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 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 aminoterminus 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 subject (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 functionally important. G-protein-coupled receptor kinase 4 polymorphisms and pravastatin on cardiovascular disease in high-risk hypertensive patients: the Genetics of Hypertension-Associated Treatment (GenHAT) study, Am Heart J 2007; 153: 54–58

References


Conflict of interest statement. None declared.