Human Population Genetics and Genomics
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Review

An anthropologist's point of view

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Abstract

The historical relationship between the cognate fields of biological anthropology and human population genetics is complicated. Of Cavalli-Sforza's contributions to this dialogue, The Human Genome Diversity Project has had some of the most interesting cultural reverberations to the present day.

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1. An Anthropological Retrospective

Long before there was a Human Genome Diversity Project (HGDP), geneticist Bruce Walsh and I [1] had written as post-docs to ridicule the idea of a "big science" project intended to sequence "the" human genome: "the conceived sequencing project violates one of the most fundamental principles of modern biology: that species consist of variable populations of organisms." The idea of mobilizing the scientific community to support and finance a mega-project to study the structure of the human gene pool never occurred to us. It was inconceivable. Moreover, we already had a pretty good idea of the general patterns in the human gene pool, thanks to the pioneering work of geneticists like William C. Boyd, Richard Lewontin, and L. L. Cavalli-Sforza.

On the other hand, a freely available database of human genetic diversity for any and all interested researchers? What a wonderfully ambitious intellectual dream! And since the idea was raised, I still think it would be a nice idea to have a central repository for the preservation and analysis of genetic diversity in our species.

Luca Cavalli-Sforza's ambition to create a Human Genome Diversity Project in the early 1990s was of course informed by his own experience, as a leader in the field of human population genetics for decades. But

just as genetic technologies had evolved since the 1960s, so too had ideas about the property rights of indigenous peoples. In retrospect, the major problem of the HGDP was that it was framed in explicitly colonial terms, at a moment when the rest of human science was becoming conscious of de-colonizing [2]. Infamously, when *Time Magazine* reported that "Cavalli-Sforza was taking blood samples from schoolchildren in a rural region of the Central African Republic, [and] was confronted by an angry farmer brandishing an ax" [3], it was intended to portray him as a swashbuckler, and not as a premodern globetrotter exploiting the lack of autonomy of children over their own bodies, and having little interest in securing anything like the "voluntary informed consent" of participants. The story certainly doesn't read as well in retrospect as it presumably was intended at the time.

The Native American Graves Protection and Repatriation Act (NAGPRA) had been passed in 1990, and identified Native American tribes as the true owners of the biological remains in the possession of science [4]. The relevance of NAGPRA to the 1991 proposal of the HGDP was clear enough to the Native Americans who began to speak out about it. I remember two points being made to me: that somehow the genetic data would be used to build "gene bombs" against indigenous peoples; and that somehow the genetic data would be used to financially exploit indigenous peoples. I dismissed both possibilities at the time, but I did find plenty of intellectual common ground to share with the other members of the Indigenous People's Council on Biocolonialism [5].

I had not heard about the 1991 *Genomics* paper, "Call for a Worldwide Survey of Human Genetic Diversity: A Vanishing Opportunity for the Human Genome Project," [6] until I was asked about it by a journalist from *Science*. Apparently there had been a disagreement at the very top of the HGDP about the nature of the sampling strategy that should be employed. Luca Cavalli-Sforza wanted the sampling to proceed according to ethnic labels; Allan Wilson noted that such a strategy would bias the project by artificially inflating the amount of between-group variation in the samples [7]. Further, the collection would be proceeding according to cultural labels rather than by following any natural patterns. Moreover, it seemed to be swimming against the decolonizing tide in science. NAGPRA was mandating the return of biological remains that had been collected without what we would now consider appropriate consent. It seemed rather short-sighted to start promoting a massive effort to collect blood from indigenous peoples.

Many anthropologists, upon hearing of the HGDP, understood its focus on indigeneity to represent a somewhat romanticized (and false) notion of a world before gene flow, when Europeans were more or less confined to Europe [8]. There seemed to be duelling narratives about the HGDP: On the one hand, it was intended to be a survey and repository of the genetic structure and diversity in our species. On the

other hand, the sampling strategy seemed designed to maximize the amount of diversity detectable between culturally - or politically-defined groups, a heavily biased "survey". The example used by the HGDP, was to "to see if, for example, the Irish are more closely related to the Spaniards or to the Swedes" [9]. But they didn't seem to be nearly as interested in the Swedes and the Irish and the Spaniards as they were in the Hopi and Maori and KhoeSan [10,11]. Moreover, appeals to be studying "our" evolution did not seem to resonate, since "we" did not evolve from the KhoeSan. So why such an interest in the genomes of indigenous peoples? Was their blood of greater historical value for our ancestry, or simply an exercise in the accumulation of hematological exotica? Why not survey the human gene pool as it is – notably, concentrated in urban centers?

The answer of course, is that the microevolution of the human species was the HGDP's first and only goal, and that was indeed Cavalli-Sforza's own research program. Biomedical applications and the knowledge of patterns of modern human diversity were always secondary; hence the strategic interest specifically in indigenous peoples. In fact, shortly after the HGDP was announced, we invited one of its leaders, Prof. Kenneth K. Kidd of Yale's Human Genetics department, to give a colloquium for our physical anthropology group at Yale. Prof. Kidd spoke to the need for the HGDP by emphasizing the archaic themes of salvage anthropology and primordial purity. His exact words, engraved forever into my consciousness, were: "We've got to sample these people before they become admixed!" My department chair at the time, who happened to work in Madagascar, responded simply, "I think you're a little late".

2. Unintended Consequences

Three decades later, of course, much has changed. The trend to decolonize science continues, and the Human Genome Diversity Project, if it ever was, is no more [12,13]. And the field of human genetic diversity studies continues to thrive, but with greater attention to the rights of indigenous peoples. Although not formally associated with the HGDP, the Havasupai case in 2012 revolved around familiar issues: informed consent, researcher responsibilities, and the rights of participants [14,15].

Back in the 1990s the most problematic colonial aspects of the HGDP did not even have a name. Now they do: "helicopter science" – that is to say, the extraction of intellectual raw materials by scientists from the Global North. The label extends beyond genomics, to other areas of exploitative biomedical sciences, although as Warwick Anderson [16] notes, "Typically, Cavalli-Sforza was the most insistent blood collector, and the least willing to spend much time with the local communities."

Today helicopter science is indeed a significant bioethical issue [17,18]. The HGDP did not invent it, but certainly put the practice in a spotlight for the next generation of practitioners to engage. But who could have imagined that 30 years later, the field of human microevolutionary genetics would be undergoing a renaissance in the public sphere, driven by widespread consumer interest in genetics ancestry testing, a billion-dollar industry [19]?

Human population genetics entrepreneurs like Bryan Sykes (Oxford Ancestors), Rick Kittles (African Ancestry) and Spencer Wells (The Genographic Project) showed the feasibility, marketability, and profitability of genetic ancestry in the earliest part of the 21st century. They also showed where the HGDP had gone astray: In seeking public financing, and thus being subject to public ethical accountability. This is not to suggest any unethical behavior on anyone's part, but simply to note that with private funding in place, the novel ethical considerations that undid the HGDP in the public eye would no longer jeopardize such an endeavor.

Genetic ancestry testing is a very rich cultural site, since it embraces several paradoxes. In the first place, nobody doubts that it is science. After all, it employs DNA and statistics. It is different from, but complementary to, the humanistic study of ancestors as revealed in old documents, and certainly distinct from the non-science of trying to talk to those ancestors. And yet, there are plenty of geneticists warning the public not to take this particular science too seriously (e.g., [20]). Or at least to take it less seriously than evolution or vaccinations. This is indeed an unusual form of science.

Second, as a primary product of corporate, rather than academic, interests, genetic ancestry introduces a conflict-of-interests that is unusual in the natural sciences. Scientific training has traditionally avoided morality as humanistic, with notable public professions of communalism, universality, disinterestedness, originality, and skepticism [21]. But what of interest conflicts? In the Sermon on the Mount (Matthew 6:24), Jesus explains that you cannot serve both God and money, for the money will inevitably corrupt the piety. If you can't serve both God and money, can you serve both science and money? Or does the profit motive collide as well against the accuracy motive in science with sufficient force as to invariably deflect it from its goal? Obviously no one would argue that academic population genetics was ever pure, but it at least doesn't have this particular conflict of interests. To sidestep this conflict, the genomic ancestry tests generally are accompanied by disclaimers specifying that the results are for entertainment or educational, rather than scientific, use. Indeed, a very unusual form of science.

Third, ancestry presumably reflects facts of nature [22,23]; and yet the results are partitioned for the client into units of culture. If the result says that you are, say, 25% French, you are encouraged to infer a French

grandparent. But what it really implies is a 25% match to the samples in their database that are labeled as French. France is neither a unit of nature, nor a genetic status. It is a geopolitical unit, whose inhabitants span a large area, from people similar in form and genes to the Flemish in the north, to people similar in form and genes to the Spanish in the south. The calculation thus depends both on your genotype and also, crucially, on the samples you are being compared to, who are the symbolic embodied representatives of France.

Even then, however, cultural identities can override genetic relationships: According to the American "one drop of blood" rule, three European grandparents would have been insufficient to classify you as white, because a single Black grandparent would make you a "quadroon" and therefore non-white. In other words, the ancestral French gene pool – whatever it was like – would have been composed, like the American gene pool, of both DNA and assumptions about history, migration, and citizenship, or more generally, of inclusion. So, whose genes today represent the population of France as it existed 300 years ago, or 1000 years ago? And does the difference between the French gene pool of the year 1100 and the French gene pool of the year 1700 matter, or is there an official French gene pool that is somehow timeless and transcendent?

There is a great deal of culture here, which is easily disguised. Indeed, somewhat ironically, this issue mirrors the intellectual division at the outset of the HGDP, with Cavalli-Sforza wanting to structure the collection of samples by ethnic groups, and Allan Wilson wanting to structure the collection of samples by geographical grid. The confusion of constructed categories for biological categories, or facts of cultural history for facts of nature, is one of the oldest and most pernicious fallacies in the study of the human species, and stretches back to the dawn of the scientific study of human diversity, in the 18th century work of Linnaeus [24]. Today we recognize that humans can be clustered in various sorts of biocultural ways, but those clusters are never naturalistic elemental units of the human species, because human populations are, and always have been, diverging, moving, merging, and being bounded or self-identified by cultural, symbolic criteria [25–28].

Nor is the public free from the message of genetic determinism, as the hungry corporate beast demands constant feeding. Your genetic roots are not the only features that your DNA might reveal, after all. Let us say that you indeed had one French grandparent, who was an artist. And you also had a Bangladeshi grandparent, who was an engineer. You are as much ¼ French and ¼ Bangladeshi as you are ¼ artist and ¼ engineer. You may understand those sets of fractions differently, depending upon how culturally pre-programmed you are to interpret ancestry as biology or destiny. In this context, 23andMe gives you much more genetic information than simply your presumptive ancestry; for example, it tells

you what time your DNA has encoded you to wake up in the morning. (Mine is 6:40 AM, although results may presumably vary depending upon occupation, latitude, and dog ownership.) In other words, the DNA is something of a Ouija board, upon which a client can read and/or project information that may or may not be true. As an educator, I don't think that is a great situation (and it is appropriate here to acknowledge Cavalli-Sforza's consistent opposition to genetic determinism and scientific racism) – but this is not about public education, it's about attracting customers.

The critical feature of "Ouijanetics" that sets it apart from ordinary science is the lack of regulatory oversight for presumptive genetic tests that are not medically related [29,30]. A genetic test for sickle-cell anemia or Tay-Sachs disease or cystic fibrosis is carefully regulated, as lives might depend on it. But a genetic test for what time you wake up comes with no medical risks, and is consequently considered as entertainment, with little oversight, like a tarot card reading. This permits companies to offer to match wines to your genotype, as the short-lived "Vinome.com" did; or a battery of DNA personality tests provided by "Orig3n.com," which had previously failed to detect that the DNA sample submitted by a local television station had come from a dog [31].

Genetic ancestry testing is very explicitly labeled by its disclaimers as being for educational or recreational use, and as having no legal validity. But isn't science supposed to be valid enough to stand up in court? Obviously the disclaimers are written by the legal departments, to absolve the company in the case of someone falsely laying claim to a political identity based on presumptive genetic grounds. But that, of course, begs the question of the legitimacy and accuracy of the scientific claims.

3. Conclusions

The 2020s are a turbulent decade for human population genetics. The public is now very interested in it, which is good; but the information they are receiving may not be very accurate, which is bad. Moreover, the client is free to reject the results, which the company won't even back up in court. That is even worse, because it undermines the public credibility of science. On the other hand, I think that the happiest long-term result of the HGDP is that, with the aid of three decades of hindsight, the leading-edge technology involving the study of ancient DNA is undergoing some proactive ethical reflections [32].

Luca Cavalli-Sforza's impact on the field is incalculable. He nobly spoke out against the racist science of the 1970s, but had difficulties comprehending the critiques of colonial science in the 1990s. He shepherded human population genetics into mainstream science, leading the way for the popular work of Spencer Wells ("The Journey of

Man") and Henry Louis Gates ("Finding Your Roots"). He surely never imagined that the field would be gobbled up by the neoliberal economy of the 21st century. But then, who did?

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Consent for Publication

Not applicable.

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