行政院國家科學委員會專題研究計畫　成果報告

血管收縮素元基因 A-217G,A-6G 與 M235T 之 haplotype 與高血壓之關連

計畫類別： 個別型計畫
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前言:
Although some single polymorphism analyses of the angiotensinogen (AGT) gene have been found to be associated with hypertension, the results are still inconsistent. The objectives of this study are to evaluate the association of the genotype and haplotype distributions of three single-nucleotide polymorphisms (SNPs) (G-217A, A-6G, and M235T) in the AGT gene with hypertension.

方法與結果:
In a sample of 461 hypertensive and 327 normotensive patients in Taiwan, we found that -217AA and-6GG homozygotes conferred independently an increased risk to hypertension (P = 0.008 and P =0.037, respectively), as illustrated by their significant associations with hypertension in both single SNP and pair-wise SNPs analyses. Meanwhile, a very weak linkage disequilibrium was found between the G-217A and the A-6G polymorphisms in terms of $r2$ (<0.05). On the basis of likelihood ratio test, only the set of haplotypes that constituted the A-6G and the M235T polymorphisms was associated with hypertension (2 =20.91, P =0.0008), which was mainly due to the increased frequency of the recombinant haplotypes (-6A≡235M and-6G≡235T), and a pathophysiological role in the predisposition to hypertension was hence indicated. In functional assays, the promoter activities of the haplotypes-217A ≡-6A and-217G ≡-6G were significantly higher than the most common haplotype-217G≡-6A.

討論:
Our analyses of population association indicate that the two promoter genotypes, -217AA and -6GG, have independent contribution to hypertension, which are supported by our functional assay and consistent with recent studies. Despite the short physical distance between the G-217A and the A-6G, in which the latter is in strong LD with the M235T as expected, the LD between them is very weak and hence implies that the two promoter polymorphisms are related to different functional expression pathways. Revealed by the increased frequency of the recombinant haplotypes between the A-6G and the M235T in the hypertensive subjects, the role of disruption in the conserved interval in the predisposition to hypertension is indicated. These results also highlight the necessity of a thorough analysis of all reported variants of a candidate gene in the elucidation of genetic susceptibility to a complex disease like hypertension, even when the variants are in the same haplotype block.

結論:
These results highlight the necessity of a thorough analysis of all reported variants of a candidate gene in the elucidation of genetic susceptibility to a complex disease like hypertension, even when the variants are in the same haplotype block.