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Brenna M Henn and Lluís Quintana-Murci

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Brenna Henn is an Associate Professor at UC Davis. With a background in anthropology, she aims to consider questions in human genetics from an interdisciplinary perspective. The primary focus of her lab is modeling how patterns of genetic diversity arose within Africa, whether by drift, migration or adaptation, and how this diversity uniquely affects susceptibility to disease in Africans.

Lluís Quintana-Murci is CNRS Research Director and Professor at the Institut Pasteur, where he heads the Unit of Human Evolutionary Genetics. His laboratory is focused on understanding how natural selection, human demography and lifestyle have shaped the patterns of diversity of the human genome, to understand how this may impact phenotype diversity, with an emphasis on immune response variation and infectious diseases.

This special issue on the Genetics of Human Origins in Current Opinion in Genetics and Development is dedicated to Luigi Luca Cavalli-Sforza who passed away last August 2018. Luca — “please, call me Luca” he always said whoever he was talking to — was the grandfather of the field of human population genetics [1], and influenced many of the perspectives we review here in foundational ways. His interests in human prehistory cut across several disciplines, as he worked to compare patterns from linguistic, cultural and archaeological data with emerging protein polymorphism, mitochondrial and Y-chromosomal data. His cross-disciplinary thinking opened new avenues of research, including that of how cultural evolution may impact biological evolution: *“If there’s any interaction between genes and languages, it is often languages that influence genes, since linguistic differences between populations lessen the chance of genetic exchange between them”*.

Cavalli-Sforza’s contributions also included developing methods for phylogeny reconstruction, scouring historical records to understand the effects of local migration on inbreeding and deleterious alleles, and describing long-range patterns of gene flow between populations (e.g. admixture). He was, notably, a vociferous advocate of understudied populations, pushing for them to be included in the emerging field of human genetics — a theme that has recently reached new urgency (see the reviews by [Alicia Martin et al.](#), and [Gillian M. Belbin et al.](#)). We especially highlight his interest in African genetic diversity, with an emphasis on the study of hunter-gatherers, which was an inspiration for many population geneticists, us included.

This issue is comprised of four main topics: population history of different regions of the world, methods for demographic inference and different modes of adaptation, population genetic perspectives on human health and disease, and interdisciplinary approaches to understanding human evolution and phenotype diversity. This issue is also unique in including multiple reviews for different regions of Africa. Our editorial discretion (perhaps unsurprisingly biased given that we are both ‘Africanists’) aimed to highlight that geographic regions of Africa have distinct population histories and, often, populations compared between regions will be as genetically differentiated as Europeans vs. East Asians. It is therefore inappropriate to lump all African populations into a single category, or use a single African population to represent ‘Africans’, and the field of human genetics will need to develop genomic resources for all regions of the continent. [Gillian M. Belbin et al.](#) make a similar point with regard to the heterogeneity among Hispanic/Latino populations.

In the African context, [Etienne Patin and Lluís Quintana-Murci](#) emphasize that despite the ancient divergence between central African rainforest

hunter-gatherers and present-day farming populations, recent interactions and gene flow between the two groups have facilitated adaptive evolution. [Ludovica Molinaro and Luca Pagani](#) provide an updated review of human evolution in eastern Africa, out-of-Africa dispersals and the extent of back-to-Africa migration from Eurasia. [Francesco Montinaro and Cristian Capelli](#) consider the history of southern African KhoeSan and Bantu-speaking populations, including multiple waves of migration into southern Africa and the extent of sub-structure in the region. Of particular recent interest in this issue is the time depth of population structure within Africa and the possibility of archaic admixture with a yet unknown *Homo* species; these two issues can be conflated. [Brenna Henn et al.](#) provide context for interpreting these ideas by laying out 4 distinct models of human origins in Africa in the context of paleoanthropological and archaeological data, and call for more formal testing of each model.

This focus on Africa is not to ignore the tremendous advances made over the past few years in increasing our understanding of population history, structure and admixture in Europe ([Iosif Lazaridis](#)), South Asia ([Mait Metspalu et al.](#)), as well as Australia and the Pacific ([Anna Gosling and Elizabeth Matisoo-Smith](#)). A common theme throughout these regions is the recent impact of, or potential for, ancient DNA from diverse Holocene sites. [Krishna Veeramah](#) takes this topic further by discussing the importance of true multidisciplinary discourse between archaeologists and geneticists, and particularly the need to move beyond broad brush patterns of migrations to understand the local processes that gave rise to present-day variation. This is especially true for the field of ancient DNA, which directly interacts by definition with archaeologists to obtain samples for subsequent sequencing ([Michael Dannemann and Fernando Racimo](#)).

We are also excited to feature several articles that describe possible approaches to demographic inference and lay out relative advantages and pitfalls for several of the most common methods. The field has experienced a proliferation of new methods recently necessitated by the computational demands and specific features of massive amounts of sequencing data from an increasing number of human populations. [Niall Cooke and Shigeki Nakagome](#) discuss the flexibility of Approximate Bayesian Computation (ABC) approaches for demographic inference and questions of local adaptation, emphasizing the importance of carefully selecting informative summary statistics. [Jeffrey Spence et al.](#) describe advances in coalescent hidden Markov modeling, as applied to whole genome sequence data, and compare the performance of several methods under population size changes. [Aaron Ragsdale et al.](#) focus on diffusion models and allele frequency spectra, and discuss how demographic inference is affected by different classes of data, like nonsynonymous and synonymous variants and intergenic loci.

[Pongsakorn Wangkumhang and Garrett Hellenthal](#) review different statistical methods to detect, quantify and date admixture events, and provide an overview on local ancestry inference, which can now be applied more broadly than just recently admixed populations. [Michael Dannemann and Fernando Racimo](#) take admixture further back in time and focus on the fascinating issue of interbreeding between modern humans and ancient, now-extinct hominins and how our ancestors may have borrowed segments of Neanderthal or Denisovan genomes to increase their adaptation . . . highlighting, again, the evolutionary advantage of admixture, as Cavalli-Sforza proposed decades ago: “*The whole world is becoming a single population, and this aspect of globalization can only be beneficial from a genetic point of view*”. In the context of adaptation, [Melissa Ilardo and Rasmus Nielsen](#) discuss three captivating cases of genetic adaptation to extreme conditions; the cold of the arctic, the hypoxic conditions of life at high altitude, and the physiological stress of breath-hold diving.

Reconstructing population structure and genetic adaptation forms a basis for interpreting phenotypic diversity and correcting for potential biases in genetic epidemiology. [Jing Guo et al.](#) discuss not only how genome-association studies have facilitated our comprehension of the genetic architecture of complex traits but, importantly, how they can be used to delineate adaptive phenotypes. As highlighted by [Gillian M. Belbin et al.](#), the strong genetic differentiation and structure of populations, such as Hispanic/Latino groups, can have important consequences for genomic medicine and health issues. An iconic phenotype whose diversity has been strongly shaped by natural deletion and that exhibits marked differences among populations is the immune response. [Joaquin Sanz et al.](#) discuss the sources of such immune response variation and highlight how past genetic adaptation can result in present-day increase risk for some disorders (‘maladaptation’). The need to be less Euro-centric, particularly when it comes to studying the architecture of complex traits and diseases, is well illustrated by [Alicia Martin et al.](#), who discuss the advantages and challenges of conducting such studies in the highly heterogeneous — both culturally and genetically — African populations. A different perspective on all these topics is provided by [Connie Mulligan](#), who addresses the interesting, though difficult, question of the role of epigenetic changes in human evolution and disease phenotypes.

Finally, three reviews provide us with interdisciplinary perspectives on human history and phenotype diversity, from an angle that goes beyond the use of human-specific DNA. Fascinating examples come from the study of human microbiome variation, as discussed by [Stephanie Schnorr](#). Nor to mention the studies of our closest living relatives, non-human primates, as reviewed

by [Leslea Hlusko](#) as well as [Noah Snyder-Mackler and Amanda Lea](#). These reviews illustrate well how the study of non-human primates and, more generally, other mammals, can offer new insights into the study of the architecture of complex traits, such as obesity or heart disease, but also how social behavior, for example, can have a profound impact of gene regulation and ultimate phenotypes.

The study of human evolution and phenotype diversity from a genetic perspective remains a deeply exciting and burgeoning field of research — owing to the increasingly affordable deep sequencing technologies, the deluge of ancient DNA studies, the improvement/development of statistical frameworks to interpret the data and the

increasing awareness of including underrepresented human groups in population genetic studies. We hope you will enjoy the different pieces in this issue as much as we did, as they provide an updated, multidisciplinary view of the use of genetic data as a means to increase our understanding of “*who we are*” [2], to paraphrase, again, the late Luca Cavalli-Sforza.

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