Hypertension Research (2012) 35, 574–581

www.nature.com/hr

REVIEW SERIES

Ethnic differences in genetic predisposition to hypertension

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Recently, large-scale meta-analyses of genome-wide association (GWA) studies have identified a number of loci significantly associated with systolic and/or diastolic blood pressure (BP). Most of the GWA studies reported to date were conducted in populations of European descent. Given the appreciable ethnic differences in clinical presentation of hypertension, studies in non-European populations allow us to assess the relevance of the findings in Europeans to other ethnic groups and to potentially discover novel variants. Before the GWA scan era, the presence of racial or ethnic differences has been widely recognized for response to antihypertensive therapies, salt sensitivity and impact of obesity on developing hypertension. Despite a limited number of genetic loci that have been proven to show substantial ethnic differences, we can assume four possible genetic mechanisms—(1) absence of target variants in other ethnic groups; (2) presence of allelic heterogeneity; (3) difference in linkage disequilibrium structure; and (4) gene–gene and gene–environment interactions. Considering such a number of potential sources of heterogeneity, we should be cautious about claiming the presence of genuine ethnic differences in genetic susceptibility to BP-related traits or hypertension. Approximately a quarter of BP-associated loci that have been reported in four meta-analyses of GWA studies (i.e., 8 out of 34 loci) appear to be common across three ethnic groups—Europeans, east Asians and south Asians. 'Transethnic' BP meta-analysis will be useful not only for revealing novel susceptibility loci and pathophysiological pathways but also for facilitating the fine mapping of common causal variants.
Hypertension Research (2012) **35,** 574–581; doi:10.1038/hr.2012.44; published online 5 April 2012

Keywords: blood pressure; genes; genetics; hypertension

INTRODUCTION

Genetic, environmental and demographic factors and their interaction determine an individual's risk for hypertension. Despite considerable efforts to investigate the genetic basis of hypertension, or elevated blood pressure (BP) levels,[1,2] the inherently complex nature hampered progress in the elucidation of the genes involved and yielded little success until 2009 when two consortia-based meta-analyses of genome-wide association (GWA) studies involving 30 000–40 000 samples in the discovery stage identified a total of 13 independent loci significantly associated with BP in populations of European descent.[3,4] Subsequently, meta-analyses of GWA studies in east Asians[5] and in a larger consortium combining the Global BPgen and CHARGE consortia[6] identified a total of 21 additional loci. The large part of the GWA studies reported to date were conducted in populations of European descent.[3,4,6,7] Given the appreciable ethnic differences in clinical presentation of hypertension,[8] studies in non-European populations allow us to assess the relevance of the findings in Europeans to other ethnic groups and to potentially discover novel variants. In addition, with the advent of massive genome-wide characterization of single nucleotide polymorphisms (SNPs), for example, $>650\,000$ SNPs, it has become clear that diversity is greater within than between races,[9] further indicating the presence of substantial genomic differences between ethnic (or racial) groups.

In the present article, I review ethnic differences known to exist for hypertension-related traits and propose possible genetic mechanisms underlying such ethnic differences. Then, I describe some findings from the meta-analyses of GWA studies on BP and hypertension thus far reported.[3–6]

ETHNIC DIFFERENCES IN HYPERTENSION-RELATED TRAITS

Antihypertensive drug response

Racial or ethnic differences in response to antihypertensive therapies have been widely recognized during the past decades.[10] In the early 1980's, clinical differences in response to the BP-lowering effects of β-blockers and diuretics were noted between whites (those of European descent) and blacks (those of African descent) based on several reports including a Veterans Administration Cooperative Trial,[11] which suggested that whites had a better antihypertensive response to β-blockers than blacks, whereas blacks had a slightly better response to diuretics than whites. Accordingly, in 1988, the fourth report of the Joint National Committee on the Detection, Evaluation and Treatment of High BP recommended consideration of

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Received 8 January 2012; revised 15 February 2012; accepted 17 February 2012; published online 5 April 2012

race/ethnicity when selecting antihypertensive therapy.[12] In 2004, a meta-analysis of 15 clinical trials that had been published between 1984 and 1998 showed that there were consistent, although modest, differences in responses between whites and blacks as depicted in Figure 1.[10,13] In general, it appears that blacks respond more favorably to diuretics or calcium channel blockers, whereas whites respond to all classes of antihypertensive drugs similarly. Among Asians and Hispanics, limited data are available on the corresponding antihypertensive drug response, in regard to ethnic comparison with whites.[14]

The prevalence of hypertension has been known to be higher among blacks than whites.[8,15] In addition, excessive target organ damages such as stroke and heart failure have been reported among blacks in the USA;[16] that is, overall mortality due to hypertension and its consequences is 4–5 times more likely in blacks than in whites. These hypertension-related target organ damages result from a combination of genetic and environmental factors. Of note, Liggett *et al.*[17] reported a pharmacogenomic interaction between β-blocker treatment for heart failure and a non-synonymous polymorphism, Leu41Gln, of the G protein-coupled receptor kinase 5 (*GRK5*) gene, which desensitizes β-adrenergic receptors. A 'protective' GRK5-Leu41 variant was shown to be common in African Americans (~10-fold higher than in European Americans) and to protect against death or cardiac transplantation among African American patients with heart failure, in contrast to its higher risk among blacks.[18] Moreover, the GRK5-Leu41 allele is not disproportionately represented in individuals with cardiac disease; that is, the allele frequencies are 0.23 among unaffected individuals, 0.24 among patients with heart failure and 0.28 among patients with acute ischemia. Thus, it has been concluded that enhanced β-adrenergic receptor desensitization of excessive catecholamine signaling by GRK5-Leu41 provides a 'genetic β-blockade' that improves survival in African Americans with heart failure, suggesting the presence of within-population diversity in response to organ protection therapies, independent of disease etiology.

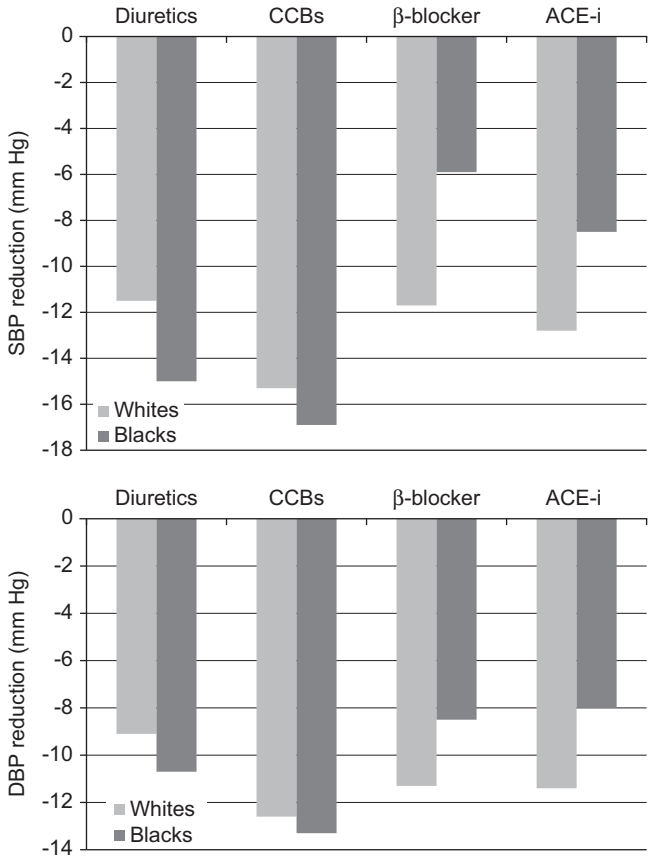


Figure 1 Ethnic differences in pooled estimates of decrement in BP with four antihypertensive drugs. The pooled estimates of BP reduction are shown for SBP (upper panel) and DBP (lower panel) separately. The data were derived from the article by Johnston[9] (originally from Brewsler *et al.*[12]). ACE-I, angiotensin converting enzyme inhibitors; CCBs, calcium channel blockers.

Salt sensitivity

It has long been recognized that dietary habits such as salt intake have an important role in the development of hypertension. A number of epidemiological studies have shown that the prevalence of hypertension increases with habitual salt intake or urinary sodium chloride excretion at the population level in various parts of the world.[19] Nevertheless, substantial heterogeneity has been thought to exist in the individual BP response to changes in sodium balance, often referred to as salt sensitivity.[20] Although there are no uniform criteria for measuring salt sensitivity as a function of BP change or for dichotomizing it to separate people into salt-sensitive and salt-resistant individuals, salt sensitivity has been assumed to be more prevalent in blacks than in whites.[21] To support this, Chun *et al.*[22] showed that there were distinct ethnic differences in renal handling of calcium and magnesium basally and in response to furosemide (loop diuretics) that were consistent with a more pronounced activity of sodium uptake by the Na-K-2Cl cotransporter in the thick ascending limb of the kidney in blacks, which could result in a greater tendency to retain sodium than whites.

It has been reported that a number of candidate gene variants, for example, those involved in the renin–angiotensin–aldosterone system and ion channels, are associated with salt sensitivity,[23] although they are difficult to replicate and remain largely inconclusive.[24]

Impacts of obesity on hypertension

Racial and ethnic differences have also been assumed to exist in terms of the components and impacts of genetic factors for obesity, and traits or disorders related to obesity, for example, type 2 diabetes.[25,26] Moreover, from an epidemiological viewpoint, it has been demonstrated that the overall impact of obesity on hypertension is greater in Chinese (east Asians) than in blacks and whites;[27] that is, the increase in the hypertension incidence associated with an one-unit increase in body mass index over ~8 years of follow-up was 2.5, 1.8 and 1.7 percentage points for Chinese, blacks and whites, respectively. Although a combination of genetic, environmental and social differences between the ethnic groups may contribute to such ethnic differences, little is known about the underlying biological mechanisms at present.

POSSIBLE GENETIC MECHANISMS UNDERLYING ETHNIC DIFFERENCES

Thus far, only a limited number of genetic loci have been reported to show robust evidence supporting the presence of ethnic differences in BP- or hypertension-associated loci.[3–6] Nevertheless, we can assume four possible genetic mechanisms as explained later.

To facilitate readers' understanding, basic concepts of genetic association are illustrated in Figure 2. It is assumed that a causal mutation was first introduced into a population at some historical point of time upon a certain phylogenetic cluster of the relevant

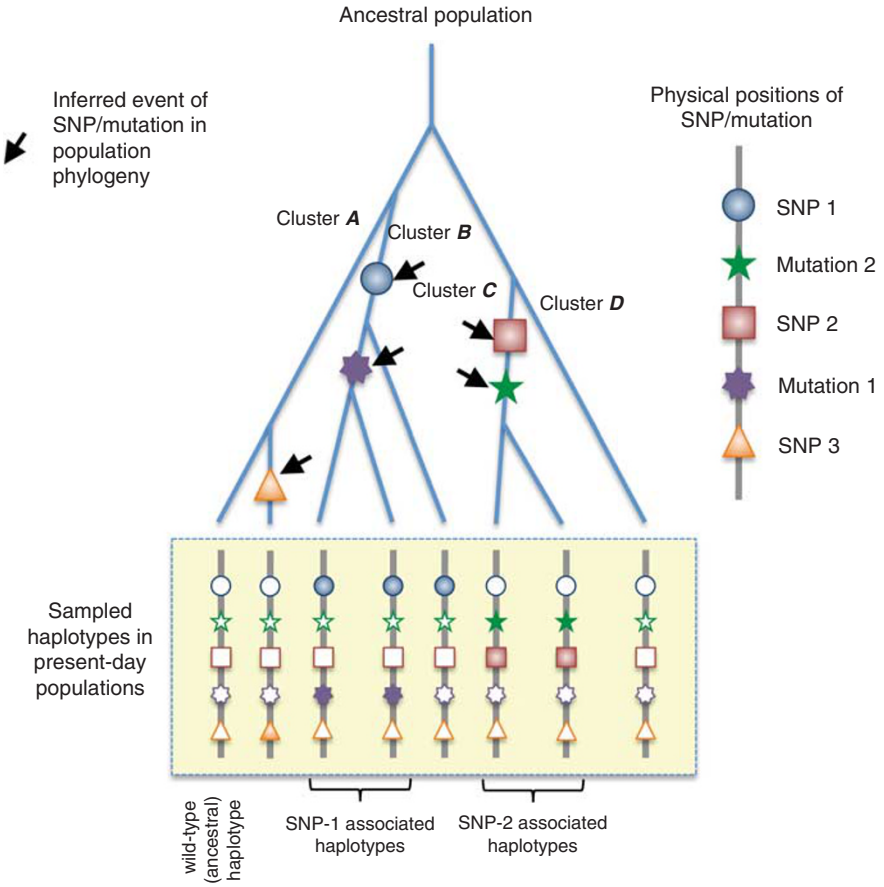


Figure 2 Illustration of basic concepts of genetic association from the viewpoint of population phylogeny. Coalescent genealogies (blue lines) are used to infer the demographic histories of sampled population, which is assumed to have differentiated into four clusters—***A***, ***B***, ***C*** and ***D***. Wild-type (or ancestral) haplotypes are preserved in the cluster ***A***, disease susceptibility haplotypes belong to the clusters ***B*** and ***C***, and neutral (in terms of disease susceptibility) but relatively new haplotypes are in the cluster ***D***. Observed sequence differences (SNPs and mutations) are indicated by colored symbols: circle, square, triangle and asterisks.

population. At a particular susceptibility locus (or gene), multiple mutations may have occurred on different phylogenetic clusters, which result in allelic heterogeneity, the phenomenon in which different mutations at the same locus (or gene) cause the same disorder. Without *a priori* knowledge about the causal variants or mutations, people attempt to identify genetic 'markers' such as SNPs, which help us to capture the association signals via linkage disequilibrium (LD), the phenomenon in which alleles of two different loci (or genes) occur together more often than would be predicted by chance, indicating that the two alleles are physically close on the DNA strand. A set of SNPs and mutations in strong LD tend to be inherited together by forming haplotypes. On performing GWA studies, we normally assay not all SNPs but a subset of SNPs that can be chosen by considering the LD structure in a particular chromosomal region (Figure 3). If the pattern and strength of LD between the SNPs (and mutations) in the target region are similar and the causal variants are commonly present among the different ethnic groups, the association in question is detectable at the SNP markers (e.g., SNP1 for mutation 1 and SNP 2 for mutation 2 in Figure 2) across the populations.

Absence of target variants in other ethnic groups

It is possible that there is a common causal variant in one ethnic group but not in another, because the variant occurred and/or spread almost exclusively among the individuals belonging to the former ethnic group, in which the resultant genetic association can be identified via GWA studies.

This has turned out to be the case with a locus associated with BP-related traits, which we have recently identified near the *ALDH2* gene at 12q24.13 in east Asians.[5] This association is likely driven by a known functional variant rs671 at *ALDH2*, which is common in east Asians and has been reported to associate with hypertension principally through modification of alcohol consumption.[28–30] In populations of European descent, on the other hand, one of the BP loci has been identified near the *SH2B3* gene at 12q24.13.[3,4,6] The SNP at 12q24.13 associated with BP in Europeans (rs3184504 at the *SH2B3* locus) is not polymorphic in east Asians, and the SNP associated with BP in east Asians (rs671 at the *ALDH2* locus) is not polymorphic in Europeans. Here, of particular note is the fact that we found modest signatures of recent selection in the corresponding region,[5] which were separately reported in Europeans.[31] Eight common SNPs (minor allele frequency = 0.23–0.24 in the Japanese population) appeared to identify a common haplotype (H5), which arose on a haplotype (H4) that is common in east Asians but is absent in Europeans and is rare in Africans (Figure 4), spanning almost the same interval length (0.7 Mb) as that of suggestive natural selection at 12q24.[5] Thus, phylogenetic analysis

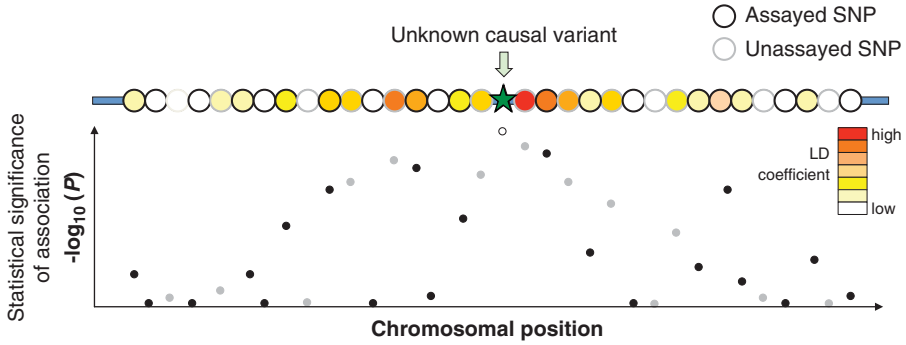
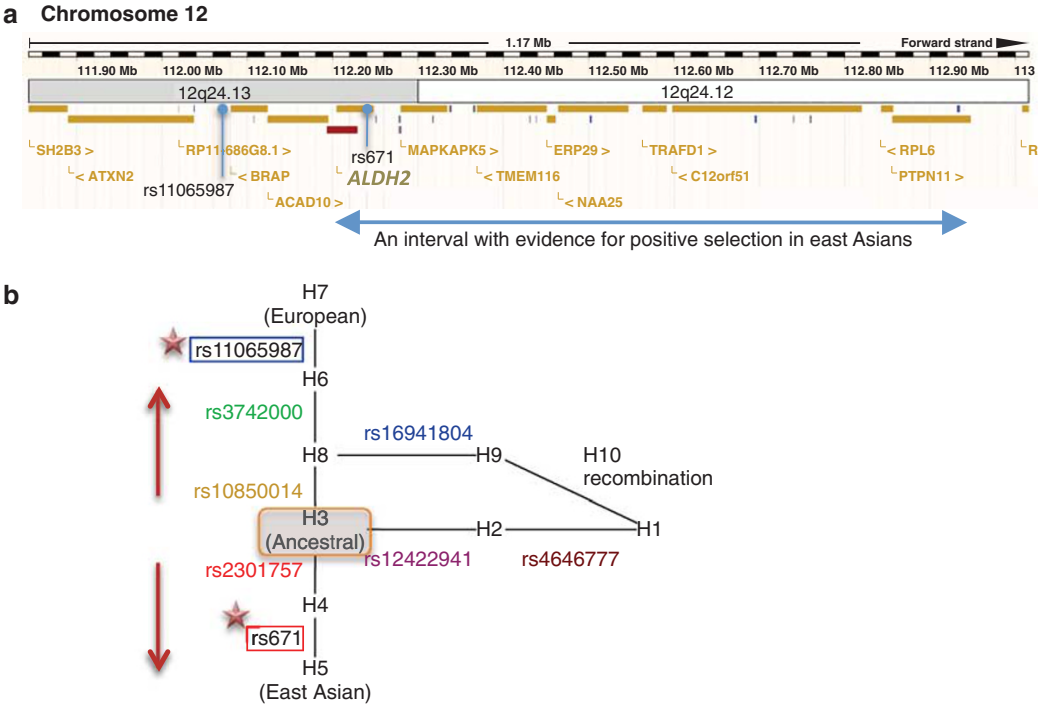


Figure 3 Illustration of LD relation between SNPs (upper panel) and regional *P*-value plots for SNP-trait association (lower panel). In an assumed chromosomal region, a subset of SNPs (dots colored in black) are assayed, whereas the remaining, unassayed SNPs (dots colored in gray) are imputed. LD coefficient between an unknown causal variant and an SNP is drawn with the shaded colors.



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Haplotype class	*Index* SNP marking individual haplotype								Haplotype frequency		
	rs11065987	rs4646777	rs3742000	rs16941804	rs12422941	rs10850014	rs2301757	rs671	Japanese	Caucasian	Black
H1	A	A	C	T	C	G	A	G	0.14	0.12	0.15
H2	A	G	C	T	C	G	A	G			0.02
H3 (Ancestral)	A	G	C	T	T	G	A	G			0.17
H4	A	G	C	T	T	G	C	G	0.38		0.04
H5 (East Asian)	A	G	C	T	T	G	C	A	0.29		
H6	A	G	T	T	T	A	A	G	0.19	0.44	0.18
H7 (European)	G	G	T	T	T	A	A	G		0.36	
H8	A	G	C	T	T	A	A	G			0.07
H9	A	G	C	C	T	A	A	G			0.29
H10	A	A	C	C	T	A	A	G		0.07	0.06

Figure 4 Phylogenetic relation of population-specific SNPs to ancestral haplotype on 12q24 involving the *ALDH2* locus.[3–6] Two phylogenetically-independent haplotypes—H5 and H7—are assumed to affect BP in the east Asian and European populations, respectively.[3–5] There are several clusters of SNPs with tight LD at 112.2–112.9 Mb (Build 37.3 drawn from Ensembl browser, http://www.ensembl.org/Homo_sapiens/), in which modest signatures of natural selection were detected[5] as indicated by a horizontal arrow (**a**). Here, positions of east Asian-specific (rs671) and European-specific (rs11065987) SNPs are also depicted in the top panel (**a**). For clusters of SNPs located in this interval that shows limited recombination across the three populations—east Asian (Japanese), Caucasian (or whites) and blacks, we chose representative SNPs of each cluster and inferred their phylogeny (**b**) and haplotypes (**c**). rs11065987 and *SH2B3* rs3184504 belong to the same cluster. Figures and tables are drawn from Supplementary materials of Kato *et al.*[5]

suggests that rs671, which is a possible, although not conclusive, causal variant in east Asians, is not responsible for the BP-association identified in the overlapping chromosomal region (near *SH2B3*) in populations of European descent. Although positive selection has been presumed to have a role in increasing the frequencies of alleles that elevate some autoimmune disease risk,[32] this possibility remains to be further explored for alleles (or variants) associated with hypertension.

Presence of allelic heterogeneity

Recent large-scale meta-analyses of GWA studies have reveled that allelic heterogeneity is not rare in the human genetics of common traits such as height and type 2 diabetes.[33,34] As for BP traits, significant association was identified at 12q24.21 in both Europeans and east Asians,[4,5] although the associated SNPs (e.g., rs2384550 in Europeans and rs35444 in east Asians) were not in LD with each other. As these two index SNPs are located in the intergenic region (350-kb and 550-kb distant from the closest gene, *TBX3*), it remains unknown whether they could exert genetic effects on the same gene (e.g., *TBX3*) or on different genes or pathways. In the former case (i.e., genetic effects on the same gene), besides allelic heterogeneity, there is another issue that each of the two index SNPs is 'specific' to an individual ethnic group, at least, in regard to genetic impacts or the feasibility of identifying genetic association.

Difference in LD structure

The common SNPs under investigation in GWA studies may not themselves contribute to phenotypic variation. Instead, it is usually assumed that these characterized variants are in high LD with common 'causal' variants. As far as the lengths and patterns of LD near the causal variants are similar across the various populations, the common causal variants can be tagged by use of standard GWA scan platforms (or SNP arrays). However, it has become known that there are substantial cross-population differences in LD structure in some chromosomal regions; where the same set of tagging SNPs is not useful across the various populations in order to identify the common causal variants, if any.[35] The development of sophisticated algorithms for imputation (estimation of some unmeasured genotypes by using the LD structure in a region, which is drawn from the data in a reference panel)[36–38] and the application of dense, reference SNP marker sets, that is, the 1000 Genomes Project data (http://www.1000genomes.org/), for imputation help to reduce the risk of missing such common association signals due to cross-population differences in LD structure.[35] Even so, imputation accuracy is still limited, in particular, for relatively rare variants, unless they are directly genotyped.[39]

Gene–gene and gene–environment interactions

Even the causal variants with 'cosmopolitan' effects may show racial or ethnic differences in the statistical power to identify disease association, which are largely influenced by the hidden effects of gene–gene or gene–environment interaction.[40] Gene–gene interaction has been frequently found to exist between loci in model organisms.[41] However, it can be difficult to detect[42] and little robust evidence has been provided for the human genetics of hypertension and/or BP traits. Assuming two interacting loci, their combined effects can be larger than and/or in the opposite direction to the individual effects of the loci. Environment may also have a substantial role in determining the effect size of a given susceptibility locus.[40,42] For example, it has been reported that allele frequencies for probable functional variants in BP-trait-associated candidate genes (such as *GNB3* and *AGT*) are correlated with latitude, which is hypothesized to result from differential exposure to selection pressure (by factors such as higher salt intake and colder environments) since the out-of-Africa expansion of human populations.[43]

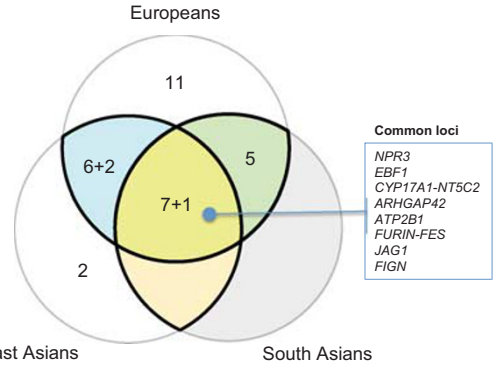

Figure 5 A schematic representation of cross-population difference (or overlapping) for a total of 34 BP-trait-associated loci that have been reported in four meta-analyses of GWA studies.[3–6] Here, an associated locus is assumed to overlap between the ethnic groups when $P \leqslant 0.05$ showing a concordant direction of genetic effect in the population tested for replication.

FINDINGS FROM GWA STUDIES OF BP TRAITS

Given a number of sources of heterogeneity,[35,40,42] we should be cautious about claiming the presence of genuine ethnic differences in genetic effects of susceptibility to BP traits or hypertension. The factors to be considered include sample size, LD structure and the potential impact of gene–gene and gene–environment interactions in the individual population. Although further investigation is required, an arbitrary picture of cross-population difference (or overlapping) can be depicted in Figure 5 as for a total of 34 BP-trait-associated loci that have been reported in four meta-analyses of GWA studies[3–6]; these were originally conducted in populations of European and east Asian descent and thereafter the signals of association were subjected to evaluation (i.e., replication) in other ethnic groups.

Approximately a quarter of the loci (8 out of 34) appear to be common across three ethnic groups—Europeans, east Asians and south Asians. Here, because the tested associations could not be generally reproducible in African Americans,[6] they were not included in this cross-population comparison. Among the remaining 26 loci, index SNPs showed BP-trait association in only two ethnic groups or in a single ethnic group, which was estimated as 38%, 13 each out of 34 loci (Figure 5).

Among the GWA scans performed to date, there has been a strong bias towards samples of European descent. The importance of extending analyses to samples from non-European populations with differing mutational and demographic histories has been emphasized.[42] 'Transethnic' meta-analysis is currently being planned and will allow for a better chance to reveal novel susceptibility loci and pathophysiological pathways, and may also facilitate the fine mapping of common causal variants by utilizing ethnic differences in LD structure.[44]

CONFLICT OF INTEREST

The author declares no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT); the Grant of National Center for Global Health and Medicine; and the Ministry of Health Labor and Welfare.

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