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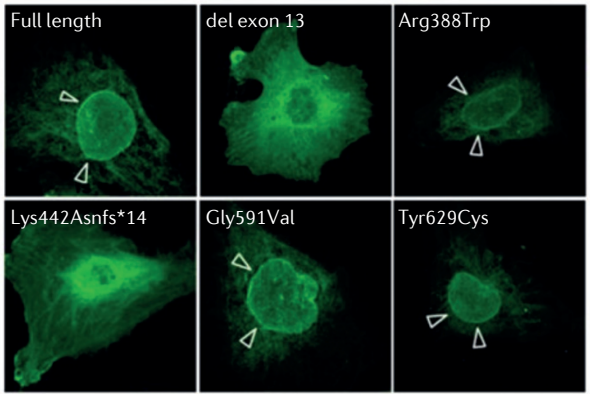
GENETICS

New link between nuclear pore genes and SRNS

A recent study has identified specific mutations in nuclear pore genes that can cause steroid-resistant nephrotic syndrome (SRNS). The new data — recently published in *Nature Genetics* — suggest a novel link between nuclear pore complex (NPC)-associated proteins and SRNS via the BMP-7-dependent SMAD signalling pathway.

Friedhelm Hildebrandt and colleagues previously demonstrated that up to 70% of cases of SRNS are of unknown genetic origin. In their latest study, they performed homozygosity mapping (to map recessive traits) and whole-exome sequencing in 160 affected families with the aim of identifying novel causative genes of SRNS. They found two homozygous mutations (p.Gly591Val and p.Tyr629Cys) in *NUP93*, which encodes nuclear pore protein 93 (NUP93), in three of these families. High-throughput exon sequencing in an additional 1,800 families with SRNS identified a further three mutations in *NUP93* (p.Arg388Trp, p.Lys442Asnfs*14 and del exon 13) in three families. The carriers of these mutations had early-onset SRNS, with end-stage renal disease by 11 years of age, signs of focal segmental glomerulosclerosis or diffuse mesangial sclerosis on renal biopsy, renal tubular phenotypes, and podocyte foot process effacement in some individuals.

> “loss-of-function mutations in *NUP93* can cause SRNS, likely as a result of aberrant SMAD signalling”



Overexpression of Myc-tagged (green) human NUP93 in human podocytes. Full length Myc-NUP93 should localise to the nuclear envelope (arrow heads). Introduction of the del exon 13 and the Lys442Asnf*14 mutations results in abberant NUP93 cellular localisation. Permission obtained from Nature Publishing Group © Braun, D. A. *et al. Nat. Genet.* http://dx.doi.org/10.1038/ng.3512

Follow-up sequence analysis of siblings from one affected family identified a homozygous missense mutation in another nucleoporin gene *NUP205* (p.Phe1995Ser); a mutation in the nuclear export gene *XPO5* (p.Val552Ile) was also detected. NUP93, NUP205, and XPO5 interact to form part of the NPC, which is essential for nuclear-cytoplasmic protein shuttling. The researchers say that mutations in such a critical cellular component would be expected to be lethal, but in these cases, mutations in nuclear pore proteins were causative of kidney disease and thus could be classified as “functionally relatively mild”.

The researchers performed a series of *in vitro* functional analyses to determine the molecular consequences of the identified mutations. Knockdown of *NUP93* in immortalized human podocytes resulted in impaired podocyte migration, a reduced rate of cellular proliferation, and increased apoptosis upon hydrogen peroxide challenge. Depletion of *NUP93* in *Xenopus laevis* egg extracts abrogated nuclear envelope and pore formation, which was restored upon add-back of wild-type *NUP93*. Furthermore, the subcellular localization of overexpressed *NUP93* was affected upon introduction of the p.Lys442Asnfs*14 and del exon 13 mutations, resulting in failure of *NUP93* to localize to the nuclear envelope.

In the last stage of their study, Hildebrandt and colleagues investigated the involvement of the BMP-7-dependent SMAD signalling pathway in SRNS, based on the reported role of NUP93 in the nuclear import of phosphorylated Smads in *Drosophila melanogaster*. Co-immunoprecipitation assays demonstrated an interaction between SMAD4 and NUP93, and between NUP93, SMAD1 and SMAD5 upon BMP-7 stimulation. Expression of some of the mutated forms of *NUP93* abrogated these interactions. BMP-7-dependent SMAD signalling was also defective as a result of *NUP93* knockdown.

Together these functional and genetic data suggest that loss-of-function mutations in *NUP93* can cause SRNS, likely as a result of aberrant SMAD signalling. The researchers propose that the link between NPC proteins and BMP-7-dependent SMAD signalling might provide a new opportunity for therapeutic intervention in this disease. They are now developing an assay by which they can monitor and record the movement of podocytes. In this way, changes in the speed and amount of movement before and after introducing a drug to the cell culture system can be assessed. They hope that this novel “podocyte migration assay” will enable them to efficiently screen for candidate drugs that might boost the activity of BMP-7 and potentially improve outcomes in patients with SRNS.

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