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Gene-mapping Strategy of Common Disease in the Post-genome Era

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As the Human Genome Project accomplishes the completed human DNA sequences, research interests have rapidly shifted from common nucleotide sequences to nucleotide diversities in human populations. Characterizing the nucleotide diversity of single nucleotide polymorphisms (SNPs), their linkage disequilibrium (LD), and haplotype structures in the human genome can help in gene-mapping of common disease. Human genome contains about 30 thousands of genes and probably about 5 millions of SNPs. It is not still realistic to analyze all the SNPs to map disease gene despite that advent of modern technology enables us large sca le typing with low cost. We apply non-parametric linkage analysis with affected sib-pairs to map disease loci, then screen the linkage region (about 10 M bp in length) by LD mapping with SNPs in the database. As an example, I will present our recent succe ss of the ossification of posterior longitudinal ligament of the spine (OPLL), which is a common Asian disease with ectopic bone formation in the spine. We have mapped OPLL to chromosome 21 by genomewide linkage analysis with 140 affected sib-pairs (maxi mum Zlr=3.97). In the linkage region, 600 SNPs of 150 genes were genotyped and LD mapping was performed. Several SNPs of collagen 6A1 gene (*COL6A1*) were strongly associated with OPLL (the best significance, p = 0.000003). The haplotype analysis with tree SNPs of *COL6A1* confers high significance (p=0.0000007). These results strongly indicate that *COL6A1* constitutes the genetic susceptibility of OPLL, and more importantly our strategy performing genomewide linkage and LD mapping of the linkage region could successfully pin-point the disease gene.

S6-4

From Analysis to Interpretation of DNA Microarray Data

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One of the major bottle necks in the genomics research using DNA microarray technology is the stage of interpretation. Here I present some publically available interpretation tools which help to resolve this problem. I specifically introduce **GenMapp** (http://www.genmapp.org/links.html), **Dragon** (http://pevsnerlab.kennedykrieger.org/dragon.htm), and **MedGene** (http://hipseq.med.harvard.edu/MEDGENE/login.jsp) which assist to study gene expression profiles associated with the diseases. GenMapp and Dragon View has comparable but different functions for pathway mapping of microarray results. MedGene helps researchers to find a list of genes associated with a disease or a list of diseases associated with a gene.