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GUEST EDITORIAL

Biomedical research in India can have a global impact provided...

The Human Genome Project unlike any other project in science, received unprecedented attention, as evident from print and visual media coverage. The reason was obvious. It was hoped that having gotten the 'first glimpse of the book of life, previously known only to God', scientists would be able to solve most of the diseases and health-related miseries afflicting mankind. The Human Genome Project was not the first genome sequencing effort undertaken by scientists. Many genomes including bacteria, viruses, fungi and microorganisms had been sequenced before the human genome was sequenced. When the complete genome sequence of *Mycobacterium tuberculosis* was published in 1998 there were hopes that the cure for the disease that kills so many persons everyday will soon be found. Have we discovered any new drug against tuberculosis even after knowing the genome sequence, or for that matter against any other pathogenic organisms for which the complete genome sequence had been made available? I am afraid I do not have a comforting answer, except in the case of some viruses for which knowledge-based inhibitors were designed with the aid of high performance computing and structural biology. Many of these are in the market and one of them has even become a blockbuster drug. The take home from genome sequencing projects is that the outcome of such projects provides us with an opportunity to further dissect the biology of the organism in a manner otherwise impossible. Knowledge gained from such analyses will one day definitely aid in the discovery of new drugs and intervention regimes against the disease process.

Going back to the Human Genome Project, what came as a big surprise was the large degree of similarity (>99%) between two humans, at the genome level. It became apparent that the difference between two individuals, which could be responsible for the way we look, behave, have a life style or succumb to a disease, is primarily because of millions of genetic differences (variants) known as Single Nucleotide Polymorphisms (SNPs) spread across the genome. It is estimated that there are over 10 million SNPs in the human genome which occur once out of every 100 nucleotides. Such gene variants are at best an indication of predisposition to common diseases and not the cause of the disease. Quite often such SNPs in the human gene are not independent of one another and are instead associated with particular variants present on the same chromosome. Haplotype is the term used to define variants that associate together. Therefore, a particular variant at a given position on the chromosome can be used to 'tag' or predict the presence of a particular variant at another position. SNP analyses have nonetheless become 'fashionable' on the assumption that these SNPs not only provide the basis for differences between any two human individuals and hence have pharmacological implications, but will also aid in understanding the evolution and migration of the human race and other related issues. In a recent study (referred to as 'The HapMap Project') involving more than one million SNPs, identified in 269 people drawn from four diverse human populations, no direct influence of these SNPs on gene function could be seen (Gibbs, R. A. *et al.*, *Nature*, 2005, **437**, 1299–1320). These analyses nonetheless provide valuable information about the overall pattern of chromosome organization of such variants and provide a new tool for finding disease-causing genes in humans. Similar association analysis with high density SNP markers could only identify susceptibility loci or other determinants for complex diseases (Cheung, V. G. *et al.*, *Nature*, 2005, **437**, 1365–1369.).

Biologists have identified yet another direct way to discover disease-causing genes. In this method, referred to as medical reconsequencing (MRS), the target genes of different patients are sequenced and these sequences are compared with those of a healthy control. Such comparisons will identify genetic variations that may contribute to the disease or may be responsible for the disease process. Clearly this exercise in itself is an ex-

ceedingly large task of humongous proportions considering the fact that not only more than 20,000 genes (that the human genome is now believed to contain) will need to be sequenced on a population-based matrix, but also identifying the right gene for a right disease to begin with, will in itself be a formidable challenge. Making a catalogue of such functional variants, as they are so called, would no doubt aid in providing the right answers to why a given gene is responsible for a disease, but unfortunately this exercise would be restricted only to Mendelian diseases. Majority of the diseases which are not caused by single gene and represent complex genetic disorders (such as cardiovascular disease, neurological disorders, cancer, etc.) will need a very different approach. It is important, however, to create data of such functional variants by MRS for a general population and not just patients and controls.

Where does India fit in, in this global disease gene hunting expedition? The HapMap report, considered as a landmark study, was carried out with contributions of about 250 authors working in different institutions spread over the world. While from China alone seven genome Centres were associated with this study, India, with over a billion plus population was conspicuous by her absence. Did we once again miss the bus? Unfortunately, with the current mindset about funding of research infrastructure, there seems to be very little hope for India. As it is our total science and technology budget for the entire country is below the budget of a moderately big size single R&D entity in the West. This tendency of our science-funding agencies (the reviewers of R&D projects are equally responsible) to prevent the replication of high technology biological infrastructure in our country deserves a serious reconsideration. It is indeed a tribute to our scientific community that today we are seeing a justifiable increase in the quality of publications. Even journals (such as those published by the *Cell* press) which had been more or less refractile to manuscripts sent from India are now accepting our papers. We are today witnessing a significant increase in the number of publications in *Nature, Science,* etc. as well, in addition to other leading biology journals such as *JBC, JMB, J. Bact., JCM,* etc. For India to truly make an impact in disease gene identification, we need dramatic and exponential expansion of our biological infrastructure. For a country of the size of India, it is indeed a pity that we have only one national publicly funded facility to sequence any genome, and similarly perhaps just one national facility for proteome analysis. China has more than half a dozen. The same is more or less true for transcriptome and gene microarray expression analysis. We are shockingly ill-equipped in the area of metabolome analysis which is a very important and powerful system with a tremendous impact for the development of new diagnostics, besides enabling an understanding of the cell physiology as a function of the disease process. The Govt of India has a vision to invest up to 2 per cent of the GDP in Science & Technology. With our strong biomedical research base we can definitely emerge successfully as a hi-tech knowledge-driven economy. We must replicate high technology infrastructure as National Facilities, more particularly in the University system and in other places where there is a proven competence, with the proviso that this should be liberally shared with other investigators. With our unique population structure and the vast spectrum of diseases, some of them existing only in this part of the world, India can really make an enormous impact, provided we prepare ourselves to address these issues immediately. The mindset of our scientific R&D managers in the government must change if we have to be globally competitive. Science, particularly biology, today is more technology driven than ever. Discovery and innovation can be greatly facilitated if modern tools necessary for scientific enquiry are available to a much larger percentage of the best-of-the-best minds.

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