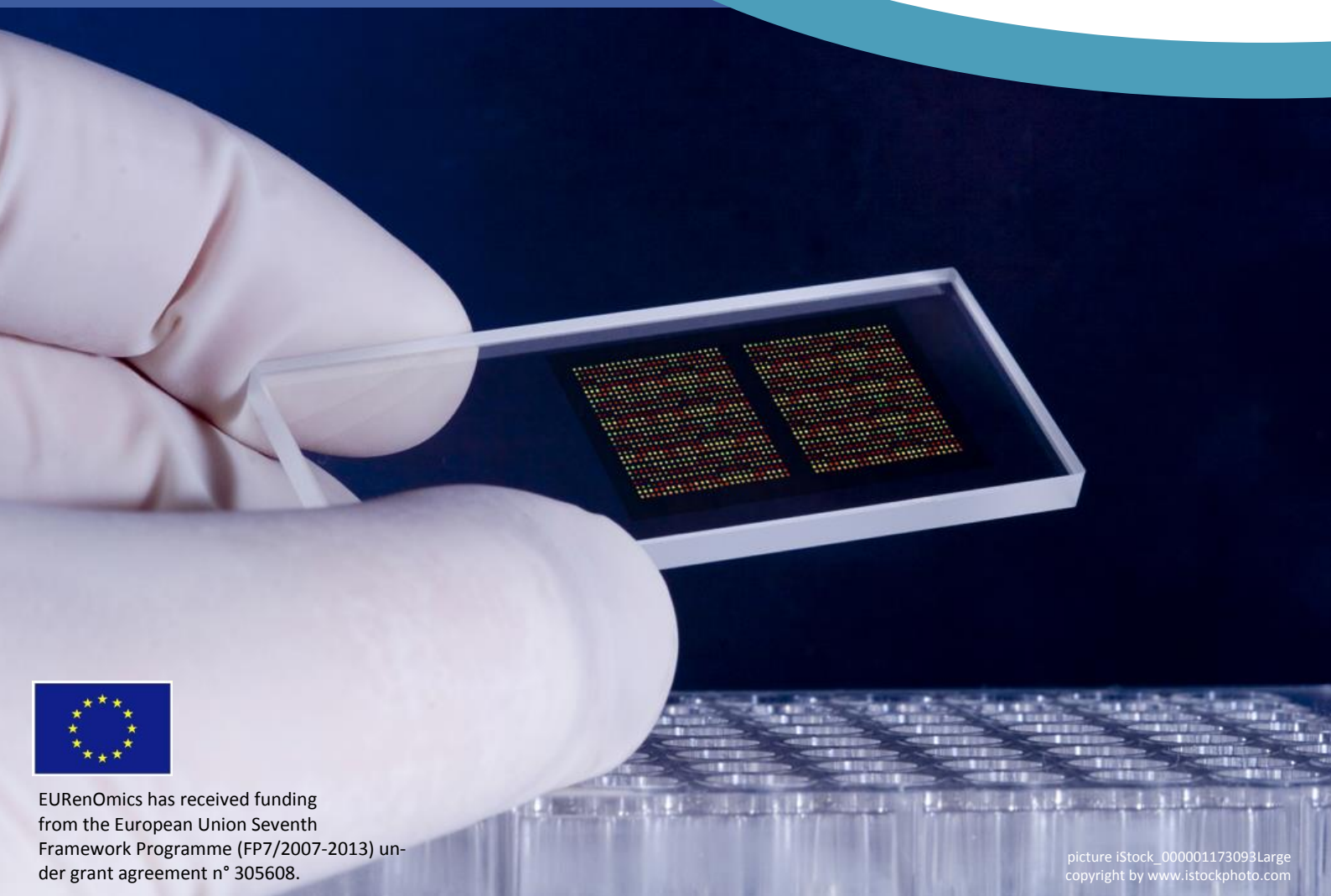
NEWS

Breaking news about rare kidney diseases

EURenOmics

ISSUE 1/2016

EURenOmics
Cutting edge technologies for rare kidney diseases



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

In the last three years the EURenOmics consortium has been working intensively on high-throughput research on rare kidney diseases. In the third periodic progress report at the end of 2015, the partners can proudly report >160 scientific publications and >450 oral and poster presentations. The next annual meeting of the project will be held in Paris from 11th-13th May 2016.

The following articles highlight publications from the major disease groups studied: focal segmental glomerulosclerosis, membranous nephropathy, atypical haemolytic uremic syndrome, tubulopathies and congenital malformations of the kidney and urinary tract.

Novel mitochondrial cause of nephrotic syndrome – treatment at the horizon

Coenzyme Q10 related mitochondropathies are among the very few causes of steroid resistant nephrotic syndrome that are amenable to treatment. Clinicians and geneticists of the PodoNet consortium, which is part of WP2, have now provided a description of the clinical course of children and adolescents with a novel, predominantly renal mitochondropathy. Loss of ADCK4 (AarF Domain Containing Kinase-4) leads to reduced cellular coenzyme Q10 levels. Podocytes are comparatively rich in ADCK4, but lack the related ACDK3 found in most other tissues, explaining the predominantly renal damage cause by mutations in ADCK4.

The 26 patients reported show a relatively late but all the more rapid onset of loss of renal function compared to two other common forms of genetically determined steroid resistant nephrotic syndrome (SRNS). The most common extrarenal manifestations were neurological problems, however these were much less pronounced than with other mitochondrial forms of SRNS. Encouragingly, oral treatment with Coenzyme Q10, which was applied in 2 patients at a very early stage, led to a significant reduction in proteinuria in both. However, many patients already had lost large parts of their renal function by the time of diagnosis.

Awareness of the clinical phenotype (adolescent onset nephrotic syndrome with chronic kidney disease) and inclusion of ADCK4 in NGS panels for diagnostic screening will hopefully increase the number of patients who are identified early on and may benefit from timely treatment.

ADCK4-Associated Glomerulopathy Causes Adolescence-Onset FSGS. J Am Soc Nephrol. 2016 Jan;27(1):63-8

Membranous nephropathy and sarcoidosis – more closely linked than previously thought

Membranous nephropathy is an important cause of chronic kidney disease in adults and may be without obvious cause (primary MN) or due to an underlying disorder (secondary MN). Discovery of auto-antibodies against PLA2R as a cause of primary MN has revolutionized understanding of the disease in recent years. PLA2R auto-antibodies are usually absent in secondary MN. However, EURenOmics partners from Paris have recently presented evidence, that they may also be involved in secondary MN. The researchers collected 26 cases of concomitant sarcoidosis and glomerular disease, of which 11 had MN with analyzable kidney biopsy in 9. In 5 sarcoidosis and MN were diagnosed within 6 months of each other. All five patients with active sarcoidosis at the time of the kidney biopsy had PLA2R antigen in immune deposits while none of those with inactive sarcoidosis had detectable PLA2R. In two patients with follow-up examinations PLA2R levels paralleled sarcoidosis activity. These very unexpected finding suggests a causal relationship between PLA2R and sarcoidosis, though the exact link still remains unclear. At the moment, clinicians should beware to not to overlook underlying disease in PLA2R-positive MN-patients, especially sarcoidosis.

Phospholipase A2 receptor and sarcoidosis-associated membranous nephropathy. Nephrol Dial Transplant. 2015 Jun;30(6):1047-50

A Randomized Controlled Trial of Rituximab for Severe Idiopathic Membranous Nephropathy

At the ASN Kidney week EURenOmics partners from Paris and across France reported interesting news from the first randomized controlled trial of rituximab for idiopathic membranous nephropathy (MN). Seeing as anti-PLA2R (and more rarely other types of) auto-antibodies are the most common cause of MN, rituximab promises clinical benefit for many patients with severe MN.

This randomized controlled trial compared non-immunosuppressive antiproteinuric treatment (NIAT) alone in 37 patients to NIAT plus 2 doses of rituximab on day 1 and 8 in 38 patients. The primary endpoint of remission at month 6 was reach by more patients in the rituximab group (n=13 (35 %)) compared to NIAT alone (n= 8 (21 %)), however this did not reach statistical significance (p=0.17). On the other hand, the composite endpoint of reduction of proteinuria >50% and increase of serum albumin >30% was reached by significantly more patients in the rituximab group (n=15 (41%)) compared to NIAT alone (n=5 (13%), (OR=0.22, 95% CI= [0.07; 0.70]; p=0.007). This was mainly due to a difference in serum albumin, rather than proteinuria.

The 6-month results are slightly disappointing, regarding the highly significant decrease of PLA2R-Ab rate and titer (P<0.001) at 3 months with PLA2R-Ab depletion achieved in 56% of patients (P<0.001). Therefore, we are looking forward to the full publication of the results for more details on the time course of antibody titers after this abbreviated regime of rituximab, as well as more details on renal function.

The fact that there was no excess of significant adverse events in the rituximab group, gives hope to the further study of this drug in MN.

A Randomized Controlled Trial of Rituximab for Severe Idiopathic Membranous Nephropathy (IMN). JASN Kidney Week, November 2015, Volume 26, Abstract Edition

Dynamic gene area holds surprises for aHUS researchers

Atypical haemolytic uremic syndrome (aHUS) is a rare disease where uncontrolled activation of the innate immune system (the complement cascade) results in damage to small vessels which can affect all organs, but particularly the kidney. Finding genetic causes of aHUS is not easy: the relevant factors that control complement activation (especially factor H) cluster on the long arm of chromosome 1, where large genomic duplications led to a number of low copy repeats encoding for factor H and five complement factor H–related proteins. Thus this cluster is prone to nonallelic homologous recombination, where DNA is altered because similar, but not identical single strands are erroneously combined to double-stranded DNA.

EURenOmcis partners from Newcastle now describe a novel Factor-H/Factor-H Related Protein-3 hybrid gene secondary to a de novo deletion that arose through microhomology–mediated end joining (a process that usually repairs broken DNA double strands by joining matching ends of overhanging single strands). They could confirm that transcription of the mutant hybrid gene takes place to produce a protein which can no longer recognizes factor H. Subsequently cell surface regulation of complement is impaired, leading to the chronic, uncontrolled activation of the complement system that is typical for aHUS. The fact that the formation of this hybrid gene arose as a de novo event suggests that this cluster is a dynamic area of the genome in which additional genomic disorders may arise to surprise aHUS researchers in the future.

A De Novo Deletion in the Regulators of Complement Activation Cluster Producing a Hybrid Complement Factor H/Complement Factor H-Related 3 Gene in Atypical Hemolytic Uremic Syndrome. J Am Soc Nephrol. 2015 Oct 21 [Epub ahead of print]

High calcium in newborns – discovery of novel cause benefits children who may now be treated

A small number of newborns suffer from abnormally high calcium levels which can make them severely unwell (idiopathic infantile hypercalcemia, IIH). In recent years hyperactivity of the enzyme which activates Vitamin D has been identified as one cause of IIH. There is little specific treatment for this Vitamin D hyperactivity, except for omitting the recommended prophylactic Vitamin D and restricting calcium intake. Researchers from Münster, Germany have now identified disease mechanism causing IIH in collaboration with EURenOmics partners. Genetic studies on consanguineous families with IIH pinpointed the SLC34A1 gene as a promising candidate. This encodes a protein channel for sodium and phosphate found in the kidney that is needed to reclaim phosphate from the primary urine into the blood. Different animal models confirmed that phosphate wasting results in inappropriate activation of Vitamin D (via FGF-23) and is essential for the secondary development of high calcium levels. High phosphate diets on the other hand could restore normal phosphate, FGF-23, Vitamin D and calcium levels. Therefore, treatment of affected infants with phosphate supplementation is a novel, promising option with few anticipated side effects and low cost. Newborns presenting with IIH therefore should undergo thorough investigation of their phosphate metabolism and genetic analysis may help to identify children who will benefit from phosphate supplements.

Autosomal-Recessive Mutations in SLC34A1 Encoding Sodium-Phosphate Cotransporter 2A Cause Idiopathic Infantile Hypercalcemia. J Am Soc Nephrol. 2016 Feb;27(2):604-14

Malformations of the kidney & urinary tract – supreme challenge to modern genetics

An impressive effort to advance the characterization of genetic abnormalities in patients with congenital abnormalities of the kidney and urinary tract (CAKUT) such as hydronephrosis, vesico-ureteric reflux or duplex kidneys was performed by EURenOmics partners from the Netherlands.

The largest set of genes associated with CAKUT so far (over 200) was analyzed with next generation sequencing in 453 Dutch patients. This identified 148 candidate variants (i.e. unusual gene sequences which may be pathogenic) which were rare and DNA-truncating, splice-site variants, or non-synonymous variants, predicted to be deleterious and conserved. However, surprisingly, in a burden analysis no significant excess of rare variants in any of the genes was found compared to healthy controls.

Also, autosomal dominant causal mutations in known genes were detected in only 6 patients (2x PAX2, SIX5 (novel frameshift variant), HNF1b (novel truncating variant), 1 UMOD).

The results suggest that the proportion of CAKUT cases with recessive inheritance in Caucasian patients is very low and that the heterogeneity of this disease is probably much higher than previously thought.

Also, the study puts into question previous claims of pathogenicity based only on novel and predicted deleterious variants in candidate genes (especially CHD1L, PKD1, and PKD2) and underlines that such claims need to be supported by statistical evidence and functional data.

Therefore this high-depth targeted sequencing study using a comprehensive list of candidate variants puts CAKUT research back to the drawing board by suggesting that the contribution of previously implicated genes to CAKUT risk is much lower than had been thought. Indeed, the influence of perinatal environmental factors such as hypoxia, may play a much greater role than was previously thought (L. Wilkinson et al, Kidney International 2015).

Prioritization and burden analysis of rare variants in 208 candidate genes suggest they do not play a major role in CAKUT. Kidney Int. 2015 Oct 21 [Epub ahead of print]

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