Renal MODY-fier genes

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It is supposed that every gene in the body has a constellation of controlling elements serving as binding sites for transcription factors working coordinately in a tissue-specific, temporal, and/or developmental fashion. These DNA elements are bound by a community of protein factors organized around transcription start sites to regulate the relative activities and levels of expression of genes in response to orchestrated programs and external stimuli.

This jumble makes understanding the regulation of gene expression very difficult. As such, it is refreshing to see a gene system boiled down to one essential transcription factor, hepatocyte nuclear factor (HNF)-1β, that binds to one DNA sequence element located in the promoter of the polycystic kidney and hepatic disease 1 (Pkhd1) gene, as critical to controlling the expression of this important kidney gene that, when mutated in humans, causes autosomal recessive polycystic kidney disease (ARPKD) (11).

In an article in a recent issue of the *American Journal of Physiology-Renal Physiology*, Williams et al. (11) showed, with exquisite precision, that the mouse transcription factor HNF-1β binds to a DNA element sitting upstream, almost on top of the transcription start site, of the Pkhd1 gene at −49 bp. They also showed that the proximal promoter region, which includes this site and is only a total of −2 kb in length, determines renal collecting duct-specific expression of the gene. To put this tiny DNA region into perspective, the Pkhd1 gene itself is over half a million base pairs in length (7, 9), and promoter elements may extend upstream to as far as −35 kb or beyond (3). The key importance of this one site for Pkhd1 expression was demonstrated by mutating four conserved nucleotides of the binding sequence at −49 bp on a transgene and showing that there was no gene expression from this DNA construct in the renal collecting ducts of numerous mice carrying this mutation, in contrast to mice with a wild-type transgene. Extension of this promoter construct downstream a little way into the gene, another 2.7 kb, supported expression in other renal tubule segments, recapitulating kidney developmental expression, and allowed expression in extrarenal locations. However, collecting duct-specific expression was controlled only by the very proximal-most, HNF-1β-dependent region. A conserved HNF-1β-binding site in the human PKHD1 gene suggests that mutation of this HNF-1β-binding sequence could be a cause of ARPKD in cases in which coding sequence mutations cannot be found (1, 11). Importantly, the critical dependence of Pkhd1 transcription on HNF-1β binding would suggest by implication that the human PKHD1 gene is uniquely vulnerable to HNF-1β mutations.

It has been known for some time that mutation of the HNF1B (TCF2) gene, which codes for the HNF-1β transcription factor, causes a variety of renal abnormalities. HNF1B gene mutations cause conditions affecting primarily the kidney, pancreas, and genitourinary tract, including diabetes and mature onset diabetes of the young type 5. However, the most common phenotype caused by dominant loss-of-function mutations in HNF1B is renal cysts and diabetes. The prominence of renal cysts was clearly established by previous work (3, 5) showing that HNF-1β regulates the expression of a cadre of “renal cystic genes,” including PKHD1, PKD2 (one of the two genes mutated in autosomal dominant polycystic kidney disease), and uromodulin mutated in medullary cystic kidney disease type 2 (UMOD). In support of this, kidney-specific homozygous deletion of the Hnf1b gene in the mouse causes severe polycystic kidney disease, probably as a result of transcriptional downregulation of these renal cystic genes (12, 13). Thus, it is likely that the mechanism responsible for renal cyst formation in HNF1B heterozygotes would involve the downregulation of the cilia genes PKHD1, PKD2, and UMOD, all of which would contribute to cyst development. In this context, it is interesting that the PKD1 gene (the other autosomal dominant polycystic kidney disease gene) does not appear to be regulated by HNF-1β, which raises questions about how polycystin-1 and polycystin-2 are coordinately regulated, as they would be expected to be.

In screening patients with unexplained renal disorders, some with early diabetes, −15–20% were found to have HNF1B mutations, with a high percentage (~50%) of these being due to new mutations (2, 4). Consistent with this, in recent large studies looking for HNF1B mutations in patients with renal cysts, a sizable fraction (~20%) was found with HNF1B mutations. Potentially, other causes would be mutations in PKD1, PKD2, PKHD1 and UMOD as well as nephronophithis and Bardet-Biedl syndrome ciliopathy genes. By far the most common or consistent feature associated with HNF1B mutations is a renal disease giving rise to cyst formation and kidney developmental abnormalities that can be very heterogeneous in nature, from multicystic kidney disease and cystic dysplasia to glomerulocystic kidney disease to renal agenesis and hypoplasia. In addition, the severity of these conditions can also be extremely variable, from fetal kidney failure to normal kidney function in adults (2, 4). The extreme variability, even among siblings with the same HNF1B mutation, and lack of a genotype-phenotype correlation suggest that there are strong genetic modifiers or environmental factors influencing disease expression.

Of considerable interest is the potential for gene-gene interactions between HNF1B, PKHD1, PKD2, and other cyst-initiating genes and how HNF1B alleles might influence their expression levels. ARPKD patients with biallelic loss-of-function mutations in PKHD1 develop severe prenatal cystic dis-
ease, which often leads to neonatal renal failure. However, ARPKD can also manifest with only a mild renal disease that patients can survive before they develop a more slowly progressive hepatoportal disease with congenital hepatic fibrosis (1). This variable phenotype for ARPKD would suggest that modifier genes might be a major contributing factor affecting the patient’s outcome. If so, could hypomorphic HNF1B nonsense alleles, which might otherwise not have a phenotype, play a role in ARPKD disease expression? This might not be possible if ARPKD is caused by two loss-of-function truncating alleles. However, if one or both of the alleles retains partial function, its expression level could be further reduced by a partially impaired HNF1B allele. Furthermore, given the high new mutation rate for HNF1B and the observation that somatic second hits can occur in HNF1B heterozygotes to cause PKD1 silencing and chromophobe renal cell carcinoma (8), could HNF1B mosaicism be occurring? Partial loss of HNF1B function, or complete loss of one allele due to early somatic deletion, could have an impact on PKD1 expression in some or many tissues, decreasing it below a critical threshold and affecting the severity of the ARPKD phenotype. The possibility that ARPKD severity can be modified has been demonstrated with the PKD1+/– PCK rat model, which has a more severe or less severe renal cystic disease depending on its genetic background (6).

Finally, another consideration is that the carrier frequency of PKD1 mutations has been estimated to be from 1:30 to 1:70 (10). While these heterozygous PKD1 carriers should have a normal phenotype, is it possible that a second, disease-causing or hypomorphic mutation in HNF1B together with the heterozygous PKD1 mutation might interact to bring down expression of PKD1 to a level that would manifest as a more severe renal cystic phenotype? Studies so far have screened patient cohorts only having renal disease. It would be interesting to know how prevalent HNF1B variants are in the general population—variants that could interact with PKD1 carriers, modify ARPKD, or interact with other renal cystic genes.

DISCLOSURES

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