Not so free associations

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Keywords: association; chronic kidney disease; genetics; hypertension; sympathetic

According to PubMed, there have been 62,872 genetic association studies published, about 2 for every gene in the human genome. That assessment is of course incorrect. Both the notorious insertion/deletion polymorphism in the angiotensin-converting enzyme (ACE) gene and polymorphisms in the angiotensinogen gene have representative papers numbering in the thousands. However, the adrenergic receptors have not been sleeping in this regard; their polymorphism paper number currently stands at 1334 reports. In this issue of Nephrol Dial Transplant appears the next such paper. Fung et al. [1] reported that adrenergic beta-1 receptor (ADB1R) genetic variation predicts the rate of estimated glomerular filtration rate (eGFR) decline in participants of the African American Study of Kidney Disease and Hypertension (AASK) study cohort. The authors obtained a similar result in a second cohort from San Diego, CA, USA, termed the ‘replication’ cohort. Do we now have the genetic basis for the decline in eGFR over time in patients with hypertension-induced kidney damage?

AASK was a (US National Institutes of Health sponsored) drug study in black Americans [2]. The study was heroic in that participants underwent a renal biopsy to verify that they indeed had hypertension-associated nephrosclerosis. The study compared two levels of blood pressure reduction and three antihypertensive drug classes and tested the effect on eGFR. Briefly, AASK detected no additional benefit of slowing progression of hypertensive nephrosclerosis with the lower blood pressure goal. The authors stated that ACE inhibitors appeared to be more effective than beta-blockers or dihydropyridine calcium channel blockers in slowing GFR decline. However, they also noted that most of the drug group comparisons showed consistent significant differences in the eGFR slope. Disappointing surely for the participants was the fact that in many AASK patients, eGFR declined relentlessly although they controlled their blood pressure to contemporary guideline goals. eGFR declined relentlessly even though they did everything their doctors asked. With such a result, we could conclude either that blood pressure control and drug classes are not as important as we all believe or that something else (genes for instance) is at fault. Large drug trials, irrespective of the sponsors, are favourite for polymorphism studies and most, if not all, feature one or more genetic ‘spin-off’ studies. For instance, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) featured an entire polymorphism consortium disingenuously entitled GENHAT. This group published the presence of an absence of an interaction between the ACE gene insertion–deletion polymorphism and pravastatin in cardiovascular disease in ALLHAT patients [3]. The AASK study has already been milked for polymorphisms. A paper on G-protein-coupled receptor kinase 4 polymorphisms and response to metoprolol in the AASK cohort has recently been published. Several authors on the current report also appear on that paper [4]. Why did the authors pick ADB1R? The hypothesis is not directly stated. However, the senior author is specifically interested in adrenergic mechanisms in hypertension and perhaps that is the reason.

Did the authors make a good choice in selecting polymorphisms? Yes, they did. First, adrenergic tone is decidedly increased with diminished renal function. The issue has been studied with direct measurement of muscle sympathetic nerve activity. Converse et al. recorded the rate of postganglionic sympathetic-nerve discharge to the blood vessels in skeletal muscle by means of microelectrodes inserted into the peroneal nerve in 18 patients with native kidneys who were undergoing long-term treatment with haemodialysis, 5 patients receiving haemodialysis who had undergone bilateral nephrectomy and 11 normal subjects [5]. They showed unequivocally that chronic renal failure is accompanied by reversible sympathetic activation, which appears to be mediated by an afferent signal arising in the failing kidneys. The literature on the issue is extensive. A recent review outlines all the findings in detail [6]. Too bad that the sympatholytic drugs are not renoprotective. Metoprolol, a predominantly ADB1R blocker, did not seem to help the AASK participants very much.

The authors got their best mileage out of the Ser49Gly polymorphism in ADB1R, with minimal decline in persons homozygous for Gly49Gly. This finding is a bit surprising, because the most highly touted polymorphism, at least for a risk of heart failure in ADB1R has been Arg389Gly [7], which was only in partial linkage disequilibrium with Ser49Gly according to the authors [1]. The authors’ polymorphism is located towards the aminoterminal of the receptor, at the other end compared to the Arg389Gly
polymorphism. Levin et al. studied the variants in detail and found that the Gly49Ser variant displayed a more profound agonist-promoted downregulation than the Ser-49 variant [8]. They propose that the stronger downregulation of the Gly49Ser variant could explain the beneficial effect of the Gly49Ser genotypes on survival, supporting the notion that ADB1R desensitization is protective in heart failure. A summary of their site-directed mutagenesis variant expression data in renal cells is outlined in Figure 1. The authors’ data are consistent in that the Gly49Gly subjects (there were 29 such happy individuals in AASK and 30 in the San Diego Veterans Cohort) had the least steep progression. The favourable variant carriers in both cohorts made up about 10% of the subjects. The authors met the criteria of an ‘adequate’ association study. The $P$ values were small, the functional importance of the genetic variants was shown and a ‘replication’ cohort was included. The replication cohort could of course not be a parallel to the AASK study. Nevertheless, the authors took the trouble of looking into the San Diego Veterans Cohort to see if they could come up with similar findings.

Could the authors have given us a better show by including more data? Could networking help us here? The sympathetic nervous system is not covered solely by the ADB1R. The ADB2R also contains functionally important polymorphisms. The norepinephrine transporter (NET) is an important aspect of sympathetic tone. G-protein couplers and regulators (regulator of G-protein signalling 2 and spinophysin) are important. Finally, the enzyme renalase degrades circulating catecholamines. Desir hypothesizes that renalase is secreted into blood by the kidney and plays a key role in regulating blood pressure and cardiovascular function [9]. Furthermore, he believes that abnormalities in the renalase pathway contribute to the heightened cardiovascular risks observed in patients with chronic renal disease. Renalase and the other above components might contribute to the overall picture at least as much as ADB1R. The authors’ cohort might be a good start to study a series of interacting genes rather than only polymorphisms in a single gene. Such an approach would make association studies not only less numerous but also more interesting.

Conflict of interest statement. None declared.

(See related article by M. M. Fung et al. Adrenergic beta-1 receptor genetic variation predicts longitudinal rate of GFR decline in hypertensive nephrosclerosis. Nephrol Dial Transplant 2009; 24: 3677–3686.)

References


