The history and variation of human genes

Global spatial patterns of infectious diseases and human evolution

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Introduction

The range of diseases to which humans have been exposed has changed considerably from early human populations nearly four millions years ago through Neolithic humans *c*.10,000–8,000 years ago to modern humans living today in megalopolises (Armalegos *et al*. 1996). Over this long period humans have constantly created new ways of living and eating, thus generating new pathways for diseases to invade and spread into communities. For most of their evolutionary history, humans lived in small, sparsely settled communities with very low population sizes and densities. Although such human communities were too small to support endemic pathogens that were constantly present, they were regularly infected by zoonoses through insect bites (e.g., sleeping sickness), by preparation and consumption of contaminated flesh, from wounds inflicted by animals (e.g., tetanus), and by direct contacts with animal reservoirs (e.g., avian tuberculosis and leptospirosis (Armalegos *et al*. 1996)). Moreover, the range of earliest hominids was probably restricted to the tropical savannah, which would have limited the number of pathogen species. As they moved into temperate zones, hominids escaped from some of the tropical diseases that had plagued their ancestors and acquired new pathogens. When, about 10,000 years ago, the agricultural revolution produced larger, less mobile human populations, infectious diseases such as influenza, measles, mumps, and smallpox increased (Armalegos *et al*. 1996). The domestication of animals also attracted more potential vectors and led to greater exposure to zoonotic diseases (Polgar 1964). Over this long period, aspects of human behavior, physiology, and genetics evolved in response to these diseases (Armalegos and Dewey 1970; Dronamraju 2004).

We consider in this chapter three main questions about the global distribution of infectious diseases and their impact, in particular the impact of their diversity, on human evolution. First, what are the global geographical patterns of the distribution of pathogen species, and how can we explain them? Second, how does parasitic diversity influence the evolution of genetic diversity and the distribution of alleles at particular genes in humans? Third, how has geographical variation in the distribution and diversity of infectious disease shaped the distribution of life-history traits observed in current human populations? We argue that while the emergence of new diseases has been a recurrent pattern since the origin of hominids, with the new emerging pathogens we now face an important epidemiological transition that potentially influences human adaptation and survival. In particular, global trade and transcontinental economic exchange and transport will considerably alter the occurrence and distribution of human infectious diseases and thus the selection they exert on humans.

Geographical aspects of human diseases

Latitude affects the diversity and distribution of many free-living organisms, but little is known about large-scale patterns of the distribution of human or animal pathogens (Finlay 2002). One

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reason large-scale patterns of human diseases have so rarely been studied is that their geographical distribution has probably changed substantially over human history, with a major transition during the late twentieth century. In particular, it is generally thought that infection chains and intercontinental transfers of microbes would homogenize their spatial distribution, so that no geographical patterns could be detected (see Haggett 1994; Finlay 2002). However, recent studies of human microbial pathogens identify several macroscale distribution patterns of human diseases.

Latitude and the species diversity of human pathogens

Disease species diversity is higher in the tropics than in temperate areas (Fig. 2.1a) (Guernier *et al*. 2004). This pattern is stronger in the northern hemisphere, where human populations are concentrated, than in the southern hemisphere. Most important parasites of humans occur in tropical and subtropical countries, and some of these species, mainly zoonotic and vector-borne diseases, are restricted to those regions because of the restricted geographical distribution of their hosts (Woolhouse and Gowtage-Sequeria 2005). Humans in temperate regions suffer from only a small subset of the

diseases affecting humans in the tropics (Guernier *et al*. 2004). But does this distribution of modern diseases reflect the environment of early humans? There are indeed several reasons to expect a similar or even stronger pattern for early human populations. First, the natural history explorations at the beginning of the sixteenth century and more recent large-scale dispersal due to intercontinental trade and transport increased the geographical ranges of diseases (McMichael 2004) and thereby weakened spatial patterns. Second, the geographic variation of temperature and rainfall affects disease ranges, in particular those of vector- and reservoir-borne diseases (Guernier *et al*. 2004). If, as we would expect, the latitudinal increase in winter severity decreases the survival of pathogens or their vectors, disease diversity would decrease as we move away from the equator. In addition, the amount of precipitation during a growing season decreases as we move away from the equator, which should affect the range of diseases and vectors that are sensitive to moisture. Finally, species richness of the parasites of non-human hosts also decreases with increasing latitude, in particular for metazoan parasites of marine fish (Rohde 1999), of primates (Nunn *et al*. 2005), and for parasites of some plant hosts, e.g., soybean (Yang and Feng 2001). Even if this rule does not apply to all microbial organisms
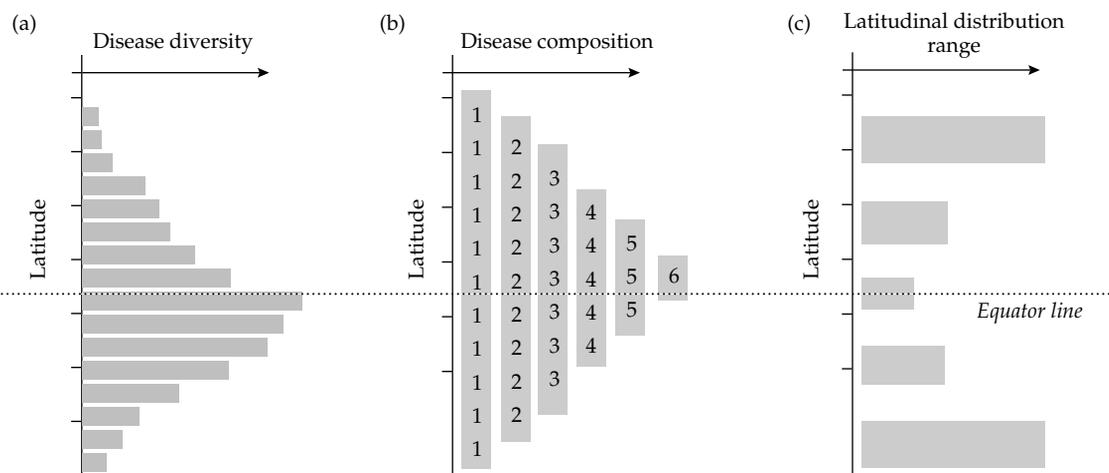
Figure 2.1 At a global scale, three macroscopic patterns for human diseases emerge: (a) the relationship between human disease species diversity and latitude; (b) the relationship between latitude and disease species composition, where disease species comprising smaller assemblages at high latitudes constitute a subset of the species in richer tropical areas (nested pattern); numbers indicate different parasite species; (c) the relationship between latitudinal geographic range of human diseases and latitudinal centroids of diseases (Rapoport's rule).

(see Finlay 2002), the similarity of the effect of latitude in these examples is striking.

Longitude and the species diversity of human pathogens

In contrast to the latitudinal gradient of species richness, the tendency for richness to vary with longitude has been largely ignored (Gaston and Blackburn 2000). Yet, the diversity of human diseases is generally highest in continental Africa and is lower in both southern America and southeast Asia (unpublished data). This spatial pattern probably reflects in part the long-distance dispersal of diseases by humans during their history of expansion and migration, as in the example of fungal pathogens that followed the American migration of humans from the north to the south (Fisher *et al.* 2001). Inevitably, increasing global travel, trade, and migration (Wilson 1995) will weaken this spatial trend.

Latitude and the nested pattern of human pathogens

As in animal and plant communities, human pathogens are distributed in a nested species structure (Guernier *et al.* 2004): some species are widely distributed and occur in many local communities, whereas others have more restricted distributions and occur only in a subset of the richest local communities (Fig. 2.1b). Together with the latitudinal gradient mentioned above, this means that some parasites only occur in tropical regions, others occur everywhere, but very few (e.g., Lyme disease) occur only in temperate areas (see Guernier *et al.* 2004). Pathogens that occur in tropical and temperate zones are generally directly transmitted viruses, bacteria and fungi, which are *internal* to the host and therefore little affected by environmental variability. This category of disease agents represents around 36% of 332 pathogen species described by Smith *et al.* (2007); their dispersal is primarily drive by contagion (Guernier *et al.* 2004). In contrast, pathogens with *external* stages (helminth worms, vector-transmitted pathogens, and reservoir-borne diseases) are more strongly influenced by environmental conditions; the ranges and environmental

requirements of their hosts restrict the range of many of these pathogens to tropical regions. According to Woolhouse and Gowtage-Sequeria (2005), 58% of 1,407 recognized species of human pathogens are zoonotic and thus constrained by the animal host's spatial range. Because many of these animal hosts are tropical, most actual and potential human pathogens are endemic to tropical zones.

Latitude and the geographical range of human pathogens

According to Rapoport's rule, species whose geographical ranges are centered at higher latitude tend to be distributed over a larger latitudinal range (Gaston and Blackburn 2000). This rule is valid for some human pathogens, for mean latitude and disease ranges (Fig. 2.1c) are positively correlated for five of the six pathogen categories considered, namely protozoa, fungi, bacteria, helminthes, and vector-transmitted viruses (Guernier and Guégan, submitted). The exceptions to the rule are directly transmitted viruses. Despite previous doubts about the existence of Rapoport's rule for the southern hemisphere (see Rohde 1999) and its generality as a common pattern in macroecology (Gaston and Blackburn 2000), the spatial trend for the five groups of human pathogens is also supported in the southern hemisphere. Moreover, this pattern also occurs in the tropics, although several previous studies suggested that it is limited to the Palearctic and Nearctic above latitudes of 40–50°N (Chown *et al.* 2004). Thus human diseases centered at higher latitudes have wider geographical ranges than what it is generally observed for diseases endemic to the intertropical belt.

Geographical area and the species diversity of human pathogens

Perhaps more than any other ecological pattern, the species–area relationship has influenced the development of ecology. Smith and collaborators (2007) identified three distinct categories of species–area relationships for human diseases (Fig. 2.2). First, directly transmitted diseases, such as measles and pertussis, do not show a significant species–area relationship (Fig. 2.2). In other words,
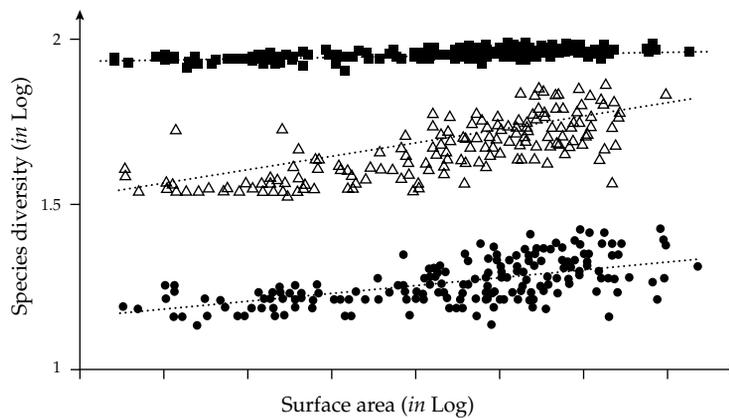
Figure 2.2 Areal species richness diversity and surface area size (double-logarithmic transformations) for three categories of human pathogens: contagious diseases (black squares), zoonotic diseases (open triangles), and multihost diseases (black circles). Each point represents a pathogen species. Modified from Smith *et al.* (2007).

the species diversity within a local community does not differ statistically from that observed at the largest scale (Fig. 2.2), and communities from adjacent sites are not more similar to each other than they are to those from more distant sites. This suggests that such parasites disperse rapidly over large distances, thus maintaining their global distribution.

Second, multihost diseases such as trypanosomiasis, with human hosts and non-human reservoirs or vectors, have a positive species–area curve (Fig. 2.2). For these diseases, increasing the size of the sampling area increases the number of pathogen species, which suggests that they are to some extent endemic to certain localities, as discussed earlier.

Third, reservoir host diseases, such as monkeypox virus or Ebola virus, which require an animal to spread, follow a positive species–area curve (Fig. 2.2). For this category of diseases, for which transmission from person to person is impossible or extremely rare and humans are unusual, accidental hosts and not part of the normal life cycle, pathogen communities from distant localities are composed of distinct pathogen species, for many zoonotic parasites are restricted to locally distributed reservoir species, such as tropical rodents. Therefore it is likely that with increasing sampling effort more zoonotic pathogen microbes will be discovered in the future.

In summary, geographical barriers rarely restrict the large-scale dispersal of directly transmitted pathogens. The local diversity of these pathogens—to which human populations are exposed—is large and probably a significant proportion of global diversity (Fig. 2.2). At the other extreme, the ranges of multihost reservoir diseases and zoonotic diseases do not differ markedly from the ranges of their macroscopic hosts, and they show some well-known biogeographical patterns: species richness and species composition gradients with latitude and longitude, range size with latitude, species richness–area curves. Within these two groups of pathogens, many novel, endemic pathogen species probably exist with spatial distributions largely driven by that of their reservoir species and with high species diversity in the tropics. New emerging diseases will likely originate from animal reservoirs, especially those in the tropics. International exotic animal trade may be an excellent pathway for disseminating such emerging diseases into 'microbe-free' regions around the globe (Di Giulio and Eckburg 2004).

Historical patterns of the distribution of disease

It is unlikely that early modern humans faced the pathogen species diversity that we know today, for many diseases—e.g., coccidioidomycosis (Fisher

et al. 2001), smallpox (Oldstone 1998), the plague (Scott and Duncan 2001), leprosy (Monot *et al*. 2005), and many zoonotic diseases (Oldstone 1998)— emerged only a few thousand years ago. Leprosy, for instance, originated in Eastern Africa or the Near East and was introduced into the Americas within the past 500 years (Monot *et al*. 2005). Similarly, the fungal disease *Coccidioides immitis* probably appeared in South America within the past 10,000 years via human migrations (Fisher *et al*. 2001). Although current macroscopic patterns of disease distribution and occurrence cannot precisely mirror the situation of early human populations, the broad macroecological patterns of diseases discussed earlier are likely to have been similar.

To summarize this section: large-scale human-pathogen interactions show two general spatial trends: (a) globally distributed pathogens selected throughout history as strains adapted to human populations, and (b) endemic pathogens, primarily zoonoses, whose species diversity is highest in the tropics.

Pathogen distribution and human genetic evolution

Did differences in levels of exposure to certain pathogens or groups of pathogens differentially affect the genetic evolution of human populations?

The answer is yes! Of several good examples, we focus here on two. The first concerns the gene that codes for the β-globin found in hemoglobin. Some mutants of this gene have been maintained at high frequencies in certain human populations— despite their obvious deleterious effects—because they confer resistance against particular pathogens. The second concerns a group of genes with immune function, the HLA (human leucocyte antigen) genes also known as major histocompatibility complex (MHC). Human populations exposed to a higher diversity of disease agents display higher genetic diversity at HLA genes than is expected under a simple neutral model. While genetic drift and demographic history have also been important in shaping their patterns of diversity, we argue that selection exerted by local pathogen communities has influenced the local evolution of these human genes.

Pathogen distribution and human genetic evolution: the case of sickle cell disease

Hemoglobin and sickle cell disease
Sickle cell disease is caused by a change in the hemoglobin protein (Pauling *et al*. 1949). Individuals with two copies of the Hb S variant of the β-globin (homozygous Hb SS) develop stiff, distorted red blood cells that have difficulty passing through the body's blood capillaries. Tissues with reduced blood flow become damaged. Eventually, the disorder causes anemia, joint pain, a swollen spleen, and often severe infections that lead to death. Homozygous individuals have a short life expectancy and rarely reproduce. Heterozygotes for this variant (individuals that present the 'normal' variant Hb A and the 'abnormal' one Hb S) produce both sickle-shaped red cells and normal ones but rarely develop any symptoms (Ashley-Koch *et al*. 2000). Because persons homozygous for the sickle cell gene very rarely reproduce, the sickle cell allele (Hb S) should decline in every generation within populations and should therefore be observed only at very low frequencies if at all. This, however, is not the case everywhere.

Sickle cell trait distribution
High frequencies of more than 20% of the sickle cell trait are found in populations across a broad belt of tropical Africa (Allison 1954a,b) (Fig. 2.3). Elevated frequencies are also found in Greece, Turkey, and India (Singer 1953). Intermediate frequencies are found in, for example, Sicily, Algeria, Tunisia, Yemen, Palestine, and Kuwait. The sickle cell gene is thus found in a large and nearly continuous region of the Old World (and in populations that have recently emigrated from there), whereas the trait is almost completely absent from northern Europe, Australia, and North America (Singer 1953). Two main hypotheses have been proposed to explain the observed high frequencies within certain populations (Neel 1951) despite its highly deleterious effects: either the sickle cell allele frequently arises by recurrent mutation within populations, or the heterozygous individuals for the sickle cell allele (Hb AS) have a selective advantage (i.e., overdominance) over both the 'normal' homozygotes (Hb AA) and the sickle cell ones (Hb SS). Overdominance would enable
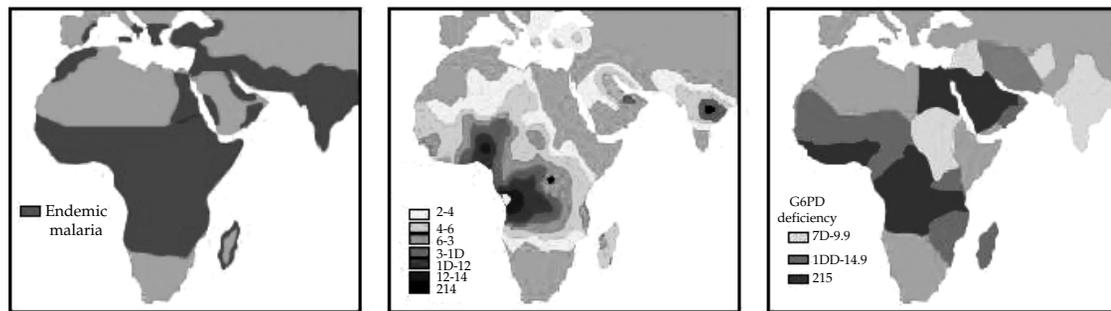
Figure 2.3 Maps showing the relation between (a) the geographic presence of malaria before 1920, (b) the frequencies (%) of the Hb S allele, and (c) the frequencies (%) of the G6PD deficiency in males in Africa, southern Europe, and west Asia. For G6PD, only the frequencies higher than 7% are reported. In many regions where malaria is prevalent but not the Hb S or the G6PD deficiency, other mutant hemoglobins may be found. Data mapping compilation from different sources by one of the authors (FP).

the deleterious allele to be maintained at a stable polymorphism.

For the first hypothesis, the mutation rate would have to be very high and confined to certain human populations. Vandepitte *et al*. (1955) demonstrated that the mutation rate in hemoglobin was not high enough to maintain the observed frequencies of the sickle cell allele within populations. Therefore selection in favour of heterozygous individuals seems the best explanation. Why, then, had the gene become common in some parts of the world but not in others? Why did human heterozygotes have an advantage only in certain communities?

Malaria and the sickle cell trait: the advantage of heterozygotes

Allison *et al*. (1952) proposed that malaria could be the selective agent behind this process by noting that the geographical distribution of the gene for hemoglobin S and the distribution of malaria in Africa virtually overlapped (see Fig. 2.3). And indeed, Allison (1954a,b) later demonstrated that the prevalence and intensity of the infectious disease were lower in Hb AS heterozygote individuals than in Hb AA homozygous individuals. Hb AS children are more likely to survive than Hb AA children in highly malaria endemic areas (Aidoo *et al*. 2002).

Mechanisms of resistance: an intimate association between malaria and red cells

Several factors are likely to contribute in varying degrees to the partial resistance of sickle cell heterozygotes to malaria. Resistance can be mediated by the reduced ability of parasites to grow and multiply in Hb AS red cells (Friedman 1978) or by their early removal from circulation (Luzzatto *et al*. 1970). Thus, parasite-infected Hb AS erythrocytes sickle more than non-parasitized Hb AS cells, which may lead to the parasites' intracellular death (Friedman *et al*. 1979) or their removal by the immune system (Luzzatto *et al*. 1970). Although the latter may be largely the result of innate immunity, recent data suggest that acquired immunity may also be involved (Williams 2006). The contributions of these processes to protection against malaria *in vivo* are still largely undetermined.

Malaria and other red cell polymorphisms

The Hb S variant is not the only polymorphism of red cell proteins that has been selected for protection against malaria (Table 2.1). As shown in Fig. 2.3, the distribution of these variants is similar to the geographical distribution of malaria. However, human double heterozygotes for some of these variants, such as Hb S and β-thalassemia, or Hb S and Hb C, also suffer from a type of sickle cell disease (as do homozygotes) that reduces their fitness, so that these variant alleles tend to be mutually exclusive in human populations (Allison 1964). By comparison, other combinations of variants, for which there is no negative interaction between mutants, can be found at high frequencies (as is the case for G6PD deficiency and the Hb S variant; Fig. 2.3).

Table 2.1 Examples of red cell genes involved in malaria resistance, and which polymorphism worldwide may have been partly determined by the presence/absence of malaria

Cell component	Variant	Gene	Protein and function	Effect on malaria	Main distribution
Hemoglobin	Hb S	HBB	β-globin (hemoglobin component)	Protects against severe malaria	Africa, Middle East, India, Mediterranean
	Hb C	HBB	β-globin (hemoglobin component)	Protects against severe malaria	Africa
	Hb E	HBB	β-globin (hemoglobin component)	Reduces parasite invasion	Southeast Asia
	α-thalassemia	HBA	β-globin (hemoglobin component)	Protects against severe malaria	Africa, Mediterranean India, Southeast Asia
	β-thalassemia	HBB	α-globin (hemoglobin component)	Protects against severe malaria	Africa, Mediterranean, India, Southeast Asia, Melanesia
Red cell enzymes	G6PD deficiency	G6PD	Glucose-6-phosphate dehydrogenase (protects against oxidative stress)	Protects against severe malaria	Africa, Mediterranean, India, Southeast Asia
Red cell membrane	FY*O	FY	Duffy antigen (Chemokine receptor)	Protects against *Plasmodium vivax*[a]	Africa

[a] *Plasmodium vivax* is one of the agents of the human malaria. The others are *Plasmodium falciparum*, *Plasmodium malariae*, and *Plasmodium ovale*. The deadliest is *P. falciparum*.

Malaria and human gene evolution

Malaria has been a major determinant in the evolution of several human genes, especially those involved in the constitution of red blood cells. It has in fact been suggested that malaria was (and still is) one of the most powerful forces of selection operating on humans. Despite the widespread use of drugs, malaria is still responsible for between 1.5 and 2.7 million deaths each year, primarily of children under the age of five years (Phillips 2001), and as such still has a major impact on human fitness in many populations. This infectious disease has shaped the evolution of several human genes.

Variations in pathogen diversity and human genetic evolution: the HLA genes

HLA is a complex of genes with a major role in the recognition and presentation of non-self (antigens) to the effector cells of the immune system (T-cells) (Zinkernagel and Doherty 1974). Class I genes (A, B, and C), which are expressed in almost all cells, are involved in the recognition of intracellular non-self (e.g., viruses); class II genes (DP, DQ, and DR), which are only expressed in the antigen presenting cells, are mainly involved in the recognition of extracellular pathogens (or non-self). HLA genes are among the most polymorphic genes, both in the human genome and in the genome of other vertebrates. For instance, more than 350 alleles are known for the Class I HLA B gene alone (Robinson *et al.* 2001).

Several pieces of evidence suggest that this extreme polymorphism is, at least in part, maintained by balancing selection (Meyer and Thomson 2001). Thus, within human populations, the number of HLA alleles is far higher than the number expected under neutrality. Furthermore, when alleles do not differ in their selective effect (Potts and Wakeland 1993), they are generally more evenly distributed within populations than expected under a pure neutral model of evolution (Hedrick and Thomson 1983), and heterozygote excesses are observed more often than predicted by Hardy-Weinberg expectations (see Markow *et al.* 1993).

Several hypotheses have been proposed to explain selection operating on HLA genes within populations, including MHC-dependent mate choice (Penn *et al.* 2002), spontaneous abortion (Thomas *et al.* 1985), and the selection imposed by the various species or strains of pathogens infecting human populations (Klein and Ohuigin 1994). This latter kind of selection, generally called 'pathogen-driven balancing selection,' is expected to operate when different alleles are selected

because of their ability to provide higher resistance against certain species of pathogens or certain strains, and is supported by several pieces of evidence. Thus, certain alleles confer more resistance against certain pathogens (e.g., against malaria or HIV) and individuals heterozygous for HLA genes are more resistant to some infectious diseases than homozygous individuals (overdominant selection) (see Penn 2002).

There is therefore little doubt that the evolution of HLA in humans is linked to pathogens. But can this link explain why HLA diversity varies among human populations worldwide? In other words, might pathogenic species richness and composition have influenced the local evolution of these immune genes in modern humans?

HLA genetic diversity and pathogen-driven selection
Across 61 populations (Fig. 2.4), there is a strong positive correlation between HLA class I diversity and pathogen species diversity, especially for genes A and B after accounting for the effect of human demography on HLA diversity (for details see Prugnolle *et al.* 2005). Note that, as HLA class I genes (A, B, C) are mainly involved in the presentation and recognition of intracellular pathogens, the analysis considered only intracellular disease agents (viruses, obligate and facultative intracellular bacteria, and protozoans with at least one
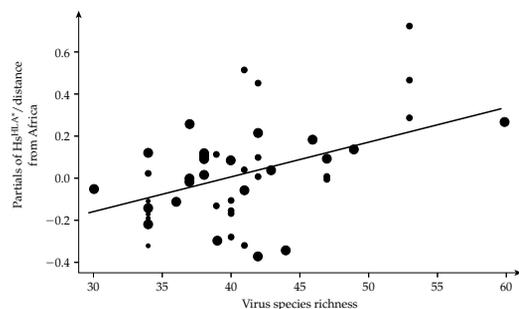
Figure 2.4 Partial residuals (after having taken into account the effect of demography) of Hs^{HLA}*($=$log[Hs/(1-Hs)]) against virus species diversity for the HLA B gene. For details refer to Prugnolle *et al.* (2005). Hs is the HLA genetic diversity. Dot size is inversely proportional to the number of human populations coming from the same region in order to avoid statistical bias due to over-representation of some human communities. Modified from Prugnolle *et al.* (2005).

intracellular stage). The relationship is stronger for HLA B than for HLA A, suggesting that the HLA B gene might be under stronger balancing selection than the other Class I genes. This finding is in good agreement with other genetic and immunological studies, which have shown a stronger involvement of HLA B than of HLA A in the recognition of non-self (Kiepiela *et al.* 2004). Subdividing the intracellular pathogens into viruses, bacteria, and protozoans shows that HLA class I diversity is mainly correlated with virus species richness, suggesting that virus diversity, which is higher in the tropics, might exert stronger selective pressure on immune genes than any other category of pathogens.

Pathogens are not distributed evenly in space (see above). They form an ecologically heterogeneous landscape in which spatially separated human populations have been submitted to different selected regimes, leading populations to adapt to their local parasitic conditions. Today, the traces of these different evolutionary histories may be found in the genomes of human populations.

Infectious diseases and human life-history traits

Human populations differ in life-history traits such as survival, fertility, age at first menstruation, and age at menarche (Thomas *et al.* 2001; Barret *et al.* 2002). Social scientists and demographers have traditionally assumed that socioeconomic variables—such as development, modernization, culture, and family planning programs—predominate in determining these differences. Variation in human life-history traits, however, might also have evolutionary explanations that rely on differences in characteristics of the environment, including biotic interactions (Stearns 1992). For instance, in many plant and animal species, parasites play an important role in the evolution of host life-history traits (see, e.g., Kris and Lively 1998; Fredensborg and Poulkin 2006). Parasites use resources that the host could otherwise use for its own growth, maintenance, or reproduction. Direct costs of this exploitation lead to variation in life-history traits among individuals and populations. Alternatively, changes in host life-history traits may be an adaptive response to

parasitism. One solution developed by many animal species against parasites is the adjustment of life-history traits to compensate for their negative effects on fitness. By analogy, we here suggest that parasitic and infectious diseases have also affected human life-history traits.

Human fertility and the species diversity of human pathogens

Guégan *et al*. (2001) performed a comparative analysis on 150 countries to explore the relationship between the diversity of infectious disease agent species and human fertility. The prediction was that humans in countries with high quantities and diversity of virulent parasites should compensate for the high offspring mortality by increasing their reproductive investment. In agreement with this prediction, human fertility was positively related to the diversity of disease types encountered by local human communities. The correlative nature of this study prohibits any conclusions about the causal mechanisms relating diseases and fertility. One important finding was that a set of co-occurring diseases rather than a unique infectious disease is the key to understanding the link between parasitism and human life-history traits.

Human birthweight and the species diversity of human pathogens

Human populations differ in birthweight (Vangen *et al*. 2002). Many variables influence prenatal growth and birthweight in humans, e.g., maternal energy supply, maternal stature, physical work, stress, temperature, disease status, smoking status, gestation length, and altitude (see Koupilova *et al*. 2000; Wells 2002). Thomas *et al*. (2004) present a theoretical model to suggest that a significant part of the variability in human birthweight results from adaptive responses among which the risk of fitness reduction predominates (this idea has not yet been formally tested). In stable, well-resourced, low-parasite environments (i.e., most modern industrialized countries), somatic (i.e., non communicable) diseases are likely to be an important source of fitness variation among individuals. Because

infants with a low birthweight are at a higher risk of expressing chronic diseases later in life (e.g., cardiovascular diseases, diabetes, certain cancers, impairment of hearing and vision; cf. Chapter 19), selection in these environments is expected to favour individuals producing larger children. Even if some of these somatic diseases occur late in life (i.e., after reproduction), they are likely to be detrimental to an individual's fitness, for they reduce its capacity to deliver grandparental care.

In countries where the risks of parasitic infections are high (i.e., numerous developing countries), women are, other things being equal, also expected to deliver infants with a high birthweight. Indeed, infants with low birthweight generally have an increased vulnerability to infectious diseases because of impaired immune function (e.g., Moore *et al*. 1999). Given that offspring mortality (due to infections), more than fertility, is likely to be the primary determinant of fitness variation between reproducing females, mothers in parasite-rich environments will have a particular reproductive interest in producing larger, more resistant, children. The study by Thomas *et al*. (2004) also predicts that once a threshold in infection risk is reached, birthweights significantly increase with the number of diseases present.

Finally, in environments where adverse environmental conditions—famine, drought, or accidents—are frequent, selective pressures for producing large offspring are likely to be relaxed because the negative impacts of environmental factors on individual fitness are largely independent of birthweight. Instead, the fitness costs incurred by the mothers when producing large children (e.g., reduced survival, lower probability of subsequent reproduction, cf Bereczkei *et al*. 2000) are less well compensated by reproductive advantages, so that natural selection should favor individuals producing smaller babies.

Human behavior and culture, and the species diversity of human pathogens

Can infectious diseases also alter human culture? One example is the protozoan *Toxoplasma gondii* (see Lafferty 2006), which lives in the nervous system. Cats are the final hosts of *T. gondii*, and

rodents are its normal intermediate hosts, but the parasite also develops well in humans. The parasite induces behavioral alterations in rodents that lead to an increased risk of predation by cats (Berdoy *et al.* 2000). In humans, *Toxoplasma* infections result in slight personality changes, for example guilt proneness, a form of neuroticism, and reduced psychomotor performance (Havlicek *et al.* 2001). Because cats do not normally prey on humans, these behavioral changes are of no apparent value to the parasite. They could be manifestations of mechanisms evolved in the past to manipulate the normal rodent hosts, or they may be mere coincidental pathology. Whatever the cause of such changes, Lafferty's results suggest that *Toxoplasma* could affect specific elements of human culture. He found that countries with high *Toxoplasma* prevalence have a higher aggregate neuroticism score, and Western nations with high prevalence

also score higher in the 'neurotic' cultural dimensions of uncertainty avoidance and of masculine sex roles (Fig. 2.5). Many infectious agents may play a role in some neuropsychiatric disorders (McSweegan 1998), and a recent study has pointed out that nearly half (49%) of all emerging viruses today are characterized by encephalitis or serious neurological clinical symptoms in humans (Olival and Daszak 2005), highlighting the importance of neurotropic disease agents in medicine and social culture. Recent investigations have illuminated the molecular mechanisms that enable neurotropic viruses to alter brain function and lead to neurobehavioural disorders (Volmer *et al.* 2006).

Although parasitic and infectious diseases have had a major impact on human population demography around the world, relatively few attempts have been made to investigate how disease-causing agents have affected human biology. The few studies above suggest that their influence might be substantial. The importance of parasites as a determinant of human life histories as compared to other factors remains to be assessed.
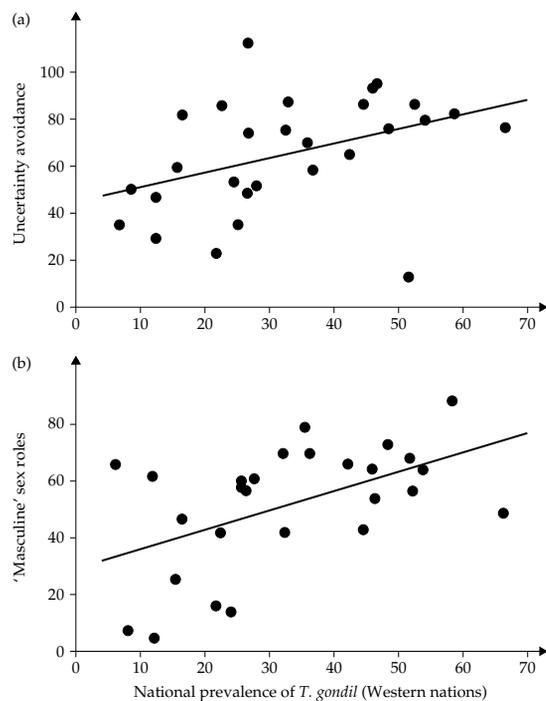
Figure 2.5 Association between (a) the cultural dimension of uncertainty avoidance and the prevalence of *Toxoplasma gondii* in Western nations, and (b) the cultural dimension of masculine sex roles avoidance and the prevalence of *T. gondii* in Western nations. From Lafferty (2006).

Summary

1. Human infectious diseases are not distributed at random: contagious diseases are everywhere; zoonotic pathogens are more locally concentrated in the tropics.

2. Therefore, human communities are not all equally exposed to disease; populations in the tropics have suffered, and are still suffering, from a greater diversity of pathogens.

3. Pathogens have exerted strong selective pressures on modern humans, which in turn have evolved resistant genotypes. Results of this evolution may be observed in the genomes of current human populations.

4. Because pathogens are not distributed homogeneously, human populations have been submitted to qualitatively and quantitatively different selective pressures. Therefore, different human populations may have followed different evolutionary pathways.

5. An allele that confers resistance against a pathogen may reduce fitness in the absence of the pathogen. The evolution of an allele conferring resistance

against a pathogen is often the result of a complex balance between costs and benefits.

6. The life-history traits of early humans (like those of many animals) were shaped by inter-actions with parasites, but to what extent those of modern humans result from selection by disease is a matter of debate. Better comparative statistics on life-history traits in humans (in addition to traits usually surveyed by anthropologists) are needed to explore this important issue.

7. Given the current epidemiological transition into which modern societies have entered (less parsitic load), analyses of the connections between life-history traits and disease biology can also help us to understand evolutionary responses in fertility, sexual dimorphism, and life span (cf. Chapter 7).

8. These considerations stimulate important ques-tions about the role of parasites in our evolution: Which kinds of pathogens are most likely to spread in human populations in the future (cf. Chapter 16)? To what extent will the homogenization of zoonotic diseases interfere with human adaptation and evo-lution? If pathogen pressure maintains much human polymorphism, what will be the effects of disease control and eradication on our own evolution?

Acknowledgments