NUS Graduate School for Integrative Sciences and Engineering
Research Project Write-up

Title of Project : Identification of functionally-important polymorphisms in drug response genes using large-scale computational and experimental strategies.

Name of Supervisor : Caroline G. Lee

Contact Details: bchleec@nus.edu.sg, Tel: 6436-8353 or 6516-3251

Short Description

With ~10 million single nucleotide polymorphisms (SNPs) occurring at >1% in humans, identifying the functionally important SNP can be likened to "finding a needle in a haystack". It is thus not practical to investigate every SNP for their functionality or disease/drug response association. Our approach is to search for signatures of recent positive selection in genes responsible for drug response. The rationale behind this approach is based on principles of natural selection and "survival of the fittest". The exodus of mankind from Africa exposed our ancestors to new/different environments/diseases. Polymorphisms in genes that facilitate better adaptation to the new environment will be retained and its frequency increased while deleterious polymorphisms are removed and its frequency reduced in that population. These "signatures of natural selection" left behind in our genome can be utilized to identify functionally important polymorphisms in "adaptive" genes that enable the individual to adapt to new environments. We propose that the drug response genes belong to this category of "adaptive" genes that leave behind these signatures which can be utilized to identify functional polymorphisms. The identification of functionally important SNPs in this functionally important category of genes will greatly facilitate future studies associating SNPs in these genes with drug response as well as complex diseases in which environment/xenobiotics play a role.

Objectives

(1) In silico approaches to mine the HAPMAP and Perlegen databases for regions in the human genome that contains genes important for drug response.
(2) Genotype selected drug response genes in our 3 local populations (Chinese, Malays, Indians).
(3) Examine the haplotype and linkage disequilibrium profile of these regions using computational methods.
(4) Utilize computation methods to search for signatures of recent positive selection in these genes.
(5) Experimentally examine candidate SNPs that show statistical evidence of positive selection to evaluate if these SNPs are associated with differences in the gene and/or protein expression/function

References

1) Bamshad M and Wooding S.P. Signatures of natural selection in the human genome. ***Nature Reviews. Genetics*** 4:99-111 (2004)
2) Kun Tang, Li Peng Wong, Edmund JD Lee, Samuel S. Chong, **Caroline G.L. Lee***. Genomic Evidence for Positive Selection at the *MDR*1 Gene Locus. ***Human Molecular Genetics*** 13(8): 783-797 (2004).

3) Zihua Wang, Baoshuang Wang, Kun Tang, Edmund JD Lee, Samuel S Chong, and **Caroline GL Lee***. A functional polymorphism within the *MRP*1 gene locus identified through its genomic signature of positive selection. ***Human Molecular Genetics*** 14(14): 2075-2087 (2005)

4) Zihua Wang, Jingbo Wang, Erwin Tantoso, Baoshuang Wang, Amy YP Tai, London L.P.J Ooi, Samuel S Chong, and **Caroline GL Lee***. Signatures of Recent Positive Selection at the ATP-Binding Cassette (ABC) Drug Transporter Superfamily Gene Loci. ***Human Molecular Genetics*** 16(11):1367-1380 (2007)