Journal of the History of Biology (2018) 51:631–655
https://doi.org/10.1007/s10739-017-9486-7

Whose Turn? Chromosome Research and the Study of the Human Genome

SORAYA DE CHADAREVIAN
Department of History and Institute for Society and Genetics
University of California Los Angeles
6265 Bunche Hall
Los Angeles, CA 90095-1473
USA
E-mail: chadarevian@history.ucla.edu

Abstract. A common account sees the human genome sequencing project of the 1990s as a "natural outgrowth" of the deciphering of the double helical structure of DNA in the 1950s. The essay aims to complicate this neat narrative by putting the spotlight on the field of human chromosome research that flourished at the same time as molecular biology. It suggests that we need to consider both endeavors – the human cytogeneticists who collected samples and looked down the microscope and the molecular biologists who probed the molecular mechanisms of gene function – to understand the rise of the human genome sequencing project and the current genomic practices. In particular, it proposes that what has often been described as the "molecularization" of cytogenetics could equally well be viewed as the turn of molecular biologists to human and medical genetics – a field long occupied by cytogeneticists. These considerations also have implications for the archives that are constructed for future historians and policy makers.

Keywords: Cytogenetics, Molecular biology, Population studies, Gene mapping, Human genetics, Human genome project, Molecularization

The work of historians very much depends on the availability of archives. A common saying goes: where there is no archive there is no history. The reverse is also true: existing narratives about events and their meanings shape the form of the archive. They can determine what is kept or discarded, included or excluded from specific collections.

This is true for scientific archives as well. To take as a concrete example the topic that interests us here: how scientists, archivists and historians understand the human genome project (HGP) will determine

The original version of this article was revised due to a retrospective Open Access order.

what material will form part of the archive that future historians will be able to consult.[1] It is with these considerations in mind that I will offer some reflections on the history of the human genome project.

The first all but trivial question is: what is the HGP? Is it to be written in capital letters or in lower case? Is there one or are there more projects? A provocative answer to these questions was formulated by the historian Michael Fortun who argued: "The Human Genome Project does not exist." The "'Human'" so Fortun, was "dispersed in a zoo blot of research organisms," each of which was supported by its own research community and commanded its own funding. The "'Genome,'" too, lost "its distinctly defined boundaries" and became dispersed in the technological process. Finally, the "postulated coherence of a localizable, definable 'Project,' with a manageable, completed endpoint" was nothing else than a rhetorical ploy aimed at convincing Congress (Fortun, 1999, p. 26). The human genome project, Fortun declared, "was nothing new, just the speeding up of research lines that already existed" (Fortun, 1999, p. 27). Other scholars agreed that there were several (national) genome projects of various kinds. The US HGP (assuming it ever existed) was constructed as an "international" project and given its high level of funding it played an important role in shaping the overall effort. Nevertheless, the US HGP only produced about a third of the sequencing data of what was hailed as the publicly funded HGP. A further third was produced by the Sanger Center (now the Sanger Institute) in the UK and a final third by a variety of other European laboratories, Japan and China. Then there was Craig Venter's and Celera Genomics' parallel effort to sequence the human genome, using a shotgun rather than a map based method. For the purpose of this essay, I will refer to the HGP as the US side of the publicly funded international project.

Early on, the project attracted the attention of historians and sociologists of science as well as science writers. An insider account of the science and politics that led to the HGP appeared as early as 1994, when the HGP was still in full swing. Under the racy title *The Gene Wars*, Robert Cook-Deegan who, in the crucial years, had directed a study of the status of genome research for the Office of Technology Assessment of the US Congress and later served as an advisor to the National Center for Human Genome Research (renamed National Human Genome Research Institute in 1997), laid out what became the standard

[1] The question how to create a historical archive of the human genome project was actively debated as part of the Human Genome Archive Project, launched by the Wellcome Library in London. The project saw the participation of different "stakeholders", including archivists, scientists and historians (Shaw, 2016).

account of the project (Cook-Deegan, 1994).[2] The story starts with Robert Sinsheimer, then Chancellor of the University of California Santa Cruz, convening a meeting of molecular biologists in 1985 where the idea of sequencing the human genome was first aired. Sinsheimer's aim was to put Santa Cruz "on the map" with a big biology project. While nothing came out of this specific plan, the seed was sown. Harvard molecular biologist and entrepreneur Walter Gilbert carried on the torch. Eventually the Department of Energy (DOE) signed on to the idea, followed by the National Institutes of Health (NIH), with the project becoming contested and changing along the road. Eventually James Watson, then Director of Cold Spring Harbor Laboratory, was called to head the NIH genome program, forcefully steering it through Congress and its initial phase. The rest is history.

There were critical responses to this account of the HGP. According to one view, what distinguished the project was not so much the aim of producing a reference sequence of the full human genome than the establishment of "large-scale biology" and the new machinery set in place to governing it. Thus, rather than being about the human genome it was a socio-technical management project (Hilgartner, 2013). Others traced the beginning of the US HGP back to the Atomic Bomb Casualty Commission, and especially its genetic arm, intended to study the mutational effect of radiation on the atomic bomb survivors. This project was funded by the Atomic Energy Commission, the predecessor of the DOE that kick-started funding for the HGP. The underlying reason for Congress to fund the HGP according to this view then can be found in the post-Cold war economic competition with Japan and deeply embedded questions of national security (Beatty, 2000).

This essay addresses one central tenet of the standard account, namely that the HGP was "a natural outgrowth" of molecular biology. The strongest formulation of this view can be found in the opening paragraph of *Gene Wars*:

> The recipe for making a human being is written out sequentially in a four-letter code, embodied in the six-feet of DNA coiled inside virtually every human cell. Amassing the scientific tools to decode that set of instructions has been a major preoccupation of molecular biology ever since 1953, when James D. Watson and Francis Crick first described DNA's double helical structure. The Human Genome Project is a natural outgrowth of this effort (Cook-Deegan, 1994, p. 9).

[2] See also Kevles (1992).

In a chapter on the science and technology behind gene mapping and sequencing science writer-turned-historian Horace Judson concurred:

> Like the oak in the acorn, the HGP was implicit in the discovery of DNA (Judson, 1992, p. 40).

These quotes establish a conceptual connection between the understanding of genes as a sequence of DNA bases and the project of sequencing the human genome. The link is made stronger by Watson's personal history that provides a biographical connection – one he himself never failed to stress – between the proposal of the double helical structure of DNA in 1953 and the announcement of the full draft of the human genome sequence 50 years later.[3]

The essay aims to complicate this neat narrative by putting the spotlight on the field of human chromosome research. The field flourished at the same time as molecular biology. It received much attention and support in the decades following World War Two but has mostly been written out of accounts of late twentieth century biology. The essay suggests that we need to consider both endeavors – the human cytogeneticists who collected samples and looked down the microscope and the molecular biologists who probed the molecular structure and functions of genes in simple model organisms – to understand current practices and aspirations in the life sciences and biomedicine.[4] Human chromosome research expanded into many directions but the essay focuses on those endeavors that most directly intersected with concerns pursued in the HGP and in the wake of it.

The first section provides a brief introduction to the study of human chromosomes in the heyday of molecular biology and traces the establishment of chromosome analysis in the clinic. The next two sections investigate the use of chromosome techniques for studies of human populations and efforts to map the human genome that preceded the HGP. The essay concludes by considering the impact of these efforts in shaping the HGP and preparing the ground for current genomic practices.

[3] Cook-Deegan supported this interpretation declaring: "James D. Watson set in motion the whole chain of events that led to the HGP when he and Francis Crick discovered the double-helical structure of DNA in 1953" (Cook-Deegan, 1994, p. 162, figure caption). The two events coincided with Watson's twenty-fifth and seventy-fifth birthdays.

[4] The argument is further developed in my forthcoming book *Heredity under the Microscope*. On the important contribution of cytogeneticists to gene mapping and in laying the "groundwork" for the HGP see also Hogan (2016, pp. 85–86).

The Study of Human Chromosomes

Today chromosomes are viewed as macromolecular assemblages of DNA and proteins and are studied with molecular techniques. Yet in the 1950s to 1980s, the study of human chromosomes was very much the province of cytogeneticists who studied the sub-cellular structures armed with an evolving set of preparation techniques and the microscope.

The study of chromosomes was not new to the postwar era.[5] Chromosomes were first described and then extensively studied since the late nineteenth and early twentieth century. Researchers followed chromosomes through the cell cycle and distinguished the sex chromosomes from other chromosomes. In the 1920s, scientists agreed that humans had 48 chromosomes, an observation often confirmed over the years. Plants and insects had fewer chromosomes and the material was more readily available and easier to handle. For these reasons – and for the potential commercial value of new chromosomal plant varieties – research focused on these organisms (Campos, 2008; Curry, 2010, 2016; Santesmases, 2013).

This changed in the aftermath of World War Two. Widespread efforts to establish the effects of radiation in humans as well as a continuing interest in the role of chromosomes in the etiology of cancer – a disease intimately connected to the risk of radiation exposure – provided new incentives to develop methods to study human chromosomes at a time when various governments were invested in the development of nuclear energy for military and civilian uses. Postwar genetics was deeply intertwined with the concerns and opportunities of the nuclear age (Beatty 1991; Lindee, 1994, 2016). This holds true specifically for human chromosome research. If we search for the nuclear connections, they are pervasive and deeply mark the history of the field (de Chadarevian, 2010).

In this context of renewed interest in the study of human heredity, the number of human chromosomes was revised from 48 to 46. Joe Hin Tjio and Albert Levan from the University of Lund first suggested the new count in 1956 (Tjio and Levan, 1956). The two researchers had been working with fetal lung tissue and, initially, were cautious in generalizing their findings. But the new count was quickly confirmed by other researchers in the field (Ford and Hamerton, 1956). Tjio and Levan combined a number of newly available techniques to achieve their soon iconic chromosome pictures. Most importantly, the technique to grow

[5] On the history of chromosome research, see Hsu (1979), Kevles (1995), Lima-de-Faria (2003), Harman (2004) and Harper (2006).

tissue samples in thin monolayers in culture allowed researchers to move away from the traditional technique of tissue sectioning and instead to observe chromosomes directly in squash preparations. The addition of colchicine and hypotonic medium increased the number of analyzable cells and spread the chromosomes apart, facilitating counting.[6]

The new preparation techniques stimulated new studies, often initiated by clinicians who provided tissue samples and case histories. The work led to a string of observations that linked unusual chromosome numbers with known clinical syndromes like Down, Turner and Klinefelter syndrome that affected the mental and sexual development of children. The causes of these complex syndromes had baffled clinicians for a long time. They were now all the more impressed by the possibility to trace the clinical pictures to a change in shape and number of chromosomes that was detectable under the light microscope. An editorial in the *Lancet*, the leading British medical journal that carried three separate reports on the new chromosome diseases in one single issue, captured the excitement declaring "what next?" was the least necessary question to be asked in this new field. There was "an enormous territory awaiting exploitation with nothing less than the first real explorations of the human chromosome map as the prize if this early promise is even half fulfilled" (Editorial, 1959). The eminent British medical geneticist Lionel Penrose echoed this view when, referring to the new chromosome findings, he announced:

> Evidently… there has been, during the last year a major breakthrough in the science of human genetics. We can now confidently look forward to the time when genes with known effects can be assigned to their correct locations on the chromosomes. We can also expect great advances in knowledge of how genes deliver their instructions to the cells both during development and in adult life. We may even expect to contribute to the problems relating chromosome anomalies to the problems of abnormal growth as in tumors. In fact it is a very encouraging period for those of us who have pursued the subject of human genetics for many years.[7]

In a lecture one year later Penrose included the new findings on the structure of DNA in his considerations on the future of human genetics, yet the decisive turning point was still marked by the fact that "now we

[6] On the history of the recount and the epistemic practice of counting, see Kottler (1974), Martin (2004) and de Chadarevian (2015a).

[7] Human chromosomes [typescript for a lecture], 22 October 1959; file 88/1, Penrose Papers, UCL.

can see our own chromosomes… and can sometimes make an exact diagnosis from them."[8] The development of a standard nomenclature for human chromosomes provided the basis for more detailed and comparable chromosomal descriptions and diagnostic categories, including a standard visual representation of the human chromosomes (Lindee, 2005, pp. 90–119).

Chromosome researchers have been hailed for having provided genetic medicine with "their organ" (McKusick, 1982, p. 7). Yet despite the collaboration of clinicians in the first detection of chromosome anomalies, the introduction of chromosome analysis in the clinic was anything but straightforward and was often resisted. One reason for this was the shift of expertise it included from the pediatrician or other health specialists to the clinical geneticist (Gaudillière, 2000). Nonetheless, with the establishment of amniocentesis and the passing of abortion laws in various countries, karyotyping became routine practice in pre-natal screening. It was accompanied by a growing apparatus of tissue collections, registries, diagnostic laboratories and counselling services that made increasing space for chromosomes in the clinic and in modern reproductive medicine (Rapp, 1999; Schwartz Cowan, 2008; Stern, 2012; Hogan, 2016). At the same time, chromosome analysis did not just make an impact on prenatal diagnosis and pediatrics but also held promise for a broad range of other fields, including cancer research, sex research, the study of mental retardation, gerontology and toxicology. In the words of one participant, cytogenetics did not only provide an experimental foundation for human genetics but also "convinced medicine itself that genetics had a place in the very foundations of medicine, along with anatomy, physiology and biochemistry". By doing so, "it expanded our understanding of disease, and even more of health… and created a new vision and new ways of prophylaxis" (Polani, 1997, p. 119).

The adoption of cytogenetics as a diagnostic tool in the clinic is important for our concerns here as it created and expanded the category of genetic diseases and put into place many of the services and infrastructures into which molecular technologies could eventually be integrated. Yet cytogeneticists also became active in two other areas of research that are of interest in this context, namely the large-scale genetic study of human populations and human chromosome mapping.

[8] Lionel Penrose, "Molecular basis of heredity" [typescript for lecture at Medical Society of London], 11 January 1960; file 88/2, Penrose Papers, UCL. In the same lecture, Penrose also noted that "a chromosome contains many strands of DNA, possibly 64 or 128." We now know that there is only one DNA strand per chromosome.

Chromosomes and Human Population Studies

Human chromosomes became amenable to large-scale epidemiological studies only after Peter Nowell and David Hungerford in Philadelphia had shown that leucocytes extracted from a blood sample could be used for chromosome preparations (Nowell and Hungerford, 1960). In fact, Soviet scientists had described a similar method to gain chromosome preparations from white blood cells in the 1930s.[9] Yet the method was not taken up at the time and with the silencing of the Soviet geneticists in the Lysenko era, it appeared to have been forgotten (Hungerford, 1978; Harper, 2006, pp. 139–140). Instead, human chromosomes continued to be prevalently prepared from testis or bone marrow samples extracted operatively or in painful breastbone punctures, hardly a procedure that could be employed for large-scale population studies. In contrast, the "peripheral blood method" described in 1960 immediately opened up chromosome analysis to wider use. Nevertheless, at the time only a few centers around the world had the capability to engage in large-scale chromosome studies. Among these the institution that most vigorously pursued the project to use chromosome techniques for population studies was the Medical Research Council Clinical Effects of Radiation Research Unit at the Western General Hospital in Edinburgh, headed by the radiologist and medical researcher Michael Court Brown. The unit soon changed its name to MRC Clinical and Population Cytogenetics Unit to capture better the actual work of its researchers.

Early in his career, Court Brown had embarked on a large follow-up study of patients that had received radiation treatment. Collaborating with the epidemiologist Richard Doll, he showed that patients that had been treated with radiation for a debilitating arthritic condition had a ten times higher chance of contracting leukemia. The study appeared in the Government White Paper *Hazards to Man of Nuclear and Allied Radiations* and made a very strong impact (Court Brown and Doll, 1956).[10] Together with the A-bomb survivor studies in Japan, this was the most important study to establish the carcinogenic effect of low doses of ionizing radiation. The study also set the course for Court Brown's future work.

[9] The Russian method did not make use of phytohemagglutinin, a protein found in bean extract that was routinely used to remove red blood cells from blood preparations but was discovered to stimulate cell division in white blood cells, making them amenable to chromosome analysis.

[10] Doll and C. Brown also collaborated on life expectancy and cancer mortality of British radiologists; on the incidence of leukemia in A-bomb survivors; and on the incidence of leukemia after exposure to diagnostic exposure in utero.

Following the leukemia study, Court Brown very quickly picked up the new cytogenetic techniques that were just being perfected. His aim was to study the mechanism by which radiation induced cancer. Yet from the beginning, he combined cytogenetic studies with epidemiological techniques. Two initiatives he started – the creation of a registry of abnormal karyotypes and an extended newborn screening program – exemplify his approach and point to the critical reception of some of these studies.

The first reports on chromosomal disorders had only just appeared, when the Edinburgh Unit started a registry of abnormal karyotypes that gathered data on a large scale in a way that opened it up for epidemiological studies. The aim was to compare cancer incidences and mortality patterns more generally in individuals with chromosome anomalies with those of the ordinary population. The number of cases in the registry grew fast and the registry soon became a central tool for a broad range of population based epidemiological studies.

Cases were provided by collaborating clinicians and through the surveys undertaken by the Unit. Data collection was extensive. Every entry consisted of a several page long form asking for personal data, medical history, detailed description of physical characteristics and physiological data, intelligence tests and family data. The unit had persons on its staff whose job it was to complete data collection through interviews with the families and cross checking with public records such as birth, death and marriage registries and census records. Their work also included annual follow-ups of the cases in the registry and the overall management of the data. Data collection focused on Scotland but with the explicit potential to be expanded to the national level. Access to the registry was open to *bona fide* researchers but Court Brown was keen to circulate the data even more broadly. A volume published in the MRC Special Report Series in 1964 introduced its readers to karyotyping, the newly identified genetic diseases and the registry and presented the full case reports of 266 anonymized patients with sex chromosome abnormalities extracted from the registry. In the preface, MRC officials expressed the hope that the volume "will serve not only as a useful handbook for workers in many different fields, but also as a source book for data and analysis and as a stimulus to speculation and further inquiry" (Court Brown et al., 1964, p. viii).

By the early 1970s, several cytogenetic registries existed in various countries. At a meeting in Edinburgh, organized by the Standing Committee of the Paris Conference on the Standardization in Human Cytogenetics, the possibility was discussed of merging these into one central registry. In the end, the committee decided against it but it

highlighted the need to standardize the way information was collected and recorded. The committee also solicited cooperation between the different institutions and the international support of the WHO in the endeavor. By this time, the aims the registries were expected to serve had vastly expanded. They reached from morbidity and mortality studies to recurrence risk and reproductive fitness studies, mutation rate estimates, etiological studies, determination of karyotype–phenotype correlations, linkage studies, the determination of break points in structural rearrangements, and the determination of health care needs of patients with chromosome anomalies (Hamerton, 1975).

An important correlate to the registry was the establishment of a newborn screening program. The systematic screening of all newborns at the Western General Hospital in Edinburgh (later expanded to a second large hospital) was meant to establish the frequency of abnormalities in the general population and thus to provide a point of reference for other studies. Data from the screening program also fed into the registry and the newborns that showed some of the known chromosome variations were enrolled in longitudinal studies.

The screening revealed an unexpected large number of chromosomal abnormalities or – as was now more carefully stated – genetic variance. Findings indicated that about 1% of children showed a chromosome anomaly in their dividing cells. This was regarded as an underestimation of the chromosomal variation present in the general population because of the limitations inherent in the available microscopic techniques.[11]

Newborn screening studies were started in other centers. In the mid-1960s, following controversial reports that the XYY karyotype predisposed to aggressive and violent behavior, screening was aimed specifically at identifying newborns with XYY and other sex chromosome anomalies and following up the children to study their physical, mental and behavioral development.[12] Between 1964 and 1979 when screening stopped, over 200,000 consecutive births in hospitals in Denver, Edinburgh, New Haven, Toronto, Aarhus, Winnipeg and Boston were screened for chromosome anomalies (nearly 35,000 of these in Edinburgh alone) and over 300 children with unusual sex chromosome

[11] W. M. Court Brown, Contributions of human cytogenetics to clinical medicine, MRC 67/357 - CR 67/26, 16 March 1967, p. 2; FD 9/1281, National Archives, Kew, UK.

[12] On the controversy surrounding the XYY karyotype see The Hastings Center (1980), Green (1985) and, more recently, Richardson (2013, pp. 81–102).

combinations (a rare condition after all) were enrolled in prospective studies.[13] The prospective studies quickly attracted controversy. The Boston study in particular was singled out for critique, with lasting impact on the other projects as well. Science for the People, a group of science activists that had formed around the protest against the use of science and technology in the Vietnam War, led the charge. Consistent with their position on other causes, notably the race and IQ debate that was re-kindled at the time by Arthur Jensen's controversial article on the issue (Jensen, 1969), members of the group exposed the "XYY syndrome" as a "dangerous myth" and criticized the hereditary explanation of social behavior. More specifically, they attacked the consent procedure of the study and the danger of "self -fulfilling prophesy" produced by telling parents of the XYY karyotype and its connected risks. This made the study not just flawed and "worthless" but also "positively harmful" for the children involved. It also provided "the opening wedge for programs with much more serious eugenic implications" (Beckwith and King, 1974). Although various bodies reviewing the charges voted for a continuation of the studies, the researchers at the center of the controversy decided to end the program. Critique elsewhere was more subdued but by the late 1970s all screening programs had stopped. The debate opens a window into emerging ethical discussions on clinical research and resistances to hereditary approaches to human behavior.

Chromosome analysis was not just used for clinical population studies but also to study genetic variation in human populations. Building on a long-standing anthropological tradition, the preferred study objects were geographically or culturally "isolated" populations (Lipphardt, 2012). Besides learning about the distribution of chromosome anomalies and genetic markers in different populations, the aim was to gain insights into human evolution. Among the first chromosome researchers to undertake such studies was Hungerford, one of the two scientists who had developed the method to prepare chromosomes from white blood cell cultures. He credited the British anthropologists Nigel A. Barnicot and his associates at University College London with having started the systematic search for chromosomal variation in human populations. The London team had compared chromosomes from people in West Africa, Greenland, and Europe, largely drawing on London's cosmopolitan population (Barnicot and Travers, 1963). Hungerford teamed up with physical anthropologists to collect and study samples of indigenous people in Eastern New Guinea, the Todas

[13] See Ratcliffe (1986). The figures given in various publications differ slightly.

in Southern India and the Ainu on Hokkaido in Japan. As Barnicot's earlier studies also Hungerford's, stretching over several years, showed no recognizable differences. Yet Hungerford remained optimistic that "microscopically visible karyotype variability" could be found and encouraged physical anthropologists and chromosome researcher to collaborate to find such variations, while "discrete isolates" still existed (Hungerford et al., 1965).[14]

Among those who headed the call was the Italian population geneticist Luca Cavalli-Sforza. In the mid-1960s, whilst undertaking his extensive population genetic study of the pygmies living in Western parts of Africa, he sent blood samples back to Pavia in Italy for chromosome analysis. Once more, the chromosomes were found to be "normal".[15] Support for Cavalli-Sforza's study and other genetic studies of "vanishing" or "primitive people" came from the World Health Organization (WHO) and the International Biological Program (IBP), both of which maintained larger programs in human heredity and human adaptability in the 1960s and 1970s.[16] Some 20 years later, Cavalli-Sforza initiated the Human Genome Diversity Project that clearly followed in the footsteps of the earlier study of indigenous people supported by the WHO and the IBP. Employing some of the same rhetoric, 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 who kept 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 (Cavalli-Sforza et al., 1991; Ventura Santos, 2002). The project encountered resistance and eventually floundered, pointing to continuities but also changing bio-economies and ethical standards of studies of human populations (Reardon, 2004; M'Charek, 2005).

[14] See also Chandra and Hungerford (1966) and Hungerford et al. (1969).

[15] L.L. Cavalli-Sforza, Research on African pygmies [1966; research report]; file G3-181–20, Grant to Istituto di genetica, Università di Pavia, Italy, in respect of population genetic studies of the Babinga pygmies, WHO Archives. See also Cavalli-Sforza et al. (1969, p. 255). The pygmies that Cavalli-Sforza studied lived in the Central African Republic and were therefore also referred to as "Western pygmies".

[16] On the chromosome studies of "vanishing populations" supported by the WHO and the IBP, see de Chadarevian (2015b); on the blood collection program of indigenous people more generally and the ethical issues involved in the collection, preservation and re-use of the samples, see Radin (2013, 2014, 2017); Kowal and Radin (2015) and Radin and Kowal (2015).

Chromosome Mapping

The *Lancet* editorial commenting on the wave of chromosome discoveries in the late 1950s set the mapping of human genes as the ultimate prize to be achieved. Human geneticists had long pursued that goal but human chromosome researchers were poised to pursue it with new vigor.

The first mapping of a gene to a human chromosome went back to 1911. Having established the X and Y chromosomes as the sex chromosomes, the American zoologist Edmund Beecher Wilson suggested that the gene for color blindness must be on the X-chromosome given the gender-specific inheritance pattern of the condition. This was before the fly group started drawing up chromosome maps for their model organism. Through linkage studies of large family pedigrees a few more genes responsible for the inheritance of diseases, including hemophilia, were located on the X-chromosome (Haldane, 1936; Bell and Haldane, 1937). In the early 1930s, the idea of using the mass of data accumulated around blood groups as markers for establishing linkage with other genes provided new impetus for the mapping of human genes. The mathematically heavy approach was embraced as an attempt to turn human genetics into an exact science and distance it from socially biased eugenic approaches while at the same time opening the possibility of identifying carriers of deleterious recessive genes, a problem that had long vexed eugenicists (Mazumdar, 1992, pp. 166–169; Kevles, 1995, pp. 193–198).

Although progress remained slow, the mapping of human genes remained an abiding interest for a dedicated group of human geneticists. J. B. S. Haldane, evolutionary biologist, statistician and "*the* moving scientific spirit" in genetic research at the time, most energetically promoted the project (Polani, 1997, p. 118). Delivering the Croonian lecture at the Royal Society in 1946, he suggested that the "final aim [of human genetics], perhaps asymptotic, should be the enumeration and location of all the genes found in normal human beings" (Haldane, 1948, p. 149). In the US Victor McKusick, studying the Amish people, collected large pedigrees and population data, including especially information on the distribution of hereditary diseases, that he submitted to elaborated statistical analysis to extract linkage information (Lindee, 2005, pp. 58–89). From the late 1950s, he started using IBM computers at the Glen L. Martin Company, an aerospace firm (later known as Lockheed-Martin) with headquarters close to his clinic in Baltimore, for

the otherwise intractable calculations (McKusick, 1966; McGovern, 2014).

By the late 1960s, 68 human genes had been assigned to the X-chromosome through genetic linkage studies. Around the same time, the development of two new cytogenetic techniques – chromosome banding and a technique based on the construction of mouse-human cell hybrids – opened the way for the mapping of human genes to proceed at a much faster pace. Banding was based on the use of fluorescent and other dyes. The dyes produced a characteristic banding pattern for every single chromosome. The staining facilitated the identification of chromosomes that had been difficult to tell apart and allowed researchers to track much finer changes like small deletions and translocations in the chromosomes. Just as banding techniques came along, researchers observed that fused cells grown in culture progressively lost chromosomes. Experimenting with human-mouse hybrids and using different stains for human and mouse chromosomes, they established that the hybrid cells tended to shed human (rather than mouse) chromosomes. Chromosome banding made it possible to identify precisely which chromosomes or chromosome fragments were lost. Correlating these microscopic observations with the presence or absence of specific cell functions allowed researchers to map the responsible genes to specific sites on the chromosomes. The method was first used successfully in 1971 when a group of researchers from Columbia University, Yale University and John Hopkins School of Medicine managed to map the gene for thymidine kinase, an enzyme involved in the synthesis of DNA, on chromosome 17. The mouse cell line used in the experiment lacked the enzyme and the hybrids were grown in a selective medium that required the enzyme for survival (Miller et al., 1971). Many more gene assignments using the same method followed in the next few years. Theoretically, the locus of any biochemical product in the cell that could be distinguished from its mouse counterpart could be mapped in this way. Although cumbersome, the method circumvented sexual reproduction and genetic crossing experiments and did away with the complex statistics of linkage studies. For all these reasons, it soon became the method of choice for human gene mapping. With the wealth of clinical data available, progress on the human gene map soon outstripped the mapping projects of traditional model organisms.[17]

With the number of gene assignments growing rapidly, Frank H. Ruddle, an early adopter of somatic cell hybridization, convened the

[17] On somatic cell hybrids and gene mapping, see Ferguson-Smith (1993), Harris (1995), Polani (1997) and Hogan (2016).

first International Workshop on Human Gene Mapping in New Haven in 1973. In the introduction of the first meeting report, published in the *Birth Defects: Original Article Series*, funded by the National Foundation, and reprinted in *Cytogenetics and Cell Genetics*, the editors underlined the promises of somatic cell genetics for the compilation of a human gene map. In conjunction with family studies, "the acquisition of new data has been rapid – and promises to become explosive". From the beginning the aim was "to map all the genes", a goal to be achieved by the year 2000.[18]

Subsequent meetings took place in Rotterdam (1974), Baltimore (1975), Winnipeg (1977), Edinburgh (1979), Oslo (1981), Los Angeles (1983), Helsinki (1985), Paris (1987), New Haven (1988 and 1989), Oxford (1990) and London (1991). A distinctive feature of the workshops was that the meetings were used for actual work on the map. Committees assigned to review particular areas of the genome confirmed valid gene assignments and flagged those that needed further confirmation. Participants also agreed on a standard terminology. In addition, there were discussions on new concepts and methodologies. Overall, the meetings were designed to contribute to the "more orderly advance of human gene mapping" (New Haven conference, 1973, pp. 9–10). The meeting reports documented the rising number of gene assignments and the growing scale of the overall enterprise. The number of assigned genes rose from just over 200 at the first meeting to over 2300 genes at the last meeting when the human genome sequencing project took off (Ferguson-Smith, 1993, p. 11, Table 2).

From the early 1980s, it became clear that recombinant DNA techniques would have a significant impact on human gene mapping. Of special importance were the provision of molecular markers known as RFLPs (restriction length polymorphisms) along the chromosomes and in situ hybridization techniques using radioactive or fluorescent molecular probes. A new committee was created to review progress in these areas.

The tenth Human Gene Mapping Workshop, convened again in New Haven, marked a transition point for chromosome mappers. Scientists had come to agree that the "complete mapping and sequencing of the human genome", in a period of time comparable to that between the first and the tenth human gene mapping workshop or about 15 years, was "both feasible and desirable" (Ruddle and Kidd, 1989). The US

[18] V. McKusick, Twenty-five years of Human Genome Meetings (HGMs): the past and the future (draft 1), 1 April 1998 [typescript], pp.1 and 7; box HGM98, file HX, Alan Mason Chesney Medical Archives, Johns Hopkins University.

government had committed significant funds to that project. The expanded effort required a new organization and a full-time permanent office that would be supported by the Human Genome Organization (HUGO). The Human Gene Mapping workshops were to be replaced by single chromosome workshops and an annual chromosome coordinating meeting, associated with a Human Genome Mapping workshop.

At least initially, Ruddle, McKusick and other cytogeneticists who had been active in convening the human gene mapping conferences, welcomed the new mapping and sequencing project that they regarded very much as a continuation of their own efforts.[19] Ruddle, especially, was centrally involved in the early discussions on the project. He acted as an effective chairperson of the Genome Sequence Workshop, a key planning meeting convened at Santa Fe in New Mexico in 1986 by the Department of Energy and the Life Sciences Division of the Los Alamos National Laboratory. He also participated in related meetings organized by the National Institutes of Health and the Howard Hughes Medical Institute, and was part of the National Research Council Committee on Mapping and Sequencing the Human Genome that recommended to Congress to commit 200 million dollars of new funding per year to the project (National Research Council (US) Committee on Mapping and Sequencing the Human Genome, 1988).[20] In 1987, together with McKusick, he founded the journal *Genomics*, dedicated to the publication of work on the mapping and sequencing of human and other genomes. "Genomics" was presented as a new discipline, but the editors did not fail to highlight the connection with the earlier gene mapping effort they had promoted since the early 1970s. The "nucleotide sequence" was presented as "the ultimate map" and a useful step towards gene mapping, a goal to which they remained committed (McKusick and Ruddle, 1987, p. 1). With the sequencing project gaining steam, Ruddle, together with a small handful of other candidates, was informally considered as possible director of the new project while McKusick became the

[19] On this point see also Theodore Puck, Memorandum on Dr Betinsky's [sic] human genome conference [Santa Fe meeting], attached to letter Puck to Betinsky, 17 March 1986; box 0102-001, Archival and Digitized materials, National Human Genome Research Institute Archive [NHGRI Archive].

[20] On Ruddle's participation at the meeting in Santa Fe, see material in box 01202-001 and box 0103-001, NHGRI Archive. On Ruddle's reflections on the workshop and his vision for the sequencing project see especially Ruddle to Bitensky, 17 March 1986; box 01202-001, NHGRI Archive. On his participation in the committee that recommended the human genome project to Congress, see interview of Frank Ruddle by Dmitriy Myelnikov, New Haven, CT, 8 December 2011. I thank Myelnikov and Nancy Ruddle for making the interview available to me.

founding president of HUGO, the coordinating agency of the international effort to sequence the human genome.[21] Ruddle supported the construction of a physical map of the whole genome and the sequencing of clinically relevant regions as well as comparative sequencing. He also argued for a distributed structure with centralized funding and management.[22] Although some of these ideas became an integral part of the publicly funded human genome project, by the late 1980s Ruddle's influence started waning and card carrying molecular biologists and directors of designated sequencing centers gained increasing influence. Exactly how this shift of power occurred warrants further research but it reflected a more general shift in the life sciences towards molecular approaches. Cytogeneticists saw molecular technologies as useful to their own goals of mapping human genes and were eager to initiate collaborations with people skilled in the new techniques or, in some instances, also re-trained themselves. In practice, however, funding for such projects tended to be handed over to young people trained as molecular biologists who, in turn, constructed projects around their own research questions and priorities. This may at least partially explain how molecular biologists started getting an upper hand.[23] The eventual decision to privilege brute force sequencing of the whole genome over gene sequencing and mapping remained controversial also among molecular biologists (Cook-Deegan, 1994; McElheny, 2010, pp. 35–74).

Despite the diminishing influence of cytogeneticists and somatic cell geneticists, the continuities between the Human Gene Mapping Workshops and the later organization supporting the international human genome project were evident – down to the use of the same abbreviation, HGM, for the workshops supporting both initiatives. The two projects also shared the international collaborative structure, the data

[21] On Ruddle as possible candidate for the directorship see for example C. Thomas Caskey to James Wyngaarden (Director, NIH), 2 March 1988; box 0102-008, NHGRI Archive.

[22] See material in box 0103-001, NHGRI Archive. Ruddle and other cytogeneticists supported physical mapping of the genome because they saw it as a step towards their goal of gene mapping. In later discussions proponents of the publicly funded HGP defended map-based sequencing as both a way to produce a reliable sequence of the whole genome and as an effective way to divide up the work and manage the multi-sited international project. In contrast, the whole-genome shotgun method, which had emerged from a sequence-based gene discovery program overseen by Craig Venter, was presented as a more risky approach to sequencing the whole genome and less amenable to a collaborative effort (Bostanci, 2004).

[23] These insights are gleaned from research on the 'molecularization' of cytogenetics in other research contexts; see de Chadarevian (forthcoming).

sharing arrangements and, connected with it, the absence of commercial funding.[24] In the view of the "gene mappers" the whole genome project depended – both technically and politically – on the previous gene mapping efforts. As Ruddle put it in a later interview:

> I don't think Congress or anyone would have accepted [the genome project] without the realization that many genes had already been mapped and that there was progress.[25]

Nevertheless, invited to deliver a keynote lecture at the 1998 human genome meeting, McKusick complained rather bitterly that the promoters of the HGP were "not familiar with what had gone on in the field of gene mapping". As others, he remained critical of the fact that the HGP as proposed by a handful of leading molecular biologists was purely based on sequencing, without any reference to gene mapping that had been the focus of activity beforehand. To underline his point, McKusick declared that, while Jim Watson wanted the HGP to be finished by April 2003 or 50 years after he and Crick first proposed the double helical model of DNA, he personally would be satisfied if the project would not be completed until 2006 or exactly 50 years after the correct chromosome number was established.[26]

As it turned out, the available genetic map proved essential to construct the physical map of the human genome and align the many DNA fragments that composed it, an essential step in producing the full sequence. Sequence annotation, including gene assignments – with all the complications attached to defining what a gene is – became a central preoccupation in the post-genomic era.[27] In this endeavor, the chromosomal maps created by cytogeneticists continued to serve as visual reference tools for genomic researchers and medical geneticists alike (Hogan, 2016, pp. 186–196).

[24] The agenda eventually embraced by the publicly funded HGP was to keep the sequence in the public domain. This was considered as ethically correct on the basis that the sequence was regarded as common human heritage (Sulston and Ferry, 2002). This did not preclude commercial exploitation of work building on the sequence information—a goal the open access policy even encouraged (Maxson Jones, Ankeny and Cook-Deegan, this issue).

[25] Interview with Frank Ruddle by Nathaniel Comfort, 4 December 1984, p. 34; http://ohhgp.pendari.com/Collection.aspx. On the technical contributions of somatic cell genetics to the human genome project and molecular biology more generally, see also Harris (1995, pp. 153–209).

[26] V. McKusick, Twenty-five years of Human Genome Meetings (HGMs): the past and the future (draft 1), 1 April 1998 [typescript], p. 6 and 10; box HGM98, file HX, Alan Mason Chesney Medical Archives, Johns Hopkins University.

[27] On the problems of defining what a gene is up to proposing the abolition of the term see Beurton et al. (2000) and Keller (2000).

Conclusions

In the late 1950s and 1960s – when molecular biologists were intent studying the mechanisms of DNA replication, protein synthesis and genetic regulation in simple model organisms – cytogeneticists expanded their techniques to work on human tissue samples. Their techniques found a place in clinical diagnostics, they were deployed in an ever expanding series of epidemiological studies and population screening programs and provided tools for the effort to construct a map of human genes. In this process, cytogeneticists were successful in pushing the boundaries of where genetic techniques mattered and in building up the necessary institutional and technical infrastructures. As molecular biologists extended their reach, they came to occupy some of the same territory. Yet what has often been described as the "molecularization" of cytogenetics could equally well be viewed as the turn of molecular biologists to human and medical genetics – a field long occupied by cytogeneticists.

Genetic engineering, together with DNA sequencing techniques, offered molecular biologists a new set of tools that made it possible to tackle questions of human heredity in the test tube. Funding opportunities and hopes for medical returns further encouraged molecular biologists to move from the entrenched work on model organisms to work on humans.[28] From the 1980s, molecular and later genomic techniques started to make an impact on human gene mapping and the development of diagnostic tests. In some areas, like for instance in prenatal testing, molecular tests have started replacing cytogenetic testing, but this is not a zero-sum game and there are resistances.[29] In other areas, like for instance in cancer diagnostics, cytogenetic testing is not only resisting but also making a comeback. The DNA changes in

[28] This move could be controversial as for instance in the case of the Max Planck Institute for Molecular Genetics in Berlin. The institute was founded in the mid-1960s with the explicit intention of marking a clear break with its predecessor, the Max Planck Institute for Comparative Genetics and Hereditary Pathology that traced its origins to the deeply tainted Kaiser Wilhelm Institute for Anthropology, Human Genetics and Eugenics. For this aim in mind, research in the new institute was to be based exclusively on the study of cells, viruses and bacteria, without any application to human genetics. This policy remained in place until the mid-1990s when, after a highly polarized debate, a re-orientation of the institute towards the analysis of human and other genomes, disease causation and medical treatments was agreed (Sachse, 2011; Sperling, 2014; Trautner, 2014) as well as "Max Planck Institute for Molecular Genetics—history", http://www.molgen.mpg.de/3498/Geschichte; accessed 29 August 2014.

[29] On the resistances to the introduction of molecular tests and the persistence of cytogenetic techniques in prenatal diagnosis, see Turrini (2014).

cancer chromosomes are too complicated and unstable to be studied with standard molecular techniques. This leads to the seemingly ironic situation that in clinical practice today, molecular geneticists perform the routine genetic diagnoses while cytogeneticists are entrusted with the complicated analyses of somatic cancer cells.

More generally, many of the population-scale genetic initiatives launched parallel to and in the wake of the HGP seem to have correlates in projects pursued by cytogeneticists in earlier decades. Sometimes, as in the case of the Human Genome Diversity Project mentioned before, there are direct biographical or historical links between the earlier and later endeavors. In other cases, the connections are more mediated. We can think here, for instance, of the UK Biobank initiative, started in 2006, that collects genetic, medical and life style information of 500,000 UK citizens. Not unlike in the case of the much more modest Registry of Abnormal Karyotypes the aim is to make correlations between genetic and environmental risk factors and disease patterns. Other examples, both launched in 2015, are the "BabySeq Project: Genomic Sequencing for Childhood Risk and Newborn Illness", funded by the U.S. National Institute of Child Health and Human Development and the NHGRI, and the "1000 Genome Project", an international project to study human genetic variation and identify candidate genes for genetic diseases. Technical, structural and ethical conditions have changed even if some basic questions that troubled cytogeneticists as, for instance, which genetic information is meaningful persist. To understand these changes and the drivers of current population projects we need to expand the historiographical scope of our analyses. Only by considering the whole spectrum of genetic practices that were pursued side by side since the 1950s can we understand the rise of the HGP and build the archives for future historians, policy makers and everyone interested in the goals and contours of current genomic practices. This includes securing the archives of human and medical geneticists next to those of molecular biologists and genomic researchers and reading them in tandem.[30]. Digital platforms that can create cross-links between different archival holdings are facilitating the task.

[30] For an important effort in this direction see the Wellcome Library digital collection "Codebreakers" that next to the archives of molecular biologists also contains the archives of several human and medical geneticists; "Codebreakers: Makers of modern genetics. Digitised archives," http://wellcomelibrary.org/collections/digital-collections/makers-of-modern-genetics/digitised-archives/. Accessed 30 April, 2017. On securing the archives of human and medical geneticists see also Harper (2009).

Acknowledgements

I wish to thank Christopher Donohue for the invitation to participate at the workshop Capturing the History of Genomics in Bethesda, MD in April 2015 and providing the brief for the talk on which this article is based as well as for facilitating access to the archival and digitized materials at the National Human Genome Research Institute Archive. Thank you also to the other participants of the meeting for vigorous discussion and to the incisive comments of two anonymous referees that helped give the essay its final shape. Research for the larger project on which this essay is based was supported by a Scholar Award from the National Science Foundation (No. 1534814, 2015–17).

References

Barnicot, N. A. and P. J. Travers. 1963. Comparison of the human karyotype in various populations. In *Proceedings of the Second International Congress of Human Genetics, Rome, September 6–12, 1961, volume II*. Rome: Istituto G. Mendel, pp. 1164–1166.

Beatty, J. 2000. "Origins of the U.S. Human Genome Project: Changing Relationships Between Genetics and National Security." P. R. Sloan (ed.), *Controlling Our Destinies: Historical, Philosophical, Ethical, and Theological Perspectives on the Human Genome Project*. Notre Dame, Indiana: University of Notre Dame Press.

Beckwith, J. and King, J. 1974. "The XYY Syndrome: A Dangerous Myth." *New Scientist* 64: 474–476.

Bell, J. and Haldane, J. B. S. 1937. "Blindness and Haemophilia in Man." *Proceedings of the Royal Society of London B* 123: 119–150.

Beurton, P. J., Falk, R. and Rheinberger, H.-J. (eds.). 2000. *The Concept of the Gene in Development and Evolution: Historical and Epistemological Perspectives*. Cambridge: Cambridge University Press.

Bostanci, A. 2004. "Sequencing Human Genomes." J.-P. Gaudillère and H.-J. Rheinberger (eds.), *From Molecular Genetics to Genomics: The Mapping Cultures of Twentieth-Century Genetics*. London: Routledge, pp. 158–179.

Campos, L. 2008. Genetics Without Genes: Blakeslee, Datura, and 'Chromosomal Mutations'. *A Cultural History of Heredity IV: Heredity in the Century of the Gene. Preprints of the Max-Planck Institute for the History of Science, No 343*. Berlin: Max Planck Institute for the History of Science, pp. 243–258.

Cavalli-Sforza, L. et al. 1969. Studies on African Pygmies. I. "A Pilot Investigation of Babinga Pygmies in the Central African Republic (With an Analysis of Genetic Distances)." *American Journal of Human Genetics* 21(3): 252–74. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1706414/.

Cavalli-Sforza, L. L., et al. 1991. "Call for a Worldwide Survey of Human Diversity: A Vanishing Opportunity for the Human Genome Project." *Genomics* 11: 490–491.

Chandra, H. S. and Hungerford, D. A. 1966. "Chromosome Studies of Todas of Southern India." *Human Biology* 38: 194–198.

Cook-Deegan, R. 1994. *The Gene Wars: Science, Politics, and the Human Genome*. New York and London: Norton & Co.

Court Brown, W. M. and Doll, R. 1956. "Appendix B: Leukaemia and Aplastic Anaemia in Patients Treated with X-rays for Ankylosing Spondylitis." In *The Hazards to Man of Nuclear and Allied Radiations*, Medical Research Council. London: Her Majesty's Stationery Office. Cmd 9780, pp. 87–89.

Court Brown, W., Harnden, D., MacLean, N. and Mantle, D. 1964. *Abnormalities of the Sex Chromosome Complement in Man*. Privy Council Medical Research Council Special Report Series No. 305. London: Her Majesty's Stationery Office.

Curry, H. A. 2010. "Making Marigolds: Colchicine, Mutation Breeding, and Ornamental Horticulture, 1937–1950." L. Campos and A. von Schwerin (eds.), *Making Mutations: Objects, Practices, Contexts. Preprint 393*. Berlin: Max Planck Institute for the History of Science, pp. 259–284.

—— 2016. Evolution Made to Order: Plant Breeding and Technological Innovation in Twentieth-Century America. Chicago: University of Chicago Press.

de Chadarevian, S. Forthcoming. *Heredity Under the Microscope*.

—— 2010. "Mutations in the Atomic Age." L. Campos and A. V. Schwerin (eds.) *Making Mutations: Objects, Practices, Contexts*. Berlin: Max Planck Institute for the History of Science. Preprint 393, pp. 179–188.

—— 2015a. "Chromosome Photography and the Recount of Human Chromosomes." *Historical Studies in Natural Sciences* 45: 115–146.

—— 2015b. "Human Population Studies and the World Health Organization." *Dynamis* 35: 359–388.

Editorial. 1959. "The Chromosomes of Man." *Lancet* 273(7075): 715–716.

Ferguson-Smith, M. A. 1993. "From Chromosome Number to Chromosome Map: The Contribution of Human Cytogenetics to Genome Mapping." A. Sumner and A. Chandley (eds.) *Chromosomes Today*, 11 vols. London: Chapman & Hall, pp. 3–19.

Ford, C. and Hamerton, J. 1956. "The Chromosomes of Man." *Nature* 178: 1010–1023.

Fortun, M. A. 1999. "Projecting Speed Genomics." M. Fortun and E. Mendelsohn (eds.) *The Practices of Human Genetics*, vol. 21. Sociology of the Sciences Yearbook. Dordrecht: Kluwer, pp. 25–48.

Gaudillière, J.-P. 2000. "Whose Work Shall We Trust? Geneticists, Pediatrics, and Hereditary Diseases in Postwar France." P. Sloan (ed.), *Controlling Our Destinies:*

Historical, Philosophical, Ethical, and Theological Perspectives on the Human Genome Project. Notre Dame: University of Notre Dame Press, pp. 17–46.

Green, J. 1985. "Media Sensationalisation and Science: The Case of the Criminal Chromosome." T. Shinn and R. Whitley (eds.), *Expository Science: Forms and Functions of Popularisation*. Boston: D. Reidel, pp. 139–161.

Haldane, J. B. S. 1936. "A Provisional Map of a Human Chromosome." *Nature* 137: 398–400.

—— 1948. "The Formal Genetics of Man." *Proceeding of the Royal Society of London B* 153: 147–170.

Hamerton, J. L. 1975. "Human Cytogenetic Registries." *Humangenetik* 29: 177–181.

Harman, O. S. 2004. *The Man Who Invented the Chromosome: A Life of Cyril Darlington*. London: Harvard University Press.

Harper, P. S. 2006. *First Years of Human Chromosomes: The Beginning of Human Cytogenetics*. Bloxham: Scion Publishing.

Harris, H. 1995. *The Cells of the Body: A History of Somatic Cell Genetics*. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Hilgartner, S. 2013. "Constituting Large-Scale Biology: Building a Regime of Governance in the Early Years of the Human Genome Project." *BioSocieties* 8: 397–416.

Hogan, A. J. 2016. *Life Histories of Genetic Disease: Patterns and Prevention in Postwar Medical Genetics*. Baltimore, MD: Johns Hopkins University Press.

Hsu, T. 1979. *Human and Mammalian Cytogenetics: An Historical Perspective*. New York: Springer.

Hungerford, D. A. 1978. "Some Early Studies of Human Chromosomes, 1879–1955." *Cytogenetics and Cell Genetics* 20: 1–11.

Hungerford, D. A. et al. 1969. "Chromosome Studies of the Ainu Population of Hokkaido." *Cytogenetics* 8: 74–79.

Hungerford, D. A., Giles, E. and Creech, C. G. 1965. "Chromosome Studies of Eastern New Guinea Natives." *Current Anthropology* 6: 109–110.

Jensen, A. 1969. "How Much Can We Boost IQ and School Achievement?" *Harvard Educational Review* 39: 1–123.

Judson, H. F. 1992. "A History of the Science and Technology Behind Gene Mapping and Sequencing." D. J. Kevles and L. Hood (eds.), *The Code of Codes: Scientific and Social Issues in the Human Genome Project*. Cambridge, MA: Harvard University Press, pp. 37–80.

Keller, E. 2000. *The Century of the Gene*. Cambridge, MA: Harvard University Press.

Kevles, D. J. 1992. "Out of Eugenics: The Historical Politics of the Human Genome Project." D. J. Kevles and L. Hood (eds.), *The Code of Codes: Scientific and Social Issues in the Human Genome Project*. Cambridge, MA: Harvard University Press, pp. 3–36.

—— 1995. *In the Name of Eugenics: Genetics and the Uses of Human Heredity. With a New Preface by the Author*. New York: Harvard University Press.

Kottler, M. J. 1974. "From 48 to 46: Cytological Technique, Preconception, and the Counting of Human Chromosomes." *Bulletin of the History of Medicine* 48: 465–502.

Kowal, E. and Radin, J. 2015. "Indigenous Biospecimen Collections and the Cryopolitics of Frozen Life." *Journal of Sociology* 51(1): 63–80.

Lima-de-Faria, A. 2003. *One Hundred Years of Chromosome Research and What Remains to be Learned*. Dordrecht and Boston: Kluwer Academic Publishers.

Lindee, M. S. 2005. *Moments of Truth in Genetics and Medicine*. Baltimore: Johns Hopkins University.

Lipphardt, V. 2012. "Isolates and Crosses in Human Population Genetics; or, a Contextualization of German Race Science." *Current Anthropology* 53(Supplement 5): S69–S82.

M'Charek, A. 2005. *The Human Genome Diversity Project: An Ethnography of Scientific Practice*. Cambridge: Cambridge University Press.

Martin, A. 2004. "Can't Any Body Count? Counting as an Epistemic Theme in the History of Human Chromosomes." *Social Studies of Science* 34: 923–948.

Mazumdar, P. M. 1992. *Eugenics, Human Genetics and Human Failings: The Eugenics Society, Its Sources and Its Critics in Britain*. London and New York: Routledge.

McElheny, V. K. 2010. *Drawing the Map of Life: Inside the Human Genome Project*. New York: Basic Books.

McGovern, M. 2014. "The London/Baltimore Link has been Severed": The Economies of Human Gene Mapping and Mainframe Computing at the Moore Clinic, 1955–1973. MPhil dissertation. Cambridge: University of Cambridge.

McKusick, V. A. 1966. "Computers in Research in Human Genetics." *Journal of Chronic Diseases* 19: 427–441.

—— 1982. "The Human Genome Through the Eyes of a Clinical Geneticist." Human Gene Mapping 6: Oslo Conference (1981), Sixth International Workshop on Human Gene Mapping. *Cytogenetics and Cell Genetics* 32: 7–23.

McKusick, V. and Ruddle, F. H. 1987. "Editorial: A New Discipline, a New Name, a New Journal." *Genomics* 1: 1–2.

Miller, O., Allderdice, D., Miller, W. Breg, and Migeon, B. 1971. "Human Thymidine Kinase Gene Locus: Assignment to Chromosome 17 in a Hybrid of Man and Mouse Cells." *Science* 173: 244–245.

National Research Council (US) Committee on Mapping and Sequencing the Human Genome. 1988. *Mapping and Sequencing the Human Genome*. Washington, DC: National Academies Press.

New Haven Conference. 1973. "First International Workshop on Human Gene Mapping. 1974." *Cytogenetics and Cell Genetics* 13: 1–216.

Nowell, P. and Hungerford, D. 1960. "Chromosome Studies on Normal and Leukemic Human Leukocytes." *Journal of the National Cancer Institute* 25: 85–93.

Polani, P. E. 1997. "Human and Clinical Cytogenetics: Origins, Evolution and Impact." *European Journal of Human Genetics* 5: 117–128.

Radin, J. 2013. "Latent Life: Concepts and Practices of Tissue Preservation in the International Biological Program." *Social Studies of Science* 43: 483–508.

—— 2014. "Unfolding Epidemiological Stories: How the WHO Made Frozen Blood a Flexible Resource for the Future." *Studies in History and Philosophy of the Biological and Biomedical Sciences* 47A: 62–73.

—— 2017. *Life on Ice: A History of New Uses for Cold Blood*. Chicago: University of Chicago Press.

Radin, J. and Kowal, E. 2015. "Indigenous Blood and Ethical Regimes in the United States and Australia Since the 1960s." *American Ethnologist* 42(4): 749–765.

Rapp, R. 1999. *Testing Women, Testing the Fetus: The Social Impact of Amniocentesis in America*. New York; London: Routledge.

Ratcliffe, S. G. 1986. Introduction. *Birth Defects: Original Article Series* 22(3): xii–xv.

Reardon, J. 2004. *Race to the Finish: Identity and Governance in the Age of Genomics*. Princeton: Princeton University Press.

Richardson, S. S. 2013. *Sex Itself: The Search for Male and Female in the Human Genome*. Chicago: University of Chicago Press.

Ruddle, F. H. and Kidd, K. K. 1989. "The Human Gene Mapping Workshops in transition." Human gene mapping 10: New Haven Conference (1989), Update to the Ninth International Workshop on Human Gene Mapping. *Cytogenetics and Cell Genetics* 51: 1–2.

Sachse, C. 2011. "Ein 'als Neugründung zu deutender Beschluss'.: Vom Kaiser-Wilhelm Institut für Anthropologie, menschliche Erblehre und Eugenik zum Max-Planck-Institut für molekulare Genetik." *Medizinhistorisches Journal* 46 (2011): 24–50.

Santesmases, M. Jesús. 2013. "Cereals, Chromosomes and Colchicine: Crop Varieties at the Estación Experimental Aula Dei and Human Cytogenetics, 1948–1958." B. Gausemeier, S. Müller-Wille, and E. Ramsden (eds.), *Human Heredity in the Twentieth Century*. London: Pickering and Chatto, pp. 127–140.

Schwartz Cowan, R. 2008. *Heredity and Hope: The Case for Genetic Screening*. Cambridge, MA: Harvard University Press.

Shaw, J. 2016. "Documenting Genomics: Applying Archival Theory to Preserving the Records of the Human Genome Project." *Studies in History and Philosophy of Biological and Biomedical Sciences* 55: 61–69.

Sperling, K. 2014. "50 Jahre Max-Planck-Institut für molekulare Genetik- Die Wende zur Humangenetik." M. Vingron (ed.), *Gene und Menschen: 50 Jahre Forschung am Max-Planck-Institut für molekulare Genetik*. Berlin: Max-Planck-Institut für molekulare Genetik, pp. 76–87.

Stern, A. M. 2012. *Telling Genes: The Story of Genetic Counseling in America*. Baltimore: Johns Hopkins University Press.

Sulston, J. and Ferry, G. 2002. *The Common Thread: A Story of Science, Politics, Ethics and the Human Genome Project*. London: Bantam Press.

The Hastings Center. 1980. Special Supplement: The XYY Controversy: Researching Violence and Genetics. *The Hastings Center Report* 10(4), 4 August, *Special Supplement: The XYY Controversy: Researching Violence and Genetics*. The Hastings Center Report - Special Supplement.

Tjio, J. H. and Levan, A. 1956. "The Chromosome Number of Man." *Hereditas* 42: 1–6.

Trautner, T. A. 2014. "Ich hätte mir gar nichts anderes vorstellen können." M. Vingron (ed.), *Gene und Menschen: 50 Jahre Forschung am Max-Planck-Institut für molekulare Genetik*. Berlin: Max-Planck-Institut für molekulare Genetik, pp. 62–71.

Turrini, M. 2014. "The Controversial Molecular Turn in Prenatal Diagnosis: CGH-Array Clinical Approaches and Biomedical Platforms." *Tecnoscienza - Italian Journal of Science & Technology Studies* 5: 115–139.

Ventura Santos, R. 2002. "Indigenous People, Postcolonial Contexts and Genomic Research in the Late Twentieth Century: A View from Amozonia (1960–2000)." *Critique of Anthropology* 22: 81–104.