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Despite our millions of years of evolution, and proud conviction that we are somehow special or superior, human beings have achieved little more than a clever reshuffling of the building blocks of life - the genes encoding essential proteins from bacteria to man. This is the conclusion that the full sequence of the human genome has finally sealed. Sure, we are smart, and complicated compared with E. coli, but all those millennia of evolution have, in large part, merely constructed a complex mosaic that reuses ancient designs, repeated, inverted, altered and refined. As Samuel Broder, Senior Vice President and Chief Medical Officer of Celera Genomics, USA, philosophised, "It's like buying a Rolls Royce, opening the bonnet expecting to see a marvel of mechanical sophistication, only to find a row of Citroën Deux Cheveaux engines one joined to the other." We may console ourselves with the fact that, as Leena Peltonen, Chair of the UCLA Department of Human Genetics, put it, "the human genome is more creatively used than that of lower species." To society this may come as a disappointment, but to scientists it is the key to understanding how we work. That we work with many fewer genes than previously though (30,000 odd as opposed to the previous estimate of up to 200,000) can only simplify the Herculean task.

The goal for medicine, in large part, consist of understanding the differences between individuals. Variation accounts for a mere 0.1 percent of the genome on average in the human population, but that amounts to 3 million base pairs. Many of these are SNPs (single nucleotide polymorphisms), and the big challenge is identifying the genetic variation associated with disease. Disease causing polymorphisms reside in a relatively small number of genes according to Jonathan Knowles, Head of Global Pharmaceutical Research, at Hoffman-La Roche. That said, he holds the conviction that "there are far to many drug targets even for the pharmaceutical companies to work on."

For society, the genetic definition of disease may mean a reassessment of what it means to have one. On average we all carry a hand-full of polymorphisms that can cause disease. Though society may fear stigmatisation and discrimination as the possible result of genotyping, revelations such as this may lead to a more balanced perception of genetic disease. "We all have genetic disease", claimed Andres Metspalu, Head of the Estonian Genome Project, who's aim it is to collect data on 1,000,000 individuals into a national health database for the purpose of high density SNP mapping. Patient support groups are eager to be involved in genetic research, and Ysbrand Poortman, Chairman of EPPOSI1 and Executive director of VSOP2 stressed the importance for science of the large numbers of individuals in patients organisations. Furthermore he is aware, as a representative of the interests of sufferers of fatal diseases, that "between the risks and options come chances."

For sufferers of a disease for which there is not yet a cure, however, a genetic test is sometimes of doubtful benefit. The distinction between breast cancer patients who are HER-2 +ve or HER-2 -ve, on the other hand, is already proving a useful indicator of treatment strategy and prognosis according to Knowles. His vision of healthcare in the future relies strongly on predisposition screening and targeted monitoring followed by prevention via life style changes, nutrition or medicines. Early surrogate markers are vital, as exemplified by Alzheimers, in which, at the time of diagnosis, already 90% of the affected neurones are dead.

In general, knowledge of the genetic profile of a patient will increasingly be power in the hand of doctors and consultants who prescribe for acute and chronic conditions. In the USA annually 2 million serious adverse events, and 90 thousand deaths are ascribed to medicaments. Pharmacogenomic approaches to drug design and administration will make feasible personalised healthcare, hence reducing adverse drug reactions, and better matching a patient with an appropriate efficacious treatment. For example, the P450 cytochromes are particularly important enzymes that degrade not only toxins, but also drugs in the liver. Polymorphisms in these enzymes cause some individuals to metabolise a drug faster than average, hence making their treatment inefficient. Others may metabolise the same drug too slowly, and as a result suffer toxic side-effects. In drug development, the reliance of a clinical trial on "average" individuals sometimes results in the definition of a less than optimal dose for a particular group of sufferers, leading to the misconception that the drug is intrinsically ineffectual for them.

This is important, because we will have to live with pharmaceutical solutions for the foreseeable future. Gene therapy, with the exception of a very restricted group of diseases and patients, does not seem likely to be the elegant fix that some believed it would be. Alain Fischer from the Hôpital Necker-enfants Malades in Paris is sober about its limited success, despite the fact that 2.5 years after gene therapy for severe combined immunodeficiency (SCID), 6 out of 7 patients in his trial have normal T-cell function, and 4 now live at home in a normal environment. Apart from the problem of finding a suitable vector, the major obstacle to gene therapy is that at present it can only work for cell types in which the presence of the gene in question imparts a survival advantage. SCID is just such a case. That said, it would be unfair to belittle the value of gene therapy, given that its success rate is no worse that that of the pharmaceutical industry when measured in terms of the percentage of products that make it from laboratory to market.

As to the question of whether the genome will live up to the expectations of the public, it is too early to say. We are not even at the end of the beginning. Indeed, according to Jonathan Knowles, "it might take us 20 years to understand the role of key genes." But already it is clear that epidemiology, genomics, proteomics and genetics in combination represent extremely powerful tools in defining the molecular pathology of common disease. We will increasingly understand molecular pathology by the intersection of many orthologous data sets. Moreover, the improved understanding of the genetic interactions of hosts and pathogens in diseases that kill millions in the 3rd world promises hope for more effective treatments. The technical limitation of sequencing has long since been overcome, such that today it is possible to sequence some microbial organisms in weeks, if not days. Some of the optimism surrounding future prospects of genetic medicine is bound to be hype, but as Knowles remarked, "I am very sympathetic to the hype surrounding genomics and proteomics." We need just be a little patientþ

1. European Platform Patients' Organisations, Science and Industry (EPPOSI)

2. Dutch Alliance of Genetic Supportgroups (VSOP)

Andrew Moore, Programme Manager for Science & Society, EMBO, and Conference Organiser