Scientific limitations and ethical ramifications of a non-representative Human Genome Project: African American response

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ABSTRACT: The Human Genome Project (HGP) represents a massive merging of science and technology in the name of all humanity. While the disease aspects of HGP-generated data have received the greatest publicity and are the strongest rationale for the project, it should be remembered that the HGP has, as its goal the sequencing of all 100,000 human genes and the accurate depiction of the ancestral and functional relationships among these genes. The HGP will thus be constructing the molecular taxonomic norm for humanity. Currently the HGP genomic baseline is almost exclusively skewed toward North Atlantic European lineages through the extensive use of the Centre d’Études du Polymorphisme Humaine (CEPH) data set. More recently, the HGP has shifted to the use of volunteer donors since adequate informed consent had not been secured from the CEPH families. No evidence exists that either the CEPH families or the current volunteers are the most appropriate demographic or evolutionary lineages for the functional genomic studies that will guide production of new DNA based drugs, targeted therapeutics and gene-based diagnostics. The lack of scientific representativeness of the HGP is a serious impediment to its broad applicability. Yet this can be remedied, and five alternative sampling strategies are presented. In response to the current exclusionary design of the HGP, there is noteworthy caution and skepticism in the African American community concerning genetic studies. The Manifesto on Genomic Studies Among African Americans reflects both a desire to be systematically included in federally funded genomic studies and a desire to maintain some control over the interpretation and application of research results. Representative sampling in the HGP is seen as an international human rights issue with domestic ethical implications.
The Human Genome Project (HGP) is a massive molecular biology effort that aims to reflect the normal sequence for 100,000 genes and accurately depict the ancestral and functional affinities among these genes.\(^1\) On par with the Apollo Space Mission, the HGP has, among its aims, to construct genetic and physical maps of the human genome, determine the sequence of human DNA, and identify the complete set of human genes.\(^2\) Under the aegis of the Human Genome Project these efforts are proceeding very rapidly. Technological advances such as the application of automated DNA sequencing, improved sample handling, advanced bioinformatics and other innovations have greatly augmented data acquisition as has the recruitment of additional researchers devoting their most productive career years to genomic studies. Together, these technological and person-power initiatives have accelerated the rate of identification and description of important genomic sequences.

The rapid progress made in characterizing genes and mRNAs have accelerated the call to interface DNA mapping and sequencing data with protein information.\(^3\) The shift to studies of functional genomics is seen as the natural sequel to the earlier focus of the HGP on structural genomics. While structural genomics provides information on disease gene sequence and expression, functional genomics represents a new paradigm to elucidate gene function and genetic pathways. Since proteins orchestrate most cellular functions, establishing the “norm” and identifying abnormal proteins is a critical step toward the control of disease-associated genes. Rapid progress in the HGP has already stimulated many promising investigations into gene therapy and DNA diagnosis of human diseases through mutation or polymorphism analysis of disease-causing genes, resulting in an array of new DNA based drugs,\(^4\) targeted therapeutics, and gene-based diagnostics.\(^5\) Indeed, gene manipulation aimed at disease control was among the most consistent early visions offered to potential funders by HGP enthusiasts.

**HGP, the disease connection, and the goal of intervention applications**

HGP backers dazzled Congressional funders with the vision of identifying (and manipulating) disease genes of broad public health significance while providing an individualized approach to health care. The diseases most frequently suggested as benefitting from funding of the HGP were those cancers having a genetic basis. The identification of disease susceptibility and intervention remains a feasible and important goal. However, our current repertoire of disease genes and genetic polymorphisms in general is highly biased toward European patterns of diversity, especially those observed among North Atlantic European groups.\(^6\) No studies suggest that these polymorphisms were ever representative for all of humanity.

The HGP’s primary human database is derived from 10 to 15 people from the Centre d’Études du Polymorphisme Humaine (CEPH) families of North Atlantic European origins.\(^7\) Founded in 1984 by Nobel Prize winner Dr. Jean Dausset, the CEPH data set consists of established cell lines from large human families from Utah,