A Functional Variant of NEDD4L Is Associated With Hypertension, Antihypertensive Response, and Orthostatic Hypotension

Fang Luo, Yibo Wang, Xiaojian Wang, Kai Sun, Xianliang Zhou, Rutai Hui

Abstract—NEDD4L is involved in the regulation of plasma volume and blood pressure by controlling cell surface expression of the kidney epithelial Na$^+$ channel. Previously, the cryptic splice variant rs4149601(G/A) A allele of NEDD4L, generating isoform I, was estimated to decrease blood pressure by downregulating Na$^+$ reabsorption. However, a recent functional study showed that isoform I should lead to abnormal Na$^+$ reabsorption increases by antagonistically downregulating epithelial Na$^+$ channel activities. To determine whether the variant rs4149601 A allele is a risk factor for hypertension, has an impact on the antihypertensive response to hydrochlorothiazide, and is associated with orthostatic hypotension, we performed a case-control study of hypertension (n = 1686), a 4-week clinical trial (n = 542), and a case-control study of orthostatic hypotension (n = 793) in Chinese subjects. We found that the A allele was significantly associated with hypertension after appropriate adjustment (odds ratio: 1.39; 95% CI: 1.13 to 1.72; P = 0.002). The blood pressure reduction in A carriers after hydrochlorothiazide treatment was greater than that in GG carriers, with differences of 6.1 mm Hg (P = 0.009) in systolic blood pressure and 2.7 mm Hg (P = 0.027) in diastolic blood pressure. The A allele was significantly associated with orthostatic hypotension after adjustment for cardiovascular risk factors (odds ratio: 0.68; 95% CI: 0.48 to 0.98; P = 0.039). In conclusion, rs4149601 is a genetic risk factor for hypertension and a protective factor against orthostatic hypotension in hypertensive subjects, and the antihypertensive response to hydrochlorothiazide is more sensitive in A allele carriers than in GG carriers. Consequently, the A allele may be a useful marker for predicting hypertension, orthostatic hypotension, and antihypertensive response to hydrochlorothiazide. (Hypertension. 2009;54:796-801.)

Key Words: NEDD4L hypertension ■ antihypertensive response ■ orthostatic hypotension ■ genetic ■ Na$^+$ reabsorption

The epithelial Na$^+$ channel (ENaC)-NEDD4L-proteasome system plays an important role in blood pressure (BP) regulation.1 NEDD4L is the key link of this system. Because of the importance of NEDD4L for Na$^+$ homeostasis, mutations in NEDD4L may be responsible for BP phenotypes. A frameshift mutation of NEDD4L, rs4149601(G/A), results in premature truncation of the NEDD4L protein2 and has been shown to be associated with ambulatory BP and progression of BP over time.3 It has also been found to be associated with salt sensitivity, an intermediate phenotype of BP.4 However, the issue of whether rs4149601 is a contributing factor to hypertension and orthostatic hypotension (OH) is poorly understood. Russo et al5 found that the A allele is a risk factor for hypertension in a case-control study. However, a later study showed that the G allele is a risk factor for hypertension in men,6 and another study showed no association between rs4149601 and hypertension.7 These controversial results may be partly derived from inadequate sample sizes. Notably, a recent functional study8 identified a great change in the knowledge surrounding rs4149601. Initially, the rs4149601 G allele was estimated to be a risk factor for hypertension on the basis of functional studies of NEDD4, a paralog of NEDD4L.3,4 A subsequent study demonstrated that NEDD4L isoform I, which is generated by the rs4149601 A allele, led to abnormally increased Na$^+$ reabsorption.8 This finding implies that the A allele may be the real risk factor for hypertension. A large case-control study needs to be carried out to clarify the effect of this important variant on hypertension.

This variant may also become involved in hypertension treatments. Manunta et al9 observed that BP responses to diuretics are greater in hypertensive patients who carry a combination of the common alleles of the ADD1, WNKI, and NEDD4L genes compared with other patients. However, the effect of rs4149601 alone on BP responses remains unclear.
Clarification of this issue may be very useful toward understanding the function of rs4149601 and providing clues for antihypertensive drug selection. The association between rs4149601 and OH also needs to be elucidated. Systematic studies of associations of the variant with hypertension, BP responses, and OH can be explained by a uniform theory, which is suggested by the recent functional study. The systematic studies strengthen the reliability of the results and provide complete insights into the function of rs4149601.

In the present study, on the basis of the results of the recent functional study, we examined whether the A allele is a risk factor for hypertension through a large-scale, case-control study. Next, we investigated whether the A allele has a greater effect on the antihypertensive response to the diuretic hydrochlorothiazide (HCTZ). Finally, we analyzed the relationship between the A allele and OH.

**Methods**

The studies were approved by the ethical committees of both FuWai Hospital and local collaborative hospitals and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from each individual enrolled before entry into the study, and all of the procedures were in accordance with institutional guidelines. All of the participants reported to be of Han Chinese descent.

**Case-Control Study of Hypertension**

A total of 833 unrelated hypertensive patients and 853 age and sex frequency-matched controls were recruited from screening in 7 communities in Henan province, China. Patients were defined as hypertensive if their systolic BP (SBP) and/or diastolic BP (DBP) levels were ≥140/90 mm Hg on 3 occasions within 2 months or if they were taking drugs for high BP. Normotensive controls were defined as having SBP and DBP levels of <140/90 mm Hg with no family history of hypertension. Subjects were excluded from entry into the study if they had evidence of previous stroke, coronary heart disease, diabetes mellitus, renal diseases, or secondary hypertension.

**HCTZ Treatment Study**

Potential subjects for the HCTZ treatment study were chosen from the hypertensive patients in the first case-control study. We only recruited the patients who stopped antihypertensive therapy themselves (noncompliance) for >1 month before our study. The exclusion criteria were as follows: inability to continue antihypertensive treatment for 4 weeks; SBP of >180 mm Hg and/or DBP of >110 mm Hg; inability to discontinue drugs that could antagonize the effect of HCTZ; allergy to HCTZ; stroke; coronary heart disease; diabetes mellitus; renal diseases; or secondary hypertension.

A total of 542 hypertensive patients were enrolled in the 4-week clinical trial from March to May 2005. By screening, we found that 4 kinds of antihypertensive drugs had been taken by 71 patients, including a diuretic, β-blocker, calcium channel blocker, and angiotensin-converting enzyme inhibitor. These patients had a 1-month washout before starting HCTZ. The patients were treated with 12.5 mg of HCTZ twice daily. BP and drug adverse effects were recorded at the end of the first 2 weeks. If the SBP/DBP levels were ≥140/90 mm Hg or drug adverse effects were detected, HCTZ was added to or replaced by other kinds of antihypertensive drugs (n=231). Otherwise, the patients continued with the treatment of 12.5 mg of HCTZ twice daily (n=311). BP was measured again at the end of the second 2 weeks of treatment. The differences in the BP levels between posttreatment and pretreatment were defined as the responses to antihypertensive drugs.

**Case-Control Study of OH**

A total of 793 hypertensive patients in the first case-control study underwent supine and standing BP measurements. The baseline readings were the BP measurements with the subject in the supine position after 5 minutes of rest. The measurements were repeated in the standing position after 1 and 3 minutes. OH was defined as a drop of ≥20 mm Hg in SBP or a drop of ≥10 mm Hg in DBP from the supine position to the standing position at any of 2 measurement points.

**Measurements**

All of the participants were asked to avoid alcohol, smoking, coffee, tea, and exercise for ≥30 minutes before the BP measurements. A standardized mercury sphygmomanometer and appropriate cuff size (regular adult, large, or thigh) were used by trained nurses to measure the BP in the patient’s right arm. The sitting BP was measured 3 times ≥30 seconds apart after ≥5 minutes of rest, and the average was defined as the BP level. Weight and height were recorded for calculation of the body mass index (BMI). Blood specimens were drawn after overnight fasting and analyzed for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and glucose. A structured questionnaire was used for data collection.

**Genotyping**

Genomic DNA was extracted from whole blood. The rs4149601 variant was amplified by allelic discrimination with a 232-bp sequence with the following primers: 5'-CCGTGTAAGCTGCTTTCTGGG3' and 5'-CCAAGGCAAAGTCTTACCGAAGTGTA3'. The resultant PCR products were digested with KpnI (New England Biolabs), which yielded 2 DNA bands for the G allele and 1 DNA band for the A allele after 4% agarose gel electrophoresis. The reproducibility of the genotyping was subsequently confirmed by randomly selected bidirectional sequencing in 10% subjects and was found to be 100%.

**Statistical Analysis**

Data are expressed as mean±SD. Quantitative variables in the clinical characteristics of the subjects in the 2 case-control studies were compared by 1-way ANOVA and Student t test. The χ² test was used to verify categorical variables and Hardy-Weinberg equilibrium of the variant frequencies. The associations of the genetic variants with hypertension and OH were analyzed by multivariate logistic regression, adjusted by age, sex, and other cardiovascular risk factors. Linear regression modeling was used to assess the associations of the BP responses with the genotypes, after adjustment for pretreatment BP, age, sex, BMI, and glucose. Differences between the rs4149601 genotypes in the effects of HCTZ treatment from baseline to 4 weeks of BP measurements were investigated by ANCOVA. A 2-tailed value of P<0.05 was considered significant. All of the analyses were performed with SPSS 13.0 for Windows.

**Results**

**A Allele of rs4149601 Is Associated With Hypertension**

The clinical characteristics of the patients and controls in the case-control study are shown in Table 1. Significantly higher frequencies of the A allele and AA genotype were significantly higher in hypertensive patients than in controls. To study the effect of the A allele on the hypertension risk, a dominant model was used to analyze the association of the rs4149601 A allele with hypertension. The results revealed a significant association of the A allele with hypertension (crude odds ratio [OR]: 1.34; 95% CI: 1.10 to 1.64; P=0.004). Multivariate analysis was used to adjust for age, sex, BMI, and other cardiovascular risk factors. The adjusted OR of the A allele was 1.34 (95% CI: 1.10 to 1.64; P=0.004).
A Allele of rs4149601 Is Associated With BP Responses to HCTZ

In the first 2 weeks of HCTZ treatment, all of the enrolled patients (n=542) took HCTZ alone. The BP reduction in A allele carriers was greater than that in GG carriers. As shown in the Figure, part A, the differences were 3.0 mm Hg for SBP and 1.7 mm Hg in DBP but did not reach statistical significance (P=0.129 and P=0.076, respectively). In the second 2 weeks of HCTZ treatment, 311 patients continued with HCTZ alone. The SBP and DBP reductions in A carriers were greater than those in GG carriers by 6.1 mm Hg (P=0.009) and 2.7 mm Hg (P=0.027), respectively (Figure, part B). However, in the patients without HCTZ or with HCTZ treatment plus another drug, the BP responses at the end of 4 weeks showed no differences between A carriers and GG carriers (Figure, part C). These results suggest that NEDD4L rs4149601 A allele carriers are particularly sensitive to HCTZ treatment, especially chronic HCTZ treatment.

A linear regression analysis showed that rs4149601 was significantly associated with both SBP and DBP responses to HCTZ (P<0.05). The associations remained after adjustment for covariates, including pretreatment BP, age, BMI, and glucose. The covariates, together with rs4149601, accounted for 35.4% of the interindividual variation in the SBP responses and 37.0% of the interindividual variation in the DBP responses to HCTZ (Table 3).

A Allele of rs4149601 Is Associated With OH

The prevalence of OH in this study was 23.46% (186 of 793). Among the clinical characteristics of the patients and controls, the only significant difference was age. The OH patients were older than the controls (P<0.05; Table 4). The genotype frequencies for rs4149601 were in accordance with Hardy-Weinberg equilibrium in both OH patients and controls. As shown in Table 5, the A allele exhibited a trend to be a protective factor against OH, but the data did not reach statistical significance (OR: 0.81; 95% CI: 0.58 to 1.14; P=0.24). The association between the A allele and OH was significant after adjustment for age, sex, and other cardiovascular risk factors by multivariate logistic regression analysis (OR: 0.68; 95% CI: 0.48 to 0.98; P=0.039). This finding implies that the A allele is a protective factor against OH and confirms the hypothesis that NEDD4L has a close relationship with OH.

Discussion

In the present study, we found that the rs4149601 variant of NEDD4L showed associations with the risk of hypertension, protection against OH, and BP responses to HCTZ. The contribution of the rs4149601 A allele to the risk of hypertension was independent of age, sex, and other conventional risk factors. After 4 weeks of continuous HCTZ treatment, the rs4149601 A allele also exhibited independent sensitive BP responses in both SBP and DBP. Previously, the A allele was estimated to decrease BP by downregulating Na+ reabsorption. However, a recent functional study showed that isofrom I would lead to abnormal Na+ reabsorption increases by antagonistically downregulating ENaC activity. Our present results are in accord with the recent functional study, which may clarify the knowledge regarding the NEDD4L rs4149601 A allele. Furthermore, to the best of our knowledge, this is the first study to reveal that A allele carriers are especially sensitive to HCTZ and is also the first to reveal that the NEDD4L A allele is a protective factor against OH in hypertensive subjects.

rs4149601 is a common variant of NEDD4L. The frequencies of allele A varied from 16% to 41% in different ethnic groups, being relatively higher in whites (33% to 41%) and lower in Asians (16% to 21%). In the present study, the A

Table 2. Association of rs4149601 With Hypertension

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Genotype, n (%)</th>
<th>Additive Model for A Allele (A&lt;--&gt;G), Crude OR (95% CI)</th>
<th>Dominant Model for A Allele (AA+AG&lt;--&gt;GG), Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AA</td>
<td>AG</td>
<td>GG</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>38 (4.6)</td>
<td>311 (37.3)</td>
<td>484 (58.1)</td>
<td>1.31 (1.11 to 1.55)</td>
</tr>
<tr>
<td>Normotensive</td>
<td>22 (2.6)</td>
<td>276 (32.4)</td>
<td>555 (65.1)</td>
<td>P=0.002</td>
</tr>
</tbody>
</table>

The OR and 95% CI values were calculated by multivariate logistic regression analyses. The adjusted OR was obtained by using multivariate logistic regression analysis after adjustment of age, sex, BMI, cigarette smoking, alcohol intake, glucose, HDL-C, LDL-C, and TC.
allele frequency was 21%. It is located at the splice junction of the putative exon 1 and results in a 10-nucleotide splicing site moving to the 3' end of NEDD4L, thereby leading to a change in the translated reading frame. This frameshift mutation generates a disrupted isoform, designated "isoform I," and produces a novel NEDD4L C2 domain.2 On the other hand, the G allele encodes an ancestral isoform and an evolutionarily conserved C2 domain.8 The C2 domain, which can be found in both NEDD4L and its paralog NEDD4 in humans, plays a significant role in the transfer of its product to the apical membrane of epithelial cells.2 The effects of the C2 domain and isoform I on Na⁺ reabsorption have become clearer over recent years. Initially, the function of the C2 domain in NEDD4L was considered to be the same as that in NEDD4. In other words, NEDD4L without the C2 domain would downregulate ENaC more potently than NEDD4L with the C2 domain.10 It was also considered that the novel C2 domain generated by the rs4149601 A allele had no function.2 Therefore, many researchers estimated that the A allele would decrease BP by downregulating Na⁺ reabsorption.3,4 However, recent studies have shown that, unlike NEDD4, NEDD4L with and without the C2 domain can robustly reduce ENaC activity.11,12 Furthermore, isoform I generated by the A allele does not downregulate ENaC activity, as proposed previously. On the contrary, isoform I has significant antagonistic activity against ENaC downregulation.8 Our present results strengthen these new lines of functional evidence, which clarify that the rs4149601 A allele is a risk factor for hypertension. Moreover, the contribution of the A allele to the risk of hypertension is independent of other hypertension risk factors.

We further found that rs4149601 predicted both SBP and DBP responses to HCTZ. HCTZ is a type of diuretic that functions by reducing Na⁺ reabsorption. It exerts this diuretic action by binding to Na⁺-Cl⁻ cotransporters in the distal convoluted tubules of the kidney. HCTZ also has effects on other ion transporters, including ENaC.13 An increase in ENaC abundance in the outer medulla induced by chronic HCTZ treatment was found in rats,14 suggesting an interaction between them. In the kidney, ENaC is primarily involved in regulating fluid and Na⁺ reabsorption by facilitating Na⁺ entry from the lumen into the cells.15 It is believed that ENaC constitutes the limiting step of Na⁺ transport through the cell and, hence, represents the major target of regulation. However, the degradation of ENaC from the cell surface is determined by NEDD4L via enhanced endocytosis or, alternatively, by induced translocation of ENaC into lysosomal multiple vesicular bodies.16 All of the above analyses suggest that HCTZ may regulate Na⁺ reabsorption together with NEDD4L. The rs4149601 A allele plays important roles in the structure and function of NEDD4L. It increases Na⁺ reabsorption through upregulation of ENaC, leading to a high BP. In addition, the patients with hypertension, which is mainly caused by abundant Na⁺ reabsorption, exhibited more

Table 3. Model Predicting BP Response to HCTZ After 4 Weeks

<table>
<thead>
<tr>
<th>Genotype</th>
<th>After 4 wk</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>∆ SBP, mm Hg</td>
<td></td>
</tr>
<tr>
<td>AA+AG (n=125)</td>
<td>23.3 (21.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>GG (n=186)</td>
<td>17.2 (18.6)</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>P=0.009</td>
<td></td>
</tr>
<tr>
<td></td>
<td>∆ DBP, mm Hg</td>
<td></td>
</tr>
<tr>
<td>AA+AG (n=125)</td>
<td>10.6 (10.7)</td>
<td>0.047</td>
</tr>
<tr>
<td>GG (n=186)</td>
<td>7.9 (10.6)</td>
<td>0.025</td>
</tr>
<tr>
<td></td>
<td>P=0.027</td>
<td></td>
</tr>
</tbody>
</table>

Rs4149601 was first considered by itself as a predictor of the BP responses and then considered after adjustment for concomitant variables, including pretreatment BP, age, sex, BMI, glucose, and rs4149601 (model). β is the standardized regression coefficient. \( R^2 \) is the percentage of interindividual variation in the BP responses explained by rs4149601 alone and by predictors in the model.
Table 4. Clinical Characteristics of the OH Patients and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OH</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>186</td>
<td>607</td>
</tr>
<tr>
<td>Age, y*</td>
<td>59.8 (7.9)</td>
<td>57.7 (8.5)</td>
</tr>
<tr>
<td>Men</td>
<td>30.1</td>
<td>33.1</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 (3.4)</td>
<td>26.1 (3.5)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>169.4 (23.9)</td>
<td>167.6 (22.0)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>98.0 (13.5)</td>
<td>99.8 (11.4)</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.4 (1.1)</td>
<td>5.5 (1.5)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>5.6 (1.2)</td>
<td>5.5 (1.1)</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>3.1 (1.0)</td>
<td>3.1 (0.9)</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>1.6 (0.3)</td>
<td>1.6 (0.3)</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>19.4</td>
<td>15.5</td>
</tr>
<tr>
<td>Alcohol intake, %</td>
<td>17.2</td>
<td>17.3</td>
</tr>
</tbody>
</table>

Values are given as the mean (SD) unless otherwise specified. *P<0.05, OH patients vs controls.

Table 5. Association of rs4149601 With OH

<table>
<thead>
<tr>
<th>Genotype, n (%)</th>
<th>Crude OR (95% CI)</th>
<th>P</th>
<th>Adjusted OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>AA+AG</td>
<td>GG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OH</td>
<td>70 (37.6)</td>
<td>116 (62.4)</td>
<td>0.81 (0.58 to 1.14)</td>
<td>0.24</td>
</tr>
<tr>
<td>Controls</td>
<td>259 (42.7)</td>
<td>348 (57.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

The OR and 95% CI values were calculated by multivariate logistic regression analyses. The adjusted OR was stratified by age, sex, SBP, DBP, family hypertensive history, BMI, cigarette smoking, alcohol intake, glucose, HDL-C, LDL-C, and TC. NA indicates not applicable.
are used to test salt sensitivity. In our large-scale study, however, it was hard to control the salt intake or acute Na⁺ load. These data will be collected in the next phase of our study. Lastly, in this study, we focused on the relationship between rs4149601 and BP. It is necessary to clarify whether other variants of NEDD4L have any effects on BP in future.

In conclusion, the present study confirms that the A allele is a risk factor for hypertension and provides evidence for a pharmacogenetic association of the NEDD4L variant rs4149601 A allele with changes in SBP and DBP after 4 weeks of HCTZ treatment. The present results are supported by the recent functional findings in Araki et al and may clarify the knowledge of the NEDD4L rs4149601 A allele. Furthermore, the present study provides the first evidence that the NEDD4L rs4149601 A allele is a protective factor against OH in hypertensive subjects. The present conclusions will be strengthened by replication in another population in an additional study and may highlight a new aspect of NEDD4L rs4149601 A allele functions.

**Perspectives**

The interactions between NEDD4L and ENaC play crucial roles in Na⁺ homeostasis and BP regulation. The NEDD4L rs4149601 A allele leads to a significant change in the NEDD4L structure, which affects ENaC regulation and leads the A allele to become involved in the interactions. Therefore, further research on NEDD4L will focus on the rs4149601 A allele. From the functional aspect, the pathophysiological mechanisms of hypertensive and hypertensive disorders related to isoform I and the novel C2 domain of NEDD4L need to be studied. From the clinical aspect, the long-term clinical outcomes will be evaluated by targeting the ENaC-NEDD4L-protesome system, with the aim of establishing an optimal approach for personalizing antihypertensive medication treatment.

**Acknowledgment**

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**Disclosures**

None.

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