Pulling the Hood off Genetic Susceptibility to Hypertensive Renal Disease

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JASN 31: 667–668, 2020.
doi: https://doi.org/10.1681/ASN.2020020139

The effect of elevated BP on morbidity and mortality is not uniformly distributed across the hypertensive population. Susceptibility to progressive hypertensive renal disease (HRD) is influenced by heritable factors: the occurrence of family members who have experienced ESKD is a robust predictor of risk[1,2] and provides the rationale for large-scale population studies that have sought to identify genetic variation contributing to loss of renal function.[3] These studies face many challenges. Risk arises from the effects within individuals of plural concurrent genetic susceptibilities. The genetic variation creating risk may differ between pedigrees and populations. The phenotypic information regarding renal function and disease that is available at the population level is limited to indirect assessments (eGFR and proteinuria) and does not include information obtained directly from kidney tissue. Finally, the impressive numbers of genetic markers assessed in genome-wide association studies do not mean that these markers saturate the genome. In fact, they leave significant parts inadequately covered. For example, the Illumina Infinium HumanCore single nucleotide polymorphism (SNP) array interrogates the human genome with an average density of approximately one SNP per 1 kb. Antibodies are known to be the pathogenic agent of several progressive renal diseases, and the Ig heavy-chain gene (IGH) is highly polymorphic. However, in this array, SNP density across IGH is 1 per 46 kb, with gaps as large as 250 kb left unexamined. In the immune-focused Infinium Immunoarray, the corresponding density of markers in this region is 1 per 260 kb with one interval of >1 Mb, representing approximately 80% of IGH, lacking markers. Consequently, alternative opportunities to understand the genetic risk of progressive renal disease are essential.

Published online ahead of print. Publication date available at www.jasn.org.

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Rodent genetic models may provide opportunities to address these challenges and identify mechanisms by which HRD arises. This is especially so when genetic risk arises from natural genetic variation that can reveal the involvement of genes or mechanisms not previously anticipated to participate in disease. Opportunities beyond the reach of human population genetics include reduced genetic complexity because the maternal and paternal autosomes in inbred rodent models are genetically identical. Both selective breeding and targeted genetic modification can be performed in model organisms to investigate specific genetic variation. These approaches include low-resolution replacement of an entire chromosome (consomic line) or a chromosomal segment (congenic line) from a rodent strain that lacks disease susceptibility. Higher resolution obtained by targeted gene deletion and replacement of single genes are also important tools after the potential target has been refined. Several useful rat models of HRD have been identified that result from natural genetic variation. Fan *et al.*[4] report in this issue of *JASN* an extensive investigation that develops convincing evidence that a single-nucleotide variant in γ-adducin, a widely expressed cytoskeletal protein encoded by the gene Add3, contributes to renal injury in the Fawn-Hooded Hypertensive (FHH) rat. They show how this variant perturbs cellular function and impairs physiologic autoregulation of renal blood flow. This inbred rat model experiences FSGS and proteinuria with increasing BP and proteinuria as animals age.[5,6] Several genomic loci have been mapped in FHH that create susceptibility, indicating polygenic inheritance. Genetic variation in Shroom3 in FHH alters its interactions with actin and contributes to podocyte foot process fusion and albuminuria.[7] Variation in Rab38 in FHH is also involved in albuminuria; however, this does not affect glomerular permeability, but rather, it acts to reduce tubular reuptake of filtered protein.[8]

The polygenic nature of HRD in FHH gains a new dimension from the study reported by Fan *et al.*,[4] which introduces an additional genetic susceptibility mechanism of HRD that arises in the vasculature. After initial mapping efforts localized a renal injury locus on chromosome 1 in FHH, a congenic line in which just 13 Mb of chromosome 1 were replaced with the corresponding region from Brown Norway (BN) rats. Among the genes located in this region, Add3 became of interest because of prior association with cardiovascular function. Narrowing of this region to approximately 2 Mb revealed that the genetic variation isolated was an important determinant of the renovascular myogenic response. Blood flow in the kidney is subject to control by autoregulation. This vessel-intrinsic, reflex vasoconstriction occurs when renal perfusion pressure increases. It buffers pressure-driven changes in renal blood flow and limits pressure transmission to the glomerulus. In the congenic line, the deficient vascular myogenic response

was restored to normal. Because this response depends on transmembrane ion fluxes, patch-clamp experiments were performed. These revealed an increase in BK channel opening probability that may act to limit depolarization-induced calcium influx into vascular smooth muscle cells, thereby preventing sufficient development of myogenic tone in response to pressure loading.

The challenge to more narrowly attribute disease causality to specific genetic variation and to establish cellular consequences of gene variation that drive pathogenesis has been rigorously addressed by Fan *et al.*[4] Sequencing revealed substitution of a highly conserved lysine to glutamine (K572Q) in Add3 in FHH. This variation is present in other inbred rat lines, although its coexistence in FHH with elevated BP and other renal injury susceptibility alleles may amplify its capacity to contribute to disease. Additional genetically modified lines were generated to prove the functional role of this variant. These lines include FHH rats that contain a large segment of the BN Chr1 containing the "wild-type" BN Add3 allele, the same FHH line in which the Add3 allele has been knocked out and a further derivative of this FHH-Add3 knockout line into which a single copy of wild-type BN Add3 (K572) was transgenically inserted. The presence of wild-type Add3 in the FHH genetic background was associated with reduced age-related proteinuria, reduced histologic measures of glomerular and tubular injury, reduced glomerular capillary pressure transmission, and reduced glomerular albumin permeability. These tissue-level injury traits correspond with restoration of wild-type Add3 in FHH to restore γ-adducin expression and subcellular distribution, to normalize actin cytoskeletal conformation, to reduce BK channel potassium flux in vascular smooth muscle cells, and to restore renovascular myogenic responses and renal blood flow autoregulation. Modeling studies support the destabilizing effect of K572G variation on actin–γ-adducin interactions. This is a remarkably diverse and coherent assembly of evidence.

There is not yet an adequate answer to the question of how susceptibility to HRD arises in humans, although some progress has emerged.[9] This new insight extends prior evidence in FHH implicating variation in Rab38 in tubular protein reabsorption and in Shroom3 in podocyte cytoskeletal function and shows how multiple, diverse genetic variants can have consonant effects to drive disease. The utility of the model organism approach to identify genetic variation, to define the molecular and cellular pathways of disease, and to prove genetic causation by genomic modification is on display with remarkable clarity in FHH and amplifies the importance of other rodent models of genetically determined HRD to extending insight into pathways in which naturally occurring genetic variants contribute to pathogenesis.

DISCLOSURES

None.

FUNDING

This work was supported by National Institutes of Health grants (NIH R01DK069632 and R01DK081866) to PAD.

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See related article, "A Mutation in γ-Adducin Impairs Autoregulation of Renal Blood Flow and Promotes the Development of Kidney Disease," on pages 687–700.

Coaxing Anti-Inflammatory Granulocytes to Prevent Ischemic Kidney Injury: A Fine Balance

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JASN 31: 668–670, 2020.
doi: https://doi.org/10.1681/ASN.2020020146

Published online ahead of print. Publication date available at www.jasn.org.

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