Gene and environmental interactions according to the components of lifestyle modifications in hypertension guidelines

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Abstract

Risk factors for hypertension consist of lifestyle and genetic factors. Family history and twin studies have yielded heritability estimates of blood pressure (BP) in the range of 34–67%. The most recent paper of BP GWAS has explained about 20% of the population variation of BP. An overestimation of heritability may have occurred in twin studies due to violations of shared environment assumptions, poor phenotyping practices in control cohorts, failure to account for epistasis, gene-gene and gene-environment interactions, and other non-genetic sources of phenotype modulation that are suspected to lead to underestimations of heritability in GWAS. The recommendations of hypertension guidelines in major countries consist of the following elements: weight reduction, a healthy diet, dietary sodium reduction, increasing physical activity, quitting smoking, and moderate alcohol consumption. The hypertension guidelines are mostly the same for each country or region, beyond race and culture. In this review, we summarize gene-environmental interactions associated with hypertension by describing lifestyle modifications according to the hypertension guidelines. In the era of precision medicine, clinicians who are responsible for hypertension management should consider the gene-environment interactions along with the appropriate lifestyle components toward the prevention and treatment of hypertension. We briefly reviewed the interaction of genetic and environmental factors along the constituent elements of hypertension guidelines, but a sufficient amount of evidence has not yet accumulated, and the results of genetic factors often differed in each study.

Keywords: Gene and environmental interaction, Hypertension, Lifestyle, Epidemiology, Hypertension guideline

Hypertension is the most influential risk factor for cardiovascular disease (CVD) [1]. Recent evidence has suggested that hypertension is also associated with common non-CVD such as dementia and renal dysfunction [2]. Risk factors for hypertension consist of lifestyle and genetic factors. Family history and twin studies have yielded heritability estimates of blood pressure (BP) in the range of 34–67% [3]. The collective effect of all BP loci identified through genome-wide association studies (GWAS) accounted for only ~ 3.5% of BP variability [4]. The most recent paper of BP GWAS has identified 901 SNPs with BP and explained about 20% of the population variation of BP [5]. An overestimation of heritability may have occurred in twin studies due to violations of shared environment assumptions, poor phenotyping practices in control cohorts, failure to account for epistasis, gene-gene (G × G) and gene-environment (G × E) interactions, and other non-genetic sources of phenotype modulation that are suspected to lead to underestimations of heritability in GWAS.

The recommendations of hypertension guidelines in major countries consist of the following elements: weight reduction, a healthy diet (dietary patterns characterized by a high consumption of fruit, vegetables, whole grains, legumes, seeds, nuts, fish, low-fat dairy, and a low consumption of meat and sweets), dietary sodium reduction, increasing physical activity, quitting smoking (including avoiding passive smoking), and moderate alcohol consumption (Table 1) [6–8]. The hypertension guidelines are mostly the same for each country or region, beyond race and culture [9]. In this review, we...
summarize gene-environmental interactions associated with hypertension by describing lifestyle modifications according to the hypertension guidelines.

**Gene-sodium interaction**

The INTERSALT study indicated an association between overdose salt intake and high blood pressure [10]. The Dietary Approaches to Stop Hypertension (DASH) study showed that sodium intake restrictions from a high level to an intermediate level and from an intermediate to a low level reduced both systolic blood pressure (SBP) and diastolic blood pressure (DBP) [11]. In a pooled analysis of data, lowering sodium intake was shown to be best-targeted at individuals with hypertension who consume high-sodium diets [12]. On the basis of these results, hypertension management guidelines recommend the following: salt intakes of < 5 g/day in Europe [6], < 6 g/day in Japan [8], and sodium intake of < 1500 mg/day (salt intake of < 3.81 g/day equivalent) in the USA [7].

Salt sensitivity is an increase in BP in response to salt intakes of < 5 g/day [6], < 6 g/day in Japan [8], and sodium intake of < 1500 mg/day (salt intake of < 3.81 g/day equivalent) in the USA [7].

Regular physical activity

Regular aerobic exercise (e.g., at least 30 min of moderate dynamic exercise on 5–7 days/week)

Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension.

Primarily periodic (30 min or longer daily if possible) and aerobic exercise should be practiced.

Smoking cessation

Smoking cessation, supportive care, and referral to smoking cessation programs

Quit cigarette smoking and second-hand smoking.

Smoking cessation should be promoted, and passive smoking must be avoided.

Moderate alcohol consumption

Men: < 14 units/week
Women: < 8 units/week
Avoid binge drinking

Adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than 28 g/day and 24 g/day as ethanol, respectively.

Alcohol intake should be restricted.

≤ 20–30 mL/day in men and ≤ 10–20 mL/day in women as ethanol.

**Table 1** Comparison between three major lifestyle modifications in the hypertension guidelines

| ESH/ESC Guideline 2018 [6] | ACC/AHA Guideline 2017 [7] | JSH Guideline 2014 [8] |
|----------------------------|----------------------------|------------------------|
| **Dietary sodium restriction** | Salt restriction to < 5 g/day | Optimal goal is < 1500 mg/day, but aim for at least a 1000 mg/day reduction in most adults. | The target of salt reduction is < 6 g/day. |
| **Other dietary changes** | Increased consumption of vegetables, fresh fruits, fish, nuts, and unsaturated fatty acids (olive oil); low consumption of red meat; and consumption of low-fat dairy products | A heart-healthy diet, such as the DASH diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension. Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or hypertension, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion. | Dietary pattern: fruit/vegetable intake should be increased, and cholesterol/saturated fatty acid intake should be reduced. Fish (fish oil) intake should also be increased. |
| **Weight reduction** | Body-weight control is indicated to avoid obesity (BMI > 30 kg/m² or waist circumference > 102 cm [men] and > 88 cm [women], as is aiming at healthy BMI (about 20–25 kg/m²) and waist circumference (< 94 cm [men] and < 80 cm [women]). | Weight loss is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese. | The target body mass index is < 25 kg/m². Even when the target is not reached, a significant decrease in blood pressure can be achieved by reducing body weight by approximately 4 kg. |
| **Regular physical activity** | Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension. | Primarily periodic (30 min or longer daily if possible) and aerobic exercise should be practiced. |
| **Smoking cessation** | Quit cigarette smoking and second-hand smoking. | Smoking cessation should be promoted, and passive smoking must be avoided. |
| **Moderate alcohol consumption** | Adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than 28 g/day and 24 g/day as ethanol, respectively. | Alcohol intake should be restricted. |

A cross-sectional study in Korea indicated that the mutant alleles of CSK rs1378942 and CSK-MIR4513 rs3784789 had the strongest protective effects against hypertension in the subjects in the middle group of the 24-h estimated urinary sodium-potassium excretion ratio (Table 1) [15]. In a cross-sectional study in China, Li et al. showed that the interaction for CLGN rs2567241 was associated with the sodium intake effects on SBP, DBP, and mean blood pressure (MBP), the impact of LST rs13211840 on DBP, and the effect of LOC105369882 rs11104632 on SBP through the examination of an SNP [16]. Also, genome-wide gene-based interactions with sodium identified MKNK1, C2orf80, EPHA6, SCOC-AS1, SCOC, CLGN, MGAT4D, ARHGAP42, CASPA4, and LINCO1478 which were associated with at least one BP variable. In Chinese Kazakh women, an interaction of ACE genotype and salt intake on hypertension was observed [17].

In a Japanese population, the interaction between salt consumption and NPPA rs5063 (Val32Met) showed a significant association with SBP [18]. In a general
Japanese population, a high sodium intake strengthened the association of \textit{AGT} T174 M [19] and \textit{ADD1} G460 W (only women) [20] polymorphisms with hypertension and SBP levels, respectively. Another cross-sectional study showed that \textit{CYP3A5} variants might be a determinant of salt sensitivity of BP in Japanese men [21]. A case-control study in Taiwan showed that \textit{GNB3} C825T polymorphism might increase the risk of hypertension among individuals who consumed a high-sodium diet [22]. Adamo et al. reviewed studies of gene-salt interaction [23], but most of those studies might have been subject to error due to their small sample sizes. Studies of gene-environmental interactions require large sample sizes as they involve the grouping of genes and environmental factors.

\textbf{Gene-healthy diet interaction}

The DASH diet study showed no significant BP lowering in the control group, and the fruits/vegetable group, but SBP and DBP lowering were observed in the DASH diet group [24]. In a meta-analysis of 17 randomized controlled trials, significant reductions of 4.3 mmHg in SBP and 2.4 mmHg in DBP were observed in healthy dietary patterns, including the DASH diet, Nordic diet, and Mediterranean diet, all of which include the high consumption of fruit, vegetables, whole grains, legumes, seeds, nuts, fish, and dairy and a low consumption of meat, sweets, and alcohol [25]. These foods or combinational foods contribute to the prevention of high blood pressure.

A 2-year-randomized intervention trial revealed significant interactions between the Neuropeptide Y (NPY) rs16147 SNP and dietary fat intake in relation to changes in SBP and DBP (Table 3) [26]. The gene-diet interactions appeared only in hypertensive patients. During the 2 years of intervention, the subjects with C allele had greater reductions in SBP and DBP in response to a low-fat diet but had greater increases in SBP and DBP in response to a high-fat diet. NPY is implicated in the regulation of BP, and NPY pathways in the hypothalamus are sensitive to dietary fat. Animal experiments indicated that fat intake and NPY activity in the hypothalamus are inversely correlated [27].

\begin{table}
\centering
\caption{Review for interaction of gene and salt intake on hypertension}
\begin{tabular}{|l|l|l|l|l|l|}
\hline
Population & Gene & SNPs/gene length, bp & Chr & Position & Trait & Reference \\
\hline
Korea & LOC101929750 & rs7554672 & 1 & 219339781 & HT & 24hUNa, K & 15 \\
& MKLN1 & rs1643270 & 7 & 130826034 & HT & 24hUK & \\
& CSK & rs1378942 & 15 & 72864420 & HT & 24hUNa/K & \\
& CSK-MIR4S13 & rs3784789 & 15 & 72869605 & HT & \\
& TENM4 & rs10466739 & 11 & 78290369 & HT & \\
\hline
Taiwan & GNB3 & rs5443 & 10 & & HT & Salt intake & 22 \\
\hline
China & CLGN & rs2567241 & 4 & 141542612 & SBP, DBP, MBP & Salt intake & 16 \\
& LOC105 & rs11104632 & 12 & 86747816 & SBP & \\
& UST & rs13211840 & 6 & 149153883 & DBP & \\
\hline
China & MKNK1 & 46889 & 1 & 46795665 & SBP & Salt intake & 17 \\
& SCOC & 39097 & 4 & 141484064 & SBP, DBP, MBP & \\
& SCOC-A51 & 89668 & 4 & 14142329 & DBP, MBP & \\
& CLGN & 39210 & 4 & 141520956 & SBP, DBP, MBP & \\
& MGA4T4D & 55004 & 4 & 141583978 & SBP, DBP, MBP & \\
& LINC01478 & 208264 & 18 & 40157397 & SBP & \\
& C2orf80 & 24704 & 2 & 208738321 & PP & \\
& EPHA6 & 429464 & 3 & 98641126 & PP & \\
& ARHGAP42 & 303251 & 11 & 100063616 & PP & \\
\hline
Japan & NPPA & rs5063 & 1 & 11907648 & SBP & Salt intake & 18 \\
Japan & CYP3A5 & rs776746 & 3 & & SBP, DBP & 24hUNaCl & 21 \\
Japan & AGT & T174 M & HT & & 24hUNa, sodium intake & 19 \\
Japan & ADD1 & G460 W & & & SBP & 24hUNa, sodium intake & 20 \\
\hline
\end{tabular}
\end{table}

\textit{HT} hypertension, \textit{SBP} systolic blood pressure, \textit{DBP} diastolic blood pressure, \textit{MBP} mean blood pressure, \textit{PP} pulse pressure, \textit{24hUNa} 24-h sodium excretion; \textit{24-h potassium excretion; 24-h salt excretion.
pronounced BP decrease over time in subjects with the \textit{CYP4F2} 433VV genotype, although there was no association between \( \omega-6 \) and \( \omega-3 \) PUFA intakes, \( \omega-6/\omega-3 \), and changes of BP [28]. A meta-analysis of interventional studies showed that the intake of fish oil caused a decrease in BP in hypertensive patients [29].

In a study of Japanese men, the Met allele of \textit{COMT} Val158Met was associated with higher BP and a higher prevalence of hypertension in the high-energy intake group but not in the low-energy intake group [30]. There was no difference in body mass index (BMI) between the low- and high-energy intake groups. The underlying mechanism of these results remains unclear.

In a Southern European study, there was an interaction between the \textit{NOS3} rs1799983 polymorphism and dietary saturated fatty acid and monounsaturated fatty acid that influenced DBP levels [31]. Martins et al. showed that nitric oxide synthase (NOS) activity was increased in an unsaturated high-fat diet group. The expressions of endothelial NOS (eNOS) and inducible NOS (iNOS) were also increased in the unsaturated high-fat diets group [32]. These changes may be involved in gene-dietary interactions.

\textbf{Gene-alcohol interaction}

Alcohol consumption is higher among East Asian men compared to Western men, but the consumption of alcohol by Western women is higher than that among East Asian women [33]. Approximately half of East Asians are found to be aldehyde dehydrogenase (ALDH) deficient, which accounts for a phenomenon called the 'Oriental flushing syndrome.' ALDH deficiency poses an increased risk of high BP [34].

In a study of middle-aged Finnish men, the apolipoprotein E phenotype significantly influenced the BP increasing effect of alcohol consumption (Table 4) [35]. A cross-sectional study of a Chinese population showed a significant interaction between the \textit{CYP11B2} genotype [36] and DNA methylation (CpG1 methylation) of the \textit{ADD1} gene promoter [37] and alcohol consumption on the risk of hypertension. In addition, the Stanford Asia-Pacific Program for Hypertension and Insulin Resistance (SAPPHIRE) study showed that \textit{ALDH2} genetic variants were associated with progression to hypertension in a prospective Chinese cohort [38]. In a cross-sectional study of 5724 Japanese participants, \textit{ALDH2} rs671 significantly and synergistically influenced the subjects’ drinking behavior and influenced the level of BP independently of the amount of alcohol consumption [39], but not in another study, in a case-control study of 532 Japanese patients, there was no significant interaction between the \textit{ALDH2} genotype and alcohol consumption overall or in Japanese male patients: this study may have had insufficient power to detect the interaction [40].

A genome-wide analysis of the effect of SNP-alcohol interactions on BP traits showed 1 significant and 20 suggestive BP loci by exploiting gene-alcohol interactions in a study from the Framingham SNP Health Association Resource [41]. The CHARGE Gene-Lifestyle Interactions Working Group has systematically shown the gene-alcohol interaction on BP in a recent and extensive meta-analysis across multiple ancestries, conducting a large two-stage investigation incorporating joint testing of main genetic effects and single nucleotide variant (SNV)-alcohol consumption interactions [42]. The study identified and replicated 54 BP loci in European ancestry and multi-ancestry meta-analyses.

\textbf{Gene-smoking interaction}

According to the Global Burden of Disease Study 2015, central and eastern Europe and southeast Asia had a higher prevalence of smoking than the global average for men, and western and central Europe had a higher prevalence of smoking than the global average for women [43]. The population-attributable fractions of coronary heart disease caused by smoking among men and women were higher in the East Asian region than in the Western Pacific region [44].

In a rural Chinese population, the cigarette smoking index and \textit{ACE} gene showed a low exposure-gene effect on essential hypertension with interaction indices (Table 5) [45]. In an eastern Chinese Han population, gene-environment interactions between rs1126742 and smoking were associated with an increased risk of essential hypertension [46]. A case-control study showed the association of \textit{KCNJ11} gene polymorphisms and BP response to the antihypertensive drug irbesartan in non-smoking
Table 4 Review for interaction of gene and alcohol intake on hypertension

| Population | Gene               | SNPs/gene length, bp | Chr | Position | Results | Drink | Ancestor | Reference |
|------------|--------------------|----------------------|-----|----------|---------|-------|----------|-----------|
| Finland    | APOE               |                      |     |          |         | SBP   | LHD      | 35        |
| China      | ADD1               | rs4961               | 4   |          | HT      |       | alcohol/w| 37        |
| China      | CYP11B2            |                      |     |          | HT      |       | alcohol/w| 36        |
| China      | ALDH2              | rs2238152            | 12  | 111776655| HT      |       | LHD      | 38        |
| Japan      | ALDH2              | rs671                | 12  |          | HT      |       | alcohol/w| 39        |
| USA        | MGC27382-PTGFR     | rs648425             | 1   | 78659796 | SBP     | Drinks/w|          | 41        |
|            | ESRRG              | rs17669622           | 1   |          | 214823444| MAP   | Drinks/w |           |
|            | RAB4A              | rs16849553           | 1   |          | 227403469| MAP   | Oz alcohol/w|         |
|            | FAM179A            | rs13008299           | 2   |          | 29101501 | DBP   | Drinks/w |           |
|            | CRIPT-SOCS5        | rs4953404            | 2   |          | 46739646 | PP    | Days drinks/w, Oz alcohol/w| |
|            | KAT2B              | rs9874923            | 3   |          | 20076567 | MAP   | Drinks/w |           |
|            | Intergenic         | rs3852160            | 5   |          | 5875647  | MAP   | Drinks/w |           |
|            | ADCY2              | rs4537030            | 5   |          | 7296981  | MAP   | Drinks/w |           |
|            | GLI3               | rs7791745            | 7   |          | 42351145 | MAP   | Drinks/w |           |
|            | ZNF716             | rs11766519           | 7   |          | 57587798 | PP    | Days drinks/w|         |
|            | SLC16A9            | rs10826334           | 10  |          | 61050488 | SBP,MAP| Oz alcohol/w|         |
|            | SLC16A9            | rs10826334           | 10  |          | 61050488 | SBP   | Drinks/w |           |
|            | SLIT1              | rs12773465           | 10  |          | 98784049 | MAP   | Drinks/w |           |
|            | SLIT1              | rs7902871            | 10  |          | 98799693 | DBP   | Drinks/w |           |
|            | Intergenic         | rs7116456            | 11  |          | 23911889 | SBP   | Drinks/w |           |
|            | Intergenic         | rs12292796           | 11  |          | 39382675 | PP    | Drinks/w |           |
|            | PDE3A              | rs10841530           | 12  |          | 20490379 | SBP   | Drinks/w |           |
|            | KERA-LUM           | rs991427             | 12  |          | 89998553 | SBP   | Oz alcohol/w|         |
|            | KERA-LUM           | rs4494364            | 12  |          | 90001245 | SBP   | Drinks/w |           |
|            | RNF219-AS1         | rs9318552            | 13  |          | 77923788 | DBP   | Oz alcohol/w|         |
|            | CLEC3A             | rs2735413            | 16  |          | 76611144 | SBP   | Drinks/w |           |
|            | WFDC1              | rs16963349           | 16  |          | 82895735 | SBP   | Drinks/w |           |
|            | FBXO15             | rs1943940            | 18  |          | 69856172 | DBP,MAP| Drinks/w |           |
|            | IGSF5              | rs2410182            | 21  |          | 40101946 | SBP   | Oz alcohol/w|         |
|            | IGSF5-PCP4         | rs2837253            | 21  |          | 40143126 | SBP   | Drinks/w |           |
| Multiple   | BLK                | rs2409784            | 8   |          | 11539347 | DBP   | CURD     | EA,HA     | 42        |
|            | BLK                | rs6983727            | 8   |          | 11558303 | SBP   | LHD      | EA        |           |
|            | BLK                | rs6983727            | 8   |          | 11558303 | PP    | CURD,LHD | EA        |           |
|            | BLK                | rs34190028           | 8   |          | 11559641 | SBP   | CURD     | EA        |           |
|            | CDH17              | rs115888294          | 8   |          | 94010516 | PP    | CURD     | AA        |           |
|            | CORO2A             | rs73655199           | 9   |          | 98145201 | PP    | CURD     | AA        |           |
|            | ELMOD1             | rs139077481          | 11  |          | 107579224| PP    | CURD     | AA        |           |
|            | ERCC6              | rs4253197            | 10  |          | 49473111 | PP    | CURD     | AA        |           |
|            | EYS                | rs80158983           | 6   |          | 65489746 | SBP   | CURD     | AA        |           |
|            | FAM167A            | rs12156009           | 8   |          | 11427710 | SBP   | CURD     | EA        |           |
|            | FAM167A            | rs13255193           | 8   |          | 11451683 | SBP   | LHD      | EA        |           |
|            | FAM167A-AS1        | rs9969423            | 8   |          | 11398066 | SBP   | CURD,LHD | EA        |           |
|            | FTO                | rs9928094            | 16  |          | 53765993 | PP    | CURD     | ASA,EA    |           |
|            | FTO                | rs55872725           | 16  |          | 53775211 | SBP   | CURD     | EA        |           |
Table 4: Review for interaction of gene and alcohol intake on hypertension (Continued)

| Population | Gene       | SNPs/gene length, bp | Chr | Position       | Results | Drink | Ancestor | Reference |
|------------|------------|----------------------|-----|----------------|---------|-------|----------|----------|
| FTO        | rs7185735  | 16                   | 16  | 53788739      | PP      | CURD  | EA,EA    |          |
| FTO        | rs62033406 | 16                   | 16  | 53790314      | MAP     | CURD  | ASA,EA   |          |
| GALNT18    | rs10741534 | 11                   | 11  | 11233360      | SBP     | CURD  | AA       |          |
| GATA4      | rs3735814  | 8                    | 8   | 11749887      | SBP     | CURD  | EA,HA    |          |
| GATA4      | rs36038176 | 8                    | 8   | 11752486      | SBP     | CURD  | EA       |          |
| LINCO00208 | rs899366   | 8                    | 8   | 11572976      | MAP     | CURD  | EA       |          |
| LINCO00208 | rs7464263  | 8                    | 8   | 11576667      | SBP     | CURD  | EA       |          |
| LINCO00208 | rs2244894  | 8                    | 8   | 11591150      | PP      | CURD  | ASA,EA   |          |
| LINCO00208 | rs1478894  | 8                    | 8   | 11591245      | SBP     | CURD  | EA       |          |
| LINCO00208 | rs4841569  | 8                    | 8   | 11594688      | PP      | CURD  | LHD,EA   |          |
| LINCO00208 | rs13249843 | 8                    | 8   | 11601509      | DBP     | CURD  | EA,HA    |          |
| LINCO00208 | rs17807624 | 8                    | 8   | 11605506      | DBP     | CURD  | EA       |          |
| LINCO00208 | rs17807624 | 8                    | 8   | 11605506      | MAP     | CURD  | LHD      |          |
| LOC10272331| rs13276026 | 8                    | 8   | 10752445      | SBP     | CURD  | EA       |          |
| LOC10272331| rs13276026 | 8                    | 8   | 10752445      | DBP,MAP | CURD  | EA,HA    |          |
| LOC10272480| rs453301   | 8                    | 8   | 9172877       | SBP     | CURD  | EA       |          |
| LOC10272480| rs453301   | 8                    | 8   | 9172877       | DBP     | CURD  | EA,HA    |          |
| LOC105372045| rs140520944| 18                  | 18  | 29508647      | PP      | CURD  | AA       |          |
| LOC105372361| rs142673685| 19                  | 19  | 31669942      | PP      | CURD  | AA       |          |
| LOC105379224| rs2980755  | 8                    | 8   | 8506173       | SBP,PP  | LHD   | EA       |          |
| LOC105379224| rs10092965 | 8                    | 8   | 8515975       | DBP     | CURD  | EA,HA    |          |
| LOC105379224| rs13270194 | 8                    | 8   | 8520592       | SBP     | CURD  | EA       |          |
| LOC105379224| rs7823056  | 8                    | 8   | 8525195       | SBP,PP  | LHD   | AA,EA    |          |
| LOC105379224| rs6995407  | 8                    | 8   | 8527137       | PP      | CURD  | EA       |          |
| LOC105379231| rs6601302  | 8                    | 8   | 9381948       | SBP     | CURD  | EA       |          |
| LOC105379235| rs9650622  | 8                    | 8   | 9946782       | DBP     | CURD  | EA       |          |
| LOC105379235| rs56243511 | 8                    | 8   | 9948185       | SBP     | CURD  | EA       |          |
| LOC105379235| rs656319   | 8                    | 8   | 9956901       | SBP,MAP | LHD   | EA       |          |
| LOC105379242| rs13280442 | 8                    | 8   | 11610048      | SBP,MAP | CURD,LHD | EA     |          |
| LOC105379242| rs13250871 | 8                    | 8   | 11610254      | PP      | CURD  | LHD      | EA       |          |
| LOC107986913| rs2979172  | 8                    | 8   | 8452998       | PP      | CURD  | LHD      | EA       |          |
| LOC107986913| rs2921064  | 8                    | 8   | 8459127       | PP      | CURD  | EA       |          |
| LOC107986913| rs2979181  | 8                    | 8   | 8465578       | SBP     | CURD  | LHD      | EA       |          |
| LOC157273  | rs10503387 | 8                    | 8   | 9293015       | SBP     | CURD  | AA,EA    |          |
| LOC157273  | rs11781008 | 8                    | 8   | 9295729       | DBP     | CURD  | EA,HA    |          |
| LOC157273  | rs11774915 | 8                    | 8   | 9331252       | SBP     | CURD  | EA       |          |
| MIR124–1   | rs483916   | 8                    | 8   | 9936091       | SBP,DBP,PP | CURD  | EA       |          |
| MIR124–1   | rs615632   | 8                    | 8   | 9938811       | SBP     | CURD  | LHD      | EA       |          |
| MIR4286    | rs7814795  | 8                    | 8   | 10661775      | SBP     | CURD  | LHD      | EA       |          |
| MIR4286    | rs7814795  | 8                    | 8   | 10661775      | MAP     | CURD  | EA       |          |
| MIR4286    | rs28680211 | 8                    | 8   | 10661935      | MAP     | CURD  | LHD      | EA       |          |
| MSRA       | rs2062331  | 8                    | 8   | 10122482      | DBP     | CURD  | EA       |          |
| MSRA       | rs11993089 | 8                    | 8   | 10152442      | PP      | CURD  | EA       |          |
| MSRA       | rs34919878 | 8                    | 8   | 10241994      | DBP     | CURD  | EA,HA    |          |
Chinese hypertensive patients [47]. As a genome-wide study, the Framingham Heart Study identified 7 significant and 21 suggestive BP loci by gene-smoking interactions in an analysis of 6889 participants [48].

The further genome-wide research was proposed to examine African American participants in the Hypertension Genetic Epidemiology Network (HyperGEN) research, and testing the association in African American participants from the Genetic Epidemiology Network of Arteriopathy (GENOA) study [49]. The results suggested that NEDD8 rs11158609 and TTYH2 rs8078051 were associated with SBP including the genetic interaction with cigarette smoking, although these two SNPs were not associated with SBP in a main genetic effect model.

Gene-obesity interaction
Globally, the prevalence of overweight or obesity for adults increased from 28.8% and 29.8% in 1980 to 36.9% and 38.0% in 2013 for men and women, respectively, which were observed in both developed and developing countries [50]. The prevalence of overweight and obesity is rising among children and adolescents in developing countries as well, rising from 8.1% and 8.4% in 1980 to 12.9% and 13.4% in 2013 for boys and girls, respectively. A meta-analysis of 25 studies has estimated that as body weight decreased by 1 kg, SBP and DBP decreased by −1.05 mmHg and −0.92 mmHg, respectively [51]. Therefore, weight loss for obese people is an essential factor in lowering BP.

The Atherosclerosis Risk in Communities Study showed a significant interaction among the GNB3 C825T polymorphism, obesity status, and physical activity in predicting hypertension in African American subjects, and those who were both obese and had a low activity level with T allele were 2.7 times more likely to be hypertensive compared to non-obese, active C homozygotes [52].

The representative SNPs related to BMI are those in FTO and MC4-R loci. SNPs in FTO were associated with hypertension in different ethnic groups [53]. The Pima Indians in Arizona have the highest prevalence of obesity in the world, but a relatively low prevalence of hypertension and atherosclerotic disease [54]. The lack of increase in muscle sympathetic nerve activity with increasing adiposity and insulinemia in Pima Indians may explain in part [55], but the reason why this population has a low tendency for hypertension despite the high prevalence of obesity and hyperinsulinemia are not yet known.

Gene-physical activity interaction
A meta-analysis that included 13 prospective studies suggested that there was an inverse dose-response association between levels of recreational physical activity and risk of hypertension [56]. A recent systematic review

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**Table 4** Review for interaction of gene and alcohol intake on hypertension (Continued)

| Population | Gene | SNPs/gene length, bp | Chr | Position | Results | Drink | Ancestor | Reference |
|------------|------|----------------------|-----|----------|---------|--------|-----------|-----------|
| MSRA       | rs4841294 | 8 | 10247558 | SBP | LHD | AA,EA | |
| MSRA       | rs17693945 | 8 | 10248500 | MAP | LHD | AA,EA | |
| MSRA       | rs7832708 | 8 | 10332530 | SBP | LHD | EA | |
| MSRA       | rs11786677 | 8 | 10406750 | SBP | CURD | EA | |
| PINX1      | rs4551304 | 8 | 10807559 | DBP,MAP | CURD | EA,HA | |
| PINX1      | rs7814757 | 8 | 10817678 | SBP | CURD | EA | |
| RP1L1      | rs4841409 | 8 | 10658864 | SBP | CURD | EA | |
| RP1L1      | rs4841409 | 8 | 10658864 | MAP | CURD,LHD | EA | |
| RP1L1      | rs10096777 | 8 | 10660990 | SBP | LHD | EA | |
| TACC2      | rs11200509 | 10 | 122256927 | PP | LHD | AA | |
| TARID      | rs76987554 | 6 | 133759717 | SBP | CURD | AA | |
| TNKS       | rs4383974 | 8 | 9761838 | SBP | CURD | AA,EA | |
| TNKS       | rs35231275 | 8 | 9762399 | PP | CURD | EA | |
| TNKS       | rs9286060 | 8 | 9795635 | DBP | CURD | AA,EA | |
| TNKS       | rs1076671 | 8 | 9822124 | SBP | CURD | EA | |
| TNKS       | rs55868514 | 8 | 9822890 | DBP | CURD | EA | |
| UNC5D      | rs70505281 | 8 | 35841899 | PP | CURD | AA | |
| XKR6       | rs4841465 | 8 | 10962344 | SBP | CURD,LHD | EA | |
| XKR6       | rs9969436 | 8 | 10985149 | MAP | LHD | AA,EA | |

HT hypertension, SBP systolic blood pressure, DBP diastolic blood pressure, MBP mean blood pressure, PP pulse pressure, CURD current drinker (yes/no), LHD light (1 ± 7 drinks/week) drinking; Ancestry, EA European ancestry, AA African American ancestry, ASA Asian American ancestry, HA Hispanic ancestry.
and meta-analysis of randomized control trials with a meta-regression of potential effect modifiers revealed that exercise was associated with a reduction in SBP of $-4.40$ mmHg and in DBP of $-4.17$ mmHg at 3–6 months after the intervention began [57]. Potential reasons for the association between physical activity and BP decreases are as follows. First, physical activity helps maintain appropriate body weight. Second, exercise decreases total peripheral resistance [58]. Physical activity has also been shown to improve insulin sensitivity [59], which increases high blood pressure via its effect in increasing sodium reabsorption and sympathetic nervous system activity [60]. An exercise habit can also help improve one’s other lifestyle habits. Individuals who exercise every day tend to focus on improving their lifestyle in other aspects of their daily lives.

In a cross-sectional study of African American women, $SLC4A5$ rs1017783 had a significant interaction with A allele and AA genotype by physical activity on SBP and DBP, respectively. In addition, $SLC4A5$ rs6731545 had a significant interaction with GA genotype by physical activity on both SBP and DBP. A study of Chinese children showed that interactions between a genetic risk score including $ATP2B1$ rs17249754, fibroblast growth factor 5 ($FGF5$) rs16998073 polymorphisms, and physical activity play important roles in the regulation of BP and the

### Table 5 Review for interaction of gene and smoking on hypertension

| Population | Gene | SNPs/gene length, bp | Chr | Position | Results | Smoking | Reference |
|------------|------|-----------------------|-----|----------|---------|---------|-----------|
| China      | ACE  | I/D                   |     |          | EH      | Smoking | 45        |
| China      | KCNJ11 |                        |     |          | HT      | Non-smoking | 46        |
| China      | CYP4A11 | rs1126742              | 1   |          | EH      | Smoking | 47        |
| USA        | LOC729336 | rs11589828             | 1   |          | 230735895 | SBP | Pack-years | 48        |
|            | LRP1B | rs1033284              | 2   |          | 141638258 | SBP | Pack-years |           |
|            | LRP2  | rs2268365              | 2   |          | 169802415 | SBP | Pack-years |           |
|            | FLJ45964 | rs11679072             | 2   |          | 240109156 | SBP | Pack-years |           |
|            | CNTN4 | rs9878978              | 3   |          | 2460969   | SBP | Pack-years |           |
|            | MECOM | rs12634933             | 3   |          | 170512673 | SBP | Pack-years |           |
|            | PRKG2 | rs17484474             | 4   |          | 82345145  | SBP | Pack-years |           |
|            | GYP-A-KRT18PS1 | rs6537278     | 4   |          | 145477389 | SBP | Pack-years |           |
|            | RPS6KA2 | rs4710117              | 6   |          | 167184091 | SBP | Pack-years |           |
|            | PPP1R3A-FOXP2 | rs12705959     | 7   |          | 113785482 | SBP | CPD       |           |
|            | COLEC10-MAL2 | rs6896884      | 8   |          | 120212220 | SBP | Pack-years |           |
|            | TRAPPC9 | rs7823724              | 8   |          | 141735111 | SBP | Pack-years |           |
|            | ADARB2 | rs6560743              | 10  |          | 1627136   | SBP | Pack-years |           |
|            | OPCML | rs7104871              | 11  |          | 132544099 | SBP | Pack-years |           |
|            | CACNA2D4 | rs2286379              | 12  |          | 1772425   | SBP | Pack-years |           |
|            | SACS-TNFRSF19 | rs2297585       | 13  |          | 22942344  | SBP | Pack-years |           |
|            | FRY   | rs9533282              | 13  |          | 31525648  | SBP | Pack-years |           |
|            | GPC5-GPC6 | rs9561252              | 13  |          | 92527286  | SBP | CPD       |           |
|            | LOC730007 | rs8010717            | 14  |          | 79480194  | SBP | CPD       |           |
|            | NRXN3 | rs8010717              | 14  |          | 79480194  | SBP | Pack-years, smoking |           |
|            | HERC2P6 | rs937741               | 15  |          | 21198852  | SBP | CPD       |           |
|            | CYB5B | rs12149862             | 16  |          | 68054704  | SBP | Pack-years |           |
|            | ZSWIM7 | rs7211756              | 17  |          | 15840400  | SBP | Pack-years |           |
|            | CDH19-DSEL | rs7234531          | 18  |          | 62721365  | SBP | Pack-years |           |
|            | MN1   | rs133980               | 22  |          | 26352728  | SBP | CPD, Pack-years |           |
|            | LOC200810 | rs7615952            | 3   |          | 127132093 | DBP | Pack-years |           |
|            | GRB10 | rs10275663             | 7   |          | 50765179  | DBP | CPD       |           |
| African American | NEDD8 | rs11158609             | 14  |          | 24688814  | SBP | Smoking   | 49        |
|            | TTYH2 | rs8078051              | 17  |          | 72251240  | SBP | Smoking   |           |

HT hypertension, SBP systolic blood pressure, DBP diastolic blood pressure, MBP mean blood pressure, PP pulse pressure, CPD cigarettes per day
development of hypertension [61]. ATP2BI is expressed in the vascular endothelium and regulates the homeostasis of cellular calcium levels, which is important in controlling the contraction and dilation of vascular smooth muscles [62]. The most commonly cited effect of FGF-5 is to promote angiogenesis in the heart. FGF-5 acts as an autocrine/paracrine mechanism of cardiac cell growth and as a cytoprotective mechanism against irreversible ischemic damage [63]. FGF-5 rs16998073 polymorphisms were significantly associated with hypertension risk in East Asians [64]. However, no evidence supports a role for this gene in the pathogenesis of hypertension.

**Perspectives**

In the era of precision medicine, clinicians who are responsible for hypertension management should consider the gene-environment interactions along with the appropriate lifestyle components toward the prevention and treatment of hypertension. The effects and contributions of other confounding and interaction factors such as race, age, other lifestyle habits (e.g., lack of sleep [65] and bathing [66]), and environmental factors (e.g., weather conditions [67] and air pollution [68]), stress [69], and social factors [70] must also be determined comprehensively.

We briefly reviewed the interaction of genetic and environmental factors along the constituent elements of hypertension guidelines, but a sufficient amount of evidence has not yet accumulated, and the results of genetic factors often differed in each study. The following requirements should be considered in future studies: (1) set of the reproducible environmental factor with simple and easy way; (2) consider the subjects’ race, gender, and age; (3) select research subjects so that bias is as small as possible; (4) use a risk score of the target disease including a simple dietary intake and physical activity questionnaire and examines genetic factors to improve the risk model; and (5) effectively provide hypertension management with precision medicine based on the components of appropriate lifestyle interventions in hypertension prevention guidelines for a cardiovascular disease model with the specific gene-environmental factors being studied.

The Genetic Epidemiology Network of Salt Sensitivity (The GenSalt) Study obtained novel implications regarding the association between BP responses to dietary sodium and potassium and hypertension and identifying an inverse relation between a BP genetic risk score and salt and potassium sensitivity of BP [71]. The UK Biobank data recently revealed 107 validated loci for BP, in a study that showed that BP which is 9–10 mmHg higher with an over twofold higher risk of hypertension (in a comparison of the top and bottom quintiles of the BP genetic risk score distribution) has potential clinical and public health implications [72]. Although the extent to which each gene contributes to BP is small, by incorporating the concept of a genetic risk score, the contribution of blood pressure has been shown by many GWAS. BP research will continue to contribute to future preventive medicine.

**Conclusion**

We summarize gene-environmental interactions associated with hypertension by describing common lifestyle modifications according to the recommendations of hypertension guidelines in major countries which consist of the following elements: weight reduction, a healthy diet, dietary sodium reduction, increasing physical activity, quitting smoking, and moderate alcohol consumption. We briefly reviewed the interaction of genetic and environmental factors along the constituent elements of hypertension guidelines, but a sufficient amount of evidence has not yet accumulated, and the results of genetic factors often differed in each study.

**Abbreviations**

ALDH: Aldehyde dehydrogenase; BMI: Body mass index; BP: Blood pressure; CHARGE: Cohorts for Heart and Aging Research in Genetic Epidemiology; CVD: Cardiovascular disease; DASH: Dietary Approaches to Stop Hypertension; DBP: Diastolic blood pressure; eNOS: Endothelial nitric oxide synthase; GENOA: Genetic Epidemiology Network of Arteriopathy; GenSalt: Genetic Epidemiology Network of Salt Sensitivity; GWAS: Genome-wide association studies; HyperGEN: Hypertension Genetic Epidemiology Network; iNOS: Inducible nitric oxide synthase; INTERSALT: International Cooperative Study on Salt, Other Factors, and Blood Pressure; MBP: Mean blood pressure; NOS: Nitric oxide synthase; PUFA: Polyunsaturated fatty acid; SAPPHiRe: Stanford Asia-Pacific Program for Hypertension and Insulin Resistance; SBP: Systolic blood pressure; SNV: Single-nucleotide variant

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**Authors’ contributions**

YK and SP conceived and wrote the paper. YI, KY, and AG contributed to the writing of the manuscript. All authors have reviewed the final version of the manuscript and approved to submit to your journal.

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Not applicable.

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**Competing interests**

The authors declare that they have no competing of interests.

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