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The Human Variome Project: Global Coordination in Data Sharing

Casimiro Vizzini

ONE way to address the global challenges of public health in developing countries is through international collaboration to share data. It's important to do this not just for humanitarian reasons but because open information is at the heart of scientific progress. One field in which this is particularly evident is genomic research, which has made revolutionary progress in recent years. Since the first genetic variation causing inherited disease (sickle-cell anemia) was defined at the protein level sixty years ago,[1] it has become possible to locate, isolate, sequence, and clone individual genes. Indeed, there has been an explosion in research to discover the function of each of the twenty thousand or so human genes.

Once the Human Genome Project—the international effort to map the genes present in the human genome—was completed, a new global project was launched in 2006 to share information about genetic variation in clinical practice. The Human Variome Project (HVP) acts as an umbrella organization, actively engaging with partners and stakeholders in each country to ensure that genetic variation information, generated during routine diagnostic and predictive testing, is collected and shared. The HVP is also instrumental in establishing and maintaining the standards, systems, and infrastructure that will embed the sharing of this knowledge in routine clinical practice.[2]

Carisimo Vizzini is an expert at the International Basic Sciences Programme of the United Nations Educational, Scientific and Cultural Organization.

The United Nations Educational, Scientific and Cultural Organization (UNESCO) serves as an important channel for the involvement of developing countries in the HVP, as it did during the Human Genome Project. One of the main goals of UNESCO is the development of international science that meets social needs in health, food, education, and other standards of living.

This goal has become increasingly relevant in the Post-2015 Development Agenda,[3] which aims to address these global challenges, including the burden of diseases on the performance and growth of many nations, particularly in developing countries where issues of public health are of major concern.[4] Formed at the end of World War II, UNESCO was one of numerous initiatives for international scientific cooperation undertaken by the nascent United Nations. These scientific cooperation initiatives were seen as diplomatic opportunities to promote collaborations among nations in hopes of fostering peace and development. The same sentiment is true today with the HVP, one of the latest efforts by UNESCO to promote collaboration.

The Variome and Data Sharing

The term "variome" refers to the sum of all the genetic variations found in different populations of the same species. The variome of the various populations of *Homo sapiens sapiens* is remarkably similar from one continent to another, suggesting that our species has evolved over the past ten thousand years from a small original gene pool.

Current methods of data sharing from research are suboptimal because they are greatly distributed across different databases. Yet, thanks to this research, we now know which genes are directly involved in some five thousand diseases.[5] What we do not yet understand, specifically for these diseases, and more broadly for all human disease, are the exact genetic changes in each gene that affect function and the changes that can be tolerated by the human body.

In order to increase our understanding of this fundamental question of biology, more research will need to be conducted. Additionally, more needs to be done to better share our current understanding of the way the human genome works. Every day researchers and clinicians are required to make decisions about genetic variants discovered in their patients and what those variants mean for the patient's health and wellbeing. Without ready access to the sum total of human knowledge about the specific variants being investigated, from both research studies and prior clinical cases, there is no way for doctors to properly diagnose and manage patients based on their genetic makeup. The lack of availability of, and access to, genetic variation information is still an impediment to diagnosis and treatment.

The Human Variome Project (HVP)

The looming need to collect and share human genetic data and the problems surrounding this was seen as far back as 1994 by a group of geneticists,

bioinformaticians, and scientists who met and established the Mutation Database Initiative under the auspices of the Human Genome Organisation (HUGO-MDI). This marked the beginning of the evolutionary pathway that eventually became the HVP. The HUGO-MDI was founded to encourage the creation of new locus-specific databases; it was successful enough that a small, but highly active, community of database curators was brought together. This community organized themselves into the Human Genome Variation Society (HGVS) in 2001 and soon began publishing recommendations on how to improve the quality of efforts to create databases of genetic variations.

One landmark achievement was the formalization on the now globally accepted HGVS nomenclature for the naming and describing of sequence variations. Richard Cotton, a world-renowned specialist in genetic variation from the University of Melbourne, was fundamental in the establishment and development of both the HUGO-MDI and HGVS, and he led the organizations for many years.

The early successes of the HUGO-MDI and HGVS highlighted the enormous challenges that need to be overcome to achieve the complete collection of information on all genetic variations from all countries. Motivated by the knowledge that collaboration across disciplines and cultures would be the only way to ensure enough data could be pooled to produce better and cheaper results for patients with genetic diseases, Cotton convened the HVP in 2006. The meeting was held in Melbourne, Australia, with financial support from Tony Abbott (the current Australian prime minister was the health minister at the time) and the Victorian government. It brought together leading geneticists, diagnosticians, researchers, and bioinformaticians from thirty countries, as well as representatives of UNESCO, the World Health Organization, the Organisation for Economic Co-operation and Development, and the European Commission.

The project sparked the immediate interest of those present, but the participants realized that to expand its global reach the project would need a formal structure and commitment at the governmental level. This led to the founding in 2010 of the Human Variome Project International Limited, a nonprofit Australian public company. The nonprofit would centralize coordination of the project. This structure allowed UNESCO to establish official relations with the organization in 2011 and to approach governments to ascertain their interest in the project—similar to the role UNESCO had fulfilled for the Human Genome Project in the late 1980s. Many governments, recognizing the benefits of global collaboration, reacted with enthusiasm to the potential of this new project in improving the diagnoses of diseases and patient care.

Unlike the Human Genetic Diversity Project, which is trying to work out the genetic differences among different ethnic populations, the HVP provides a central repository hub for genetic information with direct application to improving health. An editorial in *Nature Genetics*[6] describes the HVP as the successor to the Human Genome Project and pointed out the importance of this function: "much of the

necessary work is currently happening across the globe—but is just insufficiently coordinated."

The project aims to provide opportunities for training, education, and capacity building, especially in developing countries. The organization updates consortium members on its plans and progress through biennial meetings. At its fourth meeting in June 2012, hosted by UNESCO at its Paris headquarters in the framework of its International Basic Sciences Programme, the HVP's Project Roadmap to 2016 was presented.[7] Among its goals are the completion of high-quality gene- and disease-specific databases for at least three thousand genes by 2016 and a further five thousand genes, thus making it a total of eight thousand genes by 2022. The Project Roadmap also sets a target of forty countries—double the current total—sharing information with these international databases by 2016.

Sharing of genetic and genomic data, particularly when they are linked to patient clinical data, is almost always subject to local laws, regulations, and professional codes of practice. This makes developing a single standard approach to data collection, storage, access, and transfer almost impossible. Since public health issues transcend both domestic and international policies to encourage greater adoption of data-sharing practices while retaining local control over data and their use, the HVP works with stakeholders within individual countries, including national health systems, ministries of health, and national societies of human genetics, to establish what it calls HVP Country Nodes. An HVP Country Node acts as a national focal point for genomic data-sharing activities and has a specific role in connecting all the laboratories in a country that provide genetic testing services. Each node is managed and financed locally by a committee or organization that represents a sufficient number of national stakeholder groups, and the node enjoys the backing or support of the country's human genetics society or similar professional body.

So far, nodes have been established in twenty countries: Australia, Austria, Belgium, China, Cyprus, the Czech Republic, Egypt, Italy, Kuwait, Malaysia, Mexico, Nepal, the Netherlands, Nigeria, the Republic of Korea, Spain, the United Kingdom, the United States, Venezuela, and Vietnam. The HVP Country Nodes do not operate in isolation. As part of an international consortium, they are active in HVP activities, participating in the development of HVP Standards and Guidelines and sharing their knowledge and experience with other HVP Country Nodes. Continuing membership of the HVP Consortium and recognition as an HVP Country Node is at all times subject to the HVP Code of Conduct.

An HVP Country Node consists of three components. One is a repository or linked network of databases where information on a genetic variation within a country is collected and stored. This repository enables the sharing of the information both nationally and internationally. The second is a governance structure that ensures that the work of the node is both sustainable in the long term and consistent with all relevant national and international ethical, legal, and social

requirements and considerations. The third is a set of policies and procedures that ensures that the repository is operated and maintained in a responsible and accountable manner that is consistent with both national standards and the HVP's Standards and Guidelines.

Action in the third component is driven within the consortium by interest groups that are formed around broad topical areas, such as ethics, phenotype, and pathogenicity. Consortium members are divided into working groups around very narrow topics to produce standards and specify the systems and infrastructure required to address particular issues. This process is overseen by the HVP's International Scientific Advisory Committee, which leads the HVP in matters of strategic scientific direction for current and future activities. The committee is also responsible for managing the development and publication of all HVP Standards and Guidelines, as well as the arbitration of the dispute resolution process. Voting members of the committee are elected by the two advisory councils; one is the representative body for gene- and disease-specific databases and the other for HVP Country Nodes. Nodes in certain regions can assume a supporting, coordinating, and developing role for neighboring countries to become Regional Nodes.

The overall activities and the international management of the HVP are facilitated by the small staff of the International Coordinating Office. It is organized in a manner that ensures that the core scientific focus of the project is maintained, while retaining the necessary commercial and organizational skills to manage the project.

New Partners, New Frontiers

UNESCO is the only agency within the UN system that deals with fundamental science. Its unique combination of cultural and scientific interests makes it an ideal forum for interdisciplinary discussion and the promotion of understanding. By acting as a bridge among governments, governmental organizations, and nongovernmental agencies such as the HVP, UNESCO is able to facilitate effective international cooperation.

Through UNESCO, nations not currently involved in the HVP may gain access to it and ultimately make some contribution of their own. In its dealings with the HVP specifically, UNESCO provides a focal point for the exchange of data, technology, and samples relevant to genomic research and also for debate among scientists from different disciplines or from widely separated countries.

UNESCO's creation of the International Bioethics Committee, a body committed to ensuring respect for human dignity and freedom in the field of life sciences and its applications, with special attention to patient confidentiality, confers to the organization the legitimacy to work in such a sensitive field as the collection of genetic data. In working under UNESCO's umbrella, the HVP consequently is in compliance with the Universal Declaration on the Human Genome and Human

Rights,[8] the International Declaration on Human Genetic Data,[9] and the Universal Declaration on Bioethics and Human Rights.[10]

A tremendous step forward for the project took place in 2013 with the establishment of the HVP South East Asian Node. It represented significant recognition by Malaysian authorities that genetic and genomic healthcare is an important part of a well-developed health system, and it flagged their serious engagement with initiatives to provide these services to their citizens, as well as working closely within the region to address common challenges.

The launch of the HVP South East Asian Node was officiated by Tan Sri Muhyiddin Bin Yassin, Malaysia's deputy prime minister and minister for education, and Omar Osman, vice chancellor of Universiti Sains Malaysia. The node will assist Brunei, Malaysia, Singapore, Thailand, and Vietnam in their national efforts to share information on genetic variations in Southeast Asian populations among associated states and the rest of the world.

Nodes also are being developed in Portugal (by the Pediatric Hospital of Coimbra) and Brazil (by the University of São Paulo). UNESCO is working with both institutions to develop the HVP through the Community of Portuguese Language Countries formed by Angola, Brazil, Cape Verde, East Timor, Equatorial Guinea, Guinea-Bissau, Mozambique, Portugal, and São Tomé and Príncipe (known by its Portuguese acronym, CPLP, for Comunidade dos Países de Língua Portuguesa). The basic idea is to use the soft power of a common language as a diplomatic instrument to exchange science and technology across continents, fostering North-South and South-South cooperation. Recently, the Eduardo Mondlane University in Maputo, Mozambique, started discussions with UNESCO and the HVP to establish a country node.

The fifth biennial meeting of the HVP Consortium highlighted the diverse range of human genomics research projects being undertaken by African institutions and researchers involved in the Human Heredity and Health in Africa (H3Africa) initiative.

The projects presented ran the gamut of human genomics research from identifying the genetic variants involved in the development of diseases primarily affecting individuals of African descent to investigating the underlying genomic components of susceptibility to infectious diseases such as trypanosomiasis, or sleeping sickness. Researchers also reported on the development of a continent-spanning bioinformatics capability and a network of state-of-the-art biorepositories.

The Nigerian Country Node focal point, from the National Biotechnology Development Agency in Abuja, asserted that Africa now has the capacity to support the research that needs to be done and African scientists should be able to collaborate globally from Africa rather than subjecting the continent to further brain drain. He emphasized that the continent is now a fertile environment for science and technology development.

Challenges persist in the effort to expand the HVP in Africa, the Middle East, Asia, and Latin America, regions that need to be better represented in the HVP Consortium. Furthermore, HVP Standards and Guidelines for mutation detection methods, data collection, data curation, variation nomenclature, and genetic counseling must be applied in all the countries that join the consortium. That will mean ensuring that the infrastructure and working methods of the institutions in each of the countries that sets up a country (or regional) node would be of a level that complies with what is required in order to apply the standards and guidelines of the HVP.

There also is a need to dissipate any hesitation some scientists in the developed world may have regarding the social and political stability of countries in the developing world by familiarizing them with local conditions there.

To achieve both aims, exploratory missions have been held on-site by delegations consisting of UNESCO staff and members of the HVP's International Coordinating Office. Their goal is to establish preliminary contacts with local institutions and to discuss and negotiate the kind of interventions required *in loco*.

An accurate analysis of existing infrastructure and facilities and an open dialogue among scientists, both local and international, and local authorities has been key toward building confidence among all the stakeholders. Creating effective person-to-person communication centered on the exchange of information, ideas, and perspectives has made it possible to promote training and empowerment in developing countries and to establish a much more realistic picture of the local situation. In the process, some biased ideas, often based on misleading knowledge, have been eradicated.

Separately, national and regional issues needed to be addressed. National differences among the internal organizations of the scientific community have made a big difference in identifying the leading research group. Paradoxically, it is proving easier to proceed in countries that lack a national association of human genetics. In those countries, direct contact between permanent delegations and national commissions to UNESCO and central authorities, such as ministries of science and technology or national research institutions, typically leads to intervention at a national level that swiftly identifies an HVP focal point.

By contrast, in countries that have a national human genetics society, existing rivalries between different institutions have hindered the identification of a single national focal point. In those instances, after consultation with the central organization of the national society, missions to participate at the annual congress of the local association have been organized. UNESCO representatives presented the project to the governing body and led a process to reach consensus through participative meetings that included all the major national stakeholders in the field of human genetics. Conducting these collegial consultations has proved to be a successful strategy for UNESCO.

Once a country node is established at a national level, the challenge is to create regional awareness on the project in order to use the sharing of genetic information as a diplomatic instrument. Identifying a country that is able to play a leading role ended up being crucial in the leverage of interest at a regional level. The idea was to go through a detailed country analysis and geopolitical study of the region. The process needs to take into consideration several factors: the economic and financial condition, the political and societal landscape, the education level, and the quality of existing infrastructures, as well as some important cultural and historical elements and regional tensions. As an example, the use of the common language in the Community of Portuguese Language Countries was a successful idea to connect the scientific communities from countries across three continents and open the dialogue for a fruitful cooperation.

Ultimately, for the HVP to truly achieve its scientific aim of sharing data to promote better treatment and healthcare around the world, the nature of the work both requires and fosters diplomacy. To create more channels of communication among communities promoting free access to scientific information, to strengthen science education, and to shape international dialogue, the HVP relies on a diverse set of national and international partners. The close collaboration between the HVP and UNESCO ensures that the scientific efforts to understand human genetics fosters cooperation at the regional level, builds capacity at the national level, and addresses common challenges at the global level. SD

Endnotes

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