Editorial Commentary

Promoting Regulatory Gene Variation in Sodium Reabsorption

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Many genes in an individual genome exist as allelic variants with 1 dimorphic form inherited from each parent. Although these alleles share a common regulatory environment within the same nucleus, they do not necessarily respond to it in the same way. Variation in the promoter sequences of genes, most of which are single base substitutions, may alter the binding of transcription factors that regulate expression of the gene. The result is allelic expression, a condition in which the number of transcripts present that have been produced from 1 parental allele consistently differs from that produced from the other allele.

Allelic expression is gaining a great deal of interest in several fields. In evolutionary genetics there is a strong case to be made that the divergence of species relies more heavily on the evolution of regulatory rather than structural variation in genes. However, in genomics we are beginning to understand that homeostasis is the output of gene networks and that variation in many genes can shift the state of a gene network and alter its capacity to achieve homeostasis in its regulated outputs.

Amplifying interest in allelic expression is the fact that functional implications of genetic variation creating allelic expression extend beyond the statistical relationship betweenThe variant and phenotype that is the usual output of population genetic studies. This contrasts with some well-established associations between gene variants and complex disease susceptibility, such as that between Alzheimer disease and the epsilon 4 allele of apolipoprotein E, for which no sufficient functional relationship has yet been uncovered to explain the link between the gene variation and disease risk.

The capacity to make direct functional inferences regarding the consequence of allelic variation is certainly a good thing in complex disease genetics. The struggle to garner insight into the genetic underpinnings of susceptibility to hypertension has moved through a number of phases. The first was the guess that major genes involved in control of blood pressure would harbor sequence variation leading to hypertension. This approach was tempered and refined with a broader systematic approach to the whole genome (linkage analysis) that involved the investigation of the inheritance of chromosomal markers in families and the relationship between marker inheritance and disease in those families. In part because of the lack of traction that was generated by these evolving approaches, a new plan was brought forward that was animated by high-throughput genotyping methods and the recognition that all populations seem to have an innate susceptibility to hypertension. Synergizing with this plan was the hypothesis that a small number of common gene variants create disease susceptibility, existed before the global diaspora of contemporaneous humankind, were carried along on the journey, and would come to light by examining the association between disease and genetic variation in populations rather than in families. These approaches have been invigorated by rapid technological developments that have uncovered both the structure of common genetic variation in the human genome (HapMap) and have made possible the analysis of vast numbers of genotypes per individual.

Thus, we arrive at the current state of the art that is known as genome-wide association study. Genome-wide association study has, for the first time, brought forward the prospect of tangible and consistent progress in complex disease genetics. Unfortunately, hypertension has remained enigmatic in the face of genome-wide association study. Perhaps this reflects a need for more investigation in larger populations with better-defined phenotypes and improved controls. But hypertension is a multifaceted problem of which the genetic facet may be obscured by being broadly distributed through the multisystem control of blood pressure.

In this issue of Hypertension, Hasenkamp et al report genetic genomcs studies in a Western European population that have focused on genes involved in the regulation of proximal tubule sodium reabsorption. An interesting feature has been the use of measurements of fractional excretion of endogenous lithium as a surrogate for proximal tubular sodium reabsorption. These measurements will allow the investigative team to assess how genetic variation in multiple genes involved in dopamine signaling is related to phenotypes of tubular sodium handling and blood pressure in this population. Dopamine is a major regulator of proximal tubule sodium reabsorption that is generated locally in the nephron and acts on tubular dopamine receptors of the D1 type (DRD1 and DRD5) to provide a quantitatively dominant regulation of sodium excretion under conditions of moderately increased sodium intake. Increased dopamine signaling inhibits the sodium transporters of the proximal tubule, increases distal sodium delivery, and supports natriuresis. Dopamine sensitivity of the proximal D1 receptors is subject to modulation via the action of a G protein receptor–coupled protein kinase, GRK4. In their earlier study, the same team...
reported that nonsynonymous variation in the gene encoding the major D1 receptor, DRD1, was associated with differences in distal sodium reabsorption and fractional sodium excretion and that DRD1 alleles were also associated with blood pressure levels.9

These earlier studies have now been extended in the present report that identifies variation in the promoter of the GRK4 gene. The effect of the promoter variants on binding of nuclear proteins is shown, along with the observation that naturally occurring sequence variation in both proximal and distal regions of the promoter (−2 and −1720 bp) have powerful effects to reduce expression in the context of the transcriptional control machinery present in several renal epithelial cells lines. The effect of reducing expression of GRK4 has been investigated in hypertensive rats and was found both to lower blood pressure and promote renal sodium excretion.11 Thus, the potential implication of GRK4 promoter variation in blood pressure control in humans is unmistakable.

The study has important limitations that, hopefully, will be addressed in future. Foremost is the pressing need to examine the relationship between GRK4 variation and population blood pressure levels and renal function. This will require an understanding of the common haplotypes of GRK4. The effects of GRK4 promoter variants on expression have been studied singly in isolation. In contrast, natural alleles will be constructed with greater complexity. An understanding of how the functional variants are represented in natural human GRK4 alleles is desirable and might allow association between haplotypes of GRK4 and blood pressure and renal sodium handling to come to light. The allelic expression observed in reconstructed alleles has been observed only in transfected cultured cells that may not faithfully replicate the regulatory environment of the renal epithelium in situ. This limitation faces the challenge of estimating allelic expression of human genes in renal tissue samples. Biobanking of renal tissue samples and biopsies and RNA extracted from them provides a means to advance these insights from artificial alleles in vitro to natural alleles in vivo.

Renal dopamine signaling regulates proximal tubular sodium reabsorption and is accomplished by a gene network that may play a prime role in the pathogenesis of hypertension. Much is understood concerning the links in this network. The present article adds to this insight by revealing that nodes in the network may possess variable features that might affect network functions at baseline, under the stress of increased sodium intake, or after the effects of aging are imposed. Variation at such nodes may be bidirectional with respect to the potential for such variation to increase or decrease the risk of hypertension. Thus, individuals may possess regulatory networks composing a complex mixture of alleles that individually enhance, reduce, or are insignificant with respect to hypertension risk. Although such alleles affect individual nodes, they can interact with variation in other nodes across the regulatory network. Insight into the regulatory effects of gene variation will soon merge with growing appreciation of the features of homeostatic gene networks in determining physiological traits and the capacity of these networks to adapt to environmental change and aging.

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Disclosures

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References

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The version of the Editorial Commentary, “Promoting Regulatory Gene Variation in Sodium Reabsorption,” by Doris that was posted online on August 18, 2008 (DOI:10.1161/HYPERTENSIONAHA108.116145), was mistakenly entitled “Characterization and Functional Analyses of the Human G Protein Coupled Receptor Kinase 4 Gene Promoter.”

The correct title has been used in the final print version of the article in the October 2008 issue of the journal (Hypertension. 2008;52:623–624) and in the current online version.