Common Polymorphism rs11191548 Near the CYP17A1 Gene Is Associated With Hypertension and Systolic Blood Pressure in the Han Chinese Population

Xiaomu Li,1 Yan Ling,1 Daru Lu,2 Zhiqiang Lu,1 Ying Liu,1 Hongyan Chen,2 and Xin Gao1

BACKGROUND
The single-nucleotide polymorphism (SNP) rs11191548, near the CYP17A1 gene, has been identified as being associated with hypertension and systolic blood pressure (SBP) in genome-wide association studies (GWAS) in a European population. The CYP17A1 gene encodes cytochrome P450c17alpha and plays an important role in the steroidogenic pathway, which includes mineralocorticoids.

METHODS
We investigated the SNP rs11191548 in a case–control study of 1,102 subjects with essential hypertension (EH) and 1,109 normotensive controls.

RESULTS
The SNP rs11191548 was significantly associated with hypertension in an additive genetic model (genotypes CC vs. TC vs. TT; odds ratio (OR) = 1.27 (95% CI, 1.10–1.47; P = 0.001)). The ORs of the TC vs. TT and CC vs. TT genotypes were 1.34 (95% CI, 1.10–1.63; P = 0.003) and 1.52 (95% CI, 1.10–2.12; P = 0.014), respectively. The risk C-allele was associated with increased SBP (βadj ± SEM = 1.307 ± 0.515; P = 0.011) levels in the controls and decreased plasma renin activity (PRA) (βadj ± SEM = −0.053 ± 0.016; P = 0.001) in the subjects with EH. In a stratified analysis of renin–angiotensin–aldosterone-system (RAAS)-related antagonists, the C-allele was significantly associated with decreased serum potassium (K+) (βadj ± SEM = −0.093 ± 0.028; P = 0.001) and PRA (βadj ± SEM = −0.067 ± 0.023; P = 0.003) levels in patients with EH who were not taking RAAS-related antagonists. These results remained statistically significant after correction for multiple corrections.

CONCLUSIONS
The SNP rs11191548, near the CYP17A1 gene, was associated with hypertension and SBP in a Chinese Han population. The rs11191548 polymorphism was also related to lower PRA and K+ levels, suggesting that it has an effect on the enzymatic activity of CYP17A1.

Keywords: CYP17A1 gene; rs11191548; hypertension; renin; blood pressure.

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Hypertension is a major global public-health problem. The World Health Organization has projected that 29.2% (range, 28.8–29.7%) of the world’s population will have hypertension by 2025, and that the number will increase by approximately 60% to a total of 1.56 billion (range, 1.54–1.58 billion).1 In China, approximately 153 million (18%) Chinese adults were hypertensive in 2002.2 The pathogenetics of hypertension include both genetic factors and environmental factors, such as dietary sodium intake, obesity, and smoking. More importantly, hypertension is a typical multifactorial inherited disease in which the combination of small quantitative effects from the variants of many genes, together with several environmental factors, increases the risk of its occurrence. Genome-wide association studies (GWAS) are widely used to identify the common gene variants associated with hypertension or blood pressure (BP), and to explore the genetics of hypertension. In one large GWAS that used meta-analysis, the Global Blood Pressure Genetics (Global BPgen) study, the single-nucleotide polymorphism (SNP) rs11191548 at 10q24 was for the first time identified as being associated with hypertension and was also the strongest SNP associated with systolic blood pressure (SBP) levels.3 Recently, the association of this SNP with hypertension and BP was confirmed in two other meta-analytic GWAS involving European and East Asian populations.4,5 The SNP rs11191548 is one part of a large cluster of associated SNPs spanning a region of approximately 430 kb at 10q24, which includes the cytochrome P450c17alpha (CYP17A1) gene. This SNP is near the 3’ noncoding region of CYP17A1. Recently, the associations of SNP rs11191548 with hypertension or BP have been replicated in studies with European, East Asian, Chinese, and Japanese populations.6–9 The CYP17A1 gene is located at 10q24.32 and encodes the cytochrome P450 enzyme CYP17A1 (P450c17), which catalyzes two distinct enzymatic steps in the steroidogenic pathway: the 17α-hydroxylase and 17,20-lyase reactions.10–12
17α-Hydroxylation is a key step required for the synthesis of cortisol, and the 17,20-lyase reaction is essential for the production of sex steroids. Mutations in the CYP17A1 gene result in 17α-hydroxylase deficiency (17-OHD), a rare cause of congenital adrenal hyperplasia. With the deficiency in enzyme function resulting from mutations in CYP17A1, individuals with 46,XY karyotype experience under masculinization of the external genitalia and those with 46,XX karyotype commonly present with absent or delayed pubertal development.13-16 Genetic variation of CYP17A1 is related to estrogen levels,17,18 and has been found to contribute to sex steroid-related tumors, including endometrial,18,19 breast,20-22 and prostate cancer,23,24 in meta-analyses and several cohort studies. In addition to this, a polymorphism in the CYP17A1 gene is associated with polycystic ovary syndrome (PCOS) and insulin resistance.25 Important characteristics of 17-OHD include hypertension, abnormal levels of members of the renin–angiotensin–aldosterone system (RAAS), and electrolyte imbalance. Almost all patients with 17-OHD experience arterial hypertension and hypokalemia as a result of the accumulation of mineralocorticoids, including 11-deoxycorticosterone (DOC) and corticosterone.13-16 Therefore, 17-OHD is considered one of the causes of “monogenic low renin hypertension” because of the suppression of renin levels by the steroid precursors of renin in this condition.26 In clinical practice, hypertension, hypokalemia, suppressed plasma renin activity (PRA), and low-to-normal plasma aldosterone (ALD) levels are the most important diagnostic clues to 17-OHD, indicating dysfunction or reduced enzymatic activity of CYP17A1. However, until now, the relationship between the SNPs related to the CYP17A1 gene and the function and activity of CYP17A1, levels of components of the RAAS, and electrolyte balance were unknown.

The aim of our study was therefore to evaluate the association of the SNP rs11191548, located near the CYP17A1 gene, with hypertension. In addition, we tested rs11191548 for association with related traits including SBP, diastolic blood pressure (DBP), PRA, ALD, and serum sodium (Na+) and potassium (K+) levels in a Han Chinese population.

METHODS

Study population

All of the study participants were of Southern Han Chinese ancestry and resided in the metropolitan Shanghai region. The participants consisted of 1,115 patients with essential hypertension (EH) who were recruited from the hypertension clinic of the Zhongshan Hospital of Fudan University in Shanghai in 2009 and 2010. All of the patients met the 1999 World Health Organization criteria for isolated systolic hypertension (WHO/ISH criteria).27 Secondary forms of hypertension in the patients were ruled out by routine examinations. As a control population, 1,118 participants unrelated to the patients were selected from among individuals aged 20-65 years without any history of chronic diseases who were undergoing health examinations at the Zhongshan Hospital in 2009 and 2010. These individuals had normal BPs (defined as a systolic BP < 130 mm Hg and a diastolic BP < 80 mm Hg) and no history of taking antihypertensive medication. All of the control subjects were over 40 years of age.

Written informed consent was obtained from all of the participants in the study, and the study was approved by the ethics committee of Zhongshan Hospital of Fudan University.

Clinical measurements

The phenotypes of the study participants were extensively characterized for related anthropometric traits. The anthropometric measures used for this were performed and evaluated by trained medical personnel. Weight (kg) and height (m) were measured when the subjects were shoeless and wearing only undergarments. These measurements were then used to calculate the body mass index (BMI) as weight/height². Waist circumference was measured with flexible tape at the smallest horizontal circumference between the costal margin and the iliac crest. Systolic BP and DBP were measured by a nurse with a mercury sphygmomanometer that was adapted for arm size, following 5 minutes of rest with the participant lying in the supine position. Two BP measurements were made at 5-minute intervals, and the mean values were used for the data analysis in the study. The use of all antihypertensive medications and related medications was recorded.

Blood samples were obtained from both the controls and EH patients after an overnight fast and used to measure fasting glucose levels with standardized equipment. Additionally, the EH patients’ PRA and plasma levels of ALD were measured by radioimmunoassay. Blood samples for the measurement of PRA were obtained on the morning of admission and PRA was measured after the participant had maintained an upright posture for 90 minutes, to avoid any confounding effects of posture or diurnal variation in PRA. Levels of PRA below 1.0 μg/ml/h were used to characterize low-renin hypertension (LRH). All of the immunoassays for PRA and ALD were performed in duplicate, and the EH patients’ serum Na⁺ and K⁺ levels were also measured.

Genotyping

The single SNP rs11191548 was selected for analysis in the present study. Genotyping was performed through matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy with a MassARRAY platform (MassARRAY Compact Analyzer, Sequenom, San Diego, CA). The call rate was 99.0%, and the concordance rate of the SNP rs11191548 based on 120 duplicates was 100%.

Statistical analysis

Normally continuous variables were described as mean ± standard deviation (SD), and medians and interquartile ranges were used for non-normally distributed variables. Comparisons between groups were done with Student’s t-test and the chi-squared test for normally distributed continuous and categorical variables, respectively. Deviation
from the Hardy–Weinberg equilibrium was assessed with a chi-squared test. We tested the association of the SNP rs11191548 with hypertension through logistic regression analysis. Multivariate linear regression was used to test for the association of the rs11191548 SNP with quantitative traits. Non-normally distributed values were log-transformed before analysis. All of the models used in the study were adjusted for age, sex, and BMI unless otherwise noted. The analyses were done with SPSS for Windows version 13.0 (SPSS, Chicago, IL). We used the Bonferroni correction (0.05/number of tests performed) for multiple testing. The statistical power of our sample size was 96% for our case–control study (as calculated with G*power version 3.1).

RESULTS

Population characteristics

The characteristics of the participants in this study are presented in Table 1. Of the 2,211 participants, 1,102 were EH patients and 1,109 were normotensive controls. The EH patients were older and had greater BMI and waist circumference values and higher SBP, DBP, and fasting plasma glucose (FPG) levels than the controls. The gender distribution and percentages of subjects in different categories of smoking status were similar in the case and control groups. The general characteristics of the 354 (31.8%) patients with hypertension in both the total study population and in the normotensive controls, rs11191548 remained significantly associated with hypertension in an additive genetic model (CC vs. CT vs. TT; OR = 1.26; 95% CI, 1.10–1.44; P = 0.001). The rs11191548 SNP was significantly associated with hypertension in an additive genetic model (CC vs. CT vs. TT; OR = 1.38; 95% CI, 1.14–1.65; P = 0.001). Additionally, the ORs for TC vs. TT and CC vs. TT were 1.34 (95% CI, 1.10–1.63; P = 0.003) and 1.52 (95% CI, 1.10–2.12; P = 0.014), respectively, in the co-dominant model (Table 2). Because the fasting glucose levels of the hypertensive patients were higher than those of the control subjects, we also performed a multiple logistic regression analysis after adjusting for age, gender, BMI, smoking status, and fasting glucose levels in the 974 hypertensive patients without a history of diabetes and use of hypoglycemic agents. In the 1,109 normotensive controls, rs11191548 remained significantly associated with hypertension (in an additive genetic model: CC vs. CT vs. TT; OR = 1.21; 95% CI, 1.04–1.41; P = 0.015) (Table S1). Furthermore, gender-stratified analysis showed that the association of rs11191548 and hypertension was significant in both male and female study participants (Table S4).

In the controls, the risk-related C-allele was associated with increased SBP (βadj ± SEM = 1.307 ± 0.515, P = 0.011) level after adjustment for age, gender, and BMI (Table 3). After applying the multiple-testing correction, the association of the SNP with SBP levels in the controls (Bonferroni’s

Table 1. Population characteristics of patients with essential hypertension and normotensive controls

<table>
<thead>
<tr>
<th></th>
<th>Normotension (n = 1,109)</th>
<th>Hypertension (n = 1,102)</th>
<th>P value*</th>
<th>Low-renin hypertension and normal/high-renin hypertension in hypertension cases</th>
<th>P value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Low-renin (n = 354)</td>
<td>Normal/high-renin (n = 748)</td>
</tr>
<tr>
<td>Age, years</td>
<td>55.4 ± 10.6</td>
<td>60.9 ± 9.8</td>
<td>&lt; 0.0001</td>
<td>60.9 ± 10.2</td>
<td>60.8 ± 10.7</td>
</tr>
<tr>
<td>Men, %</td>
<td>43.7</td>
<td>46.6</td>
<td>&gt; 0.05</td>
<td>47.9</td>
<td>44.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.0 ± 2.2</td>
<td>25.2 ± 3.3</td>
<td>&lt; 0.0001</td>
<td>25.2 ± 3.3</td>
<td>25.2 ± 3.4</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>79.8 ± 8.7</td>
<td>86.5 ± 10.2</td>
<td>&lt; 0.0001</td>
<td>86.6 ± 9.9</td>
<td>86.2 ± 10.8</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>4.8 ± 0.4</td>
<td>5.5 ± 1.5</td>
<td>&lt; 0.0001</td>
<td>5.5 ± 1.1</td>
<td>5.7 ± 1.4</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114.2 ± 11.3</td>
<td>142.0 ± 17.1</td>
<td>&lt; 0.0001</td>
<td>143.6 ± 17.9</td>
<td>144.4 ± 19.3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>75.6 ± 7.8</td>
<td>83.9 ± 10.2</td>
<td>&lt; 0.0001</td>
<td>84.7 ± 10.6</td>
<td>85.0 ± 13.8</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>21.0</td>
<td>23.8</td>
<td>&gt; 0.05</td>
<td>24.1</td>
<td>23.2</td>
</tr>
<tr>
<td>Ex-smoker, %</td>
<td>9.0</td>
<td>10.9</td>
<td>&gt; 0.05</td>
<td>10.0</td>
<td>12.7</td>
</tr>
</tbody>
</table>

Continuous data are expressed as mean ± standard deviation.

*P value for comparison between hypertension and normotension groups. Adjusted for age except age and percentage of men

**P value for comparison between LRH and N/HRH, adjusted for age (except for the categories “Age” and “Men”).

American Journal of Hypertension 26(4) April 2013 467
The association of rs11191548 with SBP was significant in both male and female participants (Table S5). The associations between SNP rs11191548 and BP levels had no significant differences in hypertensive patients (Table S2).

**Associations of rs11191548 with electrolyte balance, the renin–angiotensin–aldosterone system, and low-renin hypertension in patients with essential hypertension**

After adjustment for gender, age, BMI, and antihypertensive medication, including RAAS-related antagonists (e.g. angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and spironolactone), the risk-related C-allele of rs11191548 was associated with increased Na⁺ (βadj ± SEM = 0.287 ± 0.120, \( P = 0.018 \)) and decreased K⁺ (βadj ± SEM = –0.049 ± 0.020, \( P = 0.014 \)) levels in all of the patients with EH. The C-allele was also associated with decreased PRA (βadj ± SEM = –0.053 ± 0.016, \( P = 0.001 \)) in the EH patients. After multiple-testing correction, the association of the C-allele with PRA (Bonferroni’s \( P = 0.003 \)) remained statistically significant, but the associations of the C-allele with Na⁺ and K⁺ levels became statistically nonsignificant in the EH patients. We also conducted a stratified analysis in the subgroups of 497 (45.1%) patients who were not using RAAS-related antagonists and 119 (10.8%) patients undergoing monotherapy with a calcium-channel blocker (CCB). The PRA levels of patients being treated with RAAS antagonists were slightly higher than those of patients not receiving such therapy, but the difference did not reach significance (median and interquartile range, 1.79, 0.90–3.48, vs. 1.60, 0.82–2.87, respectively; \( P > 0.05 \)). The rs11191548 C-allele was significantly associated with increased Na⁺ (βadj ± SEM = 0.450 ± 0.174, \( P = 0.009 \)) and decreased K⁺ (βadj ± SEM = –0.093 ± 0.028, \( P = 0.001 \)) and PRA levels (βadj ± SEM = –0.067 ± 0.023, \( P = 0.003 \)) in the EH patients not taking RAAS-related antagonists. Additionally, the rs11191548 C-allele was nominally associated with decreased PRA levels (βadj ± SEM= –0.110 ± 0.033, \( P = 0.033 \)) in the patients receiving monotherapy with CCBs. After multiple-testing correction, only the association of the C-allele with decreased K⁺ and PRA levels in the EH patients not taking RAAS-related antagonists (Bonferroni’s \( P = 0.003 \)) remained statistically significant (Table 4).

Our results also showed that the percentages of TC and CC carriers in the 354 patients (32.1%) with LRH were slightly higher than in those in the 748 normal subjects and patients with high-renin hypertension, but this difference did not reach statistical significance (OR = 1.19; 95% CI, 0.98–1.43; \( P > 0.05 \)). A similar analysis of the 119 patients receiving monotherapy with a CCB, of whom 45 (37.8%) had LRH, revealed that the percentages of CC or TC carriers in this LRH subgroup were also relatively higher than in the normal subjects and patients with HRH. However, the results in this population also failed to reach statistical significance (OR = 1.62; 95% CI, 0.94–2.70; \( P > 0.05 \)) (Table S3).

The distribution of hypertensive patients using a beta-receptor blocker or diuretic agent is shown in Table S2. The percentages of patients using a diuretic or beta-receptor blocker without concurrent use of an RAAS antagonist

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**Table 2. Associations of rs11191548 with essential hypertension**

<table>
<thead>
<tr>
<th>Allele Frequency</th>
<th>Controls</th>
<th>Cases</th>
<th>OR (95% CI)</th>
<th>P*</th>
<th>( P_{\text{adj}} )</th>
<th>( P_{\text{rec}} )</th>
<th>( P_{\text{dom}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>74.6</td>
<td>70.0</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>25.4</td>
<td>30.0</td>
<td>1.26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*Adjusted for age, gender, body mass index, and smoking status

\( \text{CI, confidence interval; OR, odds ratio.} \)
were higher than that of patients using an RAAS antagonist (39.8% vs. 10.9%, respectively, P < 0.001, and 16.1% vs. 11.6%, respectively, P = 0.029). The distribution of hypertensive patients using diuretics and a beta-receptor blocker was similar among patients with TT, TC or CC genotypes.

**DISCUSSION**

In the present study, we investigated the effect on hypertension and BP of an SNP that potentially affects steroid-hormone biosynthesis. The SNP rs11191548, near
the CYP17A1 gene, was analyzed in a case–control sample of a Han population in China. The results suggest that rs11191548 is associated with hypertension and SBP levels. These associations were independent of age, gender, BMI, and fasting glucose levels, which are well-established risk factors for hypertension. The GWAS study of hypertension done by the Global BPgen Consortium, which used a population of European ancestry, first reported the existence of the rs11191548 SNP. The effect size of rs11191548 on SBP was approximately 1.3 mm Hg per allele in our study, which was similar to the findings in the study done on the population of European ancestry. In the subsequent GWAS or replication studies done on different ethnic groups, rs11191548 was shown to be associated with hypertension or levels of BP. However, the population of Han ethnicity is the major nationality in China, which is a multinational country. Our results replicated the association of the CYP17A1–gene–related rs11191548 polymorphism with hypertension and SBP in Han Chinese. These results are consistent with the previously reported results in the studies of Europeans and Asians. However, in contrast to the finding in the report of a study of Chinese children, we found no sex-specific effects of rs11191548 on hypertension or BP in the present study.

Cytochrome P17A1 is a single microsomal enzyme with both 17α-hydroxylase and 17,20-lyase activities, which are key catalytic activities in the pathway essential for the production of glucocorticoids. The enzyme function of CYP17A1 is deficient in patients with 17-OHD patients who have a mutation in the CYP17A1 gene. This mutation leads to the accumulation of mineralocorticoids, including DOC and corticosterone, which directly affects electrolyte handling in the kidney and leads to LRH and hypokalemia. The renin levels of these patients have been found to be significantly suppressed, while the ALD levels may be low or normal in these patients. These clinical features reflect the dysfunction of CYP17A1 in patients with 17-OHD. To preliminarily investigate the possible effects of the SNP rs11191548 on the enzymatic activity of CYP17A1, we next examined the association of this SNP with RAAS and electrolyte balance.

We analyzed the association between rs11191548 and Na+, K+, PRA, and ALD levels in all 1,102 of the EH patients in our study. In accord with its association with BP, the C-allele of rs11191548 was associated with decreased K+ and higher Na+ levels in a distribution similar to that of the use of antihypertensive agents in the groups with different genotypes in our study. However, the association of this SNP with Na+ did not reach statistical significance after multiple-testing correction. Carriers of the C-allele also had lower PRA levels, but the ALD levels in groups with different genotypes were similar. Considering the effect of RAAS-related antagonists, we further performed the stratification analysis mentioned earlier. The trend toward higher PRA levels in the hypertensive patients treated with RAAS antagonists may have been due to the different therapeutic responses of these patients to CCBs and diuretics. The associations of rs11191548 with K+ and PRA levels remained statistically significant in the EH patients in the absence of RAAS-related antagonists. In the subgroup of patients receiving monotherapy with CCBs, the significant association of rs11191548 with PRA could not be replicated, mainly because of the relatively small sample size; however, the trend was in the same direction as that observed in all hypertensive patients.

Although the results did not reach statistical significance, the percentages of CC or TC carriers of rs11191548 were relatively higher among the patients with LRH than among normal subjects or those with HRH. It is possible that both sample size and the effects of antihypertensive agents on PRA levels may influence the analysis of the association between rs11191548 and LRH. Nevertheless, through these results, we found that the C-allele of rs11191548 was not only associated with hypertension and SBP levels, as previously described, but was also related to lower levels of K+ and PRA. These findings may explain the mechanism underlying the association of rs11191548 with hypertension and BP. The rs11191548 SNP is located on 10q24, upstream of the CYP17A1 gene and near the 3′ noncoding region, and may be involved in the transcriptional regulation of this gene. Therefore, this SNP may downregulate the expression of the CYP17A1 protein, decrease the process of 17α-hydroxylation, and further lead to the accumulation of DOC and corticosterone, both of which will result in the retention of water and Na+ and renal loss of K+. Patients with the risk-related C-allele of rs11191548 may have the characteristics of hypertension and hypokalemia, which resemble the mild clinical features of 17-OHD. These effects can in part explain the mechanism by which carriers of the C-allele of the rs11191548 SNP have relatively suppressed PRA levels and hypokalemia. However, higher corticosterone levels can also cause hypertension and affect BP. These preliminary results of clinical functional studies suggest that rs11191548, which is located near CYP17A1, may influence the enzymatic activity of CY17A1 and lead to LRH, with relative hypokalemia as a result of the accumulation of DOC and corticosterone. The rs11191548-related reduced enzymatic activity of CYP17A1 in vivo may be responsible for the effect of this polymorphism on hypertension and BP.

There were some limitations to our study. First, we did not measure the levels of DOC and corticosterone in our subjects, and measured electrolytes and RAAS only in patients with hypertension. In addition, the study was a case-controlled, hospital-based study. To overcome these limitations, the findings in the present study will be reassessed in the Changfeng study, a population-based prospective study of a Chinese population. Moreover, our study examined only one SNP, whereas other functional SNPs and tagging SNPs are worthy of study. Beyond this, functional studies at the molecular level could help determine the mechanism by which rs11191548 SNP can influence the function and activity of CYP17A1.

In summary, we replicated the associations of the SNP rs11191548, located near the CYP17A1 gene, with hypertension and SBP in a Chinese Han population. We also and consistently showed that the minor C-allele of CYP17A1 is associated with lower K+ and PRA levels in hypertensive patients, which suggests a putative role for this variant in hypertension through an effect on the enzymatic activity of CYP17A1 and the accumulation of mineralocorticoids.
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DISCLOSURE

The authors declared no conflict of interest.
Li et al.


