

## Lipid Kinase Mutations in Heritable Glomerular Microangiopathy

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Human genetic studies during the past decade have unmasked the molecular pathogenesis of several Mendelian disorders affecting glomerular integrity.<sup>1</sup> Among these disorders are heritable causes of nephrotic syndrome having either autosomal dominant or recessive inheritance, many of which are associated with mutations in genes essential for podocyte structure and function.<sup>2</sup> In addition, systemic genetic diseases that predispose to glomerular injury, such as the familial thrombotic microangiopathies including atypical hemolytic uremic syndrome, seem to be disorders of the alternative complement pathway.<sup>3</sup> Collectively, these discoveries provide new opportunities to classify glomerular pathology at a molecular and pathophysiological level, offering new tools for diagnosis and for identifying novel therapeutic targets.

In this issue of *JASN*, Ozaltin and colleagues report the discovery of a distinct gene involved in the pathogenesis of an autosomal recessive glomerular microangiopathy.<sup>4</sup> The authors describe an index Turkish family having four affected offspring born to consanguineous parents, all of whom had childhood-onset steroid-resistant nephrotic syndrome with normal serum complement levels and variable degrees of renal insufficiency. Renal histology in one affected sibling was consistent with a membranoproliferative GN (MPGN) combined with evidence of endothelial cell injury and capillary occlusion. A two-step genetic analysis (homozygosity mapping followed by exome sequencing) revealed a truncating mutation in *DGKE* (chromosome 17q22) encoding diacylglycerol kinase  $\epsilon$  (DGK $\epsilon$ ). Two additional consanguineous Middle Eastern families with similar clinical presentations

and comparable renal histologies were shown to have distinct truncating *DGKE* mutations. Additional experiments demonstrated the expression of DGK $\epsilon$  in podocytes. These findings implicate a gene involved with intracellular lipid signaling in the molecular pathogenesis of an MPGN-like glomerular microangiopathy.

Diacylglycerol kinases (DGKs) are a family of enzymes that catalyze the phosphorylation of 1,2-diacylglycerols (DAGs) to phosphatidic acid (PA), a critical step in the phosphatidylinositol cycle.<sup>5</sup> Both DAG and PA function as lipid second messengers and DGK provides a mechanism to attenuate signaling through DAG. DGK $\epsilon$  exhibits unique substrate specificity for DAG having one acyl chain derived from AA, and is the only constitutively active membrane-bound DGK isoform.<sup>6</sup> Thus, DGK $\epsilon$  appears essential for the generation and turnover of important signaling lipids in kidney cells.

*DGKE* represents the second gene associated with a heritable glomerular disease that encodes an enzyme involved with intracellular lipid signaling. Previously, Hinkes *et al.* reported that recessive mutations in *PLCE1* discovered in consanguineous families of Middle Eastern origin are associated with early onset nephrotic syndrome having histologic features of diffuse mesangial sclerosis and FSGS, but no reported evidence for microangiopathy.<sup>7</sup> *PLCE1* encodes phospholipase C  $\epsilon$ -1 (PLC $\epsilon$ 1), an enzyme that catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) to DAG and inositol triphosphate. As observed for the *DGKE* mutations, most of the reported *PLCE1* mutations cause protein truncation, consistent with a loss-of-function mechanism underlying recessive inheritance. Both genes also share expression in podocytes.

These complementary genetic discoveries implicate the phosphatidylinositol pathway as a novel pathway in the pathogenesis of glomerular injury, but the precise molecular mechanisms responsible are not obvious. It is tempting to speculate that glomerular disease arises because of a deficiency of a metabolic product or the excessive accumulation of a substrate for one or both enzymes. For *DGKE*, loss-of-function mutations conceivably cause accumulation of DAG along with reduced PA levels in podocytes. It is conceivable that higher levels of DAG evoke chronic activation of protein kinase C that drives increased activity of TRPC6, a podocyte cation channel implicated in familial glomerular disease. Indeed, Ozaltin and colleagues demonstrated that mutant DGK $\epsilon$  failed to attenuate TRPC6 current in heterologous cells presumably because of sustained DAG levels.<sup>4</sup> Gain-of-function TRPC6 mutations are responsible for hereditary FSGS,<sup>8</sup> and elevated DAG levels with resulting increased TRPC6 activity in podocytes is a plausible consequence of DGK $\epsilon$  loss of function. However, it is more difficult to connect *PLCE1* mutations to this same mechanistic cascade

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involving activation of TRPC6 because DAG production likely falls in the setting of PLC $\epsilon$ 1 loss-of-function mutations. Alternatively, deficiency of AA containing PA species might be a plausible unifying hypothesis because one would predict reduced levels of this end product from loss of function of either *DGKE* or *PLCE1*.

Additional evidence connecting lipid second messengers and glomerular injury comes from a recent study by Soda *et al.* demonstrating heavy proteinuria and podocyte foot process effacement in mice lacking synaptojanin 1, a phosphoinositide phosphatase that normally dephosphorylates PIP<sub>2</sub>.<sup>9</sup> The authors of that study implicated altered actin nucleation and defective clathrin-mediated endocytosis as the basis for podocyte dysfunction in this model. These findings raise further intrigue regarding the contributions of aberrant lipid signaling to glomerular injury. Clearly, additional work is needed to resolve these pathophysiological mechanisms. For future investigations of *DGKE*-associated glomerular disease, perhaps exploiting a previously described *Dgke* null mouse,<sup>10</sup> would be informative.

Beyond the obvious questions related to the underlying molecular mechanisms, the report by Ozaltin and colleagues<sup>4</sup> describes an interesting new entity along the spectrum of glomerular microangiopathies. Unlike other forms of glomerular disease with an MPGN histologic pattern, the glomerular syndrome described in this report does not appear to involve overt complement activation or extensive Ig deposition. The three families described in this article exhibit steroid- and immunosuppressant-resistant nephrotic syndrome, further evidence for a nonimmunologic basis. Collectively, these findings support the existence of a novel mechanism for glomerular microangiopathy. Whether the clinical and pathologic features described in this article are shared by other genetic or acquired conditions will hopefully be revealed in the future.

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## DISCLOSURES

None.

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See related article, "DGKE Variants Cause a Glomerular Microangiopathy That Mimics Membranoproliferative GN," on pages 377–384.

## A New Look at Tubulointerstitial Communication with Exosomes

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Various CKDs, regardless of initial insult, progress by a common pathway leading to renal fibrosis consisting of

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