EURenOmics has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 305608.

EURenOmics
Cutting edge technologies for rare kidney diseases

ISSUE 2018

Breaking news about rare kidney diseases
Welcome to the fourth and final newsletter of the EURenOmics project!

The final year of the project’s funding by the EU saw a real spurt in high-impact publications. This has continued after the end of the funding period in September 2017, so we want to highlight exciting results in this newsletter. Due to the large amounts of publications, we can only highlight selected studies here, aiming to cover the whole range from studies immediately relevant to treating patients to those laying the foundations for understanding and studying inherited kidney diseases. A full list of publications can be found on the EURenOmics website.

We are confident that EURenOmics has made a lasting impact on improving the outlook of patients with rare kidney diseases and fueling collaborative research across Europe.

Defining optimal treatment for patients with rare kidney diseases

A number of studies from the consortium have directly contributed to defining which treatments are most effective and safe in treating renal diseases. For idiopathic membranous nephropathy for example, EURenOmics partners from Nijmegen, The Netherlands and Bergamo, Italy cooperated to identify Rituximab as a safer and equally effective treatment to the currently recommended regime of steroids and cyclophosphamide. The study in over 200 adult patients with membranous nephropathy examined side effects and remission rates for well over 3 years follow-up.

EURenomics partners from Paris published a study in Blood that found chemotherapy is superior to immunosuppression in controlling C3 glomerulopathy in patients with monoclonal gammopathy. Their data from the French registry of C3 glomerulopathy show that controlling the production of monoclonal immunoglobulin with chemotherapy, especially if given early on, was more effective in rescuing kidney function than suppressing their production with a variety of immunosuppressants or only protecting the kidney with ACE inhibitors.

A large number of experts from EURenOmics centers in Bergamo, Jena, Madrid, Newcastle, Paris, Utrecht and Zurich were also involved in giving international treatment recommendations for both Gitelman syndrome and atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy that were organized by the Kidney Disease: Improving Global Outcomes (KDIGO) initiative. This important international organization has been instrumental in improving and standardizing care of patients with renal diseases around the world by bringing together groups of experts that issue independent, state-of-the-art advice on diagnosing and treating kidney diseases.

Improving patient care through faster diagnosis and predicting treatment response

Main projects of the EURenOmics consortium have involved devising rapid genetic diagnostic tools (so called gene panels using next-generation DNA sequencing), that enable a large number of relevant genes to be tested in one go. This is especially relevant where many genes can cause similar clinical patterns, e.g. tubulopathies with loss of varying electrolytes into the urine. University partners from London, Paris and Heidelberg devised a gene panel together with small enterprise partner multiplicom from Belgium, that identified causative mutations in two thirds of patients out of 400 children with renal tubulopathies. This helped to establish a diagnosis more rapidly than before and sometimes even changed the initial clinical diagnosis.

In Patients with membranous nephropathy, EURenOmics partners from France were able to identify different response patterns only 8 days after start
of Rituximab therapy, which identified patients who were going to respond or not. The detailed analysis of different types of B- and T-cells of the immune system may in future be useful for predicting response in patients with one of the most common immune-mediated kidney disorders.

**New treatments on the horizon**

A novel approach to a rare genetic kidney dysfunction called Dent disease showed promising results in a study by EURenOmics partners from the University of Zurich. In a mouse model, they could surprisingly **cure the genetic defect by bone marrow transplantation**. Donor cells were able to transfer healthy subcellular structures (enodosomes) to cells in the tubules of the kidney lacking healthy endosomes. Bone marrow transplantation is an invasive procedure that is currently used mainly for patients with resistant leukemia; whether its use for Dent disease in humans is helpful and justified still remains to be shown. However, the study opens a completely new perspective on the disease and may revolutionize therapy.

Bone marrow transplantation has also been shown to treat cystinosis, another rare kidney disease which effects a different kind of sub-cellular structure (lysosomes). EURenOmics partners from Zurich, Paris and Utrecht were instrumental in a recent study published in Nature Communications which demonstrated that **cystinosis is caused by defective clearance of damaged mitochondria** by the lysosomes and unraveled a pathway that leads to epithelial cell dysfunction. These important insights into the mechanisms of the disease provide new therapeutic perspectives for the whole group of disorders of lysosomal storage.

**Discovering new diseases and new genes**

EURenOmics partners from London and Munich were able to identify a new disease by observing several young children with **polycystic kidney disease and hyperinsulinemia**. Finding the genetic basis of the disease was complicated by the fact that the mutation was not in a gene itself, but in a “promotor” region of DNA that regulates how often the gene is transcribed. Despite the fact that this promotor (PMM2) has a widespread role throughout the body in glycosylating gene products, patients with this novel mutation are affected only in the kidney and pancreas.

Very young children and the unborn are also affected by another genetic disease - **Bartter syndrome** – that leads to loss of potassium and acid over the urine. This can lead to increased amniotic fluid, early delivery and growth problems. Even though some specific genetic causes are known, a number of cases remain unexplained. About 40% of these were found to carry mutations in a novel gene (MAGED2) by EURenOmics partners from Paris.

A cluster of novel genes (encoding subunits of the KEOPS complex) could be identified by a group of researchers including EURenOmics partners from Paris and Ankara. They help to elucidate previously unsolved cases of **Galloway-Mowat syndrome** – a disease that causes nephrotic syndrome in young children paired with brain anomalies. The large study published in Nature gives important insights into potential pathogenic mechanisms of the disease.

EURenOmics partners from Paris were also instrumental in sequencing the whole genome of fetuses affected by a failure of both kidneys to form (kidney agenesis). This helped to identify a novel genetic defect (in GREB1L), which also led to a variety of other, milder forms of **congenital anomalies of the kidney and urinary tract** (CAKUT) and failure of the uterus to form in girls. Interestingly, the mutation was transmitted by the mother in almost all cases, which is relevant for genetic counselling of affected families.
Understanding the molecular basis of rare kidney diseases

EURenOmics partners from Oulu, Finland contributed to an exciting study that sheds more light on renal development. Mutations in \textit{HNF1B} are well known to cause a variety of anomalies of kidney development as well as adult-onset diabetes of the young. The study published in Development could now demonstrate how \textit{HNF1B}-deletion disrupts kidney architecture in the earliest stages of development leading to the later formation of cysts.

An exciting study coauthored by EURenOmics partners from Zurich and Heidelberg shows that the integrity of small parts of transcribed genes (\textit{microRNA}) in specific kidney tissues is vital for them to keep kidney-specific properties and to prevent scar-formation that is seen in many different types of renal diseases (interstitial fibrosis).

New research tools for tomorrow's discoveries

On the way to understanding rare kidney diseases EURenOmics partners developed a number of tools that help to recapture and analyze what happens in diseases:

Researchers in Heidelberg and Paris developed an animal model of \textit{nephrotic syndrome} in which disease activity can be externally regulated to look for cures of different forms of the disease.

\textbf{Artificial miniature organs} developed in Oulu, Finland promise to increase our understanding of genes involved in kidney cancer. An \textit{innovative microscopy tool} from the group can be used to visualize development of these kidney organoids in detail over time.

The EURenOmics group from Toulouse established a standardized pathway to examine \textit{human urine for a large variety of metabolic substances} (metabolomics). This may in future help to prevent more invasive tests, e.g. in newborns with obstruction of the urine flow in the ureters.

Software developed by EURenOmics partners in London can be used by genetic researchers and clinicians alike for drawing complicated \textit{family trees with genetic information in an open source web application}.

If you would like to change your subscription status for this newsletter, please send an email with your request to info@eurenomics.eu.