Common Variants in Genes Underlying Monogenic Hypertension and Hypotension and Blood Pressure in the General Population

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Abstract—The genes responsible for several monogenic hypertensive and hypotensive disorders have been identified. Our aim was to evaluate whether common variants in these genes affect blood pressure in the general population. We studied 2037 adults from 520 nuclear families characterized for 24-hour ambulatory blood pressure and related cardiovascular traits. We genotyped 298 tagging and putative functional single nucleotide polymorphisms, achieving a median coverage of 82.4% across 11 candidate loci. Five polymorphisms in the KCNJ1 gene coding for the potassium channel, ROMK, showed associations with mean 24-hour systolic or diastolic blood pressure. The strongest association was with an intronic polymorphism, rs2846679, where the minor allele (frequency 16%) was associated with a -1.58 (95% CI -2.47 to -0.69) mm Hg change in mean 24-hour systolic blood pressure, after accounting for age, sex, and familial correlations (P = 0.00048). Polymorphisms in the gene were also associated with clinic blood pressure and left ventricular mass as assessed by ECG Sokolow-Lyon voltage (P = 0.0081 for rs675759). Associations with mean 24-hour systolic or diastolic blood pressure were also observed for variants in CASR, NR3C2, SCNN1B, and SCNN1G. The findings show that common variants in genes responsible for some Mendelian disorders of hypertension and hypotension affect blood pressure in the general population. Notably, variants in KCNJ1, which causes Bartter syndrome type 2, were strongly associated, potentially providing a novel target for intervention. (Hypertension. 2008;51:1658-1664.)

Key Words: genetics ■ risk factors ■ blood pressure ■ hypertension ■ KCNJ1 ■ ROMK

Hypertension is a major public health burden affecting around a billion people worldwide.1 Furthermore, even modest changes in blood pressure (BP) impact substantially on the risk of stroke and coronary artery disease.2 Blood pressure is a heritable trait,3,4 and the genomic revolution provides new opportunities for a better understanding of the mechanisms of BP regulation, which could facilitate improvement in the prevention and treatment of hypertension.5 The genetic bases of several rare monogenic forms of hypertension and hypotension have been elucidated (Table 1), providing important insight into the mechanisms of BP regulation, and in particular the central role of the kidney.6 More common polymorphisms in the genes underlying these disorders are obvious candidates as potential contributors to BP variation in the general population. Mutations in the WNK1 gene cause pseudohypoaldosteronism type II (PHAII or Gordon syndrome), an autosomal dominant condition characterized by hypertension and hyperkalemia.7 We have shown previously that common polymorphisms in WNK1 are associated with ambulatory BP in the general population.4 However, a systematic interrogation of the effect of common variation in other genes underlying all the known familial disorders of hypertension and hypotension on BP has not hitherto been carried out. Our aim was to evaluate comprehensively the effect of common variants in these genes on BP in the general population.

Methods

Study Population and Phenotyping

We studied 2037 white European subjects from 520 nuclear families recruited from the general population in the GRAPHIC (Genetic Regulation of Arterial Pressure of Humans in the Community) study. Families were included if both parents aged 40 to 60 years and 2 offspring ≥ 18 years wished to participate. We recruited families by writing to women aged 40 to 69 registered with participating family practitioners in Leicestershire, UK, inviting them and their family to take part. There was no preferential selection based on history of hypertension, but subjects were excluded if they had known renal disease.

Participants had a detailed history taken and were examined by research nurses following standard operating procedures. Measurements included height, weight, waist-hip ratio, clinic BP, and ambulatory BP. For clinic BP, 3 readings were made, using an Omron HEM-705CP digital BP monitor with an appropriate size cuff, on the nondominant arm, with an interval of at least 3 minutes.
between readings. Clinic BP was defined as the mean of the second and third BP readings. Ambulatory BP was measured using a Spacelabs 90207 monitor (Spacelabs, Wokingham, UK) for 26 hours. The first 2 hours of each record was discarded to avoid an alerting response. The monitor recorded BP at 30-minute intervals between 08:00 and 21:59 (“daytime”) and at 1-hour intervals between 22:00 and 07:59 (“nighttime”). If ambulatory BP profiles were less than 80% complete they were repeated when the participant consented. We summarized the ambulatory BP data by the application of a weighting to each period proportional to its length. Other measurements included 24-hour urinary electrolytes, plasma electrolytes and lipids (total and HDL cholesterol), and ECG variables including the Sokolow-Lyon voltage. Further details of recruitment and phenotyping are included in the supplemental materials (available online at http://hyper.ahajournals.org.).

The Leicestershire Research Ethics Committee approved the study, and all subjects provided written informed consent. The study adhered to the principles of the Declaration of Helsinki, and all procedures followed were in accordance with institutional guidelines.

**SNP Selection and Genotyping**

Each of the candidate loci (the gene along with the adjacent 5000 base-pairs of 5’-upstream and 3’-downstream segments) shown in Table 1 was assessed for tagging single nucleotide polymorphisms (SNPs) with unambiguous location within the HapMap database (http://www.hapmap.org/). Using Tagger software,7 we selected SNPs which tagged common variants (minor allele frequency [MAF] ≥0.1) in the HapMap CEU reference panel with r² ≥0.9. In addition, common (MAF ≥0.1) potentially functional single nucleotide polymorphisms identified in silico using the molecular categories available in the SNP Function Portal6 (http://brainarray.mbi.med.umich.edu/Brainarray/Database/SearchSNP/snpfunc.aspx) were added to the final set of tagging genetic markers at the pre-experimental stage. Altogether we genotyped 298 SNPs (Table 1).

**Quality Checking**

In family-based studies it is possible to use the family data in the quality control (QC) procedures. Before finalizing the GRAPHIC study dataset we analyzed all recruited subjects with a panel of 3 highly polymorphic microsatellites4 and multiple SNPs, and removed individuals (n=17) where Mendelian inconsistencies were suggestive of misspecified family relationships or sample mislabeling. The 2037 individuals studied here represent those that passed this QC.

Our intrastudy QC was undertaken first at the level of individuals and, second, at the level of SNPs. Of the 2037 individuals, we excluded 18 because of a low call rate (defined as an overall call rate <80% before excluding poorly performing SNPs). Therefore, association tests were based on 2019 individuals. For subsequent QC at the level of SNPs, we assessed call rates, MAF, deviation from Hardy-Weinberg equilibrium, and Mendelian inconsistencies. Because Hardy-Weinberg assumptions and MAF comparisons apply to unrelated individuals, these were assessed in the parents only. We excluded 10 Mendelian inconsistencies (n=10) which, as we had previously excluded individuals with misspecified family relationships or sample mislabeling, was indicative of poor genotyping quality.

**Statistical Analysis**

Our primary hypotheses were that SNPs in these genes would be associated with mean 24-hour systolic BP (SBP) or mean 24-hour
diastolic BP (DBP). In secondary exploratory analyses we tested whether these SNPs (1) were associated with other BP phenotypes (clinic, mean daytime, mean nighttime SBP, and DBP); (2) were associated with 24-hour urinary sodium, potassium, and calcium excretion and (3) showed interaction with 24-hour urinary sodium in their effects on mean 24-hour BP. Association tests were undertaken using generalized estimating equations (GEE) with an exchangeable correlation structure and robust standard errors to account for the correlation induced by the familial relationships.11,12 In all analyses an additive genetic model was assumed and covariates included sex, age, and age² (the latter to account for possible nonlinear effects of age). We corrected for the effects of antihypertensive therapy using a semiparametric algorithm.3 Details of this approach and justification for appropriate adjustments for antihypertensive therapy have been published previously.12 We assessed association between the SNPs and log-transformed mean 24-hour urinary sodium, potassium, and calcium, as these measures showed a nonnormal distribution. To test for interaction between each SNP and 24-hour urinary sodium, we assessed departure from additivity of the effects of urinary sodium on BP across levels of each SNP: a similar approach was used for tests of interaction between SNPs and urinary calcium and potassium. We used the statistical software STATA 9.0 (release 9.1, STATACorp LP).

Interpreting the strength of evidence in an association study depends on the likely number of true associations and the power to detect them.13 For associations reaching nominal levels of significance, we therefore also present the false-positive report probability (FPRP), that is, the probability of no true association given a significance, we therefore also present the false-positive report probability (FPRP) to account for the correlation induced by the familial relationships.11 In all analyses an additive genetic model was assumed and covariates included sex, age, and age² (the latter to account for possible nonlinear effects of age). We corrected for the effects of antihypertensive therapy using a semiparametric algorithm. Details of this approach and justification for appropriate adjustments for antihypertensive therapy have been published previously.12 We assessed association between the SNPs and log-transformed mean 24-hour urinary sodium, potassium, and calcium, as these measures showed a nonnormal distribution. To test for interaction between each SNP and 24-hour urinary sodium, we assessed departure from additivity of the effects of urinary sodium on BP across levels of each SNP: a similar approach was used for tests of interaction between SNPs and urinary calcium and potassium. We used the statistical software STATA 9.0 (release 9.1, STATACorp LP).

Interpreting the strength of evidence in an association study depends on the likely number of true associations and the power to detect them.13 For associations reaching nominal levels of significance, we therefore also present the false-positive report probability (FPRP), that is, the probability of no true association given a statistically significant finding.14,15 The FPRP depends not only on the probability value but also on the prior probability of true association and the statistical power of the test. Given the convincing priori evidence that the genes we investigated were involved in Mendelian disorders of hypertension and hypotension, we conservatively estimated a priori that one in 100 of the SNPs we genotyped in these strong candidate gene regions would be truly associated with BP ("true positives"; please see supplemental materials for more details). We conducted sensitivity analyses with different assumptions about this probability. The FPRP calculations were based on an assumed allelic effect size of 1/8 standard deviation, which is consistent with the usual effect sizes usually expected for a common variant influencing a complex trait. As a guide to the interpretation of the FPRP, it has been described previously that the overall FPRP for published molecular epidemiology studies, which tend to base reporting only on probability values, is around 0.95.14 In accordance with published recommendations we regard as noteworthy FPRP values of 0.5 or less, and as more definitive evidence FPRP values of below 0.2.14

Further details of the statistical methods, including power calculations (Table S1), are available in the supplemental materials.

Results

Subjects

The characteristics of the GRAPHIC study participants are shown in Table 2. The age of participants at interview ranged from 18 to 61 (mean 39.3, SD 14.5) years, and 50.5% of participants were male. In our population, which was unscreened for hypertension status, the prevalence of hypertension was comparable to data from the Health Survey for England 2003.16

Genotypes and Coverage

Of the 298 SNPs analyzed, 224 SNPs (75%) passed QC (Table 1). The characteristics of these SNPs are shown in Table S2. For comparison with other genotyping platforms we present the coverage as the percentage of CEU HapMap SNPs with MAF >5% captured with $r^2$ >0.8 by the genotyped SNPs which passed QC in our study (Table 1). The overall coverage was 78.9% (mean) and 82.4% (median), substantially exceeding the coverage provided by a commonly used genome-wide association platform for most loci (Table 1). As some of our functional SNPs were not in HapMap, our coverage is probably slightly underestimated.

The distribution of failed SNPs was not uniform (Table S3). Of interest, a high proportion of SNPs in the CLCNKA/CLCNKB region showed marked deviation from Hardy-Weinberg equilibrium and were excluded from our analysis, resulting in a lower coverage than intended for these genes. Copy number variation has been noted in CLCNKA/CLCNKB17–19 and this phenomenon could explain the observed deviation from Hardy-Weinberg equilibrium rather than genotyping error.

Main Association Finding: KCNJ1

Our key findings relate to the KCNJ1 gene, in which 5 SNPs showed associations with mean 24-hour SBP or DBP with FPRP <0.2 (Table 3). Two of these SNPs were located in the 3' untranslated region and the remaining 3 SNPs were intronic (Figure 1). One further SNP, rs610155 (128,232 kb), showed associations with mean 24-hour SBP and DBP with FPRP <0.5 (Table S4). The strongest association with mean 24-hour SBP was with rs2846679, each copy of the minor allele (A, frequency 16%) altering mean 24-hour SBP by an estimated $-1.58$ (95% CI $-2.47$ to $-0.69$) mm Hg after accounting for age, sex, and familial correlations ($P=0.00048$, FPRP 0.05). The strongest association with 24-hour DBP was observed for rs2186832, the minor allele (G, frequency 20%) being associated with an estimated $-0.95$ (95% CI $-1.52$ to $-0.39$) mm Hg change in mean 24-hour DBP after accounting for age, sex, and familial correlations ($P=0.00095$, FPRP 0.09). Consistent associations were seen for SNPs in KCNJ1 with mean daytime, mean nighttime, and clinic SBP and DBP (Figure 1 and Tables S4 and S5).

The association of rs2846679 with mean 24-hour SBP and rs2186832 with mean 24-hour DBP remained significant after adjustment for BMI, current smoking, and excess alcohol intake and 24-hour urinary sodium ($P=0.004$ and $P=0.002$, respectively). Interestingly, there was also an association between several SNPs in KCNJ1 and left ventricular mass as assessed by Sokolow-Lyon voltage on the ECG. The effect was in the same direction as seen with BP. The strongest association was with rs675759 (coefficient $-85.5$, 95% CI $-148.7$ to $-22.2$, $P=0.0081$).

Other Genetic Association Findings

Blood Pressure

Table S4 shows SNP associations reaching nominal significance and with FPRP <0.5 for any of the BP phenotypes. One additional SNP showed association with a FPRP <0.2—this was SNP rs3857080 in NR3C2, each copy of the minor allele (T, frequency 10%) altering mean nighttime SBP by an estimated $-1.86$ (95% CI $-2.96$ to $-0.77$) mm Hg after accounting for age, sex, and familial correlations ($P=0.00087$, FPRP 0.11). rs3857080 was also associated with mean nighttime DBP ($P=0.0032$, FPRP 0.31) and nominally associated with
sensitivity analyses for FPRP are shown in Table S5. The results of the association tests for all SNPs and NR3C2 (8 SNPs), SCNN1B (1 SNP), and SCNN1G (1 SNP) were observed for a further 12 SNPs—in CASR (1 SNP), FPRP between 0.2 and 0.5 for our secondary BP phenotypes Table 3. SNPs Showing Nominal Association for Mean 24 Hours SBP or DBP With False Positive Report Probability (FPRP) < 0.2

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Fathers (n=516)</th>
<th>Mothers (n=516)</th>
<th>Sons (n=513)</th>
<th>Daughters (n=492)</th>
<th>All Subjects (n=2037)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>2037</td>
<td>53.7 (4.3)</td>
<td>51.9 (4.4)</td>
<td>25.0 (5.1)</td>
<td>25.9 (5.4)</td>
<td>39.3 (14.5)</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean (SD)</td>
<td>2037</td>
<td>27.8 (4.0)</td>
<td>27.1 (4.6)</td>
<td>24.9 (4.1)</td>
<td>24.5 (4.9)</td>
<td>26.1 (4.6)</td>
</tr>
<tr>
<td>Waist-hip ratio, mean (SD)</td>
<td>2016</td>
<td>0.93 (0.07)</td>
<td>0.81 (0.06)</td>
<td>0.86 (0.06)</td>
<td>0.78 (0.07)</td>
<td>0.85 (0.09)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>2034</td>
<td>76 (14.8)</td>
<td>64 (12.4)</td>
<td>147 (28.7)</td>
<td>120 (24.4)</td>
<td>407 (20)</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>2037</td>
<td>292 (56.6)</td>
<td>226 (43.8)</td>
<td>203 (39.6)</td>
<td>188 (38.2)</td>
<td>909 (44.6)</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>2036</td>
<td>139 (26.9)</td>
<td>133 (25.8)</td>
<td>19 (3.7)</td>
<td>33 (6.7)</td>
<td>324 (15.9)</td>
</tr>
<tr>
<td>Hypertension (clinic BP ≥ 140/90 mm Hg or on treatment), n (%)</td>
<td>2037</td>
<td>267 (51.7)</td>
<td>184 (35.7)</td>
<td>107 (20.9)</td>
<td>23 (4.7)</td>
<td>581 (28.5)</td>
</tr>
</tbody>
</table>

mean 24-hour SBP (P = 0.014, FPRP = 0.67). Associations with FPRP between 0.2 and 0.5 for our secondary BP phenotypes were observed for a further 12 SNPs—in CASR (1 SNP), NR3C2 (8 SNPs), SCNN1B (1 SNP), and SCNN1G (1 SNP) (Table S4). The results of the association tests for all SNPs and sensitivity analyses for FPRP are shown in Table S5.

**Interactions**
Because many of the genes examined influence urinary sodium, potassium, or calcium reabsorption, we tested for associations between the SNPs and 24-hour urinary sodium, potassium, and calcium (Table S6) but found no strong associations and the number of nominal associations was

Table 3. SNPs Showing Nominal Association for Mean 24 Hours SBP or DBP With False Positive Report Probability (FPRP) < 0.2

<table>
<thead>
<tr>
<th>CHR</th>
<th>Gene</th>
<th>Position (kb)</th>
<th>SNP</th>
<th>Alleles</th>
<th>MAP*</th>
<th>HW_P*</th>
<th>Call Rate (%)</th>
<th>Mean 24 Hours SBP</th>
<th>FPRP</th>
<th>Mean 24 DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>KCNJ1</td>
<td>128213.19</td>
<td>rs675759</td>
<td>G/C</td>
<td>0.15</td>
<td>0.52</td>
<td>99.7</td>
<td>-1.44 (-2.32 to -0.55); 0.0015</td>
<td>0.15</td>
<td>-0.99 (-1.6 to -0.39); 0.0013</td>
</tr>
<tr>
<td>11</td>
<td>KCNJ1</td>
<td>128213.22</td>
<td>rs675388</td>
<td>G/A</td>
<td>0.15</td>
<td>0.54</td>
<td>99.8</td>
<td>-1.41 (-2.30 to -0.52); 0.0020</td>
<td>0.19</td>
<td>-0.99 (-1.61 to -0.38); 0.0015</td>
</tr>
<tr>
<td>11</td>
<td>KCNJ1</td>
<td>128234.75</td>
<td>rs2846679</td>
<td>G/A</td>
<td>0.16</td>
<td>0.90</td>
<td>99.2</td>
<td>-1.58 (-2.47 to -0.69); 0.00048</td>
<td>0.05</td>
<td>-1 (-1.60 to -0.39); 0.0013</td>
</tr>
<tr>
<td>11</td>
<td>KCNJ1</td>
<td>128236.16</td>
<td>rs2855800</td>
<td>A/C</td>
<td>0.28</td>
<td>0.87</td>
<td>99.6</td>
<td>-1.21 (-1.92 to -0.50); 0.0084</td>
<td>0.08</td>
<td>-0.57 (-1.06 to 0.09); 0.021</td>
</tr>
<tr>
<td>11</td>
<td>KCNJ1</td>
<td>128239.88</td>
<td>rs2186832</td>
<td>C/G</td>
<td>0.20</td>
<td>0.37</td>
<td>99.8</td>
<td>-1.42 (-2.24 to -0.6); 0.00065</td>
<td>0.07</td>
<td>-0.95 (-1.52 to -0.38); 0.0009</td>
</tr>
</tbody>
</table>

Alleles are major/minor alleles respectively.

*Minor allele frequency (MAP) and a χ² test for deviation from Hardy-Weinberg equilibrium (HW_P) were estimated in the parents. The coefficients are shown under an additive genetic model and may be interpreted as a per-allele effect (that is, per additional copy of the minor allele) having taken appropriate account of familial relationships and having adjusted for age, age², and sex as covariates.
consistent with chance. Although variants in these genes could plausibly interact with sodium intake in their effect on BP, in our exploratory tests of interaction between each SNP and 24-hour urinary sodium, potassium, or calcium on 24-hour SBP and DBP, 12 interactions were observed that reached a statistical significance threshold of \( P < 0.01 \), compared to 13.4 interactions expected by chance (Table S7). Notably, no significant interaction was observed for the \( \text{KCNJ1} \) SNPs that showed association with mean 24-hour SBP or DBP.

**Discussion**

This is the first report of a comprehensive analysis of the association of common variants in genes responsible for Mendelian forms of hypertension and hypotension with BP in the general population. Our principal finding was the association of several SNPs in the \( \text{KCNJ1} \) gene, which codes for ROMK, the ATP-sensitive inwardly-rectifying potassium channel expressed in the thick ascending limb, with mean 24-hour SBP and DBP as well as clinic BP. The observations that variants in \( \text{KCNJ1} \) were associated with several BP phenotypes and that the same variants were associated with an ECG marker of left ventricular mass in the anticipated direction for its relationship with BP add weight to the findings.

ROMK mediates potassium secretion and regulates NaCl reabsorption in the kidney.\(^{20}\) Loss-of-function mutations in ROMK are responsible for Bartter syndrome type 2, a life-threatening disorder in which both renal tubular hypokalemic alkalosis, hypercalcuiuria, and profound systemic symptoms manifest in the first few weeks of life.\(^{21}\) Dietary \( \text{K}^+ \) restriction decreases ROMK abundance in the renal
The precise nature of the variants of \textit{KCNJ1} that affect BP and the mechanisms involved remain to be elucidated. However, one of the BP-associated \textit{KCNJ1} SNPs, rs675759, shows a functional potential in silico. According to the web-based bioinformatic interfaces SNP Function Portal\(^9\) and SNPseek (http://snp.wustl.edu/SNPseek/index.cgi), rs675759 maps to an evolutionarily conserved microRNA target site within the 3' untranslated region (3'UTR) of \textit{KCNJ1}. Thus, the genetic variant may potentially affect annealing of the hsa-miR-155 microRNA molecule to its complementary \textit{KCNJ1} UTR DNA sequence and contribute to a posttranslational regulation of \textit{KCNJ1} expression. The putative physiological significance of this possible molecular mechanism is further supported by the data showing the effect of microRNA-dependent mechanism on repression of potassium inward-rectifying channel translation in the heart.\(^{26}\) Functional experiments are warranted to clarify whether a similar mechanism may explain the association between \textit{KCNJ1} SNP and BP. The stronger associations we observed for SNPs rs2846679, rs2855800, and rs2186832, which are located in a different haplotype block from rs675759 (Figure 1), may reflect the effects of an additional (untyped) functional variant.

We observed a number of further significant associations between BP and variants in other genes. Most notably rs3857080 in \textit{NR3C2} was associated with lower nighttime SBP and DBP. \textit{NR3C2} codes for the mineralocorticoid receptor and \textit{NR3C2} mutations are responsible for autosomal dominant pseudohypoaldosteronism type I\(^{27}\) and hypertension exacerbated by pregnancy.\(^{28}\) Given the large number of analyses, these findings need to be viewed as exploratory. However, they identify variants that deserve further investigation in other cohorts and settings.

The effects of variants on BP identified may seem individually modest. For example, the proportion of the variance in mean 24-hour SBP explained by the \textit{KCNJ1} SNP rs2846679 is 0.8\% (and that by all SNPs showing nominal association with mean 24-hour SBP, 2.7\%). However, the estimated magnitude of the effect is wholly consistent with that expected for a complex genetic trait. Notably, a 2-mm Hg lower usual SBP is associated with an approximately 10\% fall in stroke mortality and a 7\% reduction in mortality from ischemic heart disease or other vascular causes in middle age.\(^2\) In our study, each copy of the minor allele (A) of rs2846679 (frequency 16\%) was associated with a reduction of mean 24-hour SBP of over 1.5 mm Hg, a difference of over 3 mm Hg between homozygotes. These observations underscore the potential public health relevance of these findings, if replicated. Much larger clinical effects may be realized if improved knowledge of pathways involving the gene identifies intermediate phenotypes amenable to public health or pharmacological interventions.

**Perspectives**

We show that variants in the \textit{KCNJ1} gene are associated with mean 24-hour systolic and diastolic BP in families recruited from the general population. Evidence for association was also found for variants in \textit{CASR}, \textit{NR3C2}, \textit{SCNN1B}, and \textit{SCNN1G}. Our findings suggest that common variants in these genes, where mutations are also responsible for rare Mendelian forms of hypertension or hypotension, also play an important role in regulating BP in the general population. These findings, if replicated, could improve our understanding of the molecular regulation of BP and form the basis for further research to assess whether combinations of the relevant gene variants identify subgroups at higher risk of hypertension or predict response to antihypertensive drugs.

**Acknowledgments**

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**Disclosures**

None.

**References**


