Segmental Renal Sodium Handling in Relation to the Human SAH Gene

To the Editor:

The expression of SAH (spontaneously hypertensive rat-clone A-hypertension-associated gene) is markedly higher in the kidneys of spontaneously hypertensive rats compared with normotensive Wistar-Kyoto control rats.1 In rats, SAH is expressed mainly in proximal renal tubules.2 The human SAH gene is located on chromosome 16p13.11 and is also expressed in the kidney.3 A large number of previous studies suggested association of the human SAH gene with hypertension and related metabolic phenotypes, such as obesity, hypercholesterolemia, and hypertriglyceridemia. However, we recently analyzed blood pressure, measures of obesity, serum lipids, and blood glucose as continuous phenotypes in 2603 relatives from 560 families and 31 unrelated subjects randomly recruited from 6 populations in the framework of the European Project on Genes in Hypertension. We genotyped the G-1606A and -962D/I polymorphisms in the SAH gene. In spite of sufficient statistical power, none of the phenotype-genotype associations approached statistical significance.4

In this journal, we reported recently on the genetic association of segmental renal sodium handling with DRD1 and GRK4.5 In a family based random sample of 611 untreated white subjects, we measured the endogenous lithium clearance to assess fractional sodium excretion (FE\textsubscript{Na}) and proximal and distal tubular sodium reabsorption. Because the human SAH gene is expressed in the kidney,1–3 we used the same sample and same methods as published previously5 to explore the possible association of renal sodium handling with the aforementioned variation in human SAH. Because of progress in the examination of subjects, for the present analysis, our sample included 719 subjects (46.2% women; mean age: 41.3 years). From this sample, we had excluded all of the patients on antihypertensive drug treatment (n = 156), all of the women taking contraceptive pills or hormonal replacement therapy (n = 76), and subjects with serum or urinary lithium levels suggestive of external contamination (n = 4). The genotype frequencies were 0.7%, 21.5% and 77.8% for -1606AA, -1606GA, and -1606GG, and 9.5%, 45.4%, and 45.1% for -962DI, -962DD, and -962II, respectively. The frequencies of the common haplotypes were 11.1% for A and I, 56.5% for G and I, and 32.1% for G and D. As in our previous analyses,5 we adjusted FE\textsubscript{Na}, proximal tubular sodium reabsorption, and distal tubular sodium reabsorption for sex, age, body mass index, mean arterial pressure, and sodium excretion, and we accounted for relatedness using mixed models as implemented in SAS 9.1.3. In population-based analyses, considering single nucleotide polymorphisms, as well as haplotypes, none of the phenotype-genotype associations reached statistical significance (P > 0.13). In the family based analyses (number of informative offspring ranging from 244 to 367), the between-family component of phenotypic variance was consistently nonsignificant (P > 0.34), which excluded confounding by population structure. The within-family component was borderline significant for FE\textsubscript{Na} in relation to the transmission of the -962D allele (effect size: −0.067 ± 0.033%; P = 0.043) and the G and D haplotype (−0.067 ± 0.033%; P = 0.043). It did not reach significance for any family based analysis, involving proximal tubular sodium reabsorption (P > 0.77) or distal tubular sodium reabsorption (P > 0.14). On the assumption that our participants were in balance with regard to sodium intake and excretion, our family based findings on FE\textsubscript{Na} suggest that genetic variability in human SAH might influence salt intake. However, the more likely explanation is that the borderline significance for the family based association between FE\textsubscript{Na} and variability in SAH might have arisen by chance. We conclude that, in spite of its renal expression,1–3 the human SAH gene is unlikely to have an important role in renal sodium handling.

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Disclosures

None.

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