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Genetic analysis to identify the predisposing factors to salt sensitive hypertension

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Summary

To achieve the tailored medicine as a safeguard against these disorders, it is required to clarify their pathogenesis. Even though many papers concerning molecular mechanism of cardiovascular disease have been published, there has been little success in identifying the correlation among genome, transcriptome, proteome, and environment in the pathogenesis of cardiovascular disease. We have been examined the genotype-phenotype interactions in many candidate genes using a huge number of samples to identify several unique interactions between gene polymorphism and environmental factors. For example, T235 allele of angiotensinogen gene modulates the salt sensitivity and increases a risk for lacunar infarction and non-dipper type of blood pressure variation. Interestingly, the frequency of four candidate genes of salt sensitive hypertension, angiotensinogen (*AGT*), aldosteron synthase (*CYP11B2*), alpha adducin (*ADD1*) and G protein beta 3 subunit (*GNB3*), were significantly higher in Japanese than that in Caucasians. Arg904Gln polymorphism of thiazide sensitive sodium-chloride co-transporter (*TSC*) gene contributed to increase the predisposition to hypertension via gain of TSC function only in Japanese. We also carried out the microarray analysis to examine gene expression level in a thiazide (HCTZ) administration test, resulted that the peripheral transcriptome was altered according to *TSC* genotype and HCTZ administration. Since recent report suggested the positive association between functional polymorphisms in the beta 2- and beta 3-adrenergic receptors and cardiovascular function, our 5-year longitudinal study clarified that the beta 2-adrenergic receptor polymorphisms related to weight gain, blood pressure (BP) elevation via alteration of sympathetic nerve activity. In addition, beta-1 adrenergic receptor polymorphism was associated with heart rate and daily home blood pressure variation and increased risk for lacunar infarction in the Ohasama Study. Put together these results, we would like to propose the importance to examine the genetic factors with precise and accurate clinical phenotypes. Lessons from large genetic epidemiological studies taught us that genetic information may be able to provide the “optimal environment” suited for individual constitution. We would like to express gratitude to all collaborators of large epidemiological studies and Salt Science Research Foundation for their continuous grant support.