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The Role of Parasites in Genetic Susceptibility to Allergy

IgE, Helminthic Infection and Allergy, and the Evolution of the Human Immune System

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Abstract

There have been numerous studies in the mouse illustrating the dichotomy of T cell responses, with the common classification orchestrated around Th1 vs. Th2 responses. This classification is now widely applied to human disease as well and the generic conclusion is that the Th1 responses are more likely to occur secondary to specific microbiologic insult but also inflammatory responses. In contrast, the Th2 response is the prevalent response in subjects with atopy and allergic disease but is also the mechanism for protection against helminthic infections. Unfortunately, the paradigm of Th1 vs. Th2 is not as clear in the human as it is in mouse models. Even so, the immunological mechanisms responsible for IgE production that are protective in helminthic infections, i.e. Schistosoma, are similar to those for the production of specific IgE against allergens. In fact, there also appear to be associations in the memory T cell subpopulation CD4+CD45RO+ and the elicitation of IgE against both parasites and allergens. In this review, we present the overall contemporary scheme on the role of parasites in genetic susceptibility to allergic IgE, helminthic infections with specific discussion of its implications for the evolution of the human immune system.

Index Entries

Parasites; helminths; allergy; IgE; genetics; immune response.

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Relationship Between Th2 Responses and Parasite Disease

The role of Th2-like responses in protection against helminthic infection has been extensively documented. Studies performed in experimental models have established the absolute requirement for interleukin(IL)-4 and IL-4 receptor-dependent mechanisms in the clearance of worms *(1–3)*. Moreover, early reports have provided a wealth of information on the role of IgE resistance against these parasites, describing different immunological mechanisms including IgE antibody-dependent killing of *Schistosoma mansoni* larvae by platelets and macrophages *(4,5)* and the role of IgE-mediated local hypersensitivity in the expulsion of gastrointestinal worms *(6,7)*.

Studies Suggesting That IgE Protects From Helminthic Disease

Epidemiological studies with *Schistosoma haematobium* in the Gambian population provided the first convincing evidence that resistance to reinfection is associated with high levels of parasite-specific IgE *(8)*. Dunne et al. *(9)* demonstrated that IgE antibodies against *Schistosoma mansoni* adult worm preparations correlated negatively with reinfection. A 22.6-kDa protein derived from *Schistosoma mansoni* adult worms, recognized by human IgE, has been associated with resistance to reinfection *(10)*.

Studies performed in children belonging to low socioeconomic groups in Venezuela, and living in a helminth-endemic area, have shown striking differences in the specific IgE response against adult worm antigens between children susceptible or resistant to *Ascaris lumbricoides* reinfection. After oxantel-pyrantel treatment administered monthly to the population for 22 mo, reinfection rates were lower in those children with high initial levels of specific anti-*Ascaris* IgE. These levels increased significantly and persisted during the course of the study. In contrast, the reinfected children were unable to maintain a similar specific IgE response after antihelminthic treatment *(11)*.

Studies performed in Nigerian children have indicated that specific IgE antibody responses against the ABA-1 *A. lumbricoides* antigen may be associated with natural immunity against *Ascaris* infection *(12)*.

Very low levels of specific anti-*Ascaris* IgE have been observed in a high proportion of the children studied in various rural areas in Venezuela *(13–15)*. The most recent study performed in a Warao Amerindian community from the Orinoco Delta has shown that although 96% of a total of 260 children were parasitized by helminths, only 20% were able to mount a specific IgE response toward parasites (>0.7 PRU/mL). Different environmental and genetic factors may influence the capacity to develop a protective response against helminthic infection. Parasite polyclonal IgE stimulation may inhibit specific IgE synthesis *(13)* and helminthic infection induces the production of regulatory cytokines such as IL-10 *(16,17)* that may inhibit antigen presentation *(18)*. This immunosuppressor IL-10 cytokine has been shown to stimulate IgG4 differentially *(19)* and might thus induce the suppression of the protective response mediated by IgE.

Other Factors Influencing Immune Responses to Helminths

Other environmental factors such as malnutrition, which is frequent in endemic areas, may also modulate the immune response toward helminths. A strong association between a low proportion of the memory T cell subpopulation CD4+CD45RO+ and low levels of specific anti-*Ascaris* IgE have been found among malnourished children *(20)*.

Relationships Among Parasites, IgE, and Atopy

An atopic predisposition is generally recognized to be associated with elevated IgE synthesis. Atopic individuals with high levels of

IgE against helminth parasites demonstrated a significantly lower parasite burden than those reported in a non-atopic population *(21)*.

The possible role of helminths in the modulation of allergic reactivity has been of growing interest. The burden of helminthic infection is an important variable that may determine whether helminths act as a risk or as a protective factor against allergic diseases.

With mild helminthiasis, allergic reactivity may be elevated by the nonspecific potentiation of IgE synthesis against environmental allergens and, possibly, by direct reactivity against the parasite. This increase in allergic reactivity reaches a peak after which further stimulation would result in suppressive effects that are due to both mast-cell saturation and inhibition of specific IgE synthesis. There would be a point at which the stimulatory effects of parasitic infection would be balanced by the inhibitory influences, and thus the allergic reactivity would be equivalent to that in uninfected individuals. Beyond this point, with a heavy parasite burden suppression would predominate, causing an extremely low allergic reactivity despite a high degree of sensitization to common allergens *(22,23)*.

Indeed, active infection with any geohelminths and infection with *Ascaris lumbricoides* or *Ancylostome duodenale* are associated with significant protective effects against allergy skin test reactivity. Children with the highest levels of total IgE and with anti-*Ascaris lumbricoides* IgG4 antibodies were protected against skin test reactivity *(24)*.

As a confirmation of the modulatory effect of helminthic infections on allergic reactivity, patients with light infections had their conditions alleviated after receiving antihelminthic drugs *(21)*, but untreated individuals enhanced their allergic reactivity *(15,21)*. The situation in industrialized countries might be that as parasitic infections are light and sporadic they would produce an enhancement of the allergic phenotype. However, other sources of Th2-like enhancers must be considered *(25)*.

Importantly, other infectious agents such as gastrointestinal protozoa, bacteria, and viruses may also contribute to the development of allergic symptoms, although the association of IgE-mediated mechanisms by which these infections induce inflammation deserves further elucidation *(26–28)*.

Cross-Reactivity Between Helminths and Other Allergens

We have presented data from the studies of allergy and parasitic infections that may lead to a better understanding of this relationship and new perspectives related to the clinical outcome of allergic symptoms in humans and possibly the development of new therapies for immune-mediated disorders.

These studies, however, did not consider other factors that could contribute to a better understanding of the association between helminthic infections and allergic reactivity. The possibility of cross-reactions between house dust mites and antigen structures on helminths may play a role in understanding this complex relationship *(29)*. Another factor to be considered is the presence of a strong anti-inflammatory network, such as elevated IL-10, TGF-β, and the regulatory T cells (T3 and Tr) *(30)*. This mechanism occurs during long-term helminthic infections and has been shown to be inversely correlated with allergy *(31)* and directly correlated with parasite infection as a specific immunological phenomenon *(32)*.

Role of the Immune System in Defense From Parasitic Disease

To summarize aspects discussed thus far, immunological and clinical studies are consistent with the human immune system involving Th2 responses in defense against helminthic parasites *(33)*. This part of the immune system is also involved in allergy and asthma, but the interrelationships between resistance to parasitic infection, intensity of parasitic infection, allergy, and asthma are complex and still poorly understood.

Consequences of Need for Protection Against Helminthic Parasites

In circumstances where helminthic disease is endemic and potentially a significant cause of morbidity and mortality, a proportion of the population could be expected to die prematurely from direct effects or complications of the infection. Those with the least inherited resistance to that particular infection are more likely to die and, over many generations, the alleles responsible for increased resistance would gradually increase in prevalence in the community *(34)*. Hence, through natural selection, inherent resistance to helminthic infection would become established in populations living in endemic areas.

Initial Migration of Modern Man Around the World

Since available evidence suggests that modern man evolved from ancestors who originally resided in tropical areas *(35,36)*, antihelminth-driven natural selection could be expected to have been present at the time of the commencement of the diaspora of modern man throughout the world *(33)*. Most evidence points to the Horn of Africa as the site where this exodus commenced; the time is thought to be between 50,000 and 100,000 years ago *(35–37)*. Migrating humans reached Europe soon after this and spread east through Asia *(37)*. The first humans reached Australia nearly 50,000 years ago *(38)*, but the spread to the Pacific Islands and New Zealand was much more recent and was not completed until less than 1000 years ago *(39)*.

The weight of evidence suggests that humans crossed to the Americas via the Bering Strait land bridge during the height of the last ice age, which was around 10,000 to 12,000 years ago *(40)*. Those who crossed would have needed to have previously developed technologies strongly adapted to survival in an extremely cold climate. To do this would have required long-term residence in such regions; archeological data do support the North American ancestors as coming from the region of Siberia where they had lived for approximately 35,000 years *(40)*. However, after reaching North America, migration down through Central America and South America as far as Tierra del Fuego was rapid and completed within about 2000 years *(40)*. The eastern spread was not completed until the Inuits reached Greenland only 1000 years ago *(41)*. Human groups within the Americas, therefore, share common ancestors who originated in the tropics, spent many tens of millennia in a cold, northern, climate, and then, around 10,000 years ago moved to occupy an extraordinarily diverse range of climatic and environmental locations.

The extraordinarily rapid and widespread migration of modern humans from Africa to all corners of the globe is unique among mammalian species. It also provides an experiment of nature that allows patterns of immunological evolutionary development to be observed.

Relevance of Migration of Modern Man

The relevance of this anthropological information is that populations that were originally adapted to an environment strongly selecting toward an antihelminth defense system rapidly moved to a wide variety of regions. In these climatically diverse regions, one could expect that the balance of helminth infection and host defenses would have changed. We have speculated that these changes would be predictable and follow the same general pattern in different groups moving to different regions *(34)*. We have reasoned that in some areas, the antihelminth defense system would have continued to be of importance, particularly in those moving to the tropical areas of the Asian subcontinent, Southeast Asia, Indonesia, and northern Australia. In those moving to temperate areas, helminthic disease would have been less of a problem, as helminths thrive best where the environment is both hot and humid *(42)*. In these locations, the strong Th2 responses would have been more likely to cause problems in the form of allergies and

asthma than to have been important for defense from aggressive worm infections *(34,43)*. These allergic conditions would have resulted in an attributable increase in morbidity, but more importantly, in an increase in mortality. Although such an increase would have been small, over many generations, it could be sufficient to cause those with the strongest Th2 responses to gradually be selected out and become less prevalent. Thus, the specific population environmental selection could have changed from favoring individuals with strong Th2 responses to reducing their frequency. This process would logically have been even more rapid in those living in climates that were much colder, as helminth infection would have been much less aggressive in such places.

Speed at Which Evolutionary Changes Could Occur

How rapidly evolutionary changes that reduce Th2 responses would take place is unclear and would be difficult to calculate *(43)*. Historic evidence does show that genetic susceptibility to infectious disease can change extremely rapidly in particular circumstances. For example, within a few years of the arrival of Europeans in the South Pacific, many indigenous populations experienced very high mortality rates, presumably from European-derived viral diseases. In these circumstances, the pattern of allele distribution for key genes controlling resistance to such infections could be expected to have changed dramatically within one generation. In the case of excessive Th2 responses, an evolutionary-driven decline in the intensity of these responses would have had up to 50,000 years or more to become evident in populations living in temperate or cold regions.

The Example of the Americas

The spread of humans through the Americas allows an interesting experiment of nature to be observed in the opposite direction. In this situation, the speed at which increases in allele frequencies for key polymorphisms controlling the intensity of Th2 responses could be observed. This is because the move to the Americas most likely occurred in a well-defined period 10,000 to 12,000 years ago, when the Bering land bridge was open. At that time, those who crossed would have come from a population that had been adapted to the cold climate of Siberia for perhaps 30,000 years or more *(40)* and therefore with an expected low prevalence of alleles that augment Th2 responses. Examination of different indigenous populations in diverse climates in the Americas should therefore allow the effect of approx 10,000 years of a change in climate to be observed. In the circumstance of groups settling in tropical locations in South America, a return to a higher frequency of these alleles could be expected; these groups could be compared with groups of indigenous Americans who had remained in high northern latitudes—the Inuits in particular. One could also speculate that changes in allele frequency would occur most rapidly in the genes that are most important in controlling Th2 responses. A further prediction of interest is that one could determine whether a particular gene was important to survival in tropical areas by examining allele frequencies of polymorphisms of functional significance within that gene.

Genotypic Evidence that Climate Has Resulted in Significant Differences Between Populations With Respect to Genetic Susceptibility to Th2 or Associated Pro-Inflammatory Responses

Although there have as yet been no systematic studies comparing allele frequencies for polymorphisms in inflammatory genes between populations deriving ancestrally from diverse climatic origins, the available data are consistent with these differences being both substantial and important. Several examples of

such differences exist. The –159C allele of the CD14 C-159T polymorphism has been associated with increased IgE responses in children *(44)* and had a frequency of 82.3% in Aboriginal Australians and 50.8% in European-Australians *(45)*. The 237G allele of the high-affinity IgE receptor β-chain E237G polymorphism has been associated with asthma, and was present in 20% of blacks in South Africa, but in only 8.5% of European-Africans *(46)*. The IL 4 –589T allele has been associated with increased total IgE levels and asthma, and was present in 52.2% of African-Americans and 18.3% of European-Americans *(47)*. The IL-4 receptor Ile50 allele that has been associated with atopic asthma and increased specific IgE *(48)* was more common in African-Americans than European-Americans *(49)*. The –1903G allele of the mast cell chymase A-1903G polymorphism has been associated with increased IgE responses *(50)* and was present in 96.6% of Aboriginal Australians compared with 37.5% of European-Australians *(45)*. The 1188C allele of the IL-12B A1188C polymorphism has not been shown to be associated with clinical phenotypes to date, but the allele frequency in two studies was higher in the population with a tropical ancestry compared with the population with a temperate ancestry: 37.5% in an African population and 16.4% in a UK population *(51)*, and 67.0% in an Aboriginal Australian population and 21.3% in a European-Australian population *(52)*.

Interestingly, a similar pattern of an increased frequency of the pro-inflammatory allele is found for tropical versus nontropical populations for other genes that do not have direct Th2-related actions. The –401A allele of the RANTES G-401A polymorphism has been associated with atopic skin disease and was present in 43% in African-Americans and 15% in European-Americans *(53)*. The –308G allele of the TNFα G-308A polymorphism has been associated with asthma in Australian children *(54)* and had an allele frequency of 88% in African-Americans and 80% in European-Americans *(55)*. The M1(ala213) haplotype of the α 1-antitrypsin gene was more common in European-African asthmatics and was also more common in blacks in South Africa (controls 55%, asthmatics 53%) than in European-Africans (controls 19%, asthmatics 36%) *(56)*. The 38A allele of the Clara cell 16-Kda protein (CC16) A38G polymorphism has been associated with asthma in Australian children *(57,58)* and increased airway responsiveness in German asthmatic children *(59)* and had an allele frequency of 79% in Aboriginal Australians and 33% in European-Australians *(34)*.

Thus, there are several examples of genes involved in inflammation for which the allele that has been associated with inflammatory disease has been found to be more common in populations that have long-term ancestry in tropical regions. Not all of these genes are directly involved in Th1/Th2 responses, and as yet in most cases evidence linking them to resistance to parasite infection has not been established. However, the available data support the likelihood that adaptation to a tropical environment that includes pathogenic helminth infections results in a profile of genetic responses that is markedly more pro-inflammatory than other populations.

Prevalence of Atopic Disease in Populations Adapted to Tropical Climates

As there are major differences between "developed" and "developing" societies with respect to the prevalence of atopic disease, there are clearly potent environmental factors in developed or "Westernized" societies that make a substantial contribution to the prevalence of atopic disease. Therefore, comparisons between different racial groups should be made in different groups that live in the same society. There are many examples of studies in which allergy, atopy, and asthma were more common in African-American compared with European-American populations *(34)*. In these studies, odds ratios for asthma in African-

American children suggest that they are approximately twice as likely to develop asthma in a given Westernized society compared with children of a European origin *(60–63)*. More recently, in the large Collaborative Study on the Genetics of Asthma that was undertaken in 314 families with 2584 subjects in the United States, higher cockroach skin reactivity and increases in asthma among relatives were noted for African-American compared with European-American and other US ethnic groups *(64)*. Thus, the evidence supports a greatly increased susceptibility to allergy and asthma among populations with tropical ancestry.

Future Predictions

At least 2 billion people live in the tropics and in these regions, Westernization is proceeding rapidly and asthma appears to be increasing at a very fast rate *(65)*. Although there are still too few data on the many diverse populations in this region, the available evidence does suggest that these populations are at risk of major increases in allergy and asthma over the next few years. Studies are urgently needed to investigate this possibility and to develop strategies to cope with this problem should a generalized strong susceptibility to atopic disease be found in all tropical populations.

One explanation for population-specific differences in allele frequencies in dispersed populations is founder effect and random genetic drift. However, the consistency of the findings across multiple Th2-response-related genes in many populations in diverse regions argues for a causal relationship rather than a chance occurrence.

The rapidity with which changes in asthma prevalence occur in migrating populations has suggested a predominant environmental rather than genetic cause. However, a population with long-term residence in a region naturally selecting for a strong Th2 response might not manifest an allergic phenotype in their region of origin due to the mobilization of the system to fight parasite disease. This latent allergic diathesis would cause allergic disease immediately on exposure to the altered environmental stimulus.

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References

1 Grencis, R.K. (1997), *Philos Trans R Soc Lond B Biol Sci* **352,** 1377–1384.
2 Spencer, L., Shultz, L., and Rajan, T.V. (2001), *Infect Immun* **69,** 7743–7752.
3 Urban, J.F., Jr., Noben-Trauth, N., Donaldson, D.D., Madden, K.B., Morris, S.C., Collins, M., et al. (1998), *Immunity* **8,** 255–264.
4 Capron, A., Dessaint, J.P., Capron, M., Ouma, J.H., and Butterworth, A.E. (1987), *Science* **238,** 1065–1072.
5 Capron, A., Capron, M., Grangette, C., and Dessaint, J.P. (1989), *Ciba Found Symp* **147,** 153–160; discussion 160–170.
6 Ahmad, A., Wang, C.H., and Bell, R.G. (1991), *J Immunol* **146,** 3563–3570.
7 Negrao-Correa, D., Adams, L.S., and Bell R.G. (1999), *Parasite Immunol* **21,** 287–297.
8 Hagan, P., Blumenthal, U.J., Dunn, D., Simpson, A.J., and Wilkins, H.A. (1991), *Nature* **349,** 243–245.
9 Dunne, D.W., Butterworth, A.E., Fulford, A.J., Kariuki, H.C., Langley, J.G., Ouma, J.H., et al. (1992), *Eur J Immunol* **22,** 1483–1494.
10 Dunne, D.W., Webster, M., Smith, P., Langley, J.G., Richardson, B.A., Fulford, A.J., et al. (1997), *Parasite Immunol* **19,** 79–89.
11 Hagel, I., Lynch, N.R., Di Prisco, M.C., Rojas, E., Perez, M., and Alvarez, N. (1993), *Clin Exp Immunol* **94,** 80–83.
12 McSharry, C., Xia, Y., Holland, C.V., and Kennedy, M.W. (1999), *Infect Immun* **67,** 484–489.
13 Hagel, I., Lynch, N.R., Perez, M., Di Prisco, M.C., Lopez, R., and Rojas, E. (1993), *Parasite Immunol* **15,** 311–315.
14. Hagel, I., Salgado, A, Rodríguez, O., Ortiz, D., Hurtado, M., Puccio, F., et al. (2001), *Gac Méd Caracas* **109,** 82–90.
15 Lynch, N.R., Hagel, I., Perez, M., Di Prisco, M.C., Lopez, R., and Alvarez, N. (1993), *J Allergy Clin Immunol* **92,** 404–411.

16 Mahanty, S. and Nutman, T.B. (1995), *Parasite Immunol* **17,** 385–392.
17 van den Biggelaar, A.H., van Ree, R., Rodrigues, L.C., Lell, B., Deelder, A.M., Kremsner, P.G., et al. (2000), *Lancet* **356,** 1723–1727.
18 Lateef, Z., Fleming, S., Halliday, G., Faulkner, L., Mercer, A., and Baird, M. (2003), *J Gen Virol* **84,** 1101–1109.
19 Jeannin, P., Lecoanet, S., Delneste, Y., Gauchat, J.F., and Bonnefoy, J.Y. (1998), *J Immunol* **160,** 3555–3561.
20 Hagel, I., Lynch, N.R., Puccio, F., Rodríguez, O., Luzondo, R., Rodríguez, P., et al. (2003), *J Trop Pediatr* **49,** 136–142.
21 Lynch, N.R., Palenque, M., Hagel, I., and DiPrisco, M.C. (1997), *Am J Respir Crit Care Med* **156,** 50–54.
22. Di Prisco, M.C., Lynch, N.R., and López, R.I. (1987), *Interciencia* **12,** 300–303.
23. Lynch, N. R. (1992), *Influence of Socio-Economic Level on Helminthic Infection and Allergic Reactivity in Tropical Countries*. London: Taylor & Francis.
24 Cooper, P.J., Chico, M.E., Rodrigues, L.C., Ordonez, M., Strachan, D., Griffin, G.E., et al. (2003), *J Allergy Clin Immunol* **111,** 995–1000.
25 Yazdanbakhsh, M., Kremsner, P.G., and van Ree, R. (2002), *Science* **296,** 490–494.
26 Bachert, C., Gevaert, P., Howarth, P., Holtappels, G., Van Cauwenberge, P., and Johansson, S.G. (2003), *J Allergy Clin Immunol* **111,** 1131–1132.
27 Di Prisco, M.C., Hagel, I., Lynch, N.R., Jimenez, J.C., Rojas, R., Gil, M., et al. (1998), *Ann Allergy Asthma Immunol* **81,** 261–265.
28 Skoner, D.P. (2002), *Allergy Asthma Proc* **23,** 229–232.
29 Thomas, W.R. and Smith, W. (1999), *Clin Exp Allergy* **29,** 1583–1587.
30 McGuirk, P. and Mills, K.H. (2002), *Trends Immunol* **23,** 450–455.
31 Araujo, M.I., Lopes, A.A., Medeiros, M., Cruz, A.A., Sousa-Atta, L., Sole, D., et al. (2000), *Int Arch Allergy Immunol* **123,** 145–158.
32 Doetze, A., Satoguina, J., Burchard, G., Rau, T., Loliger, C., Fleischer, B., et al. (2000), *Int Immunol* **12,** 623–630.
33 Le Souef, P.N., Goldblatt, J., and Lynch, N.R. (1999), *Clin Exp Allergy* **29(Suppl 4),** 31–34.
34. Le Souef, P.N., Goldblatt, J., and Lynch, N.R. (2000), *Lancet* **356,** 242–244.
35 Lewin, R. (1987), *Science* **237,** 1292–1295.
36. Leakey, R.L.O. (1993) *Origins Reconsidered: In Search of What Makes Us Human*. New York: Anchor-Doubleday.
37. Stringer, C.M.R. (1997) *African Exodus: The Origins of Modern Humanity*. New York: Henry Holt & Company.
38 Roberts-Thomson, J.M., Martinson, J.J., Norwich, J.T., Harding, R.M., Clegg, J.B., and Boettcher, B. (1996), *Am J Hum Genet* **58,** 1017–1024.
39 Underhill, P.A., Passarino, G., Lin, A.A., Marzuki, S., Oefner, P.J., Cavalli-Sforza, L.L., et al. (2001), *Hum Mutat* **17,** 271–280.
40. Diamond, J. (1998) *Guns, Germs and Steel*. London: Vintage.
41 Shields, E.D. and Jones, G. (1998), *Am J Phys Anthropol* **106,** 207–218.
42 Stromberg, B.E. (1997), *Vet Parasitol* **72,** 247–256; discussion 257–264.
43 Siegel, S.C. (1987), *J Allergy Clin Immunol* **80 (3 Pt 2),** 458–462.
44 Baldini, M., Lohman, I.C., Halonen, M., Erickson, R.P., Holt, P.G., and Martinez, F.D. (1999), *Am J Respir Cell Mol Biol* **20,** 976–983.
45. Candelaria, P.V., Khoo, S.K., Laing, I.A., Judge, P.K., Hayden, C.M., Backer, V., et al. (2003), *Am J Respir Crit Care Med* **167,** A630.
46 Green, S.L., Gaillard, M.C., Song, E., Dewar, J.B., and Halkas, A. (1998), *Am J Respir Crit Care Med* **158(5 Pt 1),** 1487–1492.
47 Burchard, E.G., Silverman, E.K., Rosenwasser, L.J., Borish, L., Yandava, C., Pillari, A., et al. (1999), *Am J Respir Crit Care Med* **160,** 919–922.
48 Deichmann, K., Bardutzky, J., Forster, J., Heinzmann, A., and Kuehr, J. (1997), *Biochem Biophys Res Commun* **231(3),** 696–697.
49. Pillari, A., Lilly, C.M., Yandava, C.N., and Drazen, J.M. (1999), *Am J Respir Crit Care Med* **159,** A645.
50 Tanaka, K., Sugiura, H., Uehara, M., Sato, H., Hashimoto-Tamaoki, T., and Furuyama, J. (1999), *Clin Exp Allergy* **29,** 800–803.
51 Hall, M.A., McGlinn, E., Coakley, G., Fisher, S.A., Boki, K., Middleton, D., et al. (2000), *Genes Immun* **1,** 219–224.
52. Khoo, S.K., Candelaria, P.V., Brooks, A.S., Backer, V., Lynch, N.R., Hagel, I., et al. (2003), *Am J Respir Crit Care Med* **167,** A750.
53 Nickel, R.G., Casolaro, V., Wahn, U., Beyer, K., Barnes, K.C., Plunkett, B.S., et al. (2000), *J Immunol* **164,** 1612–1616.
54 Albuquerque, R.V., Hayden, C.M., Palmer, L.J., Laing, I.A., Rye, P.J., Gibson, N.A., et al. (1998), *Clin Exp Allergy* **28,** 578–584.
55 Hoffmann, S.C., Stanley, E.M., Cox, E.D., DiMercurio, B.S., Koziol, D.E., Harlan, D.M., et al. (2002), *Am J Transplant* **2,** 560–567.
56 Gaillard, M.C., Zwi, S., Nogueira, C.M., Ludewick, H., Feldman, C., Frankel, A., et al. (1994), *Clin Genet* **45,** 122–127.
57 Laing, I.A., Goldblatt, J., Eber, E., Hayden, C.M., Rye, P.J., Gibson, N.A., et al. (1998), *J Med Genet* **35,** 463–467.
58 Laing, I.A., Hermans, C., Bernard, A., Burton, P.R., Goldblatt, J., and Le Souef, P.N. (2000), *Am J Respir Crit Care Med* **161,** 124–127.
59 Sengler, C., Heinzmann, A., Jerkic, S.P., Haider, A., Sommerfeld, C., Niggemann, B., et al. (2003), *J Allergy Clin Immunol* **111,** 515–519.

60 Gold, D.R., Rotnitzky, A., Damokosh, A.I., Ware, J.H., Speizer, F.E., Ferris, B.G., Jr., et al. (1993), *Am Rev Respir Dis* **148,** 10–18.
61 Litonjua, A.A, Carey, V.J., Weiss, S.T., Gold, D.R. (1999), *Pediatr Pulmonol* **28,** 394–401.
62 Nelson, D.A., Johnson, C.C., Divine, G.W., Strauchman, C., Joseph, C.L., and Ownby, D.R. (1997), *Ann Allergy Asthma Immunol* **78,** 21–26.
63 Von Behren, J., Kreutzer, R., and Smith, D. (1999), *J Asthma* **36,** 575–582.
64 Lester, S., Cassidy, S., Humphreys, I., Bennett, G., Hurley, C.K., Boettcher, B., et al. (1995), *Hum Immunol* **42,** 154–160.
65. Paramesh, H. (2002), *J Pediatr* **69,** 309–312.