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GLOMERULAR DISEASE

Gain-of-glycosylation mutation in *ITGA3* causes nephrotic syndrome

Researchers in The Netherlands have identified a novel missense mutation in *ITGA3* that causes interstitial lung disease and nephrotic syndrome. The mutation causes hyperglycosylation of the integrin α3 subunit, which prevents formation of functional α3β1 integrin.

Nayia Nicolaou *et al*. initiated their study after identifying a patient with severe lung and kidney abnormalities. To identify the genetic basis of the disease, the researchers conducted genome-wide screening, which revealed a large homozygous stretch on chromosome 17 containing *ITGA3*. Sequencing of the *ITGA3* coding sequence revealed a mutation that causes an Ala349Ser substitution in the integrin α3 subunit. To study the mechanism by which this mutation causes disease, the researchers expressed human CD151 together with either the wild-type or mutant integrin α3 subunit in cultured podocytes from mice lacking both *Cd151* and *Itga3*. Introduction of the wild-type integrin α3 but not the mutant α3 subunit reconstituted expression of the α3β1 integrin and cell binding to laminin. Further biochemical experiments revealed that the mutation introduced an *N*-linked glycosylation site in the α3 subunit that prevents it from binding to the β1 subunit, but not to CD151. Consequently, the mutant α3 subunit is ubiquitinated and degraded.

The researchers hope their findings will facilitate early diagnosis in patients with severe respiratory distress and/or nephrotic syndrome and help inform appropriate genetic counselling.

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