NEWS

Breaking news about rare kidney diseases

EURenOmics

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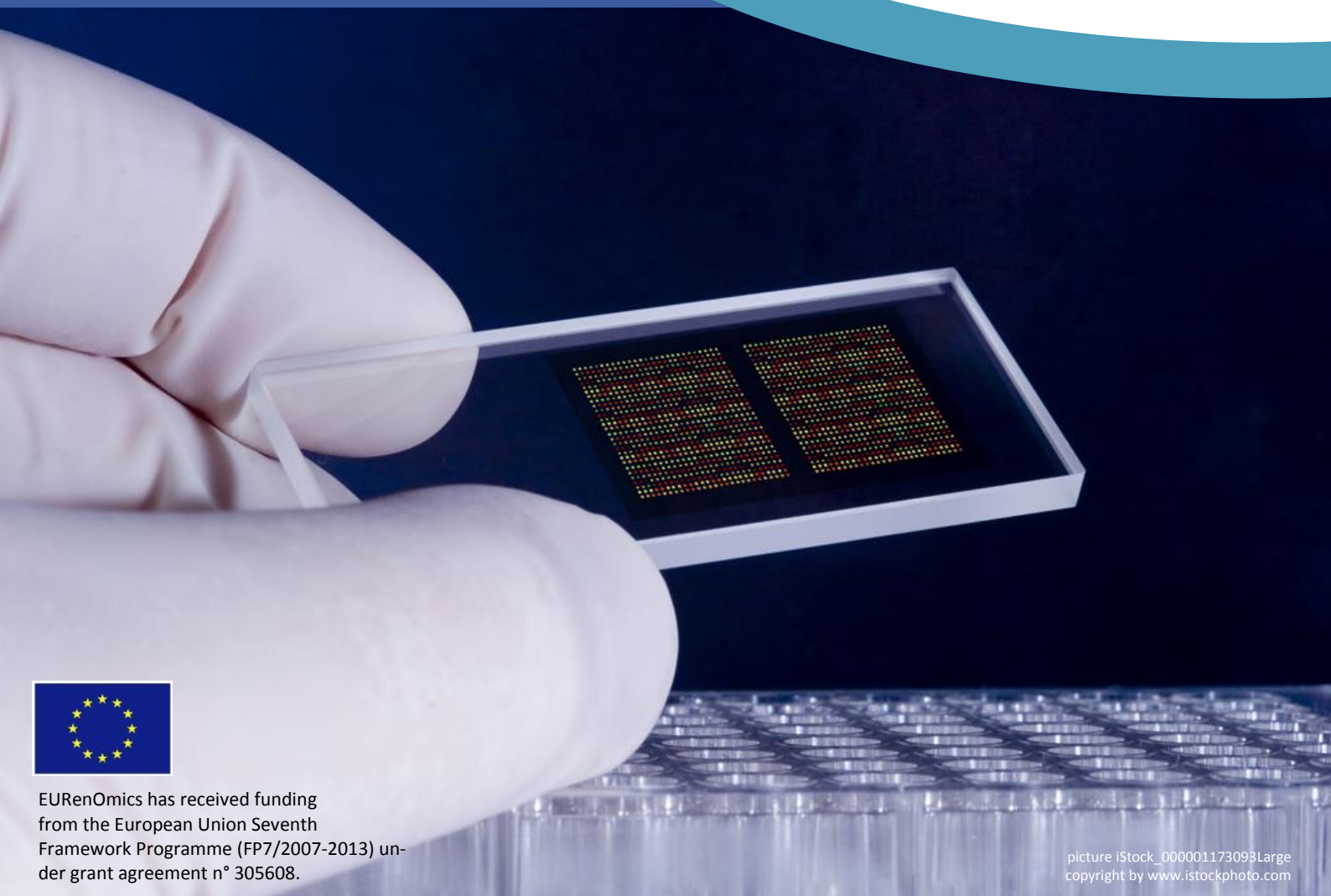
EURenOmics
Cutting edge technologies for rare kidney diseases



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In this 3rd EURenOmics newsletter, we want to present some highlights of the project in its 4th year. Within the field of rare kidney diseases, 30 university and small business partners continue to focus on steroid-resistant nephrotic syndrome (SRNS), membranous nephropathy (MN), tubulopathies, complement disorders and malformations of the kidney and urinary tract (CAKUT).

The group's publication activity reached a record high with 69 peer-reviewed articles in its 4th project year. In addition to the ones mentioned below, a complete list can be found on the project's website, with regular updates on Twitter.

The consortium continues its close collaboration with the RD-Connect and NeurOmics projects, and the next annual meeting will be held jointly with all three groups in Berlin from 3rd to 5th May 2017.

Cooperative projects of all 3 projects in the last year have included a statement on obtaining informed consent for international rare disease cooperative research and dealing with consent issues in existing biobanks collected without or with partial informed consent (Gainotti et al., European Journal of Human Genetics). All 3 groups have also contributed to the advancement of the human phenotype ontology (HPO), a system to improve the standardized description of diseases for computational use (Köhler et al., Nucleic Acid Research). It includes a phenotype vocabulary, disease-phenotype annotations and the algorithms that operate on these. The HPO is an important bioinformatical tool that helps to translate basic research findings into patient-centered medical knowledge.

Cohort studies

The integration of large EURenOmics patient databases and advances in gene diagnostics has allowed deep phenotyping and genotype-phenotype association studies (e.g., WT1 and ADCK4-glomerulopathy, Schimke syndrome, Dent disease, Bartter syndrome, familial hypercalcemic hypocalciuria, renal Fanconi syndrome, tubulointerstitial kidney diseases, C3-associated aHUS).

EURenOmics partners from Paris, Zurich and Nijmegen collaborated in a large study of patients with Dent's disease found that the changes in blood abnormalities with progression of the disease were more dependent on age than on genotype (Blanchard et al., Kidney international). A long-term study in patients with primary membranous nephropathy from EURenOmics partners at the University of Manchester, UK could identify patients at greatest risk of loss of renal function and death, underlining the importance of achieving remission and monitoring for relapses (Kanigicherla et al., Nephrology Dialysis and Transplantation). The largest cohort study to date of patients with renal disease in Bardet Biedl syndrome was published by EURenOmics partners from University College London, UK. In this study Forsythe et al. identified both genetic abnormalities and clinical parameters that predicted more severe course of renal involvement (Journal of the American Society of Nephrology).

Partners from Paris, Heidelberg and Ankara assembled the largest cohort of children with focal segmental glomerulosclerosis (FSGS) and ADCK4 mutations to date. Korkmaz et al. demonstrated several features that make ADCK4 disease unique among the hereditary glomerulopathies and among those related to mitochondrial dysfunction. This may help to identify patients earlier in future and prevent loss of renal function with oral Coenzyme Q10 treatment.

Genomic research

As part of EURenOmics, exome sequencing has been performed in 186 families, contributing to the discovery of 11 novel SRNS genes, 2 tubulopathy genes, 3 complement disease genes, 11 new genomic rearrangements in complement disorders, and 4 CAKUT genes. In addition, numerous candidate disease genes are undergoing functional characterization. In parallel, targeted next generation sequencing (NGS) assays capturing all known genes within a disease group have been developed for glomerular (34 genes), tubular (44 genes), complement diseases (13 genes) and CAKUT (two panels, 208/388 genes). NGS panels dramatically decrease the time needed for genetic diagnosis compared to conventional Sanger sequencing. So far, the EURenOmics panels have been applied to 2871 cases, identifying disease causing mutations in 21% of the SRNS, 49% of the tubulopathy, 40% of the aHUS (atypical hemolytic uremic syndrome) and 6% of the CAKUT patients.

EURenOmics partner Prof Olivier Devuyst from Zurich, Switzerland was co-senior author for an unusual genomic study with an evolutionary angle. The researchers examined changes of the uromodulin (UMOD) gene in 156 human populations, eight ancient human genomes, and in primate genomes in order to determine why a particular UMOD variant, which is associated with salt-sensitive hypertension and chronic kidney disease in the general population has remained prevalent. Their results, published in the Journal of the American Society of Nephrology, found that the risk allele did not follow the ancestral susceptibility model observed for variants associated with salt-sensitive hypertension. Rather it was significantly correlated with pathogen diversity of bacteria and helminths and prevalence of antibiotic-resistant urinary tract infections. This substantiates a link between UMOD variants and protection against urinary tract infections (UTIs). Thus it appears that the UMOD ancestral allele, associated with higher urinary uromodulin levels, hypertension and kidney disease, has been kept at a high frequency because of its protective effect against UTIs. The paper continues to enlarge the groups impressive contribution to our understanding of the physiological and clinical relevance of uromodulin since the start of the EURenOmics project (see also Brunati et al., Prujim et al., Troyanov et al., Labriola et al., Olden et al., and Trudu et al.).

Additionally, members of the consortium have contributed to a number of genome wide association studies (GWAS), which examine millions of genetic variants using single nucleotide polymorphism arrays. Because they examine the whole genome, analysis is not restricted to previously known or suspected regions (non-candidate-driven approach) but requires intense genetic testing and bioinformatic analysis. One GWAS study within the project identified claudin-14 as a novel gene involved with renal tubular calcium and magnesium handling as well as renal stones (Corre et al., Pflugers Archive). EURenOmics partners were also involved in 2 GWAS examining risk variants for membranous nephropathy (Sekula et al., Cui et al.), diabetic albuminuria (Teumer et al.) and chronic kidney disease in children (Wuttke et al.).

Complement diseases

Disorders of the complement system (an important part of the bodies innate immune system) are known to cause both atypical haemolytic uremic syndrome (aHUS) and C3 glomerulonephritis (C3GN). The latter has only been defined as a separate entity from other membrano-proliferative glomerulopathies (MPGN) in the last few years, so our pathophysiological understanding is still limited and no treatment strategies have been systematically validated.

EURenOmics partners from the Universtiy of Newcastle,UK have performed detailed genetic examination

of a specific complement protein – factor I – in 56 aHUS patients. In Immunobiology Gleeson et al. report 32 different complement factor I variants, 29 of which had not been described previously. Also, they are the first group to describe a patient with aHUS who had a complete deletion of the gene for factor I due to chromosomal rearrangement (as well as a susceptibility variant in CD46).

A different genomic rearrangement was found in collaboration with EURenOmics partners from the University of Madrid. In Molecular Immunology Xiao X. et al. report a family with a fusion gene of two factor H related proteins (CFHR5-CFHR2), who developed C3GN. This sheds new light on the role of factor H related proteins in complement regulation and how disruption of that regulation leads to C3GN.

Another genetic defect leading to familial C3GN was discovered by EURenOmics partner Dr. Véronique Frémeaux-Bacchi's group from Paris. Chauvet et al. report in the Journal of the American Society of Nephrology two individuals with mutations of C3 which decreased its binding to complement receptor1 and caused a histologically unusual type of C3GN.

Finally, EURenOmics partners from Prof. Giuseppe Remuzzi's group at the Clinical Research Center for Rare Diseases Bergamo, Italy performed complement biochemical and genetic screening in 140 patients with idiopathic Ig-MPGN or C3GN. In Molecular Immunology, Iatropoulos et al. report finding mutations in genes encoding alternative pathway complement proteins in both Ig-MPGN and C3GN patients. The presence of mutations alone did not significantly increase the risk of Ig-MPGN or C3G, but only when other susceptibility variants were also present. Patients without proven mutations had more aggressive renal disease, suggesting that different pathways exist within this group of diseases.

Model systems

In several EURenOmics workpackages new model systems could be established, which help to study the pathophysiological processes in rare renal diseases. For example, partners from the Radboud University Medical Center, Nijmegen, The Netherlands established the 1st mammalian cell-based activity assay for studies on Gitelman syndrome (Valdez-Flores et al., American Journal of Renal Physiology). The activity of the affected thiazide-sensitive NaCl cotransporter could previously only be studied in frog egg cells.

Renal involvement in the rare metabolic disease methylmalonic aciduria can now be studied in a mouse model developed by partners at the University of Zurich, Switzerland (Forny P et al., Journal biological Chemistry). Their research could already identify new biomarkers and provide the first in vivo proof of cobalamin treatment for the disease.

EURenOmics partner Prof. Seppo Vaino's group from the University of Oulu, Finland have extensively researched the role of the Wnt signal transduction pathway in kidney development. In 2016 they presented a new mouse knockout model of Wnt11, which highlighted the role of Wnt11 at the later stages of kidney development, especially in coordinating the development of the tubular system. It provides a model for studying the mechanisms behind tubular anomalies and glomerular cyst formation (Nagy et al., BMC developmental biology). In 2015 their studies highlighted the role of Wnt4 in the development of the female reproductive tract (Prunskaite-Hyyryläinen et al., Human Molecular Genetics), but this work has more than just embryological relevance. Both Prof. Vaino and EURenOmics partner Prof. Schedl from Nice, France collaborated in a study that demonstrated an important role of the Wnt pathway and its suppressor PKA in the growth of malignant tumors of the adrenal gland (Drelon et al.,

Nature Communications). Also, suppression of the Wnt signaling pathway is a promising new target for drugs against renal cell carcinoma (Xu et al., Cancers (Basel)).

A way to circumvent the use of animal models to study renal development and an exciting possibility for regenerative medicine was discovered by Prof. Elena Levtchenko's group from the University of Leuven, Belgium. Arcolino et al. report the successful isolation of kidney progenitor cells from the urine of preterm neonates in the Journal of the American Society of Nephrology. While isolating kidney stem cells proved difficult in adults and children because kidney development is largely complete 6 weeks before term birth, the urine collected non-invasively from preterm babies was a rich source of kidney progenitor cells. The investigators also confirmed the potential of these cells to reduce later toxic kidney injury and to differentiate into functional glomerular cells. These cells may therefore be a promising tool for regenerative medicine aimed at kidney repair.

Lysosomes in inborn and acquired kidney diseases

Two groups examining very different kidney diseases have shed light on the central role of lysosomes in the function of the renal tubule. These organelles are small vesicles filled with an array of enzymes and perform a number of functions within normal cells including waste disposal and secretion. In Nature Cell Biology De Leo et al. report novel findings on their role in Lowe syndrome - a rare genetic renal disease that causes kidney, eye and brain defects in boys. EURenOmics partners from the Universities of Zurich, Leuven and Manchester collaborated to discover that in the disease lysosomes were unable to clear up vesicles with internal cell debris (autophagosomes), which consequently accumulated in kidney cells. Based on this finding, they also identified selective agonists that restored the autophagic flux in cells from Lowe syndrome patients, which may be a first step to discovering a treatment to ameliorate this devastating disease.

Luciani A et al. investigated an entirely different disease: monoclonal gammopathy, which is an age-related uncontrolled production of paraprotein by plasma cells found in adults. It often, but not always, causes renal tubular damage. In the Journal of the American Society of Nephrology, EURenOmics partners from the University of Zurich report that paraproteins which induced renal tubular damage did so by accumulating in renal lysosomes which became enlarged and dysfunctional causing loss of function of tubular cells. Future studies should test whether promoting the clearance of lysosomal storage can preserve tubular cell function and therefore protect patients with monoclonal gammopathy from renal damage.