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CORRESPONDENCE

The rs3754777 polymorphism of the *STK39* gene is associated with essential hypertension in central south Chinese Han males

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Essential hypertension is a highly heterogeneous disorder that is influenced by genetic and environmental factors, and by interactions between these factors.[1] Several genes have been reported to confer susceptibility to essential hypertension in Chinese individuals.[1–3] Recently, a new hypertension susceptibility gene, serine/threonine kinase 39 (*STK39*), was identified as a candidate gene for hypertension by a genome-wide association study. We found a study providing supporting evidence that the *STK39* polymorphisms rs35929607 and rs3754777 are associated with hypertension in sex-combined Amish populations.[4] Here, we report our replication data showing a significant association of the rs3754777 polymorphism, but not rs35929607, of *STK39* with essential hypertension in a male Chinese Han population.

In this case–control study, an essential hypertensive (EH) group was composed of 560 Chinese Han patients from Hunan Province. The diagnosis of hypertension was made according to a classification based on blood pressure (BP) levels of at least 160/100 mm Hg. Patients with any history of diabetes, hyperlipidemia, stroke, chronic kidney disease or coronary heart disease were excluded from this study. In addition, 550 unrelated subjects with a BP $<140/90$ mm Hg and no history of cardiovascular disease, diabetes mellitus or other diseases were considered to be normotensive controls. The study was approved by the Ethics Committee of Kunming Medical University (http://www.kmmc.cn/). Written informed consent for genetic analysis was obtained from all subjects or their guardians. The distribution of fasting plasma glucose (FPG) levels did not differ significantly between the two groups ($P>0.05$). Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were significantly higher in the EH group than in the control group ($P<0.05$).

Genotyping of rs35929607 and rs3754777 was conducted using SNaPshot (Applied Biosystems/Life technologies, Foster City, CA, USA). All variants in the cases and controls were in Hardy–Weinberg equilibrium ($P>0.05$). Allelic and genotypic associations in our samples were then assessed using PLINK 1.9 (http://pngu.mgh.harvard.edu/~purcell/plink/), and the results are shown in Table 1. No association was found between *STK39* rs35929607 and essential hypertension in Chinese Han individuals ($P=0.16$). The results did not stratify when adjusted by gender (male: $P=0.25$; female: $P=0.37$). An analysis of the frequency of *STK39* rs3754777G revealed that the frequency was significantly higher in the EH patients (0.42) than in the controls (0.31), with an odds ratio (OR) of 1.55 ($P<0.001$, 95% confidence interval (CI): (1.31–1.85)). A significant association remained in males ($P=0.002$) but not in females ($P=0.85$). The frequencies of the *STK39* rs3754777 genotype in the EH cohorts and the controls were GG: 0.16 *vs.* 0.28, AG: 0.29 *vs.* 0.27 and AA: 0.55 *vs.* 0.45. The frequencies of the AG +AA genotype (dominant model) and the AG +GG genotype (recessive model) in the EH cohorts were significantly different from the frequencies in the control group ($P<0.05$). However, the significant association disappeared in the male and female subgroups ($P>0.05$). Regression analysis was also used to evaluate possible correlations between *STK39* rs3754777 risk genotypes and specific clinical characteristics in essential hypertension. *STK39* rs3754777 genotypes were found to be significantly associated with SBP and DBP ($P<0.01$). No significant evidence of an association between *STK39* rs3754777 and other clinical characteristic subgroups was detected ($P>0.05$) (Table 2).

STK39 encodes sterile 20-like-related proline–alanine-rich kinase, which plays a critical role in salt homeostasis in renal physiology, and is strongly implicated in BP regulation and hypertension development. Fava *et al.*[5] replicated the association of *STK39* variants with BP in Caucasians. Overall, patchy evidence has been provided in favor of a modest effect of *STK39* on hypertension prevalence in more homogeneous populations, such as the Amish[4] or African Americans.[6] The *STK39* rs35929607 A>G polymorphism was associated with hypertension, at least in females, in two very large urban-based surveys conducted in southern Sweden and Tharparkar.[5,7] rs3754777 was validated in an independent Amish sample and in four non-Amish Caucasian populations.[8] Our findings support that the single nucleotide polymorphism (SNP) rs3754777, but not the SNP rs35929607, of *STK39* is associated with hypertension in sex-combined Chinese Han populations; this finding is similar to the findings of a previous report by Wang *et al.*[8] but differs from the reports by Chen *et al.*[9] To our knowledge, this is the first time a significant association between *STK39* rs3754777 and essential hypertension in a male Chinese Han population in Hunan Province is reported. Our results are also inconsistent with a previous study by Xu *et al.*[10] This inconsistency is likely

Table 1 The association between *STK39* gene polymorphisms and essential hypertension

	Number of alleles/genotypes					
SNP rs, allele (MAF)	*Cases(n = 560)*	*Controls(= 550)*	P	*OR[a] (95% CI)*	P_{male}	P_{female}
rs3754777 (A>G)						
G	465	345	<0.001	1.55 (1.31–1.85)	0.002	0.85
AG/AA +GG	164/396	151/399	0.05	1.29 (1.00–1.67)	0.28	0.47
AA/AG+GG	306/254	243/307	0.0005	1.52 (1.20–1.93)	0.20	0.85
GG/AG+AA	90/470	156/394	<0.001	0.48 (0.36–0.65)	0.17	0.86
rs35929607 (A>G)						
G	396	348	0.16	1.23 (0.92–1.69)	0.25	0.37
AG/AA +GG	167/393	160/390	0.79	1.04 (0.80–1.34)	0.27	0.26
AA/AG+GG	303/257	273/277	0.14	1.20 (0.95–1.51)	0.46	0.43
GG/AG+AA	90/470	110/440	0.08	0.77 (0.56–1.04)	0.23	0.35

Abbreviations: 95% CI, 95% confidence intervals; OR, odds ratio; SNP, single nucleotide polymorphism.
[a]OR and 95% CI are calculated for the minor allele of each SNP.

Table 2 The association between rs3754777 and clinical features in essential hypertension

	Clinical features								
Genotype	*Age (years ± s.d.)*	*SBP (mmHg ± s.d.)*	*DBP (mmHg ± s.d.)*	*BMI ($kg\,m^{-2}$ ± s.d.)*	*FPG ($mmol\,l^{-1}$ ± s.d.)*	*TC ($mmol\,l^{-1}$ ± s.d.)*	*LDL-C ($mmol\,l^{-1}$ ± s.d.)*	*HDL-C ($mmol\,l^{-1}$ ± s.d.)*	*TG ($mmol\,l^{-1}$ ± s.d.)*
AA	61.2 ± 5.53	141.6 ± 30.6	84.7 ± 16.76	22.23 ± 4.22	5.48 ± 1.66	5.12 ± 1.08	3.47 ± 2.66	1.53 ± 0.63	1.69 ± 1.77
AG	61.6 ± 6.11	145.8 ± 31.73	87.2 ± 16.93	23.17 ± 4.14	5.65 ± 1.35	5.33 ± 1.10	3.18 ± 0.46	1.46 ± 0.32	1.64 ± 1.17
GG	61.3 ± 7.31	168.5 ± 28.61	104.5 ± 14.39	24.26 ± 3.67	5.57 ± 2.14	5.33 ± 1.03	3.15 ± 0.56	1.44 ± 0.54	1.67 ± 1.74
*P**	0.08	<0.01	<0.01	0.26	0.34	0.56	0.154	0.31	0.39

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.
*P values from Student's t-test or χ^2.
All the data were presented as mean ± s.d. No significant differences were observed for age, BMI, FPG, TC, LDL-C, HDL-C and TG ($P>0.05$).

caused by heterogeneity in the etiology of hypertension or by confounding factors in genetic association studies caused by population stratification.

In summary, the present results suggest that *STK39* rs3754777 may be a susceptibility factor for essential hypertension in a male central south Chinese Han population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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