

## EDITORIAL

# PERSONALIZED GENOMIC MEDICINE: THE WAY TO FUTURE HEALTH?

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Among the many promises that the new age of genetics offers, perhaps a major hope is that of being able to achieve a level of personal healthcare for each individual based on fundamental insight into that person's genetic profile (or genome). This is possible because of the uniqueness of each person's genome (so that no two persons are alike, identical twins being exceptions) based on inheritance of their specific genetic prototypes. This makes it likely that the contribution of their genomes to disease predisposition as well as response to environmental pathogens are also highly specific and different from others—in essence opening the door to personalized health care based on an understanding of the genomes that make them susceptible or immune to various diseases. The hope then is to provide tailor-made therapies that will be fine-tuned to individual genomic reactions and responses thereby enabling an optimal level of patient care. Since 2003, when the entire human genome was sequenced for the first time, scientists are getting optimistically closer to realizing this dream.

There are several high-level technical prerequisites to realizing this futuristic scenario. Obviously, the first step is to identify the genomes of all individuals, itself a daunting task involving technical expertise and near-prohibitive expenses. Current estimates of cost of total genome scans indicate that it could cost around US\$ 350,000 per person spread out over several months—certainly not a beacon of hope for daily medical practice! However the X-prize Initiative of the National Institutes of Health (NIH) USA has made an offer of US\$ 10 million to the first team of researchers that can sequence 100 human genomes in 10 days at a cost around US\$ 1,000.

Given that some level of affordability will occur in the future, the next enormous challenge is to identify the genes that carry the risk of acquiring diseases. This includes both the genes believed to 'predispose' to various diseases and also the genes involved in providing immunity, by whatever mechanism, to diseases. The human genome consists of approximately 25,000 genes located among 3 billion base pairs on 46 chromosomes, further defining the complexity of this task. However, due to a specific feature that promotes variations among the different alleles of genes called Single Nucleotide Polymorphisms (SNP), this task has become somewhat manageable. SNPs refer to changes in single

nucleotide (base) sequences on alleles among individuals so that different people have their own unique base sequence determining the variation in inherited characteristics (traits). A polymorphism is defined as a gene variant with 2 alleles in the population at a frequency of more than 1%.

There are approximately 10 million SNPs in the human genome. Each individual thus has a unique SNP sequence which, upon determination, will identify the presence of normal or abnormal gene complements unique to that person. Since this gene map varies among individuals and is based on heterogeneity of inherited base sequences, it is called a 'Haplotype'. Determination of the haplotypes of individuals in the population in order to probe for genetic variants predisposing to diseases has been given the name of Haplotype Mapping and the International HapMaP Project (<http://www.hapmap.org/>) was started in 2002 as a multi-country effort to identify, catalogue and make publicly available the genetic diversity in humans. Most individuals have a few haplotypes on a given chromosome thus making the task easier, as a few 'tag' SNPs can account for the variations in the individual haplotype without having to identify all SNPs. Furthermore, haplotypes also display linkage disequilibrium, whereby alleles physically situated close together on a chromosome region tend to be associated with each other during recombination events, thus getting inherited together as well. Together these two events make it possible to identify only a few tag SNP regions thereby accurately predicting the entire individual haplotype without having to identify all SNP regions—this may cut down the task of identification to as few as two SNP regions per chromosome in some instances.

SNPs would thus act as markers to identify genes in an individual's DNA sequence. It may be recalled that SNPs are already in use in Forensic Science to successfully identify or exonerate suspected criminals by enabling unique 'DNA Fingerprinting'. For geneticists, SNP changes are analogous to 'spelling mistakes' in the nucleotide alphabet sequence; some spelling mistakes confer an increased risk for the individual for diseases which would not have occurred in the normal spelling sequence. In the case of a disease, say coronary artery disease (CAD), the spelling mistakes would occur in individuals prone to develop CAD at a significantly higher frequency

than the individuals with a normal spelling sequence. It is then a simple matter to perform a case-control study of CAD patients and their normal counterparts and identify tag SNPs that would be found in the former, increasing their risk for the disease. Such studies would gradually build a databank of the tag SNPs associated with various diseases, and even all diseases, with a genetic contribution.

Among other applications of this information base would be a program of disease prevention based on the SNP profile of all newborns to provide an index of the 'risky' genes that they inherited. This is of tremendous importance as many of the diseases would develop in these individuals at various times in adult life essentially without any forewarning or clues, at which time mostly curative or remedial approaches are possible. Forearmed with the knowledge of a person's genetic risk profile, a physician could then provide specific treatment and detailed instructions to patients as to what triggering events or cumulative risk factor should be avoided by the person to either blunt the disease or prevent it altogether.

Spurred by such prospects, the world is witnessing a 'genomic gold rush' where nations and companies are spending billions in the pursuit of developing genomic databanks of their citizens. This is aided by advances in biotechnology that allow for assays of 500,000 to 1,000,000 SNPs per individuals at relatively low cost. Such Genome Wide Association (GWA) studies have given us the unheralded potential to not only study the genomic associations that contribute to complex multi-gene diseases, but also provide the hope that in future it will be possible to prevent these diseases in families and high-risk individuals. Completion of the HapMap project would further decrease the burden of GWA studies so that in the clinical setting, fewer diagnostic SNP tests would have to be ordered that would take acceptable times to report.

Only in the last few years, gene loci have been identified for many common complex diseases such as breast cancer, CAD, Myocardial Infarction, Obesity, Diabetes and Prostate cancer. Three robust studies for CAD in three different populations have identified the 9p21 gene locus as a risk factor – it is pertinent that this is a new locus which does not contain coding sequences, hence may provide newer insights into hitherto unexplained features of the disease. Type 2 diabetes has been extensively studied,

and independent genome-wide scans have identified several loci for diabetes susceptibility such as CDKN2A/CDKN2B, CDKAL1, and IGSF2BP2, as well as confirming TCF7L2, PPAR $\gamma$ , and KCNJ11, which had been previously identified by other methods. For obesity the FTO gene has been identified, while the genes for Crohn's disease, Rheumatoid Arthritis and adult macular degeneration are being identified.

Other than the area of Diagnostics, two further areas are under extensive research because of the potential to vastly improve personalized patient care—these are Pharmacogenomics and Therapeutics. Data from medical practice indicate that for many drugs, less than 50% of beneficial patient response is obtained. Additionally over 100,000 people die of drug-related adverse effects; a recent study from Britain estimated that admissions for adverse drug reactions accounted for 6.5% of all hospital admission costing the NHS about US\$ 1 billion annually. Each individual's response to any drug is also to an extent determined by the genome and identification of SNPs conferring advantageous or deleterious responses to prescribed drugs would be of great, even life-saving importance for the prescribing clinician and the patient. This information could result in prescription of tailor-made drugs, decreased dosage schedule, fewer side-effects and better quality of life during the medication period.

To conclude, it should be said that another domain of scientific and informed decision making appears in the offing as far as personalized genomic medicine is concerned. It remains to be seen to what extent it will be beneficial and how many branches of medicine will be affected or revolutionized by it. It is essential that a concerted effort be made to organize the genomic information rather than allowing companies and other vested interests to freely patent their genes of interest, thereby hindering a comprehensive health care plan meant for the greater good of all mankind. The role of the laboratory scientists is also vital in providing meaningful information about the various diagnostic tests to the clinician so that effective personalized health care is provided to the patient rather than developing the habit of routinely ordering expensive tests without any significant contribution to the betterment of the patient's disease.

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