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Personalized management of asthma exacerbations: lessons from genetic studies

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Abstract

INTRODUCTION—The genetics of severe asthma and asthma exacerbations are distinct from milder forms of asthma. Gene-environmental interactions contribute to the complexity and heterogeneity of severe asthma and asthma exacerbations, and pharmacogenomic studies have also identified genes that affect susceptibility to asthma exacerbations.

AREAS COVERED—Studies on the genetics, gene-environment interactions, and pharmacogenomics of asthma exacerbations are reviewed. Multiple individual genetic variants have been identified to be associated with asthma exacerbations but each genetic polymorphism explains only a fraction of the disease and by itself is not able to translate into clinical practice. Research is shifting from candidate gene studies and genome wide association studies towards more integrative approaches to translate genetic findings into clinical diagnostic and therapeutic tools.

EXPERT COMMENTARY—Integrative approaches combining polygenic or genomic data with multi-omics technologies have the potential to discover new biologic mechanisms and biomarkers for severe asthma and asthma exacerbations. Greater understanding of genomics and underlying biologic pathways will also lead to improved prevention and treatment, lowering costs, morbidity, and mortality. The utilization of genomic testing and personalized medicine may revolutionize asthma management, in particular for patients with severe, refractory asthma.

Keywords

asthma; gene environment interaction; pharmacogenomics; genome wide association study; candidate gene association study

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Declaration of interest

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1.0 INTRODUCTION

Asthma is a heterogeneous and genetically heritable disease composed of multiple subtypes with discrete pathogenic mechanisms[1]. Asthma affects an estimated 300 million individuals worldwide and accounts for significant morbidity and economic costs, particularly in severe or uncontrolled asthmatics[2]. The biology and genetics of severe asthma is distinct from milder forms of the disease[3]. Research has shown that the greatest predictor of future asthma exacerbations is a prior asthma exacerbation in both children and adults, which demonstrates that susceptibility toward asthma exacerbations exists beyond general asthma susceptibility[4, 5]. Greater understanding of the genetics and pathogenesis of severe asthma and in particular asthma exacerbations may lead to new targeted treatments that more effectively lower asthma morbidity.

Most genetic studies on asthma have previously focused on asthma susceptibility instead of asthma phenotypes because case-control studies are easier to conduct and genetic studies in general, as well as genome-wide association studies (GWAS) specifically, require large sample sizes for adequate power. Asthma severity studies depend on accurate phenotyping of individuals and selection of comparison measures. The genetics of asthma exacerbations are complex and heterogeneous, influenced by multiple genes and the environment[3]. While individual genes and environmental loci can provide biologic insights into the pathogenesis of severe asthma, it is likely that a combination of these factors interact to contribute to the full spectrum of severe asthma. Integrating these multiple components will require novel pathway and network approaches to discover underlying interactions and gain new insights into biologic mechanisms and therapeutic targets.

In this review, we will discuss the genetics of severe asthma focusing on research that has studied asthma exacerbations and advanced the understanding or clinical management of severe asthma. Asthma exacerbations are an acute or sub-acute worsening of symptoms and lung function, and exacerbations in research studies are often measured as emergency department (ED) visits, hospitalizations, and use of oral corticosteroids[6]. Asthma severity classifications are defined by the Global Initiative for Asthma (GINA) and National Asthma Education and Prevention Program[6, 7]. Research on human genetics, gene-environment interactions, and pharmacogenomics will be reviewed. When available, the genomic reference sequence is given. We will also outline current and future directions in the field as research is rapidly progressing toward individual genetic profiling and integrated pathway approaches.

2.0 ASTHMA EXACERBATION GENES IDENTIFIED BY CANDIDATE GENE STUDIES

Candidate genes are selected via their influence on the known biology of the disease process of interest. The gene *IL-4* and its receptor *IL-4R* have emerged as major candidates not only for regulating asthma susceptibility, atopy, and serum total IgE levels but also for asthma exacerbations[8, 9]. The *IL*-4 gene is located on chromosome 5q31 and maps within the chromosome 5q31-33 locus, where several other candidate genes for asthma severity are located[8]. These other genes, including the β_2-adrenoreceptor (*ADRB2*), *RAD50*, and *IL-9*

genes will be discussed later. A multinational study from Australia, New Zealand, and Canada found the rs2243250:C>T SNP in the IL-4 promoter to be associated with fatal or near-fatal asthma exacerbations (Table 1)[10]. The rs2243250 polymorphism has also been associated with a lower predicted ratio of forced expiratory volume in 1 second to forced vital capacity (FEV1/FVC) in Caucasians in a multicenter cohort of moderate to severe asthmatics in the United States (US) and with increased severity of airway hyperresponsiveness (AHR) as measured by methacholine challenge in a study from Taiwan[11, 12]. *IL-4R* is located on chromosome 16p12, and polymorphisms in *IL-4Rα* (rs1801275:A>G and rs1805011:A>C) are associated with severe asthma exacerbations and lower predicted FEV1/FVC in Caucasians and African Americans in the US[13]. These findings were replicated in an independent multicenter cohort that found African Americans to have a higher prevalence of severe exacerbations and polymorphisms in *IL4-Rα*[13]. The association of the rs1801275 polymorphism in *IL-4Rα* with a decrease level of lung function has also been demonstrated in multinational study from Australia, New Zealand, and Canada[10]. The rs1801275:A>G SNP in *IL-4R* is associated with enhanced signaling through the IL-4R and an increased number of bronchial mast cells, suggesting a mechanism by which variation in *IL-4R* may modify asthma severity and atopy[13, 14].

Polymorphisms in the *ADRB2* gene are common and associated with distinct forms of severe asthma[15, 16, 17]. Two nonsynonymous polymorphisms are associated with agonist-promoted downregulation in human airway smooth muscle cells and measurements of asthma severity: the rs1042713:G>A SNP resulting in substitution of Gly for Arg at codon 16 (Arg16Gly) and the rs1042714:G>C SNP resulting in substitution of Glu for Gln at codon 27 (Glu27Gln)[18]. A third coding SNP (Thr164Ile) has also been described but is uncommon and not associated with asthma severity[19]. A candidate gene study in a US population found Arg16Gly to be associated with steroid-dependence and use of allergen immunotherapy, and a separate US cohort identified Arg16Gly to be associated with frequent nocturnal awakening due to asthma[15, 16]. Glu27Gln was associated with history of asthma-related hospitalizations in a study from New Zealand, and the prevalence of the Glu27Gln polymorphism was demonstrated to be higher in moderate-to-severe Caucasian asthmatics compared with those with mild disease in an independent population from Canada[20, 21]. Furthermore, in a cohort of 65 steroid-dependent asthmatics from the United Kingdom (UK), Glu27Gln was associated with increased AHR in a gene-dose dependent manner[17]. Lastly, a study from Australia on *ADRB2* haplotype pairs, which allows for observation of interactions between individual SNPs and haplotypes, found no association between individual polymorphisms and severe asthma as defined by American Thoracic Society guidelines but a strong correlation between the heterozygous haplotype pair containing Arg16Gly and Glu27Gln and severity of asthma in Caucasians[19]. Polymorphisms in *ADRB2* have not been found to be associated with fatal or near-fatal asthma[21]. Despite the association of *ADRB2* polymorphisms with β2-adrenergic receptor downregulation, *ADRB2* polymorphisms and haplotypes have not consistently demonstrated an association with β_2-agonist treatment response, and their role in the pathogenesis of severe asthma and asthma exacerbations remains unclear[22, 23, 24].

Polymorphisms rs1801282:C>G and rs3856806:C>T in the peroxisome proliferator-activated receptor gamma (*PPARG*) gene were shown to be protective against asthma

exacerbations in Caucasian children and young adults in the UK[25]. Individuals who were homozygous haplotypes for the C allele at both rs1801282 and rs3856806 had an increased risk for asthma exacerbations, courses of oral steroids, school absences, and hospital admissions[25].

Transforming growth factor beta 1 (TGF-β1) and interleukin-10 (IL-10) are an anti-inflammatory cytokines that are secreted by T regulatory cells to drive peripheral tolerance and suppress airway inflammation[26]. Polymorphisms rs1800469:A>G and rs2241712:C>T in the *TGFβ1* promoter have been associated with increased AHR in a cohort of Costa Rican children and replicated in a US pediatric Caucasian cohort, and the exonic SNP rs1800470:G>A was associated with lower risk of asthma hospitalizations in both cohorts in a gene-dose dependent manner[27]. In addition, a study of Caucasian asthmatics in the UK found the rs1800469 polymorphism to be associated in a gene-dose dependent manner with asthma severity[28]. Three SNPs are common in the *IL-10* promoter–rs1800896:T>C, rs1800871:A>G, and rs1800872: T>G[29]. Two haplotypes, CGG and TAT, were discovered to be associated with severe asthma in Caucasians in the UK[30]. Furthermore, the C allele at rs1800896 is associated with higher IL-10 production versus the T allele in peripheral blood mononuclear cells[29]. Fewer severe asthmatics had the low IL-10 producing CGG haplotype, and more severe asthmatics had the high IL-10 producing TAT haplotype[30].

In summary, multiple biologic candidate genes have demonstrated association with asthma exacerbations and asthma severity. Many of these studies have further demonstrated a functional role behind the associated variants. However, none of the individual variants by themselves have been identified to uniquely differentiate individuals with frequent exacerbations from those without or been translatable to clinical diagnostic and therapeutic agents.

2.1 ASTHMA EXACERBATION GENES IDENTIFIED BY GWAS

In contrast to candidate gene studies, GWASes provide an unbiased approach to genetic association by interrogating potential associations across the genome. The gene *CHI3L1* encodes for chitinase-like protein YKL-40, also known as human cartilage glycoprotein 39 [HCgp-39] or chitinase 3-like 1[31]. Chitin is the second most abundant polysaccharide in nature and provides protection for pathogens[32]. Mammalian chitinase hydrolyzes chitin and increases during T-helper type 2 airway inflammation and hyperresponsiveness[32]. The rs4950928:G>C SNP in the *CHI3L1* functional promoter was first found to be positively associated with asthma prevalence, AHR, and serum YKL-40 levels in a founder population of European ancestry and replicated in a German case-control population[31]. Serum YKL-40 levels were found to inversely correlate with FEV1 and were a significant predictor of both asthma and decline in lung function[31]. The protective effect of the minor G allele against asthma susceptibility and exacerbations was replicated in Caucasian adults and children in the UK[33]. Several other SNPs in *CHI3L1* have been found to be associated with asthma severity and YKL-40 levels, including the intronic rs12141494:G>A SNP with lower predicted post-bronchodilator FEV1/FVC in two independent populations of

European ancestry and the SNPs rs1538372:A>G and rs10399931:T>C in a gene-dose dependent manner with lower FEV1/FVC in a Taiwanese study[34, 35].

The chromosome 17q12-21 locus containing the *ORMDL3* and *GSDMB* genes has been widely replicated to be associated with childhood and adult asthma in multiple ethnically diverse populations[36, 37]. ORMDL proteins are transmembrane proteins localized to the endoplasmic reticulum that regulate sphingolipid biosynthesis, and GSDM proteins regulate epithelial cell autophagy[38, 39]. In a case-control study of children and young adults of European ancestry with asthma in the UK, the SNP rs7216389:C>T, located within the first intron of the *GSDMB* gene, was found to be associated with an increased risk of asthma exacerbations, school absence, and oral corticosteroid use over the previous 6 months[40]. TT homozygotes were at increased risk over both CT and CC genotypes[40]. Another SNP rs2305480:G>A in *GSDMB* has been associated with asthma-related hospitalizations in both Caucasian and non-Caucasian children and replicated in three European cohorts[41]. Finally, the SNP rs4794820:A>G was associated with increased risk of severe asthma according to GINA classification compared to mild to moderate asthma in individuals of European ancestry in the UK[42]. This association was replicated in an independent cohort of subjects from the UK and Western Australia of European ancestry[42].

Our research group has recently conducted a GWAS meta-analysis of two pediatric cohorts of Caucasians, identifying polymorphisms in alpha-T-catenin (*CTNNA3*)–rs7915695:T>C, rs7923078:A>C, rs7923279:G>T, and rs6480203:A>C–to be associated with asthma exacerbations[43]. The alpha catenin family of proteins is critical to the function of epithelial cell adherens junctions and mediates cell-cell adhesions[44]. The GWAS also found a non-significant association with semaphorin 3D (*SEMA3D*) SNP rs993312:C>A and asthma exacerbations in the two pediatric Caucasian cohorts but a significant association in an African American adult and pediatric replication cohort[43]. Semaphorins are transmembrane and secreted proteins, and class 3 semaphorins regulate endothelial cell motility and migration[45, 46]. SEMA3D is necessary for normal vascular patterning and may play a role in airway remodeling[43, 46].

A GWAS of early childhood asthma with severe exacerbations identified rs928413:G>A near *IL33*, rs6871536:T>C in *RAD50*, and rs1558641:G>A in *IL1RL1* to be associated with increased risk of asthma-related hospitalizations in Caucasian children in Denmark[41]. These findings were replicated in three cohorts in Europe, two of European ancestry and one of mixed ancestry[41].

In summary, like candidate gene studies, GWASes have identified several novel loci in multiple genes associated with asthma severity and exacerbations. Current work is focused on further defining the biology behind these associations. However, no single GWAS association is sufficient by itself to provide a model for clinical translation as it relates to asthma exacerbations or severity.

2.2 GENE-ENVIRONMENT INTERACTION STUDIES

Studies focusing on gene-environment interactions and exposures have identified novel asthma genes and led to greater understanding of underlying biologic mechanisms. A GWAS

of early childhood asthma with severe exacerbations was the first to identify the SNP rs6967330:G>A in the cadherin-related family member-3 (*CDHR3*) gene to be associated with increased risk of asthma-related hospitalizations (Table 2)[41]. The findings were replicated in three cohorts in Europe, two of European ancestry and one of mixed ancestry[41]. CDHR3 is a member of the cadherin family of transmembrane proteins and was recently discovered to facilitate rhinovirus C binding and replication[47]. Furthermore, the rs6967330 SNP in *CDHR3* mediates enhanced rhinovirus C binding and increased progeny yields *in vitro*[47].

Vitamin D insufficiency affects asthma outcomes through gene-environment interactions. The cytotoxic and regulatory T-cell molecule (CRTAM) regulates the interaction between T cells and antigen presenting cells and enhances NK cell adhesion and cytotoxicity[48, 49]. Our GWAS in Caucasian children found individuals who were homozygous at the minor alleles of rs7941607:C>T, rs2272094:A>G, and rs2140151:A>C in *CRTAM* to have increased likelihood of asthma exacerbations when stratified by low serum levels of vitamin D[50]. Asthma exacerbations were defined as ED visits or hospitalizations, and high serum vitamin D levels were protective for the same variants. These findings were replicated in a cohort of Costa Rican children. One of the SNPs, rs2272094, is a nonsynonymous polymorphism in *CRTAM*, and a functional cell line study showed *CRTAM* expression in the presence of vitamin D to be significantly increased in the rs2272094 homozygous minor allele group compared to the homozygous major allele group[50].

House dust mite exposure has been found to modify polymorphisms in *IL-10*, *TGFβ1*, and *IL-9* to increase the risk of asthma exacerbations. Among Costa Rican children exposed to high levels of dust mite allergen (Der p 1 allergen >10μg/g), those who were homozygous for the minor allele at rs1800896:T>C, rs3024492:T>A, or rs3024496:A>G in *IL-10* had higher odds of asthma hospitalizations[51]. The major allele at rs1800896, rs3024492, or rs3024496 was protective against asthma exacerbations in a gene-dose dependent manner in asthmatic children exposed to high levels of dust mite allergen. The results for rs1800896 and rs3024496 were replicated in a US pediatric Caucasian cohort[51]. In another study, dust mite exposure was found to modify the effects of SNPs in *TGFβ1* in Costa Rican children and an independent cohort of US Caucasian children[27]. Higher levels of dust mite allergen exposure led to SNP-specific effects of increased AHR for the exonic SNP rs1800470:G>A and increased asthma exacerbations for the promoter SNP rs2241712:C>T[27]. Similarly, elevated dust mite exposure has been also shown to increase the odds of a severe asthma exacerbation by three to four-fold in US Caucasian and Costa Rican children who have the *IL-9* polymorphism rs11741137:C>T or rs2069885:G>A[52]. Of note, the polymorphisms rs11741137:C>T and rs2069885:G>A in IL-9 are in linkage disequilibrium ($r^2 = 0.99$) and measure the same effect. In children exposed to low dust mite levels, the same polymorphisms were associated with 30% reduced odds of severe asthma exacerbation, as defined by asthma-related ED visit or hospitalization, and a meta-analysis combining these two cohorts with a third cohort of children from the US and Puerto Rico replicated the association in rs2069885[52].

The 20p13 locus contains the genes a disintegrin and metalloproteinase 33 (*ADAM33*) and sialic acid-binding Ig-like lectin 1 (*SIGLEC1*)[53]. In a pediatric case control study from

Croatia, asthmatic children who were homozygotes for the G allele at rs512625:A>G in *ADAM33* and T allele carriers at rs532448:A>T in *SIGLEC1* had 2.61 times odds and 1.99 times odds, respectively, of having two or more asthma-related hospitalizations compared to other genotypes. The increased odds of asthma-related hospitalizations were augmented by early life exposure to tobacco smoke, defined as having a mother who smoked during pregnancy. Asthmatic children who were homozygotes for the G allele at rs512625 in *ADAM33* and had early life exposure to tobacco smoke had 9.15 times odds of having two or more asthma-related hospitalizations. These children also had lower lung function compared to asthmatic children who were non-exposed and did not have the rs512625 polymorphism[53]

2.3 PHARMACOGENOMIC STUDIES

Pharmacogenomic studies relate the interaction of genes with response to medications and have identified multiple genetic polymorphisms associated with asthma exacerbations in children and adults treated with inhaled corticosteroids (ICSs), including variations in *ST13*, Fc epsilon RII (*FCER2*), *P2RX7*, and cap methyltransferase 1 (*CMTR1*) (Table 3). *ST13* encodes for heat shock protein 70 interacting protein, a co-chaperone in the glucocorticoid receptor complex that promotes functional maturation of the receptor[54]. In a meta-analysis of three independent Northern European cohorts, rs138335:C>G and rs138337:A>G in *ST13* increased the odds of asthma-related hospital visits in children and young adults on ICSs[55]. The G allele in rs138335 was also associated with oral corticosteroid use in a gene-dose dependent manner. These data were combined with three independent cohorts of Caucasian and Hispanic children and young adults from the UK, US, and Puerto Rico into a six cohort meta-analysis. The rs138335 SNP in *ST13* remained associated with asthma-related hospital visits and oral corticosteroid use but was under the threshold for significance when corrected for multiple testing[55].

FCER2 (or CD23) is the low-affinity IgE receptor, which can induce cellular responses to specific allergen, and cell surface expression is upregulated in the airways of individuals with allergic asthma[56]. In Caucasian and African American children taking ICSs, we previously reported that the rs28364072:A>G SNP in *FCER2* is associated with a 3 to 4-fold higher risk of severe asthma exacerbations respectively and with lower *FCER2* expression in a gene-dose dependent manner[57]. The increased risk for asthma exacerbations was not present in children not taking ICSs[57]. These results were replicated in an independent cohort of Caucasian children and young adults on ICSs in the Netherlands and the UK which demonstrated the rs28364072 variant to be associated with severe asthma exacerbations defined by hospital visits, higher risk of uncontrolled asthma, and increased daily dose of ICS[58].

Extracellular ATP increases in human airways after allergen challenge and activates $P2X_7$ receptors on epithelial cells and leukocytes[59]. The *P2RX7* gene encodes a homotrimeric, ATP-gated non-selective cation channel that can reversibly dilate to a larger pore[60]. Attenuated whole blood monocyte $P2X_7$ pore activity in mild-intermittent asthmatics is associated with 11 times odds of developing an asthma exacerbation and 15 times odds of developing an asthma exacerbation in the presence of rhinovirus and use of ICS[61]. In a

case-control study, the rs2230911:C>G SNP in *P2RX7* was significantly associated with a history of prednisone use in African American asthmatics adjusted for ICS and long-acting beta-agonist use[62]. In a multi-ethnic population of moderate severe asthmatics, individuals with attenuated $P2X_7$ pore function were found to have a higher rate of asthma exacerbations despite medium-dose ICS use[62].

In a case-control study of US Caucasian children and adults, polymorphism rs2395672:G>A in the *CMTR1* gene was associated with an increased risk of asthma exacerbations in patients taking ICSs in two independent populations[63]. *CMTR1* mRNA expression was found to be differentially expressed during asthma exacerbations, suggesting that *CMTR1* may have a potential role in the pathogenesis of asthma exacerbations.

Pharmacogenomic studies have also identified variations in leukotriene pathway genes that modify asthma risk and response to leukotriene receptor antagonists[64]. Polymorphisms in the arachidonate 5-lipoxygenase (*ALOX5*) gene promoter, LTA_4 hydrolase (*LTA4H*) gene, and LTC4 synthase (*LTC4S*) gene reduced the risk of asthma exacerbations in a study of Caucasians taking montelukast for 6 months[65]. Individuals with a variant number (either 2, 3, 4, 6, or 7) of repeats in the *ALOX5* promoter in one allele had a 73% reduction in risk of asthma exacerbations compared to homozygotes for five repeat alleles. Individuals who were heterozygotes and GG homozygotes for the rs2660845:G>A SNP in *LTA4H* had a 4 to 4.5-fold higher risk of having at least one asthma exacerbation, and individuals who were carriers of the C allele at the rs730012:A>C SNP in *LTC4S*, including both heterozygotes and homozygotes, had an 80% reduced risk of having an asthma exacerbation[65]. These results demonstrate the complex biologic and genetic pathways underlying asthma exacerbations and leukotriene antagonist treatment response and need to be replicated in larger and more diverse populations.

In summary, genetic variants can influence the asthmatic response to environmental exposures, such as rhinovirus, vitamin D, house dust mite, and tobacco smoke as well as medications. Relevant pharmacogenomic studies, including those involving *ST13*, *FCER2, P2RX7*, and *CMTR1* for ICS and *ALOX5, LTA4H*, and *LTC4S* for leukotriene modifiers, may have direct translational relevance in terms of predicting pharmacodynamic response, but further replication studies will need to be performed to assess feasibility and performance of such testing.

3.0 CONCLUSION

Research on the genetics of asthma exacerbations has identified multiple individual genetic variants associated with this phenotype and advanced the scientific understanding of biologic pathways underlying asthma severity and disease progression. Candidate gene and GWAS approaches have described multiple genetic variants associated with asthma exacerbations and severe asthma, several of which have proven functional significance. Not only is determining function important, a challenge of genetic association studies is also to translate newly detected genetic polymorphisms into biologically or clinically significant information. A successful example of how genetic research has elucidated underlying biologic mechanism is the discovery of the polymorphism in *CDHR3* which led researchers

to identify the receptor for rhinovirus C[41, 47]. Current studies on the genetics of asthma severity and exacerbations have also reflected the inherent complexity and heterogeneity of asthma. Individual genetic variants explain only a fraction of the heritability of severe asthma and asthma exacerbations. This 'missing' heritability is common in complex diseases, and in genetic studies of asthma exacerbations, the small sample sizes, insufficiently comprehensive arrays, and lack of ethnic diversity contribute to the missing heritability[66]. In addition, part of the missing heritability has more recently been explained by gene-environment interaction and pharmacogenomic studies, and some of these studies have begun to translate their findings into potential diagnostic or therapeutic targets. However, many studies were not performed or replicated in diverse populations because of difficulty identifying defined phenotypes or exposures which limits the generalizability of results and calls for large-scale international collaborations in the field going forward[67]. Finally, the future of research in the field as we continue to discover new genes that regulate asthma exacerbations and severity requires the integration of individual genetic information with polygenic models and multi-omics technologies to predict prognosis and treatment response.

4.0 EXPERT COMMENTARY

Approximately 5–10% of asthmatics have severe disease refractory to combination ICS and bronchodilator medications[3]. This subgroup of patients disproportionately consumes up to 50% of health care resources and accounts for the majority of asthma-related morbidity[68]. As the global burden of asthma continues to increase with urbanization, severe asthma will become a growing problem with a need for improved risk prediction and biomarkers to guide management decisions, in addition to new targeted therapies[69]. Currently, there are multiple individual genetic variants that singularly provide insight into asthma biologic pathways but do not translate into meaningful, practice changing information impacting patient morbidity and mortality.

The use of genomic testing has the potential to revolutionize asthma management, much like it has for the field of oncology. The ultimate goal of genotype or other 'omic profiling is to provide both medically effective and cost-effective treatment regimens that improve morbidity and mortality, particularly for the sickest patients who are refractory to current treatment regimens. To do so, biomarkers that predict prognosis and response to expensive medications will be needed. This is the basis of personalized (precision) medicine, where the understanding of genomics and biologic pathways guides and individualizes diagnosis and treatment. Genetic and genomic studies in asthma have laid the foundation for precision medicine, but research thus far has not yet been able to translate genetic findings into clinical practice. Several current research approaches may lend themselves to enhancing the potential for precision medicine as applied to asthma exacerbations. First, a prevalent hypothesis in the asthma literature is that asthma may not represent one disease but rather comprises a syndrome of multiple disease subtypes or endotypes[70]. The derivation of endotypes is typically done by clustering algorithms centered around multiple clinical inputs and universally has demonstrated that some clusters tend to be more severe or exacerbation prone than others[71, 72]. In turn, each endotype is likely to be determined by distinct genetic and molecular mechanisms. Therefore, molecular biomarkers may identify disease

severity and optimal therapies targeting the underlying pathophysiology of the endotype. Indeed, gene expression microarray studies have begun to uncover genes and pathways specific to severe asthma endotypes and inhaled corticosteroid treatment response[73, 74]. A second approach to prediction is to use integrative approaches focused on specific and in particular severe phenotypes. For instance, our group has used random forest modeling in a Caucasian pediatric population to predict severe asthma exacerbations with an area under the curve score of 0.66 by combining 160 SNPs[75]. Markov modeling has also been used to predict hospitalizations, ED visits, and need for oral corticosteroid therapy in childhood asthma[76]. Next, the utilization of systems biology to understand asthma exacerbation is another potential methodology emerging in the field of precision medicine. Systems biology has the ability to incorporate multi-omics interactions to model complex diseases such as asthma. One multi-center study profiling gene expression during acute asthma exacerbations in adults described separate exacerbation-associated gene expression signatures in three asthma phenotypes, each pointing to a different immune signaling pathway upregulated during exacerbations[77]. Finally, epigenetic variation and regulation likely accounts for interindividual susceptibility to asthma severity and exacerbations. Research has demonstrated DNA methylation patterns in response to exposure to IL-13 to be correlated with asthma severity and lung function[78].

We are now faced with the challenge of integrating available technologies in an efficient and clinically meaningful manner. Furthermore, new findings, whether it be a genotype risk score, biomarker, or therapeutic target, will need to be validated in large clinical trials or across well phenotyped asthma cohorts. The future use of personalized data for management of severe asthma and asthma exacerbations is possible as it has been for other fields, such as oncology, and once established, validated diagnostic tests and treatments will need to be integrated into the health care system. Eventually, genotype profiling and personalized medicine will become more cost-effective for the management of severe asthma exacerbations by improving prevention and decreasing morbidity and mortality associated with the disease.

4.1 FIVE-YEAR VIEW

In five years, genomics research on asthma exacerbations will use more integrative methods to discover biologic pathways. Both systems biology and epigenetics research on severe asthma and asthma exacerbations have the potential to elucidate new mechanistic insights and treatment targets. Furthermore, research focused specifically on the sub-phenotypes of severe asthma and asthma exacerbations is important to reduce sample heterogeneity and improve power. Some of the gene products discussed in this review, such as $P2X_7$ activity, are easily measurable with a known functional role and serve as excellent biomarker candidates[62]. In the future, functional roles and biomarkers will not only be elucidated from individual candidate genes but also from polygenic and systems biology models. Finally, genotype profiling will become more widely available to researchers, patients, and health care systems as our understanding of the genomics and biologic mechanisms of asthma improves in the coming years.

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Papers of particular interest have been identified using one or two asterisk symbols (* = of interest, ** = of considerable interest).

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KEY ISSUES

- The biology and genetics of severe asthma and asthma exacerbations are distinctive, complex, and heterogeneous, influenced by multiple genes and the environment.
- Multiple individual genes have been identified by candidate gene studies, genome wide association studies, gene-environment interaction studies, and pharmacogenomic studies to be associated with asthma exacerbations, but no individual gene by itself can provide a model for clinical translation relating to disease management.
- The integration of individual genetic information with polygenic models, epigenetic data, and multi-omics technologies is of ongoing research interest with the goal to translate findings into tools for clinical prevention and treatment of severe, refractory asthma.

Table 1

Asthma exacerbation genes identified by candidate gene and genome-wide association studies

	Gene	Chromosome Location	SNP(s)	Population(s)	HGVS Name	Reference
1	*IL-4*	5q31.1	rs2243250	US[a] (Caucasians but not African Americans); Australia, New Zealand, and Canada; Taiwan	NC_000005.10:g.132673462C>T	[10, 11, 12]
2	*IL-4Rα*	16p12.1-p11.2	rs1801275 rs1805011	US (Caucasians and African Americans); Australia, New Zealand, and Canada US (Caucasians and African Americans)	NC_000016.10:g.27363079A>G NC_000016.10:g.27362551A>C	[10, 13]
4	*ADRB2*	5q31-q32	rs1042713 rs1042714	US; Australia (Caucasians) UK[b]; Canada (Caucasians); New Zealand (Caucasians); Australia (Caucasians)	NC_000005.10:g.148826877G>A NC_000005.10:g.148826910G>C	[15, 16, 19, 20, 21]
5	*PPARG*	3p25	rs1801282 rs3856806	UK (Caucasians)	NC_000003.11:g.12393125C>G NC_000003.11:g.12475557C>T	[25]
6	*TGFβ1*	19q13	rs1800469 rs2241712[c] rs1800470[c]	UK (Caucasian); US (Caucasians); Costa Rica US (Caucasians); Costa Rica US (Caucasians); Costa Rica	NC_000019.10:g.41354391A>G NC_000019.10:g.41363851C>T NC_000019.10:g.41353016G>A	[27, 28]
7	*IL-10*	1q31-q32	rs1800896 rs1800871 rs1800872	UK (Caucasians)	NC_000001.10:g.206946897T>C NC_000001.11:g.206773289A>G NC_000001.10:g.206946407T>G	[30]
8	*CHI3L1*	1q32.1	rs4950928 rs12141494 rs1538372 rs10399931	Germany (Caucasians); UK (Caucasians) US (Caucasians); UK (Caucasians) Taiwan Taiwan	NC_000001.10:g.203155882G>C NC_000001.10:g.203151425G>A NC_000001.10:g.203154532A>G NC_000001.10:g.203156080T>C	[31, 33, 34, 35]
9	*ORMDL3/GSDMB*	17q12-12	rs7216389 rs4794820 rs2305480	UK (Caucasians) UK (Caucasians); Australia (Caucasians) UK (Caucasians); Denmark (Caucasians); Netherlands (Caucasians and non-Caucasians)	NC_000017.10:g.38069949C>T NC_000017.10:g.38089344A>G NC_000017.10:g.38062196G>A	[40, 41]
10	*CTNNA3*	10q22.2	rs7915695[c] rs7923078[c] rs7923279[c] rs6480203[c]	US (Caucasians)	NC_000010.10:g.68444734T>C NC_000010.10:g.68430828A>C NC_000010.10:g.68430672G>T NC_000010.10:g.68448403A>C	[43]
11	*SEMA3D*	7q21.11	rs993312	US (African Americans)	NC_000007.14:g.85118528C>A	[43]
12	*IL-33*	9p24.1	rs928413[c]	Denmark (Caucasians); UK (Caucasians); Netherlands (Caucasians and non-Caucasians)	NC_000009.12:g.6213387G>A	[41]
13	*RAD50*	5q31	rs6871536[c]	Denmark (Caucasians); UK (Caucasians); Netherlands (Caucasians and non-Caucasians)	NC_000005.10:g.132634182T>C	[41]
14	*IL1RL1*	2q12	rs1558641[c]	Denmark (Caucasians); UK (Caucasians); Netherlands (Caucasians and non-Caucasians)	NC_000002.12:g.102149405G>A	[41]

[a] United States

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[b] United Kingdom

[c] studied only in pediatric population(s)

Table 2

Asthma exacerbation genes identified by gene-environment interaction studies

	Gene	Chromosome Location	SNP(s)	Population(s)	HGVS Name	Reference
1	*CDHR3*	7q22.3	rs6967330[c]	Denmark (Caucasians); UK[a] (Caucasians); Netherlands (Caucasians and non-Caucasians)	NC_000007.14:g.106018005G>A	[41]
2	*CRTAM*	11q24.1	rs7941607[c] rs2272094[c] rs2140151[c]	US[b] (Caucasians); Costa Rica	NC_000011.10:g.122867102C>T NC_000011.10:g.122867553A>G NC_000011.10:g.122866145A>C	[50]
3	*IL-10*	1q31-q32	rs1800896[c] rs3024492[c] rs3024496[c]	US (Caucasians); Costa Rica	NC_000001.10:g.206946897T>C NC_000001.10:g.206944112T>A NC_000001.10:g.206941864A>G	[51]
4	*TGFβ1*	19q13	rs1800470[c] rs2241712[c]	US (Caucasians); Costa Rica	NC_000019.10:g.41354391A>G NC_000019.10:g.41363851C>T	[27]
5	*IL-9*	5q31.1	rs11741137[c] rs2069885[c]	US (Caucasians); Costa Rica US (Caucasians); Costa Rica; Puerto Rico	NC_000005.10:g.135890448C>T NC_000005.10:g.135892476G>A	[52]
6	*ADAM33*	20p13	rs512625[c]	Croatia	NC_000020.10:g.3648378A>G	[53]
7	*SIGLEC1*	20p13	rs532448[c]	Croatia	NC_000020.10:g.3666838A>T	[53]

[a]United Kingdom

[b]United States

[c]studied only in pediatric population(s)

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Table 3

Asthma exacerbation genes identified by gene-environment interaction studies

	Gene	Chromosome Location	SNP(s)	Population(s)	HGVS Name	Reference
1	*ST13*	22q13.2	rs138335 rs138337	Netherlands (Caucasians), UK[a] (Caucasians)	NC_000022.10:g.41227086C>G NC_000022.10:g.41231053A>G	[55]
2	*FCER2*	19p13.3	rs28364072	US[b] (Caucasians and African Americans); Netherlands and UK (Caucasians)	NC_000019.10:g.7690399A>G	[57, 58]
3	*P2RX7*	12q24	rs2230911	US (African Americans)	NC_000012.11:g.121615131C>G	[61]
4	*CMTR1*	6p21.1	rs2395672	US (Caucasians)	NC_000006.12:g.37460801G>A	[63]
6	*ALOX5*	10q11.2	repeat variant	US (Caucasians)	N/A	[65]
7	*LTA4H*	12q22	rs2660845	US (Caucasians)	NC_000012.12:g.96044775G>A	[65]
8	*LTC4S*	5q35	rs730012	US (Caucasians)	NC_000005.10:g.179793637A>C	[65]

[a] United Kingdom

[b] United States

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