shows association to the same traits (Tables 1 and 2). These overlapping loci may at least in part explain the concept of the 'atopic march' e.g. childhood AD leads to an increased risk of developing asthma later in life, as there is overlapping genetic susceptibility (Fig. 2). There is clearly concordance of specific IgE loci with self-reported/doctor-diagnosed allergic disease-based approaches for asthma, AD and AR, e.g. *C11orf30, SLC25A46, HLA-DQB1, IL1RL1, MYC, IL2* and *HLA-B*. It is important to note that there is also discordance for several loci, most evident for trait-specific associations, e.g. the *FLG* locus for AD. Due to the common occurrance of co-morbidities, it is difficult to dissect which susceptibility loci are truly shared and which are specific. One recent study aimed to do this for asthma and AD by stratifying these patients based on AD (all), AD and asthma, and AD (no asthma) [48]. Using a cohort of 1563 childhood onset AD cases and 4054 controls, five loci were identified as genome-wide significant in all subjects; of interest, the 1p21 (*FLG*) and 5q31 (*RAD50/IL13*) loci achieved markedly greater significance in the AD plus asthma compared to the AD (no asthma) group [48]. In a similar approach, a recent study using GWAS data from 1716 asthma cases and 16 888 controls identified association to multiple known loci including *IL1RL1*; however, no significant effect of AR status was observed [32]. Similarly, in a recent study examining both AR and grass pollen-specific IgE in the same patients, there was some concordance between these outcomes and loci identified, e.g. 11q13 (*C11orf30/LRRC32*) and 5q22.1 (*TMEM232/SLC25A46*); however, other loci appeared to be phenotype-specific, e.g. 20p11(*ENTPD6*) for AR and 1p32 (*EPS15*) for grass sensitisation [37]. These data suggest larger prospective studies are required to establish the different components of the

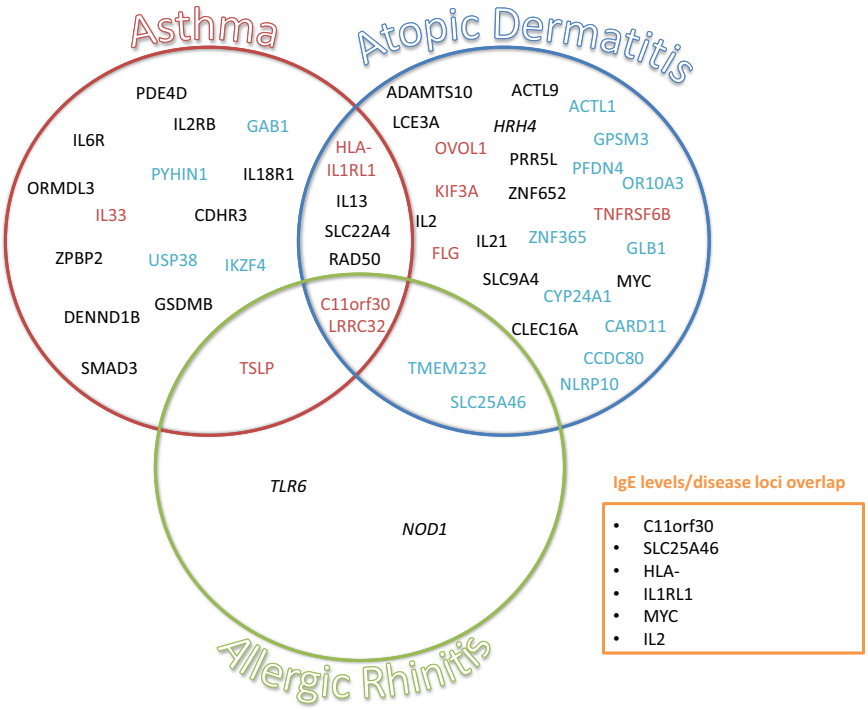

Fig. 2. Venn diagram illustrating genes identified through genome-wide association studies as associated with the allergic diseases asthma, atopic dermatitis and allergic rhinitis. Genes highlighted in black identify those discovered in Caucasian populations, with italics defining promising genes that nearly achieved genome-wide significance. Genes highlighted in blue identify those genes discovered in non-Caucasian populations, while those in red identify those genes discovered in both Caucasian and populations of other ancestry.

allergic phenotype and provide a greater understanding of heterogeneity in the underlying mechanisms.

Results of GWAS in other ethnic populations

While we have focussed to the Caucasian population in Tables 1 and 2, it is important to note that several GWAS for allergic conditions and traits have been completed in a range of populations, including African American, Mexican, Korean and Japanese cohorts. Torgerson and colleagues used diverse North American populations including 5416 individuals with asthma of European, American, African American or African Caribbean, and Latino ancestry with replication in 12 649 individuals from the same ethnic groups [56]. Four previously described loci associated in Caucasian studies were identified, 17q21, *IL1RL1*, *IL33* and *TSLP* [56]. Importantly, there appears to be some ancestry-specific loci, e.g. the 17q21 locus was particularly relevant to the Caucasian and Latino populations but not African descent populations and the novel locus, *PYHIN1* was restricted to individuals of African descent only. *PYHIN1* encodes pyrin and HIN domain family, member 1 and is an interferon-inducible protein shown to regulate IFN-β and NO production in macrophages [57]. In the largest GWAS of asthma in the Japanese to date, 7171 cases and 27 912 controls were used to identify five loci, 4q31 (*USP38-GAB1*), 5q22 (*TSLP*), 6p21 (*HLA*), 10p14 (intergenic) and 12q13 (*IKZF4*) [58]. Likewise, a recent study of paediatric asthma in Japanese and Korean subjects identified significant association with the *HLA-DPA1/HLA-DPB1* locus but failed to replicate several of the loci identified in the Caucasian population [59]. Overall, these data show some concordance with asthma susceptibility loci identified in the Caucasian population, but also identify potential ancestry-specific loci.

Similarly, a GWAS of AD in a Chinese Han population using a discovery sample of 1012 cases and 1362 controls followed by multiple replication cohorts identified loci at 1q21 (*FLG*), 5q22.1 (*TMEM232/SLC25A46*), 10q21 (*ZNF365*) and 20q13 (*TNFRSF6B*) [60]. The 1q, 10q and 20q loci are now convincingly replicated for AD in the Caucasian population (Table 1). Interestingly, the 5q22.1 (*TMEM232/SLC25A46*) locus only just failed to reach genome-wide significance for AR in a recent meta-analysis in the Caucasian population but was associated with IgE sensitisation to grass suggesting this locus is of relevance for allergic disease in the multiple populations [37]. In a GWAS for AD in a Japanese population using 3328 cases and 14 992 controls, associations were observed for several of the loci identified in Caucasian and Chinese populations, including *FLG, C11orf30, TMEM232/SLC25A46, TNFRSF6B, OVOL1, ACTL1* and *KIF3A* [61]. Importantly, several new loci for AD were reported, including 6p21.3

(*GPSM3*), 11p15.4 (*OR10A3-NLRP10*), 3p21 (*GLB1*), 3q13 (*CCDC80*), 7p22 (*CARD11*), 10q21 (*ZNF365*) and 20q13 (*CYP24A1-PFDN4*) [61].

In an attempt to further define ancestry-specific markers of serum IgE levels, a GWAS meta-analysis has been carried out that investigated genetic variation across African American (n = 2469), Caucasian (n = 1564) and Latino (n = 259) racial groups in the EVE asthma genetics consortium [62]. Here, the authors analysed a total of 4292 subjects and identifed ten unique regions of association with serum total IgE levels (*HLA-DQB1 PTB2*, *SUCLG2*, *MAT2B*, *TBX18*, *SOBP*, *TLE4*, *CCDC82*, *WWP2* and *LINC00469*) [62]. Interestingly, several of these loci showed ancestry effects, e.g. the key SNP in *TBX18* may be of particular relevance in African and Latino groups but was not informative in the Caucasian population. Very recently, a GWAS of serum IgE levels in Japanese subjects identified significant association with the MHC class I locus; however, interestingly 9/32 genes previously identified in the Caucasian population as determinants of serum IgE showed evidence of association indicating some cross-ethnic group associations [63].

While further studies are required, these data suggest there may be overlapping allergic disease susceptibility loci spanning multiple ethnic groups, e.g. *IL33/IL1RL1*, *HLA* locus and *TSLP*, as well as ancestry-specific susceptibility loci, e.g. *PYHIN1* in asthma.

Summary

GWAS has provided a unique insight into the genetic basis of allergic disease, including novel information regarding the role of potential pathways and mechanisms. Associated genes include those involved in epithelial/barrier function (e.g. *FLG*, *CDHR3*), cytokines, their receptors and other inflammatory genes (e.g. *IL13*, *IL1RL1*, *IL33*, *IL2RB*, *TSLP*), those involved in T-cell differentiation and function (e.g. *IL6R*, *LRRC32*, *HLA* genes) or those with functions relevant to specific tissues affected by allergy (e.g. *PDE4D*, *ADAMTS10*). However, these genes only account for a small proportion of genetic heritability of these traits and a large degree of genetic influence remains unaccounted for. GWAS investigates associations to common variants (> 5%), not rare variants or structural polymorphisms such as insertion, deletion or copy number variation, which may explain this missing heritability. Similarly, gene–gene interactions and epigenetic mechanisms have not been adequately addressed to date and may be important considerations.

Future directions

GWAS of allergic diseases have been highly successful in identifying genetic variation of relevance to disease susceptibility albeit with modest effect sizes. The future holds great promise to extend these studies particularly beyond case–control to further define endotypes within these complex diseases as recently reported via the use of childhood severe asthma with exacerbation, which lead to the discovery of a novel locus, *CDHR3* [23]. In addition, a recent family exome sequencing [64] and candidate gene resequencing [65] suggested an increased heterogeneity in asthma and the importance of rare variants. As costs for targeted resequencing and whole genome sequencing continue to decrease, this makes approaches to investigate variation *per se* on a large scale a real possibility. The integration of environmental factors, known to be an important contributing factor in allergy will be a focus for research efforts allowing gene x environmental interaction to be identified, with more recent studies incorporating these parameters, e.g. interactions of AD and smoking with asthma [32]. The environment is particularly important for epigenetic changes driving disease, with accumulating evidence that the epigenome may be important in allergic disease [66]. As novel loci and polymorphisms are identified with confidence, the long road to translate the biology of these genetic changes begins; however, initiatives such as the Encyclopaedia of DNA elements consortium (ENCODE), aimed at identifying regulatory regions of the genome and the use of expression quantitative trait loci (eQTL) approaches will provide further insight to functional mechanisms.

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Conflict of interest

The authors declare no conflict of interests.

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