

Personalized Medicine: A Pediatric Perspective

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The aim of pediatric personalized medicine is to uniquely combine genetic variation with developmental stage and environmental exposure to provide a tailored preventive, diagnostic, and therapeutic regimen. Recent advances in genomic research have identified many genetic variants that may be related to allergic and inflammatory disease and therapeutic response. These include variants involved in immune response, barrier proteins, and medication response. Current evidence also suggests that the effect of genetic variation often depends on the developmental stage of a child and environmental exposure such as infection or tobacco smoke during a specific stage. Personalized medicine is a new and exciting field with the potential to significantly improve medical care for children and adults.

Introduction

The concept of personalized medicine generally is discussed as an application of genomic information to predicting a disease, disease severity, and therapeutic response. This “new vision of medicine” has been described as the three “Ps”: predictive, personalized, and preventive [1]. In children, this takes on a new meaning. Pediatric personalized medicine should consider genetic variation and ontogeny and environmental exposures that often have overlapping and additive effects (Fig. 1).

Advances in genomics—the study of genes—have yielded a better understanding of how genetic variation influences disease and therapeutic response. The identification of single nucleotide polymorphisms (SNPs)—single base-pair substitutions that occur within genes—signaled the beginning of personalized medicine; however, complex diseases such as asthma cannot be explained by this simplified approach. New techniques allowing examina-

tion of large amounts of genomic data may identify new genes and biologic pathways that contribute to disease and therapeutic response (Table 1).

Ontogeny—the path of development—is an important consideration in children. The field of pediatric clinical pharmacology demonstrated that developmental differences exist between children and adults whereby absorption, distribution, and clearance of drugs differ based on developmental stage [2]. Evidence also suggests that gene expression varies along the developmental spectrum whereby children may be at increased or decreased risk for a disease or have a different therapeutic response depending on developmental status.

Environmental exposure is generally unique to individuals. This is particularly important in children, as some exposures encountered at a specific time may confer risk for disease, worsen severity of disease, or alter response to treatment. Environmental exposures may not always allow intervention, but awareness of the potential impact in vulnerable children may improve diagnosis and allow earlier treatment of a specific disease.

Pediatric personalized medicine must consider genetic, developmental, and environmental differences that are unique to children. In this review, we discuss recent advances that address this aim of pediatric personalized medicine in the field of allergy and immunology and have the potential to lead to personalized diagnostic and treatment modalities.

Asthma and Allergic Disease Gene–Environment Susceptibility

Environmental exposures are known triggers of asthma and allergic disease in susceptible people. However, the complexity of allergic/inflammatory disease makes discerning the environment's role difficult. Environmental exposures, such as tobacco smoke, air pollution, infectious agents, allergens, chemical exposure, and even nutrition, are related to asthma and allergic disease. However, little is known about the complex interaction between environmental exposure and genetic variation in the development of these diseases. Recent evidence suggests that environmental exposures, especially in genetically and developmentally susceptible children, have an impact on disease pathogenesis.

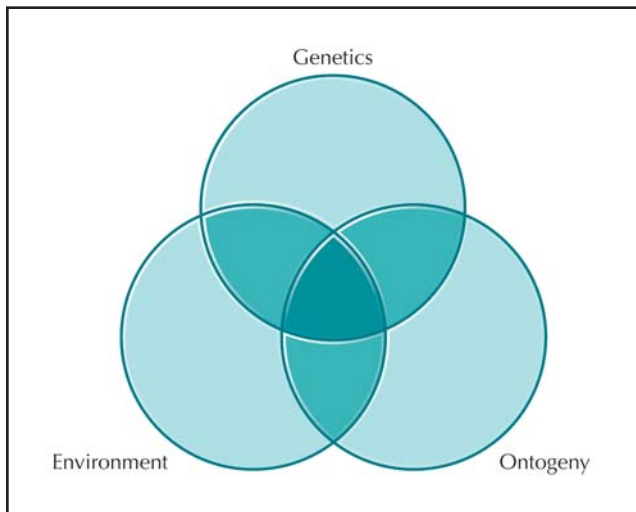


Figure 1. The overlapping but additive aspects of the environment, genetics, and ontogeny in the pursuit of pediatric personalized medicine.

17q12-21 locus

Genome-wide association studies have identified several asthma susceptibility genes. A notable and highly replicated finding is the link between asthma and atopy and the 17q12-21 locus. A study in children identified multiple markers on chromosome 17 at the 17q21 locus that were strongly associated with childhood asthma. This locus is associated with expression of the *ORMDL3* gene, which encodes a protein of unknown function belonging to a family of transmembrane proteins anchored in the endoplasmic reticulum [3]. A recent study demonstrated an association between variants at chromosome 17q21 and increased risk of asthma. This study used a large, family-based dataset with extensive phenotypic and environmental data. Thirty-six SNPs in the 17q21 region in 1511 individuals from 372 families in five French cities were examined. Eleven SNPs were significantly associated with asthma, and three SNPs (rs8069176, rs2305480, and rs4795400) were strongly associated with asthma occurring before the age of 4 years. These SNPs were located in the *ORMDL3* region, regulating transcription levels of this gene, and also included three other genes: *ZPBP2*, which encodes zona pellucida-binding protein 2; *IKZF3*, which is involved in leukocyte development and regulation of IgE production; and *GSDML*, or *GSDMB*, which is involved in epithelial barrier function. No association was found between the 17q21 SNPs and late-onset asthma. In this cohort, asthma risk was further increased by early-life exposure to environmental tobacco smoke in individuals with six SNPs in the 17q21 locus (rs8069176, rs2305480, rs11557467, rs2305479, rs4795400, and rs4795405). One SNP (rs8069176) was associated with a threefold increase in risk for development of early-onset asthma in children exposed to tobacco smoke [4••].

This study was the first to demonstrate that SNPs in the 17q21 region appear to be specifically associated with the early-onset asthma phenotype in children exposed

to tobacco smoke. A recent longitudinal study examined asthma and atopy phenotypes in childhood and their association with an SNP (rs7216389) located at the 17q12-21 locus. The investigators found that variation at the 17q12-q21 locus was associated with a twofold increase in risk for recurrent wheeze, asthma, asthma flare-ups, and bronchial hyperreactivity from early infancy through school age. However, rs7216389 did not increase the risk for eczema, rhinitis, or allergic sensitization in that same group [5]. These findings support the results of Bouzigon et al. [4••] that indicate that the 17q12-21 locus is associated with the early nonatopic asthma phenotype. These discoveries highlight the gene–ontogeny–environment interaction in disease pathogenesis and may allow predictive and preventive measures in a subset of children.

CD14

The 5q31 locus includes the *CD14* gene, which encodes CD14, a receptor with specificity for lipopolysaccharide and other bacterial-wall components. *CD14* is constitutively expressed on monocytes, macrophages, and neutrophils in a membrane-bound form and also exists in a soluble form (sCD14) in the serum. Because of the receptors' involvement in innate immunity and response to infections such as respiratory syncytial virus, genetic variations within the *CD14* gene have been investigated as potential causes of asthma susceptibility [6]. The role of sCD14 in allergic disease was explored in a cohort of 2-year-old children [7]. In this cohort, mean sCD14 levels did not differ between atopic and nonatopic children. Also, female gender was associated with higher sCD14 levels. Furthermore, girls with antenatal maternal smoking and parental asthma had lower sCD14 levels, and recurrent middle ear infections were associated with increased sCD14 levels [7]. A polymorphism within the promoter region of the *CD14* gene (CD14-159C/T) has been associated with variation in circulating levels of sCD14. In individuals who are TT homozygotes at position -159 of the gene, circulating sCD14 levels are higher than they are in CC homozygotes [8]. Whether the T allele is associated with an increased or decreased risk of atopic disease has not been elucidated, as conflicting reports exist. It has been hypothesized that presence of the T allele may be protective or confer risk, depending on degree of exposure to microbial products. Martinez [9] found that endotoxin exposure in the presence of the C allele was protective in the development of atopy compared with the presence of the T allele. Furthermore, at low levels of exposure, CC homozygotes were at the highest risk for atopy, although at high endotoxin levels, the CC homozygotes were at the lowest risk [9]. A study conducted in adults from the French Epidemiological Study on the Genetics and Environment of Asthma sought to identify an association among SNPs in *CD14*, Toll-like receptors (TLRs), country living during childhood, and asthma [10]. It found that in the presence of atopy, the CD14/-260CC genotype was protective against asthma, whereas there was no association between country living and asthma in atopic individuals with the -260 T allele. In nonatopic individuals

Table 1. Techniques used in genomic research

Technique	Description
Candidate gene study	Genetic association study that determines if a specific genetic variant is more common in individuals with a particular disease than in individuals without that disease.
Genome-wide association study	Compares the genomes of 2 groups of participants: those with a disease and a similar group without the disease. Sites of genetic variation in the disease group are identified, which could indicate disease-associated genes. This technique of genome analysis may reveal truly novel candidate genes and may identify novel biologic pathways for disease.
Genome-wide linkage study	Identifies genetic regions within the genome containing a high number of shared alleles among family members with a particular disease. These regions of shared alleles may indicate where a disease allele is located.
Haplotype analysis	Molecular genetic testing identifies a set of closely linked segments of DNA; this is used in linkage analysis.

with the -260CC allele, country living was not associated with asthma, although it was associated with a lower risk of asthma in atopic individuals with the -260 T allele [10]. A longitudinal investigation conducted in children sought to identify an association between the CD14-159CC polymorphism and early-onset atopy. Children with the -159CC allele were more likely to have early-onset atopy (odds ratio [OR], 2.2; $P = 0.018$) compared with those with the -159TT and -159CT allele. Early-onset airway hyperresponsiveness was also associated with presence of the -159CC genotype (OR, 2.6; $P = 0.019$). The impact of the genetic variation of CD14 appears to rely on environmental exposure and age, although the biologic mechanism remains to be determined.

CCR5

Respiratory infections are another major trigger for asthma exacerbations in children, and early viral exposure is linked to asthma susceptibility [11]. CCR5 is a chemokine receptor expressed on monocytes, macrophages, and T-helper type 1 cells that is involved in the immune response against viruses, including influenza A. CCR5 expression increases during *Mycoplasma pneumoniae* infection. A 32-bp deletion (832) in the CCR5 receptor gene causes loss of CCR5 receptors on lymphoid cells and altered immunity. A recent study revealed an association between the CCR5-832 mutation and reduced risk of nonatopic asthma in Slovenian children. Investigators genotyped 111 children with mild or moderate persistent asthma for the CCR5-832 mutation. A total of 75 children were atopic, and 36 had nonatopic asthma. Compared with 365 children without atopy or asthma, the study found that presence of the CCR5-832 mutation protects against nonatopic asthma [12]. Another study identified an association between chronic *Mycoplasma* infection and asthma. Children with the CCR5-832 mutation were more susceptible to *Mycoplasma* infection; however, infected children with the CCR5-832 mutation had a reduced incidence of asthma compared with similar children without the CCR5 mutation [13]. These studies offer new insights into the pathogenesis of the infection-associ-

ated asthma phenotype in children. They may also have implications in the future development of CCR5 blocking agents in the treatment of this asthma phenotype.

Toll-like receptors (Xp22)

TLRs are a class of proteins that recognize structurally conserved molecules derived from microbes and activate immune cell responses. TLRs play an important role in the innate immune response and may also play a role in asthma pathogenesis. *TLR7* and *TLR8* are encoded on chromosome Xp22, which was previously linked to asthma and other atopic disorders. A recent genome-wide association study identified *TLR7* and *TLR8* as novel risk genes in atopic disease. The study found significant associations between SNPs in *TLR7* and *TLR8* and asthma, rhinitis, atopic dermatitis, and increased specific IgE. The most significant association with asthma was seen with the *TLR8* rs2407992 SNP, which potentially affects *TLR8* splicing. The *TLR7* rs179008 SNP, which affects *TLR7* processing, also demonstrated a strong association with atopic disease [14]. This finding identifies the novel biologic pathway of TLRs in innate immunity and suggests that response to infection by TLRs is implicated in the pathogenesis and susceptibility of allergic/inflammatory disease.

Polyaromatic hydrocarbons

Although there is convincing evidence that air pollution triggers asthma exacerbations, increases asthma hospitalizations, and impairs lung function, few studies have investigated whether an association exists between air pollution and genetic susceptibility in the risk for asthma. Fossil fuel combustion releases polyaromatic hydrocarbons, which induce oxidative stress and have been associated with asthma and wheeze. Enzymes responsible for metabolism and detoxification of polyaromatic hydrocarbons include microsomal epoxide hydrolase (EPHX1) and glutathione S-transferase (GST) M1, P1, and T1. These enzymes are polymorphically expressed in humans, with some variants resulting in increased enzyme activity and others associated with reduced or absent enzyme function. Salam et al. [15]

recently conducted a study in children in an effort to identify a possible association among SNPs within the *EPHX1*, *GSTM1*, *GSTP1*, and *GSTT1* genes, *EPHX1* enzyme activity, and asthma in children. They found that high *EPHX1* activity was associated with increased occurrence of asthma in children, perhaps due to an overwhelming effect of the downstream metabolic pathways that increased oxidative stress. Increased *EPHX1* activity may also be a marker for increased exposure to pollutants. However, the association varied depending on the *GSTP1* Ile105Val genotype and distance from the residence to a major road. Among children with early persistent asthma, the increased risk associated with high *EPHX1* activity was only found in those with the *GSTP1* 105Val/Val allele or who lived near a major road. The children at highest risk were those with high *EPHX1* activity, the *GSTP1* 104Val/Val allele, and who lived within 75 meters of a major road. *GSTM1* and *GSTM1* null variants were not associated with asthma [15]. These data suggest that a group of children are at increased risk of early-onset asthma resulting from exposure to traffic-related pollution, which further defines the impact of pollution on children with asthma. Furthermore, the data identify a possible mechanism by which fossil fuel combustion is involved in the pathogenesis of asthma.

Socioeconomic status

Low socioeconomic status (SES) is associated with increased asthma prevalence and severity in childhood. Potential reasons for this association include lack of access to quality medical care, environmental exposures in urban areas, and poor medication adherence. However, a recent study demonstrated that the social environment may actually alter gene transcription in children with asthma. Specifically, gene transcription control pathways that regulate inflammation and catecholamine signaling were found to vary by SES in children with asthma. Children with asthma with high SES showed overexpression of T-cell genes involved in chemokine activity, stress responses, and wound responses compared with children with asthma from low SES. Children in the lower SES group also had poorer clinical outcomes, including greater asthma symptoms [16]. These findings support previous reports indicating an association between economic status and asthma. However, this study reveals that SES has its effect at the genomic level. Future investigations are needed to identify the components and related biologic pathway(s) associated with low SES that are linked to this finding.

Impact of Other Genetic Variants on Asthma and Allergic Disease

Interleukin-13

Several polymorphisms linked to asthma have been identified on chromosome 5 at the 5q31 locus. The interleukin (*IL*)-13 gene, located at 5q31, encodes the IL-13 cytokine produced by activated T-helper type 2 cells. IL-

13 upregulates major histocompatibility complex class II expression, promotes IgE isotype switching, and is critical to the pathogenesis of allergen-induced asthma. Studies have identified associations between genetic variation in the *IL-13* gene region with atopy and asthma. Howard et al. [17] reported that SNPs in the *IL-13* gene promoter region (-1111) were significantly associated with asthma, bronchial hyperresponsiveness, and skin test responsiveness. *IL-13* polymorphisms also have been implicated in pharmacogenetics—how genetic variation affects drug response. One investigation found that polymorphisms within the *IL-13* gene may be linked to response to montelukast. The investigators conducted a prospective evaluation of children with asthma and exercise-induced bronchospasm (EIB) in which they looked at previously studied *IL-13* polymorphisms (-1512A/C, -1112C/T, +2044G/A). Among children with asthma and EIB ($n = 100$) who were treated with 8 weeks of montelukast, 53 were homozygous for the *IL-13* -1112 C allele. Furthermore, among those who were homozygous, 41 (77.4%) were responders to montelukast, whereas 12 (22.6%) were nonresponders. The investigators also found an association between the variant allele +2044G/A, IgE level, and maximum percentage fall in forced expiratory volume in 1 second after exercise [18]. This was the first study to reveal an association between the -1112C/T allele and montelukast response in children with asthma and EIB.

Leukotriene pathway

Polymorphisms within the leukotriene pathway also are associated with response to montelukast. In a retrospective analysis of 174 patients, Drazen and colleagues [19] found that polymorphisms in the 5-lipoxygenase gene (*ALOX5*) promoter were associated with a variable response to 5-lipoxygenase inhibitors. Another study examined the *ALOX5* promoter genotype in patients with asthma and their response to leukotriene receptor antagonists such as montelukast. The investigators included 61 children and adults with atopic, moderate, persistent asthma. Participants were assessed before and after a 6-month treatment period with montelukast. The study found decreased asthma exacerbations, improved forced expiratory volume in 1 second, and decreased β_2 agonist use in patients with 5/5 or 4/5 tandem repeats in the *ALOX5* promoter region while they were on montelukast [20•]. Genetic screening for *ALOX5* promoter polymorphisms may be useful in identifying patients with asthma who will most likely respond to montelukast. These findings may help to elucidate the variable drug response to montelukast observed in children and may lead to prediction of drug response by genotype.

Genetic Susceptibility in Atopic Dermatitis

Atopic dermatitis, a common chronic skin condition, affects about 15% of children. Genetic variability is apparent in this heterogeneous disease [21]. The most significant

and replicated genetic associations have been observed when evaluating mutations in the filaggrin (*FLG*) gene and atopic dermatitis/eczema. New discoveries involving the histamine pathway also have been associated with atopic dermatitis.

Filaggrin

FLG (filament-aggregating protein) is an important component of epidermal barrier differentiation and function in the outer layer of the skin. *FLG* aggregates the keratin cytoskeleton, thus forming a barrier to prevent water loss and minimize entry of allergens and microorganisms. Several null mutations have been identified within the *FLG* gene, resulting in *FLG* deficiency and atopic dermatitis [22]. Two of these mutations (R501X and 2282del4) were identified as the mutations that most significantly contribute to disease, although other less common mutations (R2447X, S3247X, 3702delG) may also contribute in some populations and/or phenotypes [23].

Henderson et al. [24••] conducted a longitudinal, population-based study in a birth cohort of more than 14,000 children. They evaluated the association between the R501X and 2282del4 mutations and development of atopic dermatitis, asthma, and hay fever in the cohort. They found a strong association with presence of a variant allele and persistent eczema. In children with an *FLG* mutation, the mean time that eczema persisted was 76.7 months, compared with 65.6 months in children without the mutation. The presence of an *FLG* mutation was also associated with the phenotypes for asthma plus eczema (OR, 3.42; $P = 1.95 \times 10^{-12}$), early wheeze with eczema (OR, 3.01; $P = 1.1 \times 10^{-18}$), and allergic sensitization with history of eczema (OR, 2.12; $P = 5.42 \times 10^{-27}$) [24••]. This suggests that children with asthma and eczema have a distinct phenotype rather than a progression of disease from eczema to asthma (ie, “the allergic march”).

Another study conducted in 800 children 7 to 9 years of age from a population-based birth cohort aimed to determine if five common *FLG* null mutations (R501X, 2282del4, R2447X, S3247X, and 3702delG) are associated with mild to moderate atopic eczema. The investigators found that children who carry two copies of the *FLG* mutation (homozygote and compound heterozygote) have a 27-fold greater chance of having eczema (OR, 26.9; 95% CI, 3.3–217.1) than children who carry only one mutation (heterozygotes) (OR, 1.2; 95% CI, 0.7–1.9). The investigators reported no association of the asthma with eczema phenotype. Before this study, most investigations included children with severe eczema [25]. This study indicates that the *FLG* mutation is also related to pathogenesis of mild to moderate eczema, the most common form of the disease.

Another population-based study of 3099 German children 9 to 11 years of age aimed to determine the probability that children with a known *FLG* mutation (R501X, 2282del4, R2447X, S3247X, and 3702delG) will develop atopic disease and the proportion of cases in

the population attributable to the mutant *FLG* alleles. The investigators found a strong association between atopic eczema (OR, 4.57; $P = 3.2 \times 10^{-14}$) and allergic rhinitis (OR, 2.64; $P = 2.5 \times 10^{-6}$). Again, the asthma-plus-eczema phenotype was strongly associated with presence of a mutant allele (OR, 3.49; $P = 1.0 \times 10^{-5}$). For eczema, the penetrance of *FLG* null alleles (probability that a person carrying a mutation will develop a disease) was 38.5%, and the percentage of eczema cases in the population attributed to presence of mutant *FLG* alleles was 13.5%. The percentages for allergic rhinitis with eczema and asthma with eczema were 20.1% and 15.6%, respectively [26]. These findings indicate a strong and reliable association between an *FLG* defect and atopic dermatitis and identified a novel biologic pathway of disease in patients with atopic dermatitis.

As in asthma, there is a clear gene–environment–ontogeny interaction in the pathogenesis of atopic dermatitis. Bisgaard et al. [27] sought to determine if there is an interaction between *FLG* loss-of-function mutations (R501X and 2282del4) and early-life exposure to potential environmental allergens (ie, pets, dust mites) that leads to development of eczema. The investigators used data obtained from two birth cohorts (Copenhagen Prospective Study on Asthma in Childhood and Manchester Asthma and Allergy Study). The effect of the presence of an *FLG* mutation in both cohorts on development of eczema occurred early in life, with hazard ratios (HRs) of 2.90 and 2.06 in the first year of life, respectively, compared with 0.71 and 1.01 after age 1 year. In the Copenhagen Prospective Study on Asthma in Childhood cohort, the overall risk of developing eczema was increased in the presence of a mutation (HR, 2.26; $P = 0.05$), and this risk was further increased if there was early-life (1 month of age) cat exposure in the home (HR, 11.11; $P < 0.0001$). Analysis including only children carrying variant alleles demonstrated a significant effect of cat ownership on development of eczema (HR, 7.49; $P = 0.006$). In the Manchester Asthma and Allergy Study cohort, the risk of eczema also increased in children with the *FLG* mutation and a cat in the home early in life (within 4 weeks after birth) (HR, 3.82; $P = 0.011$). In an analysis including only children with a variant allele, the risk was also further increased in those with a cat in the home (HR, 2.47; $P = 0.03$). However, allergic sensitization was considerably low early in life in both cohorts [27]. These investigations revealed important considerations in the pathogenesis of atopic dermatitis in children: 1) the risk of eczema in children with *FLG* null mutations is most significant in the first year of life, 2) environmental exposure early in life is an important disease modifier in children with the presence of an *FLG* variant allele, and 3) the mechanism by which cat exposure drives development of eczema may not be IgE mediated. These findings and future research based on these findings are important in revealing important gene–environment–ontogeny interaction in children with eczema.

Table 2. Gene variants with potential impact on the future of pediatric personalized medicine

Gene(s)	Chromosome location	Polymorphism(s)	Consequence
<i>HLA-DQB1, HLA-DQA1</i>	6p21	*0104 allele and *0201 allele	Associated with asthma and atopy susceptibility
Secretoglobulin 1A1	11q12-13.1	A38A	Associated with persistently elevated specific IgE level and house dust mite skin test positivity
<i>IL-17RB</i>	3p21.1	5661G > A	May protect against asthma development
Chitinase 3-like 1	1q32.1	-131C > G	Associated with elevated levels of chitinase-like protein (YKL-40), asthma, and bronchial hyper-responsiveness
IL—interleukin.			

Histamine-N-methyltransferase

Histamine is a key mediator in the pathogenesis of atopic dermatitis. It induces itch, a central symptom of atopic dermatitis, via interaction with the H_1 -receptor. Histamine metabolism is mediated primarily by the enzyme histamine-N-methyltransferase (HNMT). SNPs within the *HNMT* gene, which result in decreased enzyme activity, are associated with reduced histamine metabolism. A recent study conducted in children 6 months to 5 years of age ($n = 256$) investigated the association between presence of *HNMT* SNP (C314T) and atopic dermatitis. The frequency of the T314 variant allele was higher in children with atopic dermatitis than in controls (0.12 vs 0.06; $P = 0.04$). The combined frequency of genotypes associated with reduced *HNMT* activity (CT or TT) was also significantly increased in children with atopic dermatitis compared with controls (0.24 vs 0.12; $P = 0.02$) [28]. Variation in the histamine metabolism pathway may provide another biologic pathway to predict disease and therapeutic response in children with atopic dermatitis, allergic rhinitis, and allergic asthma.

Other

Many genetic variations have been associated with allergic/inflammatory disease. It would be impossible to discuss them all in this review. We have attempted to focus on advances that in our opinion may have near-future potential for clinical relevance. Other relevant findings that may also contribute to the realization of personalized medicine in the future are listed in Table 2 [29–32].

Conclusions

The field of pediatric personalized medicine represents a unique opportunity to combine knowledge of genetics, ontogeny, and environmental exposure in understanding the pathophysiology and natural history of allergic and inflammatory disease in children. Future investigations should focus on better defined phenotypes to recognize potential associations. Studies also should be conducted in diverse groups of ethnic populations, as the application of genetic variation will likely vary between ethnic groups. Translation of the idea of personalized medicine from the

bench to the bedside will also require more efficient and economical genomic techniques in addition to standardized and feasible techniques for assessing and remediating environmental exposures. Investigations that integrate genetics, ontogeny, and environment will provide the best opportunity for achieving personalized medicine in children.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Boat TF: The future of pediatric research. *J Pediatr* 2007, 151(5 Suppl):S21–S27.
 2. Kearns GL, Abdel-Rahman SM, Alander SW, et al.: Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003, 349:1157–1167.
 3. Moffatt MF, Kabesch M, Liang L, et al.: Genetic variants regulating *ORMDL3* expression contribute to the risk of childhood asthma. *Nature* 2007, 448:470–473.
 - 4.•• Bouzigon E, Corda E, Aschard H, et al.: Effect of 17q21 variants and smoking exposure in early-onset asthma. *N Engl J Med* 2008, 359:1985–1994.
- This study identified genetic variants associated with early-onset asthma in a genetic subset of children exposed to cigarette smoke.
5. Bisgaard H, Bonnelykke K, Sleiman PM, et al.: Chromosome 17q21 gene variants are associated with asthma and exacerbations but not atopy in early childhood. *Am J Respir Crit Care Med* 2009, 179:179–185.
 6. Kurt-Jones EA, Popova L, Kwinn L, et al.: Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. *Nat Immunol* 2000, 1:398–401.
 7. Lodrup Carlsen KC, Lovik M, Granum B, et al.: Soluble CD14 at 2 yr of age: gender-related effects of tobacco smoke exposure, recurrent infections and atopic diseases. *Pediatr Allergy Immunol* 2006, 17:304–312.
 8. Baldini M, Lohman IC, Halonen M, et al.: A polymorphism* in the 5' flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum immunoglobulin E. *Am J Respir Cell Mol Biol* 1999, 20:976–983.

9. Martinez FD: CD14, endotoxin, and asthma risk: actions and interactions. *Proc Am Thorac Soc* 2007, 4:221–225.
 10. Smit LA, Siroux V, Bouzigon E, et al.: CD14 and Toll-like receptor gene polymorphisms, country living, and asthma in adults. *Am J Respir Crit Care Med* 2009, 179:363–368.
 11. Murray CS, Simpson A, Custovic A: Allergens, viruses, and asthma exacerbations. *Proc Am Thorac Soc* 2004, 1:99–104.
 12. Berce V, Repnik K, Potocnik U: Association of CCR5-delta32 mutation with reduced risk of nonatopic asthma in Slovenian children. *J Asthma* 2008, 45:780–784.
 13. Ungvari I, Tolgyesi G, Semsei AF, et al.: CCR5 Delta 32 mutation, *Mycoplasma pneumoniae* infection, and asthma. *J Allergy Clin Immunol* 2007, 119:1545–1547.
 14. Moller-Larsen S, Nyegaard M, Haagerup A, et al.: Association analysis identifies TLR7 and TLR8 as novel risk genes in asthma and related disorders. *Thorax* 2008, 63:1064–1069.
 15. Salam MT, Lin PC, Avol EL, et al.: Microsomal epoxide hydrolase, glutathione S-transferase P1, traffic and childhood asthma. *Thorax* 2007, 62:1050–1057.
 16. Chen E, Miller GE, Walker HA, et al.: Genome-wide transcriptional profiling linked to social class in asthma. *Thorax* 2009, 64:38–43.
 17. Howard TD, Whittaker PA, Zaiman AL, et al.: Identification and association of polymorphisms in the interleukin-13 gene with asthma and atopy in a Dutch population. *Am J Respir Cell Mol Biol* 2001, 25:377–384.
 18. Kang MJ, Lee SY, Kim HB, et al.: Association of IL-13 polymorphisms with leukotriene receptor antagonist drug responsiveness in Korean children with exercise-induced bronchoconstriction. *Pharmacogenet Genomics* 2008, 18:551–558.
 19. Drazen JM, Yandava CN, Dube L, et al.: Pharmacogenetic association between ALOX5 promoter genotype and the response to anti-asthma treatment. *Nat Genet* 1999, 22:168–170.
 20. Telleria JJ, Blanco-Quiros A, Varillas D, et al.: ALOX5 promoter genotype and response to montelukast in moderate persistent asthma. *Respir Med* 2008, 102:857–861.
- This study revealed a potential pharmacogenetic determinant for montelukast response in children and adults with asthma.
21. Dold S, Wjst M, von Mutius E, et al.: Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child* 1992, 67:1018–1022.
 22. Sandilands A, Terron-Kwiatkowski A, Hull PR, et al.: Comprehensive analysis of the gene encoding filaggrin uncovers prevalent and rare mutations in ichthyosis vulgaris and atopic eczema. *Nat Genet* 2007, 39:650–654.
 23. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al.: Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006, 38:441–446.
 24. Henderson J, Northstone K, Lee SP, et al.: The burden of disease associated with filaggrin mutations: a population-based, longitudinal birth cohort study. *J Allergy Clin Immunol* 2008, 121:872.e9–887.e9.
- This study revealed that *FLG* mutations are strong indicators of eczema and other allergic/inflammatory diseases in the context of eczema.
25. Brown SJ, Relton CL, Liao H, et al.: Filaggrin null mutations and childhood atopic eczema: a population-based case-control study. *J Allergy Clin Immunol* 2008, 121:940.e3–946.e3.
 26. Weidinger S, O'Sullivan M, Illig T, et al.: Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008, 121:1203.e1–1209.e1.
 27. Bisgaard H, Simpson A, Palmer CN, et al.: Gene-environment interaction in the onset of eczema in infancy: filaggrin loss-of-function mutations enhanced by neonatal cat exposure. *PLoS Med* 2008, 5:e131.
 28. Kennedy MJ, Loehle JA, Griffin AR, et al.: Association of the histamine N-methyltransferase C314T (Thr105Ile) polymorphism with atopic dermatitis in Caucasian children. *Pharmacotherapy* 2008, 28:1495–1501.
 29. Ober C, Tan Z, Sun Y, et al.: Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. *N Engl J Med* 2008, 358:1682–1691.
 30. Laing IA, de Klerk NH, Turner SW, et al.: Cross-sectional and longitudinal association of the secretoglobin 1A1 gene A38G polymorphism with asthma phenotype in the Perth Infant Asthma follow-up cohort. *Clin Exp Allergy* 2009, 39:62–71.
 31. Gao J, Lin Y, Qiu C, et al.: Association between HLA-DQA1, -DQB1 gene polymorphisms and susceptibility to asthma in northern Chinese subjects. *Chin Med J (Engl)* 2003, 116:1078–1082.
 32. Jung JS, Park BL, Cheong HS, et al.: Association of IL17RB gene polymorphism with asthma. *Chest* 2009, 135:1173–1180.