Genomic Med (2007) 1:3–7
DOI 10.1007/s11568-007-9003-8

EDITORIAL

# Genomic medicine: a new frontier of medicine in the twenty first century

**Dhavendra Kumar**

Received: 21 January 2007 / Accepted: 19 March 2007 / Published online: 24 April 2007


Although the concept of heredity has been in existence since ancient times, the science of genetics began to evolve only around 150 years ago. The Darwinian theory of evolution by natural selection made clear reference to hereditary factors that reflect at least some of the present-day concepts of the genetic basis of life. Mendel's laws of inheritance, and successive discoveries in various aspects of genetics, laid the foundation for a number of disciplines covering different areas within the modern science of genetics. The emergence of *human genetics* was no exception.

It has taken six decades since the recognition of DNA as the carrier of hereditary information to arrive at our present state in the science of genetics. The future now appears bright, opening up many new and challenging opportunities. During the last four decades, medical genetics has established itself covering clinical and laboratory diagnostic applications. The basis of medical genetics is grounded in a sound knowledge and understanding of principles governing 'human genetics'. Clinical genetics is now a recognized medical specialty among several disciplines comprising the current spectrum of modern medicine.

Fifty years after the discovery of the double-helical structure of the deoxyribonucleic acid [DNA] molecule (Watson and Crick 1953), the characterization of the virtually complete sequence and organization of the human genome was successfully accomplished (Lander et al. 2001; Venter et al. 2001). This major scientific achievement laid the foundation of 'human genomics'; that section of the biological sciences which studies variations, mutations and functions of genes and controlling regions, and their implications for human variation, health and disease. This is strengthened by developments in the other areas of genomics relating to micro-organisms, animals and plants.

The identification of all human genes and their regulatory regions provides the essential framework for understanding the molecular basis of disease. This advance has also provided a firm foundation for the future development of genomic technologies that can be applied to medical science. Rapid developments in global gene analysis, gene product analysis, medical bioinformatics, and targeted molecular genetic testing are destined to change the practice of medicine. However, many practicing clinicians perceive developments in genomics as primarily confined to the research arena with little clinical applicability. DNA/RNA-based methods of disease susceptibility screening, molecular-based disease diagnosis and prognosis, and genomics-based therapeutic choices and prediction of treatment outcome are some of the key areas that are likely to influence the practice of modern clinical medicine.

Undoubtedly, the science of genomics has tremendous potential for improving human health. The World Health Organization [WHO] has recently made several recommendations for the scope and application of genomics on global health (WHO 2002). It is acknowledged that the information generated by genomics will provide major benefits in the prevention, diagnosis and management of communicable and genetic diseases as well as other common medical diseases, including cardiovascular diseases, cancer, diabetes and mental illnesses (Cardon and Bell 2001). Together these constitute a major health burden, as reflected in chronic ill-health and mortality. In addition, a number of infectious diseases are associated with genomic mutations manifesting in the form of increased susceptibility, clinical severity, favorable and unfavorable response

D. Kumar (✉)
Institute of Medical Genetics, University Hospital of Wales, Cardiff University, Heath Park, CF14 4XN Cardiff, UK
e-mail: kumard1@cardiff.ac.uk

to anti-microbial therapy and in conferring protection. It is possible that the protective effect of a microbial vaccine might be influenced by genomic variation.

The sequence of the entire human genome is now virtually complete. Each person carries a distinct sequence. The variation among all humans is reflected in sequence polymorphisms scattered across the whole genome. The genomic variation between individuals together with environmental factors probably determines disease susceptibility and protection, and is important in drug efficacy and side effects (Holden 2000; Chakravati 2000). The key to genomic variation lies in deciphering single nucleotide polymorphisms [SNPs] and copy number variations [CNVs] and their use in studying disease mechanisms (Stephens et al. 2001). The mapping of the disease susceptibility loci depends upon the successful application of haplotype associations. This is strengthened by valuable data emerging from the International Haplotype Mapping [HapMap] and the Human Variome projects. This is likely to be promising in conducting clinical studies to find individuals in whom a drug is likely to be efficacious. The use of SNPs and CNVs in pharmacogenetics and pharmacogenomics is currently restricted to studying genes encoding drug-metabolizing enzymes, such as P450s, and variation in genes that encode drug receptor target proteins. The newly emerging dynamic field of pharmacogenomics is an exciting application of genomic variation in drug discovery and drug development.

Developments in human genomics or, to be precise, in medical genomics, will have a powerful impact on our understanding of pathogenesis and management of common medical diseases of complex etiology. The recent identification of a number of susceptibility genes for multifactorial diseases is encouraging. Examples include the identification of *NOD2* as a susceptibility gene for Crohn's disease, an inflammatory bowel disease [IBD] (Hugot et al. 2001 and Ogura et al. 2001). This is a major development in understanding the pathophysiology of IBD. Similar studies are likely to unravel the genetic mechanisms in other complex medical diseases. A comprehensive SNP map will allow the cloning of other susceptibility alleles. However, this will depend upon the population sample size, the method employed, linkage disequilibrium or association studies rather than the technology used (Cardon and Bell 2001). Some of the impressive genetic studies of this kind include susceptibility to infectious disease, for example an association between chemokine receptors (CCR5) and HIV susceptibility, and between the bacterial transporter protein Nramp and resistance to macrophage-infecting bacteria such as *Mycobacterium tuberculosis*. Similarly, various alleles at the *G6PD* locus determine malaria susceptibility (Tishkoff et al. 2001).

These kind of studies and the clinical applications of the resulting outcomes are not without ethical concerns. Some of the questions and concerns are related to ownership of the genes and freedom to use collected DNA for such studies. These are complex and emotional issues, especially when dealing with populations who may have been exploited or perceived to have been exploited. These issues should always be dealt with carefully under the statutory requirements and rules.

There has been a tremendous surge in various sub-specialties and technologies with names ending in *-omics*. We are rapidly moving into the ''omics'' era. In addition to genomics, several new specialist fields with an 'omics' suffix have recently appeared, for example, pharmacogenomics, nutrigenomics, metabonomics, metabolomics, transcriptomics, proteomics, micribiomics, glycomics, toxicogenomics, and many more. Whatever the basis of distinction might be, the driver of all these specialist fields is *GENOMICS*—the study of genomes in their entirety.

Genomics is not just about genome sequencing. Apart from full-length cDNAs and their sequences, copies of mRNAs that encode different proteins are probably equally important. The study of proteins thus derived falls within the broad field of proteomics which encompasses *functional genomics*. It is likely that eventually *proteomics* will have more practical applications in clinical medicine. This is rapidly moving ahead with the completion of the HapMap project (Nature 2005) and the future 'functional-variant database', a natural outcome of the HapMap project (Gibbs 2005).

It is vital that existing gaps in our knowledge about various 'omics' disciplines are filled to ensure efficient use of the valuable information emerging from research. It is also important that the gap between 'genetic professionals' and the 'primary-care community, as well as the 'public health community', is narrowed (Khoury et al. 2003). Integration of this knowledge in the medical education curriculum and in continued professional education programs is urgently required to ensure applications of genomics in the provision of healthcare.

During the last two decades, the practice of medical genetics or clinical genetics, has found its niche within the broad horizon of clinical medicine (Collins and Guttmacher 2001). Genetic services now constitute a small, but important, component of modern medical practice and public health. Currently, genetic services focus on providing information on chromosomal and single-gene diseases with limited contribution to multifactorial/polygenic diseases. How would this then be different from genomics? Already there is tremendous enthusiasm for the recently introduced term of 'genomic medicine'. In a primer on genomic medicine, Guttmacher and Collins (2002) viewed

genetics ''as the study of single genes and their effects'' and genomics as ''the study not just of single genes, but of the functions and interactions of all the genes in the genome.'' In simple terms, there is a quantitative difference between the two fields—the study of multiple genes as opposed to one gene. Few would argue for genetics to be part of genomics. This distinction is not yet fully understood and accepted. However, there is a qualitative difference between genetics and genomics in medical and health applications ranging from the concept of disease in genetics to the concept of information in genomics (Khoury et al. 2003).

The practice of medical genetics has traditionally focused on those conditions that result from specific alterations or mutations in single genes (e.g., inborn errors of metabolism, Duchenne muscular dystrophy and Huntington's disease), abnormal chromosomal constitution involving whole or part of chromosomes (e.g., trisomy 21 in Down syndrome and multiple malformation syndromes associated with a chromosomal microdeletion or microduplication) and a wide range of conditions resulting from genetic and environmental interactions such as single or multiple congenital malformations and developmental disabilities. The existing model of medical genetic services for these conditions includes laboratory diagnosis, genetic counseling and management. This is supported by public health measures to ensure delivery of genetic services and genetic screening (e.g., newborn screening or screening high-risk population groups). On the other hand, the practice of genomics in medicine and public health will focus on information resulting from variation at one or multiple loci and strong interactions with environmental factors, for example diet, drugs, infectious agents, chemicals, physical agents, and behavioural factors (Khoury et al. 2003).

What medical and public health applications could one foresee following the completion of the human genome sequence in 2003? How could these be applied and delivered to the 95% of human diseases that do not fall under the rubric of genetic disorders? These are some of the likely questions related to genomic medicine. Medical and public health professionals urgently need to make the changes necessary to accommodate rapid identification and characterization of the numerous genomic variants at multiple loci which increase or decrease the risks for various diseases, singly or in combination with other genes, and with various chemical, physical, infectious, pharmacologic, and social factors (Khoury 1999). This genetic and genomic information is crucial in assessing disease susceptibility among healthy individuals, and in personalized primary and secondary prevention planning. Collins and McKusick (2001) stated that ''By the year 2010, it is expected that predictive genetic tests will be available for as many as a dozen common conditions, allowing individuals who wish to know this information to learn their risks for which interventions are or will be available. Such interventions could take the form of medical surveillance, lifestyle modifications, diet, or drug therapy. Identification of persons at highest risk for colon cancer, for example, could lead to targeted efforts to provide colonoscopic screening to those individuals, with likelihood of preventing many premature deaths.''

One of the major areas of clinical medicine is pharmacotherapy. It has been argued and largely agreed in principle that individual genetic variation could play a significant role in drug response. Arno Motulsky put forward the term ''pharmacogenetics'' in the 1950s which essentially refers to the role of genetic variation influencing the drug response or adverse drug reactions (Motulsky 1957; Weinshilbourm 2003). Several monogenic disorders are now linked to drug response variation or alternatively drug response being dependent upon possessing a specific allele affecting drug metabolism. Examples include primaquine-induced hemolytic anaemia in G6PD deficiency and prolonged muscle relaxation and apnea following administration of succinylcholine during general anesthesia. Variation to drug response was also observed in twin studies comparing the drug response in identical (monozygotic, MZ) and non-identical (dizygotic, DZ) twins (Vesell and Page 1968). However, despite such a promising and encouraging beginning, the progress in pharmcogenetics has been very slow. This was largely due to technological limitations and difficulties in conducting family studies due to lack of appropriately matched controls.

With the completion of the Human Genome Project, our ability to understand and analyze individual genomic variation has vastly improved with the prospect of massive improvements in the future. This has opened doors to an entirely new approach to drug discovery, drug development and studying drug response based on specific genomic make up. This field is appropriately called pharmacogenomics. In a real sense this promises to be the basis of personalized medicine in the future. Apart from dealing with drug discovery and drug development, similar techniques could also be applied in studying an individual's response to various environmental agents (ecogenomics) including foreign biological material (xenobiotics) and toxic agents (toxicogenomics). Undoubtedly, this approach would attract attention of the public major interest to public health professionals and health care managers.

Several examples of personalized pharmacotherapy are now available. This is good evidence that modern clinical medicine is rapidly adopting and assimilating developments resulting from the Human Genome Project. A notable example includes fatal myelosupression following the administration of thiopurine medications (azathioprine, 6-mercaptopurine and thioguanine) linked to relative

differences in the activity of the enzyme thioprine S-methyltransferase (TPMT) which is completely absent in about 1 in 300 white Caucasians and partially deficient activity in about 10% of the same population. This is related to genetic polymorphisms influencing TPMT enzyme activity. A simple assay to measure TPMT enzyme activity will allow the clinician to modify the drug dose in patients with low enzyme activity and thus minimize the risk of the fatal complication of myelosupression. The TPMT polymorphism is probably an excellent model for *translational genomics* in guiding the patient therapeutics or in other words supporting the concept of *personalized medicine* (McLeod and Siva 2002).

The age of personalized medicine has begun. Clinicians will be able to tailor treatment and to understand response to treatment better than ever before (Thrall 2004). The power of personalized medicine lies in understanding and deciphering genetic and genomic variation. The potential of personalized medicine is enormous. However, other powerful factors should not be ignored. Powerful factors that also influence health and wellbeing include personal choice, economic and political constraints, lifestyle, diet, misuse and abuse of toxic substances and alcohol, environmental pollution and the impact of natural climate change. Perhaps more importantly, the potential for misuse of genetic and genomic information and outright discrimination are legitimate concerns (Collins and Watson 2003).

Personalized medicine will encompass not only common medical diseases, but as well as a broad range of preventable diseases [www.genovations.com]. In future, testing for disease susceptibility using multiple genomic variants will be possible and affordable with the application of 'high throughput' genome-based (for example, array-comparative genome hybridization, array-CGH) genetic testing.

A wealth of information on genomics is rapidly being acquired with the potential for a major impact on human health. However, these data are scattered through multiple scientific journals, reviews and state-sponsored reports and bulletins. A clinician or health professional often has difficulty in accessing and assimilating this information for application in medical and public health practice. More importantly, an inability to assimilate and interpret leads to frustration and avoidance of potentially useful information.

In view of the above developments and the rapidly increasing gulf in the available literature resource, the need for a dedicated journal on genomic medicine was appreciated and is thus appropriately entitled ''Genomic Medicine''. It is anticipated that the series of articles and original papers that will appear in this new bio-medical journal will facilitate the acquisition of factual information on genomics, developing concepts on the genomic basis of human disease, and in providing a practical basis to enable an interested clinician and health professional to develop an understanding of applications of genomics in clinical medicine and health. This journal is aimed at providing a suitable platform and resource to a wide-range of genetic scientists, genetic clinicians, clinicians in both primary and specialist practice and a broad range of health professionals. The success of this journal will be judged by the quality of the published material covering a broad remit in applied or translational genomics research in clinical diagnosis, therapeutics and teaching and training in medicine and health.

Finally, the practice of Medicine is an art based on sound scientific principles. It would be appropriate to quote Sir William Osler's remarks, ''If there were no individual variability, medicine would have been science not an art.'' Genomics in this context provides the basis of individual variability and the modern *genomic era* clinician will need to ensure that this is applied as an art.

## References


Cardon LR, Bell JI (2001) Association study designs for complex diseases. Nat RevGenet 2:91–99

Chakravati A (2000) To a future of genetic medicine. Nature 409:822–823

Collins FS, Guttmacher AE (2001) Genetics moves into medical mainstream. JAMA 286:2322–2324

Collins FS, McKusick VA (2001) Implications of the Human Genome Project for medical science. JAMA 285:540–544

Collins FS, Watson JD (2003) Genetic discrimination: time to act. Science 302:745–746

Genovations - the advent of truly personalized healthcare. http://www.genovations.com

Gibbs R (2005) Deeper into the genome. Nature 437:1233–1234

Guttmacher AE, Collins FS (2002) Genomic medicine: a primer. N Engl J Med 347:1512–1520

Holden AL (2000) The SNP consortium: a case study in large pharmaceutical company research and development collaboration. J Com Biotech 6:320–324

Hugot JP et al (2001) Association of NOD2 leucine-rich variants with susceptibility to Crohn's disease. Nature 411:599–603

Khoury MJ (1999) Human genome epidemiology: translating advances in human genetics into population-based data for medicine and public health. Genet Med 1:71–73

Khoury MJ, NcCabe LL, McCabe ER (2003) Population screening in the age of genomic medicine. N Engl J Med 348:50–58

Lander ES et al (2001) Initial sequencing and analysis of the human genome. International human genome sequencing consortium. Nature 409:860–921

McLeod HL, Siva C (2002) The thrioprine S-methyltransferase gene locus: implications for clinical pharmacogenomics. Pharmacogenomics 3:89–98

Motulsky AG (1957) Drug reactions, enzymes and biochemical genetics. JAMA 165:835–837

Nature (2005) A haplotype map of the human genome-report from the International HapMap Consortium. Nature 437:1299–1320

Ogura Y et al (2001) A frameshift in NOD2 associated with susceptibility to Crohn's disease. Nature 411:603–606

Stephens C et al (2001) Haplotype variation and linkage disequilibrium in 313 human genes. Science 293:489–493
Thrall JH (2004) Personalized medicine. Radiology 231:613–616
Tishkoff SA et al (2001) Haplotype diversity and linkage disequilibrium at the human G6PDH: recent origin of alleles that confer malarial resistance. Science 293:455–461
Venter JC et al (2001) The sequence of the human genome. Science 291:1304–1351
Vesell ES, Page JG (1968) Genetic control of drug level in man: phenylbutazone. Science 159:1479–1480
Watson JD, Crick FHC (1953) Molecular structure of nucleic acids. Nature 171:737–738
Weinshilbourm R (2003) Inheritance and drug response. N Engl J Med 348:529–537
World Health Organization (2002) Genomics and World Health-report from the Advisory Committee on health research. WHO, Geneva