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Recent Progress in the Genetic and Epigenetic Underpinnings of Atopy

Carolyn H Baloh, MD[1,2], **Rasika A. Mathias, ScD**[3]

[1]The Immune Tolerance Network; Benaroya Research Institute at Virginia Mason; Seattle, WA 98101.

[2]Department of Medicine, Harvard Medical School, Division of Allergy and Clinical Immunology, Brigham and Women's Hospital; Boston, MA 02115.

[3]Department of Medicine, School of Medicine, Johns Hopkins University, Division of Allergy and Clinical Immunology; Baltimore, Maryland, USA.

Abstract

In the past two years there continue to be advances in our understanding of the genetic and epigenetic underpinnings of atopy pertaining to disease risk and disease severity. The joint role of genetics and the environment has been emphasized in multiple studies. Combining genetics with family history, biomarkers, and comorbidities is further refining our ability to predict development of individual atopic diseases as well as the advancement of the atopic march. Polygenic risk scores will be an important next step for the field moving towards clinical translation of the genetic findings thus far. A systems biology approach, as illustrated by studies of the microbiome and epigenome, will be necessary to fully understand disease development and to develop increasingly targeted therapeutics.

Keywords

Genetics; Polygenic risk score; Family history; Genome wide association; Methylation; Atopy; Atopic march; Asthma; Food allergy; Atopic dermatitis

Introduction

The etiology of atopic diseases is polygenic and complex as evidenced by the finding of many genetic risk loci each with small cumulative risk for disease, the interplay between genes themselves, and notably genes with environment. The degree to which heritability contributes to disease varies by specific diagnosis and by study, with

Corresponding author Rasika Mathias, rmathias@jhmi.edu. 5501 Hopkins Bayview Circle, Baltimore, MD 21224. Phone: 410-550-2487.

Conflicts of Interest

CHB & RAM have no relevant conflicts of interest.

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heritability estimates for asthma ranging from 35 to 70% (1). Atopic diseases are a function of environmental interactions with genomic variation, and often elucidated by epigenetic evidence. Environmental factors are numerous and include in-utero exposures, pollution, aeroallergens, infectious pathogens, and dietary components. Recent advances in understanding atopic disease risk and disease trajectory have continued to leverage the genome wide association study framework and there is promising evidence for clinical translation as the field is in the early stages of implementing polygenic risk scores. Many studies emphasize the importance of combining genetics with family history, other biomarkers, and comorbidities to further improve diagnostic capability. This publication, while not exhaustive, highlights some of the most impactful recently published studies in the genetics and epigenetics of atopy (Tables 1 & 2).

Family history and its ability to predict disease risk

A positive family history (e.g. a parent or sibling with disease) has been a well-documented risk factor for allergic disease, and recent publications continue to demonstrate its importance in predicting risk for disease and disease severity for asthma; while for food allergy and sensitization, the presence of atopic dermatitis may outweigh the importance of family history. In a study of 1,676 children 4–18 years of age referred for asthma evaluation, a family history of asthma in a first degree relative resulted in an increased odds (OR 2.08) of the child having uncontrolled asthma, regardless of other atopic comorbidities (2). Recurrent upper or lower respiratory tract infections also increased risk of uncontrolled asthma (OR 2.4) (2). In contrast to asthma, the likelihood of developing food and aeroallergen sensitization has been shown to be most well predicted by the presence of the first step of the atopic march, atopic dermatitis (AD), rather than by family history of asthma and/or sensitization to at least 1 allergen. Kroner et al. performed a comparison of two birth cohorts: The Cincinnati Childhood Air Pollution Study (CCAAPS) comprising a cohort of children with parental atopy placing them at higher risk for asthma development, and The Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH) which is a cohort of children with atopic dermatitis that had a similar rate of parental atopy to the CCAAPS cohort (3). They found that children in MPAACH were found to have higher rates of sensitization to both aeroallergens and food allergens indicating that AD increases the risk of atopy above parental atopy (3). In a cohort of 321 babies 4–11 months of age who had not yet eaten peanut and were are at high risk of peanut allergy, Keet et al. found that both the presence of eczema and older age before introduction of peanut increased the risk of peanut allergy, and in the absence of eczema, family history of food allergy conferred very little risk of peanut allergy (4).

A recent advancement in the field of precision medicine is the use of the polygenic risk scores (PRS) to predict disease risk, allowing for risk stratification and tailored intervention (5). In an interesting approach, Park et al. tested specifically to see if family history had added value over genetic risk scores for disease prediction. Risk models using genetic variants alone compared to those with genetic variants plus a family history and found thelatter were significantly better at identifying children who progressed through the atopic march to develop atopic dermatitis (AD) and asthma (6). Interestingly, when they used a similar comparison of models to predict atopic dermatitis alone, the genetics-only model

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was superior (6). Participants with asthma were older than the participants with only AD, and potentially had more time for environmental factors, reflected in family history, to influence advancement of the atopic march (6).

Genetic Predictors of Disease Risk: asthma, atopic dermatitis, and food allergy

There have been numerous publications in the candidate gene and genome wide association (GWAS) era that have identified genetic loci associated with asthma, AD and food allergy over the last two decades (7–9). Barriers to advancement in this area include residual heritability (i.e. there is more genetic signal to be uncovered that comes from rare variation, gene interactions with environment and interactions between genes, etc), and limited functional understanding of the genetic loci that have stemmed from the somewhat siloed approaches (e.g. genetics, transcriptomics and epigenetics are often considered in parallel and not interactively). The availability of large biobanks with high numbers of individuals having both genetic data and detailed electronic health records (EHR) has recently offered the opportunity to look across the atopic march and also greatly increase power in genetic discovery. Additionally, the recent inclusion of genetics in clinical trials of therapy allow us to expand our understanding of the role of genomics in disease risk, response to intervention, and disease management. In the more recent publications reviewed here, there is a transition to approaches that are advancing our understanding of how genes interact in elevating disease risk, greater functional mapping of genetic loci with disease, and greater extension to epigenetic determinants of disease risk and severity.

The Chr17q12–21.2 locus has been associated with asthma in multiple studies but determining which gene(s) within this locus are most important has been a challenge due to high linkage disequilibrium. Li et al. used samples from the Severe Asthma Research Program to address this problem. They identified *gasdermin B* (*GSDMB*) to be associated with asthma exacerbations and asthma severity. Functionally, *GSDMB* SNPs act through alteration of IFN signaling and MHC class I antigen presentation (10). Eliason et al. leveraged the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) cohorts, UK Biobank, and iPSYCH study to identify and replicate gene-gene interactions associated with early childhood asthma. They identified an interaction between the *cadherin related family member 3* (*CDHR3*) and *GSDMB* genes that increased asthma risk. The mechanism of these SNPs leading to asthma is predicted to be through increased IL-17A production in response to viral infections (11). SNPs in *thymic stromal lymphopoietin* (*TSLP*) and elevated tissue levels of TSLP mRNA have independently been associated with asthma and AD. Murrison et al. recruited a cohort of children with and without asthma and confirmed that the combined effect of TSLP mutations and increased TSLP mRNA in the nasal epithelium increased asthma risk. They also confirmed that circulating TSLP protein levels were not significantly altered in patients with asthma suggesting that circulating TSLP protein is less important in disease pathogenesis (12).

Sliz et al. identified 30 loci correlating with risk of AD leveraging data from 796,661 individuals, 22,474 of whom had AD, combined from three large European Biobanks - FinnGen Study, UK Biobank, and Estonian Biobank. Beyond replication of the well-known loci (e.g. *Filaggrin (FLG), IL-6R, IL-13, and CLEC16A*) this approach identified novel

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genes including *desmocolin 1* (*DSC1*) and *serpin family B member 7* (*SERPINB7*), both of which are important for the epidermal barrier function (13). Like the functional fine-mapping advances for asthma, there have been advances in mapping non-coding genetic variants from AD GWAS loci to genes with functional relevance. Using chromosome conformation capture (Capture HiC) Sahlen et al. were able to identify 118 target genes of 82 non-coding SNPs previously linked to AD. Notably, about half of the target genes identified were upregulated in the lesional skin of patients with AD and psoriasis (14). This is an important advancement in knowledge, as this study provides biological understanding of the AD genetic loci and identifies candidate pathways for further mechanistic study and therapeutic intervention.

Recent advances in the genetics of food allergy have come from the Learning Early About Peanut (LEAP). This clinical trial setting controlling for sustained oral exposure of peanut in high-risk children is unique as it allows the modeling an early life environmental exposure critical in the determination of peanut allergy. Kanchan et al. (15) confirmed the previously documented association of HLA-DQA1*01:02 with peanut allergy in the peanut avoidance arm of the study. Interestingly, in the presence of oral peanut exposure, the very same HLA-DQA1*01:02 allele was associated with increased peanut-specific IgG4 which in turn was associated with protection from peanut allergy development. This is an illustration of how both genetics and environmental exposures are relevant in allergy, and importantly how they interact in predicting risk or protection of peanut allergy (15). *FLG* variants, another well-known risk factor for AD and consequently food allergy, was further confirmed by The German Genetics of Food Allergy Study Cohort in which the presence of these variants associated with allergies to multiple food allergens including egg, milk, and peanut after adjustment for eczema status. *FLG* variants were associated with persistence of food allergy (16).

Epigenetic Predictors of Disease Risk: atopic dermatitis, food allergy, asthma, and allergic rhinitis.

Epigenetic modifications, which can be induced by environmental factors, have been linked to atopic disease. Most recent studies of epigenetics in atopy have focused on DNA methylation, or the addition of methyl groups to cysteine residues that are in the context of a CpG (17). Differentially methylated positions have been recently identified in nasal epithelium (18) and peripheral blood mononuclear cells (19–23). Levels of enzymes that regulate DNA methylation have also been examined in bronchial epithelium (24). Environmental exposures examined include the intrauterine environment (19), exposure to common environmental allergens (18, 20), pollution (24), and infections (21) have been associated with atopic disease development. An understanding of epigenetic modifications can improve our ability to alter the environment for primary prevention of atopic disease, allow for disease endotyping, and can contribute to improving risk scores for individual diseases and progression of the atopic march.

Asthma is known to have a parent-of-origin mode of transmission with asthmatic mothers more likely to transmit the disease than asthmatic fathers, and a proposed model for this is immune interactions in-utero (25). Assessment of methylation in maternal PBMCs

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during pregnancy in the Assessment of Lifestyle and Allergic Disease During Infancy (ALADDIN) birth cohort revealed differentially methylated regions (DMRs) associated with atopy development in their children suggesting that in utero and/or early life events shape methylation and subsequent development of aeroallergen sensitization (19). The role of the environment has also been implicated in the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort. Methylation profiles in nasal epithelium were largely driven by aeroallergen sensitization, and methylation of cg03565274 was positively associated with having a cat or dog in the home and protection from developing asthma and/or allergic rhinitis (18). More general environmental aspects such as residential proximity to green space, a proxy for aeroallergen exposure in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults (SAPALDIA) study support the role of epigenetic changes in peripheral blood leading to allergic rhinitis development (20).

To further buttress the evidence of the environment on methylation profiles from epidemiological settings, a controlled human exposure crossover study, where allergen exposure altered levels of DNA methylation regulation enzymes in participants with underlying airway hypersensitivity, but not healthy controls, was recently undertaken. Li et al found an association between better lung function (as measured by FEV1/FVC ratio) in response to allergen challenge associated with higher levels of DNA regulation enzymes (DNMT1, DNMT3B, TET2, pTET) in bronchial epithelium, and this effect was not altered with concurrent exposure to diesel exhaust (24). Recent studies have also continued to support the importance of methylation changes related to helminth infections (21). Methylations profiles were also shown to differ by sex and to vary during adolescence contributing to altered incidence of asthma in male and females pre- and post-adolescence (22, 23).

Taken together with pre-existing knowledge, these recent publications continue to showcase the importance of combining family history, genetics, environment, and other clinical factors in understanding allergic disease development in young children. This is best seen in a study of the Canadian CHILD birth cohort study that identified four wheezing trajectories, and found numerous factors including family history, genetics, birth factors, child growth, outdoor and indoor exposure, blood eosinophils, allergies, and respiratory infections to be positively associated with wheezing trajectories. In contrast, breast-feeding was the only negative association with wheezing trajectories (26).

Genomic signatures implicating gene networks in allergy

Alterations in networks of genes related to immune and barrier dysfunction have also been associated with the atopic diathesis, and recent advances have continued to highlight the role of these genes within gene networks. While this review is limited in general to genetics and epigenetics of allergy, the best illustration of advances in gene networks comes from a transcriptomic study in The Inner City Asthma Consortium. Altman et al. identified 6 clinical endotypes of asthma based on wheeze, atopy, and lung function within the Urban Environment and Childhood Asthma (URECA) birth cohort study and relied on network-based gene expression approaches to identify genomic signatures related to these endotypes. One phenotypic group, high wheeze, high atopy, low lung function was subsequently

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correlated with higher expression of Th2 pathway genes as well as a module of *mucin 5AC* (*MUC5AC*) hypersecretion and lower expression of innate and antiviral immunity pathways. Another phenotypic group with medium wheeze and low atopy consistent with T2 low had decreased expression of genes involved in epithelial integrity and increased expression of genes in the PI3K/Akt signaling pathway. The PI3K/Akt signaling pathway has previously been shown to be important for Th17 inflammation in asthma. Taken together, this study suggests therapeutic targets of mucus hypersecretion for a high wheeze, high atopy, low lung function asthma phenotype and Th17 inflammation for a medium wheeze, low atopy asthma phenotype (27).

Three recent studies evaluated the role of early life DNA methylation in the development of IgE mediated food allergy also homing in on networks of genes related to inflammation. Differentially methylation regions (DMRs) were identified in PBMCs from children in the ALADDIN birth cohort. Thirty-eight DMRs correlated with sensitization to food allergens and functionally are involved in focal adhesion, bacterial invasion of epithelium, and leukocyte migration (19). In a study of monozygotic and dizygotic twins, differential methylation of 12 genes was associated with peanut allergy, with 7 of the 12 genes being novel to peanut allergy. The other five genes were associated with immune function, either Th1/Th2 or innate immune pathways.

Furthermore, a comparison of the methylation profiles in twins suggested that genetics may influence the DNA methylation profiles (28). In a comparison of children with asthma born to mothers with and without asthma, Magnaye et al. found differential methylation of genes involved in T cell signaling and response to viral and bacterial response in primary bronchial epithelial cells from the children further supporting the importance of the in-utero environment and epigenetic modifications as a mechanism predisposing to asthma (29). Additionally, childhood AD has been associated with global hypomethylation, and decreased methylation in the golli-mbp locus was recently associated with higher severity of childhood AD and higher IgE levels. This locus is hypothesized to be involved in Th2 cell function and Th2 cytokine production, although further functional validation in AD, and expansion to Th2 networks is still needed (30).

Genomics has also implicated alterations in the respiratory epithelium around gene networks related to ciliary function and airway remodeling. A study of the nasal transcriptome in children with severe asthma from the Airway in Asthma (ARIA-1) cohort and adults with mild-to-moderate asthma from the Airway Transcriptome (ATOM) cohort identified master regulator genes for asthma regardless of severity (*FOXJ1*), in mild-to-moderate asthma (*C1orf38, FMNL1*), and in severe persistent asthma (*LRRC23, TMEM231, CAPS, PTPCRC, FYB*). These genes are functionally important for ciliary assembly and the inflammatory response (31). DNA methylation profiles of asthma have been shown to partially normalize in remitted asthma and methylation of genes involved in ciliary function remains different from healthy controls in subjects with remitted asthma(32). Similarly, treatment refractory asthma (neutrophilic asthma) has been associated with upregulation of gene expression in pro-neutrophilic pathways and a downregulation of gene expression in ciliary function compared to non-refractory asthma in respiratory samples (33). Overall, transcriptomic and epigenetic alterations have been linked to the development of asthma,

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asthma endotypes, and asthma disease severity and functionally point to alterations in Th2 inflammation, non-Th2 inflammation, and alterations in the airway epithelium.

Genomic signatures and response to therapy

Recent advances in omics have improved our understanding of why certain patients do or do not response to existing and novel asthma therapeutics. These findings can be leveraged to advance personalized treatment of allergy. Kan et al. used a multi-omics approach to elucidate SNPs responsible for variation in response to inhaled corticosteroids (ICS). They also leveraged a combination of several studies to increase their power. The *baculoviral IAP repeat containing 3* (*BIRC3*) gene was identified as a candidate for further investigation in ICS response (34). The transcriptome was evaluated in patients who participated in a placebo-controlled trial of OM85, an IT agent which includes a polybacterial extract from a mixture of respiratory pathogens. Treatment response was characterized by improved innate immunity including increased coordination of TLR4 expression, segregation of TNF and IFN-γ and reduced size/complexity of a pro-inflammatory module containing IL-1 and IL-6 (35).

Omics approaches have also been used to improve our understanding of how immunotherapy works in patients with allergic rhinitis. Sharif et al. examined chromatin accessibility in a group of grass allergic participants who received either subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). ATAC-seq identified alterations in chromatin accessibility in circulating T follicular helper cells and T follicular regulatory cells in participants who received SCIT or SLIT. SCIT and SLIT treated participants had a decrease in accessibility to regions involved in metabolic processes and cytokine secretion. Participants treated with SLIT had more accessibility to regions involved in protein transport and secretion than those who received SCIT. Participants who received SCIT or SLIT also had a decrease in Th2 cytokine production and circulating T follicular helper cells with a concurrent increase in T follicular regulatory cells (36).

Genomics across the Atopic March

In addition to understanding genetics and epigenetics of individual atopic diseases, it is important to understand their contribution to the atopic march – *FLG* is for example is an excellent example of a barrier gene that increases risk across the allergic diathesis (15). The Mechanisms of Progression of Atopic Dermatitis to Asthma in Children (MPAACH) cohort was used to evaluate atopic trajectories of Black and White children with atopic dermatitis using longitudinal endotypes. African American children had higher rates of asthma and lower rates of food and aeroallergen sensitization. A combination of heritability and environment were found to contribute to higher rates of asthma in the African American children. White children had an opposing trend with higher rates of food and aeroallergen sensitization and lower rates of asthma. Additionally, White children were found to have more alteration to skin barrier function and decreased keratinocyte filaggrin expression (37). As described earlier, the work by Park et al. emphasized that both genetic SNPs and family history are needed to best predict progression of the atopic march in children with AD (6). Gabryszewski et al. identified specific SNPs associated with progression from AD to asthma and from AD to AR using GWAS in a birth cohort of 158,510 babies(38). Additionally,

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DeVore et al. identified a SNP in *caspase recruitment domain family member 14* (*CARD14*) which regulates *FLG* expression in AD non-lesional skin of MPAACH participants, thereby has the potential to increase the risk of food and aeroallergen sensitization in children with AD (39). Recent work in epigenetics also document shared mechanisms across atopic diseases (40, 41), and the added value of leveraging genomics across the atopic march is further illustrated below in new advances with respect to risk prediction and PRS.

Interaction of epigenetics with the microbiome

While the primary scope of this review is on advances in genetics and epigenetics, the importance of a multi-omics approach must be emphasized. Recent advances combining genetics and/or epigenetics with the microbiome and/or metabolome illustrate this extremely well. Data exploring the correlation between genetics and microbiome in atopy is conflicting. In one cohort of asthmatics, genetics and nasal microbiome were not able to be correlated (42). In another study of asthmatics, a SNP in *vanin 1* (*VNN1*) correlated with the metabolome, assessed in serum (43).

Other studies have correlated infections or the microbiome to alterations in the epigenome and/or gene transcription. Decreased microbial diversity early in life, at 1 week of age, in the COPSAC 2010 cohort correlated with AR development at 6 years of age. This is mediated through altered methylation of genes involved in the lysosome and bacterial invasion of epithelial cell pathways (44). In a cohort of pet dander sensitized children, sensitization was associated with lower microbial diversity, decreased abundance of Corynebacterium sp and Staphylococcus epidermidis, and lowered fatty acid elongation in mitochondria. A causal mediation analysis showed that these alterations led to allergic rhinitis through altered nasal gene expression (45). Streptococcal and staphylococcal infections have been shown to alter *SMAD family member 3* (*SMAD3*) transcription in the nasal epithelium and increase the odds of asthma exacerbations (46).

Eosinophilic esophagitis (EoE)

Development of EoE is known to be multifactorial with genetics and environment both contributing. The genetic contribution to disease is estimated to be 15% (47). Two recent meta-analyses replicated identification of loci previously reported in association with EoE including 5q22 (*TSLP*), 2p23 (calpain 14 (CAPN14)), and 11q13 (leucine rich repeat containing 32 (LRRC32) (48, 49). Notably, overlap in risk loci for EoE and other atopic disease continues to be identified (49). They also identified new loci providing additional information for generating a PRS and for therapeutic targeting (48, 49). While not directly a PRS, Min et al. leveraged a panel of known risk genes to predict EoE recurrence. They combined a severity scoring algorithm and transcriptomics of known EoE risk genes from a single biopsy in the distal esophagus and were able to accurately predict concurrent eosinophilia in the proximal esophagus and subsequent EoE relapse (50). In yet another study a combination of endoscopy and genetics were informative. SNPs in *calpain 14* (*CAPN14*), basal zone hyperplasia, eosinophilic inflammation, esophageal strictures, and increased likelihood of attaining a histologic remission with dietary restriction were all associated with very early onset EoE (51). Together, these advances are improving our

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ability to predict disease development and trajectory and suggest that combinations of genetics and biopsies can be more informative than either alone.

Risk prediction scores – the translation of genomics into clinical practice

The utility of PRSs to risk stratify individuals and tailor intervention is now an often-discussed aspect of complex disease risk prediction (5), PRS are intended to improve biomedical outcomes via precision medicine. A PRS is a cumulative score to predict disease risk that is generated for each individual and it is constructed as the weighted sum of a collection of genetic variants identified through large discovery GWAS (Box 1). An important feature of the PRS is that it is often derived only from European ancestry individuals, and therefore does not perform as well in non-European individuals (52); this is a particular problem in asthma where there are notable health disparities. Prior asthma PRS leveraged all-European studies, and recently, Namjou et al. developed a multi-ancestral PRS for childhood asthma using data from Electronic Medical Records and Genomics (EMERGE) and the UK Biobank. They found that pediatric participants with the top 5% PRS had 2.80 to 5.82 increased odds of asthma compared to the bottom 5%, and the prediction was high across all ancestry groups demonstrating the utility of risk prediction from asthma (53) and doing so in an equitable manner considering race and ethnicity.

As mentioned previously, common genomic networks across the atopy march would suggest greater ability to predict risk for any single allergic outcome when genomics signatures across the allergic diathesis are combined. This was recently documented for genetic scores to predict AD cases and AD severity (54). While an AD-*only* PRS performed well at prediction, accuracy was first improved when PRSs were built off the larger ‘atopy’ genetic signal and further improved when including specific *FLG* loss of function (LOF) mutations. The best prediction to distinguish individuals with severe AD from control subjects with OR of 3.86 (95% CI, 2.77–5.36) came from building scores across the ‘atopy’ signal and including *FLG* (54). Methylation risk scores have also been recently developed for atopy phenotypes (e.g. total IgE, asthma, allergy) and tested in the Influence of Life-style factors on Development of the Immune System and Allergies in East and West Germany (LISA) birth cohort. The methylation risk scores had a good ability to cross-sectionally identify atopic participants in the LISA birth cohort. There was also a dose response relationship between methylation and aeroallergen sensitization (55).

Together these advances offer promise into the ability to use genomic and epigenetic signatures to predict disease risk and severity provided the discovery studies from which these scores are derived are well-representative and inclusive. Genomic interrogations in the recent two years continue to drive home the importance of representation and diversity in studying allergy. For example, *deoxyribonuclease 1 like 3* (*DNASE1L3*) variation was associated with increased risk of asthma exacerbations in those of African American or Latinx ancestry but not those with European ancestry (56); GWAS in Japanese participants with AD identified genetic susceptibility loci unique to the Japanese population (57), GWAS in Peruvian children identified a novel locus mapping to a long noncoding RNA that associated with lung function (58), and meta-analysis in the recent National Heart Lung and Blood Institute Trans-Omics for Precision Medicine program, Consortium on Asthma

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among African-ancestry Populations in the Americas (CAAPA), and the Atopic Dermatitis Research Network (ADRN) identified HLA-DQB1*03:02 as being associated with lower total IgE levels in Hispanic/Latinx ancestry populations (59).

The importance of population differences is also noted in epigenetics. DNA methylation was assessed in a cohort of Latinx children and identified 25 genomic regions with differential methylation in those with and without asthma. The TGF-b pathway was identified as the most significantly altered biological pathway in asthma. CpG's near calcium/calmodulin dependent protein kinase 1D (*CAMK1D*) and *T cell immunoreceptor with Ig and ITIM domains* (*TIGIT*), genes related to inflammatory signaling, were altered in those with asthma (60). Zhu et al. identified differentially methylated positions (DMPs) and DMRs associated with asthma in a cohort of African American children. DMPs were identified that correlated with traffic-related air pollution or second-hand smoke exposure (61). Both of these studies report novel findings that add to our understanding of the role of epigenetics in disease risk and ratify the importance of diversity and inclusion in our genomic interrogations of allergic disease.

Conclusion

With significant advances in the genetics of atopy in recent years, the field is poised to expand to translational aspects such as polygenic risk scores to facilitate disease risk stratification, identification of severity trajectories, and potentially even response to therapy and intervention (Figure 1). To accomplish this, however, strategies that combine genetics with additional omics approaches (e.g. epigenetics, microbiome, transcriptomics, and metabolomics), and include clinical and laboratory data within a systems biology approach to understand risk of disease, disease trajectories, and responses to therapy (Box 2) is key. Existing genomics resources coupled need to be coupled with integration from biobank initiatives that bring together the electronic health record with genetics, analysis methods that allow the inclusion of smaller studies in under-represented populations, and an emphasis on new initiatives in under-represented groups in genomics research are all approaches that should be considered (Box 2). Finally, to achieve success, there needs to be an emphasis on this translation to clinical practice in an equitable manner.

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Abbreviations

AD	atopic dermatitis
CCAAPS	Cincinnati Childhood Air Pollution Study
MPAACH	The Mechanisms of Progression of Atopic Dermatitis to Asthma in Children

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PRS	polygenic risk scores
GWAS	genome wide association
EHR	electronic health records
GSDMB	*gasdermin B*
COPSAC	Copenhagen Prospective Studies on Asthma in Childhood
CDHR3	*cadherin related family member 3*
TSLP	*thymic stromal lymphopoietin*
FLG	*Filaggrin*
DSC1	*desmocolin 1*
SERPINB7	*serpin family B member 7*
Capture HiC	chromosome conformation capture
LEAP	Learning Early About Peanut
DMRs	differentially methylated regions
PIAMA	Dutch Prevention and Incidence of Asthma and Mite Allergy
SAPALDIA	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults
URECA	Urban Environment and Childhood Asthma
MUC5AC	*mucin 5AC*
ALADDIN	Assessment of Lifestyle and Allergic Disease During Infancy
ARIA-1	Airway in Asthma
ATOM	Airway Transcriptome
ICS	inhaled corticosteroids
BIRC3	*baculoviral IAP repeat containing 3*
SCIT	subcutaneous immunotherapy
SLIT	sublingual immunotherapy
CARD14	*caspase recruitment domain family member 14*
VNN1	*vanin 1*
SMAD3	*SMAD family member 3*

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CAPN14	calpain 14
LRRC32	leucine rich repeat containing 32
EMERGE	Electronic Medical Records and Genomics
LOF	loss of function
LISA	Influence of Life-style factors on Development of the Immune System and Allergies in East and West Germany
DNASE1L3	*deoxyribonuclease 1 like 3*
CAAPA	Consortium on Asthma among African-ancestry Populations in the Americas
ADRN	Atopic Dermatitis Research Network
CAMK1D	*calcium/calmodulin dependent protein kinase 1D*
TIGIT	*T cell immunoreceptor with Ig and ITIM domains*
DMPs	differentially methylated positions

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Box 1.

Polygenic Risk Prediction.

A polygenic risk score (PRS)(5, 62, 63) is the weighted sum of the risk for disease conferred by many disease-associated genetic variants across the genome, each with a small additive effect. The selection of variants and their weights generally relies on external and well-powered genomewide association studies. The selection of variants and their weights requires careful consideration to account for correlation between genetics variants and thresholds of the PRS to maximize prediction. The utility of the derived PRS for the disease under consideration is then judged based on its ability to accurately predict disease in an independent sample. Often, the value of the PRS is also judged based on its added value at predicting disease beyond pre-existing tools; for example the value of a PRS in addition to the Pooled Cohort Equation for cardiovascular disease(62, 63). Risk prediction scores can expanded to be a combination of multiple features predicting a phenotypic trait including genetics, epigenetics, biomarkers, histology and clinical risk factors. Importantly, the current generalizability of risk prediction scores is often limited in non-European individuals because to date, these scores heavily on pre-existing genetic studies where the overwhelming majority representation is European ancestry. To address this limitation, methods that maximize the available data in under-represented populations need to be considered in conjunction with investment in new and expanded genomic studies in these individuals.

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Box 2.

Key next steps in the genetics and epigenetics of atopy

- The continued use of large biobanks and meta-analyses of large cohorts is needed to obtain confidence in genetic and epigenetic findings.
- Increased incorporation of genetic and epigenetics in clinical trials is needed to improve risk prediction scores in response to treatment.
- Additional studies assessing for epigenetic modifications are needed to improve our understanding of gene*environment interactions. Studies should involve multiple types of epigenetic modifications, not just methylation.
- Additional interrogation functional networks associated with genetics and epigenetics will provide new therapeutic targets.
- Further examination of the genetics/epigenetics of atopic march progression will aid in development of primary and secondary prevention strategies for atopy.
- A focus on under-represented minorities in genomics research.
- Polygenic risk scores, methylation risk scores, and other risk prediction scores are needed to best predict risk of disease development, prognosis, and response to treatment.

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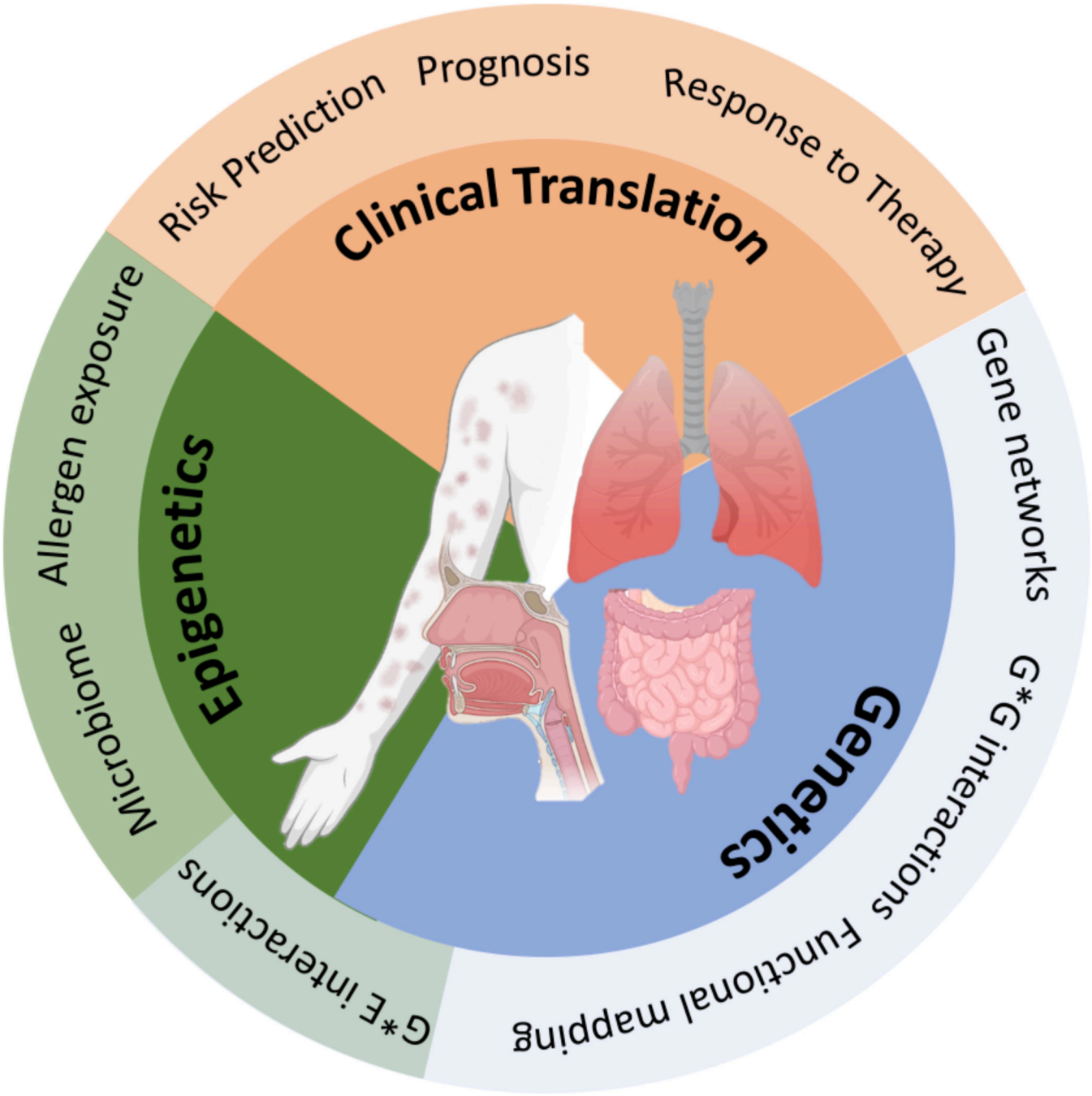


Figure 1. A Systems Biology Approach Leveraging Genetics & Epigenetics.

Recent advances in the field of genetics and epigenetics of atopy are beginning to illustrate the importance of risk prediction scores and combining multiple datasets in a systems biology framework. Use of integrative approaches across genetics, epigenetics, other omics, and clinical data in systems biology frameworks will be needed to advance our ability to predict risk of atopic disease development, prognosis, and response to therapy.

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Table 1.

Key messages in genetics and epigenetics of atopic disease

Family history to predict disease risk	Family history confers an increased risk of uncontrolled childhood asthma regardless of other atopic comorbidities (2), but does not add much beyond AD for aeroallergen/food allergen sensitization (3) and peanut allergy (4).
Genetics in development of atopic diseases	Recent studies have uncovered gene-gene interactions (11), gene-environment interactions (15), and functional mapping on previously poorly understood genetic loci [(10), (12), (14).]
Epigenetics of atopic diseases	Epigenetic studies illustrate the importance of environmental interactions in-utero (19) and in early life (18). Epigenetic studies can be combined with family history, genetics, environment, and other clinical factors (26) to predict disease risk, prognosis and response to intervention.
Gene networks in atopic diseases	(27)(29)[(31)(32)(33)]Networks of genes involved in epithelial barrier function [(31), (32), (33)], Th2 inflammation (27), and Th17 inflammation (27) have been associated with asthma development and with specific asthma endotypes.
Genomic signatures corresponding to therapeutic response	*BIRC3* mutations (34), methylation across networks of innate immunity genes(35) and increased chromatin accessibility to regions involved in protein transport and secretion (36) have been recently implicated in mechanism of response to therapy.
Genetics of atopic march progression	Filaggin (*FLG)* remains a notable contributor to risk across the atopy march, and *CARD14*, a regulator of *FLG* expression, was linked to increased risk of atopic march progression (39). DNA methylations profiles common to multiple atopic diseases were identified (40, 41).
Risk prediction scores	Clinical translation of genomic signatures are manifesting in polygenic risk scores in the recent years, (53) (54). Methylation risk scores for atopic phenotypes (55) offer the ability to bring the importance of environmental exposures, a factor for atopic disease into these applications. Race and ethnicity are important considerations as new work continues to show differences in genetic [(56), (57), (58), (59)] and epigenetic [(60), (61)] underpinnings of atopic disease.

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Table 2.

Advances in genetics and epigenetics by atopic disease

	Asthma	Allergic rhinitis/ Aeroallergen sensitization	Atopic Dermatitis	Food Allergy	Eosinophilic esophagitis
Family history to predict disease risk	A first-degree relative increased likelihood of asthma development in child (2). Family history has added value beyond genetics in predicting risk (2). Family history in conjunction with genetics, environmental factors, and respiratory infections relates to wheezing trajectories in children (26).	Presence of atopy in a child was more important than family history in predicting development of aeroallergen sensitization (3).	Family history does not have added value beyond genetics (6).	Presence of atopy in a child was more important than family history of food allergy(4). Family history of food allergy had little impact on predicting risk of a child developing peanut allergy in the absence of AD (6).	
Genetics in development of atopic disease	SNPs in *CDHR3 & GSDMB* were associated with increased risk of asthma development. SNPs in *GSDMB* were associated with asthma exacerbations and asthma severity (10). SNPs in *TSLP* & elevated tissue levels of TSLP mRNA were associated with asthma development (12).		SNPs in *TSLP* & elevated tissue levels of TSLP mRNA were associated with AD development (12). Novel findings for *DSC1* and *SERPINB7* (13).	HLA-DQA1*01:02 has prominent interaction with peanut consumption: increased risk of peanut allergy in absence of consumption and protection through IgG4 in presence of consumption (15). *FLG* were associated with food allergy development and persistence (16).	Overlap in genetic risk loci for EoE and other atopic disease is increasing (49). A severity score comprised of known EoE risk genes and interrogation of a esophageal single biopsy was able to predict disease relapse (50).
Epigenetics of atopic diseases	Having a dog or cat may confer protection through methylation (18).	Methylation in maternal PBMCs suggeste in-utero and/or early life events impact development of aeroallergen sensitization (19). Having a dog or cat may confer protection through gene methylation (18). Exposure, or lack thereof, to aeroallergens may impact risk through methylation (20).			
Gene networks in atopic diseases	High wheeze, high atopy, low lung function correlate with higher expression of Th2 pathway, a module of *MUC5AC* hypersecretion, and lower expression of innate and antiviral immunity pathways (27). Medium wheeze and low atopy correlate with decreased expression of epithelial integrity genes and increased expression of genes related to Th17		Decreased methylation of the golli-mbp locus, a locus involved in Th2 inflammation, was associated with disease severity and higher IgE levels (30).	Methylation at genes involved in focal adhesion, bacterial invasion of epithelium, and leukocyte migration correlated with sensitization to foods (19). Methylation of genes involved	

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	Asthma	Allergic rhinitis/ Aeroallergen sensitization	Atopic Dermatitis	Food Allergy	Eosinophilic esophagitis
	inflammation (27). Differential methylation of genes involved in T cell signaling and response to viral/bacterial response link between maternal asthma and risk of disease in their child (29). Increased transcription of genes involved in ciliary assembly and the inflammatory response were associated with development, severity, and remission (31). Treatment refractory asthma was associated with upregulation of gene expression in pro-neutrophilic pathways and a downregulation of ciliary function (33).			in Th1/Th2 or innate immune pathways associated with peanut allergy (28).	
Genomic signatures and response to therapy	BIRC3 was identified as a candidate gene for involvement in ICS response (34). A transcriptomic signature for response to OM-85, an IT agent with a polybacterial abstract, was identified (35).	Grass allergen SCIT and SLIT led to a decrease in accessibility to regions involved in metabolic processes and cytokine secretion (36).			SNPs in *CAPN14* in combination with specific endoscopy findings associated with likelihood of achieving histologic remission in response to dietary restriction (51).
Risk prediction scores	A multi-ancestral PRS for childhood asthma was developed (53).	A methylation risk score was developed that identified atopic children and specifically children with aeroallergen sensitization (55).	A PRS comprised of FLG LOF mutations and genetic signatures of ‘atopy’ was superior to using FLG LOF mutations alone to identify participants with atopic dermatitis (54).		