

genomic states affect the topological organization of chromosomes. Exciting progress has been made recently in mapping the three-dimensional (3D) chromatin architecture. Growing evidence suggests that long-range chromatin interactions are crucial for transcriptional regulation and genome rearrangement, for example, in cancer cells. Ten years ago, the linear composition of the genome was spelled out; I anticipate that in the next 5 to 10 years, we will be able to reveal the 3D topographic map of the human genome within cells, which will help us uncover new insights into development, as well as into the basis for disease.

The Meaning of the Human Genome Project for Neuropsychiatric Disorders

Steven E. Hyman

Provost, Harvard University and Professor of Neurobiology, Harvard Medical School Boston, MA, USA

The past 3 years have witnessed a series of replicable, credible, and increasingly useful genetic discoveries in autism, schizophrenia, and bipolar disorder. I cannot emphasize enough the significance of this progress. Neuropsychiatric disorders are outsized contributors to global disease burden, yet treatment development has reached a near standstill. The problem is that the brain, with its myriad cell types and complex circuitry, represents such a difficult scientific frontier. Because genes play powerful roles in neuropsychiatric disorders, identification of causal variation could provide invaluable clues to their pathogenesis. Sadly, the genetic architecture of neuropsychiatric disorders is fiendishly complex, but unlike other areas of medicine wrestling with genetic complexity, psychiatry lacks objective phenotypic markers.

When I became director of the National Institute of Mental Health (NIMH), NIH, in 1996, I did not foresee quite how complex the genetics would prove, but did recognize that the contemporary technologies were overmatched. (I ruefully joked that I had the only institute with no low-hanging Mendelian fruit to pluck.) With expert advice, I decided that the only rational approach was to amass large collections of patient DNAs with extensive phenotype information. Some investigators resisted sharing of samples, but for most, that day has long passed. I am pleased that these NIMH collections have proven useful, albeit as only a small fraction of the needed sample sizes.

It was not, of course, the first human sequence per se that turned the tide for neuropsychiatric disorders. As for much of medicine, the associated technologies and analytic approaches (above all, the availability of

ever cheaper and more accurate DNA sequencing) are proving decisive. These advances have given investigators, clinicians, and patients hope that genetics will finally yield tools that neurobiologists have dreamt of to study the brain in health and in illness.

A Healthy Son

Mary-Claire King

Professor of Genome Sciences and of Medicine (Medical Genetics) University of Washington, Seattle, WA, USA

Gutenberg must have felt like this: the sense of endless possibilities, of infinite applications exploiting the new technology, of the world having changed forever. It seems audacious, but is, I think, correct, to compare his time to ours. I offer a single case study to explain.

K is the youngest of eight siblings. Three of her five brothers were severely developmentally delayed, with cognitive impairment and intractable behavioral disorders. No one else in their large extended family was affected. The most likely explanation for her brothers' condition was X-linked inheritance following a new mutation in their mother. Fragile X was excluded, and the critical gene had eluded detection. The region of the X-chromosome shared by the three affected brothers was 40 megabases, too long to enable prenatal diagnosis.

K despaired of having a healthy son. Then early last spring, targeted X-exome sequencing of constitutional DNA from the affected brothers revealed a nonsense mutation in a gene known to be implicated in mental retardation. The mutation had not been detectable by conventional technologies but was transparent to massively parallel sequencing. K carried the mutant allele. Armed with knowledge of the mutation, K and her husband undertook pregestational diagnosis (PGD), which involves in vitro fertilization of their egg and sperm, then genotyping of embryos via the polar bodies, and implanting a normal embryo in the mother's uterus. In experienced hands, PGD works very well. K and her husband have a healthy newborn son.

Genetics is a way of thinking. Genomics is a set of tools. If we think rigorously about genetics and use these tools well, the resolution of inherited disorders on behalf of our patients will be bounded only by our imaginations. One healthy infant at a time is not a bad way to begin.

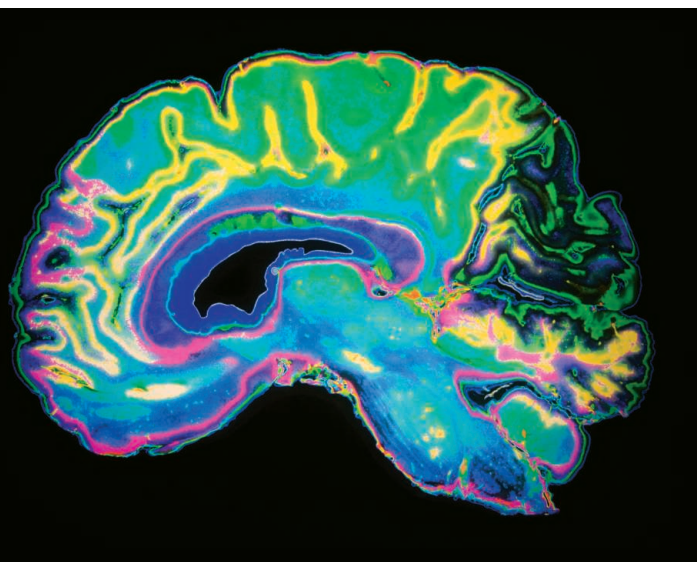
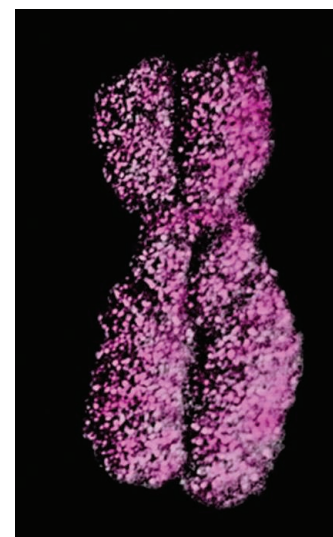
Socializing Genetic Diseases

Vololona Rabeharisoa

Professor of Sociology, Centre de sociologie de l'innovation, MINES ParisTech, Paris, France

The sequencing of the human genome has been a major scientific adventure of the late 20th and early 21st centuries. It has played a decisive role in the development of biomedicine and has led to numerous partnerships between researchers, clinicians, and the pharmaceutical and biotech industries.

Patient organizations have also been involved in these partnerships from the very beginning. In France, for instance, the French muscular dystrophy organization, the AFM (Association Française Contre les Myopathies), is a classic example. To step up the struggle against neuromus-



CREDITS: (LEFT) HEMERA/THINKSTOCK; (RIGHT) EPHRAIM LEVY-LAHAD/SHARE ZEDEK MEDICAL CENTER, JERUSALEM

Downloaded from www.sciencemag.org on April 3, 2011



cular diseases, it created its own laboratory, Généthon, which published the first physical maps of the human genome and handed them over to the United Nations Educational, Scientific, and Cultural Organization (UNESCO) in 1993, as a heritage to humanity.

Numerous patient organizations concerned with rare diseases (80% of which are of genetic origin), national alliances, and a European umbrella organization (Eurordis—European Organization on Rare Diseases) have been created and have adopted and adapted this model of partnership with research and health institutions. The “Marche des Maladies Rares” (shown in the photo above) is an annual charity walk organized by the French Alliance on Rare Diseases. This collective mobilization is what led the European Union in 2009 to ask its member states to consider rare diseases a public health issue.

The fact that the complete genome sequences are now available has had effects on patient advocacy. First, from my observations in France, patient organizations have multiplied, notably because many genetic abnormalities (and not only genes) have been discovered. Second, thanks to knowledge derived from the sequencing of the complete genome, patient organizations are confronting the complexity of their diseases in their multiple, heterogeneous, and sometimes singular manifestations. As a consequence, the very definition and contours of the conditions they are concerned with sometimes become strategic elements in their self-descriptions. Third, because the same biological pathways might be involved in different conditions, patient organizations are considering cross-condition research subjects and issues.

What lessons can be learned from patient organizations’ active participation in genetic and now genomic research? First and foremost, it has shown lay people’s ability to engage in activities that were considered for a long time as the preserve of specialists. Second, patient organizations have made a crucial contribution to the socialization of genetic diseases. Through their involvement in research, they have fostered a strong sense of solidarity with patients whose diseases were, until recently, considered to be shameful defects that excluded them from a common humanity.

The Genome Dances

Liz Lerman

Liz Lerman Dance Exchange, Takoma Park, MD, USA

As the work to map the human genome was finishing, I began to contemplate a performance piece exploring some of the meanings inherent in genetic discovery. As often happens, my research endeavors yielded too much data, and I soon recognized that a dance about the human genome could be a dance about religion, capitalism, policy, race, population control, or a dozen other topics. But after exploring the subject for a year through encounters with scientists, I settled on a format that framed the surprising commonalities of art and science and ventured to use the medium of dance as a science delivery system, setting up three topics: aging, ancestry, and perfection. The dance eventually premiered in 2006 as *Ferocious Beauty: Genome*, a work combining live dance with video projections that capture the faces, voices, and moving bodies of some of our wonderful science collaborators.

So for me, having the genome in hand meant that scientists were ready to talk to an artist—an essential element in my ability to create this work. Amid sensationalistic speculations and Frankenstein scenarios, the geneticists, biologists, and ethicists I engaged seemed eager for a platform that would bring a personal voice, a sense of beauty and history, and a range of feeling to bear on this most human of topics. Audiences throughout North America have responded in kind: “I didn’t expect it to be so emotional.” “I didn’t realize how human scientists were.” “I expected to be confirmed in my hatred for science, but now I have to reconsider.” Along this path, I encountered amazing scientists pursuing knowledge with passion, creativity, and leaps of imagination that were akin to those of my own art-making colleagues. I found a commitment to embracing wide paradoxes, such as how we humans are both common and unique. I discovered both a profound interest in personal inquiry in the lab and a commitment to preparing the larger public to handle the outcome of all of this research. After 5 years of taking this dance to communities throughout North America, I have made many new friends in a field that is not so far from my own, although we have been trained to think we are separate.



CREDIT: (LEFT) DURAND FLORENCE/SIPA/NEWSCOM; (RIGHT) MICHAEL MAZZOLLA