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Genetic and evolutionary determinants of human population variation in immune responses

Joaquin Sanz[1,2,4], Haley E Randolph[1,2,4] and Luis B Barreiro[2,3,5]

Humans display remarkable immune response variation when exposed to identical immune challenges. However, our understanding of the genetic, evolutionary, and environmental factors that impact this inter-individual and inter-population immune response heterogeneity is still in its early days. In this review, we discuss three fundamental questions concerning the recent evolution of the human immune system: the degree to which individuals from different populations vary in their innate immune responses, the genetic variants accounting for such differences, and the evolutionary mechanisms that led to the establishment of these variants in modern human populations. We also discuss how past selective events might have contributed to the uneven distribution of immune-related disorders across populations.

Addresses
[1] Department of Biochemistry, Faculty of Medicine, Université de Montréal, QC H3T 1J4, Canada
[2] Department of Genetics, CHU Sainte-Justine Research Center, Montreal, QC H3T 1C5, Canada
[3] Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, QC H3T 1C5, Canada

Corresponding author: Barreiro, Luis B (lbarreiro@uchicago.edu)
[4] These authors contributed equally to this work.
[5] Current address: University of Chicago, Department of Medicine, Genetics section, Chicago, IL 60637, USA.

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Introduction

Pathogens are one of the strongest selective pressures on the human genome [1–3]. As modern humans migrated out of Africa ~60 kyr ago and traversed new territories, they encountered markedly different pathogenic environments, likely resulting in population-specific selection of immune phenotypes ([4–6], Figure 1a). Consistent with this hypothesis, some of the most compelling evidence for local positive selection in the human genome has been detected among genes involved in immunity and host defense [2,7,8]. Yet, our understanding of the role that local adaptation plays in shaping phenotypic variation in immune responses across populations is still in its infancy.

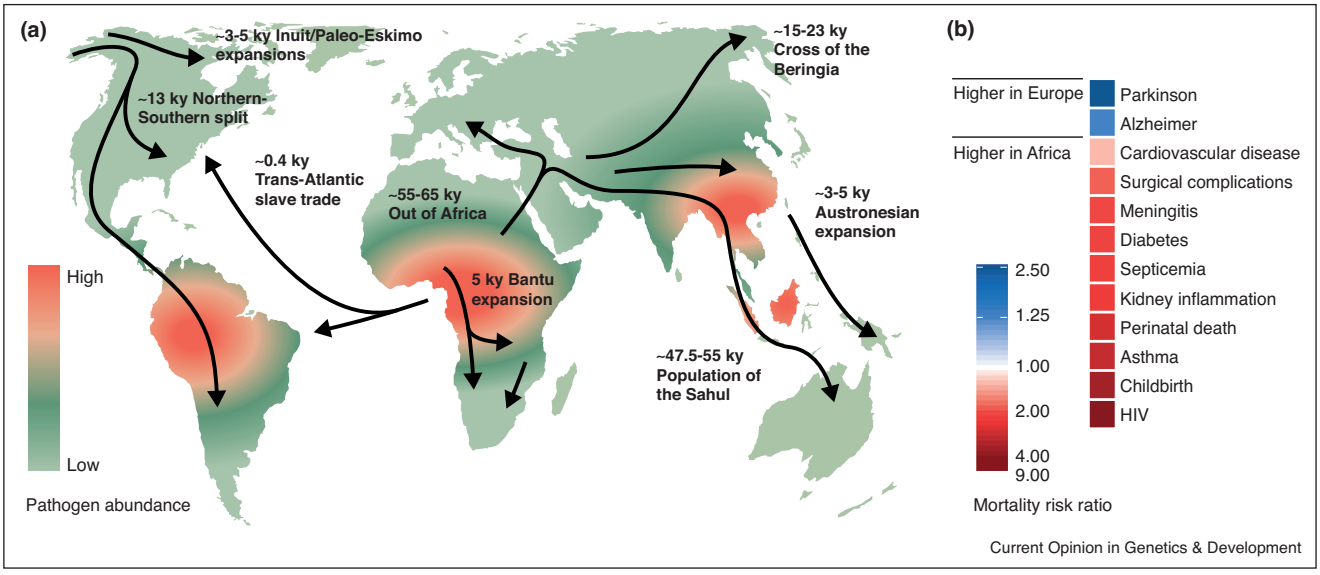
The innate immune system is the earliest immune defense mechanism activated upon pathogen invasion. Pathogen-induced signaling through innate immune receptors prompts pervasive changes in gene expression that subsequently trigger the activation of inflammatory and/or antiviral immune effectors involved in pathogen clearance [9]. Inter-individual differences in innate immune responses are common and presumably contribute to varying susceptibility to infection, inflammation, and autoimmune disorders (Figure 1b) [10–12]. Although a substantial fraction of transcriptional heterogeneity in response to infection is likely attributable to environmental factors, a large portion is also due to host genetics. Recently, the contribution of host genetics to innate immune response diversity among individuals has been demonstrated using expression quantitative trait loci (eQTL) mapping [13] on diverse subsets of immune cells both at baseline and after exposure to immune stimuli and live pathogens [13,14•,15,16••,17,18••,19•,20•,21,22••,23,24•] (Figure 2a,b). These 'immune response eQTL' studies have identified a large number of host genetic variants that underlie differential innate immune responses to infection, some of which have been associated with increased susceptibility to sepsis, inflammatory bowel disease, viral hepatitis, typhoid fever, and tuberculosis [19•,25–27]. Recently, several studies have implemented similar eQTL mapping approaches to determine the extent to which disparities in immune phenotypes between populations are due to genetically-controlled transcriptional response variation (Figure 2c) [16••,18••].

Here, we do not attempt to provide a comprehensive overview of the myriad of genetic and non-genetic determinants of inter-individual variation in immune phenotypes (see [24•,28•]), for which outstanding reviews have been published elsewhere (e.g., [29]). Instead, we focus specifically on recent genomic studies characterizing the functional differences in immune response between populations as well as the genetic determinants partially controlling such differences. Further, we discuss the role of natural selection in driving present-day disparities in immune response between populations, considering cases of local adaptation and adaptively-introgressed alleles.

Inter-population variation in disease susceptibility and immune phenotypes

Individuals from distinct regions of the world differ in their susceptibility to infectious diseases as well as chronic inflammatory and autoimmune disorders

Figure 1



(a) Major migratory routes followed by the ancestors of present-day humans who originated in Africa around 200 kyr, adapted from Refs. [4,5]. The spread of humans throughout the world led to the settlement of populations in geographical areas with variable environments. Ultimately, these migrations imposed novel and heterogeneous adaptive pressures on the human genome. The existence of varying levels of pathogen diversity (geographic distribution sketched from results summarized in Ref. [6]) is linked with many significant signatures of adaptation found in relevant immune system genes [2,7,8]. **(b)** Age-adjusted death rate ratios associated with different diseases and fatality causes between individuals of African versus European ancestry in the USA, as summarized in Ref. [10].

(reviewed in [11,30]). Recent studies suggest that such disparities in disease susceptibility can in part be explained by differences in immune response between individuals of varying genetic ancestry. Nédélec *et al.* [18••] used RNA-sequencing to characterize the manner in which primary macrophages derived from a panel of 175 healthy individuals who self-identified as either African or European American responded to *Listeria monocytogenes* or *Salmonella typhimurium* infection. Using a similar approach, Quach *et al.* [16••] tested for the effect of African versus European ancestry on monocyte response to several Toll-like receptor (TLR) ligands, including TLR1/2, TLR4, and TLR7/8, and the human seasonal influenza A virus. Both studies revealed marked ancestry-associated differences in gene expression and immune responses to infection. Across the experimental conditions tested, on average, 21.3% of the genes appeared to show differential expression between European and African individuals (i.e., population differentially-expressed or popDE genes) (Figure 3a, left). In addition, up to 16.1% of the genes responding to immune stimulation showed a significant divergence in the intensity of response between European and African individuals (i.e., population differentially-responsive or popDR genes) (Figure 3a, right).

The number of genes exhibiting significant differences in immune regulation between individuals of African and European descent is substantial. Yet, the proportion of immune response variation due to genetic ancestry remains modest — on average ~7% (Figure 3b). In other words, for most genes, two individuals from different populations tend to manifest more similar phenotypes than two individuals from the same population (Figure 3c). Despite this, the additive effect of subtle shifts in the distribution of many immune phenotypes (i.e., in the expression levels of many genes across the genome) between populations may be sufficient to explain the reported ethnic disparities in inflammatory and autoimmune disease susceptibility. Supporting this hypothesis, Nédélec *et al.* showed that genes differentially-expressed between populations are significantly enriched for genes associated with immune-related disorders identified by genome-wide association studies. Such diseases include rheumatoid arthritis, systemic sclerosis, and ulcerative colitis, all of which have been reported to differ in incidence or disease severity between African American and European American individuals [10,31].

Several lines of evidence from genetic, epidemiological, and functional genomic studies indicate that individuals of African descent engage a stronger transcriptional response to immune stimulation as compared to individuals of European descent, particularly among genes related to the activation of inflammatory responses. As compared to European Americans, African Americans have higher frequencies of alleles associated with