GENOME-SEQUENCING ANNIVERSARY

A Celebration of the Genome, Part II

During the month of February, we are celebrating the 10th anniversary of the first publications of the human genome sequence. This week, the commentaries explore the impacts of sequence information on our understanding of ourselves, as well as look at future directions for research and medicine.

–Barbara R. Jasny and Laura M. Zahn

My Genome

Desmond Tutu

Archbishop Emeritus of Cape Town, South Africa

This is a monumental month for human genomics as we celebrate 10 years since the publications of the human genome. It is time to reflect on the advances that this endeavor has brought to mankind. The ability for scientists to generate a complete human genome sequence meant that, for the first time, an individual's entire genetic code could be read from beginning to end. For the first time, these amazing men and women could use the code to study disease, to make sense of inherited risks, and to assess how the body responds to medicines. These advances, however, were biased because the available information provided limited benefit to the African continent and the people of Southern Africa. I have been known to refer fondly to my country as the "Rainbow Nation," a land of wealth in its many diverse peoples and cultures. The majority of us have experienced many years of oppression, emerging as a free nation only in 1994. As a nation, however, we need to continue to fight against racial inequalities and socio-economic disparities on a daily basis. My participation in the Southern African Genome Project was a step in this direction, generating the first Southern African genome to be sequenced—exactly 9 years after the publication of the human genomes.

My reasoning was simple. Southern Africans are victims of many devastating diseases whose eradication requires immediate attention and international resources. My hope is that my genetic code may provide a voice for the region and serve as the starting point for a map of DNA variation significant for Southern African peoples, to be used for medical research efforts and effective design of medicines. I implore the scientific community to continue what I hope was just a first step to further medical research within the region.

Many may ask if I learned anything significant from having my genome sequenced. I was certainly not expecting anything dramatic. I have been blessed to be alive for 79 years; we have four beautiful, healthy children and seven gorgeous grandchildren. Wonderfully, I discovered that I was related to my fellow sequenced Southern African in this project, !Gubi, a Kalahari Bushman from Namibia. Meeting !Gubi and his wife Anna in Windhoek in February 2010 was for me a highlight of this project. Anna bore an uncanny resemblance to my mother. It was a truly uplifting experience to discover that I was genetically related to a long line of peaceful and gentle people that have trod the soils of Southern Africa for centuries.

My dream is that by including all peoples in understanding and reading the genetic code we will realize that all of us belong in one global family—that we are all brothers and sisters. Wow!

Genome Literacy

Emmanouil T. Dermitzakis

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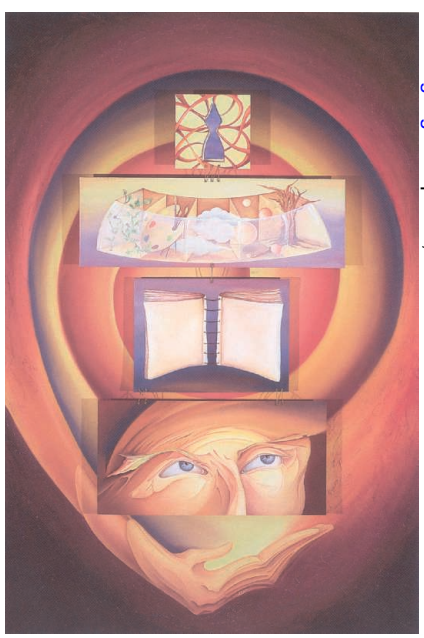

The transition from knowing small patches of the genome to having whole human genomes available to explore has been a unique experience. The biggest surprise initially came from the number of protein-coding genes—estimates anywhere from 15,000 to 160,000 had appeared in the literature before the publications came out in 2001 and settled at 20,000 to 30,000 genes. Although protein-coding genes were the most identifiable functional elements in the human genome, 10 years ago, the exact location of regulatory regions was unknown, and only a small fraction of the variations existing within the human population had been characterized. Ten years later, the ability to use the complete human genome backbone to map sequence variation and the availability of technologies to interrogate genome function are driving our ability to read the compendium of functional elements and to understand how population variation effects them. The basic components in each genome are largely the same, but the way they are used differs from tissue to tissue and person to person. Understanding the rules of gene regulation, the grammar of the genome, is key to the understanding of the human body. And it is only with the full sequence that we will

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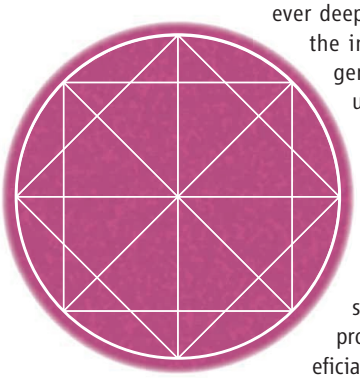
be able to learn the grammar of the genome. Each person's genome tells slightly different stories, and fascination comes with the discovery of the differences in those stories. To cite from the original papers: "The sequence is only the first level of understanding of the genome" and "Finally, it is has not escaped our notice that the more we learn about the human genome, the more there is to explore."

Personal Genomes: For One and for All

Jun Wang
Executive Director, Beijing Genome Institute

Thanks to immense technological improvements in the 10 years since the draft of the first human reference genome was published, we are now seeing the dawning of the personal genomics era. Breakthroughs in medical genomics and genomics-guided medicine allow ever deeper interpretation and application of the information contained in a personal genome. The accumulation of individual genomes with clearly documented phenotypes that are available for research significantly facilitates such breakthroughs and discoveries. This virtuous circle is likely to spin faster in the coming years.



Although the benefits of a personal genome for the owner are clear, profiling everyone's DNA is mutually beneficial, acting with a strong network effect. Human populations are largely phylogenetically related as a result of recent population explosion. Considering that any two of us have common ancestry back to a certain point, people nearly always share a significant fraction of genetic variation sites and allele types. Therefore, the health profile and personal genetic information of one individual will, to a certain extent, provide clues to better understand other's genomes and their medical implications. In this sense, a personal genome is not only for one, but also for all humanity.

The Landscape of Human Evolution

Pardis Sabeti
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In the pregenomic era, evolutionary genetics was a painstaking process. From observations of the natural world, scientists hypothesized instances of selection and sought confirmation on a case-by-case basis. As of 2000, only a handful of such cases had been identified. Technological and analytical advances in the past decade, however, have enabled us to progress from hypothesis-testing to hypothesis-generating science. Rather than examining single-candidate genes, we can scan the entire genome to identify variants under natural selection. In the initial phase of the postgenomic era, we have confirmed earlier hypotheses of evolution for malaria resistance, skin pigmentation, and lactose tolerance, and we have identified new adaptations for the formation of hair, resistance to trypanasomes, and response to high altitude. The challenge now is to uncover how hundreds of newly discovered candidate loci have shaped our evolution. In my laboratory's own recent scans, we identified more than 200 loci with strong evidence of selection. Of these, roughly half point to genes, and the other half point to large, intervening, noncoding RNAs (lincRNAs), other regulatory elements, and many yet-unknown regions. It is intriguing that whole new adaptive pathways are coming into view, such as those regulating sensory perception and thermoregulation in Asia, and metabolism and infectious disease in all populations. In the next decade, scientists can look forward to investigating these pathways and many other new hypotheses being generated through genome scans to uncover the vast landscape of human evolution.

My Genome, My Identity, My Health

Charmaine D. M. Royal
Associate Research Professor, Institute for Genome Sciences & Policy and Department of African and African American Studies, Duke University, Durham, NC, USA.

As a genetic counselor and human geneticist, I am in awe of the human genome—the nucleus of our field. Its potential to enlighten us about ourselves, our relationship to one another, and our place in the scheme of life makes it a distinctive reservoir for ground-breaking science and personal reflection.

Advances in genomics have taught us much about the biological underpinnings of disease. Nevertheless, the research itself is confirming that genome sequence does not tell the full story about human health and illness. Indeed, individual and group differences are the result of many variables. What is my socioeconomic status? Where do I live? Do I have supportive social networks? Access to health care? How do others perceive and treat me? Humans are so much more than a genome! If we truly want to decipher disease mechanisms and practice personalized medicine to achieve optimal health, we must adopt a more holistic approach.

Genomic research has also prompted new, and resurrected old, conversations about "race," ancestry, ethnicity, and identity. The findings that human genetic variation is primarily continuous and that living humans have not subdivided into biological races (subspecies) mean that

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the (mis)use of the term "race" to refer to the groups and populations of national censuses and various geographical origins should cease. There are groups, populations, and lineages—defined in a variety of ways—but no human races.

My enduring dream is that, over the next 10 years and beyond, there will be an upsurge in authentic and critical interdisciplinary and transdisciplinary biomedical research that breaks with previous paradigms of categorical thinking. In this dream, droves of biological, social, behavioral, and clinical scientists are stepping out of their silos, reaching across the corridors, transcending lip service—maximizing our capacity to understand and prevent disease and to enhance the quality of human life. Our moral obligations and scientific integrity demand it.

What Will Drive Genomics Over the Next 10 Years?

Arthur Caplan
Director, Center for Bioethics, University of Pennsylvania, Philadelphia, PA, USA.

When the announcement was made that teams led by Francis Collins and J. Craig Venter had jointly produced a rough map of the human genome, I was way in the back of a room crowded with a starry-eyed horde of media, NIH officials, representatives from the White House, and a variety of university and corporate scientists. I am fairly certain I was the only person at that press conference from the field of ethics. In the decade since the human genome map was published, efforts to apply that knowledge to human health have greatly and appropriately increased the presence of ethics in the world of human genomics.

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Efforts to move personalized risk-testing to the Internet and into pharmacies did quickly follow the publication of the map and the creation of better array-based technology. A variety of companies jumped on the "spitomics" bandwagon—encouraging individuals to spit in a cup in order to find out whether they were at risk for cancer, diabetes, and drug dependency; to gain insight into the identity of their forebears; or to find out if their kids were likely to have food allergies or become star athletes.

These activities met with little enthusiasm. The lack of standards about the accuracy and sensitivity of claims about genetic tests, the absence of serious efforts to ensure competent counseling, and indifference to simply having information about risk slowed the growth of interest in personal risk assessment.

Fear of repercussions has been an obstacle as well. Only in the past few years, with the enactment of the Genetic Information Nondiscrimination Act of 2008 and the Patient Protection and Affordable Care Act last year, has the requisite ethical and legal infrastructure for personal genetic risk analysis been created.

It is not the analysis of risk factors that shows the most immediate promise for human genomics but the application of genetic information to permit the safer and more efficacious use of drugs. Pharmacogenomics is poised to capture the promise of the discovery and publication of our genome. Cure, not diagnosis, is the value driving human genetics and is likely to do so into the future.

An Anniversary Party

Kári Stefánsson
President and CEO, deCode Genetics in Reykjavik, Iceland

The decision to sequence the human genome constituted an unparalleled commitment on behalf of humanity. Ten years ago, it was announced that the sequencing of the reference human genome had been completed. Although it could be argued that the decision to do this was somewhat arbitrary, it is a reason for us to throw an anniversary party in 2011. The sequencing had been going on for years, yielding data that empowered the field of human genetics to make discoveries as never before, and the sequencing has continued ever since. However, still today, we do not have "the complete sequence" of the reference human genome as parts (such as the centromeres or regions of copy number variation) are still incomplete. The suboptimal quality of the reference sequence is one of the limiting factors in the work of those who are using whole-genome sequencing to understand human biology. Hence, this is an anniversary of a moment in the history of our quest for an instrument (the reference sequence) to use in better understanding ourselves.

First Steps on a Long Road

Eric Schadt
Chief Scientific Officer, Pacific Biosciences of California, Menlo Park, CA, USA.

DNA variations and their interaction with diverse environmental pressures are how nature's fundamental forces shape nearly every facet of life. The first human genome sequence, published in 2001, provided a canonical reference from which to understand genome structure, as well as a registry of functional units. Before 2001, only a handful of examples of genetic risk factors existed for common human diseases. At present, thousands of genes that influence susceptibility to hundreds of disease-associated phenotypes have been identified. Today, with advanced, low-cost technologies, we have embarked on the characterization of genomic variation and associated gene networks. However, our understanding of complex phenotypes is far from complete. Knowledge of the human genome has led to a wave of discoveries (e.g., transgenerational epigenetic inheritance) that have shaken some of the foundations upon which biology is built. We have learned that the human genome is much more dynamic than previously thought. Elucidating its complexity will require a more systems-level approach, including comprehensive integration with other data dimensions, such as RNA, metabolite, protein, and clinical data. For me, although this past decade has exposed many amazing aspects of the genome, it has revealed the existence of a world about which we know very little. We will have to become masters of information if we ever hope to go from the big data sets coming to dominate biology to knowledge and to understanding.

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