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Pharmacogenomics of antihypertensive drugs: past, present and future

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Abstract

Hypertension pharmacogenomics holds the promise of leading to individualized drug treatment approaches for the approximately 1 billion individuals worldwide with hypertension. Prior to 2000, the literature on hypertension pharmacogenomics was quite limited. The last decade has seen a substantial growth in the literature, with several examples of genes that appear to play an important role in antihypertensive response. The last decade has also made apparent the numerous challenges in hypertension pharmacogenomics, and addressing those challenges will be important. Moving forward, it seems clear that collaboration among researchers to allow replication or joint analyses will be essential in advancing the field, as will the use of genome-wide association approaches. The next decade should clearly define the clinical potential for hypertension pharmacogenomics.

Keywords

β-blockers; ACE inhibitors; angiotensin receptor blockers; antihypertensive; calcium channel blockers; hypertension; pharmacogenetics; pharmacogenomics; thiazide diuretics

Hypertension is the most common of the chronic diseases, affecting an estimated 1 billion adults worldwide [1]. Hypertension represents a major public health burden as it is a major risk factor for coronary artery disease and myocardial infarction, heart failure, stroke and renal failure. Despite knowledge about certain preventive measures that can be taken, the prevalence of hypertension is rising, owing in part to the increasing age of the population and increased rates of obesity [1,2]. Thus, hypertension is a major global health problem and drug therapy is the major tool for reducing risk associated with its adverse sequelae.

Numerous effective antihypertensive drug classes are available, and common first-line therapies include the thiazide diuretics, β-blockers, ACE inhibitors, angiotensin receptor blockers and calcium channel blockers. Despite numerous efficacious drug classes, and

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many drugs within each class, blood pressure (BP) control rates among hypertensives are dismal. Global estimates suggest less than 35% of hypertensives have both systolic and diastolic BP control [3], with similar estimates from the USA [4] and other countries [5,6]. These poor rates of BP control are not explained by lack of treatment, as one study estimated approximately 30% of treated hypertensives take one antihypertensive drug, 40% take two antihypertensives and 30% take three or more antihypertensives [3]. These data suggest the current trial and error approach to the management of hypertension is suboptimal and alternative approaches for identifying the optimal antihypertensive regimen in a specific patient are needed. One potential approach for individualizing antihypertensive therapy is through the use of genetic information, or pharmacogenomics, to identify the most appropriate therapy for individual patients. Given the health burden associated with hypertension and the poor rates of BP control, hypertension pharmacogenomics holds great potential.

Hypertension pharmacogenomics: progress up to 2000

This issue of *Pharmacogenomics* celebrates the journal's anniversary, and considers the past, present and future of pharmacogenomics. With a view 10 years into the past, one could argue the dawn of the new millennium was also an important launching point for hypertension pharmacogenomics. Prior to 1995, there were essentially no papers in the literature that focused on hypertension pharmacogenomics. There were studies focused on drug-metabolizing enzymes, and, as it relates to antihypertensive drugs, the most important was the cytochrome P4502D6 enzyme, which has numerous common genetic polymorphisms, some of which lead to absence of functional protein. This enzyme is important for the metabolism of a number of β-blockers and is the prominent drug-metabolizing enzyme for metoprolol. Thus, a number of studies described the impact of these polymorphisms on β-blocker pharmacokinetics and response as assessed by the negative chronotropic response to exercise [7,8]. However, they did not focus on antihypertensive responses and subsequent studies have demonstrated that the *CYP2D6* genotype has little impact on the antihypertensive response. This is likely to be explained by the upward dose titration typically utilized and the wide therapeutic index of β-blockers [9].

Studies focused on hypertension pharmacogenetics/pharmacogenomics began to appear around 1995, and prior to 2000 the literature was focused almost exclusively around two genes and a specific polymorphism in each gene; *ACE* and its insertion/deletion (I/D) polymorphism, and *ADD1*, and its Gly460Trp polymorphism [10]. Studies had consistently shown an association between ACE levels and the I/D polymorphism, making this an excellent pharmacogenetic candidate for ACE inhibitors. By 2000, there were approximately a dozen papers in the literature assessing the response to ACE inhibitors relative to the I/D polymorphism, and even then it was clear that there were not consistent associations with response (either BP lowering or clinical outcomes) [10]. The literature on the *ADD1* Gly460Trp polymorphism looked more promising in 2000, with several studies demonstrating an association between genotype and BP lowering with thiazide diuretics, and solid supporting data from functional and animal studies [10]. Thus, at the close of the 20th Century, hypertension pharmacogenomics literature was quite limited, and the two genes for which there was a body of literature presented a mixed message about its potential.

Hypertension pharmacogenomics: 2000 to present

The last decade has seen substantial growth in the literature surrounding hypertension pharmacogenomics, and several reviews provide an insight into this body of literature [11–14]. These studies have advanced our understanding of the potential role of genetics in variable response to antihypertensive drugs, but the field is perhaps not at the point many investigators would have hoped for 10 years ago. The bulk of the literature continues to focus around candidate genes; primarily those that are direct protein targets of a drug or involved in the physiological or pharmacological signaling pathways relevant to a drug's action. Several dozen genes have now been evaluated in multiple studies, and in contrast to the approach in 2000, there is increasing use of a tag SNP approach. By contrast to 2000, pharmacogenomic studies have now been published on all five major antihypertensive drug classes, although the smallest literature base continues to be that of the the calcium channel blockers.

To date, there are no clear hypertension pharmacogenomics examples ready for translation in to practice. As was the case in 2000, there continues to be studies focused on the *ACE* gene and overall the literature has yet to discern a polymorphism in this gene, or any genes of the renin angiotensin system pathway, that are clearly important in response to antihypertensive drugs [11–15]. For *ADD1*, a paper published in 2002 suggested differential outcomes (myocardial infarction or stroke) with thiazide treatment based on the Gly460Trp genotype [16], raised enthusiasm not only for this gene, but also for the potential of utilizing genetic information to select drug therapy that would lead to the best patient outcomes. However, subsequent outcomes-based analyses from controlled clinical trials did not replicate this finding [17,18]. Of interest, a recent investigation of *ADD1* considered together with *NEDD4L* revealed a significant association with BP response to a thiazide, while neither gene alone showed such an association [19]. These data suggest promise may remain for this gene, and that methods for considering gene–gene interactions may be needed to detect important pharmacogenetic effects.

There are some examples where the literature seems quite promising as it relates to hypertension pharmacogenomics. Perhaps, most promising are associations between β-blocker response and SNPs in the *ADRB1* gene, which encodes the β1-adrenergic receptor. Most commonly studied is the Arg389Gly polymorphism, for which many, but not all, studies show a significant association with antihypertensive response to β-blockers [13,20]. In addition, two independent studies have suggested an association between treatment-related hypertensive outcomes and *ADRB1* SNPs [21,22]. These data are also consistent with numerous papers on *ADRB1* associations with β-blocker response and outcomes in heart failure [20]. While these findings represent the strongest body of literature in hypertension pharmacogenomics, additional studies are needed to confirm the role of the *ADRB1* gene in antihypertensive response and outcomes, along with elucidating how such data might be utilized in a clinical setting.

Another potentially interesting gene is *KCNMB1*, for which SNPs have been associated with BP response in three independent populations, and treatment-related outcomes in one

[23,24]. There are other genes with promising findings in large cohorts, but these require replication in independent samples.

In a shift away from the candidate gene approach, Turner *et al.* published the first hypertension pharmacogenomics genome-wide association study (GWAS) [25]. They discovered and validated a region on chromosome 12 that was associated with the response to hydrochlorothiazide. The association mapped most closely to *YEATS4* but this (or nearby) genes have not been previously implicated in ways that are obvious for a role in hypertension or thiazide response. However, this important paper highlights the potential power of a GWAS approach. Other groups have ongoing pharmacogenomic studies that will also utilize GWAS [26].

Overall, there have been significant advances in hypertension pharmacogenomics in the past decade. While the data to date provide promise for detecting genetic variants that are strongly associated with response to antihypertensive drugs, studies from the last decade also highlight some of the challenges for work in this field.

One of the challenges in interpreting the hypertension pharmacogenomics literature is the phenotype that is studied. Presently, the studies can be divided into two broad categories; those focused on the genetic association with the BP lowering effect of the drug, and those focused on long-term cardiovascular outcomes with antihypertensive therapy. While the literature on *ADRB1* and *KCNMB1* suggest it is possible that genetic associations might be consistent across these very different phenotypes, it should not be presumed that all polymorphisms important to the antihypertensive response would necessarily be associated with outcomes.

Within the BP response studies, there are differences in the study populations that might influence the genetic association and lead to the disparate findings across studies. For example, some groups focus on newly diagnosed, never-treated hypertensives, while others enroll untreated and treated hypertensives, with the latter almost always going through a washout period. However, whether these population differences would impact the association is unclear. There is also variability in the BP phenotype, where some focus on the clinic or office BP, while others focus on 24 h ambulatory or home BP. The latter two have been shown to be more strongly associated with long-term outcomes, and probably reduce the measurement error that is part of a single clinic BP measurement [26]. These differences in BP phenotype might also importantly impact the consistency of findings across the various studies.

The outcomes-based studies typically arise from two data sources – large randomized controlled trials and population databases. The randomized controlled trials theoretically have advantages over the population samples since the treatment of interest is randomized, thus reducing many potential sources of bias that can arise in a population based sample. Unfortunately, most of the large hypertension clinical trials were conducted in a pregenomics era, and so only a small portion have genetic samples available. To our knowledge, only the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [15], International Verapamil/trandolapril (INVEST) study [21],

Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) [27] and Losartan Intervention For End point reduction in hypertension (LIFE) [28] trials collected DNA. This limits the opportunities for discovery of those drugs included in these four trials. It also limits opportunities for replication across these trials, given the differences in treatment regimens studied. Nonetheless, these genetic cohorts are likely to represent the best opportunity for the discovery of genetic polymorphisms that are truly important to the treatment-related outcomes in hypertension.

One of the challenges of all genetics research is sample size, and this is certainly the case for hypertension pharmacogenomics. While the sample sets available from the clinical trials are reasonably sized (thousands to tens of thousands), they still have limited numbers of cases (individuals suffering the cardiovascular outcome of interest) and so power, particularly for efforts based on large numbers of SNPs (e.g., GWAS), may still be limited to relatively large effect sizes (e.g., hazard ratio >1.4 or 1.5). However, this may not be a major limitation, since for hypertension pharmacogenomics to have predictive ability in the clinic, it is likely to require an effect size in this range. For the studies focused on BP response, they tend to be much smaller, ranging from the 40s to high 100s.

Hypertension pharmacogenomics: moving forward & predictions for 2020

As highlighted earlier, there are numerous challenges in hypertension pharmacogenomics that may make interpretation of the literature or discovery of important genetic variants for the antihypertensive response difficult. Thus, the next decade will be critical for hypertension pharmacogenomics, and overcoming some of the challenges that have been clearly defined in the past decade.

Perhaps, the most important step in hypertension pharmacogenomics moving forward is for there to be increased international collaboration among hypertension pharmacogenomics investigators. As has been made clear in hypertension genomics (and other diseases) recently, there are enhanced opportunities for discovery when groups collaborate for replication, meta-analyses or joint analyses. It seems the same approach will have to be taken for hypertension pharmacogenomics to advance, and such collaborations are beginning. Focusing on the most promising examples that have arisen from candidate gene studies and attempting to replicate these findings across multiple studies is an important first step.

Also, following the successes in disease genetics, it seems imperative for hypertension pharmacogenomics to move toward GWAS, and, based on discussions with multiple hypertension pharmacogenomics research groups, this is also happening. While each group may have limited power to detect anything but very large effect sizes in their individual population, collaborative efforts with other groups conducting GWAS will have a much greater likelihood of success. Given the few examples in hypertension pharmacogenomics that seem promising based on relatively small studies, it seems likely that the very large sample sizes (i.e., many tens of thousands) that have been required for hypertension genomics to be successful will not be required for hypertension pharmacogenomics. Thus,

based on the existing cohorts across the globe, it seems there is great potential for important discoveries, particularly through increased collaboration.

By 2020, the clinical potential for hypertension pharmacogenomics should be much clearer. Given the advances in the past decade, and the number of promising examples that have arisen in this decade, it seems likely that, by 2020, there will be some genetic variants that can be used to guide antihypertensive therapy. Such an approach might be particularly enhanced if the prediction that patients will increasingly have their SNP genome or whole-genome data available in their medical records comes to pass [29]. If this occurs, it will facilitate the use of hypertension pharmacogenomic data in practice, since the clinician could look at the SNP data of interest before selecting an antihypertensive drug; delays for a genetic test and the inherent costs would be avoided. In the absence of the genetic data already being available, it seems that hypertension pharmacogenomics might have a harder path for translation to practice in the short term. Specifically, a genetic test is likely to not be attractive to clinicians if it only addresses a single drug. Therefore, to be of value to clinicians, such a test is likely to have to cover the spectrum of the first-line drug classes, and it seems unlikely that the level of evidence will be at that standard for all major classes within 10 years.

Conclusion

In summary, the next decade will be important for more clearly defining hypertension pharmacogenomics, and whether it has a role in clinical practice. The studies that are planned and ongoing should allow this to be clearly elucidated in the next 10 years. Even if these studies reveal there are not genetic variants of sufficient effect size and predictive value to be utilized in practice, it is almost certain that this work will advance our understanding of how the various drugs work in hypertension, and in so doing will advance our understanding of hypertension. In addition, it is possible that such work could identify new drug targets through our advancements in understanding the mechanisms by which the current drugs work. The next decade should be an exciting one for hypertension pharmacogenomics.

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Biography

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