The recent discovery of inverted formin 2 (INF2) as a major gene for focal segmental glomerulosclerosis (FSGS) focused the spotlight on this gene as important for understanding renal disease. New findings reveal that the same gene causes an uncommon neurologic disorder, Charcot-Marie-Tooth disease (CMT), in a subset of the same patients.

The finding has important clinical implications for FSGS patients, and it sheds light on the crucial role of the actin cytoskeleton in the structure and function of the podocyte, a property it appears to share with the Schwann cells that绝缘 axons.

"We do not know exactly why some mutations lead only to the renal disease, while others cause renal plus neurologic disease," said Corinne Antignac, MD, PhD, lead author of the study and a researcher at the French National Institute of Health and Medical Research and the Necker Hospital in Paris. However, the study was published late last year in the New England Journal of Medicine.

The clinical implication of the finding is quite clear, Antignac said. "If you have patients with familial-dominant FSGS, you have to check whether they might have a neurologic disorder." Patients suspected of having peripheral neuropathy should be referred to a neurologist for further evaluation and treatment.

The CMT disease causes progressive weakness and atrophy of distal muscles and reduced tendon reflexes. Over time, patients typically experience deformities of the foot, including high arches and hammertoes, along with hand deformities.

Mutations in the INF2 gene were originally linked to FSGS in 2010 by Martin Pollak, MD, and colleagues. In early 2011, Antignac and her team reported that out of 54 French families with autosomal-dominant FSGS, 17 percent carried INF2 mutations. By contrast, only one patient in 84 sporadic cases carried a mutation. These results indicated that INF2 mutations are a major cause of autosomal-dominant FSGS but are unlikely to account for a significant fraction of sporadic disease.

The gene encodes a formin protein, a family of proteins involved in remodeling of the actin and microtubule cytoskeleton. In fulfilling this role, INF2 interacts with myelin and lymphocyte protein (MAL), which, as its name implies, is found in both myelin and lymphocytes, along with podocytes. "When we read the literature, we saw that INF2 was interacting with MAL, and that reminded me that we had heard about patients with both FSGS and Charcot-Marie-Tooth disease," Antignac said.

That led her to wonder whether the two diseases might have a common cause in these patients. She and her colleagues enrolled 16 patients with both FSGS and CMT from 16 unrelated families, including seven with autosomal-dominant FSGS and nine with sporadic disease. They also obtained DNA from an additional four families from previously published cases. They ruled out mutations in the two genes that account for the large majority of CMT cases, called PMP22 and MPZ, both of which are crucial for myelin stability in Schwann cells.

They found heterozygous mutations in INF2 in 12 of the 16 patients. In most patients, though not all, symptoms of CMT developed earlier than or at the same time as proteinuria, in patients ranging from age 5 to age 28 (median, age 13). Several patients had both sensorineural hearing loss and muscle weakness. Patients were classified as having an intermediate CMT phenotype, with a combination of both axonal and demyelinating changes.

The nine different mutations were all located in exons 2 and 3 of the gene, which encode a protein domain crucial for interacting with multiple other proteins. "All of the mutations for both CMT and FSGS are located in a more central part of the protein" compared with those causing FSGS alone, Antignac said. This may account for the more widespread clinical phenotype arising from these mutations, although much work remains to be done to test that hypothesis.

In the kidney, INF2 is predominantly expressed in podocytes, where it interacts with MAL, among other targets, as it does in Schwann cells. In Schwann cells, the disease-causing mutations do not disrupt INF2-MAL binding but instead, Antignac showed, cause MAL to be mislocalized away from the nucleus and diffused throughout the cytoplasm. Cells with mutant INF2 had less cortical actin and a reduced number of long actin stress fibers, and their microtubule network was disorganized.

"INF2 is involved in polymerization and depolymerization of actin," Antignac said, and it is well known that the cytoskeleton is crucial for the shape of the podocyte. You can very well imagine if this system is interrupted, it could lead to abnormalities of the cytoskeleton, and to disease."

Her group is currently investigating the role of the INF2-MAL complex in intracellular transport in the podocyte.

"It has been shown that the complex is involved in transport in lymphocytes, and we are trying to figure out whether it is critical for the podocyte. It is very important to try to understand how INF2 works," she said, and how it goes awry when mutated, because it may give clues to the development of treatments for both primary and secondary FSGS.

"I think this is a fascinating finding," said Pollak, who discovered the INF2-FSGS link. "It emphasizes the importance of taking a careful family history." Pollak is chief of nephrology at Beth Israel Deaconess Medical Center in Boston.

"It’s a great paper," Pollak said. "People have long noted there are certain similarities between podocytes and some cells of the nervous system, in terms of structure and biology, and this is consistent with that at a genetic level." Those similarities are especially acute in the "architectural complexity" of the two cell types, made possible by actin and other cytoskeletal elements.

James Lupski, MD, PhD, professor and vice chairman of molecular and human genetics and professor of pediatrics at Baylor College of Medicine in Houston, who is an expert on CMT, agreed that the article is important.

"In both the neuropathy and the glomerulat disorder, you are dealing with cells that have had to specialize, creating very unusual membrane structures. The Schwann cell wraps many times around the axon, while the podocyte must have a very large surface area to deal with filtration." The remarkable thing, he said, is "that one protein is involved in solving this problem in both."

Suggested Reading

ASN Introduces... eJC Offers:
• Topics that will be innovative and controversial
• An interactive and timely journal club experience
• Promotion of discussion among nephrologists
• Stimulating interactions with authors

Visit http://ejc.cjasn.org today!