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Normalization and the Search for Variation in the Human Genome

ABSTRACT

This essay reflects on the tension between standardization and the search for variation in the human genome. The stabilization of the human chromosome count in the 1920s was based on the consensus that "Whites," "Negroes," and "Japanese," as well as women and men, had the same number of chromosomes. Yet the idea that there might be chromosomal differences between various groups of people was never quite abandoned. When in the mid-1950s the human chromosome number was revised from 48 to 46, the new count was tested in populations around the world. The description of the "normal human karyotype" that was negotiated in the 1960s was driven by the search for a standard against which the genetic variation revealed by the flurry of testing could be measured. And although the human genome project in the 1990s promised to provide the genetic blueprint that all humans shared, it has in fact led to an increased focus on the genetic variation that distinguishes the history, identity, and health outcomes of various human populations. Following concrete examples, this essay investigates the historically contingent quests that have been driving the search for common standards and variation, and the role Pacific and Indigenous populations have played in these endeavors.

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KEY WORDS: normal human karyotype, human genome, human genome project, genetic variation, racial variation, genetic study of human populations, racial cytogenetics, Indigenous peoples

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The following abbreviation is used: UNESCO, United Nations Educational, Scientific and Cultural Organization.

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In 1958, David Harnden, a postdoctoral student in Charles Ford's cytogenetics laboratory at the Radiobiological Research Unit at Harwell (UK), developed a new technique for growing a skin biopsy from his own arm that could be used to study the chromosomes in the cells. This was an important development as until then chromosome analysis was mostly performed on testis or bone marrow samples that required surgical intervention. Harnden maintained that he was probably the first person in the world who looked at his own chromosomes. Later he recalled the exhilarating experience and the feeling that he was now "able to explore areas not reachable by anyone else."[1] One of the first projects he pursued with his new technique was to test the hypothesis that different human populations carried different numbers of chromosomes. He assumed that if such variation existed, it would most likely occur in populations that had been "geographically isolated for some time."[2] With the help of a colleague in Adelaide he organized for a skin biopsy of an "assuredly 'full-blooded' aborigine" to be flown to him for testing from the Australian "Outback" with the Flying Doctor Service.[3] As he reported, the culture "grew beautifully but the chromosomes were quite normal." Harnden mused that this was a "disappointment, I suppose, but still fun to do."[4] Although not too much should be made from a single utterance, the use of the term "normal" here is nevertheless significant.

Shortly after Harnden's exploit, human cytogeneticists gathered to achieve a standard description of the human karyotype.[5] Against expectation perhaps, the establishment of the standard karyotype further encouraged the search for variations. Following Harnden's lead, cytogeneticists teamed up with anthropologists to study the chromosomes of populations around the world, often returning to the Pacific. Every new technique that was introduced raised the

1. David G. Harnden, "Early Studies on Human Chromosomes," *BioEssays* 18 (1996): 165.

2. David G. Harnden, "The Chromosomes," in *Recent Advances in Human Genetics*, ed. L. S. Penrose and Helen Lang Brown (London: J. & A. Churchill, 1961), 23.

3. Possibly the colleague in question was Andrew Arthur Abbie, Professor for Anatomy and Histology at the University in Adelaide. Originally from Britain, he kept in close contact with British colleagues, especially with Grafton Elliot Smith at University College, London. From the 1950s, his research interest shifted to the anthropology of Aboriginal people, and he conducted many expeditions to Aboriginal communities in South Australia and the Northern Territory. I thank Warwick Anderson for this suggestion.

4. Harnden, "Early Studies" (ref. 1), 165.

5. "A Proposed Standard System of Nomenclature of Human Mitotic Chromosomes (Denver, CO)," *Annals of Human Genetics* 24 (1960): 319–25; M. Susan Lindee, *Moments of Truth in Genetics and Medicine* (Baltimore, MD: Johns Hopkins University Press, 2005), 90–119.

hope to find the elusive differences that scientists seemed to expect. A similar dynamic developed around the human genome project. Originally celebrated as the common blueprint of all humanity, it has in fact focused attention on the 0.1 percent of the genetic information that supposedly distinguishes individuals and is differently reflected in various human populations.

This essay aims to analyze the dynamic between the efforts to define the "normal genome" and the continued search for genetic variation, as well as the persistence of this tension in the study of human heredity throughout the twentieth and into the twenty-first century. The focus will be on two historical moments: the search for the "normal human karyotype" in the 1950s and the declaration of the human genome sequence as the common heritage of humankind fifty years later. All along, the essay will reflect on the role of the Pacific as a site for genetic research.

THE NORMAL HUMAN KARYOTYPE

In the 1910s and 1920s, researchers studying the chromosomes of a variety of organisms, included those of humans, considered the possibility that "Whites" and "Negroes" had a different number of chromosomes. Thomas Hunt Morgan, who headed the celebrated fly genetics laboratory at Columbia University and was an outspoken critic of eugenic ideas and policies, suggested this possibility as a way to explain the different human chromosome counts presented by Belgian cytologist Hans von Winiwarter, who had been working on tissue of men of European descent, and Michael F. Guyer, a zoologist at the University of Wisconsin, who had been studying samples from African Americans.[6] Guyer later supported Morgan's suggestion, reporting higher chromosome counts in samples of "two Caucasians."[7]

6. Thomas Hunt Morgan, *Heredity and Sex* (New York: Columbia University Press, 1913), 245; Thomas Hunt Morgan, "Has the White Man More Chromosomes Than the Negro?," *Science* 39 (14 Jun 1914): 827–28.

7. Michael F. Guyer, "A Note on the Accessory Chromosomes of Man," *Science* 39 (15 May 1914): 722. Although not further pursued in this essay, it is important to note that next to the search of chromosome variation in human populations, the comparative study of chromosome and later genomic variation between humans and other organisms remained an abiding interest of researchers throughout the twentieth century. For an early and later example in the chromosome field, see Theophilus S. Painter, "A Comparative Study of the Chromosomes of Mammals," *The American Naturalist* 59 (1925): 385–409, and J. L. Hamerton et al., "Somatic Chromosomes of the Gorilla," *Nature* 192, no. 4799 (1961): 225–28. For the genomic field it will suffice to recall that the

By the mid-1920s, the possibility considered by Morgan was laid to rest, and it was generally accepted that "Whites" and "Negroes" as well as "Japanese" and women and men had the same number of chromosomes.[8] The consensus was part of the effort to stabilize the human chromosome count, which was set at 48. Scientists agreed on this point at the height of the eugenic movement and of Jim Crow segregation. Nevertheless, the idea that there might be chromosomal differences between various populations was never quite abandoned. For instance, in the mid-1930s, Soviet cytogeneticists, comparing published cytogenetic data with their own measurements, found variations in the length of single chromosomes in samples of Russian, Japanese, European, and African-American individuals. They suggested that finding "racial variations" (*Rassenunterschiede*) was the next task for human cytogeneticists.[9] Their findings and call to action were rejected at the time. Yet when, in the mid-1950s, the number of human chromosomes was revised from 48 to 46 and improved karyotyping techniques became available, the issue was raised again and put to the test.[10]

An early challenge to the still tenuous consensus on the new chromosome count came from Masuo Kodani, a Japanese emigré who worked both in the US and with the Atomic Bomb Casualty Commission in Japan. Kodani reported counts of 46, 47, and 48 chromosomes in samples of Japanese males. The higher counts depended on the presence of either a single or a pair of what the author described as small inert "supernumerary" chromosomes. Kodani expected—and later confirmed—that the same three counts also existed in Whites. He suggested that these observations could explain the divergent chromosome numbers reported in the literature. Moreover, his studies

international human genome project included the sequencing of a number of model organisms for comparison with the human genome; see, for instance, NIH News Release (20 May 2003), "Progress made in sequencing of model organisms' genomes: Chimp, honeybee genome nears completion; Dog project begins," https://www.genome.gov/11007358/2003-release-model-organisms-update (accessed 25 Jun 2020).

8. Theophilus S. Painter, "The Sex Chromosomes of Man," *The American Naturalist* 58, no. 659 (1924): 506–24.

9. A. H. Andres and M. S. Navashin, "Ein Beitrag zur morphologischen Analyse der Chromosomen des Menschen," *Zeitschrift für Zellforschung und mikroskopische Anatomie* 24 (1936): 411–26.

10. On the complex and protracted process that led to the recount of the human chromosome number, see Aryn Martin, "Can't Any Body Count? Counting as an Epistemic Theme in the History of Human Chromosomes," *Social Studies of Science* 34 (2004): 923–48; Soraya de Chadarevian, "Chromosome Photography and the Human Karyotype," *Historical Studies in Natural Sciences* 45 (2015): 115–46.

indicated that the proportion of the three possible chromosome numbers could vary in different ethnic groups, with a 48-chromosome count being more likely in Japanese people than in Whites.[11]

Kodani was an experienced cytogeneticist. Nevertheless, Charles Ford, an authority in the field of mammalian cytogenetics, who had the opportunity to study photographs of Kodani's chromosome preparations, quickly decided that a count of 23 bivalents (or paired chromosomes) was the more "plausible" interpretation in all preparations.[12] The case seems to have rested there, but in fact Ford did not dismiss Kodani's suggestion altogether. Rather, he encouraged further studies of chromosomal variation, contending:

> Comparison of the chromosome sets of different ethnic groups immediately suggests itself as the most likely method of revealing polymorphism if it exists. It is unnecessary to stress the interest for anthropology if any form of chromosome polymorphism should be revealed.[13]

Considering this statement, we can surmise that Ford may well have inspired or would at least have supported Harnden's testing of the Aboriginal sample in his laboratory. The statement also provides evidence that geneticists and physical anthropologists held on to notions of biological differences in human populations even while embracing the broader critique of biological racism as expressed, for instance, in the first UNESCO Statement on Race of 1950.[14] Thus, the search for chromosomal differences and other biological

11. Masuo Kodani, "Three Diploid Chromosome Numbers in Man," *Proceedings of the National Academy of Sciences of the Unites States of America* 43, no. 3 (15 March 1957): 285–92; Masuo Kodani, "Three Chromosome Numbers in Whites and Japanese," *Science* 127 (1958): 1339–40; Masuo Kodani, "The Supernumerary Chromosome of Man," *American Journal of Human Genetics* 10 (1958): 125–40.

12. Ford corresponded on the matter with Levan; see Ford to Levan, 15 Jan 1957, and Levan to Ford, 17 Jan 1957; Correspondence folders, Albert Levan Papers, Special Collections, Lund University Library. Researchers suggested later that Kodani's unusual chromosome counts might be due to atomic radiation exposure of the people he sampled. On this point and on Kodani's difficult career as an émigré scientist from Japan in America, including his internment in Manzanar during World War II, see Vassiliki Betty Smocovitis "Genetics Behind Barbed Wire: Masuo Kodani, Émigré Geneticists, and Wartime Genetics Research at Manzanar Relocation Center," *Genetics* 187, no. 2 (2011): 357–66.

13. C. E. Ford, "Human Cytogenetics: Its Present Place and Future Possibilities," *American Journal of Human Genetics* 1960, no. 12 (1960): 105.

14. On the debate among social and physical anthropologists around the concept of race in the context of the UNESCO statements on the subject in the early 1950s, see *The Race Concept: Results of an Inquiry* (Paris: UNESCO, 1952), online https://unesdoc.unesco.org/ark:/48223/pf0000073351 (accessed Aug 2020); and Michelle Brattain, "Race, Racism, and Antiracism:

polymorphisms in human population research persisted despite the concerted efforts by social anthropologists to undercut the biological reality of race.

The flurry of new work on human chromosomes called for a common human chromosome classification system so that results from different laboratories could be compared. With this aim in mind human cytogeneticists gathered in Denver, Colorado, for a three-day discussion on chromosome nomenclature in 1960. Participation at the conference was restricted to researchers who had already published a human karyotype showing 46 chromosomes. This was a small club of thirteen people, coming from a handful of countries, namely Britain, France, Sweden, the US, and Japan. Also invited were a "secretary" and three "wise men" (David Catcheside from Birmingham, Herman Muller from Indiana University, and Curt Stern from the University of Berkeley), who were to act as arbiters in any possible dispute. All three were distinguished geneticists, but none of them had direct experience with human chromosome analysis. As the organizers saw it, this made them impartial judges.

The participants set as their task to agree on a nomenclature that was simple, free of ambiguities, and flexible to accommodate future changes. The work accomplished by the group was condensed in three tables included in the brief final report. First, chromosomes—with exception of the X and Y chromosomes that kept their names—were serially numbered, "as nearly as possible" in descending order of length, "consistent with operational conveniences of identification by other criteria."[15] The chromosomes were then subdivided into seven groups, into which they could be readily assigned. The first table provided a "conspectus" of the groups. Each group was characterized by the serial number of the chromosomes it contained (for instance, group 1–3, group 4–5, group 6–12) and a brief verbal description of their main characteristics, including some additional practical hints for distinguishing them.

A second table displayed the actual work that had gone into defining the normal karyotype. It also shows the difficulty of the task the conference participants had set themselves. In neatly arranged columns the table listed the measurements of every single chromosome made from cells of "normal individuals" (except in one case) by groups in Denver, Oak Ridge, Lund, Uppsala, Paris, and Edinburgh. Each chromosome was characterized by three

UNESCO and the Politics of Presenting Science to the Postwar Public," *The American Historical Review* 112, no. 5 (2007): 1386–1413.

15. "A Proposed Standard System" (ref. 5), 320.

parameters: its relative length, calculated in respect to the total length of all the chromosomes contained in a normal haploid set with an X chromosome; the arm ratio, expressed as the length of the longer arm relative to the shorter arm; and the centromere index, indicating the relation of the length of the shorter arm to the length of the whole chromosome. A final column gave the range for each measurement provided by the various groups, showing substantial variation. This variation was explained by the intrinsic difficulties in measuring small objects with fuzzy contours and by differences in preparation method, as it was noted that for every individual worker measurements were more consistent. Finally, a third table provided an overview about the correspondence of each chromosome in the new nomenclature with the numbering or naming proposed in previously published work.

Among the many journals that reprinted the report with the proposed standard nomenclature was the *Annals of Human Genetics*, published at the Galton Laboratory under Lionel Penrose's editorship. In his editorial comment Penrose included a diagram of a set of chromosomes drawn using the means of the six sets of values published in the report.[16] Penrose, who had not participated in the Denver conference, had gone through all the chromosome measurements submitted for inclusion in the report and had found various arithmetic mistakes, as duly reported in the editorial. Researchers welcomed the diagrammatic representation of the new standard nomenclature. An enlarged version of the diagram, slightly corrected, titled "Average measurements of human chromosomes—Denver System, Galton Laboratory 1960," multiple pinholes in the corners clearly visible, was among the treasured papers of a former postdoctoral researcher in the laboratory.[17] Looking well used, with various annotations added in pencil, it clearly had served as a reference tool for chromosome identification.

Somewhat inadvertently perhaps, what started off as a nomenclature meeting ended in the definition of the "normal karyotype."[18] From the beginning the aim had been to provide a standard against which anomalies in the number and size of chromosomes could be described and measured. Leading up to the meeting, researchers had been able to correlate such chromosome anomalies with specific clinical syndromes. Yet it also became increasingly clear that there

16. "A Proposed Standard System" (ref. 5), 319 (editorial comment).

17. See Marco Fraccaro, Personal collection of papers and manuscripts, file "Normal karyotype," Collegio Fratelli Cairoli, Università di Pavia, Italy. The letters later assigned to each chromosome group were added in pencil.

18. This was also the name of the file in which I found the reference diagram; see note 17.

was much more chromosomal variation in apparently healthy individuals than previously expected, throwing easy distinctions between normal and abnormal into question. Things became even messier when chromosome techniques were used to find chromosomal variations among human populations. Improved tools for chromosome analysis, including the standard nomenclature, stimulated a new series of such studies. The following longer passage, drawn from the scientific report of one of these, points to the assumptions guiding the research:

> Since 1956, when a new era in the study of human chromosomes commenced, considerable effort has been invested in trying to define the morphology of the normal chromosome complement (karyotype) at metaphase of somatic cell division. This new era was heralded by Tjio's and Levan's discovery (1956) that the normal diploid number in man was 46. Progress since then, not only in defining the normal human karyotype, but in the description of chromosome abnormalities and their correlation with phenotypic effects, has been impressive and is still continuing. . . .
>
> Since most of the subjects used in these investigations have been drawn from relatively cosmopolitan populations (intended to mean those which have participated in recent extensive genetic outcrossing), sufficient attention may not have been paid to the possibility that microscopically visible karyotypic variability is present in other populations. That such variability might exist is suggested by previously described gross (i.e. detectable with methods presently in use) chromosome abnormalities, the presence of which is compatible with an apparently normal phenotype. . . . If the assumption is granted that an occasional instance of karyotype change would confer on its carrier a selective advantage within a particular environment, such change should be perpetuated in one way or another, the frequency with which the altered karyotype appears in the population depending on chance and on the balance of selective forces operating.[19]

Significantly, a different range of measurements in samples from New Guineans would not be incorporated into the calculation of the averages of the "normal human karyotype." Rather, as the scientists readily acknowledged, what was "normal" was defined as such "on the basis of studies in people of

19. David A. Hungerford, Eugene Giles, and Charlotte G. Creech, "Chromosome Studies of Eastern New Guinea Natives," *Current Anthropology* 6 (1965): 107. On Tjio and Levan's work, see Joe Hin Tjio and Albert Levan, "The Somatic Chromosomes of Man," *Hereditas* 42 (1956): 1–6. See also note 10.

European origin."[20] As a result, any observed variation in the chromosome picture, even if interpreted as evolutionarily meaningful, could easily slip into being labeled an "abnormality," as in the quoted passage.

In searching for chromosomal variation, David Hungerford, a cytogeneticist from the Fox Chase Cancer Center in Philadelphia, and Dr. Charlotte Creech from the same institution teamed up with anthropologist Eugene Giles from the University of Illinois, who was already carrying out fieldwork in Northeastern New Guinea to "sample cytologically subjects from this relatively isolated area." Skin biopsies were taken, placed in sterile vials containing growth medium, packed in vacuum flasks containing water ice and brought out on foot and by motor vehicle to Lae.[21] From there the flasks were re-iced and flown to Sydney in a scheduled commercial flight. They were re-iced again and flown to Philadelphia on a commercial jet air-freight. Overall, between 85 and 109 hours elapsed between biopsy and arrival in Philadelphia. In the laboratory in Philadelphia the skin cells were cultured and prepared for chromosome preparation. Nine specimens were successfully established in culture. None of the cells studied showed unusual chromosome numbers, and the karyotypes looked "normal."[22] This confirmed Harnden's result and two other studies, one performed on Aboriginal Australians and one on Indigenous people from Kundiawa, Eastern Highland District, Territory of Papua and New Guinea, all of which were cited in the paper.

The researchers were adamant that the "apparently negative results" should not deter "further work on isolated groups, many of which are rapidly disappearing," as the finding of "karyotypically distinct populations" would be of the greatest interest to the study of human genetics and evolution. The present study had shown the feasibility of such investigation even though the cytological laboratory facilities were "half way around the world." Although the field worker had no previous training in cytology, tissue culture, and biopsy techniques, she had been able to obtain "adequate samples from non-

20. Hungerford et al., "Chromosome Studies" (ref.19), 110.

21. Hungerford was the co-inventor of the peripheral blood method that allowed chromosome analysis to be performed on leukocytes isolated from peripheral blood samples. Although blood samples were easier to obtain than skin samples, the latter had the advantage that they resisted transport periods of more than seven days (the maximum allowable for blood samples). They were thus "the method of choice in more remote areas"; see J. S. Weiner and J. A. Lourie, *Human Biology: A Guide to Field Methods. IBP Handbook No. 9* (Oxford and Edinburgh: Blackwell Scientific Publications, 1969), 131–39.

22. Hungerford et al., "Chromosome Studies" (ref. 19), 108.

institutionalized primitive New Guineans, who were unexpectedly cooperative in every way." In addition, the study was carried out at relatively low cost as it piggybacked on an ongoing field study. The paper ended with a strong call for more such collaborative studies. Meanwhile, samples from the study were frozen and stored in liquid nitrogen, "pending the development of improvements in cytological techniques which would permit greater precision in karyotype analysis."[23] Karyotyping was only the most recent tool employed for the study of human variation, but because of its "hidden" character and the supposedly direct inspection of the full human genome, it promised to be of special importance for the study of human genetics.

Hungerford, the lead author of the paper, participated in at least two further studies with anthropologists. One study concerned the Todas in Southern India, another one the Ainu population of Hokkaido in Japan. The studies did not show any microscopically visible variations. Yet by the mid-1960s, researchers started reporting ethnic differences in the length of the Y chromosomes.[24] Motivated by these reports, Roslyn Angell, from the Cytogenetics and Cell Biology Unit at the Prince of Wales Hospital in Randwick, New South Wales, undertook a new study of "full-blood aborigines" from at least two locations with the explicit aim to look for minor chromosomal variants, such as variation in the length of chromosomes rather than in their number or gross morphology.[25] Angell quite unashamedly referred to her study as "racial

23. Ibid., 110. On the importance of freezing technologies for transporting and preserving samples for future unpredictable uses, especially in the context of "salvage anthropology," see Joanna Radin, *Life on Ice: A History of New Uses for Cold Blood* (Chicago: University of Chicago Press, 2017).

24. See, for example, M. M. Cohen, Margery W. Shaw, and Jean W. MacCluer, "Racial Differences in the Length of the Human Y Chromosome," *Cytogenetics* 5 (1966): 34–52; Monica N. Starkman and Margery W. Shaw, "Atypical Acrocentric Chromosomes in Negro and Caucasian Mongols," *American Journal of Human Genetics* 19 (1967): 162–73; and H. A. Lubs and F. H. Ruddle, "Chromosome Polymorphism in American Negro and White Populations," *Nature* 233 (1971): 134–36.

25. In the mid-1960s, Angell, who at the time was pursuing her graduate studies at Guy's hospital in London, had also participated in the genetic studies of the islanders of Tristan de Cunha. The thinly populated island in the Atlantic was presented as the "most remote inhabited location on Earth." Following a volcano eruption on the island in 1961, the whole population of 264 people was evacuated to Britain. In the two years they spent in Britain, the islanders became the subject of extensive scientific and medical investigations. Over fifty researchers participated in the studies. The results of the cytogenetic studies were published in a paper in *Nature* under the title "Chromosome investigation of a small isolated human population." Despite widespread congenital malformations present in the population, no chromosome anomaly was found; see John L. Hamerton et al., "Chromosome Investigations of a Small Isolated Human Population:

cytogenetics." Halfway through the study, new fluorescent banding techniques became available. Researchers determined that every human chromosome displayed a characteristic pattern of narrow and broader stripes. This made it possible to identify each chromosome with much more confidence. It also made it easier to spot and locate minor differences. A particularly strong band appeared in the distant arm of the Y chromosomes. Applying the new staining method to her samples, Angell observed that the Y chromosome band was much weaker in Aboriginal samples than in control white Australian samples. This indicated that the mean length of the Y chromosome was significantly smaller in Aboriginal samples, and that the difference lay specifically in the fluorescent segment of the longer Y chromosome arm.[26]

When in the mid-1970s Patricia Jacobs, one of the doyen of the "re-birth" of human chromosome studies, wrote a review article on the potential of karyotyping for studies of human variation, she could point to a significant number of studies that had reported "racial variations" in chromosome studies.[27] A few years earlier, Jacobs had moved from Edinburgh to Hawai'i to join her husband, population geneticist Newton Morton. In a later biographical essay, Jacobs pointed out the "fortunate" circumstance that Hawai'i offered an ethnically highly diverse study population that comprised people of Chinese, Japanese, Filipino, Hawaiian, and Caucasian ancestry. This enabled her to study the different prevalence of various conditions among the ethnic groups.[28] The same circumstance may explain her interest in "chromosome heteromorphisms" in various population groups.

Chromosome Abnormalities and Distribution of Chromosome Counts According to Age and Sex Among the Population of Tristan Da Cunha," *Nature* 206 (1965): 1232–34. After her stint in London (1963–69), Angell returned to Australia before setting out to Hawai'i (1974–76) and then settling in Edinburgh (from 1978); http://prabook.com/web/person-view.html?profileId=550299 (accessed Aug 2020).

26. Rosyln Angell, "The Chromosomes of Australian Aborigines," in *The Human Biology of Aborigines in Cape York. Australian Aboriginal Studies No. 44: Human Biology Series No. 5*, ed. R. L. Kirk (Canberra: Australian Institute of Aboriginal Studies, 1973), 103–09.

27. Patricia A. Jacobs, "Human Chromosome Heteromorphisms (Variants)," in *Progress in Medical Genetics; New Series: Volume II*, ed. A. G. Steinberg et al. (Philadelphia: W. B. Saunders Company, 1977), 251–74.

28. Patricia A. Jacobs, "An Opportune Life: 50 Years in Human Cytogenetics," *Annual Review of Genomics and Human Genetics* 15 (2014): 38. On Hawai'i as a laboratory for population studies, see also Warwick Anderson, "Racial Hybridity, Physical Anthropology, and Human Biology in the Colonial Laboratories of the United States," Supplement, *Current Anthropology* 53, no. S5 (2012): S95–S107; and Joan H. Fujimura and Ramya M. Rajagopalan, "Discourses and Practices of Race, Ethnicity, Ancestry, and Genomics in Hawai'i" (this issue).

Jacobs concluded that the frequency of chromosome variations differed in various racial groups and suggested that further investigation of the phenomenon would provide valuable information "on the origin, migration and kinship" of these different groups.[29] She predicted that when "objective methods of mensuration" would become available, "heteromorphisms will take their place alongside conventional blood group and enzyme polymorphisms as tool in formal and population cytogenetics."[30] Other researchers echoed this view.[31]

As this brief survey suggests, the search for genetic differences in human populations was an abiding interest for human geneticists in the 1960s and 1970s. Chromosome analysis (and eventually banded chromosomes) were merely the latest tool, next to blood grouping techniques and protein variant determinations, enrolled in the ongoing quest to map such differences.[32] Later standardization meetings continued to provide ever more detailed descriptions of "normal chromosomes" that served as a standard against which finer differences could be gauged. Research focused on populations that were constructed as geographically or culturally isolated, and thus as reservoirs of unique genomic histories that preserved traits from the early evolutionary history of humans. Many of these populations were already subjects of intense study and exploitation in colonial and post-colonial settings. Existing infrastructures and scientific networks and the continuing positioning of the Indigenous populations as remote and different facilitated research in Australia and its territories as well as in the Pacific more generally.[33]

29. Jacobs, "Human Chromosome Heteromorphisms" (ref. 27), 266.

30. Ibid., 271.

31. See, e.g., G. A. Harrison et al., *Human Biology: An Introduction to Human Evolution, Variation, Growth and Ecology*, 2nd ed. (Oxford: Oxford University Press, 1977), 294.

32. On the use of blood groups for the analysis of racial differences, see Lisa Gannett and James Griesemer, "The ABO Blood Groups: Mapping the History and Geography of Genes in Homo Sapiens," in *Classical Genetic Research and Its Legacy: The Mapping Cultures of Twentieth-Century Genetics*, ed. Hans-Jörg Rheinberger and Jean-Paul Gaudillière (London: Routledge, 2004), 119–72; Jenny Bangham, "Blood Groups and Human Groups: Collecting and Calibrating Genetic Data After World War II," *Studies in History and Philosophy of Biological and Biomedical Sciences* 47A (2014): 74–86; Jenny Bangham, *Blood Relations: Transfusion and the Making of Human Genetics* (Chicago: University of Chicago Press, 2020).

33. One important international node for genetic studies of Indigenous Australians, notably in the context of the International Biological Program and for blood collection, was Robert L. Kirk's laboratory in Perth and later in Canberra; see Emma Kowal and Joanna Radin, "Indigenous Biospecimen Collections and the Cryopolitics of Frozen Life," *Journal of Sociology* 51 (2015): 63–80. See also Projit Bihari Mukharji, "Bloodworlds: A Hematology of the 1952 Indo-Australian

From the 1990s, molecular biologists turned increasingly toward human and medical genetics, bringing a new set of tools to the field.[34] Yet some of the fundamental tensions in the study of human heredity remained the same.

99.9 PERCENT THE SAME

The first complete human genome sequence was presented as that of a "composite person." It had an X and Y chromosome, which technically made it a man, but the "he" was comprised of autosomes taken from men and women of several nations, including especially the US, Europe, and Japan, representing the main sequencing centers. He was "a multinational and multiracial melange, a kind of Adam II, his encoded essence revealed for the twenty-first century and beyond."[35] Announcing the "first survey of the human genome" at a press conference at the White House in 2000, President Clinton—framed by Francis Collins and Craig Venter, the heads of two competing projects to sequence the genome who had agreed to a truce—declared, "all human beings, regardless of race, are more than 99.9 percent the same."[36]

Venter followed up, bolstering the claim:

> The method used by Celera has determined the genetic code of five individuals. We have sequenced the genome of three females and two males, who have identified themselves as Hispanic, Asian, Caucasian or African American. We did this sampling not in an exclusionary way, but out of

Genetical Survey of the Chenchus" (this issue). Reportedly, the growth of human genetics in Australia was stimulated by the development of diagnostic clinical cytogenetics in the early to mid-1960s. The cytogenetics community met annually from 1966; see Grant R. Sutherland, "The history and development of the Human Genetics Society of Australasia" (n.d.), https://www.hgsa.org.au/documents/item/65 (accessed Aug 2020). On Oceania as a laboratory for the study of difference, see Bronwen Douglas and Chris Ballard, eds., *Foreign Bodies: Oceania and the Science of Race 1750–1940* (Canberra: ANU E Press, 2008); and Warwick Anderson, "Hybridity, Race, and Science: The Voyage of the Zaca, 1934–1935," *Isis* 103 (2012): 229–53. On the construction of Indigenous people as "living fossils," see Pratik Chakrabarti, *Inscriptions of Nature: Geology and the Naturalization of Antiquity* (Baltimore, MD: Johns Hopkins, 2020), ch. 4.

34. On the turn of molecular biologists to human genetics, see Soraya de Chadarevian, *Heredity under the Microscope: Chromosomes and the Study of the Human Genome* (Chicago: University of Chicago Press, 2020).

35. Daniel J. Kevles, "Out of Eugenics: The Historical Politics of the Human Genome Project," in *The Code of Codes: Scientific and Social Issues in the Human Genome Project*, ed. Daniel J. Kevles and Leroy Hood (Cambridge, MA: Harvard University Press, 1992), 36.

36. White House, Office of the Press Secretary, "June 2000 White House Event" (transcript), June 26, 2000; https://www.genome.gov/10001356/ (accessed Aug 2020).

> respect for the diversity that is America, and to help illustrate that the concept of race has no genetic or scientific basis. In the five Celera genomes, there is no way to tell one ethnicity from another.[37]

The covers of *Nature* and *Science* that published the first full draft of the sequence of the human genome a year later conveyed the same supposedly post-racial message, even if race was very much on display in the cover images.

Soon there were rumors (later confirmed) that the DNA used by Celera Genomic was in fact largely Venter's own. Also the publicly funded sequence was less composite than claimed, relying to 71 percent on the DNA of one (unnamed) male individual, presumably from the Buffalo, NY, area.[38] Apart from the obvious problem of constructing the "normal human genome" from mostly two North American men, it is well known that, despite all the rhetoric, much of the postgenomic research effort focused on the 0.1 percent difference between individuals. The promise of genomics—scientifically, clinically, and commercially—lay in the correlation of specific genetic variations with particular disease patterns, and in mapping the distribution of genetic differences in different populations, variously defined in epidemiological, geographical, or cultural terms. Scientific programs, biotech enterprises, national genomic programs, and ancestry testing companies were built on these premises that all too often, unwittingly or intentionally, became entangled with the resurrection and biological re-inscription of racial categories the human genome project had promised to overcome.[39]

Setting out from a population genetical and evolutionary rather than a molecular biological and biomedical context, the Human Genome Diversity Project, launched shortly after the US human genome sequencing project was coming into gear, explicitly planned to collect samples from "diverse populations in order to understand human variation." Luca Cavalli-Sforza, the driving force behind the project, had participated in the genetic studies of "primitive people" supported by the WHO and the International Biological Program (IBP) in the 1960s and 1970s. Employing some of the same rhetoric,

37. Ibid.

38. Lisa Gannett, "The Normal Genome in Twentieth-Century Evolutionary Thought," *Studies in History and Philosophy of Biological and Biomedical Sciences* 34 (2003): 144–45.

39. Dorothy Roberts, *Fatal Invention: How Science, Politics, and Bio-Business Re-Create Race in the Twenty-First Century* (New York: New Press, 2011); Catherine Bliss, *Race Decoded: The Genomic Fight for Social Justice* (Stanford, CA: Stanford University Press, 2012); Jenny Reardon, *The Postgenomic Condition: Ethics, Justice, and Knowledge* (Chicago and London: University of Chicago Press, 2017).

Cavalli-Sforza and his colleagues, in their call for action, pointed to the "vanishing opportunity" to collect blood samples from quickly disappearing "isolated human populations" around the world, which held the key to the study of human diversity. They also called on the WHO, next to the Human Genome Organization (HUGO) and other institutions, to support the urgent international effort.[40] In a tightly argued analysis, Lisa Gannett has shown that the population-based Human Genome Diversity Project suffered from similar essentialist assumptions as the human genome project. In other words, population-based approaches do not necessarily avoid the pitfalls of typological approaches and problematic notions of "normality."[41] Yet in contrast to earlier studies, the project encountered resistance and eventually floundered. Among those who contested the project were the Indigenous groups included in the study, who protested their description as vanishing isolates of historical interest and opposed the scientific exploitation of their genetic heritage.[42] This signaled an important historical change in Aboriginal Australians and other Indigenous groups from objects of studies to considering their own interests as communities in such knowledge.[43]

Nevertheless, the search for patterns of variability and population based approaches remains widespread in genomic research and beyond.[44] The HapMap project, launched in 2003 with the aim of determining common patterns

40. L. L. Cavalli-Sforza et al., "Call for a Worldwide Survey of Human Diversity: A Vanishing Opportunity for the Human Genome Project," *Genomics* 11 (1991): 490–91; Ricardo Ventura Santos, "Indigenous Peoples, Postcolonial Contexts and Genomic Research in the Late Twentieth Century: A View from Amazonia (1960–2000)," *Critique of Anthropology* 22 (2002): 81–104.

41. Gannett, "The Normal Genome" (ref. 38).

42. Jenny Reardon, *Race to the Finish: Identity and Governance in the Age of Genomics* (Princeton, NJ: Princeton University Press, 2004); Amade M'charek, *The Human Genome Diversity Project: An Ethnography of Scientific Practice* (Cambridge: Cambridge University Press, 2005). For a more general critique of the often implicit racial assumptions that underpin the study of Indigenous DNA, see also Jenny Reardon and Kim TallBear, "'Your DNA is Our History': Genomics, Anthropology, and the Construction of Whiteness as Property," *Current Anthropology* 53, no. S5 (2012): S233–S245.

43. Joanna Radin and Emma Kowal, "Indigenous Blood and Ethical Regimes in the United States and Australia since the 1960s," *American Ethnologist* 42, no. 4 (2015): 749–65.

44. Next to the search of genomic variation (although not unrelated to it), blood groups and blood proteins, including especially the highly variable human leukocyte antigen system, have been used to study variation in human populations. In the case of blood groups we can see a similar dynamic at work. The determination of a common set of blood groups was followed by wide-ranging studies on the geographical distribution of blood group frequencies as a means to distinguish different populations; see Bangham, "Blood Groups and Human Groups" (ref. 32).

of DNA sequence variations in parts of Africa, Asia, and Europe (whittled down to samples from the Yoruba, Chinese, Japanese, and Northern and Western Europeans), in many respects functioned as the successor of the Human Genome Diversity Project.[45] The uses of genetic technologies in forensics, in ancestry testing, and in "personalized medicine" are all population based. Individuals are tested against populations that are characterized by patterns of genomic differences (for instance, the frequency of singular nucleotide polymorphisms). As several scholars have shown, categories of race and ethnicity often unwittingly enter the analysis rather than resulting from it, as sometimes claimed.[46] In biomedical research in the US, it is mandated that data are collected in accordance with the Office of Management and Budget categories of race and ethnicity. Affiliation to any of these categories is by self-identification (by selecting from a list of offered options). Nevertheless, there is the danger that the social categories become biologically re-inscribed.[47] Thus, once again, the establishment of a "reference genome" (*the* human genome sequence) stimulated the search for genetic difference, including the re-introduction of racial differences that the promoters of the human genome project had declared as defunct. In this context also falls the controversial announcement of the first genome sequence of an Aboriginal Australian from a historic hair sample.[48] Here and in other studies Indigenous samples remain at the forefront of current research.

45. The International HapMap Consortium, "The International HapMap Project," *Nature* 426 (2003): 789–96.

46. See, for instance, Amade M'charek, "Technologies of Population: Forensic DNA Testing Practices and the Making of Difference and Similarities," *Configurations* 8 (2000): 121–58; Ramya Rajagopalan and Joan Fujimura, "Making History via DNA, Making DNA from History: Deconstructing the Race-Disease Connection in Admixture Mapping," in *Genetics and the Unsettled Past: The Collision Between DNA, Race, and History*, ed. Keith Wailoo, Alondra Nelson and Catherine Lee (New Brunswick, NJ: Rutgers University Press, 2012), 143–63; Lisa Gannett, "Biogeographical Ancestry and Race," *Studies in History and Philosophy of Biological and Biomedical Sciences* 47 (2014): 173–84. See also the references in note 39.

47. Steven Epstein, *Inclusion: The Politics of Difference in Medical Research* (Chicago: Chicago University Press, 2007); Troy Duster, "A Post-Genomic Surprise: The Molecular Reinscription of Race in Science, Law and Medicine," *The British Journal of Sociology* 66 (2015): 1–27.

48. Emma Kowal, *Haunting Biology: Science and Indigeneity in Australia* (Durham, NC: Duke University Press, forthcoming), ch. 3. As Kowal argues, the genomic study of the hair sample of an Aboriginal man, collected in a British expedition to Australia in 1923, in a Danish laboratory eighty years later, remained entangled with the racial studies of the interwar years. Yet the same story also encapsulates the changed sensibilities and consent requests of postcolonial genomic science that confronted the lead researcher Eske Willerlev and that he came to embrace, following

CONCLUSIONS

How, then, can we explain the continuing search for genetic variation, including the resurgence of racial categorizations, in light of the simultaneous negation of such differences? Posing the question with respect to the persistence of racial concepts that have been denounced again and again, Staffan Müller-Wille has suggested that these notions are reiterated because they have been "indelibly inscribed into the conceptual architecture that has supported and continues to support, all attempts at describing and controlling human variation on a global scale since the early modern period."[49] Expanding on this thought, the analysis presented in this essay suggests that the study of variation itself is inextricably linked to the study of biological heredity. As Hans-Jörg Rheinberger and Müller-Wille have argued, the emergence of an epistemic space for a concept of biological inheritance was predicated on plants, animals, and people moving in space in the age of colonial explorations. Variable traits (like the height of a plant or the color of the human skin) that persisted in these moves could be recognized as heritable rather than depending on environmental factors.[50] More generally, for a certain characteristic to be recognized as a heritable trait, it had to exist in a variety of forms. Similarly, Mendel's breeding project was aimed at producing stable new plant varieties, whereas hereditary variation was at the basis of Darwin's theory of heredity and natural selection. Finally, for a gene to be identified and mapped, it must exist in a mutant form. The search for variation, then, seems to be built deeply into the study of heredity. Yet how variation is interpreted—as variation on a theme or deviation from a norm, in a hierarchical or inclusive manner—and how it is acted upon, is a matter of interpretation and historical contingency. This is of particular consequence for the study of variation in humans that has been the focus of this essay. In this case, the continuing search for variation and the persistence of racial categories often re-enforced and re-inscribed each other. Such assumptions often informed genetic studies of Pacific populations. Yet

a visit to the Aboriginal communities from which the hair sample originated. I thank Emma Kowal for making the chapter available to me pre-publication.

49. Staffan Müller-Wille, "Reproducing Difference: Race and Heredity from a Longue Durée Perspective," in *Reproduction, Race, and Gender in Philosophy and the Early Life Sciences*, ed. Susanne Lettow (Albany, NY: SUNY Press, 2014), 218. On this point, see also Terence Keel, *Divine Variations: How Christian Thought Became Racial Science* (Stanford, CA: Standford University Press, 2018).

50. Staffan Müller-Wille and Hans-Jörg Rheinberger, *A Cultural History of Heredity* (Chicago: Chicago University Press, 2012).

traveling to the Pacific could also open the eyes to other perspectives, as recounted for researchers in the 1930s and 2010s alike.[51] A critical, reflexive, and participatory approach in the study of human variation is of paramount importance not to betray the basic consensus that, in all respects that matter, all humans are the same.

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51. Anderson, "Hybridity" (ref. 33); Kowal, *Haunting Biology* (ref. 48), ch. 3. See also note 48.