# Genomics and the Changing Profile of Human Disease

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## Introduction

Within the last decade, much has been written on the impending impact of the Human Genome Project on human health. A typical perspective was offered in 1995 as part of the submission of the Royal College of Physicians to the Science and Technology Committee of the U.K. House of Commons. In describing the future contribution of genetics to medical practice it was stated that, '*The process has scarcely begun and may not have a major clinical impact for many years; however it represents the change from empirical to rational management of disease and hence its significance can hardly be exaggerated'*. Clearly, any body of knowledge that could effect such a change would be of global importance, and if this and similar predictions prove to be correct, they would match in significance the revolution in medical practice provoked by the anatomical discoveries of the Renaissance period.

The Human Genome Project was initiated in 1991, and by 2001, the first consensus sequence of the human genome was simultaneously published by publicly supported researchers (International Human Genome Sequencing Consortium 2001) and the privately financed Celera Genomics (Venter *et al*. 2001). Access to the growing database on genome structure and function made available through the Human Genome Project has greatly assisted medical researchers, and as a result, by March 2003 over 14,000 single gene disorders affecting both the human nuclear and mitochondrial genomes had been identified (OMIM 2003).

Of itself, the recognition of specific and often very rare mutations is unlikely to change medical practice or to impinge on the everyday lives of the vast majority of the world's population. Data on the contribution of predisposing genes to common diseases is still rudimentary, and there is limited information on non-biological factors that influence the genetic structure of human populations and thereby govern the distribution and transmission of disease mutations. An appreciation of the importance of these topics has, however, gradually been emerging, accompanied by the establishment of two new academic disciplines, Community Genetics and Public Health Genetics. The aim of this article is to briefly review the potential influence and effects of these changes on the future profile of genetic disease in industrialized and developing countries.

## The prevalence of genetic disease in industrialized and developing countries

Preliminary evidence of a major change in the profile of human disease in industrialized countries was provided by a record-based study conducted in the U.K. at the Great Ormond Street Hospital for Children, London (Carter 1956). Genetic disorders had been diagnosed in 16.5% of childhood deaths in the hospital in 1914, but by 1954 this figure had risen to 37.5%. Over the same period, deaths described as 'environmental' had decreased from 68.0% of the

total to just 14.5%, reflecting the beneficial preventive effects of vaccination programmes for infectious diseases and the successful introduction of antibiotic therapy. This epidemiological transition was affecting all industrialized countries, and by the 1970s, the growing social and financial burden of childhood genetic disease had already become a source of concern in the U.S.A. (Hall *et al.* 1978).

Current estimates suggest that in the industrialized countries approximately 5% of individuals will exhibit symptoms of genetic disease by young adulthood. However, if congenital anomalies are included the prevalence increases to some 8% of all live births (Baird *et al.* 1988). Comparable data are not separately available for developing countries, but in global terms it has been suggested that at least 7.6 million children per year are born with a severe congenital or genetic disorder (Alwan and Modell 2003).

Because of the continuing importance of infectious disease and nutritional disorders in developing countries, it has been assumed that their burden of genetic disease is relatively unimportant. While it is undoubtedly true that in proportional terms genetic disorders are responsible for a minority of childhood disease diagnosed in developing countries, in many parts of the world up to 40% of the population are carriers of an inherited haemoglobin disorder (Livingstone 1967). Overall, this means that an estimated one in seven of the world's population are carriers of a gene either for thalassaemia or a haemoglobin variant (WHO 2002). In both types of disorder, individuals who have inherited the causative mutations from each parent commonly have severe anaemia, and the vast majority of these people are resident in tropical regions.

## Demography, population genetics and genetic disease

The social and demographic structures of populations play very significant roles in the distribution patterns of specific inherited disorders, albeit with marked differences between the industrialized and developing countries. For example, following the onset of the Industrial Revolution in Europe, there was widespread population movement from the countryside into the rapidly expanding towns and cities. These large-scale population changes resulted in the dissolution of historical local, regional and national boundaries, which in turn helped to exert a partial homogenizing effect on national gene pools. Likewise, through time, large-scale migration from Europe to the Americas and Australasia resulted in significant mixing of previously distinct populations (Bittles 2002a).

The situation is very different in most developing countries, where local and regional clan, tribal and ethnic groupings have largely remained intact. Thus in India, Pakistan and Bangladesh, which collectively account for more than 20% of the world's population, marriage continues to be arranged within caste and *biraderi* boundaries that probably date back some 3,000 years. In India alone, there are an estimated 50,000 to 60,000 separate endogamous communities (Gadgil *et al.* 1998). Furthermore, some 25% of the population of 1,050 million are members of the 1,600+ scheduled tribes and castes that exist outside the Hindu caste system (Bhasin *et al.* 1992), and a further 130 million persons are Muslim. In effect, each of these groupings, whether Hindu caste or non-caste, Muslim, Christian, Buddhist, Sikh, Jain or Parsi, form separate breeding pools. The net result is that while disease mutations of ancient origin may be distributed throughout the population, those which have arisen more recently may be restricted or even unique to individual ethnic groups, sub-castes, tribes or clans (Bittles 2002b).

Gene mutations can be rapidly transmitted and increase to high frequency via genetic drift within social, religious and geographical isolates of this type, especially in communities that are numerically small. Due to the restricted nature of their gene pools, there also is a high probability that by chance alone, couples who marry are biological relatives, an extreme example being the remote island of Tristan da Cunha in the South Atlantic, which was colonized in the early 19th century (Roberts 1992). In many developing countries, there also is a strong preference for consanguineous marriage, and so in North and Sub-Saharan Africa, the Middle East, West, Central and South Asia, 20% to over 50% of marital unions are intra-familial, most commonly contracted between first cousins (http://www.consang.net ; Bittles 2001).

## Community Genetics and Public Health Genetics

The influence of these various factors and the increasing contribution of genome-based information to health studies have led to the development of new, multidisciplinary approaches to the role of genetics in medicine. Community Genetics starts from a medical genetics/community medicine perspective and seeks to provide guidelines for the establishment and surveillance of programmes to prevent and control the adverse effects of human genetic disorders (Henneman *et al.* 2001). These programmes can variously be run at local, national and regional levels, and they emphasize strengthening the role of primary health care, integrating interventions into reproductive health programmes, and ensuring the feasibility and cost-effectiveness of preventive strategies (Alwan and Modell 1997). As its name suggests, Public Health Genetics derives from a broader public health background and aims to prevent mortality, morbidity and disability of genetic origin by integrating genome-based information into existing public health practice (Khoury *et al.* 2000; Beskow *et al.* 2001). The perceived remit of Public Health Genetics thus encompasses single locus disease genes, polygenic, multifactorial disorders, and pharmacogenomics, i.e. the interaction of genes with therapeutic agents.

Community Genetics has tended to concentrate on providing services to populations where genetic disorders are present at high frequency and on establishing community-specific care programmes. This includes communities in developing countries. By comparison, Public Health Genetics has been more concerned with providing solutions to the growing genetic problems faced by the populations of industrialized countries and calls on the services of a wider range of non-clinical, health-related professionals, including groups such as anthropologists, lawyers and social workers. Both disciplines are dependent on population- and subpopulation-based studies, and they also share a strong emphasis on the need for informed public consultation and the development of rigorous ethical guidelines.

The sharp community-based subdivisions characteristic of most developing countries can effectively delineate the distribution and frequency of specific disorders, ranging from inherited anaemias (de Silva *et al.* 2000), to cancers (Shanmugaratnam *et al.* 1989), and pre-disposition to major infectious diseases (Pitchappan 2002). Although data on regional origins are collected from patients in many of these countries, very limited attention has been paid to genetic differences between ethnic groups or specific communities. Where disorders are community-specific, this type of information is essential if efficient preventive programmes are to be introduced. However, any such information-gathering exercise has to be conducted with due caution and discretion, lest families or even entire communities become inadvertently stigmatized on the grounds that they carry a gene(s) for a particular genetic disorder (Bittles 2003b).

Similar problems stemming from inadequate definitions of ethnic subpopulations have been a major problem in the industrialized countries, with a common tendency to broadly refer to individuals as being of 'Maghrebian' or 'South Asian' origin. By ignoring the very marked genetic subdivisions that exist within these supra-regional categories, disease prevalence surveys may be of little practical relevance. There also has been over-emphasis on the adverse effects of consanguineous marriage, perhaps fuelled by historical suspicions of inbreeding in western countries (Bittles 2003a). This prejudice is commonly accompanied by a failure to recognize the potential effects of community endogamy and the outcomes of random inbreeding on the prevalence of genetic disorders.

## Discussion

The changing profile of human disease has been especially apparent in the countries of the Gulf region, where traditional tribal and clan endogamy and high levels of consanguineous marriage have resulted in the accumulation of specific disease mutations within individual communities (Teebi and Farag 1997). In previous generations, the adverse outcomes of these mutations would largely have been obscured by the high rates of infant mortality typical of developing countries. But since development of the oil and petrochemical industries within the region during the mid- to late 20$^{th}$ century and the introduction of high technology health care programmes, a wide range of genetic disorders has increasingly been diagnosed.

The financial and health infrastructure problems associated with genetic diseases have yet to fully emerge in developing countries. However, two examples illustrate their potential scale. In Pakistan 5,000+ infants with β–thalassaemia, an usually severe inherited form of anaemia, are born each year and require regular blood transfusions to survive. The yearly blood requirement of each annual birth cohort of affected children is 90,000 units of blood, with an associated cost per patient for chelation therapy to remove excess iron of US$4,400 (Ahmed *et al.* 2002). This compares with the annual GNP per person in Pakistan of US$1,860 (PRB 2002). In related terms, in Indonesia it has been estimated that the blood transfusion requirement for patients with severe forms of β–thalassaemia is now approaching 1.25 to 1.5 million units per year (WHO 2002). Demands of this nature will be extremely difficult to sustain, especially in developing countries where blood may be infected with a range of viruses and blood banking and testing facilities are limited, hence the central emphasis on disease prevention in Community Genetics programmes.

In fact, a similar if less acute scenario also applies in many industrialized countries, where β–thalassaemia mutations have been maintained in the gene pool of countries such as Italy and Greece as a historical protective response to the selective pressure of the malaria parasite *Plasmodium falciparum*. In Northern Europe, North America and Australasia, α- and β–thalassaemia mutations also may be present at high frequency within migrant communities from regions of the world where malaria was or remains endemic, once again placing major demands on supplies of blood for remedial transfusion.

Besides social and economic considerations, the growing changes in human disease profiles have exposed poor levels of understanding of genetic disorders among many clinicians in major industrialized countries (Baird 2001). This problem is even greater in developing countries, in part because genetic disease is still mistakenly considered to be of limited significance and accordingly, training in genetics is given low priority. As a result, the need for the formal

training of clinicians and non-clinical support staff and for effective public education programmes is all the more pressing in many less affluent countries (Verma and Bijarnia 2002).

Although genetics can be expected to contribute positively to future programmes for the maintenance of human health, and particularly to the prevention of currently intractable age-related disorders, these goals will not be achieved as a matter of course. There are major concerns that the principal targets for genomic research will be chosen primarily on commercial grounds rather than on the basis of need, and the patenting of disease mutations has served to heighten these suspicions. As a current example, the tactics employed in the marketing of BRCA1 mutation testing for breast cancer, the lack of ensured provision for pre-and post-test counselling, and the scale of charges involved all have been subject to strong criticism, but as yet to limited avail. Although these matters have so far principally affected the industrialized world, in developing countries there are worries that medical staff may be encouraged to adopt expensive therapeutic treatments when prevention would provide a more appropriate and low-cost, if less glamorous, alternative (Alwan and Modell 2003).

A recent World Health Organization publication proposed that the health rewards expected to flow from the commercial development of genomics should be equitably distributed between the industrialized and developing countries (WHO 2002). Recent experience would tend to suggest that while such altruistic behaviour would be welcomed by many, the proposal might not receive unreserved support from the companies concerned and their shareholders. In part, difficulties have arisen because of legal discrepancies between the countries and political and trade groupings most immediately concerned. It is also a fact of life that a highly focused and financially robust private company, with good international connections and offering substantial financial returns to potential backers, can act with a determination and dispatch that governmental agencies simply cannot match.

If genome- and proteome-based research is to proceed for the greater good of all, decisions as to the targets and directions of research, its timing, sources and extent of funding, and how outcome benefits can be efficiently and equitably distributed, require informed and non-partisan counsel. Manifestly, this is neither the realm nor the primary concern of commercial enterprises, and in recent years the governments of most industrialized countries have demonstrated a greatly diminished interest in tackling issues of this nature. It is, however, precisely the type of critical area where IUBS, ICSU and other representative international scientific and medical bodies are uniquely placed to act, given their ready access to the requisite cross-disciplinary, trans-national expertise. Far-sighted and principled decision-making on the future course of genomic research across the Biological Sciences is sorely needed. This is surely a task that merits the urgent attention of IUBS.

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