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Identification of Genes Contributing to Salt Sensitivity in Japanese

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Summary

The purpose of the present study was to identify genes contributing to salt sensitivity. We at first attempted to identify genes contributing to salt-sensitive hypertension in Dahl-salt sensitive rats. We performed QTL analysis for blood pressure by using 107 male F2 rats produced from Dahl salt sensitive and Lewis rats, and identified Klk1 gene in chromosome 1 and Ccl2 gene in chromosome 10 as candidate genes for salt sensitivity. However, association studies in the Suita cohort did not support that these genes contributed to salt sensitivity in Japanese.

We performed association studies between candidate genes for salt sensitivity and hypertension using the Suita cohort. The Suita cohort sample consisted of 14,200 men and women recruited randomly from the Suita city municipal population registry. They were then invited by letter to attend regular cycles of follow-up examination (every 2 years). We analyzed 2,000 - 4,000 samples in the present study. Among the many genes analyzed, *SLC12A3* and *CYP11B2* appeared to be intriguing.

SLC12A3 is known to be responsible for Gitelman's syndrome, characterized by NaCl loss from the urine. We identified 7 loss-of-function mutations in this gene in Japanese, and the combined allele frequency of these 7 mutations was as high as 2%. This indicates that one in 25 Japanese is heterozygous for Gitelman's syndrome mutations. These heterozygotes appear to be salt-resistant and vulnerable to dehydration.

CYP11B2 is known to be aldosterone synthetase. The promoter polymorphism T(-344)C appears to determined sensitivity to angiotensin II. The C type is sensitive to angiotensin II, while the T type is insensitive to angiotensin II. Thus, even under low angiotensin II concentration, such as in high salt intake situations, the promoter activity of the subjects with the TT genotype appeared to produce excess amounts of aldosterone. In fact, systolic blood pressure in subjects with the TT genotype was positively correlated with salt excretion in the urine, which was not observed in subjects with the CC genotype. The genotype frequency of the TT genotype was around 0.5, and therefore, this genotype appears to have great clinical implications.