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SERIES: "GENETICS OF ASTHMA AND COPD IN THE POSTGENOME ERA"
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Evolution and respiratory genetics

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ABSTRACT: Evolution is a plausible explanation for between-population differences in particular allele frequencies if: the genes involved have related functions; the heterogeneous alleles involved have similar functional consequences; the involved genes are not linked chromosomally; and the patterns observed would result in a biologically plausible, survival-enhancing gene–environment interaction. However, possible evolutionary effects have to be differentiated from founder effects and random genetic drift.

The current authors have noted the existence of a consistent pattern of allelic frequencies in genes related to T-helper 2 (Th2) immune responses in humans of different ancestral backgrounds, residing in climatically similar regions. Th2 responses are thought to have evolved in mammals to resist infection by parasites, particularly helminths. Modern man arose in tropical Africa where helminths thrived. Relatively recently, humans migrated to cooler or drier climates where most helminths struggled to reproduce. The genetic tendency to strong Th2 responses may have become a health liability, the reduction in risk from parasites being counterbalanced by an increased inherited propensity to atopic or allergic diseases.

The pattern noted by the present authors includes specific alleles of interleukin-4 and its receptor, interleukin-13, interleukin-10, the β chain of the high-affinity receptor for immunoglobulin E, the β_1-adrenergic receptor, and the alpha chain of tumour necrosis factor. These population-specific polymorphism profiles are likely to be relevant in current disease patterns. The high incidence of asthma in migrants from tropical locations to affluent temperate countries is likely to be related to these patterns. Of even more concern is the possibility that increasing westernisation among the ~2 billion people living in the tropics will produce rapidly increasing levels of asthma, as these populations have a high genetic predisposition to allergic disease.

KEYWORDS: Asthma genetics, evolution, parasites, T-helper 2 responses

If a series of genes related by the functional interaction of their coded proteins, but not by their chromosomal location, show systematic patterns of differences in allele frequencies between geographically isolated groups of the same species, there is a possibility that these patterns have been formed by Darwinian evolution. For the immune system, such distinct patterns could have important implications for host resistance to disease, and, given the multiple roles of each part of the immune system, there could also be corresponding consequences for disease susceptibility. Additionally, changes in local environmental exposures could determine the balance of these two outcomes. In the case of the respiratory system, recent evidence suggests that these scenarios have played a critical role in producing the current patterns of respiratory phenotypes.

However, where differences in polymorphism frequencies are found between populations, the possibility that these changes occurred by chance must be addressed. Chance variations in allele frequencies can occur from either a founder effect or from random genetic drift. A founder effect may occur when a group of individuals move away from, and lose contact with, their population of origin. If the distribution of a particular allele in that group happens to differ significantly from the population of origin, their descendants may continue to exhibit this difference provided the allele does not affect survival. The chance of a founder effect influencing allele frequencies is

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clearly greater for a smaller founder population, which would be less likely to reflect the allele distributions of the larger population. In practice, for human ethnic groups, the number of founders and the time that they diverged from their ancestral population can be estimated, to some degree, by comparing the mathematical distribution of alleles in the population of interest and the population from which its founders are likely to have emigrated [1]. Genetic drift, however, is caused by the nature of sexual reproduction, in which each individual allele in a parent has a 50% chance of being passed on to each offspring. The chance of the allele surviving in that parent's offspring depends on how many children he or she has, but even with four children the allele has a 6.25% chance of not surviving one generation. For a single nucleotide polymorphism (SNP), a reduction in the frequency of one allele means an increase in the frequency of the other. Therefore, the random survival of a particular allele may by chance reduce or increase the frequency of the allele in that population. Again, the chance of this happening is inversely related to the size of the population. Thus, founder effect and/or genetic drift are more likely to result in differences in allele frequencies between populations if the founder, and breeding, population is small. However, in contrast to Darwinian selection of alleles, both founder effect and genetic drift operate randomly and they should not produce a systematic pattern of allele frequencies in genes that are not chromosomally co-located.

If for a particular allele, a difference in allele frequencies is observed between two different populations, there is no easy way to determine whether this difference arose from a founder effect, genetic drift or natural selection. If, however, alleles from a group of genes show a systematic pattern of differences in frequencies between two populations, that pattern may be due to either linkage disequilibrium (LD) or evolution. LD occurs when different alleles are inherited together because they are close enough to each other on a chromosome (genetically linked) not to have been separated by recombination events during multiple meioses. Recombination is the naturally occurring phenomenon where alleles of two linked genes can segregate independently during meiosis owing to a random crossover with the break-point between them. Thus, the possibility that LD could be responsible for different alleles being inherited together can be dismissed if the genes are on different chromosomes (LD only occurs with closely linked genes on the same chromosome), or viewed as unlikely if they are separated by a large distance on the same chromosome (recombination is likely to have occurred between the alleles). Conversely, Darwinian evolution would produce a pattern of allele frequencies if a group of alleles all contributed to enhanced survival with respect to a particular environmental threat, and this would not depend on the physical location of the alleles in the genome.

In summary, evolution is the most plausible explanation for systematic differences in frequencies of particular alleles between populations if: 1) the genes involved code for proteins with related functions; 2) the alleles involved are from different genes but have similar functional consequences; 3) the alleles are on different chromosomes or far apart on the same chromosome; and 4) the patterns observed produce a biologically plausible improvement in survival.

With respect to the respiratory system, patterns of allele frequencies in genes related to respiratory status may provide new insight into the genetic factors underlying respiratory disease susceptibility. Since genes can have multiple roles within living systems, there is no reason to expect that a series of genes affecting a particular organ, such as the lung, would have evolved to a particular pattern of responses due to the evolutionary effects on that organ alone.

OBSERVED PATTERNS OF ALLELE FREQUENCY DISTRIBUTION

Many studies have found that populations of different ethnic origin have substantially different allele frequencies for many different genes [2–5]. Although other authors observed that these differences may have resulted in a survival advantage, they usually have not drawn any further conclusions. The current authors recently hypothesised that ''pro-inflammatory'' alleles in genes related to T-helper (Th)2 lymphocyte responses could become more frequent in tropical climates, owing to the need for defence against helminthic infection, and less frequent in cool or dry climates, owing to a modest long-term increase in mortality from allergic disease [6]. This hypothesis was based on the data available at the time, but since then further data has become available, providing the opportunity to explore the hypothesis in greater detail. Why would allele frequencies in genes related to Th2 function show differences between populations? A convincing body of evidence has accumulated suggesting that Th2 function is important in host resistance to helminthic disease.

THE DEVELOPMENT OF HOST RESISTANCE TO INFECTIOUS DISEASE

Helminthic infection is ubiquitous in all tropical areas of the planet and is considered to be present in >1 billion people [7]. Although many people who harbour helminths live with them in relative harmony, helminthic infection is still a major cause of morbidity [8], with common symptoms, (depending on the worm involved) including anaemia, failure to thrive and malabsorption. It is also a significant cause of mortality [8].

An important part of host protection from helminthic infection is provided by the immunological responses of the Th2 lymphocyte system [9]. Immunoglobulin (Ig)E is the main antibody involved in the Th2 immune system and protection from parasite infection appears to be the dominant role of IgE antibodies [9]. Several studies have shown that serum levels of helminth-specific IgE are associated with reduced parasite load. For example, in subjects from a Caribbean island, higher levels of anti-ascaris IgE were associated with reduced stool egg counts for this large roundworm compared with children from city slums, who had much higher parasite load, but lower levels of anti-ascaris IgE [10]. In another study, Nigerian children infected with ascaris had high levels of anti-ascaris IgG, but these levels did not correlate with protection; levels of IgE specific to Ascaris were higher in children with natural immunity to this infective agent [11]. In another study, people infected with both *Strongyloides stercoralis* and human T lymphotropic virus type 1 exhibited increased interferon (IFN)-γ secretion and reduced interleukin (IL)-4 secretion from peripheral blood mononuclear cells (PBMC). In this study, the authors suggested that IL-4 down-regulation may contribute to

more severe strongyloidiasis [12]. More recently, the role of the Th2 system has been underlined by a study of signal transducer and activator of transcription (STAT) 6. STAT6 has a central role in mediating Th2 activity and a variant of STAT6 has been associated with reduced ascaris infection in China [13]. These studies have established a strong link between the Th2 immune pathway and protection from helminthic infection. Hence, all genes involved in this pathway are likely to be candidate genes for the genetics of host protection from this form of infection.

COMPARISON BETWEEN MECHANISMS OF IMMUNE FUNCTION FOR HOST PROTECTION FROM HELMINTHIC INFECTION WITH ATOPY AND ASTHMA

The Th2 pathway is strongly linked to asthma [14] and the same genes that are candidates for host protection from helminthic disease are also candidate genes for asthma [15]. The involvement of a common part of the immune system for each of these processes is emphasised by a number of studies showing that immunological factors associated with increased host protection from parasite disease are also associated with increased asthma. For example, reduced IFN-γ secretion from PBMC has not only been associated with more severe helminthic infection, as mentioned above, but it has also been reported to be associated with asthma in a study of Xhosa children from South Africa [16]. The same variant of STAT6 that has been associated with a reduced burden of ascaris infection has been associated with asthma [17].

ARE PRO-TH2 ALLELES MORE FREQUENT IN POPULATIONS WITH PROLONGED EXPOSURE TO HELMINTHS?

The current authors have previously noted examples of a higher frequency of alleles that either directly or indirectly promote Th2 activities in populations whose most recent long-term ancestry was in the tropics [6].

The genes for IL-4 and its receptor are important for Th2 function. The –589T allele of the IL-4 gene [18], which has been associated with raised serum IgE concentrations [19], had an allele frequency of 0.544 in African-Americans (whose origins lie mostly in tropical West Africa) compared with 0.183 in European-Americans [20].

The Ile50Val polymorphism of the IL-4 receptor gene has been associated with increased specific IgE levels [21], and the haplotype Ile50Arg551, which has been associated with ''enhanced signalling'' and increased IgE production, was more common in African-Americans than in European-Americans [22].

IL-13 is also an important Th2 cytokine and its gene has many polymorphisms, most of which are rare [23]. The C-1111T polymorphism is more common and the –1111T allele has been associated with allergy to inhaled antigens and atopic dermatitis [24]. The frequency of this allele was 12% in Caucasians and 48% in Africans [23].

IL-10 is a regulatory cytokine that can affect both Th1 and Th2 function and its gene has several polymorphisms [3]. The C-571A polymorphism has been examined in several studies and the –571A allele has been associated with increased total IgE levels [25]. In a study from the USA, its allele frequency was reported to be 52% in Asian-Americans, 41% in African-Americans and 23% in European-Americans [3].

The 237G allele of the gene for the β chain of the high-affinity IgE receptor has been associated with asthma-related phenotypes in European-Australians [26]. One study found that 20% of black South Africans were heterozygous for the 237G allele *versus* 8.5% of European-South Africans [27].

Although not generally regarded as a gene involved with IgE production, variations in the β_2-adrenergic receptor gene have been associated with altered specific IgE levels. The arg16 allele is associated with increased levels of ascaris-specific IgE in a tropical Caribbean population [28]. This allele has been shown to be more common in African-North Americans (50% allele frequency) than European-North Americans (39%) [29].

The gene for the α chain of tumour necrosis factor has a promoter polymorphism G-308A. The G allele has been associated with asthma in Australian children [30]. This allele was present in 90.1% of a Gambian population and 77% of an English cohort [4].

The evidence that multiple genes show consistent population-specific frequency differences in alleles, which similarly perturb their coded protein's function in a related pathway, suggests the action of a natural selection process. These findings also suggest that if allele frequencies of an SNP in a gene involved in protection from helminthic disease do not differ between populations with tropical *versus* temperate origins, then the polymorphism may not be important in protection from that disease.

HOW COULD DIFFERENCES IN PRO-TH2 ALLELE FREQUENCIES HAVE ARISEN BETWEEN POPULATIONS?

Since pro-Th2 responses are likely to be an asset in the tropics, the differences in allele frequencies between populations would appear logically to have arisen through natural selection. However, the question is not why genetic variations that promote Th2 activity are more common in the tropics, but why they are less common elsewhere. The most consistent anthropological evidence points to central Africa as the site of emergence of modern humans, with dispersion to all parts of the globe beginning between 100,000 and 50,000 yrs ago [31, 32]. Interestingly, no other large mammal has ever spread so rapidly over such a large area, so there are no parallels to draw from in nature. No doubt this great migration to all corners of the Earth was facilitated by humans' unique intelligence and their ability to adapt their behaviour through invention rather than their physiology through evolution.

Why would pro-Th2 alleles become less frequent in these circumstances? The most likely explanation is that they were no longer an advantage to survival as human population groups moved to a wide variety of climatic locations. Human population groups moving to cooler, and in some cases drier, climates would have encountered a reduction in the chances of infection from helminths, which generally require hot, moist conditions to thrive. However, to become significantly less frequent, an allele would have also had to have a negative impact on survival. While there can be no definitive answer to this problem, a small increase in mortality in young

individuals from allergic reactions, including asthma, could have, over a number of millennia, reduced the frequency of alleles promoting overly active Th2 inflammatory responses. At present, there is no other more plausible explanation for the pattern of pro-Th2 allele frequencies.

IF POPULATIONS WITH LONG-TERM TROPICAL ANCESTRY HAVE A GENETIC PROFILE THAT IS RELATIVELY PRO-TH2, WHY ARE ALLERGY AND ASTHMA NOT MORE COMMON IN THESE REGIONS?

When the first asthma prevalence studies were carried out in more remote regions asthma was striking by its rarity. For instance, in rural Gambia in 1975, no cases of asthma were seen among children or adults [33]. Around the same time, the incidence of asthma in New Guinea was less than one per 1,000 [34]. These studies led to the view that asthma was an environmental disease of ''western'' civilisation. However, more recent investigations of the global incidence of asthma-related symptoms have produced less clear-cut results. This is particularly true with the largest study of this kind, the International Study of Asthma and Allergies in Childhood (ISAAC). In general, a strong pattern was observed with asthma being most common in developed areas and less common in developing regions [35], but there were some obvious exceptions. For example, symptoms of asthma in children were very common in Peru, but rare in Greece [35]. The ISAAC model has to date been unable to explain how these differences arose. A glaring deficiency in current knowledge is the lack of understanding of the environmental factors that are responsible for producing the high levels of asthma in the developed world. Although some progress has been made in determining which risk factors are involved, particularly in relation to living in proximity to animals, the critical environmental factors that have produced asthma in the developed world have largely escaped identification. Whatever these factors are, they clearly are much less of a problem in the least developed societies, so much so that asthma is almost absent despite an apparently strong genetic tendency to develop this condition.

WHAT ARE THE CONSEQUENCES OF THESE DIFFERENCES IN PRO-TH2 ALLELE FREQUENCIES?

The argument that the observed increase in frequency of pro-Th2 alleles in people of African origin is of functional consequence is supported by recent cellular stimulation studies. An immunological study of lymphocyte responses to stimulation has reported that CD4+ expression of the Th2 cytokines IL-4 and IL-13 was much greater in African than European adults [36]. The authors suggested that the differences could be a consequence of the Africans having undergone more continuous challenges with antigens that drive Th2 responses, since the differences were greater in adults than in children, but the findings could also have been the result of inherent differences in lymphocyte responses.

The evidence that having inherited an increased number of pro-Th2 alleles is a risk factor for asthma is now very strong. The best epidemiological evidence for this possibility comes from the USA. Several recent large epidemiological studies have shown that African-Americans have an increased risk of allergy and asthma compared with European-Americans after odds ratios have corrected for all other known risk factors. Increased sensitisation to allergens important in asthma was observed in African-American compared with European-American children [37]. The authors noted that these differences in indoor allergen sensitivity were consistent with ethnic differences in asthma morbidity, but suggested that the findings were due to adverse environmental factors. In the Collaborative Study on the Genetics of Asthma, African-American sibling pairs were found to have had a lower baseline forced expiratory volume in one second and a higher rate of skin test reactivity to cockroach allergen than the other groups in the USA [38]. A large study of 12,388 children from 89 centres across the USA found that the risk of asthma was 1.64 times as great in African-American children as in the rest of the population [39]. The higher rate of asthma in African-American children has not always been present, as a recent study has shown that asthma hospitalisations increased 20-fold in African-Americans between 1960 and 1990, but only five-fold in European-Americans [40]. Other investigations examining populations migrating from their tropical origins to a more developed society have revealed similar patterns. For instance, compared with British controls, migrants from the Indian subcontinent to the UK have been observed to have higher consultation rates [41] and higher admission rates [42] for asthma. Although this changing incidence of disease in migrants has been explained as an environmental risk issue, it is also likely that the new environmental exposures experienced on relocation have exposed a covert, inherited, high-risk genetic status. A similar example would be the rapidly increasing frequency of clinical manifestations of porphyria when populations at high genetic risk, such as Afrikaners, were exposed to certain drugs, such as barbiturates, for the first time.

IMPLICATIONS FOR THE FUTURE: A LARGE INCREASE IN ALLERGY AND ASTHMA IN DEVELOPING NATIONS

Although there is insufficient evidence to determine whether all populations with long-term tropical ancestry have a pro-Th2 profile of immune responses, the data that are available at present suggest this possibility. If correct, then ~2 billion people who live in the tropics would have an augmented risk of developing allergy and asthma. They may also be at risk of developing other respiratory diseases, including chronic obstructive pulmonary disease, but the relationship between Th2 responses and other respiratory diseases is not as clear-cut as it is for asthma. The data that are available increasingly suggest that a major increase in allergy and asthma can be expected as ''westernisation'' continues to increase across the world. By the late 1980s, asthma prevalence in the South Fore region of Papua New Guinea had increased from its previous level of 0.1% to 7.3% [34]. In a more recent, and worrying, study from Bangalore in India, asthma prevalence increased from 9% in 1979 to 29.5% in 1999 [43]; over the same period, Bangalore had made impressive economic progress.

Unless the environmental factors that have caused the rapid increase in asthma in recent decades can be identified and removed, which seems unlikely, a third of the world's population appears to be at risk of a large increase in the prevalence of allergy and asthma, and indeed this is already

happening. Of great concern is the possibility that asthma rates may end up much higher in tropical regions than in temperate locations if the populations there do have a greatly increased genetic profile of T-helper 2 responses. Much more data are required in this area and researchers and scientific funding bodies should appreciate the urgent need to address this issue. Studies are needed to determine the extent of the risk in different population groups and to develop appropriate strategies to cater for the increases in asthma prevalence in these groups.

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