Association of Genetic Variants of Klotho with BP Responses to Dietary Sodium or Potassium Intervention and Long-Term BP Progression

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Keywords
Klotho · Single-nucleotide polymorphisms · Salt sensitivity · Potassium sensitivity · Blood pressure

Abstract
Objectives: Klotho (KL) plays pivotal roles in the progression of salt-sensitive hypertension. Salt-sensitive hypertension was associated with KL genotypes. We aimed to explore the association of common genetic variants of KL with individual blood pressure (BP) responses to sodium and potassium through a dietary intervention study as well as long-term BP progression. Methods: We conducted family-based dietary interventions among 344 participants from 126 families in rural villages of northern China in 2004. Subjects sequentially underwent a baseline diet, a low-salt diet (51.3 mmol/day Na), a high-salt diet (307.8 mmol/day Na), and a high-salt + potassium supplementation diet (307.8 mmol/day Na + 60 mmol/day K). After dietary intervention, we followed up with these participants in 2009 and 2012. The associations between 6 single-nucleotide polymorphisms (SNPs) of KL and phenotypes were analyzed through a linear mixed-effects model. Results: SNPs rs211247 and rs1207568 were positively correlated with the BP response to high-salt diet in the dominant model after adjusting for confounders (β = 1.670 and 2.163, p = 0.032 and 0.005, respectively). BPs rs526906 and rs525014 were in a haplotype block. Block rs526906-rs525014 was positively correlated with diastolic BP response to potassium and potassium sensitivity in the additive model (β = 0.845, p = 0.032). In addition, regression analysis indicated that rs211247 was associated with long-term systolic BP alterations after 8 years of follow-up in the recessive model (β = 20.47, p = 0.032). Conclusions: Common variants of the KL gene might modify individual BP sensitivity to sodium or potassium and influence the long-term progression of BP, suggesting a potential role in the development of salt-sensitive hypertension. Thus, KL may be a new early intervention target for salt-sensitive hypertension.

Introduction
Salt sensitivity refers to the divergent responses of blood pressure (BP) to changes in salt, which is an intermediate phenotype of hypertension. This trait is a product of the interaction between genetic and environmental effects. Current evidence indicates that genetic compo-
Klotho SNPs and BP Responses to Sodium and Potassium

Therefore, we conducted a family-based dietary intervention to examine the influences of genetic variations of the KL gene on salt sensitivity in Chinese adults and assessed the interactions between KL SNPs and BP responses to potassium supplementation. Furthermore, we followed up with these participants twice to explore the associations of KL gene polymorphisms with long-term BP progression.

**Methods**

**Study Population**

A community-based BP screening was conducted to identify probands in 7 villages of Baoji in northern China from October 2003 to October 2004. Participants of Han ethnicity aged 18–60 years with a BP of 130–160 mm Hg/85–100 mm Hg and free from antihypertensive treatments were included as probands. Their parents, siblings of 2-generation families, their spouses, and offspring in 3-generation families were also recruited in this study. Individuals who had stage 2 hypertension, secondary hypertension, severe cardiovascular disease or diabetes mellitus, liver or renal dysfunction, alcohol abuse, or pregnancy were excluded. Informed written consent was obtained in accordance with the Declaration of Helsinki and the policy of the Ethics Committee of Xi’an Jiaotong University Medical School.

**Dietary Intervention**

The probands, their siblings, spouses, and offspring underwent dietary sodium and potassium interventions. As previously described [9], participants first received a baseline diet for 3 days. During this period, standard questionnaire and anthropometric data collection were administered by trained staff at baseline. After that, they sequentially received a low-salt diet (51.3 mmol/day sodium) for 7 days, a high-salt diet (307.8 mmol/day sodium) for 7 days, and a high-salt plus potassium diet (307.8 mmol/day sodium + 60 mmol/day potassium) for another 7 days (Fig. 1). To ensure the dietary compliance, each participant was required to have their breakfast, lunch, and dinner in research kitchen with professional chefs under the supervision of staff. Prepackaged salt and potassium pills were given to participants before each meal which was free from salt while cooking. Participants were instructed to avoid extra food or beverages out of the study kitchen. Besides, we collected 24-h urine during each period to verify the dietary compliance.

**BP Measurement**

Sitting BP was obtained by qualified physicians using a standard mercury sphygmomanometer for 3 times with 1-min interval during each day of baseline and at the fifth–seventh day of each period. Systolic BP (SBP) and diastolic BP (DBP) were the first and fifth Korotkoff sounds, respectively. All staff were blinded to the intervention protocol. Participants were instructed to avoid alcohol, coffee, tea, and cigarette, and rest in sitting position for >30 min prior to BP measurement. Mean arterial pressure (MAP) was calculated as 1/3 SBP + 2/3 DBP. The average of 9 BP measurements was used as the BP of each participant.
The responses of BP to dietary sodium and potassium intervention were analyzed as continuous variables and categorical variables, respectively. As a continuous variable, BP responses were defined as the absolute changes in BP during each intervention period and the percentage of BP alterations. To date, there is no consistent standard to define salt sensitivity. We adopted the concept of salt sensitivity index (SSI). SSI = (MAP of high-salt diet – MAP of low-salt diet)/MAP of low-salt diet. We used 2 cutoff values to define salt-sensitive subjects, namely, 10% and 5%. SSI ≥5% were recognized as initially salt sensitive. We then used 10% as the cutoff value to further validate our results. Similarly, to define potassium-sensitive subjects, we used the following: (MAP of high-salt diet – MAP of high-salt plus potassium diet)/MAP of high-salt plus potassium diet. Those with a value ≥10% or 5% during high-salt plus potassium period were defined as potassium-sensitive subjects.

Follow-Up Data Collection
We followed up all the participants who underwent dietary intervention twice in 2009 and 2012 to explore the effects of genetic variants on long-term BP progression. Anthropometric data were collected, and BP was measured 9 times during each follow-up. A standard questionnaire was conducted to determine the history of hypertension and use of antihypertensive medications.

SNP Selection and Genotyping
In this study, 9 tagSNPs from KL were selected as the study sites according to previous studies. The minor allele frequency (MAF) of each SNP <5% in the HapMap Chinese Han Beijing population was excluded from this study. Genomic DNA was extracted and purified from fresh/frozen whole blood samples by a commercial kit (GoldMag Co. Ltd., Xi’an, China) according to the manufacturer’s instructions. All genotyping experiments were conducted by Genesky Biotechnologies Inc. (Shanghai, China). Genotyping was performed by using an improved ligase-based multiplex SNP genotyping system (iMLDR), the accuracy of which was higher than 98%. The raw data were analyzed in GeneMapper 4.1.

Statistical Analyses
The Mendelian consistency of the SNP genotype data was assessed by PLINK. Parental SNP data were used to assess the Hardy-Weinberg equilibrium through Haploview software (version 4.2, http://www.broad.mit.edu/mpg/haploview) to estimate the extent of pairwise linkage disequilibrium between SNPs. Variables at baseline, during intervention, and follow-up are presented as the means ± standard deviations for continuous variables and as percentages for categorical variables. The associations of SNPs with BP responses to dietary intervention and longitudinal BP alterations were analyzed through a linear mixed-effects model in 3 genetic models (additive, dominant, and recessive). We used a sandwich estimator to account for the nonindependence of family members in this family-based study, which presumed that all family members were at the same degree of dependency. The false discovery rate method was used for the adjustment of multiple testing. A p value of 0.05 was used as the threshold for statistical significance.

Results
Characteristics of Participants
A total of 515 participants from 126 families were included in this study, and 344 underwent dietary intervention. Baseline characteristics were determined as previously reported (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000519839) [10]. Individual BP decreased during low-salt diet and increased while shifting to high-salt diet. Potassium supplementation could significantly attenuate high-salt-induced BP elevation. The absolute changes in BP during each intervention period were more pronounced in the probands and are summarized in Table 1. The 24-h urinary Na and K of each period were as follows: 215.7 ± 19.2 mmol, 37.6 ± 12.1 mmol at baseline; 54.9 ± 11.2 mmol, 37.0 ± 9.8 mmol at low-salt diet; 310.0 ± 27.0 mmol, 41.1 ± 11.9 mmol at high-salt diet; and 325.8 ± 27.4 mmol, 87.1 ± 12.9 mmol at high-salt plus potassium supplementation period. These results depicted the unhealthy dietary pattern of northern China characterized by high salt and insufficient potassium intake as well as the good compliance of participants to dietary intervention.

KL SNPs and BP Responses to Dietary Intervention
Detailed information on the 9 KL SNPs, including genomic location, MAF, and HWE test, is shown in Table 2. The MAFs of rs9536314, rs9527025, and rs9527026 were <5%, so they were excluded from the subsequent analysis.

We failed to find any statistical correlation of 6 KL gene SNPs with BP parameters at baseline and during...
The associations of *KL* SNPs with the BP responses to dietary high-salt and high-salt plus potassium periods are summarized in Table 3. After adjusting for age, sex, BMI, and multiple testing, rs211247 and rs1207568 were positively correlated with the BP response to high-salt diet in the dominant model (\( \beta = 1.670 \) and \( 2.163 \), \( p = 0.032 \) and \( 0.005 \), respectively). In addition, rs526906 and rs525014 SNPs were in a haplotype block. Block rs526906-rs525014 was positively correlated with the DBP response to potassium in the additive model (\( \beta = 0.8452 \), \( p = 0.005 \)).

While salt and potassium sensitivity were set as categorical variables and 10% and 5% MAP alterations were set as standards, we found that rs211247 was correlated with salt sensitivity when 10% was set as the standard. SNP rs1207568 was significantly associated with salt sensitivity regardless of the standard. Furthermore, block rs526906-rs525014 and potassium sensitivity showed a positive correlation regardless of the standard in the additive model (Table 4).

### KL SNPs and Long-Term BP Progression

In 2009 and 2012, we followed up with participants undergoing dietary interventions twice to determine the influence of *KL* SNPs on long-term BP progression. There were 344 participants in 2004, 277 in 2009, and 265 in 2012. No significant difference was observed between the remaining participants and those lost during follow-up.
As shown in Table 5, the BP of probands and siblings significantly increased in 2009. The SBP of all participants showed a prominent increase in 2012 compared with that in 2004. There were 3.5% hypertensive participants at baseline and 23.4% in 2012. Regression analysis showed that rs211247 was associated with long-term SBP alteration from 2004 to 2012 in the recessive model ($\beta = 20.47$, $p = 0.032$) (Table 6).

### Table 3. Association of $KL$ SNPs with BP responses to dietary intervention

| SNP         | Allele | $\Delta$SBP | $\Delta$DBP | $\Delta$MAP |
|-------------|--------|--------------|--------------|-------------|
|             | $B$    | $p$ value    | $B$          | $p$ value   | $\beta$     | $p$ value |
| High sodium intervention |        |              |              |             |
| rs211247    | C      | 0.2914       | 0.7354       |             |            | 1.6700     | 0.0319a   |
| rs1207568   | A      | 0.9048       | 0.2854       |             |            | 2.1630     | 0.0046a   |
| rs526906    | A      | 0.4466       | 0.5471       |             |            | 0.2740     | 0.6833    |
| rs525014    | A      | 0.4466       | 0.5471       |             |            | 0.2740     | 0.6833    |
| rs564481    | T      | 0.2109       | 0.7816       |             |            | 0.6633     | 0.3357    |
| rs650439    | T      | 0.6427       | 0.4430       |             |            | 0.1935     | 0.7724    |
| High sodium plus potassium intervention |        |              |              |             |
| rs211247    | C      | 0.3153       | 0.6719       |             |            | 0.2997     | 0.6243    |
| rs1207568   | A      | 0.6730       | 0.9213       |             |            | 0.7917     | 0.1877    |
| rs526906    | A      | 0.4514       | 0.4818       |             |            | 0.8452     | 0.0322b   |
| rs525014    | A      | 0.4514       | 0.4818       |             |            | 0.8452     | 0.0322b   |
| rs564481    | T      | −0.2241      | 0.7331       |             |            | 0.0102     | 0.9849    |
| rs650439    | T      | 0.5175       | 0.4173       |             |            | 0.6977     | 0.1831    |

$p$ values were corrected for age, gender, BMI, and multiple testing (FDR <0.05). For those associations that were not significant under any model, $\beta$ and $p$ values for the additive model were listed. Bold values are statistically significant. SNP, single-nucleotide polymorphism; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BP, blood pressure; $KL$, Klotho. a Dominant model. b Additive model.

### Table 4. Associations of $KL$ SNPs with salt and potassium sensitivity

| SNP         | Allele | Salt sensitivity | Potassium sensitivity |
|-------------|--------|------------------|-----------------------|
|             |        | 10% $B$          | 5% $B$ | 10% $\beta$ | 5% $\beta$ |
|             |        | $p$ value        | $p$ value | $p$ value | $p$ value |
| rs211247    | C      | 0.5525          | 0.0360a | 0.6565 | 0.1116 | 0.6894 | 0.3180 | 1.0880 | 0.7532 |
| rs1207568   | A      | 0.5654          | 0.0399a | 0.5907 | 0.0276a | 0.6606 | 0.2577 | 0.8810 | 0.6282 |
| rs526906    | A      | 0.6562          | 0.1390 | 0.8355 | 0.4358 | 0.5000 | 0.0463b | 0.6269 | 0.0444b |
| rs525014    | T      | 0.6562          | 0.1390 | 0.8355 | 0.4358 | 0.5000 | 0.0463b | 0.6269 | 0.0444b |
| rs564481    | T      | 0.7886          | 0.4062 | 0.7538 | 0.2290 | 1.6110 | 0.1991 | 1.0480 | 0.8432 |
| rs650439    | T      | 0.6111          | 0.0848 | 0.8768 | 0.5663 | 0.5831 | 0.1193 | 0.6933 | 0.0536 |

$p$ values were corrected for age, gender, BMI, and multiple testing (FDR <0.05). For those associations that were not significant under any model, $\beta$ and $p$ values for the additive model were listed. Bold values are statistically significant. SNP, single-nucleotide polymorphism; $KL$, Klotho. a Dominant model. b Additive model.

Discussion

In the present study, we revealed the intimate relationship between $KL$ gene SNPs and salt sensitivity of BP. To the best of our knowledge, this study is the first to identify the correlations between $KL$ SNPs and potassium sensitivity as well as long-term BP progression. These results would greatly deepen our recognition of the genetic ar-
Salt sensitivity refers to the heterogeneous responses of BP to salt intake. Generally, BP decreases during low-salt diet but increases after high-salt diet. Nevertheless, the BP of some individuals may increase after salt restriction or

Table 5. BP alterations during follow-up

| Indexes       | Probands       | Siblings       | Spouses        | Offspring      |
|---------------|----------------|----------------|----------------|----------------|
| 2004          |                |                |                |                |
| Age, years    | 41.8±8.4       | 39.8±7.4       | 47.4±6.1       | 23.3±6.9       |
| SBP, mm Hg    | 120.9±12.5     | 107.6±11.1     | 108.6±12.2     | 102.7±10.7     |
| DBP, mm Hg    | 78.9±8.3       | 70.1±8.1       | 70.6±6.9       | 63.4±8.9       |
| MAP, mm Hg    | 93.0±9.0       | 82.6±8.7       | 83.3±7.9       | 76.5±9.2       |
| 2009          |                |                |                |                |
| Age, years    | 46.5±7.2       | 45.1±7.1       | 52.4±6.1       | 29.5±7.4       |
| SBP, mm Hg    | 124.6±14.6*    | 113.6±13.0*    | 119.0±19.9     | 101.1±11.5     |
| DBP, mm Hg    | 81.5±9.6*      | 75.9±9.9*      | 74.8±10.2      | 68.7±8.4*      |
| MAP, mm Hg    | 95.9±10.5*     | 88.5±10.5*     | 89.6±12.5      | 79.5±9.3       |
| 2012          |                |                |                |                |
| Age, years    | 49.5±7.2       | 48.0±7.0       | 54.8±5.6       | 33.3±7.8       |
| SBP, mm Hg    | 133.5±16.2*,#  | 123.5±15.3*,#  | 126.6±16.2*    | 110.4±13.2*    |
| DBP, mm Hg    | 83.2±10.9*     | 78.9±9.7*,#    | 74.0±11.0      | 70.1±11.9      |
| MAP, mm Hg    | 100.0±11.6*,#  | 93.7±10.8*,#   | 91.5±10.0      | 83.5±11.7*     |

Continuous variables were expressed as mean ± standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BP, blood pressure. * Compared with BP of 2004, \( p < 0.05 \). # Compared with BP of 2009, \( p < 0.05 \).

Table 6. Associations between KL SNPs and long-term BP progression

| SNP            | Allele | SBP   |       |       |       | DBP   |       |       |       | MAP   |       |       |       |
|----------------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                |        | \( \beta \) | \( p \) value |       |       | \( \beta \) | \( p \) value |       |       | \( \beta \) | \( p \) value |
| BP of 2012     |        |       |       |       |       |       |       |       |       |       |       |       |       |
| rs211247       | C      | 14.75 | 0.0798 | 5.846 | 0.2805 | 9.014 | 0.1479 |
| rs1207568      | A      | 6.887 | 0.3623 | 2.132 | 0.6609 | 3.919 | 0.4833 |
| rs526906       | A      | 3.536 | 0.3062 | 0.2342 | 0.9161 | 1.555 | 0.5431 |
| rs525014       | T      | 3.536 | 0.3062 | 0.2342 | 0.9161 | 1.555 | 0.5431 |
| rs564481       | T      | 3.904 | 0.4696 | 4.137 | 0.2326 | 4.265 | 0.2850 |
| rs650439       | T      | 1.037 | 0.7855 | 0.6740 | 0.7830 | 1.011 | 0.7198 |
| BP alterations from 2004 to 2012 |        |       |       |       |       |       |       |       |       |       |       |       |       |
| rs211247       | C      | 20.47 | \textbf{0.0355} | 7.524 | 0.2559 | 12.80 | 0.1341 |
| rs1207568      | A      | 16.24 | 0.0630 | 5.367 | 0.3660 | 9.956 | 0.1938 |
| rs526906       | A      | −0.7383 | 0.8512 | −3.056 | 0.2518 | −1.226 | 0.7221 |
| rs525014       | T      | −0.7383 | 0.8512 | −3.056 | 0.2518 | −1.226 | 0.7221 |
| rs564481       | T      | 1.848 | 0.7676 | 1.778 | 0.6750 | 2.787 | 0.6108 |
| rs650439       | T      | −0.7619 | 0.8599 | −1.525 | 0.6023 | −0.2359 | 0.9502 |

This table showed the associations between KL SNPs on long-term BP progression. We did not find any positive results of KL SNPs with BP or the incidence of hypertension in 2009 (not listed in this table) or 2012. SNP rs211247 was associated with long-term SBP alteration from 2004 to 2012 in the dominant model. \( p \) values were corrected for age, gender, BMI, and multiple testing (FDR <0.05). The \( \beta \) and \( p \) values of the recessive model were listed. SNP, single-nucleotide polymorphism; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BP, blood pressure; KL, Klotho. * Recessive model.

Architecture of salt-sensitive hypertension. In addition, these SNPs might provide potential genetic targets for salt-sensitive hypertension and contribute to individualized treatment.
was positively correlated with the BP response to high-salt diet and salt sensitivity in the dominant model. The frequency of the A allele was 0.14 in this study, which was in line with previous reports in Asian populations. Based on previous evidence, we speculated that rs1207568 could influence individual salt sensitivity through this mechanism. However, there is still no agreement on the role of the A allele. Other studies reported higher SBP in A allele carriers of rs1207568 in Korean and Japanese populations. A meta-analysis also concluded that individuals with the G allele had significantly lower CVD susceptibility [19]. The heterogeneity of the cohort such as age, rate of hypertension, and number of participants might contribute to the inconsistent findings from previous studies. In addition, our report provides the first evidence of an association of rs211247 and the BP response to high-salt diet and salt sensitivity in the dominant model. There was also a significant association with the long-term progression of BP over the 8-year follow-up. SNP rs211247 was located nearly 8 kb upstream from the first noncoding KL exon. A Korean study reported it at the promoter region [20]. To our knowledge, few studies have referred to this SNP. A Canadian study reported that KL SNPs may contribute to susceptibility to acute coronary syndromes in some NSAID users [21]. However, further studies are warranted to verify the function of rs211247 and the regulatory role of rs211247 in KL expression, as well as its influences on salt-sensitive hypertension.

KL is involved in the regulation of several ion balances, including potassium balance [22]. Cha et al. [23] showed that KL could increase potassium reabsorption through renal outer medullary potassium channel 1 (ROMK1). The extracellular domain of KL infusion contributed to the accumulation of ROMK1 on the plasma membrane by removing terminal sialic acids from N-glycan of ROMK1, thus preventing clathrin-mediated endocytosis [23]. Our study was the first to investigate the association between KL gene polymorphisms and the BP response to potassium supplementation. Through dietary intervention study, we found the block rs526906-rs525014 was positively correlated with the DBP response to potassium and potassium sensitivity in the additive model. SNPs rs526906 and rs525014 were located in intron 1 of KL, and rs526906 was 7.6 kb from 3′ of exon 1. Studies have shown that individuals homozygous for protective alleles of rs526906 and rs525014 could upregulate KL expression compared with those who were heterozygous or homozygous for the alternative alleles [24]. Recent studies have indicated that NCC plays a pivotal role in regulating potassium secretion as a response to dietary potassium in-
take [25, 26]. $KL$ is involved in the regulation and phosphorylation of NCC as a coreceptor of FGF23. The FGF23/$KL$ pathway could also inhibit the ENaC expression through the suppression of aldosterone secretion. Therefore, different regulations under different genotypes may greatly influence potassium excretion and reabsorption. Another possible mechanism might be that these 2 intronic SNPs could induce a splicing abnormality and lead to a change in $KL$ protein construction and function. However, further studies are warranted to clarify the exact mechanisms.

C1818T, namely rs564481, is located in exon 4 of $KL$. This SNP was reported to be associated with a decreased risk of hypertension [24]. In healthy Japanese women, T carriers of C1818T were prone to have a high SBP compared with homozygous individuals of the C allele [27]. However, there was a lower T allele frequency among the Asian population. Similar to a previous study in Asian population, the frequency of the T allele was 0.21 in this Chinese cohort. We did not find any significant correlations of C1818T with salt or potassium sensitivity or long-term BP progression.

There were some limitations of this study that should be mentioned. First, our novel findings were restricted to the Chinese Han population, and the study population was quite small. Thus, the results should be replicated in other multicenter studies of large cohorts with different genetic backgrounds. Unfortunately, we did not measure serum $KL$ to explore the influence of $KL$ genotypes on serum $KL$ levels.

In summary, the current study indicated that genetic variants in $KL$ were associated with BP responses to salt intake and salt sensitivity in the Chinese Han population. In addition, we reported for the first time that $KL$ polymorphisms were associated with BP responses to potassium supplementation as well as long-term BP progression over an 8-year follow-up. The findings depict the genetic architecture of salt-sensitive hypertension and provide new clues for the regulation of salt and potassium sensitivity by $KL$. Nevertheless, basic studies are warranted to clarify the potential molecular mechanisms.

Statement of Ethics

This study was approved by the Ethics Committee of the First Affiliated Hospital of Medical School, Xi’an Jiaotong University (XJTU1AF-CRF-2015-006) and strictly complied with the Declaration of Helsinki. All participants or their parents provided written informed consent. The trial registration numbers were NCT00721721 and NCT02734472 (http://www.clinicaltrials.gov).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jiawen Hu contributed to conceptualization, data curation, investigation, and writing – original draft. Tao Shi contributed to conceptualization, methodology, and writing – review and editing. Jianjun Mu contributed to intervention design, supervision, and writing – review and editing.

Date Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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