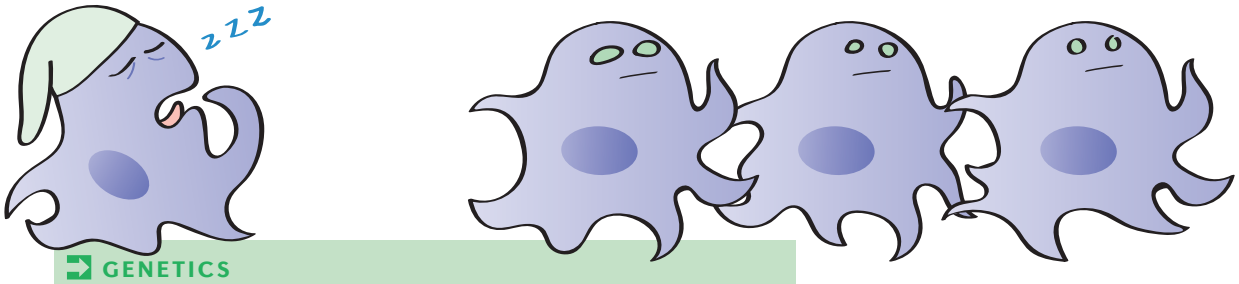
Nature Reviews Nephrology | Published online 20 Feb 2017; doi:10.1038/nrneph.2017.19



GENETICS

SGPL1 mutations cause a novel SRNS syndrome

Two new studies published simultaneously by different research groups report that recessive mutations in *SGPL1*, which encodes sphingosine-1-phosphate (S1P) lyase, cause a syndromic form of steroid-resistant nephrotic syndrome (SRNS) with adrenal insufficiency. SGPL1 degrades the intracellular signalling molecule S1P, which has roles in the regulation of various physiological processes, including cell migration, survival and differentiation.

In their study, Friedhelm Hildebrandt and colleagues used whole exome sequencing to investigate recessive causes of SRNS. They identified nine different recessive mutations in *SGPL1* in seven families. "Many of the affected individuals had extrarenal manifestations of disease, including ichthyosis, adrenal insufficiency, immunodeficiency and peripheral neurologic defects," says Hildebrandt. "We were assured that *SGPL1* mutations are the cause of this disease when comparing the clinical presentation with published findings in mice that lack *Sgpl1* activity."

Hildebrandt and colleagues show that the mutations they identified cause subcellular mislocalization, decreased expression and loss of function of SGPL1. Knockdown of *Sgpl1* resulted in reduced migration of rat mesangial cells, which could be partially reversed by a S1P receptor antagonist. Fibroblasts from patients with *SGPL1* mutations had a similar migration defect. In *Drosophila*, deficiency of the *SGPL1* ortholog *Sply* resulted in functional defects in nephrocytes; expression of wild-type *Sply,* but not of the disease-associated variants, rescued this phenotype.

"We hope that discovery of S1P metabolism as a new pathway of SRNS pathogenesis will help to develop treatment opportunities for individuals with this type of SRNS," says Hildebrandt. "If S1P signalling represents a mechanism on which other forms of monogenic SRNS converge, targeting S1P metabolism may benefit a broader group of individuals with SRNS."

Louise Metherell and colleagues are interested in the genetics of adrenal insufficiency. They first identified a *SGPL1* mutation in a family with primary adrenal insufficiency in which two individuals had SRNS. "Collaborations with adrenal colleagues from around the world allowed the identification of mutations in other families with a similar clinical picture and uncovered the truth — both pathologies are part of a single disorder," says Metherell. In total, these researchers identified four different recessive *SGPL1* mutations in five families. They also report that *Sgpl1*$^{-/-}$ mice phenocopy the major features of the human disorder. The adrenal glands of these mice had histological abnormalities and altered expression of steroidogenic enzymes, whereas the kidneys showed mild mesangial hypercellularity, glomerular hypertrophy and fibrosis.

"*SGPL1* is the causative gene for a novel syndrome, probably representing an unrecognised, progressive sphingolipidosis, incorporating adrenal and renal dysfunction with skin abnormalities and neurological deficit, amongst other features," comments Metherell. "Although most features of this syndrome have been documented in other sphingolipidoses, adrenal insufficiency is a novel finding." She explains that some patients with *SGPL1* mutations do not exhibit all features of the syndrome and suggests that in those in whom the renal phenotype seems to exist in isolation, the adrenal insufficiency might be masked owing to initial steroid treatment for the kidney disease. "Our findings highlight the importance of the sphingolipid metabolic pathway not only in kidney function, but also in the adrenal gland and other organ systems," she concludes. "A genetic diagnosis for patients with SGPL1 defects will be important for correct treatment, genetic counselling and screening for comorbidities."

Ellen F. Carney

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ORIGINAL ARTICLES Lovric, S. *et al.* Mutations in sphingosine-1-phosphate lyase cause nephrosis with ichthyosis and adrenal insufficiency. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI89626 (2017) | Prasad, R. Sphingosine-1-phosphate lyase mutations cause primary adrenal insufficiency and steroid-resistant nephrotic syndrome. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI90171 (2017)