Genetic factors in hyperuricemia and gout

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Gout is a clinical syndrome caused by an inflammatory response to monosodium urate crystal deposition, which may be formed by hyperuricemia. Manifestations of gout include recurrent attacks of acute inflammatory arthritis, tophi, uric acid urolithiasis and renal impairment. Environmental risk factors for gout include diet, alcohol intake, high level of serum uric acid, age and male gender.

The Pacific Austronesian population, including Taiwanese aborigines, has a remarkably high prevalence of hyperuricemia and gout, which suggests a founder effect across the Pacific region. Gout in the Taiwanese aborigines is found to be family aggregation and more than 85% of gouty result from under-excretion of purine in kidney. The genetic statistical analysis was shown that there is genetic component responsible for the familial aggregation of hyperuricemia and gout in Taiwanese aborigines. The upper bound for heritability (h2) was 0.8 while the sib recurrence risk ratio (λs) was estimated to be as high as 10.

We started the gene search with the candidate gene approach by examining hypoxanthine guanine phosphoribosyltranserase (HPRT). A new point mutation, nucleotide change from G to A at nucleotide 152 resulting in amino acid change, was found. However, this variant only accounted for 1.4% to 4.5% of the gout in different Taiwanese aboriginal tribes.

In 2004, we have reported a genome-wide linkage study of 21 multiplex pedigrees with gout from an aboriginal tribe in Taiwan. A average of 10 cM genomewide scan using 382 microsatellite markers spread across 22 autosomes, we demonstrated a highly significant linkage for gout at marker D4S2623 on chromosome 4q25 and hypothesized that a major gene, *GOUT1* (Gout Susceptibility 1; MIM 138900), plays a role in this trait. Based on results of linkage analysis, we also found the allele 6 of D4S2623 has a high frequency transmitted from affected parents to affected child by transmission disequilibrium test (TDT).

For addressing accurate physical mapping of the *GOUT1*, we have applied SNP technology and genomic information to identify susceptibility alleles of candidate gene associated with gout in Taiwanese aborigines. Simultaneously, all extended studies are proceeding now, including proteomics and metabolitism of gout. Further novel findings will be reported.