A Beginner's Guide to the New Population Genomics of *Homo sapiens*: Origins, Race, and Medicine

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Abstract: It is important to understand the science underlying philosophical debates. In particular, careful reflection is needed on the scientific study of the origins of *Homo sapiens*, the division of current human populations into ethnicities, populations, or races, and the potential impact of genomics on personalized medicine. Genomic approaches to the origins and divisions of our species are among the most multi-dimensional areas of contemporary science, combining mathematical modeling, computer science, medicine, bioethics, and philosophy of biology. The best evidence suggests that we are a young species, with a cradle in Africa. While prejudice, misunderstanding, and violence grow in many corners of the world, our best genomic science suggests a deep biological connection among all peoples.

A Thought Experiment

Imagine landing in the largest city of an alien planet. Let us say it is the planet's capital. Every person is within a few centimeters of the same height, everyone has a nearly identical, muscular body, and everyone's facial features are similar. Perhaps most surprising to you, every person you see has purple skin. You learn from the ambassador

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The Harvard Review of Philosophy, Volume XXVI (2019) pp. 135–151
DOI: 10.5840/harvardreview201971321

accompanying you that every person on the planet actually looks the same. She is no exception.

Why the purple skin? The ambassador says it is a developmental consequence of the double sun of that planetary system acting upon interacting skin pigment proteins. These proteins, she continues, are coded for by a few genes (most of which have only one allele, or version) shared by all individuals. "After all, exactly 619 years ago," she whispers, "we experienced the *Great Tragedy*, when ecological catastrophe and civil war decimated us, and only the tiniest group managed to survive, which then agreed to generation upon generation of voluntary, totally random breeding, in order to minimize possible future ethnic strife."

Call this planet "Unity."

Now consider the natural experimental laboratory where Darwin studied evolution, the Galápagos islands, with its wide variety and number of finch and tortoise species. In your mind, populate these islands—or any analogous archipelago—with identical small populations of early humans. Add a few more dozen islands that are larger, have distinct environments, and are distant and mutually unreachable. Throw in tens of millions of years of evolution. Populations on the islands of this thought experiment will come to be quite different from each other indeed, in body and behavior as well as culture.

Call this scenario "Galápagos-Writ-Large."

Modern genomics teaches that our species is much closer to Unity than Galápagos-Writ-Large. Our species is relatively young, expanded quickly, and is fairly continuous in genomic variation across its entire geography. And yet, controversies about the nature and scope of our genomic variation fuels our hopes and fears about critical issues including the reality and relevance of race, the possibilities of personalized medicine, and more.[1]

Why Genomics? Philosophers of Race Speak

Much scientific practice today on the origin, population structure, and biomedicine of *Homo sapiens* is at the genomic level.[2] The thrust of this piece is therefore to explore this level.

While some details in this article are technical, it is crucial to cover genomics so that the reader may think critically about statements such as the following ones made by philosophers in prestigious venues:

> The lack of fixed traits for each so-called race means that race cannot be inherited as is popularly thought. Rather, the specific physical characteristics variably associated with races in cultural contexts are inherited through family descent as is the rest of human biology. Race, therefore, supervenes on human genealogy or family inheritance.[3]

> There are no racial genes responsible for the complex morphologies and cultural patterns we associate with different races.[4]

> The "logical core" of the "ordinary concept of race" involves identifying a "group of human beings" "(1) distinguished from other groups . . . by visible physical features of the relevant kind," "(2) . . . whose members are linked by a common ancestry," and "(3) . . . who originate from a distinctive geographic location."[5]

What is the scientific status of philosophical claims such as these? In order to understand what terms such as "fixed trait" or "racial genes" or "common ancestry" denote, we need to understand the concepts of genotype and phenotype, and we must develop an appreciation for the structure and dynamics of evolution.

Consider the concept "racial gene." What does it mean? Is it a gene—or, more accurately, allele—that is present in all individuals in a human population, but not in any other, thus defining the former population genetically as a unified race? Or might there be a lower-bound of frequency (90 percent or 60 percent?) under which that allele would no longer conceptually delimit or identify a race? And if races are defined relative to one another, must it then be 0 percent (or 10 percent or some other low number) in *other* races (or populations)? To complicate things, is one racial gene with multiple alleles sufficient, or should races be identified by two, five, or fifteen distinct and unique genes, together with their respective, associated alleles?

Taking a step back, does "race" here refer to standard US American racial categories, or to categories as conceptualized elsewhere, in any variety of languages and cultures (India, the Caribbean, or South Africa?), or to human population groups as defined by researchers studying human population genomics? How many ways of slicing up *Homo sapiens* into races should we countenance?

This article builds on my prior work by providing a roadmap of the basic phenomena and processes of human population genomics.[6] Scholars in this area take a broad variety of political and ethical positions. Regardless of our ideological and moral stance on human populations, clusters, or races, I believe that we must understand the existing science on human origins, population structure, and medicine. Our arguments will be stronger for it.

Human Genetic Variation: The General Pattern

Given the manifest differences among humans across the world, it may seem that we are closer to Galápagos-Writ-Large than to planet Unity. However, this is not the case. Our young species originated in Africa from very few and highly related populations, each with few individuals. Small groups left Africa, expanded in size and range, and were modified somewhat by natural selection, random genetic drift, and mutation. Thus we populated the world, occasionally interbreeding across wide distances throughout our history. While parts of this picture are suggested by fossil evidence, it is the genomics of the last few decades that has fine-tuned and confirmed, often in surprising ways, a number of our beliefs about the global distribution of human genetic diversity: *Homo sapiens* has relatively little genomic variation as compared to many other species; non-African genomic variation is basically a subset of African variation; most genomic variation is found within local human populations, with only about 5 percent found across continental groups; and "private alleles," or those found *only* in a subset of all human populations, are quite rare. In an important sense, we are all Africans.

Unity and the Galápagos-Writ-Large are extreme points at the ends of a spectrum of genetic differentiation. When we examine *Homo sapiens* in general and on average, as if surveying a map of the entire world on a single sheet of paper, our species fits the Unity model well. And at least in some places on Earth—especially big multicultural cities—our children are becoming even more Unity-like. But if we zoom in to a finer grain, as peering at a map of Boston or Mexico City on the same size sheet of paper, exploring specific

genes or contextual comparisons of just a few small populations, our species exhibits many Galápagos-Writ-Large properties. For many genes, there are at least small frequency differences in populations from Africa, Central/South Asia, East Asia, Europe, the Middle East, Oceania, and the Americas. And for some genes, there are enormous frequency differences in different parts of the globe.

This smidgen of Galápagos-Writ-Large is what makes the population genomics of our species so fraught. Might alleles associated with cancer, sprint speed, or intelligence be unevenly distributed across the globe? If so, what consequences would knowledge of this have for self-knowledge and tailored therapies on the one hand, and for social control and surveillance on the other?

Out of Africa: Three Basic Genomic Patterns

Turn now to three basic patterns of human genetic variation that support our likely genealogical story: the *Out-of-Africa* scenario of human evolution.

1. Low average nucleotide diversity. Of species whose genomes have been extensively mapped, *Homo sapiens* has unusually low average nucleotide diversity. All members of *Homo sapiens* are basically identical at—on average and approximately—999 base pairs out of 1000.[7] Given a total genome size of 3 billion nucleotides, and an average difference of about .1 percent between any two humans, two individuals will typically differ at approximately 3 million nucleotides. For comparison: *Drosophila* fruit flies, the standard workhorse for genetic studies, differ from each other on average by 1 percent, which is 10 times our diversity;[8] bonobos differ by .077 percent, chimpanzees by .134 percent, and gorillas by .158 percent.[9] Maize has even more nucleotide diversity than *Drosophila*, and soybeans have slightly more than humans.[10] Admittedly, *Homo sapiens* has more diversity than most big cats—roughly twice that of lions and leopards (cheetahs have near 0 percent diversity, unfortunately).[11] Wherever you may be from, you and I are genetically quite similar. Unity indeed.

2. Non-African genomic variation is basically a subset of African variation. Sub-Saharan African populations are much more genetically variable than the rest of the world, both in the number and kinds of alleles they have, and in the total distribution of those alleles. Much of the rest of the world's variation is a *sub-set* of African genetic variation, meaning that it is variation that also exists among African populations. African populations have approximately twice the nucleotide diversity of non-African populations. That is, two people whose recent ancestors are of sub-Saharan African origin differ on average by about 1:900 nucleotides (.11 percent), whereas two people whose recent ancestors are of European origin differ on average only by approximately 1:1600 (.063 percent).[12] Ethnically sub-Saharan African individuals also harbor approximately half of the total number of geographic "private alleles"—i.e., types of genes at a locus that are unique to a particular population, or populations—with the rest distributed across the other six regions; note that only about 8 percent of all common alleles are private.[13]

As a third measure of variation, consider the distribution of the approximately 8000 alleles (some of which are private) surveyed in Rosenberg 2011. Of these, roughly 82 percent were found in Africa, much more than any other single continent. Furthermore, to a first approximation, most alleles (87 percent to 90 percent) found in one non-African continent were also found in Africa, but not the converse. For example, only 74 percent of alleles

observed in Africa are also observed in Europe, and only 63 percent of alleles identified in Africa are also located in the Americas. Indeed, the number of alleles diminishes as we move farther from Africa, in the following ranked order: Middle East, Europe, Central/South Asia, East Asia, Oceania, and America.

The loss of (i) nucleotide diversity, (ii) private alleles, and (iii) alleles, as we move away from sub-Saharan Africa can be explained in terms of *serial founder effects*, which are explained by the *isolation by distance* model, to be explored below. As *Homo sapiens* migrated out of Africa we went through a series of genetic bottlenecks in which small groups colonized new areas (see below).[14] These groups represented only some of the genetic variation of the parental population, as measured by (i) through (iii).[15] People reaching the Americas via the Bering Strait went through this bottleneck process the highest number of times (though indigenous Oceanian populations also experienced almost as many). Is Africa like the capital of the Unity world?

3. Genomic diversity and heterozygosity diminish along human migration routes with increasing distance from Africa, the cradle of humanity. Although genetic differences between any two populations are relatively small, there is a consistent pattern: a reduction in diversity and heterozygosity—having two different alleles at a gene locus—in populations as they get increasingly far from Africa.

First, and as we saw above, African populations have by far most genetic diversity, measured in various ways: (i) nucleotide diversity, (ii) private alleles, and (iii) common alleles.

Another theoretical measure relevant here is *heterozygosity*. This is a measure of how evenly distributed different alleles at each locus are *across* different populations. We assess the allelic frequencies at every locus and compare them across populations. If alleles are fairly (exactly) evenly distributed, then they will have similar (identical) distributions in the different populations. Here the average heterozygosity across individual populations will be slightly lower, but almost the same as (at the extreme: identical to) the *total* aggregate heterozygosity in the entire population.

Consider two kinds of populations: first, an almost infinitely large one, in which every female has an equal chance of mating with any male; second, a very large one subdivided into many small populations, where females mate almost exclusively with males within their small sub-population.

In the first case, the heterozygosity in different "parts" of the population will be effectively identical. In evolutionary theory we would say that the first population has little, if any, *population structure*.

In the second case, the allelic frequencies of the different sub-populations will become increasingly different, especially (i) the longer they have been separated, (ii) the smaller the populations are, and (iii) the more distinct and unique the selective environments of the respective populations are. It can be mathematically shown that the total or global heterozygosity (*Aa*) calculated from the allelic frequencies (*A* and *a*) theoretically pooled across all sub-populations, for each mapped locus, is *always greater* than the heterozygosity calculated by simply averaging the actual heterozygosities across all sub-populations, for each mapped locus. Thus, compared to the total, mathematically idealized population, the sub-populations each have allelic frequencies deviating from the global heterozygosity; that is, they have a relative excess of homozygotes. Thus, the second population has *significant* population structure.

Humans have some population structure, but not very much. (The technical number is on the order of .1 F_{st}.)[16] Say that we compare pairs of human populations spread across the world. For each pair, we compare the total or *global* heterozygosity of the mathematically pooled pair to the averaged actual heterozygosities of the two populations. One hypothesis, borne out by the data, is that the further apart two populations are from each other along human migration routes from sub-Saharan Africa (in particular from Addis Ababa in modern Ethiopia) the more different they are from each other, and thus the more population structure they have with respect to each other. Ramachandran et al. (2005) found that there was a very strong positive correlation ($R^2 = .78$) between the geographic distance (along human migration routes) of any two human populations and the relative population structure of those two populations.[17]

Evolutionary theory appeals to a set of forces or processes to explain why population structure emerges, especially when comparing populations increasingly far from one another. This is the *isolation by distance* model.[18] Very roughly, the model postulates *limited migration* between far-flung populations, with migration (gene exchange) being a fairly linear function of distance, with small discontinuous jumps in population structure associated with movement across geographic barriers such as the oceans, the Himalayas, and the Sahara.[19] Furthermore, when new adjacent sub-populations are established by migration—a "splitting off"—the sub-population tends to be significantly smaller than the parental population.

This population size difference has two important consequences. First, the sup-population is a probabilistic sample of the larger population. Allelic frequencies will differ between the two, and they will be increasingly different (on average) the smaller the sub-population is. This is called *the founder effect*. And if we take multiple small samples, the allelic frequencies will by statistical law differ among samples, as compared to the pooled, global allelic frequencies across loci.[20] Second, *random genetic drift* is increasingly important the smaller a sub-population is. Genetic drift, or chance variation in relative gene frequencies, will practically guarantee that the allelic frequencies across generations within each sub-population will not be the same. As an analogy, think of a fair coin: If you flip it only a few times, the chance that you will get exactly 50/50 heads/tails is very small; the more you flip it, the closer your average comes to that ideal. Similarly, allelic frequencies are conserved across generations only when many parents randomly reproduce to make many offspring.

Additionally, allele frequencies come to differ across sub-populations due to *natural selection*. The populations will likely have distinct ecological environments that each select for different suites of phenotypic characters and their associated (developmentally causal) alleles.

In a nutshell, the isolation by distance model nicely accommodates the data of human population structure, explaining and illuminating human migration from Africa to Europe and Asia, via the Middle East, and then finally to Oceania and the Americas.

But much discovery awaits. Which exact migration routes did humans take? There are various Out-of-Africa scenarios, including humans heading from Africa's horn to the Arabian peninsula ("the southern route"), or moving through Egypt and into the Levant ("the northern route").[21] The precise geographical origin or cradle of humans is also controversial. Some argue for an eastern African, Ethiopian origin, based on genomic as well as significant archaeological and paleontological evidence (e.g., Ramachandran et al. 2005;

Skoglund et al. 2017). Others argue for a more southern African origin, with contemporary Khosians possibly being direct descendants of these ancient peoples (Henn et al. 2011; Schlebusch et al. 2017). Pagani and colleagues eloquently frame the issues at play:

> [Genetic] analyses pointed to click [Khosian] speakers, Pygmies, and a Nigerian-Congolese group as all having a deeper population history than both the whole genome and the African component of the East Africans sampled. Although this result might seem inconsistent with the outstanding fossil record available from Ethiopia, it may illustrate that genetic diversity assessed from modern populations does not necessarily represent their long-term demographic histories at the site. Alternatively, the rich record of human fossil ancestors in Ethiopia, and indeed along the Rift Valley, may reflect biases of preservation and discovery, with more fossils being exposed in regions of geological activity. Fluctuations in effective population size in the past and dispersals within Africa may have further confounded our analyses and their correlation with the fossil record. (Pagani et al. 2012: 93)

It is unclear whether the genetic signatures we might continue discovering using contemporary humans as well as DNA from ancient human remains across Africa will, ultimately, tell us the full story about the migration and occasional interbreeding of very old hominid populations in Africa.[22] Further interdisciplinary study is required to piece together various kinds of evidence, including bones and fossils found across the world; whatever genetic information we can extract from these; the artifacts, technology and even waste that humans have left behind; clues in spoken and written languages; and the presence and distribution of physiological and epidemiological adaptations in contemporary humans worldwide.

The Impact of Genomics I: Origins

As we saw above, the scientific evidence shows that humans originated in Africa. However, most peoples across the globe have an origin story of their own, perhaps centuries or millennia old. In Europe, think of Romulus and Remus for the Roman Empire; or Arminius (or Hermann), a contemporary of Jesus, known as a unifier of the German tribes in his victory over the Romans at the Battle of the Teutoburg Forest; or narratives of deep pre-historic uniqueness among the Basques. Genetic studies of archaic human remains (for example, Neanderthals, or Bronze Age skeletons in Europe, Central Asia, and the Middle East) cast doubt on such stories. National, ethnic, and cultural origin narratives play important social and political functions, but they are for the most part grossly misleading. In point of fact, archaic humans cross-mated significantly, migrated dramatically and relatively recently, and consisted of many more groups than these myths represent.

For instance, evidence suggests that Europe was born during the Bronze Age (roughly 3000–500 BCE). Although origin myths remain strong throughout different European countries and ethnicities, particularly in the rhetoric adopted by far-right anti-immigrant political parties gaining power there, the history is rather complex: Yamnaya peoples moved into Europe on horses from the Caspian Steppes and mixed with Stone Age farmers. In (roughly) northeastern Europe, this mingling gave rise to the Corded Ware culture, within which the Proto-Germanic and Proto-Slavic languages likely arose and spread. This basic pattern of migration and mixing in Bronze Age Europe has been corroborated using DNA evidence.[23] Allentoft and co-authors write: "Our results imply that much of the basis of the Eurasian genetic landscape of today was formed during the complex patterns of ex-

pansions, admixture and replacements during this [Bronze Age] period."[24] This multimodal story, with genetic gradients and genetic pockets across Europe, belies any story of single or pure (national) genetic stock. Cultural and biological genealogies rarely match.

Using genetics as an "assumption detector" of origin narratives, incomplete and fallible as genetic methodologies may be,[25] often undermines standard tribal or national origin myths and furthers understanding and explanation of contemporary population genetic landscapes.[26]

The Impact of Genomics II: The Reality or Reification of Race?

Philosophers interested in biological aspects of race often focus on the metaphysics or ontology of race. Following my earlier work, some of it in collaboration with philosopher Jonathan Kaplan, let me distinguish four *ontological attitudes* to race: realism, anti-realism, conventionalism, and reification. These attitudes can be applied at three *levels of analysis*: biogenomic race, biological race, and social race, respectively.[27]

The biogenomic racial realist (e.g., Theodosius Dobzhansky and A. W. F. Edwards; consult Winther and Kaplan 2013; Kaplan and Winther 2014; Winther 2018) cares about whether human sub-populations should be considered biological, and whether these correspond to social categories of, say, racial, national, or ethnic designation (and identity, prejudice, etc.). In contemporary literature, Sesardić (2013) should, in my view, be interpreted as a biogenomic racial realist. His defense of biological race in *Homo sapiens* distances itself from both standard conceptions of race and from social concerns.[28] He effectively argues that we are more like Galápagos-writ-large than most everyone else admits. In contrast, when Hochman denies the reality of human races by noting that human F_{ST}'s would hardly force the identification of distinct populations in non-human species, he is critiquing biogenomic race,[29] endorsing a Unity scenario. A third option, defended by Winther (2011, 2014), Kaplan and Winther (2013, 2014), Winther and Kaplan (2013), and Ludwig (2015) is conventionalism about biogenomic race. Under this analysis, the reality (or not) of biogenomic races depends on the variety of "explanatory interests" deployed (Ludwig 2015: 245–247), and the measures and models used, in particular analyses. A fourth option also exists: the ontological *reification* of race (Gannett 2004, Kaplan and Winther 2013, Winther 2014; critique in Spencer 2013). Here, "what is cultural or social is represented as natural or biological, and what is dynamic, relative, and continuous is represented as static, absolute, and discrete" (Gannett 2004: 340); or, alternatively, mathematical models are "conflated and confused with the world" (Winther 2014: 204; Winther forthcoming).

The existence (or not) of biogenomic race—i.e., a sufficiently high population structure in *Homo sapiens*—would be a wholly intellectualist and detached endeavor if there were not political, ideological, and morally relevant consequences.[30] The sticking point is about the reality (or not) of *biological* race. Biological races exist when a correlational—or, more accurately, a causal mapping—can be drawn between group genetic differences and socially significant phenotypic characters such as cognitive abilities and biomedical disease proclivities.

In contrast, social races exist when there are psychologically and communally perceived stable kinds of racialized people, often leading to systematic discrimination, prejudice, and oppression.[31]

Again, the entire issue of biogenomic groups, populations, or "races," if you will, would not be so politically, socially or morally challenging if nothing social and moral rode on it (Helen Longino, personal communication). If putative group membership only determined relatively insignificant characters such as toenail width, normative concerns would hardly be as important. Lewontin concludes his influential 1972 paper thus: "since . . . racial classification is now seen to be of virtually no genetic or taxonomic significance . . . no justification can be offered for its continuance."[32] Elsewhere he makes his position more explicit:

> The taxonomic division of the human species into races places a completely disproportionate emphasis on a very small fraction of the total of human diversity. That scientists as well as nonscientists nevertheless continue to emphasize these genetically minor differences and find new "scientific" justifications for doing so is an indication of the power of socioeconomically based ideology over the supposed objectivity of knowledge.[33]

Lewontin's sustained ire on this topic has not been aimed so much at biologists interested in human genetic variation (Lewontin 1978 is a brief response to Mitton 1977), but more at hereditarians including Jensen (1969), Herrnstein and Murray (1995), Lynn and Vanhanen (2002), Wade (2014), and others. Hereditarians argue that many contemporary social, political, and economic inequalities are causally due to hereditary differences in the (average) innate capacities of different continental races. They endorse a Galápagos-writ-large picture of biological race. As non-scientists, they are less concerned with the details of biogenomic race. In addition to Lewontin, many commentators, such as Coop et al. (2014) and Kaplan and Winther (2014) deny biological race.[34]

Still, there is a *5 percent conundrum*. That is, at least 5 percent of the total genetic variation (in some sense) among humans can be attributed to being from the five different continental regions (Africa, Asia, Americas, Europe, Oceania).[35] In this difference there may lie genes that play at least *some role* in the differential development of cognitive or physical characters, or differential susceptibility across individuals, and populations, to diseases. We just do not know (yet), much to the chagrin on what could be called the *liberal consensus*, which heralds that humans are all basically the same—and much to the joy of hereditarians who wish to find such genetic differences. In this set of ongoing arguments between the liberal consensus and the hereditarians (latest salvos include pros and cons about Noah Carl's controversial work[36]), rhetorical strategies include *burden of proof arguments*. That is, both the ideological left and right can argue that the burden of proof lies on the other side. While the left might utter "the hereditarians must show that there is a gene of major effect to cognitive development, or at least that certain genes associated with cognitive differences in each population act causally in the same way across different populations" the right might declaim "the liberal consensus must show that in fact *none* of the genetic differences between populations is associated with any cognitive differences that are stable across human populations."

Here we should be cautious. We still have very much to learn, and GWAS statistical analysis (genome wide association studies) and CRISPR interventionist biotechnology are almost certain to surprise both sides of the ideological spectrum. When we meet such surprises, we should encourage better and deeper critical dialogue rather than insist—without empirical proof—that genes with significant effects on morally, socially, and medically relevant phenotypes differ in presence and frequency across human populations.

Meanwhile, in my view, we must do what we can to bolster the legal and moral justification of human equality and justice regardless of the existence of systemic genetic differences, whether between or *within* large populations.

The Impact of the New Genomics III: Personalized Biomedicine

An annotated nucleotide map of *Homo sapiens* was published in 2001. This was a watershed moment. Interestingly, the article in *Science* included a foldable functional gene map poster, and showed a New England Biolabs advertisement on the page opposite the first article page.[37] The advertisement exudes power and profit, which are dynamics central to the making of contemporary worlds. One perspective on the hype, hope, and promise of genomic technologies that was supported by the Human Genome Project is that it is the dawn of a new millennial era, with sexualized (woman; Eve) and racialized (Out of Africa) overtones, energizing and perhaps titillating the mostly male advertisement consumer base. The shape of the Africa map draped over the woman's body invites us to visualize a sail and a "cutter ship," pushing us forward into unexplored territory of the potentials of genetic engineering and personalized medicine.

In the ad, New England Biolabs offered custom restriction enzymes for the selective amplification of nucleotide sequences. With amplified DNA, powerful genetic tools in a brave new world could be birthed. The awe-inspiring authority of the advertisement invokes the possibilities of gene therapy and genetic engineering controlling diseases and heightening cognitive capacities, while discovering new realms and new corporate profits. In *When Maps Become the World*, I call this *CartoPower*.[38]

This heady atmosphere of excitement depends largely on the idea that certain traits or conditions are *genetic*, as opposed to environmental. But what do these categories even mean? Two examples will help motivate intuitions.

Huntington's Disease is a late-onset neurodegenerative disease. Its expression follows an inheritance pattern consistent with the existence of a single dominant and autosomal (non-sex-linked) gene in affected individuals. Perhaps the most solid evidence for genetics as an explanatory factor for Huntington's Disease emerged in the early 1980s from villagers living along the shores of Lake Maracaibo in Venezuela. A family-tree analysis of more than three thousand interrelated Venezuelans confirmed the dominant, autosomal allele pattern. Furthermore, a molecular study using DNA from lymph cell lines taken from this large family helped map the gene (allele) responsible for Huntington's Disease to a particular location on the fourth human chromosome.[39]

This 1983 study was a watershed moment in the development of risk analysis and testing methods for genetic diseases, as well as of biomedical ethics.[40] There remains no cure for Huntington's Disease, and actual clinical diagnostic tests were not available until the 1990s. However, this was one of the first times researchers had identified the etiology of a disease caused largely by genetic differences, mapping it onto a specific and identifiable place on the chromosome.

Interestingly, Huntington's Disease is strongly ethnically correlated: it affects almost entirely people of European descent. For instance, it has never been documented in indigenous American populations. (The Lake Maracaibo case can almost certainly be traced to a single European ancestor.) As a result, only individuals from certain populations need be

tested. While there are few therapies available today, biomedical interventions will likely focus on certain kinds of individuals and certain molecular pathways.[41]

A more environmentally sensitive disease is lung cancer. Two influential statistical studies investigating risk factors for lung cancer were Doll and Hill's 1950 preliminary report on the role of smoking and Cornfield and colleagues' careful 1959 study of relative risks.[42] Drawing on enormous amounts of survey and medical data, these studies showed that various kinds of carcinomas had much higher relative incidence in smokers than in non-smokers, and that lung cancer incidence had increased dramatically in the twentieth century alongside an increase in smoking behavior.[43]

These studies received serious pushback from the tobacco industry, not surprisingly. They were also challenged by eminent statistician R. A. Fisher, who appealed to the possibility of a *spurious correlation* between smoking and lung cancer, owing to a separate independent factor—e.g., a genetic basis—that was explanatory of both smoking and lung cancer.[44] However, the robust and well-argued large-scale statistical studies won the day. This case shows that doubt and skepticism, while often useful in scientific inquiry, can be severely harmful when poorly thought out, especially in cases where the consequences are high. A similar lesson can be drawn about the role of fossil fuels in the environment today.

Neither lung cancer nor smoking habits are spread evenly across racial and ethnic groups in the USA.[45] Personalized medicine could therefore make significant progress by focusing on susceptible ethnic and behavioral groups, and trying to figure out how best to help individuals in those groups.

There is much else to say about meanings of *genetic* vs. *environmental* disease, particularly with respect to statistical methodologies such as Analysis of Variance,[46] other ethnically linked diseases such as sickle-cell anemia and Tay-Sachs disease, and the increasingly genomic bent of cancer research.[47] For now, it bears keeping in mind that all traits and conditions are both genetic and environmental. No gene creates a trait without environmental support, and no environment creates a trait without genetic support. The difference between Huntington's Disease and lung cancer is that a single gene is essential to making a difference to the expression of the former, while the practice and amount of smoking is highly predictive of the development of the latter (even given genomic variation in susceptibility).

Now What?

Careful reflection is required on the study of the origins of *Homo sapiens*, the division of current human populations into ethnicities, populations, or races, and the potential impact of genomics on personalized medicine. In particular, it is important to understand the science underlying philosophical debates. Otherwise, we are arguing in the dark.

The evidence shows that we are a young species, with a cradle in Africa. Three basic genomic patterns of our species help us understand this: (1) low average nucleotide diversity, (2) non-African genomic variation as a subset of African variation, and (3) a reduction in genetic diversity and heterozygosity along human migration routes with increasing distance from Africa. Humans are more like the inhabitants of Unity than of Galápagos-Writ-Large.

Genomic approaches to the origins and divisions of our species are among the most multidimensional areas of contemporary science, combining mathematical modeling, computer science, medicine, bioethics, and philosophy of biology, among other fields. This nexus of theories

and practices is complicated but highly significant, impacting human origin narratives, ideas about the existence (or not) of races and ethnicities, and biomedical technologies and therapies.

Given our increasingly globalized world, with an accelerating flow of information, trade, and (both voluntary and uprooted) migrants, we find ourselves exposed to an ever-broader variety of languages, behaviors, sights, and smells. While prejudice, misunderstanding, and violence grow, our best genomic science suggests a deep biological connection among all peoples. We may exhibit some Galápagos-Writ-Large properties, but basic human physical and cognitive properties are universal.

Notes

Jonathan Kaplan, Lucas McGranahan, and Siavash Zamirpour provided critical feedback on this manuscript. Mette Bannergaard Johansen helped with project management. I am grateful to *The Harvard Review of Philosophy* for inviting me to submit this piece to their journal.

1. For example, for two relatively recent salvos in the "IQ wars," from *The New York Times* by population geneticists, see https://www.nytimes.com/2018/03/23/opinion/sunday/genetics-race.html and https://www.nytimes.com/2014/08/10/books/review/letters-a-troublesome-inheritance.html. See also Winther, Millstein, and Nielsen 2015.
2. Less reductionist approaches exist: Maturana and Varela 1980, Levins and Lewontin 1985; Maynard Smith and Szathmáry 1995; Oyama 2000; Winther 2008; and Pigliucci and Müller 2010.
3. Zack 1999: 84.
4. Haslanger 2000: 43.
5. Hardimon 2003: 451–452.
6. See Winther 2014 and the introduction to Winther 2018.
7. Li and Sadler 1991; Yu, Chen, et al. 2002.
8. Li and Sadler 1991; Winther forthcoming.
9. Yu, Jensen-Seaman, et al. 2004.
10. Brown et al. 2004.
11. O'Brien et al. 1985.
12. Yu, Chen, et al. 2002; Campbell and Tishkoff 2008; Wall et al. 2008.
13. Rosenberg 2011.
14. Ramachandran et al. 2005; Lawson Handley et al. 2007.
15. Kaplan and Winther 2013.
16. For further explication on the concept and mathematics of population structure, especially as it concerns humans, see Winther 2014; and Hartl and Clark 1989.
17. This can be clearly seen in Figure 1B of Ramachandran et al. 2005: 15943.
18. Wright 1943; Malécot 1955.
19. Ramachandran et al. 2005; Rosenberg 2011; Rosenberg et al. 2005.
20. This is also known as the *Wahlund effect*.
21. See, e.g., Pagani et al. 2012. For further details, also including highly relevant archaeological, anthropological, and paleontological evidence, consult Bellwood 2013.
22. There is now an *African Genome Variation Project*; see Gurdasani et al. 2015.
23. Allentoft et al. 2015; Haak et al. 2015.
24. Allentoft et al. 2015: 170. See also Haak et al. 2015: 210.
25. E.g., Weitzman 2017: chap. 8 provides a balanced perspective external to both genetics and archaeology.

26. I explore *assumption archaeology* in detail in genetics and across the sciences in *When Maps Become the World* (forthcoming).
27. What follows is not a complete survey of every position possible in this 4 x 3 matrix. I merely highlight some noteworthy positions in the philosophical debates.
28. Spencer 2012, 2013, 2014.
29. Hochman 2013.
30. Lewontin 1970; Hacking 2005; Kitcher 2007.
31. Mills 1998; Haslanger 2000; Hacking 2005.
32. Lewontin 1972.
33. Lewontin 1974: 156.
34. Another option would be to remain silent and withhold judgment until individual genes for socially and morally significant traits such as cognitive abilities are identified and clear and explicit selective scenarios and mechanistic, developmental penetrance established.
35. Consult Winther 2014 and Winther 2018 for this way of putting the point.
36. Carl 2018.
37. Venter et al. 2001; see Dupré 2004; Gannett 2008.
38. Winther forthcoming.
39. Gusella et al. 1983.
40. On the relation between the history of Huntington's Disease and systematic social discrimination, see Wexler 2010.
41. There are molecular genetic reasons for this pattern. A slightly old, but still relevant discussion, with a useful bibliography can be found at https://hopes.stanford.edu/population-genetics-and-hd/. For a more contemporary perspective, see Dayalu and Albin 2015.
42. Doll and Hill 1950. Doll 2002; Cornfield et al. 2009.
43. Non-statistical evidence included "additional confirmations . . . on the induction of cancer of the skin in mice painted with tobacco-smoke condensates" (Cornfield et al. 2009: 1176).
44. Strictly speaking, this does not rule out the smoking as a possible "co-factor" of lung cancer, something Fisher apparently admitted as his death approached (Doll 2002: 505), even though he was much more skeptical of this while writing his interventions collected in Fisher 1959. Stolley 1991 discusses the incoherence of Fisher's arguments against the causal links, and Oreskes and Conway 2011 addresses the general strategy of moneyed corporate interests in defending their bottom line.
45. On lung cancer rates of incidence as a function of ethnicity, see https://gis.cdc.gov/Cancer/USCS/DataViz.html. On smoking habits, see https://www.cdc.gov/tobacco/campaign/tips/resources/data/cigarette-smoking-in-united-states.html and https://www.kff.org/other/state-indicator/smoking-adults-by-raceethnicity/. I welcome feedback on international data. See also Schabath, Cress, and Muñoz-Antonia 2016.
46. See Winther 2014 and the references therein.
47. E.g., Berger and Mardis 2018.

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