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Translating the genetics of blood pressure

PROFESSOR EMERITUS STEPHEN HARRAP

Past President of the International Society of Hypertension
Department of Anatomy and Physiology, The University of Melbourne, Australia

As much as 40% of blood pressure (BP) variability is "genetic"[1] and the genome is trying to tell us something about BP. There is an active "conversation" going on within the genome, between the genome and the body and with the external environment, but we need help in understanding what's being said.

Of the two strategies for translating the genomic conversation, one attempts to decipher the raw text – the DNA - and the other pieces together the transcribed text – the RNA.

DNA studies, from the early candidate gene studies[2] to the modern genome-wide association analysis (GWAS),[3] have accumulated a compendium of changes in single letters of the genetic alphabet (single nucleotide polymorphisms – SNPs) that are associated with BP differences. However, other than the discoveries of major genetic mutations affecting BP,[4] reading one letter at a time reveals neither the nature of genetic influence on BP, nor the full extent of the conversation.

For common BP variation, SNPs are most often in the "noncoding" DNA outside the genes that make proteins. These SNPs are likely part of networks that control the time and place where genes are expressed – perfect vehicles for coordinating BP control. By their nature, networks are unlikely to be revealed by individual SNPs. Furthermore, the effect on BP of a network may be greater than the sum of its part because of amplification by interaction (known as epistasis). In this case, network SNPs may not be revealed individually but only when considered together. Evidence of such interaction exists from simple analyses of genes in the renin-angiotensin system (RAS).[5] However, more complex genome-wide searches of the DNA text for networks present significant statistical and computational challenges.

On the other hand, the advantage of studying the RNA transcript of the genome is that it can pinpoint the distilled genomic conversation. The challenge is that one must choose the appropriate tissue and stage of development in which an RNA network transcript is influencing BP. Here is an example.

The spontaneously hypertensive rat (SHR), the archetype of experimental genetic hypertension, exhibits a remarkable phenomenon: short-term treatment with a RAS blocking drug will lower the BP **(Figure 1)** for the life of the SHR.[6,7] This suggests that the genetic hypertensive program of SHR is reset to a lower BP by such treatment. This well-established paradigm is not seen with

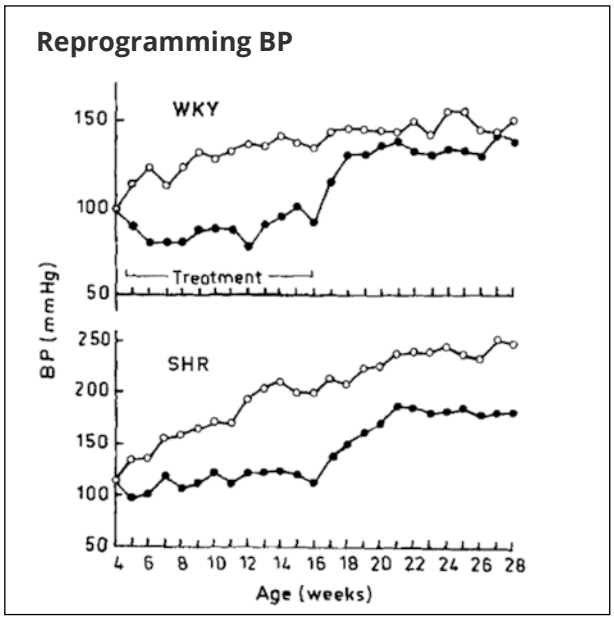
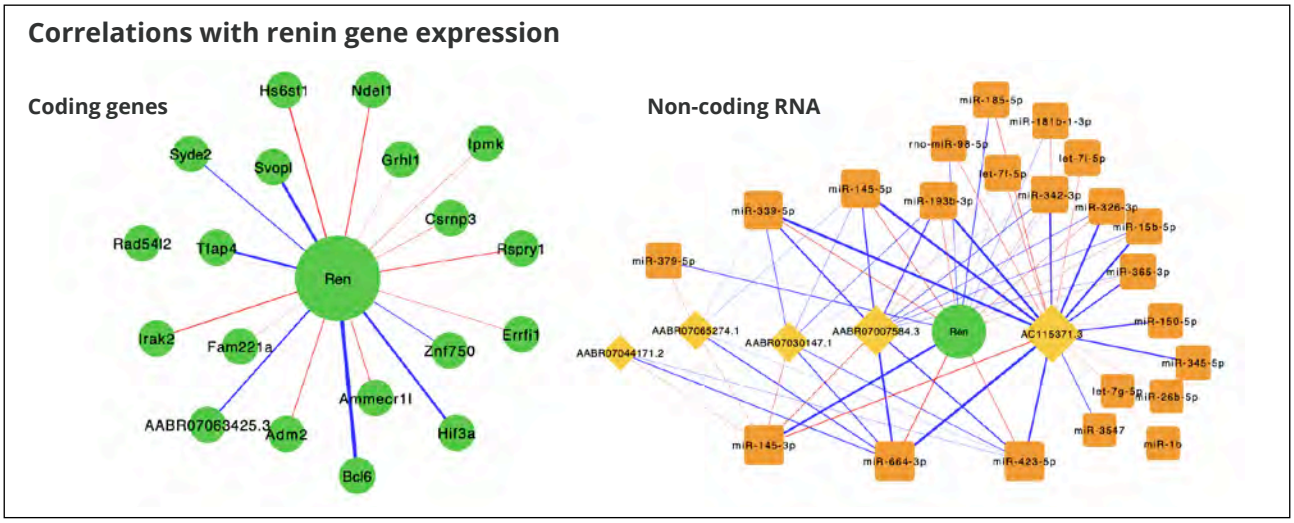


Figure 1. Treatment of young WKY and SHR animals with perindopril is followed by a persistent reduction in BP only in SHR. From ref. 7

Figure 2. The long-term reduction in renal renin gene (Ren) expression after RAS blockade in SHR correlates with changes in expression of cognate genes and non-coding RNA. From ref. 9.



other antihypertensive drugs and the kidneys are centrally involved.[8] Fifty years on, focussing on genetic expression in the kidney, the mystery may have been solved.[9] RAS blockade induces very high renin gene expression during treatment, but in SHR this is followed by a persistent reduction in renin gene expression and protein levels in the renal cortex. A priori, the persistently lower BP would normally be expected to induce a homeostatic increase in renin. Instead, the lower renal renin is the likely cause of BP reduction. It was possible to define expression networks of genes and non-coding RNA (involved in controlling gene expression) that were altered long-term after RAS blockade and were associated directly with the reduced renal renin (**Figure. 2**). These networks are known to have biological functions related to the kidneys, RAS and BP. It was also revealed that renin and other key network genes showed evidence of increased DNA methylation. This is a recognised epigenetic mechanism by which environmental exposure – in this case RAS blockade – can leave a legacy to lower gene expression. Finally, DNA sequence differences were identified in the SHR renin gene – many in putative binding site for transcription factors that control gene expression.

Such experimental strategies can uncover something of the integrated genetic language controlling BP including the interaction within the genome and between the genome and the environment. Let's keep our ears open!

Stephen Harrap – s.harrap@unimelb.edu.au

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