

## Advances in asthma and allergy genetics in 2007

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This review discusses the main advances in the genetics of asthma and allergy published in the *Journal* in 2007. The association studies discussed herein addressed 3 main topics: the effect of the environment and gene-environment interactions on asthma/allergy susceptibility, the contribution of  $T_H2$  immunity gene variants to allergic inflammation, and the role of filaggrin mutations in atopic dermatitis and associated phenotypes. Other articles revealed novel, potentially important candidate genes or confirmed known ones. Collectively, the works published in 2007 reiterate that allergy and asthma are typical complex diseases; that is, they are disorders in which intricate interactions among environmental and genetic factors modify disease susceptibility by altering the fundamental structural and functional properties of target organs at critical developmental windows. (*J Allergy Clin Immunol* 2008;122:267-71.)

**Key words:** Allergy, asthma, genetics, single nucleotide polymorphisms, association studies

The year 2007 witnessed a significant strengthening of asthma and allergy genetics, and the *Journal of Allergy and Clinical Immunology* served as a premiere conduit for cutting-edge analyses of the genetic determinants of asthma/allergy susceptibility. Among the 26 genetics articles published in the *Journal* in 2007, some highlighted the remarkable effects of the environment and gene-environment interactions on immune functions and immune-mediated mechanisms of asthma and allergy, whereas others focused on variants in  $T_H2$  inflammatory pathways. A third group of articles examined the effect on atopic dermatitis-associated phenotypes of variants in the filaggrin gene (*FLG*) (Table I). A fourth, more heterogeneous group of articles highlighted novel candidate genes or novel roles of known genes (outlined in Table II).<sup>1-14</sup>

### ENVIRONMENT, GENES, AND GENE-ENVIRONMENT INTERACTIONS IN ASTHMA AND ALLERGY

Although it is now well established that being raised on a farm protects against hay fever and atopic sensitization, the evidence for an effect of farming on asthma and wheeze remains conflicting.

#### Abbreviations used

|           |  |
|-----------|--|
| FLG:      | Filaggrin  |
| LRTI:     | Lower respiratory tract infection  |
| MYLK:     | Myosin light chain kinase  |
| PARSIFAL: | Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle |
| RSV:      | Respiratory syncytial virus  |
| SNP:      | Single nucleotide polymorphism   |
| SPT:      | Skin prick test  |
| TLR:      | Toll-like receptor   |

Differences in farming practices and hence in microbial exposures might lead to discrepant results. Indeed, the multicenter Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Lifestyle (PARSIFAL) study recently revealed substantial heterogeneity in the protective ability of farming environments across study regions.<sup>15</sup> It was therefore critical to assess whether distinct farm-related exposures have distinct effects on specific asthma-related phenotypes.

For their analysis, Ege et al<sup>16</sup> relied again on the PARSIFAL study, which includes 8263 school-age children from rural areas in 5 European countries. A strong inverse relation with a lifetime diagnosis of asthma was found for pig keeping, farm milk consumption, frequent stay in animal sheds, child's involvement in haying, and agriculture (the latter only in Germany). Use of silage strongly protected against nonatopic asthma. Interestingly, protective exposures correlated with higher expression of innate immunity genes (Toll-like receptors [TLRs] and *CD14*), and even more interestingly, distinct exposures correlated with increased expression of distinct genes; for example, haying was strongly related to increased *TLR7* and *TLR10* expression, whereas keeping pigs and feeding pressed hay were associated with higher levels of *TLR5*, and feeding silage was associated with increased *TLR6* and *TLR8* expression. Although the mechanisms responsible for the differential effects of exposure on distinct members of the *TLR* gene family remain unclear, it is tempting to speculate that these gene expression signatures point to the involvement of distinct microbial components in distinct ecologic niches within a complex farm environment.

Levels of endotoxin and extracellular polysaccharides were inversely related to atopic sensitization and asthma, respectively, independent of farm exposure. The protective effect of being a farm child on current wheeze was explained by the levels of exposure to endotoxin, glucans, and extracellular polysaccharides; however, these exposures did not explain the protective effect of farming on asthma and atopic sensitization. Also important was the identification of potential risk factors for asthma and wheeze, such as keeping hares and rabbits and the presence of sheep. Notably, after adjusting for the child's

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**TABLE I.** Major advances in asthma and allergy genetics in 2007

1. Distinct exposures associated with farming affect the expression of distinct *TLR* family genes, pointing to the involvement of distinct microbial components in distinct ecologic niches within a complex farm environment.
2. The child's activities and farm characteristics fully explain the effects of farming on asthma, wheeze, and atopy.
3. *MYLK* variants and haplotypes that confer risk for severe sepsis reduce the risk of allergic asthma in populations of African descent.
4. A functional *IL13* promoter polymorphism modifies the risk of asthma exacerbations and response to treatment. A functional *IL13* coding polymorphism is associated with late, but not early, wheezing after RSV infection.
5. The effect of *FLG* variants on the risk of atopic dermatitis exceeds that of any other candidate gene investigated thus far and makes *FLG* one of the strongest genes known to date for complex diseases.

**TABLE II.** Novel asthma/allergy candidate genes and novel roles of known genes

1. A *TNFA* promoter polymorphism (−308G/A) appears to be associated with severe bronchial hyperresponsiveness in Korean children with asthma, possibly in synergism with *CD14*−159CT.<sup>1</sup>
2. An SNP in the *FcεRIα* promoter appears to be associated with aspirin-intolerant chronic urticaria and increased gene expression in mast cells.<sup>2</sup>
3. Leukotriene C<sub>4</sub> synthase (*LTC4S*) −444AC is associated with IgE antibodies to *Dermatophagoides pteronyssinus* in a Colombian population.<sup>3</sup>
4. Genetic variation in integrin β3 (*ITGB3*)/*CD61* affects asthma susceptibility and allergic sensitization, beginning early in life. Interestingly, different SNPs in the gene are associated with asthma and IgE.<sup>4</sup>
5. Chronic *Mycoplasma pneumoniae* infection appears to be associated with physician-diagnosed asthma and the defective chemokine (C-C motif) receptor 5 (*CCR5*) variant *CCR5Δ32*.<sup>5</sup>
6. SNPs in S-nitrosogluthione reductase (*GSNOR*) modulated asthma susceptibility in children from Mexico City.<sup>6</sup>
7. A common mitochondrial haplogroup is associated with increased total serum IgE levels in white children participating in the Childhood Asthma Management Program.<sup>7</sup>
8. *HLA-DRB1* alleles control allergic bronchopulmonary aspergillosis-like pulmonary responses in humanized transgenic mice.<sup>8</sup>
9. SNPs in both the signaling lymphocytic activation molecule (*SLAM/CD150*) and *CD46* genes are associated with measurable and significant variations in antibody response after measles vaccination.<sup>9</sup>
10. Infant frequent wheezing is associated with Clara cell protein 10 (*CC10*) +38GA and lower CC10 levels, but not allergic sensitization, in a perinatal cohort study.<sup>10</sup>
11. A common *IL31* haplotype is associated with increased *IL31* expression and nonatopic eczema.<sup>11</sup>
12. Variants in chemokine (C-C motif) receptor 3 (*CCR3*) are associated with eosinophil counts, particularly in combination with IL-5 receptor α (*IL5RA*) polymorphisms.<sup>12</sup>
13. *FCER2*, which encodes the low-affinity IgE receptor, predicts the likelihood of treatment success in asthmatic children. The associations of *FCER2*/2206 TC with IgE level, severe exacerbations, and *FCER2* expression might provide a mechanistic basis for these findings.<sup>13</sup>
14. Polymorphisms in *IL4R* appear to be associated with Stevens-Johnson syndrome in Japanese patients.<sup>14</sup>

activities and farm characteristics, being a farm child was no longer inversely related with asthma, wheeze, or atopy. In other words, the variables included in the final models fully explained the effect of farming on asthma, wheeze, and atopy.

Collectively, these data point to complex biologic effects of farming on the immune and respiratory systems, a conclusion well attuned to the biologic complexity and heterogeneity of a farming environment. Most striking, though, was the demonstration that factoring in distinct and specific farm-associated exposures, activities, or both was sufficient to fully explain the protective effect of farming. This result implies that all the relevant variables have been identified, and adequate mechanistic models can now be devised to dissect the biology underlying the asthma/allergy-protective effects of farming.

One such model sought to define which farm microbial organisms, microbial products, or both might induce or influence allergy-protective mechanisms. Among a number of bacterial species identified in farm cowsheds, Debarry et al<sup>17</sup> selected, isolated, and characterized *Acinetobacter lwoffii* F78 and *Lactococcus lactis* G121. Both bacterial isolates upregulated costimulatory molecules and inflammatory cytokines and induced a T<sub>H</sub>1-polarizing program in dendritic cells *in vitro*. Moreover, intranasal administration of bacteria before and during ovalbumin sensitization reduced allergen-specific IgG1 (but not IgE) levels, eosinophil infiltration, peribronchial and perivascular inflammatory cell infiltration, mucus metaplasia, and airway hyperreactivity. The authors propose that the protective

effects of these bacteria against allergic inflammation might be mediated by their T<sub>H</sub>1-promoting activity.

Work from the same European consortium also highlighted the contribution of gene-environment interactions to allergy susceptibility. Consumption of farm milk in early life is known to confer strong protection against asthma and allergies.<sup>18</sup> Bieli et al<sup>19</sup> hypothesized that single nucleotide polymorphisms (SNPs) in *CD14*, the coreceptor for several TLRs, might modify the association between farm milk consumption and asthma and atopy. By investigating farmers' and nonfarmers' children from 2 European populations (Allergy and Endotoxin study, n = 576; PARSIFAL study, n = 1539), the authors detected a significant interaction between *CD14*−1721AG (rs2915863) and farm milk consumption. Interestingly, the asthma-protective effects of farm milk consumption were dramatic for the AA genotype, less strong but still readily detectable in −1721AG individuals, and undetectable in −1721G homozygotes. Similar patterns were observed for allergic rhinoconjunctivitis and pollen sensitization. Importantly, *CD14*−1721 also modified the association between farm milk and *CD14* expression, which was significantly increased in −1721A homozygotes but not in carriers of the other −1721 genotypes. The authors conclude that the protective effects of farm milk consumption on allergic diseases might be mediated through farm milk-induced upregulation of *CD14* expression.

A different but equally intriguing example of gene-environment interactions affecting allergic inflammation susceptibility

was provided by a study of myosin light chain kinase (MYLK), a multifunctional protein involved in the regulation of smooth muscle contraction and airway hyperreactivity.<sup>20</sup> After showing that *MYLK* variants confer risk for sepsis and acute lung injury,<sup>21</sup> the same group investigated the association between *MYLK* SNPs and asthma-related traits among African Caribbean and African American populations<sup>20</sup> and compared findings from the asthmatic populations with findings in the African American sepsis and acute lung injury groups.

Significant associations between *MYLK* SNPs and asthma and total serum IgE concentrations were observed in the African Caribbean families: a promoter SNP (rs936170) in the smooth muscle form resulted in the strongest association. A haplotype including the same SNP significantly decreased asthma risk in both the American and Caribbean families. Interestingly, the same haplotype conferred risk for severe sepsis. RNA expression studies in peripheral blood monocytes pointed to a significant decrease in *MYLK* expression among asthmatic subjects who carry rs936170.

The authors note that several candidate genes for asthma and allergic diseases, such as *CD14*, *TLR4*, acylglycerol hydroxylase, and now *MYLK*, are also associated with sepsis. These coassociations support the “common variant/multiple disease” hypothesis<sup>22</sup> and underscore the pleiotropic effects of innate immunity genes in that variants conferring risk of sepsis under one set of genetic and environmental conditions reduce risk in a different (but possibly related) clinical setting (ie, allergic asthma).

Studies investigating the immunogenetics of asthma, atopy, or both have thus far only involved populations residing in the developed world.<sup>23</sup> Given that populations can be genetically diverse, environmental conditions different, and causal pathways of allergic diseases not the same, the question is whether genetic associations found in the developed world also hold in the developing world, where the frequency of allergic diseases is low but increasing. Because parasite-induced IL-10 responses protected Gabonese schoolchildren from atopic reactivity,<sup>24</sup> van den Biggelaar et al hypothesized that human *IL10* variants that promote high IL-10 levels would be associated with reduced atopy in populations residing in Africa. To test their hypothesis, the authors genotyped 100 Gabonese schoolchildren with known skin prick test (SPT) reactions to house dust mite for 8 biallelic SNPs and 1 insertion/deletion polymorphism in the 5'-flanking region of *IL10*. Associations with SPT reactivity and PHA-induced IL-10 levels were investigated for individual polymorphisms and phased haplotypes. Although the results will need to be extended to a much larger population, these studies provided the first evidence that *IL10* variants promoting high IL-10 responses are associated with reduced risk for atopic reactivity in children living in Africa. Therefore in populations continuously exposed to infectious pathogens, the IL-10-mediated risk for atopy might be regulated both at an environmental (infection) and a genetic level. Considering the progressive urbanization of the developing world, it will be important to establish the relative role played by genetic and environmental mechanisms in the activation of IL-10 responses and the consequent risk for allergies and other inflammatory diseases in populations in transition.

## T<sub>H</sub>2 INFLAMMATORY PATHWAYS AND THEIR VARIANTS

A second group of articles examined the effect of T<sub>H</sub>2 cytokine gene variants on susceptibility to allergic inflammation. The central

effector role of IL-13 in this process is well established, and the effect of polymorphisms on the effector properties of IL-13 has also been highlighted by several studies.<sup>25</sup> Two articles published in 2007 focused on the role of *IL13* variants in asthma and wheeze. Hunninghake et al<sup>26</sup> used family-based methods to test for associations between *IL13* SNPs and asthma severity, morbidity, or both in 2 well-characterized, ethnically and geographically distinct groups of asthmatics: Costa Rican children and white non-Hispanic children in the Childhood Asthma Management Program.

*IL13*+2044GA (rs20541), a coding SNP that leads to the synthesis of an IL-13 variant with enhanced biologic activity,<sup>27</sup> was significantly associated with an increase in eosinophil counts and serum total IgE levels in both populations. Interestingly, *IL13*-1112CT (rs1800925), which results in increased *IL13* transcription and expression in T<sub>H</sub>2 cells,<sup>28</sup> appeared to be inversely associated with asthma exacerbations in Costa Rica but was associated with increased risk of asthma exacerbations among children receiving inhaled corticosteroids. These results highlight a potentially novel aspect of *IL13* biology: an effect on asthma exacerbations and response to treatment. That *IL13*-1112CT (rs1800925), a gain-of-function SNP, protects against exacerbations is puzzling but might reflect the involvement of different cell types in basal allergic inflammation and asthma exacerbations.<sup>29</sup>

Interesting insights into the role of *IL13* in airway disease were also provided by Ermers et al,<sup>30</sup> who studied the clinical, immunologic, and genetic determinants of persistent or late wheezing after a lower respiratory tract infection (LRTI) caused by respiratory syncytial virus (RSV). Following a cohort of 101 children hospitalized for an RSV-induced LRTI prospectively for 6 years, these authors found that atopic family history was associated with late, but not early, wheezing. Most importantly, the minor A allele at *IL13*+2044 (rs20541) was also strongly associated with late, but not early, wheezing, raising the possibility that early and late wheezing after RSV LRTI might be caused by distinct pathophysiologic mechanisms. The effect of *IL13*+2044GA (rs20541) on IL-13 function was further supported by another study showing increased activity of the IL-13 R130Q protein variant on cells expressing low IL-13 receptor  $\alpha$ 2 levels.<sup>31</sup>

Replication of results across studies remains the gold standard to assess the robustness of genetic associations. However, virtually no genetic association has been universally replicated, especially using strict criteria (same polymorphism, same phenotype, and same direction of the effect).<sup>25</sup> This is why meta-analyses that reassess published association data according to well-defined, strict criteria are useful to define the extent to which variants in a given gene truly modify disease susceptibility. One such meta-analysis was recently performed by Loza and Chang<sup>32</sup> for *IL4R*, which encodes the  $\alpha$  chain of the IL-4 and IL-13 receptors. After reviewing multiple case-control association studies that met specified inclusion criteria (9 and 8 studies for *IL4R*I50V and Q551R, respectively), the authors concluded that *IL4R*R551, but not *IL4R*I50V, is significantly associated with increased risk of asthma, most notably atopic asthma. Interestingly, according to Baynam et al,<sup>33</sup> the effects of *IL4R* appear to be context dependent: in a study of infant vaccine responses, the *IL4R* 551QR/QQ genotypes were associated with significant decreases in IgG levels and T-cell responses (IFN- $\gamma$ , IL-10, and IL-13) to tetanus toxoid and parallel reductions in polyclonal T-cell responses and innate immune responses but only in tobacco smoke-exposed infants, pointing to a gene-environment interaction between an *IL4R* variant and passive smoke exposure in early life.

## FLG, A NOVEL CANDIDATE GENE FOR ATOPIC DERMATITIS

Null mutations in *FLG*, a member of the epidermal differentiation complex on chromosome 1q21, were recently reported to be strongly associated with atopic dermatitis and eczema.<sup>34,35</sup> According to the meta-analysis performed by Baurecht et al,<sup>36</sup> the effect of *FLG* variants on the risk of atopic dermatitis exceeds that of any other candidate gene investigated thus far and makes *FLG* one of the strongest genes known to date for complex diseases. Yet the *FLG* mutations that predispose to atopic dermatitis are extremely rare. Indeed, their association with the disease was tested only because these mutations are known to cause ichthyosis vulgaris,<sup>37</sup> a common recessive Mendelian disorder of skin keratinization, and atopic dermatitis was highly prevalent among patients with ichthyosis vulgaris who were null or heterozygous for *FLG*.<sup>34</sup> These findings underscore both the critical role of an intact epithelial barrier in protecting against environmental agents<sup>38</sup> and the complexities of candidate gene discovery.

Mutations in *FLG* were initially identified in European families. Nomura et al<sup>39</sup> studied the role of *FLG* mutations in ichthyosis vulgaris and atopic dermatitis in Japan. Interestingly, the R501X and 2282del4 mutations originally identified in Europeans were absent in the Japanese population, but 2 novel mutations (3321delA and S2554X) were identified by means of resequencing. Both mutations led to a striking reduction of keratohyalin granules in the epidermis and were significantly associated with atopic dermatitis. Thus *FLG* mutations in Japan are distinct from those found in European populations but have a comparable effect on disease susceptibility.

The ability of *FLG* mutations to influence asthma susceptibility directly or through an effect on atopic dermatitis is still controversial. Palmer et al<sup>40</sup> showed that *FLG* mutations are associated not only with eczema-associated asthma susceptibility but also with asthma severity independent of eczema status. In contrast, Rogers et al<sup>41</sup> concluded that *FLG* loss-of-function mutations do not appear to influence either susceptibility to asthma or asthma severity phenotypes. These discrepancies are likely due to the current lack of populations in which the atopic dermatitis and asthma phenotypes exist independently in groups large enough to allow for a robust statistical analysis. Targeted prospective studies might therefore be necessary to resolve this issue. Of note, *FLG* is expressed in the epidermis and in the oral and nasal mucosa, although not in the bronchial mucosa.<sup>42</sup> If true associations between asthma and *FLG* variants were to be found only in patients with atopic dermatitis, asthma in individuals with atopic dermatitis might then be secondary to allergic sensitization that occurs after the breakdown of the epidermal skin barrier.<sup>43</sup>

## REFERENCES

- Hong SJ, Kim HB, Kang MJ, Lee SY, Kim JH, Kim BS, et al. TNF- $\alpha$  (-308 G/A) and CD14 (-159T/C) polymorphisms in the bronchial responsiveness of Korean children with asthma. *J Allergy Clin Immunol* 2007;119:398-404.
- Bae JS, Kim SH, Ye YM, Yoon HJ, Suh CH, Nahm DH, et al. Significant association of Fc $\epsilon$ R1 $\alpha$  promoter polymorphisms with aspirin-intolerant chronic urticaria. *J Allergy Clin Immunol* 2007;119:449-56.
- Acevedo N, Vergara C, Mercado D, Jimenez S, Caraballo L. The A-444C polymorphism of leukotriene C4 synthase gene is associated with IgE antibodies to *Derma-tophagoides pteronyssinus* in a Colombian population. *J Allergy Clin Immunol* 2007;119:505-7.
- Thompson EE, Pan L, Ostrovskaya I, Weiss LA, Gern JE, Lemanske RF Jr, et al. Integrin  $\beta$  3 genotype influences asthma and allergy phenotypes in the first 6 years of life. *J Allergy Clin Immunol* 2007;119:1423-9.
- Ungvari I, Tolgyesi G, Semsei AF, Nagy A, Radosits K, Keszei M, et al. CCR5 Delta 32 mutation, *Mycoplasma pneumoniae* infection, and asthma. *J Allergy Clin Immunol* 2007;119:1545-7.
- Wu H, Romieu I, Sienra-Monge JJ, Estela Del Rio-Navarro B, Anderson DM, Jenchura CA, et al. Genetic variation in S-nitrosoglutathione reductase (GSNOR) and childhood asthma. *J Allergy Clin Immunol* 2007;120:322-8.
- Raby BA, Klanderman B, Murphy A, Mazza S, Camargo CA Jr, Silverman EK, et al. A common mitochondrial haplogroup is associated with elevated total serum IgE levels. *J Allergy Clin Immunol* 2007;120:351-8.
- Koehn S, Slavin RG, Hutcheson PS, Trejo T, David CS, Bellone CJ. HLA-DRB1 alleles control allergic bronchopulmonary aspergillosis-like pulmonary responses in humanized transgenic mice. *J Allergy Clin Immunol* 2007;120:570-7.
- Dhimian N, Poland GA, Cunningham JM, Jacobson RM, Ovsyannikova IG, Vierkant RA, et al. Variations in measles vaccine-specific humoral immunity by polymorphisms in SLAM and CD46 measles virus receptors. *J Allergy Clin Immunol* 2007;120:666-72.
- Yang KD, Ou CY, Chang JC, Chen RF, Liu CA, Liang HM, et al. Infant frequent wheezing correlated to Clara cell protein 10 (CC10) polymorphism and concentration, but not allergy sensitization, in a perinatal cohort study. *J Allergy Clin Immunol* 2007;120:842-8.
- Schulz F, Marenholz I, Folster-Holst R, Chen C, Sternjak A, Baumgrass R, et al. A common haplotype of the IL-31 gene influencing gene expression is associated with nonatopic eczema. *J Allergy Clin Immunol* 2007;120:1097-102.
- Lee JH, Chang HS, Kim JH, Park SM, Lee YM, Uh ST, et al. Genetic effect of CCR3 and IL5RA gene polymorphisms on eosinophilia in asthmatic patients. *J Allergy Clin Immunol* 2007;120:1110-7.
- Tantisira KG, Silverman ES, Mariani TJ, Xu J, Richter BG, Klanderman BJ, et al. FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma. *J Allergy Clin Immunol* 2007;120:1285-91.
- Ueta M, Sotozono C, Inatomi T, Kojima K, Hamuro J, Kinoshita S. Association of IL4R polymorphisms with Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2007;120:1457-9.
- Alfven T, Braun-Fahrlander C, Brunekreef B, von Mutius E, Riedler J, Scheynius A, et al. Allergic diseases and atopic sensitization in children related to farming and anthroposophic lifestyle—the PARSIFAL study. *Allergy* 2006;61:414-21.
- Ege MJ, Frei R, Bieli C, Schram-Bijkerk D, Waser M, Benz MR, et al. Not all farming environments protect against the development of asthma and wheeze in children. *J Allergy Clin Immunol* 2007;119:1140-7.
- Debarry J, Garn H, Hanuszkiewicz A, Dickgreber N, Blumer N, von Mutius E, et al. *Acinetobacter lwoffii* and *Lactococcus lactis* strains isolated from farm cowsheds possess strong allergy-protective properties. *J Allergy Clin Immunol* 2007;119:1514-21.
- Riedler J, Braun-Fahrlander C, Eder W, Waser M, Maisch S, Carr D, et al. Early life exposure to farming environment is essential for protection against the development of asthma and allergy: a cross-sectional survey. *Lancet* 2001;358:1129-33.
- Bieli C, Eder W, Frei R, Braun-Fahrlander C, Klimecki W, Waser M, et al. A polymorphism in CD14 modifies the effect of farm milk consumption on allergic diseases and CD14 gene expression. *J Allergy Clin Immunol* 2007;120:1308-15.
- Gao L, Grant AV, Rafaels N, Stockton-Porter M, Watkins T, Gao P, et al. Polymorphisms in the myosin light chain kinase gene that confer risk of severe sepsis are associated with a lower risk of asthma. *J Allergy Clin Immunol* 2007;119:1111-8.
- Gao L, Grant A, Halder I, Brower R, Sevransky J, Maloney JP, et al. Novel polymorphisms in the myosin light chain kinase gene confer risk for acute lung injury. *Am J Respir Cell Mol Biol* 2006;34:487-95.
- Gao L, Tsai YJ, Grigoryev DN, Barnes KC. Host defense genes in asthma and sepsis and the role of the environment. *Curr Opin Allergy Clin Immunol* 2007;7:459-67.
- van den Biggelaar AH, Hua TD, Rodrigues LC, Kremsner PG, Yazdanbakhsh M, Kube D. Genetic variation in IL-10 is associated with atopic reactivity in Gabonese schoolchildren. *J Allergy Clin Immunol* 2007;120:973-5.
- van den Biggelaar AH, van Ree R, Rodrigues LC, Lell B, Deelder AM, Kremsner PG, et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 2000;356:1723-7.
- Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008;8:169-82.
- Hunninghake GM, Soto-Quiros ME, Avila L, Su J, Murphy A, Demeo DL, et al. Polymorphisms in IL13, total IgE, eosinophilia, and asthma exacerbations in childhood. *J Allergy Clin Immunol* 2007;120:84-90.
- Vladich FD, Brazille SM, Stern D, Peck ML, Ghittoni R, Vercelli D. IL-13 R130Q, a common variant associated with allergy and asthma, enhances effector mechanisms essential for human allergic inflammation. *J Clin Invest* 2005;115:747-54.
- Cameron L, Webster RB, Stremple JM, Kiesler P, Kabesch M, Ramachandran H, et al. Th2-selective enhancement of human IL13 transcription by IL13-1112C>T, a polymorphism associated with allergic inflammation. *J Immunol* 2006;177:8633-42.



29. Kim EY, Battaile JT, Patel AC, You Y, Agapov E, Grayson MH, et al. Persistent activation of an innate immune response translates respiratory viral infection into chronic lung disease. *Nat Med* 2008;14:633-40.
30. Ermers MJ, Hoebee B, Hodemaekers HM, Kimman TG, Kimpen JL, Bont L. IL-13 genetic polymorphism identifies children with late wheezing after respiratory syncytial virus infection. *J Allergy Clin Immunol* 2007;119:1086-91.
31. Andrews AL, Bucchieri F, Arima K, Izuhara K, Holgate ST, Davies DE, et al. Effect of IL-13 receptor alpha2 levels on the biological activity of IL-13 variant R110Q. *J Allergy Clin Immunol* 2007;120:91-7.
32. Loza MJ, Chang BL. Association between Q551R IL4R genetic variants and atopic asthma risk demonstrated by meta-analysis. *J Allergy Clin Immunol* 2007;120:578-85.
33. Baynam G, Khoo SK, Rowe J, Zhang G, Laing I, Hayden C, et al. Parental smoking impairs vaccine responses in children with atopic genotypes. *J Allergy Clin Immunol* 2007;119:366-74.
34. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
35. Marenholz I, Nickel R, Ruschendorf F, Schulz F, Esparza-Gordillo J, Kerscher T, et al. Filaggrin loss-of-function mutations predispose to phenotypes involved in the atopic march. *J Allergy Clin Immunol* 2006;118:866-71.
36. Baurecht H, Irvine AD, Novak N, Illig T, Buhler B, Ring J, et al. Toward a major risk factor for atopic eczema: meta-analysis of filaggrin polymorphism data. *J Allergy Clin Immunol* 2007;120:1406-12.
37. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y, et al. Loss-of-function mutations in the gene encoding filaggrin cause ichthyosis vulgaris. *Nat Genet* 2006;38:337-42.
38. Cookson W. The immunogenetics of asthma and eczema: a new focus on the epithelium. *Nat Rev Immunol* 2004;4:978-88.
39. Nomura T, Sandilands A, Akiyama M, Liao H, Evans AT, Sakai K, et al. Unique mutations in the filaggrin gene in Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J Allergy Clin Immunol* 2007;119:434-40.
40. Palmer CN, Ismail T, Lee SP, Terron-Kwiatkowski A, Zhao Y, Liao H, et al. Filaggrin null mutations are associated with increased asthma severity in children and young adults. *J Allergy Clin Immunol* 2007;120:64-8.
41. Rogers AJ, Celedon JC, Lasky-Su JA, Weiss ST, Raby BA. Filaggrin mutations confer susceptibility to atopic dermatitis but not to asthma. *J Allergy Clin Immunol* 2007;120:1332-7.
42. Ying S, Meng Q, Corrigan CJ, Lee TH. Lack of filaggrin expression in the human bronchial mucosa. *J Allergy Clin Immunol* 2006;118:1386-8.
43. Hudson TJ. Skin barrier function and allergic risk. *Nat Genet* 2006;38:399-400.

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