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COMMENTARY

Association between the p22^{phox} −930A/G polymorphism and blood pressure in normotensive subjects

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Hypertension is the most common cardiovascular condition and a major risk factor for myocardial infarction, heart failure, stroke and renal failure. Remarkable advances in drug therapy have made it possible to lower blood pressure in almost every hypertensive patient. Nevertheless, hypertension continues to be a major public health problem, and its prevalence is increasing worldwide. Moreover, the number of patients with uncontrolled blood pressure is also increasing, despite the therapeutic advances.[1] New knowledge regarding the pathogenesis of hypertension will be valuable in the development of better options for controlling elevated blood pressure.

It is well known that high blood pressure tends to cluster in families. In other words, genetic factors clearly contribute to the elevation of blood pressure. Analyses of blood pressure patterns in families suggest that genetic factors account for 40–50% of blood pressure variance, whereas shared environmental factors account for 10–30% of variance.[2] In addition, single genes can have major effects on blood pressure, accounting for the rare Mendelian forms of hypertension, such as Liddle's syndrome.[3] There is also considerable evidence implying a genetic influence on blood pressure. Studies of blood pressure in the general population are complicated by multifactorial determination, with a variety of demographic, environmental and genetic factors contributing to the elevation of an individual's blood pressure.[4] As a result, the numerous studies on the genetics of hypertension have failed to find a specific gene responsible for the increase of blood pressure in the general population.

Hypertension is considered a multifactorial disease; that is, it is influenced by multiple genetic loci as well as environmental factors, including diet, salt intake, smoking and physical activity. In most cases, complex interactions of genetic, environmental and demographic factors are also involved in the pathogenesis of hypertension. In fact, gene–environment interactions are reported to be more important for the pathogenesis of elevated blood pressure than genetic influence alone. For this reason, it is difficult to identify specific genetic factors contributing to the variation in blood pressure levels and susceptibility to hypertension in the general population.

Earlier studies attempting to identify genes predisposing to hypertension in the general population have focused mainly on analysis of candidate loci in pathways implicated in blood pressure variation. The candidate gene approach typically compares the prevalence of hypertension or the level of blood pressure among individuals of contrasting genotypes at candidate loci in pathways known to be involved in blood pressure regulation.[5]

Although, 90% of hypertension is essential hypertension, meaning that there is no specific cause in the elevation of blood pressure, major pathophysiological mechanisms of hypertension include impairment of renal salt and water handling as well as activation of the renin–angiotensin–aldosterone system (RAAS). Thus, the most frequently studied candidate genes in hypertension association studies have involved the RAAS.

Common variants in the genes of RAAS, such as an I/D polymorphism in the angiotensin I-converting enzyme, an M235T variant in angiotensinogen and an A1166C polymorphism in angiotensin II type 1 receptor genes, have been associated with hypertension and a greater risk of target organ damage in hypertensive patients. Meta-analyses failed to show consistent findings regarding the association between polymorphisms in the RAAS genes and hypertension or elevation in blood pressure.[6–9]

Oxidative stress is a status of excessive production of reactive oxygen species overwhelming antioxidant defense mechanisms. A number of studies have suggested that oxidative stress is deeply involved in the pathogenesis of hypertension.[10]

Nicotinamide adenine dinucleotide phosphate oxidases have emerged as major sources of reactive oxygen species in the vasculature and have been shown to have a major role in mediating atherosclerosis and vascular diseases such as hypertension.[11] There are several polymorphisms in genes of the nicotinamide adenine dinucleotide phosphate oxidase system, and a significant association between genetic polymorphisms in these genes and hypertension has been reported.[12–14]

As reported in this issue, Xaplanteris *et al.*[15] investigated the association of the p22^{phox} −930A/G polymorphism with peripheral and central pressure in healthy normotensive individuals. Although an association between the p22^{phox} −930A/G polymorphism and hypertension has been reported, no data have been published regarding the relationship in healthy subjects.

Xaplanteris and colleagues show that the G allele is associated with higher central and

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peripheral blood pressure. It is interesting that a $p22^{phox}$ −930A/G polymorphism is associated with blood pressure within the normal range even in the absence of a significant difference in the level of oxidized low-density lipoprotein, a marker of oxidative status, among the different $p22^{phox}$ −930A/G genotypes.

Interestingly, GG homozygotes have been shown to produce excess superoxide as a consequence of $p22^{phox}$ upregulation in hypertensive patients; however, protein levels and nicotinamide adenine dinucleotide phosphate activity did not differ across the three genotypes in a normotensive group.[13] In addition, the exact significance of G and A alleles of this single-nucleotide polymorphism remain to be elucidated because non-uniform results regarding dominance have been reported in various populations with different risk factors. Accordingly, further investigation is required to verify the clinical significance of the $p22^{phox}$ −930A/G polymorphism in normotensive individuals.

The results of a large number of association studies conducted on blood pressure have been inconsistent, suggesting a high locus and inter-population heterogeneity and trait complexity. The lack of associations in blood pressure candidate genes may be attributed to inadequate marker coverage, small phenotypic effects of the loci and/or complex interaction with lifestyle and metabolic parameters. In addition, differences in recruitment strategies between the original and replication studies may affect the results,[16] and targeting candidate genes for a complex disease needs prior knowledge of the single-nucleotide polymorphism coverage on the genotyping array of choice. However, the major limiting factors in blood pressure association studies seems to be the small phenotypic effect of causal loci and the complex interaction with lifestyle, general health status and age-associated metabolic parameters.

Recent advances in techniques of genetic analysis, especially genome-wide linkage analysis, have enabled the search for genes that contribute to the development of hypertension in the population. Unlike a genetic association study examining the relationship between one or two individual single-nucleotide polymorphisms and hypertension, genome-wide association-based studies simultaneously explore a large number of genomic loci. This novel approach has shown great promise in identifying common polymorphisms responsible for a complex disease such as hypertension.[17]

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