Genetic Determinants of Retinal Vascular Caliber
Additional Insights Into Hypertension Pathogenesis

Jie Jin Wang, Tien Yin Wong

It has long been hypothesized that the peripheral microcirculation plays a critical role in hypertension pathophysiology. In its initial stages, elevated blood pressure (BP) elicits an autoregulatory process that results in an increased arteriolar tone, narrowing of precapillary arterioles, and an increase in peripheral vascular resistance. This process, in turn, augments additional BP elevation, creating a vicious cycle that is well known to hypertension researchers. However, scientific progress in this area has been partly limited by difficulties in evaluating the human peripheral microcirculation in vivo. In the last few years, advances in retinal photography and computing technologies have made feasible objective measurement of small vessel size from digital retinal images. Several large, population-based studies have applied these new techniques to quantitatively measure retinal vessel diameters and have documented a consistent gradient association between elevated BP and narrowed retinal arterioles. Of greater significance, these studies now show that retinal arteriolar narrowing may also predict future BP elevation in previously normotensive persons. Thus, generalized arteriolar narrowing seen in the retina may be viewed as a preclinical marker of hypertension.

A key question then is whether retinal arteriolar diameter or the susceptibility of these small vessels to hemodynamic insults, including BP levels within a normal range, is genetically determined. The study by Xing et al in this issue of Hypertension is, therefore, important as being the first study to investigate the genetic basis of retinal vessel diameters using genome-wide linkage. In their population-based sample, Xing et al found that retinal arteriolar and venular diameter was linked to multiple genetic loci. Some loci were unique for arterioles or venules, and others were common to both. Additionally, the linkage regions for retinal vessel diameters appeared to overlap with regions that have been associated previously with essential hypertension, endothelial dysfunction (endothelial nitric oxide synthase–related pathways) or vasculogenesis (regions of growth factors or their receptors; Table 2 in Reference 11). These findings are novel and may contribute additional insights into the pathogenesis and the clinical management of hypertension in a number of ways. First, the study provides one of the first lines of evidence that structural changes in the microcirculation of retina may have genetic determinants, supporting the concept that peripheral vascular resistance may be the initial site for hypertension development. Second, these results potentially allow other researchers to use the retinal circulation as a microvascular bed to better understand the complex genetic–environmental interaction pathways involved in the pathogenesis of hypertension. For example, it is possible that individuals who are genetically susceptible to retinal arteriolar narrowing may also be more reactive to environmental triggers (eg, high dietary salt intake), thus having an increased likelihood of entering the vicious cycle of increased peripheral vascular resistance and elevated BP. Third, the genetics of retinal small vessel disease may provide analogies to understanding the genetics and etiology of other microvascular diseases and closely related conditions (eg, nephropathy). Finally, these data may have potential implications for future hypertension treatment. There is already some evidence that pharmacological agents that have direct beneficial effects on microvascular structure (eg, angiotensin-converting enzyme inhibitors) would reduce cardiovascular end points beyond the effects of lowered BP alone. Gene therapy targeted at the microcirculation offers an attractive alternative to conventional empirical antihypertensive pharmacological therapy.

As the authors state, replication of their results in other populations, fine mapping of candidate genes, and understanding specific genetic functions will help to additionally clarify the genetic basis of retinal vessel diameter. Ultimately, the elucidation of the genetic basis of hypertension and gene–environmental interactions responsible for the development of hypertension is a major challenge. With the collaboration of epidemiology and genetics research teams, the use of currently advancing genetic and statistical techniques, and basic science experiments in vivo and in vitro, this goal is apparently achievable, and we have moved one important step ahead with these new findings by Xing et al.

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