The biological implications of regulatory genetic variation and the definition of “normal”.

Peter Little

NUS Dept of Biochemistry and Office of Deputy President (Research and Technology) peter.little@nus.edu.sg

The past decade has seen an explosion of variation data demonstrating that diversity of both protein-coding sequences, and of regulatory elements of protein coding genes, is common and of functional importance. In this presentation, we argue that genetic diversity can no longer be ignored in studies of human biology, even those without ostensible genetic outcomes, and that this knowledge can, and must, inform research.

The concept of a “normal” biology is embedded deeply in research thinking but the reality is that diversity of gene sequence is common and is the rule rather than the exception- we will use the DNA sequence of Craig Venter and James Watson as an illustration of this. Our analyses suggest about 46% of genes contain at least one amino acid change in >5% of the population, 30% of genes have a common variant found in >25% of the population and 18%, have a variant in >40% of the population. More remarkably still the data of Byoko et al. (2008) show that about 1/3rd of these changes are functionally neutral or nearly neutral, about 1/3rd are moderately deleterious, and about 1/3rd are highly deleterious or lethal.

We will show that regulatory genetic variation has complex, shared effects upon gene expression that can have different outcomes within the different tissues of an individual as well as creating significant inter-individual differences.

By way of illustration, we will discuss the potential role of genetic data in case control studies to identify and validate cancer protein biomarkers. We argue that a consideration of genetic diversity in biomarker biology should improve the proportion of biomarkers that can accurately classify patients.

Speaker biography: Professor Peter F. R. Little is presently Research Director and Professor in the Department of Biochemistry, National University of Singapore; he was previously Director of Research, UNSW Asia, Professor of Medical Biochemistry, UNSW and Reader in Molecular Genetics, Imperial College.

I am a present member of Editorial Board of Genome Research, Comparative & Functional Genomics, Briefings in Functional Genomics and Proteomics. I extensive experience in scientific research management of national and private agencies and at the governmental levels and have conducted extensive consultancy work in both genomic and non- genomic fields, working with major pharmaceutical, biotechnology and legal companies. In my research, I have authored or co-authored ~115 papers and have written a popular science book on genetics, Genetic Destinies, that was translated into 3 languages.

Research interest: I am a molecular geneticist with 30 years post PhD experience. My research is presently focused at the interface of biology and computing and combines genetic, microarray, statistical and bioinformatic expertise, building upon my past research strengths in genomics and molecular genetics. Our goal is to characterise the key factors underpinning the influence of genetic variation on the control of gene expression. To do this we have set up unique human and mouse model systems, and have created powerful genetic, statistical and quantitative genetic tools, featuring microarray analyses in a genetic context. My research has always been highly collaborative and I have worked and published with leading research groups in the USA, the Netherlands, France, Germany, Japan and Australia. I have lectured and taught extensively at all levels from school children to professional research scientists and the general public.