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REVIEW

Genetic basis of hypertension for the development of tailored medicine

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Similar to a tsunami wave, a new surge of genome-wide association studies in common complex diseases has succeeded in identifying the causative genetic risk factors of hypertension. The current status of genomic studies in hypertension, however, remains disorganized, and there are no clear solutions in sight. One possible reason for this disorganization is the small effect of each genetic variant on the predisposition to hypertension. Another reason could be that the morbidity of hypertension is typically used as a target to assess genetic contribution, which could be resolved by introducing new technology into the classical genetic analysis. In this review, we reaffirm the genetic basis of hypertension and outline recent progress in genomics. In addition, we discuss both the possibility and usefulness of genomic information in the development of tailored medicine.
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INTRODUCTION

In Japan, physicians frequently refer to the guidelines of hypertension in daily clinical practice. The latest version of the guidelines was recently published by the Japanese Society of Hypertension (JSH2009).[1] The number of hypertensive patients in Japan was estimated to be ~40 million. It was also found that a 2 mm Hg decrease in systolic blood pressure (BP) led to a >5% decrease in the occurrence of stroke or ischemic heart disease. Thus, there is no question that the primary goal of hypertension treatment is to prevent cardiovascular disease by achieving a specific BP level. The response to antihypertensive treatment and the grade of targeted organ damage vary significantly among individuals, and the standard therapy described in the guidelines does not always achieve the final goal of treatment. A reason for this diversity is that a large proportion of hypertension cases are essential hypertension, of which the cause is not yet defined. This indicates that the identification of certain causes or predisposing factors for hypertension could lead to the development of more specific and efficient treatments. For example, if physicians could diagnose 'salt-sensitive hypertension' accurately, a reduction in the dietary intake of salt and a small dose of diuretics should be prescribed with confidence. In this study, we review publications with regard to the genetic basis of hypertension and discuss the clinical application of the results.

HERITABILITY OF BP

Both genetic and environmental factors are involved in the pathogenesis of hypertension. The genetic factors contribute to approximately 30–70% of disease susceptibility. The proportion of hypertensive patients with affected siblings was studied in 6000 Caucasian patients,[2] showing a recurrence risk of ~3.5 for hypertension. The heritability (H^2) of systolic and diastolic BP in 6148 Sardinians was estimated to be 0.253 (0.156–0.651) and 0.186 (0.121–0.449), respectively.[3] As aging has been found to be the most influential on BP in covariate analysis, the effect of genetic factors should be discussed after adjusting for age.

Previous studies with regard to monogenic hypertension and hypotension showed the importance of rare genetic variations in the electrolyte channels and transporters of renal tubules (Table 1). It is interesting that the same gene, such as the one encoding the β- and γ-subunit of the epithelial sodium channel (*SNCC1B/G*), contributes to both hypertension (Liddle's syndrome) and hypotension (pseudohypoaldosteronism type 1, or PHA1), depending on the mutation. The importance of rare genetic variations receives significant attention not only in cases of monogenic hypertension/hypotension but also in essential hypertension. In the Framingham Heart Study, rare genetic variations in three genes, solute carrier family 12 member 3(*SLC12A3*) (thiazide-sensitive Na–Cl co-transporter, TSC), *SLC12A1* (NKCC2) and *KCNJ1* (ROMK), were found to be associated with lower BP in the general population.[4] Thus, rare genetic variations may explain, at least in part, the complex genetics of human hypertension.[5] In JSH2009, Table 12-7 lists information regarding rare genetic variations in essential hypertension and includes a list of congenital diseases with BP abnormalities, the name of the causative genes and their clinical features.[1]

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SALT SENSITIVITY AND GENETIC PREDISPOSITION TO HYPERTENSION

The most popular approach to identifying hypertensive genes involves genetic association studies, which are population-based and compare cases and controls. The candidate gene approach is a classical but powerful method to examine the predisposing genetic factor of hypertension. Many studies have examined the association between gene variants of the renin–angiotensin system and hypertension. Among these, M235T, T174M and G-6A polymorphisms of the *angiotensinogen* gene (*AGT*) have been determined to increase the genetic risk not only for hypertension but also for ischemic heart disease,[6] lacunar infarction and non-dipper type of BP variation.[7] These results suggest the possibility that a polymorphism in *AGT* modulates the sensitivity to salt through an enhancement of sympathetic nerve activity or insulin resistance, thereby increasing the risk for ischemic heart disease. Indeed, *AGT* is considered to be a thrifty gene that has the advantage of surviving in a harsh environment; however, it increases the risk for cardiovascular disease through sodium and body fluid retention. In addition to *AGT*, the risk allele frequencies of popular candidate gene polymorphisms of salt-sensitive hypertension, such as *alpha adducin* (*ADD1*), the *G-protein beta-3 subunit* gene (*GNB3*) and the *aldosterone synthase* gene (cytochrome P450, subfamily Y XIB, polypeptide 2, *CYP11B2*), are higher in the Japanese population than in Caucasians.[8] Hunt *et al.*[9] reported that the effect of salt reduction and weight loss on the prevention of hypertension in pre-hypertensive individuals with the risk allele was much greater than in individuals with the normal allele. Therefore, a reduction in salt or a small dose of diuretics should be an effective approach in the treatment of hypertension in Japanese patients. On the basis of the comparable effectiveness for the treatment of hypertension and the advantage of pharmaco-economics, JSH2009 encourages physicians to use diuretics more frequently.

The thiazide-sensitive Na–Cl co-transporter has an important function in the treatment of hypertension with diuretics. Kokubo *et al.*[10] and our group[11] have reported a positive association between the TSC gene (*SLC12A3*) and a predisposition to hypertension. Matayoshi *et al.*[12] showed that the C1784T polymorphism of *SLC12A3* was significantly associated with the antihypertensive effect of diuretics. As a functional single-nucleotide polymorphism (SNP) of *SLC12A3*, Keszei *et al.*[13] showed the difference in renal tubular sodium transport by an Arg919Cys substitution of *SLC12A3*, using the *Xenopus laevis* oocyte expression system. The TSC gene not only indicates a genetic risk for hypertension but is also a causative gene for monogenic hypotensive disease (Gitelman's syndrome)[14] (Table 1).

Molecules with similarly important functions in salt homeostasis are WNK kinases (WNK1 and WNK4), which are also causative genes for monogenic hypertension with hyperkalemia (Gordon's syndrome)[15] (Table 1). WNK kinases bind and phosphorylate two Ste20-related protein kinases, OSR1 and STK39, which bind and phosphorylate TSC to increase their activity. This results in WNK kinases modulating the electrolyte and water transport pathways in the distal nephron.[16,17] A recent genome-wide association study (GWAS) in Amish and non-Amish Caucasians showed strong association signals with common variants in STK39, a *serine/threonine kinase* gene. STK39 interacts with WNK kinases and cation-chloride co-transporters, mutations of which cause monogenic forms of BP dysregulation.[18] This indicates that TSC, STK39, OSR1 and WNK kinases are key molecules in the pathogenesis of hypertension and are the new targets of treatment for hypertension.

Table 1 Genes involved in monogenic hypertension and hypotension

Locus	*Gene symbol*	*Diseases*
Monogenic hypertension		
4p31.1	*NR3C2*	Early-onset hypertension with severe exacerbation in pregnancy
8q21	*CYP11B1*	Adrenal hyperplasia due to 11-β-hydroxylase deficiency
8q21	*CYP11B1&2*[a]	Glucocorticoid-remediable aldosteronism (GRA)
10q24.3	*CYP17*	17-α-hydroxylase/17, 20-lyase deficiency
12p13	*WNK1*	Gordon's syndrome (PHA IIC)
16p13-p12	*SCNN1B/G*	Liddle's syndrome
16q22	*HSD11B2*	Apparent mineralocorticoid excess (AME)
17q21-q22	*WNK4*	Gordon's syndrome (PHA IIB)
Monogenic hypotension		
1p36	*CLCNKB*	Bartter's syndrome, type 3
1p31	*BSND*	Bartter's syndrome, type 4
4p31.1	*NR3C2*	Pseudohypoaldosteronism, type 1, autosomal dominant (PHA1)
11q24	*KCNJ1*	Bartter's syndrome, type 2
12p13	*SCNN1A*	Pseudohypoaldosteronism, type 1, autosomal recessive (PHA1)
15q15-q21.1	*SLC12A1*	Bartter's syndrome, type 1
16p13-p12	*SCNN1B/G*	Pseudohypoaldosteronism, type 1, autosomal recessive (PHA1)
16q13	*SLC12A3*	Gitelman's syndrome

CYP11B1&2, cytochrome P450, subfamily Y XIB, polypeptide 1&2; PHA, pseudohypoaldosteronism; *SLC12A1*, solute carrier family 12 member 1; *SLC12A3*, solute carrier family 12 member 3.
[a]GRA is caused by chimeric gene in which the 5′-regulatory sequences of the *CYP11B1* are fused to the coding region of the *CYP11B2*.

GENETIC BASIS FOR HYPERTENSION

Blockade of the renin–angiotensin system improves not only hypertension but also insulin sensitivity and adipocytokine abnormalities.[19] The recent TROPHY trials[20] suggested that an early blockade of the renin–angiotensin system prevents the onset of hypertension. High normal BP, obesity and impaired glucose tolerance are independent predictors of the onset of hypertension.[21] BP was shown to be significantly associated with lower adiponectin concentrations, regardless of insulin resistance. In individuals with a TC genotype of an I164T polymorphism of the *adiponectin* gene (*ADIPOQ*), adiponectin concentrations were one-third the normal level in individuals who had the homozygous wild allele. Moreover, these individuals were highly predisposed to cardiovascular diseases.[22]

Endothelial dysfunction due to reactive oxygen species (ROS) is also considered to be a cause of hypertension.[23] The genetic variants of the endothelial *nitric oxide synthase* gene (*NOS3*) have been determined to increase the genetic risk for coronary spasms[24] and to increase pulse pressure and senile cognitive dysfunction.[25] The C677T polymorphism of the *methyleneteterahydrofolate reductase* (*MTHFR*) gene was also found to be significantly correlated with hyperhomocysteinemia and carotid atherosclerosis in Japanese women, and the significance increased when the women smoked.[26] Thus, in individuals who are genetically sensitive to ROS, a recommendation to cease smoking and to modify lifestyle, or drug administration to reduce oxidative stress, should be given. Recent pharmacological studies have shown that the combination of pioglitazone and candesartan exerts more beneficial effects on hypertensive cardiovascular damage by increasing the suppression of ROS.[27]

The modulation of sympathetic nerve activity has a key function in the pathogenesis of cardiovascular diseases. We reported in a 5-year longitudinal study that *beta2-adrenergic receptor* gene (*ADRB2*) polymorphisms in association with exaggerated sympathetic nerve activity could predict the future onset of obesity and hypertension.[28] Furthermore, higher plasma norepinephrine levels that are associated with β2-adrenoceptor polymorphisms predict future renal damage in non-obese, normotensive individuals.[29] Leptin is another unique molecule to be considered as the common denominator between obesity and problems in the sympathetic nervous system. We have also pointed out that *leptin-receptor* gene (*LEPR*) polymorphisms have a function in the development of obesity through leptin resistance and blunted leptin-mediated sympathetic nerve activity.[30] As the Gly16 allele of *ADRB2* polymorphisms is linked to weight gain-induced BP elevation and is associated with leptin resistance,[31] the genotype information of adrenoceptors and leptin receptor gene polymorphisms may be useful for determining optimal diet and exercise.

RECENT PROGRESS OF GWASS IN HYPERTENSION GENETICS

In recent years, GWASs have surpassed classical genetic investigations using a candidate gene approach. First, a result obtained from the Wellcome Trust Case Control Consortium (WTCCC) using 14 000 cases of 7 common diseases and 3000 shared controls was published in *Nature* in 2007.[32] Even though hypertension was included in the seven major diseases, no significant independent associations were detected in cases of hypertension. This was in contrast to diabetes, Crohn's disease, rheumatoid arthritis and coronary artery disease. Only haplotype analysis showed a marginal association with hypertension on the 15q26.2 locus, but this was unable to pass WTCCC's stringent genotype quality filters.[33] Ehret *et al.* carried out a replication study using the top six SNPs from the WTCCC data in 11 433 individuals from the US National Heart, Lung, and Blood Institute-funded Family Blood Pressure Program. They found that only one SNP, rs1937506, was significantly associated with hypertension; however, its location was in a 500-kb gene desert on 13q21.[34] In the Hypertension Genetic Epidemiology Network, Shi *et al.* examined gene–age interactions using genome-wide linkage analysis. The highest logarithm of odds score was identified on the chromosomal region 1p36, and supporting evidence was confirmed in three separate studies. This investigation also showed that genetic effects on BP varied by age.[35]

The Japanese Millennium Genome project succeeded in identifying several loci and genes responsible for hypertension. In this project, Japanese researchers shared the samples and examined the genetic variants using 18 977 microsatellite markers and 80 795 SNPs. This resulted in 19 allelic loci using the microsatellite approach,[36] and 3 genes using the SNP approach[37] were identified as susceptible genes for hypertension. The genes identified were the *beta-adducin* gene (*ADD2*) on 2p14-p13, KIAA0789 on 12q23.3 and the *mannose-6-phospate* gene (*M6PR*) on 12p13.

Recently, a GWAS in the Kooperative Gesundheitsforschung in der Region Augsburg (KORA) S3 cohort study of 1644 Germans showed a significant association between BP and a common variant, rs11646213, upstream of *CDH13*. This gene encodes for an adhesion glycoprotein QJ;T-cadherin, a regulator of vascular wall remodeling and angiogenesis.[38] The significant association was reconfirmed in KORA S4 (Germans) and HYPEST (Estonians), and a similar trend was observed in BRIGHT (British). It is interesting that T-cadherin is also a receptor for the hexameric and high-molecular-weight species of adiponectin, but not for the trimeric or globular species.[39] In addition, methylation of the promoter region of *CDH13* was found to be significantly associated with the recurrence of non-small-cell lung cancer.[40] A similar association was observed in the *cyclin-dependent kinase inhibitor 2A* gene (*CDKN2A*) on 9p21, a current interest as the candidate locus of myocardial infarction.[41] These results indicate that the genes considered to be candidates for tumorigenesis or metastasis also act as the modifiers of vascular remodeling, atherosclerosis and metabolic signals.

Another recent breakthrough of the GWAS in hypertension appeared as three articles in an issue of *Nature Genetics*.[42–44] The first paper[42] identified the association of the common variants in the natriuretic peptide precursor A and B genes (*NPPA*, *NPPB*) with circulating natriuretic peptide and BP. The second[43] examined 34 433 individuals of European ancestry from the Global BPgen consortium and found that common variants in eight loci were significantly associated with systolic or diastolic BP. In the third paper,[44] 10–20 loci were identified as the candidates responsible for BP and hypertension using the participants of the CHARGE consortium (n=29 136). Some of these loci were found to be significantly associated with BP or hypertension in a joint meta-analysis with the Global BPgen Consortium. The final candidate genes obtained from GWAS are listed in Table 2.

ANTIHYPERTENSIVE MEDICATION BASED ON PHARMACOGENOMICS

Salt sensitivity and genetic predisposition to hypertension are different between races. In the United States, for example, BiDil (isosorbide dinitrate and hydralazine, NitroMed. Inc., Lexington, MA, USA) is currently a standard therapy for African Americans, but not for other races, with heart failure.[45] Thus, it is not difficult to anticipate that the response to antihypertensive medication also varies greatly between individuals with different racial or genetic backgrounds. Brown[46] pointed out the function of ethnicity in the pathogenesis of hypertension, and emphasized the usefulness of measuring renin activity in choosing the most appropriate antihypertensive drug.[46] In this review, age was discussed as a critical modifier in the response to antihypertensive medication. For example, usage of diltiazem or diuretics is recommended for senile African Americans, but not for young Caucasians. In individuals with the salt-sensitive allele of *ADD1*, diuretic therapy was preferred to reduce the risk of myocardial infarction or stroke compared with other antihypertensive therapies.[47]

Table 2 Candidate hypertensive genes supported by recent genome-wide association studies

Gene symbol	*Gene name*	*Locus*
NPPA-NPPB	Natriuretic peptide precursor A, B	1p36.2
ADD2	Beta-adducin	2p14-p13
ULK4	Unc-51-like kinase 4 (*C. elegans*)	3p22.1
CACNB2	Calcium channel, voltage-dependent, beta 2 subunit	10p12
CYP17A1	Cytochrome P450, family 17, subfamily A, polypeptide 1	10q24.3
PLEKHA7	Leckstrin homology domain containing, family A member 7	11p15.1
M6PR	Mannose-6-phospate	12p13
ATP2B1	ATPase, Ca^{++} transporting, plasma membrane 1	12q21.3
KIAA0789	WSC domain containing 2 (*WSCD2*)	12q23.3
TBX3-TBX5	T-box 3, 5	12q24.1
SH2B3	SH2B adaptor protein 3	12q24
CSK-ULK3	c-src tyrosine kinase, unc-51-like kinase 3 (*C. elegans*)	15q23-q25
CDH13	H-cadherin (heart)	16q24.2-q24.3

The racial difference in the response to antihypertensive medication affected the results of major clinical trials, such as the ALLHAT or INSIGHT trial. The genetic background of the participants in ALLHAT was examined as a GenHAT study. It was found that the G-6A polymorphism of *AGT* was significantly associated with pulse pressure change after 6 months of antihypertensive treatment in a gender-specific manner.[48] Another interesting result in GenHAT was obtained from the genotype determination of the two polymorphisms in the precursor of the atrial *natriuretic polypeptide* gene (*NPPA*).[49] The C-allele carriers of the *NPPA* T2238C polymorphism experienced more favorable cardiovascular disease outcomes when randomized to receive a diuretic, whereas the TT-allele carriers had more favorable outcomes when randomized to receive a calcium channel blocker. Most candidate gene polymorphisms, however, did not show any significant association in response to antihypertensive treatment in the GenHAT study.

In contrast, there are many reports suggesting the effect of adrenoceptor gene polymorphisms on β-blocker treatment, cardiovascular risk and mortality. For example, Pacanowski *et al.*[50] reported in the INVEST study that the ADRB1 haplotype variation was associated with mortality risk, and β-blockers may be preferred in subgroups of patients defined by β1- or β2-adrenoceptor gene polymorphisms.

Genome-wide association studies are already incorporated into pharmacogenomic investigations. Turner *et al.* compared the genetic background between good and poor responders for thiazide diuretic treatment using Affymetrix GeneChip Human Mapping 100K arrays (Affymetrix, Santa Clara, CA, USA). Haplotype trend regression analysis showed that the 12q15 locus was significantly associated with diastolic BP response.[51] The same group also proposed a new investigation, known as the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study, by recruiting 800 hypertensive individuals and randomizing them to atenorol or hydrochlorothiazide.[52]

In Japan, two major pharmacogenomic cohort studies of antihypertensive therapy are currently in progress. One is the Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) Study, which is a large-scale intervention trial using a PROBE design to determine an optimal target BP level on the basis of self-measured BP with an optimal initial dose of antihypertensive medication.[53] We are carrying out a sub-study of HOMED-BP, known as the HOMED-BP-GENE study, which is a GWAS to examine the genetic background of the response to antihypertensive medication. The preliminary results after a month of treatment suggest that different genes may be responsible for a reduction in BP in the morning and in the evening. Another GWAS is the GEANE (Gene Evaluation for Antihypertensive Effect of drugs) study, which is a multicenter trial to examine the response to a 3-month treatment of diuretics, an angiotensin II receptor blocker and a calcium channel blocker.

CONCLUSIONS

In comparison with the recent surge of positive results in other common complex diseases, a clear answer has not yet been elucidated for the genetic etiology of hypertension. The continuous efforts of researchers, however, will make progress by small, incremental advances (Figure 1). The chaos observed in hypertension genomics is resolvable by the introduction of new technologies in the place of classical genetic analysis. GWASs, epigenetics, pharmacogenomics and accurate phenotyping of clinical features (for example, home BP measurement) are issues that are critical to the success of investigations. In addition, fresh ideas are also crucial in finding a novel way to clarify the pathogenesis of hypertension. To consider hypertension from the viewpoint of aging, arteriosclerosis and volume retention, paying close attention to salt sensitivity, the renin–angiotensin system, atherosclerosis, ROS and sympathetic nerve activation, as well as cell growth, apoptosis, immune reaction and adipocyte differentiation, could be the solution for resolving hypertension genomics.

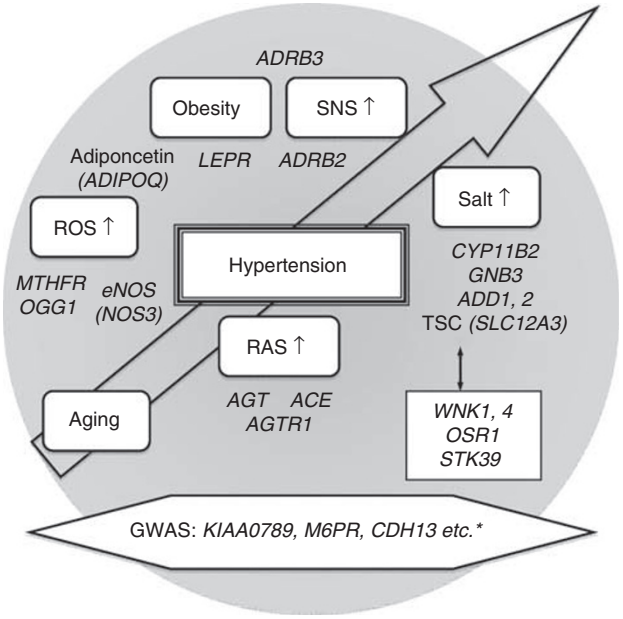

Figure 1 Prevalence of hypertension increases with age. Various genes, indicated in italics as gene symbols, affect the onset and development of hypertension. *Other candidate genes from GWAS are listed in Table 2. SNS, sympathetic nervous system; ROS, reactive oxygen species; RAS, renin–angiotensin system, GWAS, genome-wide association study. Gene symbols: *LEPR*, leptin receptor; *ADRB2*, beta-2-adrenergic receptor; *ADRB3*, beta-3-adrenergic receptor; *MTHFR*, 5,10-methlenetetrahydrofolate reductase; *OGG1*, 8-oxoguanine DNA glycosylase; *CYP11B2*, cytochrome P450, subfamily Y XIB, polypeptide 2; *GNB3*, guanine nucleotide-binding protein, beta-3; *ADD1*, alpha-adducin; *ADD2*, beta-adducin; *SLC12A3*, solute carrier family 12 (sodium–chloride transporter), member 3; *WNK1*, protein kinase, lysine-deficient 1; *WNK4*, protein kinase, lysine-deficient 4; *STK39*, serine/threonine protein kinase 39; *AGT*, angiotensinogen; *ACE*, angiotensin I-converting enzyme (peptidyl-dipeptidase A) 1; *AGTR1*, angiotensin II receptor, type 1; *KIAA0789* (*WSCD2*), WSC domain containing 2; *M6PR*, mannose-6-phosphate receptor (cation dependent); *CDH13*, cadherin 13 (H-cadherin (heart)).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**: 3–107.
2 Brown MJ. The causes of essential hypertension. *Br J Clin Pharmacol* 1996; **42**: 21–27.
3 Pilia G, Chen WM, Scuteri A, Orru M, Albai G, Dei M, Lai S, Usala G, Lai M, Loi P, Mameli C, Vacca L, Deiana M, Olla N, Masala M, Cao A, Najjar SS, Terracciano A, Nedorezov T, Sharov A, Zonderman AB, Abecasis GR, Costa P, Lakatta E, Schlessinger D. Heritability of cardiovascular and personality traits in 6,148 Sardinians. *PLoS Genet* 2006; **2**: e132.
4 Ji W, Foo JN, O'Roak BJ, Zhao H, Larson MG, Simon DB, Newton-Cheh C, State MW, Levy D, Lifton RP. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 2008; **40**: 592–599.
5 Wagner CA. How much is blood pressure in the general population determined by rare mutations in renal salt-transporting proteins? *J Nephrol* 2008; **21**: 632–634.
6 Katsuya T, Koike G, Yee TW, Sharpe N, Jackson R, Norton R, Horiuchi M, Pratt RE, Dzau VJ, MacMahon S. Association of angiotensinogen gene T235 variant with increased risk of coronary heart disease. *Lancet* 1995; **345**: 1600–1603.
7 Fujiwara T, Katsuya T, Matsubara M, Mikami T, Ishikawa K, Kikuya M, Ohkubo T, Hozawa A, Michimata M, Suzuki M, Metoki H, Asayama K, Araki T, Tsuji I, Higaki J, Satoh H, Hisamichi S, Ogihara T, Imai Y. T+31C polymorphism of angiotensinogen gene and nocturnal blood pressure decline: the Ohasama study. *Am J Hypertens* 2002; **15**: 628–632.
8 Katsuya T, Ishikawa K, Sugimoto K, Rakugi H, Ogihara T. Salt sensitivity of Japanese from the viewpoint of gene polymorphism. *Hypertens Res* 2003; **26**: 521–525.
9 Hunt SC, Cook NR, Oberman A, Cutler JA, Hennekens CH, Allender PS, Walker WG, Whelton PK, Williams RR. Angiotensinogen genotype, sodium reduction, weight loss, and prevention of hypertension: trials of hypertension prevention, phase II. *Hypertension* 1998; **32**: 393–401.
10 Kokubo Y, Kamide K, Inamoto N, Tanaka C, Banno M, Takiuchi S, Kawano Y, Tomoike H, Miyata T. Identification of 108 SNPs in TSC, WNK1, and WNK4 and their association with hypertension in a Japanese general population. *J Hum Genet* 2004; **49**: 507–515.
11 Matsuo A, Katsuya T, Ishikawa K, Sugimoto K, Iwashima Y, Yamamoto K, Ohishi M, Rakugi H, Ogihara T. G2736A polymorphism of thiazide-sensitive Na-Cl cotransporter gene predisposes to hypertension in young women. *J Hypertens* 2004; **22**: 2123–2127.
12 Matayoshi T, Kamide K, Takiuchi S, Yoshii M, Miwa Y, Takami Y, Tanaka C, Banno M, Horio T, Nakamura S, Nakahama H, Yoshihara F, Inenaga T, Miyata T, Kawano Y. The thiazide-sensitive Na(+)-Cl(−) cotransporter gene, C1784T, and adrenergic receptor-beta3 gene, T727C, may be gene polymorphisms susceptible to the antihypertensive effect of thiazide diuretics. *Hypertens Res* 2004; **27**: 821–833.
13 Keszei AP, Tisler A, Backx PH, Andrulis IL, Bull SB, Logan AG. Molecular variants of the thiazide-sensitive Na+-Cl- cotransporter in hypertensive families. *J Hypertens* 2007; **25**: 2074–2081.
14 Ogihara T, Katsuya T, Ishikawa K, Matsuo A, Rakugi H, Shoji M, Yasujima M. Hypertension in a patient with Gitelman's syndrome. *J Hum Hypertens* 2004; **18**: 677–679.
15 Wilson FH, Disse-Nicodeme S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, Gunel M, Milford DV, Lipkin GW, Achard JM, Feely MP, Dussol B, Berland Y, Unwin RJ, Mayan H, Simon DB, Farfel Z, Jeunemaitre X, Lifton RP. Human hypertension caused by mutations in WNK kinases. *Science* 2001; **293**: 1107–1112.
16 Huang CL, Yang SS, Lin SH. Mechanism of regulation of renal ion transport by WNK kinases. *Curr Opin Nephrol Hypertens* 2008; **17**: 519–525.
17 San-Cristobal P, Ponce-Coria J, Vazquez N, Bobadilla NA, Gamba G. WNK3 and WNK4 amino-terminal domain defines their effect on the renal Na+-Cl- cotransporter. *Am J Physiol Renal Physiol* 2008; **295**: F1199–F1206.
18 Wang Y, O'Connell JR, McArdle PF, Wade JB, Dorff SE, Shah SJ, Shi X, Pan L, Rampersaud E, Shen H, Kim JD, Subramanya AR, Steinle NI, Parsa A, Ober CC, Welling PA, Chakravarti A, Weder AB, Cooper RS, Mitchell BD, Shuldiner AR, Chang YP. From the cover: whole-genome association study identifies STK39 as a hypertension susceptibility gene. *Proc Natl Acad Sci USA* 2009; **106**: 226–231.
19 Iwai M, Horiuchi M. Role of renin-angiotensin system in adipose tissue dysfunction. *Hypertens Res* 2009; **32**: 425–427.
20 Julius S, Nesbitt SD, Egan BM, Weber MA, Michelson EL, Kaciroti N, Black HR, Grimm Jr RH, Messerli FH, Oparil S, Schork MA. Feasibility of treating prehypertension with an angiotensin-receptor blocker. *N Engl J Med* 2006; **354**: 1685–1697.
21 Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Sato K, Kimura G. Metabolic disorders predict development of hypertension in normotensive Japanese subjects. *Hypertens Res* 2008; **31**: 665–671.
22 Iwashima Y, Katsuya T, Ishikawa K, Ouchi N, Ohishi M, Sugimoto K, Fu Y, Motone M, Yamamoto K, Matsuo A, Ohashi K, Kihara S, Funahashi T, Rakugi H, Matsuzawa Y, Ogihara T. Hypoadiponectinemia is an independent risk factor for hypertension. *Hypertension* 2004; **43**: 1318–1323.
23 Puddu P, Puddu GM, Cravero E, Rosati M, Muscari A. The molecular sources of reactive oxygen species in hypertension. *Blood Press* 2008; **17**: 70–77.
24 Suzuki S, Yoshimura M, Nakayama M, Abe K, Yamamuro M, Nagayoshi Y, Kojima S, Kaikita K, Sugiyama S, Yasue H, Ogawa H. A novel genetic marker for coronary spasm in women from a genome-wide single nucleotide polymorphism analysis. *Pharmacogenet Genomics* 2007; **17**: 919–930.
25 Katsuya T, Sugimoto K, Hozawa A, Ohkubo T, Yamamoto K, Matsuo A, Ishikawa K, Matsubara H, Rakugi H, Tsuji I, Imai Y, Ogihara T. Genetic risk factors for cerebral infarction using data from a large scale genetic epidemiological study: the Ohasama Study. *Geriatr Gerontol Int* 2003; **3**: 150–153.
26 Inamoto N, Katsuya T, Kokubo Y, Mannami T, Asai T, Baba S, Ogata J, Tomoike H, Ogihara T. Association of methylenetetrahydrofolate reductase gene polymorphism with carotid atherosclerosis depending on smoking status in a Japanese general population. *Stroke* 2003; **34**: 1628–1633.
27 Nakamura T, Yamamoto E, Kataoka K, Yamashita T, Tokutomi Y, Dong YF, Matsuba S, Ogawa H, Kim-Mitsuyama S. Beneficial effects of pioglitazone on hypertensive cardiovascular injury are enhanced by combination with candesartan. *Hypertension* 2008; **51**: 296–301.
28 Masuo K, Katsuya T, Fu Y, Rakugi H, Ogihara T, Tuck ML. Beta2- and beta3-adrenergic receptor polymorphisms are related to the onset of weight gain and blood pressure elevation over 5 years. *Circulation* 2005; **111**: 3429–3434.
29 Masuo K, Katsuya T, Sugimoto K, Kawaguchi H, Rakugi H, Ogihara T, Tuck ML. High plasma norepinephrine levels associated with beta2-adrenoceptor polymorphisms predict future renal damage in nonobese normotensive individuals. *Hypertens Res* 2007; **30**: 503–511.
30 Masuo K, Straznicky NE, Lambert GW, Katsuya T, Sugimoto K, Rakugi H, Socratous F, Hastings J, Lambert EA, Ogihara T, Esler MD. Leptin-receptor polymorphisms relate to obesity through blunted leptin-mediated sympathetic nerve activation in a Caucasian male population. *Hypertens Res* 2008; **31**: 1093–1100.
31 Kawaguchi H, Masuo K, Katsuya T, Sugimoto K, Rakugi H, Ogihara T, Tuck ML. Beta2- and beta3-adrenoceptor polymorphisms relate to subsequent weight gain and blood pressure elevation in obese normotensive individuals. *Hypertens Res* 2006; **29**: 951–959.
32 Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007; **447**: 661–678.
33 Browning BL, Browning SR. Haplotypic analysis of Wellcome Trust Case Control Consortium data. *Hum Genet* 2008; **123**: 273–280.
34 Ehret GB, Morrison AC, O'Connor AA, Grove ML, Baird L, Schwander K, Weder A, Cooper RS, Rao DC, Hunt SC, Boerwinkle E, Chakravarti A. Replication of the Wellcome Trust genome-wide association study of essential hypertension: the Family Blood Pressure Program. *Eur J Hum Genet* 2008; **16**: 1507–1511.
35 Shi G, Gu CC, Kraja AT, Arnett DK, Myers RH, Pankow JS, Hunt SC, Rao DC. Genetic effect on blood pressure is modulated by age: the Hypertension Genetic Epidemiology Network Study. *Hypertension* 2009; **53**: 35–41.
36 Yatsu K, Mizuki N, Hirawa N, Oka A, Itoh N, Yamane T, Ogawa M, Shiwa T, Tabara Y, Ohno S, Soma M, Hata A, Nakao K, Ueshima H, Ogihara T, Tomoike H, Miki T, Kimura A, Mano S, Kulski JK, Umemura S, Inoko H. High-resolution mapping for essential hypertension using microsatellite markers. *Hypertension* 2007; **49**: 446–452.
37 Kato N, Miyata T, Tabara Y, Katsuya T, Yanai K, Hanada H, Kamide K, Nakura J, Kohara K, Takeuchi F, Mano H, Yasunami M, Kimura A, Kita Y, Ueshima H, Nakayama T, Soma M, Hata A, Fujioka A, Kawano Y, Nakao K, Sekine A, Yoshida T, Nakamura Y, Saruta T, Ogihara T, Sugano S, Miki T, Tomoike H. High-density association study and nomination of susceptibility genes for hypertension in the Japanese National Project. *Hum Mol Genet* 2008; **17**: 617–627.
38 Org E, Eyheramendy S, Juhanson P, Gieger C, Lichtner P, Klopp N, Veldre G, Doring A, Viigimaa M, Sober S, Tomberg K, Eckstein G, Kelgo P, Rebane T, Shaw-Hawkins S, Howard P, Onipinla A, Dobson RJ, Newhouse SJ, Brown M, Dominiczak A, Connell J, Samani N, Farrall M, Caulfield MJ, Munroe PB, Illig T, Wichmann HE, Meitinger T, Laan M. Genome-wide scan identifies CDH13 as a novel susceptibility locus contributing to blood pressure determination in two European populations. *Hum Mol Genet* 2009; **18**: 2288–2296.
39 Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Natl Acad Sci USA* 2004; **101**: 10308–10313.
40 Brock MV, Hooker CM, Ota-Machida E, Han Y, Guo M, Ames S, Glockner S, Piantadosi S, Gabrielson E, Pridham G, Pelosky K, Belinsky SA, Yang SC, Baylin SB, Herman JG. DNA methylation markers and early recurrence in stage I lung cancer. *N Engl J Med* 2008; **358**: 1118–1128.
41 Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, Dixon RJ, Meitinger T, Braund P, Wichmann HE, Barrett JH, Konig IR, Stevens SE, Szymczak S, Tregouet DA, Iles MM, Pahlke F, Pollard H, Lieb W, Cambien F, Fischer M, Ouwehand W, Blankenberg S, Balmforth AJ, Baessler A, Ball SG, Strom TM, Braenne I, Gieger C, Deloukas P, Tobin MD, Ziegler A, Thompson JR, Schunkert H. Genomewide association analysis of coronary artery disease. *N Engl J Med* 2007; **357**: 443–453.
42 Newton-Cheh C, Larson MG, Vasan RS, Levy D, Bloch KD, Surti A, Guiducci C, Kathiresan S, Benjamin EJ, Struck J, Morgenthaler NG, Bergmann A, Blankenberg S, Kee F, Nilsson P, Yin X, Peltonen L, Vartiainen E, Salomaa V, Hirschhorn JN, Melander O, Wang TJ. Association of common variants in NPPA and NPPB with circulating natriuretic peptides and blood pressure. *Nat Genet* 2009; **41**: 348–353.
43 Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der Harst P, Polidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McArdle WL, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergmann S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Groop L, Orho-Melander M, Allione

A, Di Gregorio A, Guarrera S, Panico S, Ricceri F, Romanazzi V, Sacerdote C, Vineis P, Barroso I, Sandhu MS, Luben RN, Crawford GJ, Jousilahti P, Perola M, Boehnke M, Bonnycastle LL, Collins FS, Jackson AU, Mohlke KL, Stringham HM, Valle TT, Willer CJ, Bergman RN, Morken MA, Doring A, Gieger C, Illig T, Meitinger T, Org E, Pfeufer A, Wichmann HE, Kathiresan S, Marrugat J, O'Donnell CJ, Schwartz SM, Siscovick DS, Subirana I, Freimer NB, Hartikainen AL, McCarthy MI, O'Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilst WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, Syvanen AC, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dorr M, Ernst F, Felix SB, Homuth G, Lorbeer R, Reffelmann T, Rettig R, Volker U, Galan P, Gut IG, Hercberg S, Lathrop GM, Zelenika D, Deloukas P, Soranzo N, Williams FM, Zhai G, Salomaa V, Laakso M, Elosua R, Forouhi NG, Volzke H, Uiterwaal CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund G, Bingham SA, Kooner JS, Connell JM, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Jarvelin MR, Mooser V, Melander O, Loos RJ, Elliott P, Abecasis GR, Caulfield M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet* 2009; **41**: 666–676.

44 Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet* 2009; **41**: 677–687.

45 Tutton R, Smart A, Martin PA, Ashcroft R, Ellison GT. Genotyping the future: scientists' expectations about race/ethnicity after BiDil. *J Law Med Ethics* 2008; **36**: 464–470.

46 Brown MJ. Hypertension and ethnic group. *BMJ* 2006; **332**: 833–836.

47 Psaty BM, Smith NL, Heckbert SR, Vos HL, Lemaitre RN, Reiner AP, Siscovick DS, Bis J, Lumley T, Longstreth Jr WT, Rosendaal FR. Diuretic therapy, the alpha-adducin gene variant, and the risk of myocardial infarction or stroke in persons with treated hypertension. *JAMA* 2002; **287**: 1680–1689.

48 Lynch AI, Arnett DK, Davis BR, Boerwinkle E, Ford CE, Eckfeldt JH, Leiendecker-Foster C. Sex-specific effects of AGT-6 and ACE I/D on pulse pressure after 6 months on antihypertensive treatment: the GenHAT study. *Ann Hum Genet* 2007; **71**: 735–745.

49 Lynch AI, Boerwinkle E, Davis BR, Ford CE, Eckfeldt JH, Leiendecker-Foster C, Arnett DK. Pharmacogenetic association of the NPPA T2238C genetic variant with cardiovascular disease outcomes in patients with hypertension. *JAMA* 2008; **299**: 296–307.

50 Pacanowski MA, Gong Y, Cooper-Dehoff RM, Schork NJ, Shriver MD, Langaee TY, Pepine CJ, Johnson JA. Beta-adrenergic receptor gene polymorphisms and beta-blocker treatment outcomes in hypertension. *Clin Pharmacol Ther* 2008; **84**: 715–721.

51 Turner ST, Bailey KR, Fridley BL, Chapman AB, Schwartz GL, Chai HS, Sicotte H, Kocher JP, Rodin AS, Boerwinkle E. Genomic association analysis suggests chromosome 12 locus influencing antihypertensive response to thiazide diuretic. *Hypertension* 2008; **52**: 359–365.

52 Johnson JA, Boerwinkle E, Zineh I, Chapman AB, Bailey K, Cooper-DeHoff RM, Gums J, Curry RW, Gong Y, Beitelshees AL, Schwartz G, Turner ST. Pharmacogenomics of antihypertensive drugs: rationale and design of the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study. *Am Heart J* 2009; **157**: 442–449.

53 Hosohata K, Saito S, Asayama K, Ohkubo T, Kikuya M, Metoki H, Obara T, Kato T, Hashimoto J, Totsune K, Miura Y, Imai Y, The H-BPSG. Progress report on The Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) study: status at February 2004. *Clin Exp Hypertens* 2007; **29**: 69–81.