Pharmacogenetics of Antihypertensive Response

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The widespread variation in individual response to antihypertensive treatment motivates a search for genetic factors associated with this variation. Pharmacogenetics evaluates the role of genetic variation in drug response, and pharmacogenomics applies pharmacogenetics to variants throughout the entire genome. The report by Turner et al1 in this issue of *Hypertension* is a pharmacogenomic study that identifies polymorphisms associated with blood pressure response to candesartan and hydrochlorothiazide. Knowledge of genetic factors that predict antihypertensive drug response may eventually enable clinicians to choose the most effective drug for each individual patient based on his or her genetic profile. This tailored therapy may help patients achieve better blood pressure control and may help to reduce the costs and adverse effects of antihypertensive therapy.

Pharmacogenetic studies have identified numerous potential genetic variants associated with response to antihypertensive drug treatment. Potential variants identified thus far include variants in the renin-angiotensin system, variants in other genes involved in blood pressure regulation, and variants in regions with no known role in blood pressure regulation.2–5 Many of these potential variants have not been replicated in subsequent follow-up studies. This lack of replication has prevented the translation of these findings into current clinical practice.

The search for genetic variants associated with hypertension has also been somewhat disappointing. Potential genetic variants associated with hypertension have been identified.6–12 As with the pharmacogenetic studies for antihypertensive medications, however, many of the potential hypertension variants have not been replicated in subsequent studies.13 Interestingly, the large genome-wide association study of hypertension by the Wellcome Trust Case Control Consortium found no associations with hypertension that met criteria for genome-wide significance.14

Turner et al1 performed a 2-tiered approach to identify single nucleotide polymorphisms (SNPs) associated with blood pressure response to candesartan and associated (in the opposite direction) with blood pressure response to hydrochlorothiazide. Knowledge of SNPs that predict an opposite-direction blood pressure response to candesartan and hydrochlorothiazide may help to select the most effective antihypertensive medications for patients with these polymorphisms. Patients with these polymorphisms may have a better blood pressure response to a diuretic than an angiotensin II receptor blocker or vice versa.

Turner et al1 performed a genome-wide association analysis to identify SNPs associated with blood pressure response to candesartan. None of the associations were significant using the accepted threshold for genome-wide significance ($P<5\times10^{-8}$). A total of 285 SNPs in whites and 272 SNPs in blacks were associated with blood pressure response to candesartan using a threshold of $P<10^{-4}$; 273 of the 285 SNPs in whites and 264 of the 272 SNPs in blacks were then tested in independent samples of patients treated with hydrochlorothiazide.

Using this approach, the authors identified several SNPs in whites that had a strong association with blood pressure response to candesartan and were also associated with an opposite-direction blood pressure response to hydrochlorothiazide. They also identified SNPs in blacks that were associated with blood pressure response to candesartan, but they did not find a significant association between these SNPs and opposite-direction blood pressure response to hydrochlorothiazide in blacks.

This racial/ethnic variation in the pharmacogenetic association patterns identified in whites versus blacks highlights the importance of performing genetic studies in diverse populations. Whites and blacks have substantial differences in allele frequencies and linkage disequilibrium patterns. Because of these differences, genetic association patterns observed in whites are often different from the genetic association patterns observed in blacks.

One of the SNPs with opposite blood pressure response in whites is in the sodium channel subunit SCNN1G, which is involved in renal sodium reabsorption and blood pressure regulation and has been shown previously to be associated with blood pressure response to hydrochlorothiazide.15 The other SNPs have not been identified previously in antihypertensive pharmacogenetic studies, and the mechanism behind these SNP associations with response to candesartan and hydrochlorothiazide is unclear.

This study was underpowered, with 300 participants treated with candesartan in each racial/ethnic group and 300 participants treated with hydrochlorothiazide in each racial/ethnic group. With genome-wide association studies, much larger sample sizes are needed to have adequate power. Measurement error because of blood pressure variability also limits study power; continuous blood pressure readings could be considered in future studies to improve the accuracy of blood pressure measurements.
In summary, these authors have identified SNPs that may be associated with response to candesartan and hydrochlorothiazide. This study and other pharmacogenetic studies of antihypertensive response offer hope for a personalized approach to hypertension treatment, whereby genetic factors are used to select the most effective blood pressure medication for each individual patient. Further studies will be needed, however, to replicate these genetic associations with blood pressure response before applying these findings to clinical practice.

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Disclosures
None.

References
Wellcome Trust Case Control Consortium. Genome-wide association studies of 14,000 cases of seven common diseases and 3000 shared controls. Nature. 2007;447:661–678.