IDENTIFICATION OF ABCG2/BCRP AS A MAJOR CAUSE FOR GOUT
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Gout based on hyperuricemia is a common disease and has long been known to have heritable component. Recent genome-wide association study also showed that serum uric acid (SUA) levels and gout relates to ABCG2 gene, which is reported to locate in a gout-susceptibility locus (MIM 138900) on chromosome 4q revealed by a genome-wide linkage study. We have previously reported that ABCG2 is an exporter that has polymorphic reduced functionality variants. Since ABCG2 exports nucleotide analogs that is structurally similar to urate, we hypothesized that ABCG2 transports urate and its genetic variants cause hyperuricemia and gout.

Transport assays were performed using membrane vesicles prepared from ABCG2-overexpressing cells, and showed ATP-dependent transport of urate in ABCG2-expressing vesicles but not in control vesicles. Kinetic analysis revealed that ABCG2 mediated a high-capacity transport of urate (calculated Km: 8.24 ± 1.44 mM), suggesting a physiological role of ABCG2 as a high-capacity urate exporter, maintaining its function even under high-urate conditions. Mutation analysis with 90 Japanese hyperuricemia in ABCG2 detected six non-synonymous variants: V12M, Q126X, Q141K, G268R, S441N and F506SfsX4. ATP-dependent urate transport was reduced about by half (46.7%) in Q141K and was nearly eliminated in Q126X, G268R, S441N and F506SfsX4. Among these five dysfunctional variants, relatively frequent two dysfunctional variants, Q141K (31.9%) and Q126X (2.8%), were then analyzed.

Quantitative trait locus analysis of 739 Japanese individuals showed that the Q141K of ABCG2 increased SUA as the number of minor alleles of Q141K increased (P=6.60x10^-5). The association study with 871 Japanese male control showed that Q126X increased the risk of hyperuricemia (OR, 4.25; 95% CI, 2.44–7.38; P=3.04x10^-7) and gout (OR, 4.25; 95% CI, 2.44–7.38; P=3.04x10^-7). Haplotype frequency analysis revealed that there is no simultaneous presence of Q126X and Q141K in one haplotype. Since Q126X and Q141K are assigned to nonfunctional and half-functional haplotype, respectively, the six patterns of genotype combinations are divided into five functional groups. Gout risk of 75% function was increased with an OR of 3.02 (95% CI, 1.96–4.65; P=2.29x10^-7) and that of 50% function was with an OR of 4.34 (95% CI, 2.61–7.24; P=2.23x10^-9). Gout risk of ≤25% function was remarkably increased with an OR of 25.8 (95% CI, 10.3–64.6; P=3.39x10^-21) and 10.1% of gout patients had these genotypes combinations while only 0.9% of control males have the same combinations. In addition, genotype combinations of full function are detected in 50.8% of the control subjects but only in 21.4% of gout patients.

Our function-based genetic analysis showed that combinations of dysfunctional two variants are major causes for gout, thereby providing a new approach for prevention and treatment for the high-risk population of gout.

References:

Biography
1995 Graduated from National Defense Medical College (NDMC)
1995-1997 Resident in NDMC Hospital
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