An Expanding Universe of FSGS Genes and Phenotypes: LMX1B Mutations Cause Familial Autosomal Dominant FSGS Lacking Extrarenal Manifestations

Jeffrey B. Kopp
Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

doi: 10.1681/ASN.2013060661

At present, there are 24 genes associated with FSGS that follow Mendelian patterns of inheritance. These patterns of inheritance include autosomal recessive, autosomal dominant, and X-linked as well as inheritance of mitochondrial DNA. The phenotypes include syndromic FSGS, in which manifestations occur in other tissues, and nonsyndromic FSGS, in which disease is limited to the kidney. The list of FSGS genes continues to lengthen, and in this age of whole-exome scans, it is likely to expand considerably in the next few years. To date, all of the FSGS genes are expressed in the podocytes, but they are rarely specific to the podocyte; this finding constitutes part of the evidence that FSGS is a podocytopathy.

The FSGS genes can be classified according to the cellular organelle or activity where the gene product plays a particularly notable role. These organelle/activity clusters include the following clusters: cell/extracellular matrix (ITGB4 and LAMB2), slit diaphragm components or interacting proteins (NPHS1, NPHS2, CD2AP, PTPRO, and MYO1E), cytoskeleton (ACTN4, INF2, MYH9, ARHGAP24, and ARHGDA), mitochondria function (IN2F, tRNA-Leu, COQ2, COQ6, and PDSS2), DNA repair/transcription (WT1, NEIL1, LMX1B, SMARCAL1, and NXF5), cell signaling (PLCE1 and TRPC6), and lysosome (SCARB2). IFN2 appears in two functional groups, and therefore, this list totals 25 genes. Some genes are reported to cause only nonsyndromic FSGS, other genes are reported to cause only syndromic FSGS, and others may cause both syndromic and nonsyndromic FSGS (e.g., INF2 and WT1). The current issue of JASN adds LMX1B to this list of switch-hitting genes that may cause both syndromic and nonsyndromic FSGS. Boyer and Werner (1) studied an extended pedigree with autosomal dominant FSGS but lacking extrarenal manifestations.

LMX1B encodes the Lin-11, Isgi-1, and Mec3 (LIM) homeodomain 1 β-transcription factor. The protein possesses two LIM domains (each with two zinc finger domains involved in protein–protein interactions; e.g., with E47 and LDB1 [NL1 and CLIM2]) at the amino terminus and a homeodomain involved in DNA binding (to a defined FLAT element in gene enhancers) in the middle portion of the molecule. LMX1B mutations associated with nail patella syndrome are clustered in the LIM and DNA binding domains, underscoring the functional importance of these domains (2).

LMX1B is a dorsoventral regulator in development, determining cell motility during limb formation as well as contributing to development of the calvaria, anterior elements of the eyes, and neurons in the central nervous systems and podocyte maturation (3). Lmx1b expression begins in the mouse kidney at embryonic day 14.5, because the visceral epithelium is undergoing differentiation into podocytes, and expression persists throughout embryonic development and adult life. Lmx1b knockout mice manifest several features indicating impaired podocyte differentiation and diminished podocyte production of collagen IV α3 and collagen IV α4 chains.

The pathways that are downstream of LMX1B are complex, including the following genes: (1) genes that control laminin gene expression, at least in the spinal cord (4); (2) podocyte genes with products that include neprhin, podocin (5), CD2AP, and collagen IV chains; (3) Wnt and Pax family genes involved in cell survival; (4) genes involved in 5-hydroxytryptamine synthesis and function; and (5) inflammation-associated genes, including IL-6 and IL-8, leading to NF-κB activation. Although these genes constitute a diverse set of pathways, they suggest the specific ways in which LMX1B may be critical to optimal podocyte function under various physiologic and pathologic situations.

The nail patella syndrome is an autosomal dominant condition with a pleiotropic phenotype and a long history. Cases were first described in 1897, familial and sporadic forms were described in 1912, autosomal dominant inheritance was described in 1933, and linkage to the ABO blood group was made by Renwick in 1955. The syndrome was finally attributed to LMX1B mutations in 1998 by Dreyer, who noted similarity to Lmx1b knockout mice; this attribution was arrived at independently by Vollrath (this interesting investigative history is reviewed by McIntosh et al. [6]). Limb abnormalities include a diagnostic tetrad: dysplasia of patellas, nails, and

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

Correspondence: Dr. Jeffrey B. Kopp, National Institutes of Health, 10 Center Drive, Bethesda, MD 20892-1268. Email: jbkopp@nih.gov

Copyright © 2013 by the American Society of Nephrology
elbows together with the presence of iliac horns. Other musculoskeletal abnormalities can affect muscles, tendons, and ligaments. Additional manifestations, more recently recognized, include normal pressure glaucoma and sensorineural hearing loss (7). There is considerable inter- and intrafamily variability with regard to the range of tissue manifestations (8).

At present, 164 heterozygous LMX1B mutations are reported to cause nail patella syndrome, which was summarized by Boyer et al. (1), and most of these mutations are in the LIM domain or homeodomains (2). The genetic mechanism is very likely haploinsufficiency; indeed, the complete absence of one LMX1B copy has been shown in two cases (9). Recently, a family was reported in which parental somatic mosaicism was noted; thus, some tissues, including presumably germ cells, have the mutated allele, but other tissues do not. This finding would explain the de novo appearance of nail patella syndrome in a family and some cases of intrafamilial heterogeneity (10). Renal penetrance is incomplete, with 30%-50% of nail patella patients manifesting kidney disease and ~5% progressing to end stage kidney disease (11). Bongers et al. (7), in a study of 32 families, suggested that glomerular disease is more common among families with homeodomain mutations. Affected patients typically develop proteinuria, with or without hematuria, at an extraordinary range of ages from birth to childhood, adolescence, or early adulthood. Progression to end stage kidney disease may occur rapidly or after a long course of proteinuria. Nephrotic proteinuria may occur, but nephrotic syndrome is not common. Characteristic findings on electron microscopy suggest the diagnosis; these findings include irregular thickening of the glomerular basement membrane accompanied by lucencies, which rise to a moth-eaten appearance, and partial foot process effacement followed over time by segmental glomerulosclerosis.

In the study by Boyer et al. (1), linkage analysis and exome sequencing in a family with autosomal dominant FSGS led unexpectedly to an LMX1B coding variant (R246Q) present only in the cases as the cause of the kidney disease. Four family members had undergone kidney biopsy, which showed FSGS in three cases and end stage kidney disease in the fourth case, but only one biopsy was analyzed by electron microscopy; also, the glomerular basement membranes were found to be normal. Boyer et al. (1) then sequenced LMX1B in 73 additional families with glomerular disease occurring with autosomal inheritance and found two additional families with LMX1B mutation; one family had R246Q (associated with FSGS), and one family had R246P (associated with minimal change disease). Nail patella syndrome has been associated with a stop codon at position 246, but these two nonconservative mutations are novel. Thus, it is possible that this arginine residue has particular specificity for regulating expression of podocyte genes. Arginine 246 is highly conserved and a component of a particular motif (signature of interest containing a five-residue random coil), and Boyer et al. (1) suggest that it may be critical for stabilizing LMX1B homeobox domain/DNA interaction, with arginine bearing a positive charge interacting with negatively charged DNA. Nonetheless, the renal-limited phenotype remains unexplained. Previously, a case report from 1982 described a single patient with typical renal features of nail patella syndrome but without extrarenal features; genetic testing was not available at that time, and therefore, it is not clear whether an LMX1B mutation was responsible (12).

In conclusion, LMX1B now joins the growing list of genes to consider when evaluating autosomal dominant FSGS with or without distinctive syndromic features. Given the incomplete penetrance that LMX1B mutations may manifest in families, it is possible that this variant or other LMX1B variants might be a rare cause of some cases of what appears to be sporadic FSGS.

ACKNOWLEDGMENTS

The author gratefully acknowledges the critical review by Dr. Cheryl Winkler.

This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases Intramural Research Program.

DISCLOSURES

None.

REFERENCES

2. Clough MV, Hamlington JD, McIntosh I: Restricted distribution of loss-of-function mutations within the LMX1B genes of nail-patella syndrome patients. Hum Mutat 14: 459–465, 1999
4. Ding YQ, Yin J, Kania A, Zhao ZQ, Johnson RL, Chen ZF: Lmxb1 controls the differentiation and migration of the superficial dorsal horn neurons of the spinal cord. Development 131: 3693–3703, 2004

