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The Red Queen's long race: human adaptation to pathogen pressure

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Pathogens, and the infectious diseases they cause, have been paramount among the threats encountered by humans in their expansions throughout the globe. Numerous studies have identified immunity and host defence genes as being among the functions most strongly targeted by selection, most likely pathogen-driven. The dissection of the form and intensity of such selective pressures have increased our knowledge of the biological relevance of the underlying immunological mechanisms in host defence. Although the identities of the specific infectious agents imposing these selective pressures remain, in most cases, elusive, the impact of several pathogens, notably malaria and cholera, has been described. However, past selection against infectious diseases may have some fitness costs upon environmental changes, potentially leading to maladaptation and immunopathology.

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Introduction

''Now, here, you see, it takes all the running you can do, to keep in the same place.''

The words of the Red Queen to Alice in Lewis Carroll's Through the Looking Glass [1] reflect the need for species to continually evolve in the face of competition and changing environments, most notably pathogen presence. This competition leads to an evolutionary arms race, driving constant adaptation and counter-adaptation of competing species, as predicted by the Red Queen hypothesis [2].

Throughout their history, humans have co-existed and co-evolved with a wide range of microorganisms, both pathogenic and harmless, shaping genetic variation in both populations today. In humans, the study of biological adaptation has entered a golden era with the availability of genome-wide (GW) datasets, such as those provided by the HapMap project and the 1000 Genomes project [3,4]. This has enabled the evaluation of the extent of selection acting on the genome and the occurrence of genetic adaptation to environmental pressures, with an unprecedented level of resolution. Likewise, improvements in statistical methods to detect the different forms that selection can take [5••] (Figure 1) have helped to separate the confounding effects of demography and selection and to elucidate the evolutionary trajectories involved in human adaptation. In this review, we explore the human side of the long race predicted by the Red Queen hypothesis. We highlight both the benefits and trade-offs of past selection against infectious diseases, and discuss the challenge of pinpointing the microbial agents exerting a selective pressure.

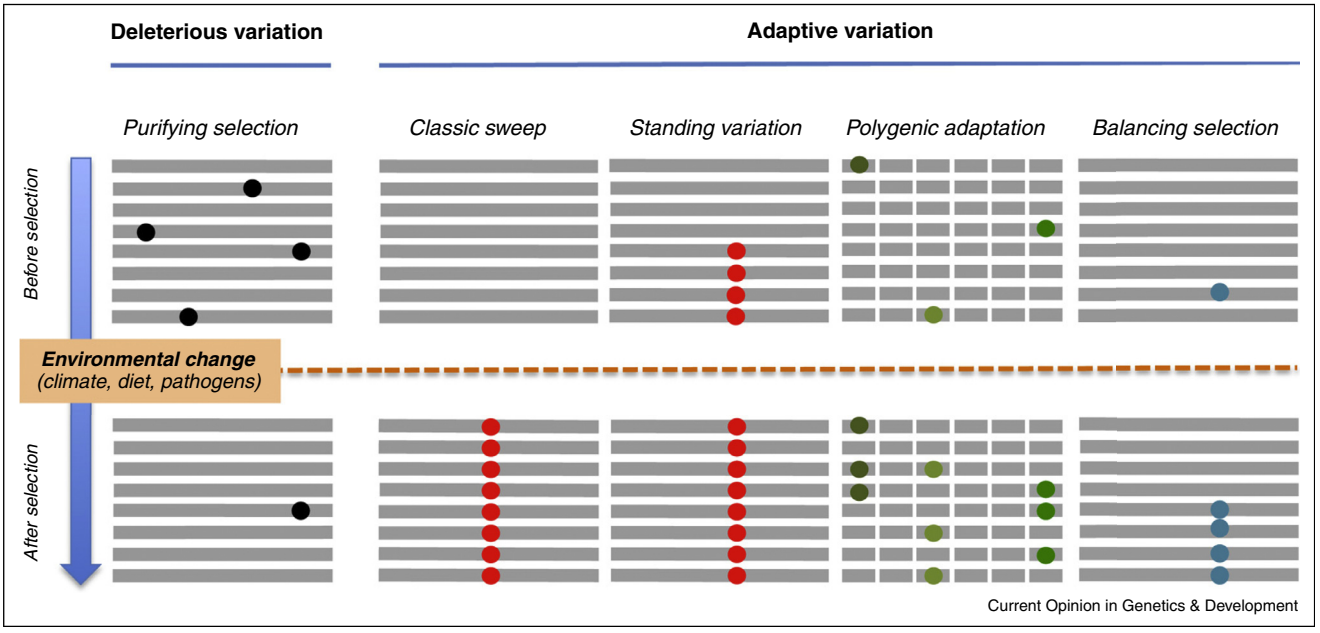
Pathogen pressure and human genome diversity

The pressure imposed by pathogens has been massive throughout human evolution. Before the advent of vaccines and antibiotics at the beginning of the 20th century — 'yesterday' from an evolutionary standpoint — diseases killed half of all children by the age of 15 and resulted in an average life expectancy of around 20 years [6] (Figure 2). It is thus not surprising that genes and functions related to immunity and host defence are among those exhibiting the strongest signatures of selection [7–9]. The hypothesis that pathogen pressure is the underlying cause of such signatures has gained considerable support at the GW level.

Proof of the importance of pathogen-driven selection comes from studies correlating genetic variability in human populations and pathogen diversity in the corresponding geographic regions. Although these studies make a number of important assumptions (i.e. constant pathogen richness over time and equal virulence of all pathogens), significant correlations have been detected for the Human Leukocyte Antigen (HLA) class I genes [10], blood group antigens [11], and interleukin genes and their receptors [12]. Other studies have identified genetic variation that correlates with specific groups of microbes, such as viruses, protozoa and parasitic worms [13–15].

Pathogen presence can correlate with other variables, so it is important to separate the selective role of pathogens from other ecological factors. To do so, Fumagalli and

Figure 1



Modes of action of natural selection. Selection can come in many different forms, some of which are subtle variants of each other and are referred to by multiple, sometimes misleading, terms. Purifying selection, also known as negative selection, refers to the selective removal of, more or less, deleterious alleles (here in black) from the population, and is the most pervasive form of selection acting on genomes. Advantageous mutations can increase in frequency in the population by positive selection, a selective regime that can take different forms and intensities. Under the model of a classic sweep (or hard sweep), following an environmental change, a newly arisen advantageous mutation (in red) will be targeted by positive selection and will, ultimately, reach fixation. There are, however, alternative modes of positive selection that do not adhere to the simple, classic sweep model. For example, selection on standing variation refers to the scenario where, due to a change in selective pressures, an allele that is already segregating in the population (in red) becomes selectively favoured, and increases in frequency. In polygenic adaptation, adaptation occurs by simultaneous positive selection of variants at many loci, each allele (here in different shades of green) making a (relatively) small contribution to overall fitness. Finally, under a model of balancing selection, one or more alleles are maintained at an appreciable frequency within the gene pool, as a result of heterozygote advantage (overdominance) or frequency-dependent selection. In the figure is shown a case of heterozygote advantage at a given position, where both alleles (the ancestral and the derived, the latter here in turquoise) are maintained at intermediate frequencies. Each form of selection leaves specific molecular signatures in the genomic region targeted, which can be detected with a variety of statistical tests (extensively reviewed in [5••]).

colleagues have tested for genetic correlations with a large variety of environmental variables, including climatic conditions, subsistence strategies, diet regimes and pathogen load [16•]. They found that, of these variables, pathogens are the primary drivers of local adaptation, and detected a large number of genes whose diversity strongly correlates with pathogen diversity, after correcting for demography. These genes are enriched in functions such as inflammatory responses and innate immunity, supporting the major role that pathogens have played in human evolution, particularly that of the immune response.

Learning immunology through population genetics

An increased understanding of the degree of essentiality, redundancy or adaptability of immunity genes can be obtained from the dissection of the form and intensity of selection that these genes have been subject to over time. The additional insight brought by the integration of such selection studies into a clinical and epidemiological framework has established the value of population genetics in delineating the biological relevance of immunity genes *in natura*, and in predicting their involvement in disease [8,17,18].

Genes evolving under purifying selection are likely to be involved in essential mechanisms of host defence, variation in which should lead to severe disorders [19]. This prediction is supported by GW studies, as Mendelian disease genes are enriched in signals of purifying selection [20,21•,22]. In the context of immunity, purifying selection is widespread, particularly among innate immunity genes [23]. Microbial sensors such as endosomal Toll-like receptors (TLRs) and many Nod-like receptors (NLRs) [24–26], adaptors such as MYD88 and TRIF [27,28], and effectors such as some type-I IFNs and IFN-γ [29] have been targeted by purifying selection, attesting to the essential nature of their involvement. Conversely, genes evolving under weak negative selection are likely to be involved in more redundant processes. For example, among innate immunity receptors that sense nucleic acids, the weaker constraints