



HEREDITARY DISEASES PROGRAMME  
 DIVISION OF NONCOMMUNICABLE DISEASES AND HEALTH TECHNOLOGY

Pennsylvania, USA, 28-31 October 1992

THE HUMAN GENOME DIVERSITY PROJECT

Report of WHO Temporary Adviser

by

Professor E.K. Ginter  
 Research Centre for Medical Genetics  
 Russian Academy of Medical Sciences  
 Moscow  
 Russian Federation

Contents

	Page
1. Introduction . . . . .	2
2. General Idea of Human Genome Diversity Project . . . . .	2
3. Human Genome Diversity Project - First Workshop . . . . .	3
4. Human Genome Diversity Project - Second Workshop . . . . .	4
5. Human Genome Diversity Project - Third Workshop . . . . .	4
6. Concluding Remarks . . . . .	4

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced or translated, in part or in whole, but not for sale or use in conjunction with commercial purposes.

The views expressed in documents by named authors are solely the responsibility of those authors.

Ce document n'est pas une publication officielle de l'Organisation mondiale de la Santé (OMS) et tous les droits y afférents sont réservés par l'Organisation. S'il peut être commenté, résumé ou cité sans aucune restriction, il ne saurait cependant être reproduit ni traduit, partiellement ou en totalité, pour la vente ou à des fins commerciales.

Les opinions exprimées dans les documents par des auteurs cités nommément n'engagent que lesdits auteurs.

## 1. Introduction

The Human Genome Diversity Project is proposed as the further development of the Human Genome Project (HGP). It is well-known that HGP is designated to map, clone and finally to determine the entire nucleotide sequence of the DNA in human genome. The priority of the Project is to study the location and fine structure of functional genes, some of which being mutated give a pathological effect, and the control elements that influence the activity of functional genes. There was a strong criticism that the Human Genome thus determined will be a composite reference of DNA sequences that will not consider the genetic variation that is widely spread in human populations. As was mentioned, the part of this variation is represented by pathological mutations, the other part - by genes that are associated with common diseases. As a response to criticism, the Human Genome Organization recently appointed a committee to examine the possibility of establishing a Human Genome Diversity Project. This committee includes well-known population geneticists and anthropologists, L.L. Cavalli-Sforza, M.-C. King, K.M. Weiss, K.K. Kidd, M. Siniscalco, J. Bodmer and the President of HUGO, Sir Walter Bodmer, serving *ex officio*.

## 2. General Idea of Human Genome Diversity project

Understanding of genetic variation is very important for many problems of interest to medicine because the diagnosis of genetic diseases depends on the identification of specific mutations at loci whose functions are related to a given disease. It has become clear that mutations for a specific locus differ among populations. The mutations that cause PKU and cystic fibrosis in Asia are probably different from those in Europe. The same is true for almost all hereditary disorders, at least autosomal recessive ones. This pattern for rare diseases caused by single gene defect contrasts with the situation for common polymorphisms. The genetics of more common but also more complex diseases such as diabetes mellitus or neuropsychiatric disorders is still badly understood. We do not even know which loci (or how many) control such diseases, but it is possible that mutations (or normal polymorphisms) of different loci could be important in different populations. For example, susceptibility to diabetes mellitus could have a substantially different genetic basis in European populations and in Amerindians. But all these proposals need to be confirmed in the course of the Human Genome Diversity study.

Genetic variation is also very important for some anthropological problems such as: (1) genetic reflection of mating related social patterns, (2) reconstruction of human population relationships, origins and prehistory, (3) adaptation, and, (4) forensic anthropology and medicine.

All the studies outlined above depend on the analysis and understanding of genetic variation within the species on the level of genome and DNA variation.

The above-mentioned ad hoc committee was funded for a series of international workshops from a consortium of agencies including the National Institutes of Health, National Science Foundation, and the Department of Energy (in the USA), and additional support is being sought from agencies in Europe. These workshops have begun to formulate specific plans for how the HGD project should be organized. Initially, the problem is to rationalize the collection of genetic resources so that the data used for a variety of research questions can use common resources.

### 3. Human Genome Diversity Project - First Workshop

The first workshop was held in Stanford, California, 16-18 July 1992. It was focused on sampling strategies and analytic methods from population genetics. The topics discussed were sampling and population structure; analysis of population; drift versus natural selection; modelling migration and population subdivision. There was general agreement that the best way for the study of the human genome diversity is the collection and maintenance of a resource of cell lines and DNA samples from numerous individuals from populations all over the world that could be available to investigators worldwide. Immortalization has the advantage of making the material available almost indefinitely. Its disadvantages are that the procedure is expensive and the cells must be immortalized within a few days of collection. To collect and store the whole blood or DNA is easier, but it provides only a finite supply that can eventually be used up.

A major component of discussion centred around a desirable sample size from the groups whose cells were to be immortalized. Many population geneticists suggested that the samples as small as 25 unrelated individuals (corresponding to 50 autosomal genomes) per population could be extremely informative, especially for genome-wide problems, but of course this sample is insufficient to study the rare genetic variation such as mutations for rare recessive hereditary disorders. It has also been suggested that for a few selected populations, a larger number of cell lines could be established, including not only unrelated individuals but also some small nuclear families. The ability to study many loci made possible by the availability of immortalized cells more than compensate for the apparently small sample size.

It is proposed that a total of 10,000 individuals, 25 from each population, will be sampled for cell immortalization. This figure was assumed because it would require a somewhat modest total cost for the project. It follows that some 400 populations should be sampled which corresponds to about eight percent of the number of tribes, estimated approximately from the number of languages.

Samples for immortalization are to be transformed into cell lines with duplicates in two or three major cell banks. It is proposed that the project should encourage the development of laboratories in the countries in which the samples are collected and where the facilities for immortalization and testing did not exist but could be established.

During the first workshop some general criteria were determined concerning how the populations should be selected and questions to be studied. Among these were:

- a. How are the genes for disease susceptibility distributed within and between populations?
- b. What accounts for important genotype-phenotype relations and for genotype-by-environment interactions?
- c. What is the history of migration and population subdivision?
- d. What is the relative importance of random drift and selection?
- e. Is there a spatial patterning among populations?

#### 4. Human Genome Diversity Project - Second Workshop

The second workshop was held in the Pennsylvania State University, 28-31 October 1992. Biological anthropologists, archaeologists and geneticists, whose task was to identify sampling needs and priorities, such as populations in danger of disappearance, populations important for understanding the genetic history and diversity of modern huge populations, and some other problems of population sampling, participated in this meeting. All the main regions of the globe were under study: North, Central and South America, Northern Africa, Southern and Central Africa, Southwestern Asia and the Middle East, India and the Himalayan region, Southeast Asia, Australia and the Pacific, East Asia and the Arctic (including the Siberia region). It should be mentioned that there is a special Project of Human Genome Diversity for Europe, which had been proposed by 14 laboratories and that there is close contact between these two project organizers. Because of this work a list of populations in different continents with definite priorities was prepared. It includes approximately 400 populations with a short description of their history, linguistic characteristics, some genetic data and remarks about blood samples collections and other relevant data, including ethical and legal issues. It is to be expected that the chosen populations would represent the human genome diversity most adequately for the homosapiens as a species.

#### 5. Human Genome Diversity Project - Third Workshop

The third workshop will take place in 1993 in Europe to discuss the organizational, logistic, funding, ethical and other related issues.

#### 6. Concluding remarks

The initial planning phase of the HGD Project is intended to establish a worldwide set of population sampling priorities, and to consider the sample size and design to be used in assembling the cell and DNA resources. The drafts prepared during workshops will be circulated broadly as summaries that will be published. The final documents as it was proposed would include the responses to these publications and will consist of the framework for research around the world to apply to funding agencies and governments for financial support to collect and maintain the samples.

The HGD Project can make fundamental contributions to applied as well as basic knowledge about human genome, but it will depend upon future scientific programmes that will be based on enormous materials of established cell lines and DNA samples representing the principle genetic diversity of mankind.

The organizers of the project expressed their optimism that contacts between the Project and such International Organizations as UNESCO and WHO, and some others, could be of great value for the successful development of the Project.

#### 7. References

1. L. Roberts. Science, 1992, vol. 257, 1204-1205;
2. K.M. Weiss, K.K. Kidd and J.R. Kidd. Human Genome Diversity Project. Evolutionary Anthropology, 1992, 80-82.