

Faulty gene regulation triggers the kidney disease FSGS

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The Clinical Institute of Pathology at the MedUni Vienna has discovered a previously unknown mechanism in the regulation of gene expression that leads to the development of a chronic renal condition known as focal segmental glomerulosclerosis (FSGS). Primary FSGS is currently untreatable and can lead to secondary conditions ranging from nephrotic syndrome with severe oedema to the destruction of renal function.

"The build-up of substances that are normally excreted in the urine in the patient's blood poisons the entire body and can only be prevented through long-term dialysis or renal transplant," says Donscho Kerjaschki, Head of the Clinical Institute of Pathology at the MedUni Vienna.

FSGS is a [chronic condition](#) in which parts of the urine-forming, microscopically small organs (known as renal glomeruli) gradually become more and more scarred. This slowly causes the kidneys' filtering function to deteriorate, even though the patient may not notice it. The renal glomeruli – of which we have around one million in each kidney – contain highly specialist [cells](#) that monitor filtration output and prevent important proteins (such as

[albumin](#)) from being lost from the blood into the urine.

These cells are the target of FSGS. One international "hot topic" in the research of [kidney disease](#) is the discovery of the molecular causes of this condition, as a basis for developing a targeted form of therapy that is not yet currently available. "In around 20 per cent of cases of FSGS, there is a [genetic cause](#), and in around 30 per cent there is an obvious circulatory factor that can trigger the recurrence of the disease in a transplanted organ. But for the remaining 50 per cent, we have so far been unable to determine any cause," says Kerjaschki.

In collaboration with the group led by Javier Martinez at the IMBA (Institute of [Molecular Biotechnology](#)), the scientists at the MedUni Vienna have discovered the direct cause of the damage in the largest group of cases. They have demonstrated that a certain micro-RNA (mir-193a) is massively over-produced in the critical glomerular cells and switches off the entire spectrum of essential, coordinated gene regulation in these cells. This damages the cells of the filtration system so badly that it can lead to the collapse of their filtration capacity and the blood-urine barrier is destroyed. Building on these results, further studies are planned which aim to determine "why mir-193a is overexpressed", says Kerjaschki, "what causes this and how we can find a targeted way to switch off this disease-causing system."

Kerjaschki summarises the outcome of the study, which has now been published in the highly respected journal *Nature Medicine*, as follows: "Micro-RNA mir-193a switches off the vital regulation of the most important cells for [renal function](#). This publication in *Nature Medicine*, the most competitive journal in translational medicine with an impact factor of 22.4, is now the sixth from the MedUni Vienna's Clinical Institute since 2004. Each year, around 1,600 renal biopsies are

performed every year at the MedUni Vienna's Clinical Institute of Pathology, one of the largest centres for renal biopsies in Europe, and around 50 of these yield a diagnosis of FSGS.

More information: Gebehuber, C. et al. Focal and segmental glomerulosclerosis is induced by microRNA-193a and its downregulation of WT1, *Nature Medicine*. [doi:10.1038/nm.3142](https://doi.org/10.1038/nm.3142)

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