GWAS in Nephrology

Reconstructing CKD

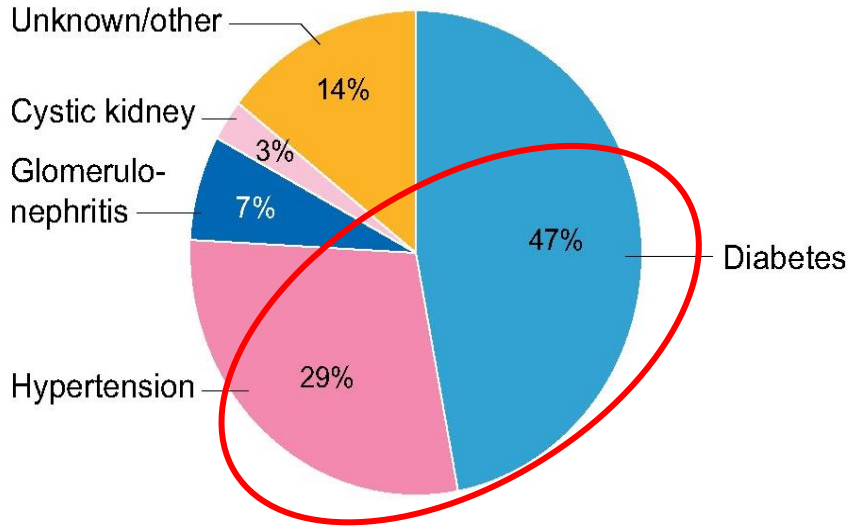
CKD “storm”

850.000.000 patients with CKD

10-13% of the general population

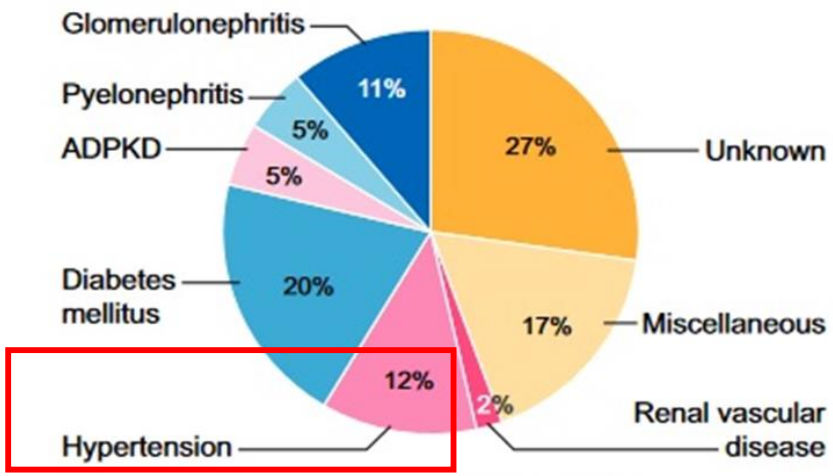
Diabetes, hypertension, cardiovascular disease, obesity

Diabetic kidney disease, hypertensive kidney disease

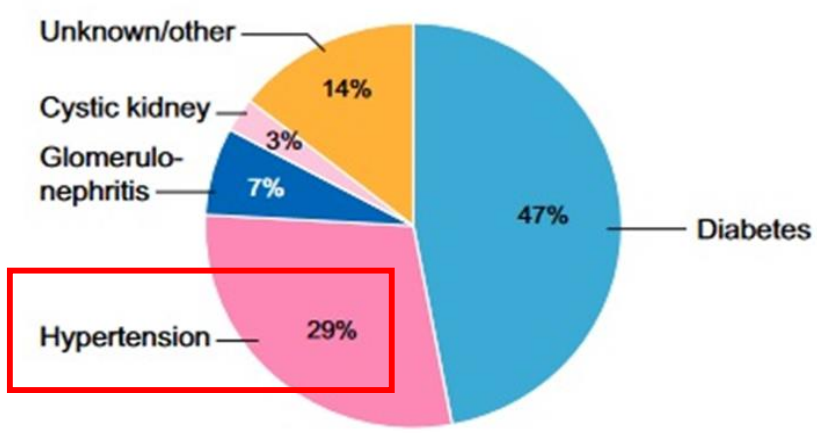



CKD
(Chronic Kidney Disease)
Diabetes
High blood pressure
Heart problems or stroke
Obesity
Family history
Tobacco use
60
60+ years old

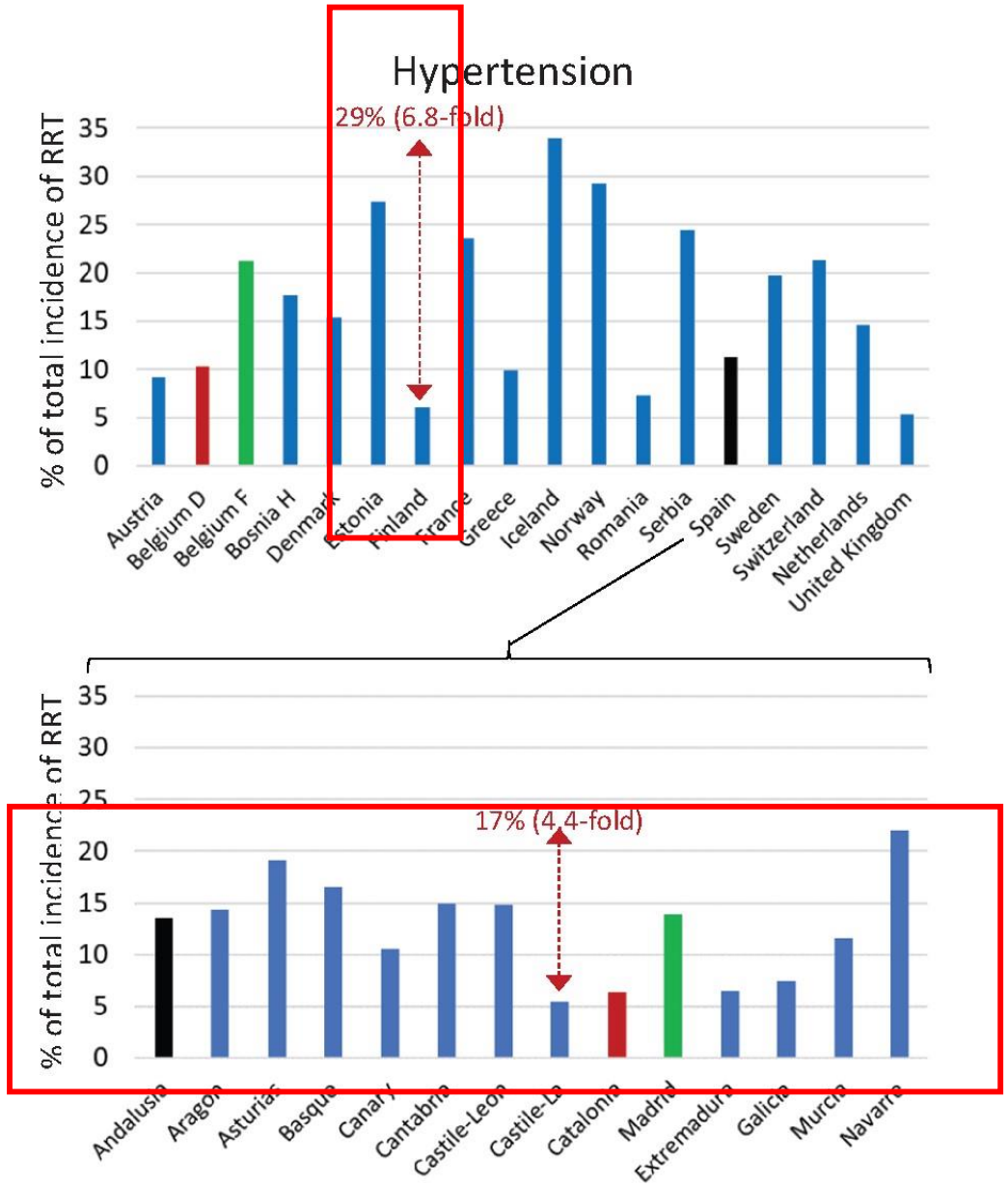
1. Hypertensive kidney disease

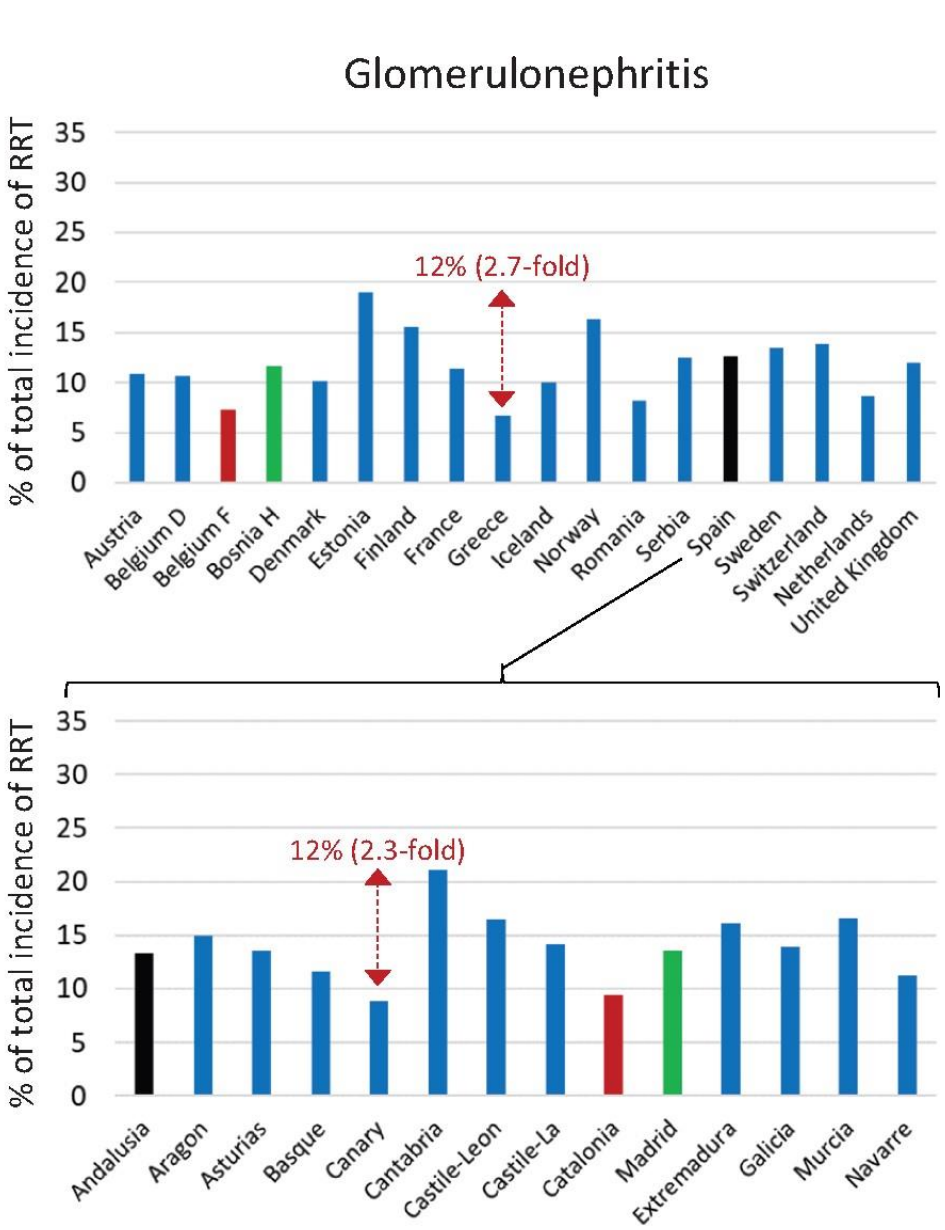


ERA-EDTA registry 2018



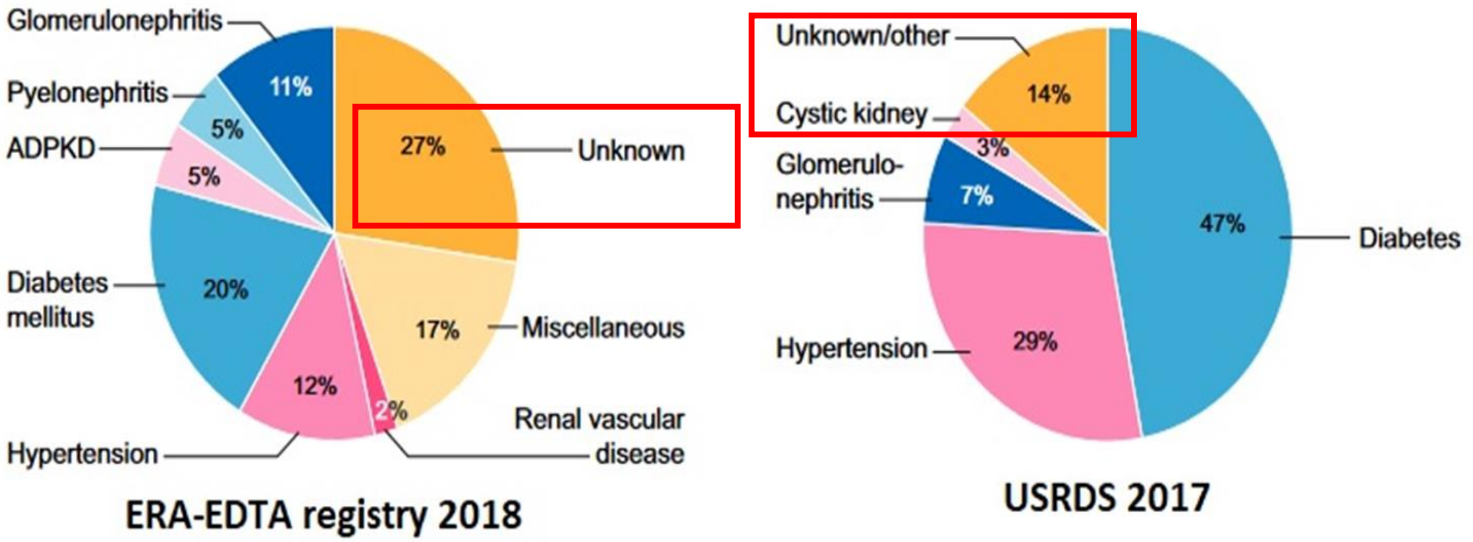
USRDS 2017


Hypertension
29% (6.8-fold)
% of total incidence of RRT
0
5
10
15
20
25
30
35
Austria
Belgium D
Belgium F
Bosnia H
Denmark
Estonia
Finland
France
Greece
Iceland
Norway
Romania
Serbia
Spain
Sweden
Switzerland
Netherlands
United Kingdom
17% (4.4-fold)
Andalusia
Aragon
Asturias
Basque
Canary
Cantabria
Castile-Leon
Castile-La
Catalonia
Madrid
Extremadura
Galicia
Murcia
Navarre


Glomerulonephritis
12% (2.7-fold)
% of total incidence of RRT
0
5
10
15
20
25
30
35
Austria
Belgium D
Belgium F
Bosnia H
Denmark
Estonia
Finland
France
Greece
Iceland
Norway
Romania
Serbia
Spain
Sweden
Switzerland
Netherlands
United Kingdom
12% (2.3-fold)
Andalusia
Aragon
Asturias
Basque
Canary
Cantabria
Castile-Leon
Castile-La
Catalonia
Madrid
Extremadura
Galicia
Murcia
Navarre

- most hypertensive patients do not develop kidney disease
- countries with a higher percentage of hypertensive patients has a lower impact of hypertensive nephropathy on RRT registries
- lack of clear benefit of intensive SBP lowering on incidence and progression of CKD
- familial aggregation of CKD independent of major risk factors such as diabetes and hypertension

2. CKD of unknown etiology



The NEW ENGLAND JOURNAL of MEDICINE

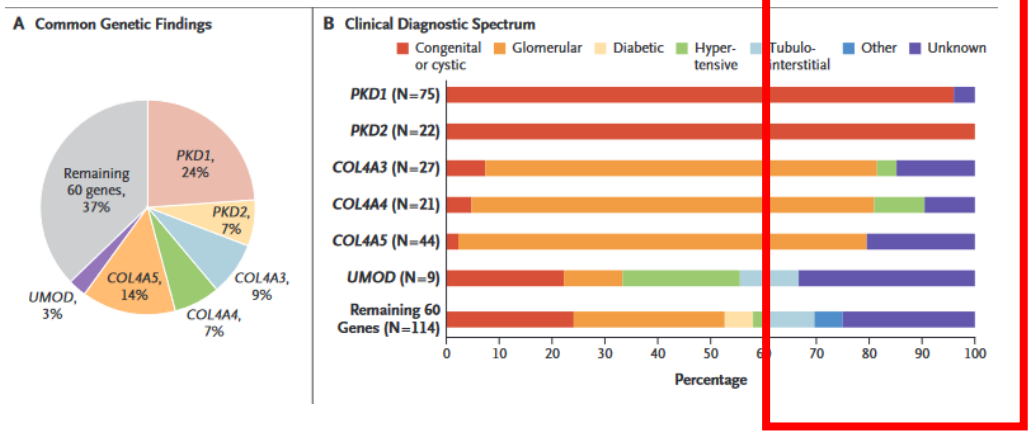
ORIGINAL ARTICLE

Diagnostic Utility of Exome Sequencing for Kidney Disease

E.E. Groopman, M. Marasa, S. Cameron-Christie, S. Petrovski, V.S. Aggarwal, H. Milo-Rasouly, Y. Li, J. Zhang, J. Nestor, P. Krithivasan, W.Y. Lam, A. Mitrotti, S. Piva, B.H. Kil, D. Chatterjee, R. Reingold, D. Bradbury, M. DiVecchia, H. Snyder, X. Mu, K. Mehl, O. Balderes, D.A. Fasel, C. Weng, J. Radhakrishnan, P. Canetta, G.B. Appel, A.S. Bomback, W. Ahn, N.S. Uy, S. Alam, D.J. Cohen, R.J. Crew, G.K. Dube, M.K. Rao, S. Kamalakaran, B. Copeland, Z. Ren, J. Bridgers, C.D. Malone, C.M. Mebane, N. Dagaonkar, B.C. Fellström, C. Haefliger, S. Mohan, S. Sanna-Cherchi, K. Kiryluk, J. Fleckner, R. March, A. Platt, D.B. Goldstein, and A.G. Gharavi

CONCLUSIONS

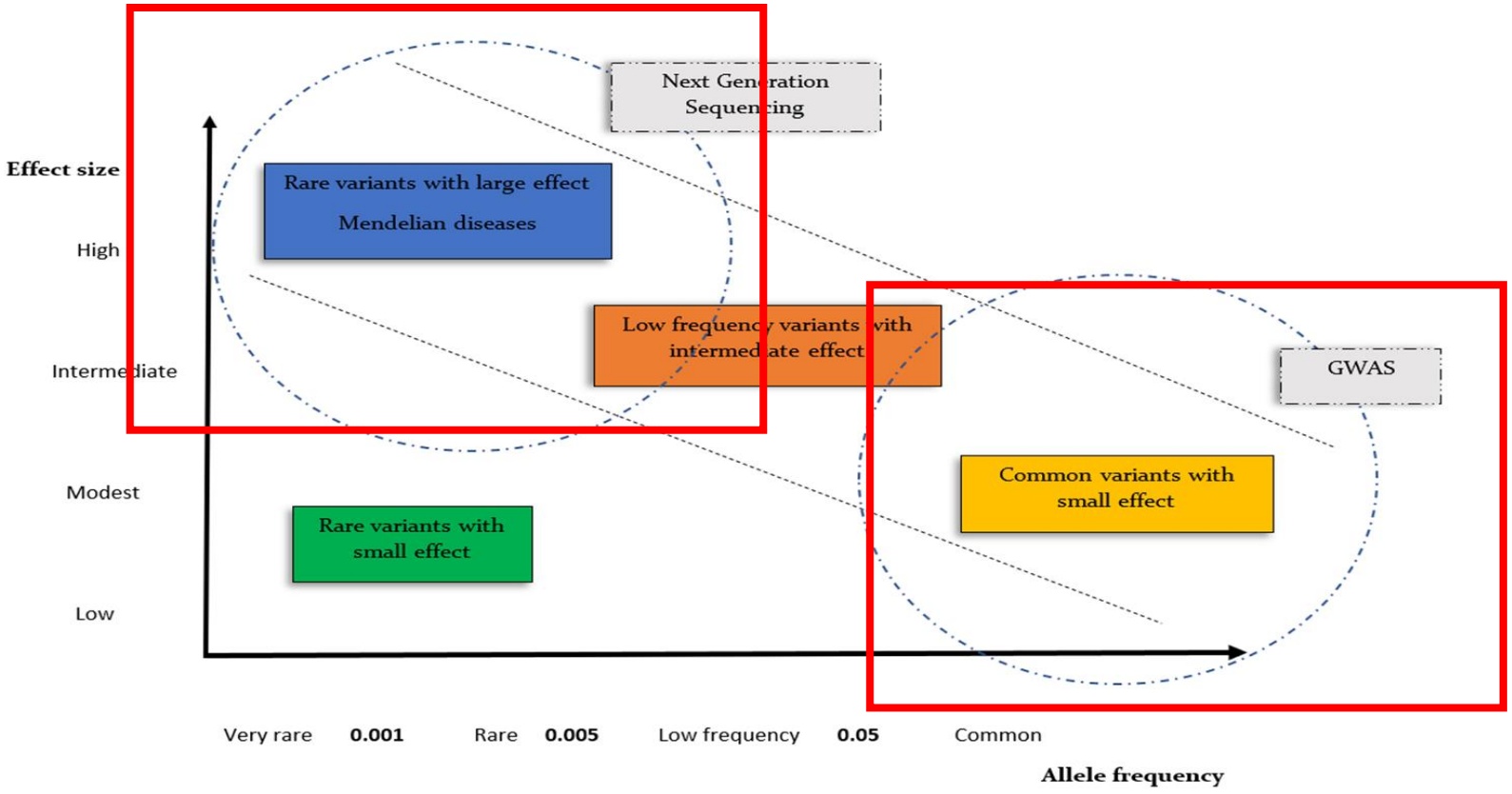
Exome sequencing in a combined cohort of more than 3000 patients with chronic kidney disease yielded a genetic diagnosis in just under 10% of cases. (Funded by the National Institutes of Health and others.)



diagnosis, a range of clinical diagnoses. Moreover, we noted diagnostic variants in 48 of the 281 patients (17.1%) with nephropathy of unknown origin, a population that may comprise up to 15% of patients with newly diagnosed


Ferdi Rizkiyan

genetic architecture of CKD



Monogenic nephropathies

> 600 genes

10-15% of CKD and ESRD

NGS/Next Generation Sequencing

Polygenic nephropathy

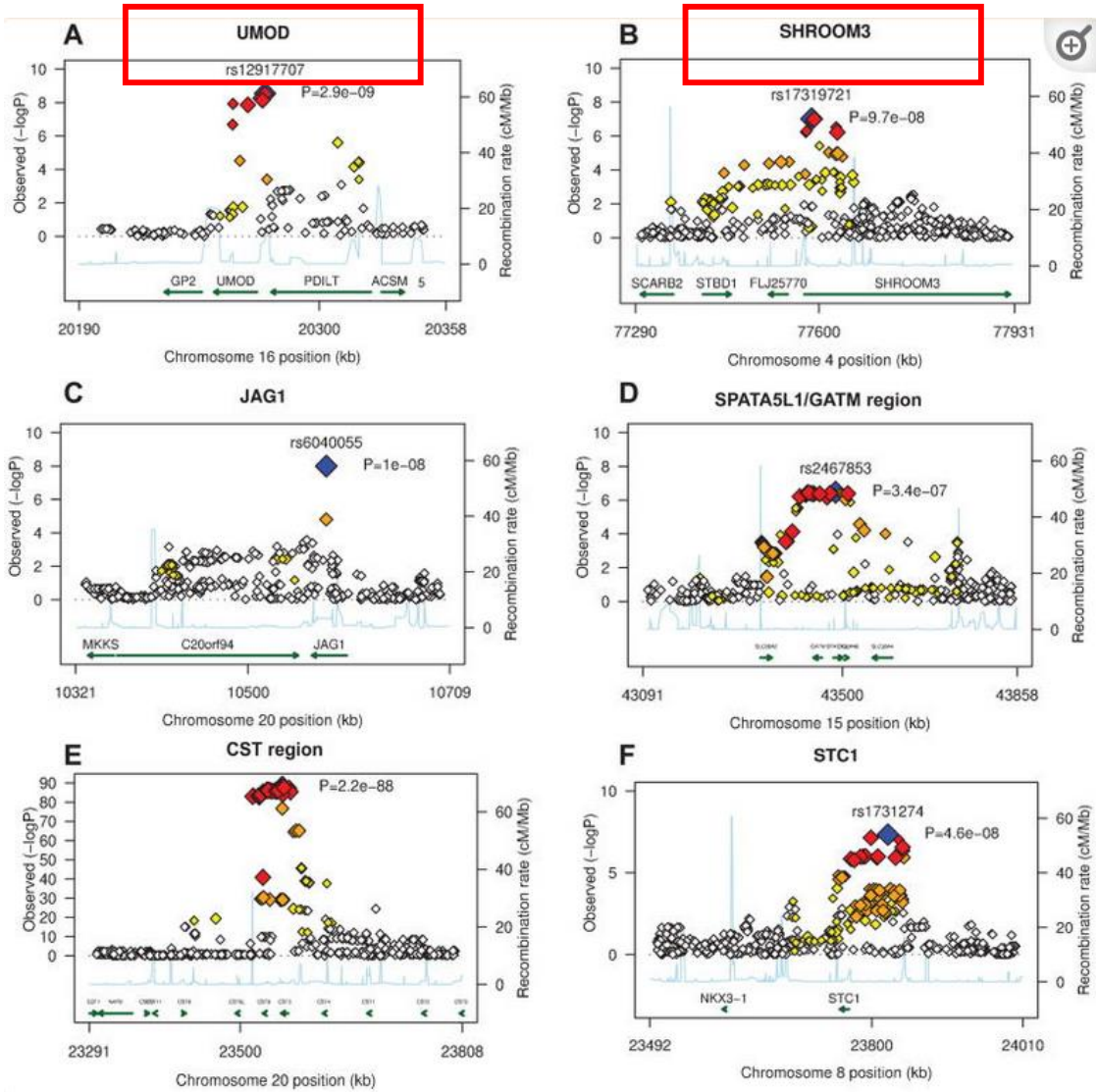
> 300 genetic loci

Genetic susceptibility to kidney disease

GWAS studies

Genome-wide association studies

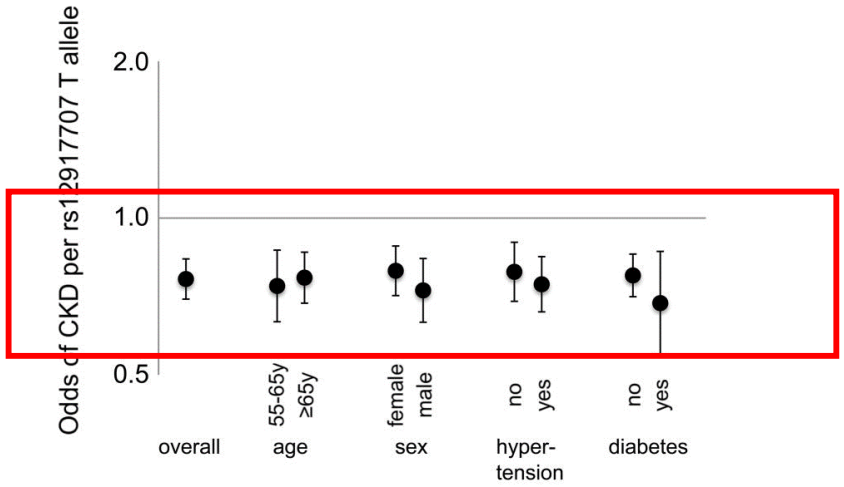
- mapping methods that identify genetic variants associated with an outcome across the genome in an unbiased manner
- do not focus on specific genes but screen entire genome
- try to find a statistical association between a genotype, typically an SNP, and an outcome, typically a kidney marker or disease
- finding a SNP in a patient group that shows a significantly different frequency from that in the control group identifies a candidate genetic locus that is likely associated with a kidney phenotype



Multiple loci associated with indices of renal function and chronic kidney disease

Anna Köttgen [1], Nicole L Glazer, Abbas Dehghan, Shih-Jen Hwang, Ronit Katz, Man Li, Qiong Yang, Vilmundur Gudnason, Lenore J Launer, Tamara B Harris, Albert V Smith, Dan E Arking, Brad C Astor, Eric Boerwinkle, Georg B Ehret, Ingo Ruczinski, Robert B Scharpf, Yii-Der Ida Chen, Ian H de Boer, Talin Haritunians, Thomas Lumley, Mark Sarnak, David Siscovick, Emelia J Benjamin, Daniel Levy, Ashish Upadhyay, Yurii S Aulchenko, Albert Hofman, Fernando Rivadeneira, André G Uitterlinden, Cornelia M van Duijn, Daniel I Chasman, Guillaume Paré, Paul M Ridker, W H Linda Kao, Jacqueline C Witteman, Josef Coresh, Michael G Shlipak, Caroline S Fox

UMOD → SNP rs12917707 → minor T allele was associated with 20% reduced risk of CKD

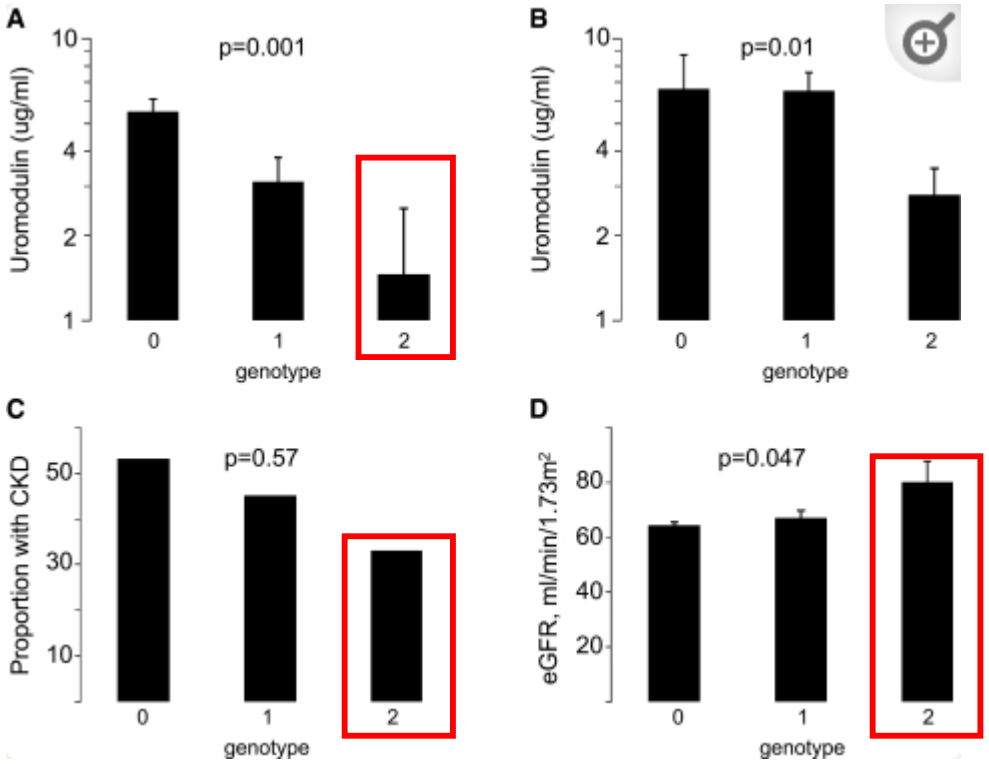


J Am Soc Nephrol. 2010 Feb;21(2):337-44. doi: 10.1681/ASN.2009070725. Epub 2009 Dec 3.

Uromodulin levels associate with a common UMOD variant and risk for incident CKD

Anna Köttgen [1], Shih-Jen Hwang, Martin G Larson, Jennifer E Van Eyk, Qin Fu, Emelia J Benjamin, Abbas Dehghan, Nicole L Glazer, W H Linda Kao, Tamara B Harris, Vilmundur Gudnason, Michael G Shlipak, Qiong Yang, Josef Coresh, Daniel Levy, Caroline S Fox

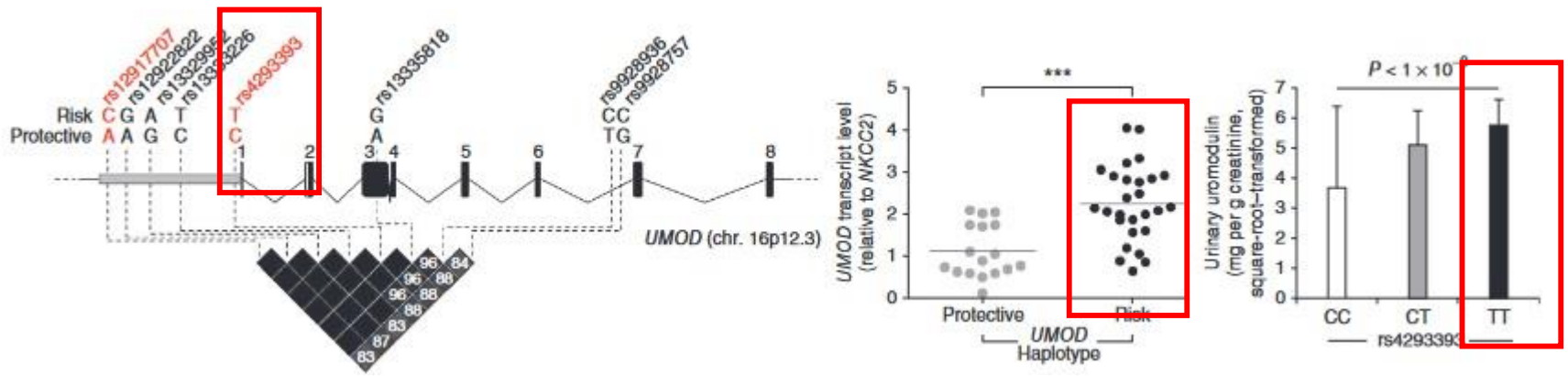
UMOD → SNP rs4293393 → minor C allele was associated with lower urine uromodulin levels, higher GFR and reduced risk of CKD



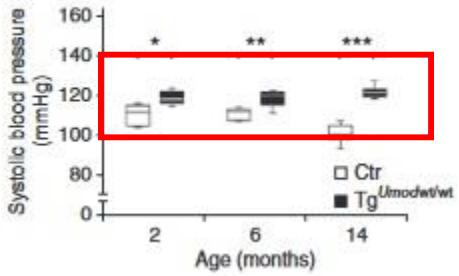
Nat Med. 2013 Dec;19(12):1655-60. doi: 10.1038/nm.3384. Epub 2013 Nov 3.

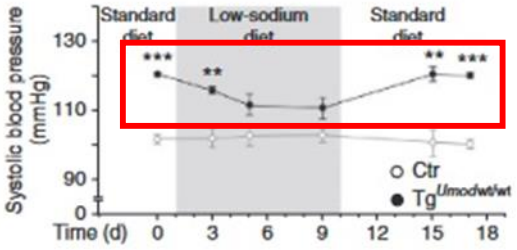
Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression

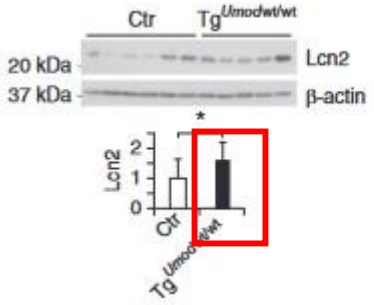
Matteo Trudu [1], Sylvie Janas [2 3], Chiara Lanzani [4], Huguette Debaix [2 3], Céline Schaeffer [1], Masami Ikehata [5], Lorena Citterio [4], Sylvie Demaretz [6], Francesco Trevisani [7], Giuseppe Ristagno [8], Bob Glaudemans [2], Kamel Laghmani [6], Giacomo Dell'Antonio [9]; SKIPOGH team; Johannes Loffing [10], Maria P Rastaldi [5], Paolo Manunta [7], Olivier Devuyst [# 2], Luca Rampoldi [# 1]

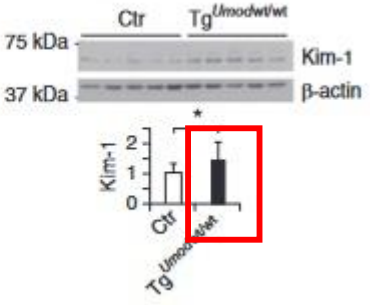


What;

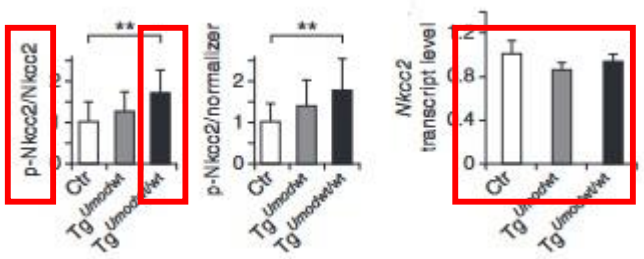

Systolic blood pressure (mmHg)
160
140
120
100
80
0
*
**
***
2
6
14
Age (months)
Ctr
Tg Umodwt/wt

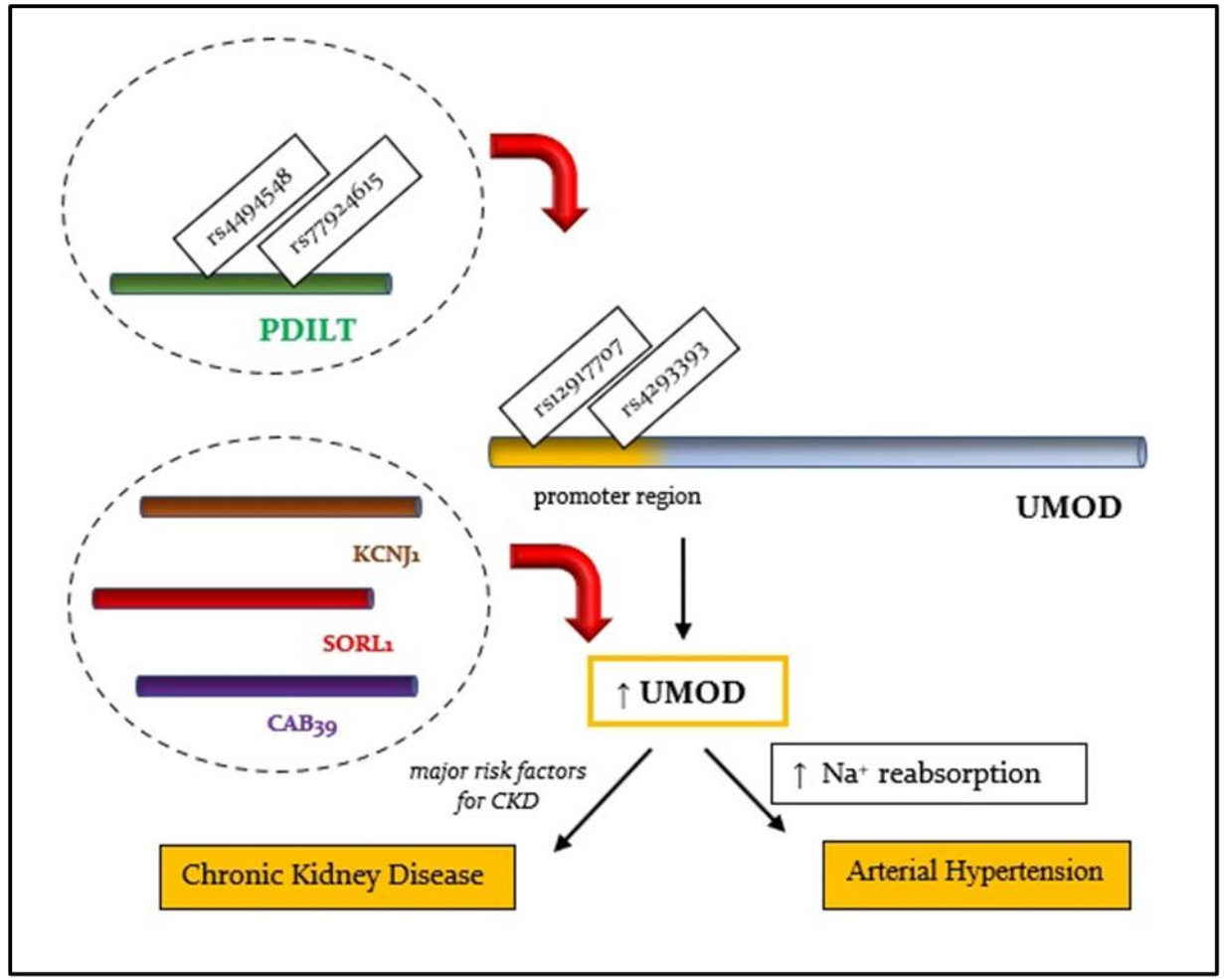

Standard diet
Low-sodium diet
Standard diet
Systolic blood pressure (mmHg)
130
110
90
0
***
**
**
***
Time (d)
0
3
6
9
12
15
18
Ctr
Tg Umodwt/wt


Ctr
Tg Umodwt/wt
20 kDa
Lcn2
37 kDa
β-actin
Lcn2
2
1
0
*
Ctr
Tg Umodwt/wt


Ctr
Tg Umodwt/wt
75 kDa
Kim-1
37 kDa
β-actin
Kim-1
2
1
0
*
Ctr
Tg Umodwt/wt

How;


p-Nkcc2/Nkcc2
**
Ctr
Tg Umodwt
Tg Umodwt/wt
p-Nkcc2/normalizer
**
2
1
0
Ctr
Tg Umodwt
Tg Umodwt/wt
Nkcc2 transcript level
1.2
0.8
0.4
0
Ctr
Tg Umodwt
Tg Umodwt/wt

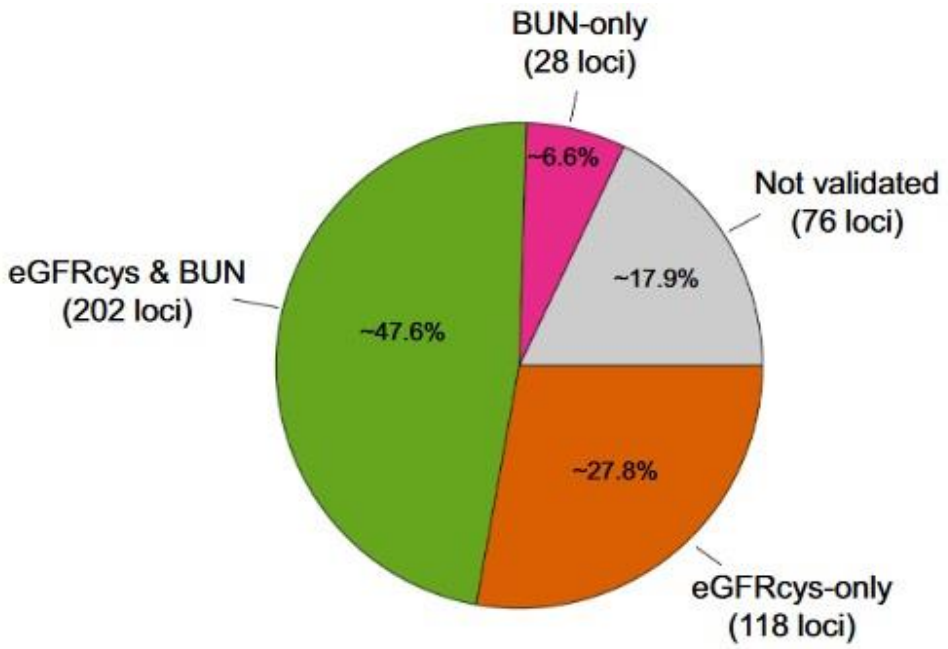

rs4494548
rs77924615
PDILT
rs12917707
rs4293393
promoter region
UMOD
KCNJ1
SORL1
CAB39
↑ UMOD
major risk factors
for CKD
↑ Na+ reabsorption
Chronic Kidney Disease
Arterial Hypertension

	Chr	position (b36)	Genes Nearby	modeled allele[#]	OR CKD [§]	95% CI	p-value
rs267734	1	149218101	ANXA9;FAM63A,PRUNE,BNIPL,LASS2,SETDB1	c	0.93	0.88–0.97	2.6E-03
rs1260326	2	27584444	**GCKR**;IFT172,FNDC4	t	0.96	0.93–1.00	8.7E-02
rs13538	2	73721836	**NAT8**;NAT8B,ALMS1	g	0.93	0.89–0.98	6.3E-03
rs347685	3	143289827	TFDP2	c	0.93	0.89–0.97	1.2E-03
rs11959928	5	39432889	**DAB2**;C9	a	1.08	1.04–1.12	1.5E-05
rs6420094	5	176750242	**SLC34A1**;GRK6,RGS14,LMAN2,PRR7,F12,PFN3	g	1.08	1.03–1.12	2.1E-04
rs881858	6	43914587	VEGFA	g	0.93	0.89–0.97	3.7E-03
rs7805747	7	151038734	**PRKAG2**	a	1.19	1.13–1.25	4.2E-12
rs4744712	9	70624527	**PIP5K1B**;FAM122A	a	1.06	1.02–1.10	7.0E-04
rs653178	12	110492139	**ATXN2**	t	0.96	0.92–1.00	5.8E-02
rs626277	13	71245697	**DACH1**	c	0.94	0.91–0.98	4.7E-03
rs1394125	15	73946038	**UBE2Q2**;FBXO22	a	1.08	1.04–1.13	8.0E-05
rs12460876	19	38048731	**SLC7A9**;CCDC123,ECAT8	c	0.93	0.89–0.96	2.6E-04

› Nat Genet. 2010 May;42(5):376-84. doi: 10.1038/ng.568. Epub 2010 Apr 11.

New loci associated with kidney function and chronic kidney disease

Anna Köttgen [1], Cristian Pattaro, Carsten A Böger, Christian Fuchsberger, Matthias Olden, Nicole L Glazer, Afshin Parsa, Xiaoyi Gao, Qiong Yang, Albert V Smith, Jeffrey R O'Connell, Man Li, Helena Schmidt, Toshiko Tanaka, Aaron Isaacs, Shamika Ketkar, Shih-Jen Hwang, Andrew D Johnson, Abbas Dehghan, Alexander Teumer, Guillaume Paré, Elizabeth J Atkinson, Tanja Zeller, Kurt Lohman, Marilyn C Cornelis, Nicole M Probst-Hensch, Florian Kronenberg, Anke Tönjes, Caroline Hayward, Thor Aspelund, Gudny Eiriksdottir, Lenore J Launer, Tamara B Harris, Evadnie Rampersaud, Braxton D Mitchell, Dan E Arking, Eric Boerwinkle, Maksim Struchalin, Margherita Cavalieri,

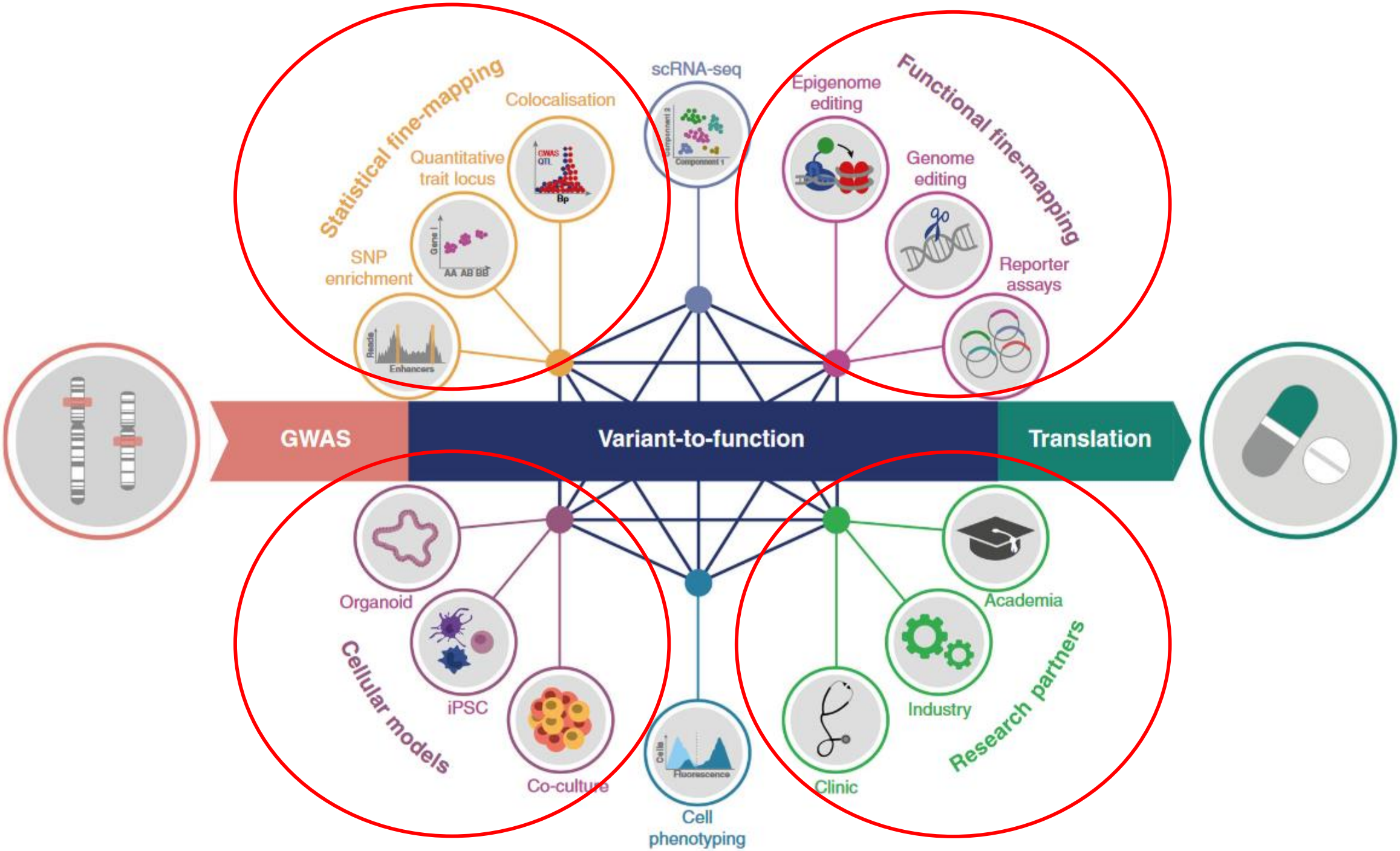


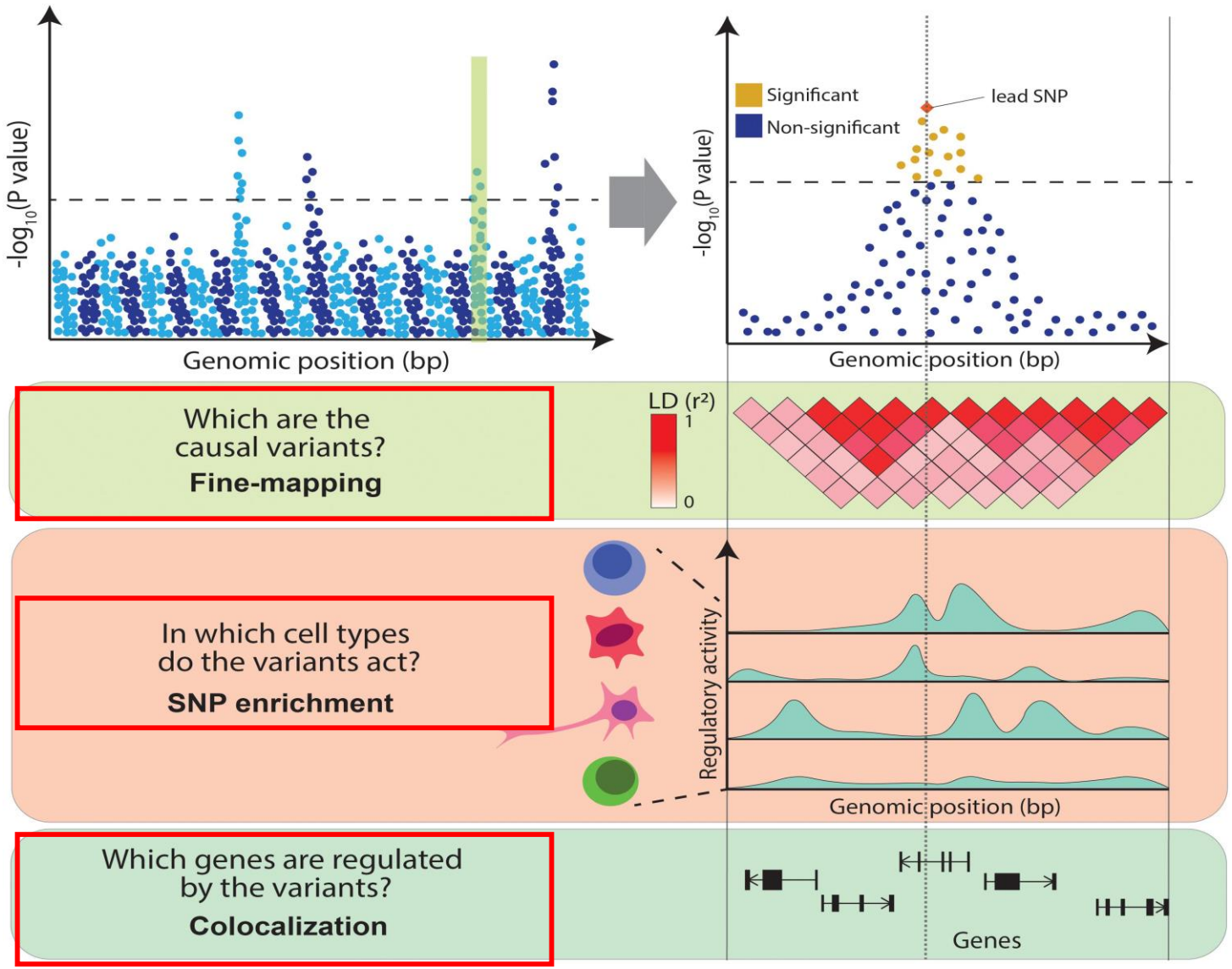
Meta-Analysis > Nat Commun. 2021 Jul 16;12(1):4350. doi: 10.1038/s41467-021-24491-0.

Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals

Kira J Stanzick [1], Yong Li [2], Pascal Schlosser [2], Mathias Gorski [1], Matthias Wuttke [2], Laurent F Thomas [3 4 5], Humaira Rasheed [3 6], Bryce X Rowan [7 8], Sarah E Graham [9], Brett R Vanderweff [10 11], Snehal B Patil [10 11 12]; VA Million Veteran Program; Cassiane Robinson-Cohen [8 13], John M Gaziano [14 15], Christopher J O'Donnell [16], Cristen J Willer [9 12 17], Stein Hallan [4 18], Bjørn Olav Åsvold [3 19], Andre Gessner [20], Adriana M Hung [8 13], Cristian Pattaro [21], Anna Köttgen [2 22], Klaus J Stark [1], Iris M Heid [1], Thomas W Winkler [23]

- associations of eGFRcre with 424 lead variants
- 348 loci were validated by association with at least one alternative biomarker and thus classified as likely relevant for kidney function


GWAS
Variant-to-function
Translation
Statistical fine-mapping
Colocalisation
Quantitative trait locus
SNP enrichment
Enhancers
scRNA-seq
Component 2
Component 1
Functional fine-mapping
Epigenome editing
Genome editing
Reporter assays
Organoid
Cellular models
iPSC
Co-culture
Cell phenotyping
Fluorescence
Academia
Industry
Clinic
Research partners


-log10(P value)
Genomic position (bp)
Significant
Non-significant
lead SNP
-log10(P value)
Genomic position (bp)
Which are the causal variants?
Fine-mapping
LD (r2)
1
0
In which cell types do the variants act?
SNP enrichment
Regulatory activity
Genomic position (bp)
Which genes are regulated by the variants?
Colocalization
Genes

Nephrol Dial Transplant, 2023, **0**, 1–8
https://doi.org/10.1093/ndt/gfad209
Advance access publication date: 0 2023

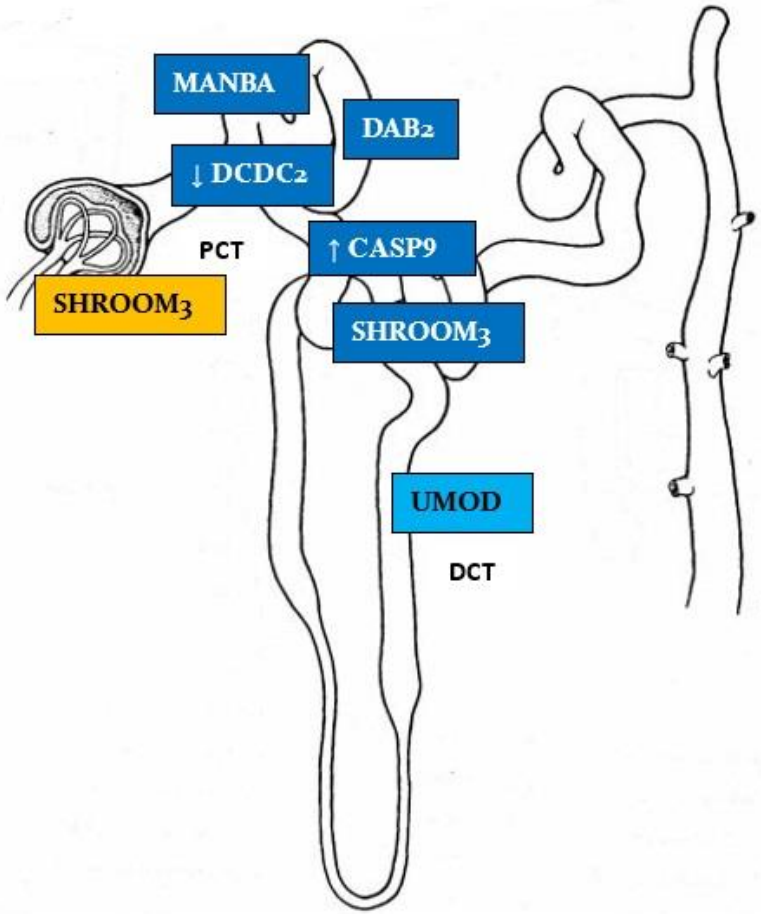
Genome-wide association studies reconstructing chronic kidney disease

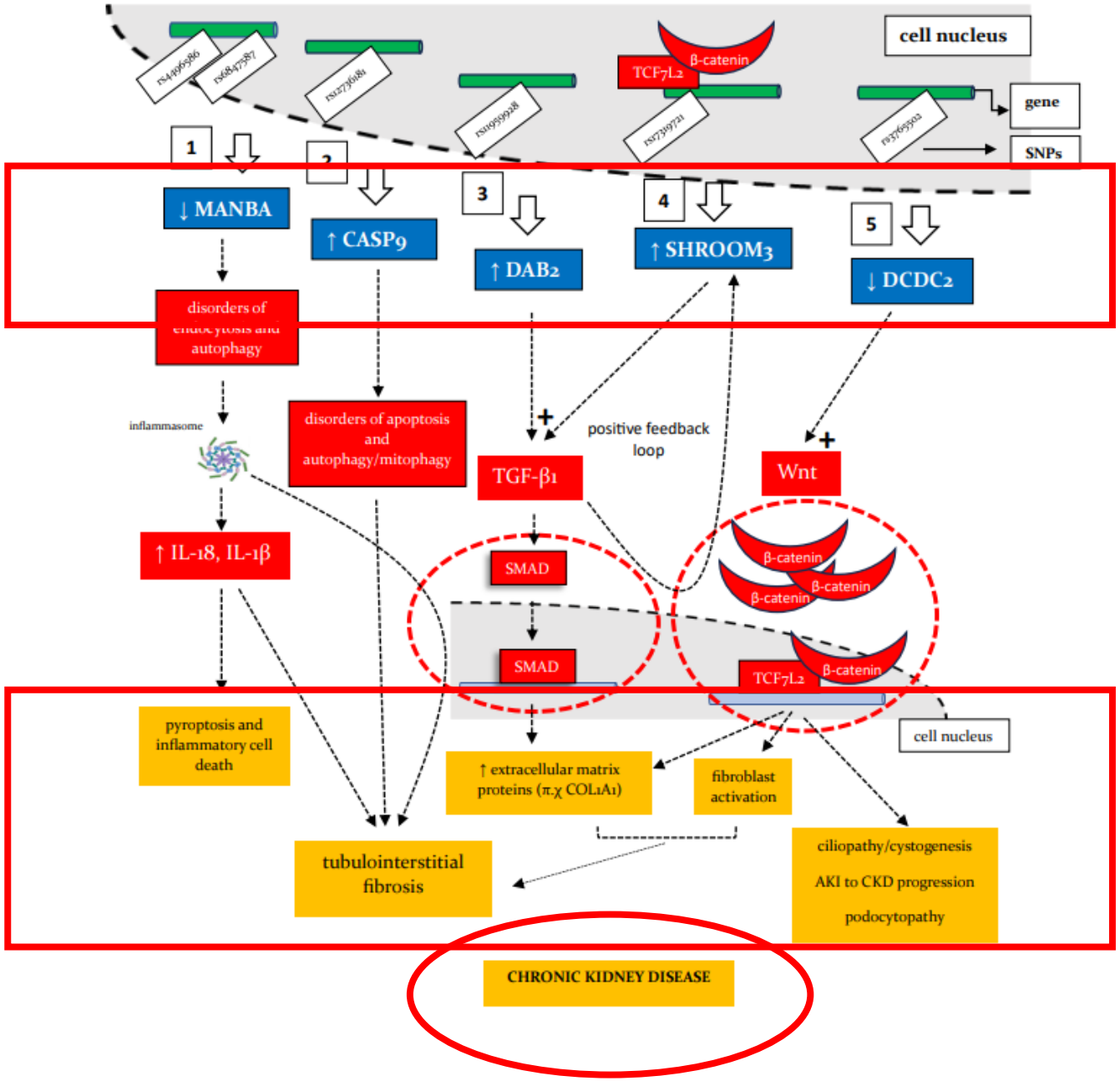
Anastasios Fountoglou[1], Constantinos Deltas[2], Ekaterini Siomou[3] and Evangelia Dounousi[1]

[1]Department of Nephrology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Dialysis Center, Nephroxenia Ioannina, Ioannina, Greece
[2]School of Medicine and biobank.cy Center of Excellence in Biobanking and Biomedical Research, University of Cyprus, Nicosia 2109, Cyprus
[3]Department of Pediatrics, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece
Correspondence to: Evangelia Dounousi; E-mail: evangeldou@gmail.com

ABSTRACT

Chronic kidney disease (CKD) is a major health problem with an increasing epidemiological burden, and is the 16th leading cause of years of life lost worldwide. It is estimated that more than 10% of the population have a variable stage of CKD, while about 850 million people worldwide are affected. Nevertheless, public awareness remains low, clinical access is inappropriate in many circumstances and medication is still ineffective due to the lack of clear therapeutic targets. One of the main issues that drives these problems is the fact that CKD remains a clinical entity with significant causal ambiguity. Beyond diabetes mellitus and hypertension, which are the two major causes of kidney disease, there are still many gray areas in the diagnostic context of CKD. Genetics nowadays emerges as


MANBA
DAB2
↓ DCDC2
PCT
↑ CASP9
SHROOM3
SHROOM3
UMOD
DCT


cell nucleus
β-catenin
TCF7L2
gene
SNPs
rs4496586
rs6847387
rs2736681
rs1959928
rs739721
rs3765502
1
2
3
4
5
↓ MANBA
↑ CASP9
↑ DAB2
↑ SHROOM3
↓ DCDC2
disorders of endocytosis and autophagy
inflammasome
disorders of apoptosis and autophagy/mitophagy
positive feedback loop
TGF-β1
Wnt
↑ IL-18, IL-1β
SMAD
SMAD
β-catenin
β-catenin
β-catenin
β-catenin
TCF7L2
β-catenin
cell nucleus
pyroptosis and inflammatory cell death
↑ extracellular matrix proteins (π.χ COL1A1)
fibroblast activation
tubulointerstitial fibrosis
ciliopathy/cystogenesis
AKI to CKD progression
podocytopathy
CHRONIC KIDNEY DISEASE

what we have learned so far;

- genetic risk variants are not associated with the occurrence of major risk factors for CKD such as diabetes and hypertension
- kidney damage appears to be mediated through a possible increase in the vulnerability of the renal parenchyma to the action of these nephrotoxic risk factors
- multiple “small” damage hits to the structural and functional integrity of kidney make the latter particularly vulnerable to the major stress from the action of major CKD risk factors
- the majority of the genes that are implicated in this vulnerability are expressed at tubulointerstitial level of the kidney (tubulo-centric view of CKD)

Jenga theory of CKD

Normal kidney

Kidney with risk SNPs and genetic predisposition of CKD

Genetic predisposition and/or a dominant genetic variant

Major risk factor

Chronic kidney disease


THANK
YOU
FOR
YOUR
ATTENTION