

A review of the genetic epidemiology of resistance to parasitic disease and atopic asthma: common variants for common phenotypes?

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Purpose of review

An inverse relationship between resistance to certain parasitic diseases and measures of atopy and asthma has long been observed. A possible explanation is that genetic determinants which confer protection against detrimental worm burdens are the same determinants involved in atopic asthma. The focus of this review is to consider the potential candidate genes that have been elucidated as part of molecular, genomic and genetic studies of parasite biology, host–parasite interactions and classic genetic epidemiology studies on parasitic disease and allergic asthma.

Recent findings

Comparative studies of the *Plasmodium* and *Schistosoma* spp. genomes have revealed a number of proteins that are homologous to humans. A number of linkage and association studies on susceptibility/resistance to parasitic diseases, including malaria and schistosomiasis, overlap with associations that have been identified for susceptibility to atopy and asthma.

Summary

In response to parasitic approaches in maintaining survival, the human host has evolved genetic adaptations that minimize severe manifestations of disease, which conversely appear to contribute to allergic disease. A clearer understanding of this process will elucidate the complex pathways and mechanisms involved in these traits.

Keywords

atopy, genes, parasite

Introduction

Atopic asthma is a disease of chronic inflammation of the airways, for which there is a strong genetic basis. The most probable source of the inflammation is a specific immunoglobulin E (IgE)-mediated reaction initiated by chronic exposure to innocuous environmental allergens, such as those associated with house dust. It has long been observed that in regions endemic for extracellular parasitic (helminthic) diseases, such as schistosomiasis, there is a lower prevalence of atopy overall and, among asthmatics, a less severe form of disease, even in settings where exposure to domestic allergens (such as house dust mite) is comparable to that which atopic asthmatics are exposed to in non-endemic regions. Interestingly, it has also been noted [1,2] that individuals with a history of atopy appear to be ‘protected’ from helminthic parasites to the extent that they mount a stronger IgE-mediated response to worm antigen and demonstrate a lower intensity of parasitic infection than non-atopic individuals with the same exposure.

Why is this? One possibility is that genetic determinants which confer protection against detrimental worm burdens are the same determinants involved in atopic asthma. A potential relationship between intracellular parasitic infection (a primarily Th1-driven phenomenon) and asthma/atopy is less clear, just as, currently, there is intense discussion and debate regarding the Th1/Th2 paradigm and the development and progression of atopic asthma [3–5]. Importantly, there is a growing body of literature suggesting a protective role of IgE subsequent to clinical malaria [6•] as well as interest in the impact of co-infection with malaria and extracellular parasitic diseases on the development of acquired immunity associated with the susceptibility or resistance to disease [7].

Characterization of parasite genomes and subsequent genomic comparison of parasites to more complex species such as mammalian hosts have contributed to our understanding of the mechanisms of parasite evolution and have provided compelling evidence for the role of host–parasite interaction in genetic adaptation. An understanding of that genetic adaptation has elucidated candidates which may drive susceptibility to other diseases of the immune system, including atopy and asthma. In consideration of the practical division of parasites into intracellular (or ‘microparasites’), which comprise bacteria,

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Abbreviations

ADA adenosine deaminase
IgE immunoglobulin E

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viruses and protozoa, compared with the extracellular (or 'macroparasites'), and which include but are not limited to helminths, the primary focus of this review is on the protozoa and helminths models for dissecting host-parasite interactions as they relate to human evolution, particularly in the context of allergic disease, and their overall impact on the human immune system. Germaine to the discussion is a brief review of the extent to which human molecular adaptations in the form of genetic variation as a response to parasitic infection have potentially mediated our response to seemingly innocuous antigens and whether or not these variants are similarly contributing to susceptibility to allergic asthma.

Host-parasite interactions

As described by Hafner and Nadler [8], there has been a long-standing postulate (Fahrenholz's rule) that speciation of parasites and hosts occurs, to a certain degree, in synchrony, sustaining the symbiotic host-parasite relationship. The human malaria parasite, *Plasmodium falciparum*, is ancient, diverging from the chimpanzee parasite *P. reichenowi* some 5–7 million years ago, about the time that humans and chimpanzees diverged [9]. The collective species *Schistosoma mansoni*, *S. japonicum* and *S. haematobium* are responsible for the extracellular parasitic disease, schistosomiasis – a major public health concern given that more than 200 million people are infected worldwide. Morbidity is associated with intestinal manifestations for *S. mansoni* and *S. japonicum* and urinary tract manifestations for *S. haematobium* are generally chronic and not typically fatal. The considerable disease burden has been estimated to cause diarrhea in ~780 000 individuals for *S. mansoni*, blood in stool in 4.4 million and hepatomegaly in 8.5 million [10]. Similarly to malarial parasites, schistosomes, as members of a group that diverged from the metazoan lineage [11], are also ancient.

The long-standing enigma whereby the majority of a population living in a region endemic for a given (or many) parasitic disease(s) may be infected, but only a minority of that population will present with clinical illness and, furthermore, only a small proportion of infections within the population will be life-threatening, is the strongest support for the evolution of successful host-parasite interactions, but also implies natural variation within populations that confers risk versus protection. In the case of filarial worms or schistosomes (flukes), an individual from an endemic region will be infected for most of his or her life as a result of repeated exposure and the inability to develop protective immunity [12]. Host immunity is typically acquired slowly and is almost never complete.

Similarly, even in the case of the virulent parasite *P. falciparum* in sub-Saharan Africa, severe disease and

death relative to the population infected are rare, despite a large host population base, stable transmission and widespread endemicity. In this environment, most children are infected after the passive immunity conferred by their mothers diminishes, but the severity of infection is controlled in part by the host immune response, leading to a steady state of chronic asymptomatic parasitaemia and a situation wherein most children carry parasites most of the time [13]. This is not to suggest that the pervasiveness of the deadly *P. falciparum* parasite is without consequences, as some 1 million children die in African each year as a direct result of this parasite [14].

Although it is not apparent how parasites such as *Plasmodium* spp. or helminths might benefit human hosts, symbiotic relationships have, nevertheless, been formed. Parasites are intimately tied to the mammalian host's immune and endocrine signals for their own development. *S. mansoni* is dependent on host cytokines for growth and reproduction, including tumor necrosis factor (TNF- α) for fertility of female schistosome worms [15] and IL-7 for proper maturation and development dermal endothelial cells [16]. Steroid and thyroid host hormones have been shown [17] to affect parasite growth, metabolism and maturation of larvae *in vitro*.

The evolutionary success of these parasites is thus owed largely to their clever approaches in maintaining infection of their vectors and mammalian hosts in order to ensure their survival. Parasitic survival is constantly threatened by the functional immune responses of vectors and hosts, and this environment has, in turn, selected for the development of intricate strategies for immune evasion. The ability to escape the effects of adaptive humoral and cellular immunity of the host (intermediate and final) differs between extracellular parasites (e.g. helminths) and protozoans, and is dictated, to a certain extent, by their reproductive strategies and life cycles. Defense strategies of extracellular parasites are aimed primarily against humoral effector mechanisms (e.g. complement lysis), whereas the strategies of intracellular protozoa are targeted toward (but not limited to) resistance to toxic metabolites and lysosomal enzymes [18]. The simplest approaches of evasion are those for which the parasite avoids host antibody responses by adopting an intracellular life style (e.g. *Toxoplasma gondii*, *Leishmania*, *Trypanosoma cruzi*), or for which life stages include the liver and blood, as in the case of malaria.

The complexity and level of evasion are heightened with elaborate approaches including clonal antigenic variation of parasite-derived red cell surface proteins (e.g. *Plasmodium falciparum* erythrocyte membrane protein-1 [PfEMP1], rifins) [13]. The *var* gene family, which encodes PfEMP1, is especially divergent in sequence, and all 14 chromosomes of the malarial

genome contain at least one member [19]. Surface antigens are an important evasion mechanism in extracellular parasites as well, and include transmembrane antigens such as erythrocyte membrane protein, leukocyte surface antigen and tissue-specific transplantation antigen identified in *S. japonicum* [20]. The host's immune system can be 'tricked' and, subsequently, immune attack can be avoided by *molecular mimicry* – the phenomenon in which a parasite shares antigens with its host in an attempt at immune evasion – or inhibition of immune reactions beyond surface antigens [21,22].

The convergent evolution of tropomyosins 1 and 2 from *S. mansoni* and its intermediate host, *Biomphalaria glabrata*, respectively, which share homology ~63%, has been proposed as one form of molecular mimicry [23]. Tropomyosin belongs to a family of proteins associated with contractile activities of actin and myosin. It is ubiquitously expressed in vertebrates and invertebrates but there are many isoforms which differ structurally and functionally. A relatively high degree of homology and functional similarity between tropomyosins of phylogenetically distantly related spp., including helminthes (*S. mansoni*, *O. volkulus*, *Brugia pahangi*) [24–27] exists. In the field of clinical immunology, there has been interest in the highly conserved muscle protein tropomyosin as a cross-reactive protein between many common allergens, including mites, shrimp and insects [24,28–30], and it has been suggested [31] that 'pan allergy' to insects may exist in individuals who have previously been sensitized to one or several insects and that allergenic similarities possibly extend to other non-insect arthropods. Particular attention has been directed towards the role of homologous antigens to the domestic cockroach, *Blattella germanica* and *Periplaneta americana*, and dust mites, *Dermatophagoides pteronyssinus* and *D. farinae*, given their prominent role in allergy morbidity. Figure 1 illustrates, for example, the substantial homology between cockroach (Bla g 7, Per a 7) and dust mite (Der p 10, Der f 10) tropomyosin to their distantly related parasitic cousins.

While the innate immune system constitutes the most ancient arm of antimicrobial host defense in humans, and appears to be a critical and similarly conserved armament in parasites, in an analysis of comparative and functional genomics of the innate immune system of *Anopheles gambiae*, one of the species of mosquitoes that is the primary intermediate host of malaria, many of the components of immune-signaling pathways were found to be highly conserved between *A. gambiae* and the very distant relative *Drosophila* [32], despite the divergence of these two insects from a common ancestor some 250 million years ago [33**]. Of even greater interest is the pace at which the putative innate immunity system components (or gene families including these components) have

evolved in *A. gambiae* compared with the rest of its genome, suggesting selective adaptation of the mosquito immune system to the pressures of various immune challenges [33**].

Comparative genomics: parasite genomes and beyond

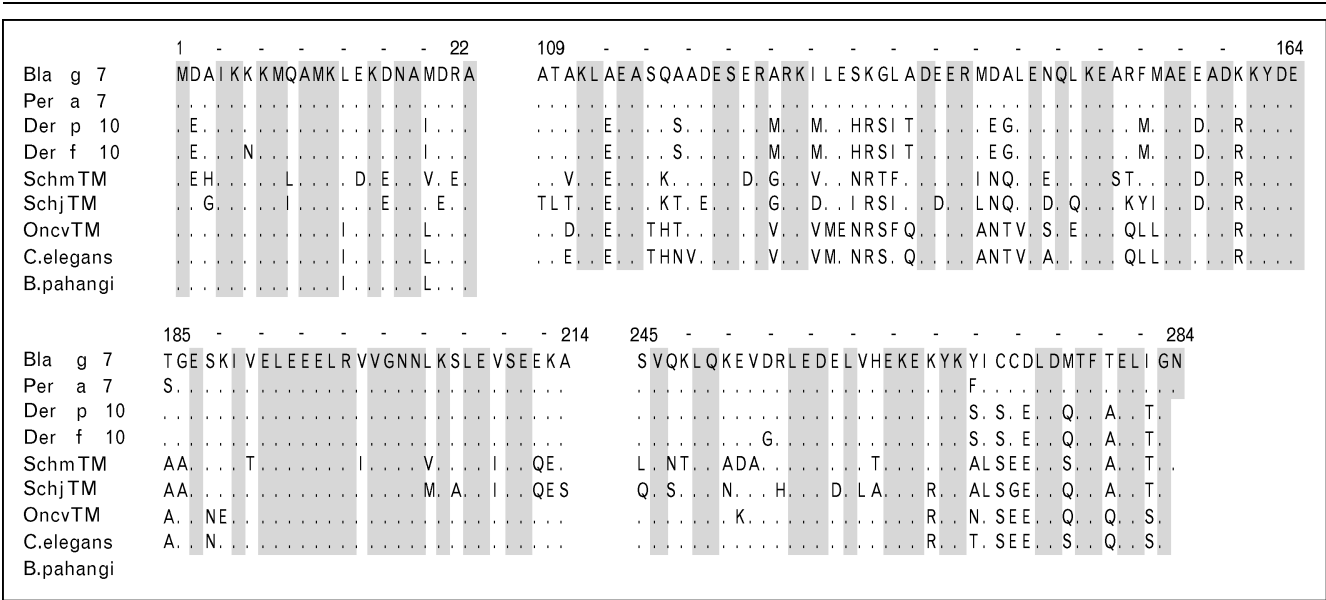
The much anticipated report [34] on the genome sequence of *P. falciparum*, the most deadly of the four species of *Plasmodium* that naturally infect humans, revealed a 23-megabase nuclear genome encoding only ~5300 genes, the majority of which are devoted to immune evasion and host–parasite interactions, and almost two-thirds of which appear to be unique to *Plasmodium*. In contrast, the *Schistosoma* genome and consequential gene ontology assignments [20,35] conjure a very different picture, with a relatively large genome (~15 000 genes [36]) of which a substantial proportion of genes (~65%) are homologous with known and highly conserved genes.

Of interest in the field of immunogenetics is the identification of many parasite-encoded receptors that are highly homologous to their mammalian hosts, which are insulin, progesterone and cytokines. Homologues of the human proinflammatory cytokine macrophage migration inhibitory factor (MIF), which has the potential of modifying the activity of human monocytes and macrophages, have been identified in both *P. falciparum* [34] and the more complex extracellular parasites *Wuchereria bancrofti*, *Onchocerca volkulus* and *Brugia malayi* [37]. Prominent homologies in the schistosomes genome include the complement C1q protein, insulin-like receptor, insulin-like growth factor binding protein, and tumor necrosis factor family, as well as homologs of genes associated with B and T-lymphocytes, such as pre-B-cell enhancing factor (PBEF) [20,35]. A high degree of sequence homology and structural similarities between helminths and humans has also been demonstrated for C-type lectins (C-TLs) [38] – a large family of cell surface receptors involved in immune cell signaling and trafficking. One interpretation [20] from these findings is that these host hormones are in fact a key mechanism that supports worm development and maturation, including sexual development.

Implications for immunogenetics in the human host

From studies on evasion of the host's immune system, we have learned much about diversification of recognition, modulation and effector components as they relate to human host–parasite interactions. Not surprisingly, the ever-evolving and dynamic host–parasite relationship has conferred adaptations at the level of genetics among human hosts. Consider, for example, epidemiological data [39] demonstrating substantial heterogeneity in

Figure 1. Comparison of Bla g 7 (AAF72534) with different tropomyosins



The tropomyosins compared were: Per a 7 (*P. americana*, AAD19606), Der p 10 (*D. pteronyssinus*, AF016278), Der f 10 (*D. farinae*, CAA75141), trematode: SchmTM (*S. mansoni*, AAA29942), trematode: SchjTM (*S. japonicum*, AAA88531), nematode: OncvTM (*Onchocerca volvulus*, AAC28900), nematode (*Brugia pahangi*, CAA12259) and nematode (*Caenorhabditis elegans*, BAA07543) (in parentheses for each of the above are the genus species, followed by the Swiss-Prot number). Points indicate the identities of residues with respect to Bla g 7. Highlighted areas indicate residues conserved in all the tropomyosins.

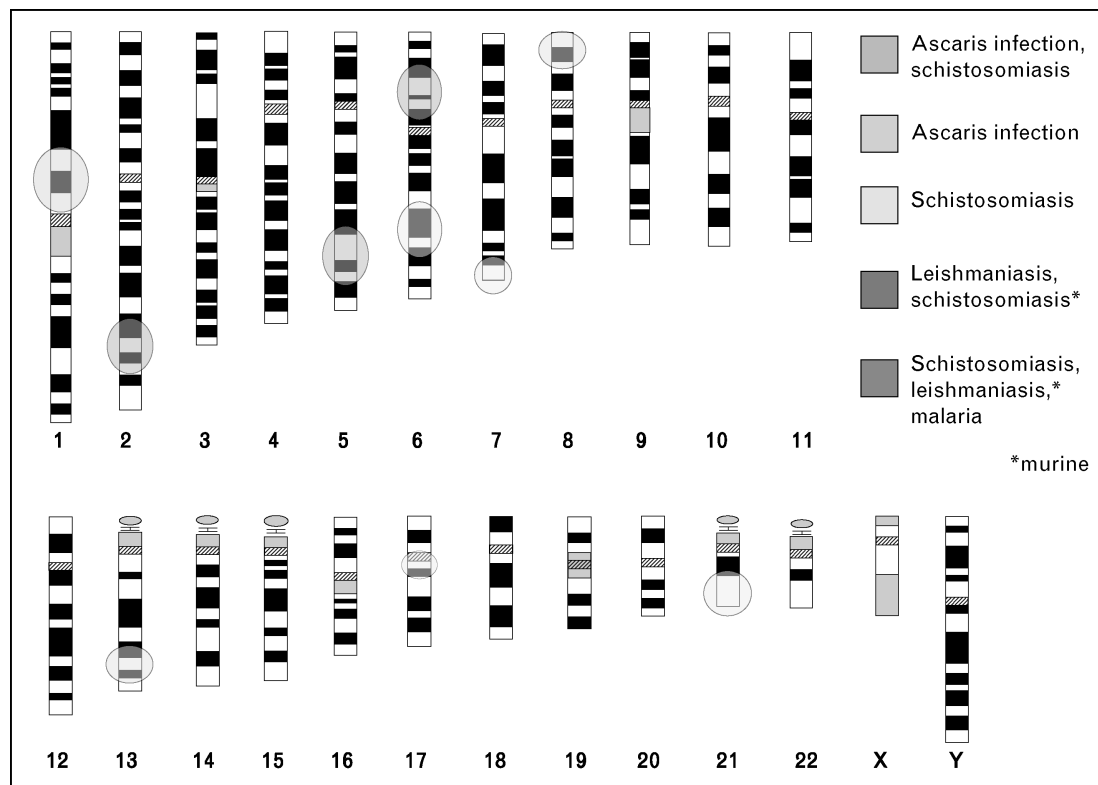
infection within a given population living in areas endemic for worm disease, by which as few as 20% of the population may be affected. Alternatively, a large portion of the population may be infected (as in the case of *Plasmodium*), but few present clinical manifestations of infection. Why is this? Given the same degree of exposure, the distribution of infection or morbidity suggests that factors conferring protection from infection itself or, at the very least, significant compromises to overall health are in play.

Many examples of genetic variation associated with host resistance (or, conversely, susceptibility) for both extra-cellular and intracellular parasitic disease abound, but perhaps several of the best examples are those related to the immune response as it confers risk for asthma or atopy are loci associated with susceptibility/resistance to ascaris, schistosomiasis and malaria. Indeed, family-based linkage studies of the two phenomena have identified similar susceptibility loci (Fig. 2). Thus, a situation emerges which suggests that a genetic adaptation in one context (e.g. 'protective' variant selected for in environments endemic for parasitic disease) may be a 'risk' variant in another setting (e.g. contemporary setting in which antigens homologous to worm antigens abound).

From a study in the Chinese population, Gao and colleagues [40] characterized a significant association between an asthma-associated genetic variant (G4219A) within the 3' regulatory element of the gene-encoding

signal transducer and transactivating factor (STAT6) and low intensity of infection by *Ascaris lumbricoides* ($P = 0.0002$) [41]. STAT6 is an important candidate because of its role in signaling for the differentiation of CD4⁺ T-cells to a Th2 type of immune response, which is associated with immunity against intestinal nematode infections [42,43]. Similar associations for both ascariasis [44] and asthma [45–48] have also been observed for a common polymorphism in the gene encoding the beta2-adrenoreceptor (Arg16Gly). These studies implicate an evolutionary explanation for the prevalence of asthma, and will be important for the interpretation of the complex phenotypic interactions between helminth infection and asthma.

The strongest evidence for linkage to schistosomiasis intensity of infection has been found for chromosome 5q31–q33 [49], the same locus for which some of the most compelling evidence for linkage to asthma and atopy had been reported (Fig. 1). Other loci which overlap with evidence for linkage to asthma include 7q and 21q [50]. Specific variants in candidate genes for schistosomiasis have not been identified at the same pace as have associations in other extracellular parasitic diseases, possibly due to the unique complexity and natural history of schistosomiasis, the fact that appropriate controls that best match the reference population have not been agreed upon, and complexities associated with the natural history of the disease and definition of the phenotype. 'Schistosomiasis' as a trait is typically defined

Figure 2. Clustering of susceptibility candidate loci in parasitic disease and human asthma

Representation of the 23 human chromosomes (syntenic regions from murine studies), highlighting those loci for which genome screens or candidate gene studies have identified linkage to a locus previously identified as a candidate locus in asthma genetics studies. Loci are mapped to short or long chromosomal arms and color-coded according to the legend. (Please see the front cover of this issue for a coloured version of this figure.)

quantitatively as the intensity of infection through a measure of egg count per gram of fecal matter (*S. mansoni*) or a measure of worm antigen in urine (*S. hematobium*). Kouriba *et al.* [51^{••}] recently identified two SNPs in the *IL13* gene that conferred increased risk for high infection intensity in a population endemic for *S. hematobium*. Specifically, IL13-1055C ($P = 0.05$) and IL13-591A ($P = 0.01$) were identified as risk alleles for schistosomiasis [51^{••}].

Focusing on factors associated with the development of periportal fibrosis (PPF) as a complication of chronic schistosomiasis in a Sudanese population, Chevillard and colleagues [52] tested for association of polymorphisms in the gene-encoding interferon- γ because of observations that high IFN- γ levels are associated with a marked reduction in the risk of fibrosis [53]. Similarly, another group focusing on hepatic fibrosis in schistosomiasis, also in Sudan, observed a marker in the interferon gamma receptor 1 (IFNGR1) gene (rs1327475) on chromosome 6q22–q23 [54], where strong evidence of linkage had previously been reported [55] and the gene for which modest association has been reported for total serum IgE levels in a British population [56].

Although the disorder vis-à-vis the human immune system in malarial infection is markedly different from that observed with extracellular parasites and also allergic disease (e.g. Th1-type milieu versus Th2-type, respectively), striking overlaps in susceptibility loci between malaria and asthma/allergic disease have been observed, including associations observed for variants in candidate genes for other extracellular parasitic diseases, such as IFNGR1 [57] and IL4 [58].

A primary receptor on the red blood cell for optimal invasion of *P. falciparum* by its 175 kD protein (EBA-175) ligand via sialic acid-dependent binding is glycophorin A – a glycoprotein controlled by the MN blood group [59] (note: EBA-175 is part of the same *var* gene family of binding proteins as the Duffy antigen, essential for *P. vivax* and *P. knowlesi* [60], described above). Another major player in the pathology of malaria is adenosine deaminase (ADA) – an enzyme that converts adenosine to inosine which, in turn, regulates the adenosine levels in tissues and cells; because malarial parasites lack a de-novo purine synthetic pathway, purines for energy metabolism are salvaged from the host erythrocyte via the metabolism of adenosine [61]. Elevations in adenosine

have also been associated with asthma and chronic obstructive pulmonary disease [62]. In a study focusing on the interactive relationship between an ADA polymorphism and past malarial morbidity in Sardinia, Bottini and colleagues [63**] demonstrated a modest but significant correlation between the combined genotype of MN (*L^M) and ADA (ADA*2) and past malarial morbidity in one region of Italy and a negative correlation to allergic asthma in a population from Rome, implicating an inverse relationship between this polymorphism and supporting, again, the notion that what is protective (or deleterious) in one context is a disadvantage (or advantage) in another. Looked at another way, the converse genotype of these alleles would be protective against malaria and lead to susceptibility of asthma.

Taken together, these findings support the notion that genetic determinants that originally arose as an adaptive mechanism in minimizing morbidity associated with parasitic infection, both intracellular and extracellular, are associated with a 'contemporary' manifestation such as asthma and allergic disease – conditions that are rarely observed in regions endemic for parasitic disease.

Conclusion

In summary, both intracellular and extracellular parasites have evolved a variety of sophisticated and ingenious approaches in immune evasion and molecular mimicry in order to maintain their survival in the human host, which has also resulted in a symbiotic host–parasite relationship. An important consequence of this relationship is the evolution of a genome for which there is considerable homology with the human immune response system. Importantly, the human host has evolved, in response, specific genetic adaptations that minimize severe manifestations of parasitic disease which, conversely, appear to contribute to allergic disease and asthma. A clearer understanding of the genetic etiology of contemporary diseases such as asthma and atopy (e.g. protection against parasitic disease) will elucidate the complex pathways and mechanisms involved in these diseases.

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