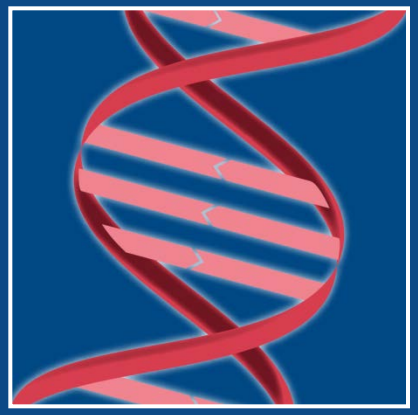
Nephro Update Europe 2018

5-6 October, Budapest

Genetic Diseases



Olivier Devuyst, Switzerland

Conflicts of Interest

Research Support/Lecturing/Consulting:

Otsuka Pharmaceuticals, SANOFI, Goldfinch Bio

Genetic causes of kidney diseases are increasingly recognized

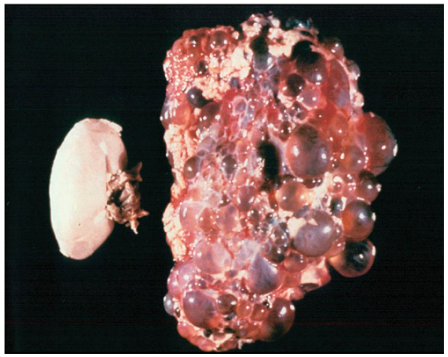
More than 200 different inherited kidney disorders have been described.

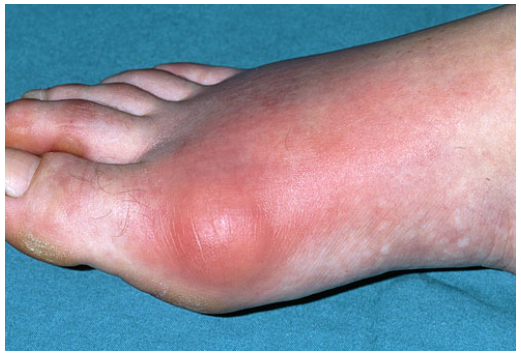
Collectively, these disorders are involved in

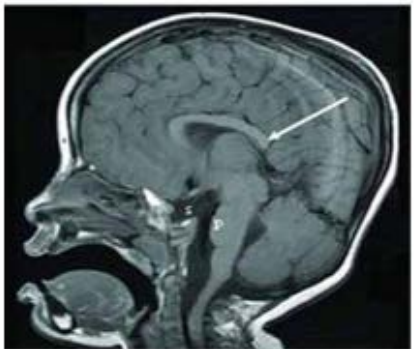
up to 20% of patients with end-stage renal disease.

Some of the inherited disorders affect only a handful of people whereas

others, such as ADPKD, affect more than 750.000 patients in Europe.







Devuyst O et al. Lancet 2014; 383: 1844-59

ERKNet

The European Rare Kidney Disease Reference Network

ERKNet is a consortium of 38 expert pediatric and adult nephrology centers in 12 European countries providing healthcare to more than 40,000 patients with rare disorders of the kidneys.

Subtopics:

1. Next Generation Sequencing in kidney disorders
2. Novel pathways in genetic disorders
3. Polycystic kidney disease: New genes & treatment
4. New technologies

Subtopic 1

Next Generation Sequencing in kidney disorders

State of the Art

• Genetic disorders are involved in up to 20% of adult and in the vast majority of pediatric kidney disorders.

• Obtaining a genetic diagnosis may be critical for the management of a disease (work-up, follow-up, prognosis,…). It will inform on disease mechanism.

• Recent advances in next-generation sequencing allow to perform genome-wide analysis at a modest cost. Whole-exome sequencing (WES) allows selective sequencing of the protein-coding regions of the genome, enriched for disease-associated variants.

• Application of these methods offers perspectives for precision medicine: individualized diagnosis and prognosis, risk stratification, and optimized work-up and follow-up.

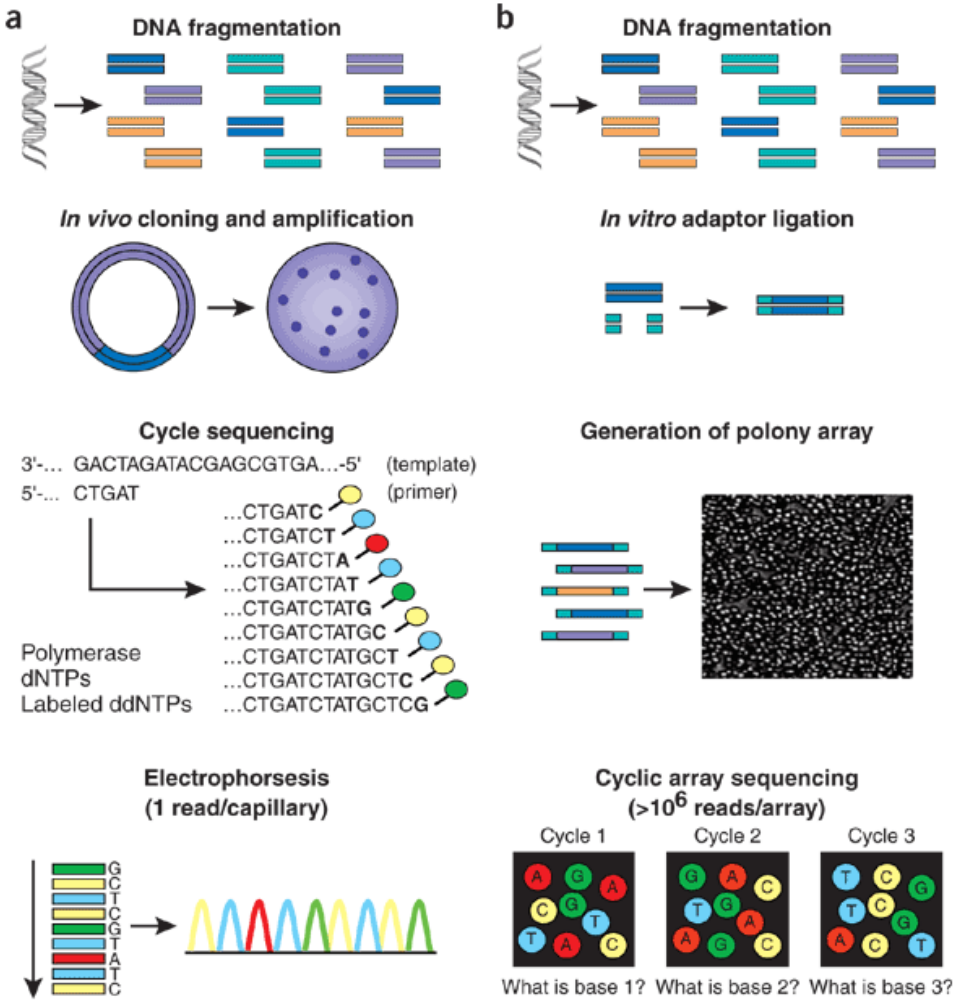
• The clinical utility of these approaches to a broad spectrum of kidney diseases remains unclear.

Renkema et al. Nat Rev Nephrol 2014; 10: 433-44
Groopman et al. Nat Rev Nephrol 2018; 14: 83-104

Next-generation DNA Sequencing

Sanger Sequencing

Next-generation Sequencing

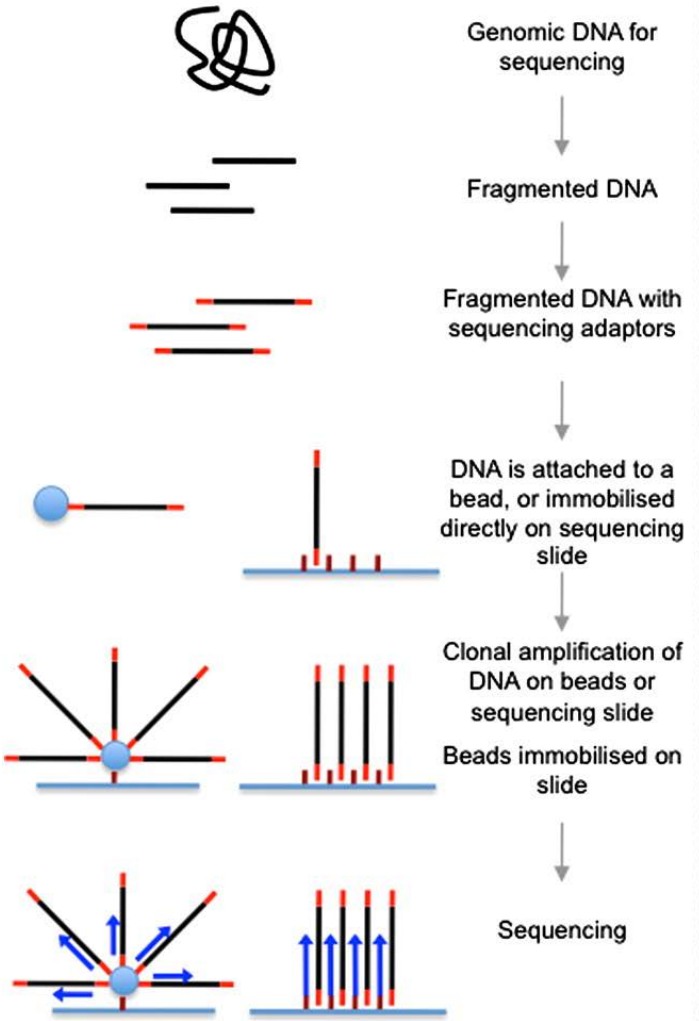


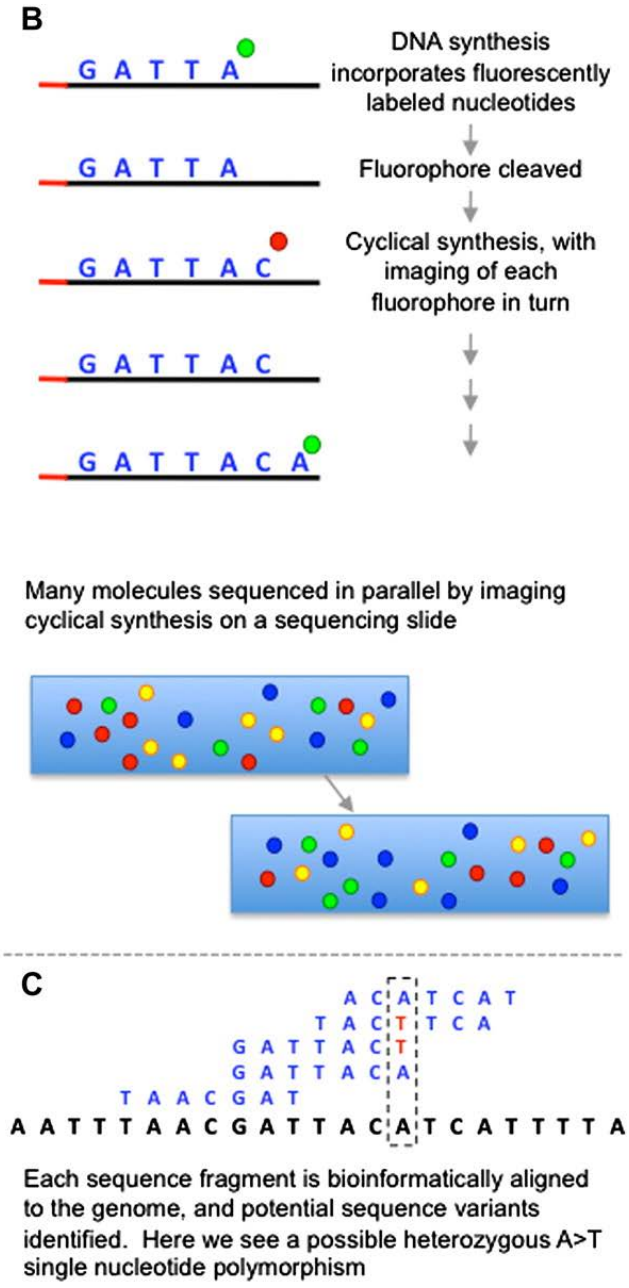
Advantages:

- Construction of a sequencing library → clonal amplification to generate sequencing data
  - No in vivo cloning, transformation, colony picking, etc…
- Array-based sequencing – multiple reads
  - Higher degree of parallelism than capillary-based sequencing

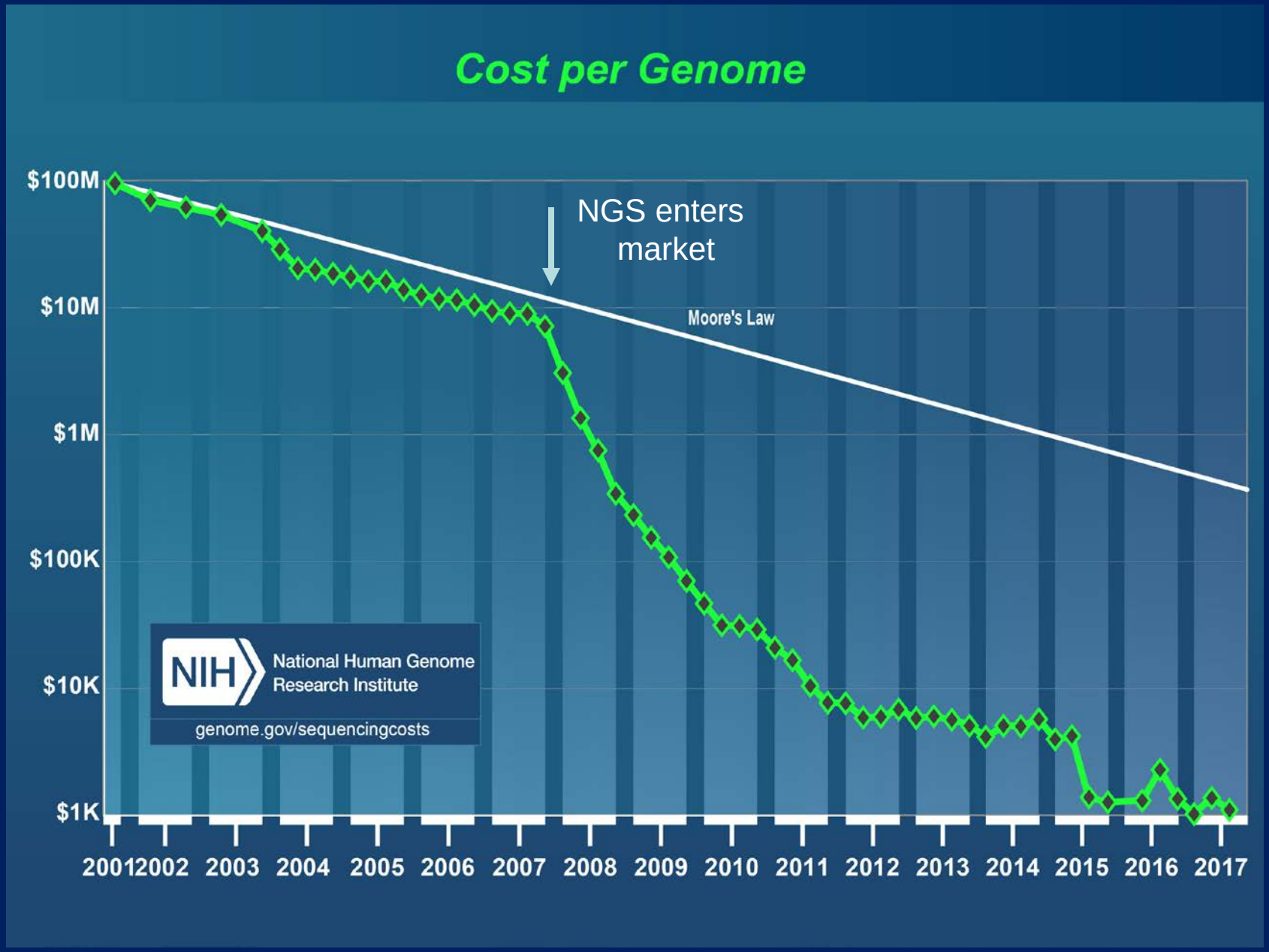
Shendure & Ji, Nat Biotechnol 2008; 26: 1135-45

NGS Basics





Ware JS et al. BMJ Heart 98: 4


Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
NGS enters market
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
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Next-generation Sequencing: Impact for Rare Diseases

- Development and validation of multigene panels: *simultaneous investigation of all relevant genes for a given phenotype*

  → Reduced costs and turn-around times

- Successful application multigene panels/NGS for diagnostic:
  - Alport syndrome
  - Steroid-resistant nephrotic syndrome
  - Nephronophthisis - ciliopathies
  - Tubulopathies

EURenOmics

Simultaneous sequencing of 37 genes identified causative mutations in the majority of children with renal tubulopathies

Emma J. Ashton[1,12], Anne Legrand[2,3,12], Valerie Benoit[4], Isabelle Roncelin[2], Annabelle Venisse[2], Maria-Christina Zennaro[2,3,5], Xavier Jeunemaitre[2,3,5], Daniela Iancu[6], William G. van't Hoff[7], Stephen B. Walsh[6], Nathalie Godefroid[10], Annelies Rotthier[8], Jurgen Del Favero[8], Olivier Devuyst[9,10], Franz Schaefer[11], Lucy A. Jenkins[1], Robert Kleta[6,7], Karin Dahan[4,10], Rosa Vargas-Poussou[2,3,12] and Detlef Bockenhauer[6,7,12]

- *These results demonstrate a high diagnostic yield of genetic testing in children with a clinical diagnosis of renal tubulopathy.*
- *Genetic testing established a definitive diagnosis in almost two-thirds of patients – informing prognosis, management and genetic counseling.*

Ashton EJ et al. Kidney Int 2018; 93:961-7

Multiplex Testing for Tubulopathies: Key Points

• This kit produced 571 amplicons covering 37 genes associated with tubulopathies followed by massive parallel sequencing and bioinformatic interpretation. Identified mutations were confirmed by Sanger sequencing.

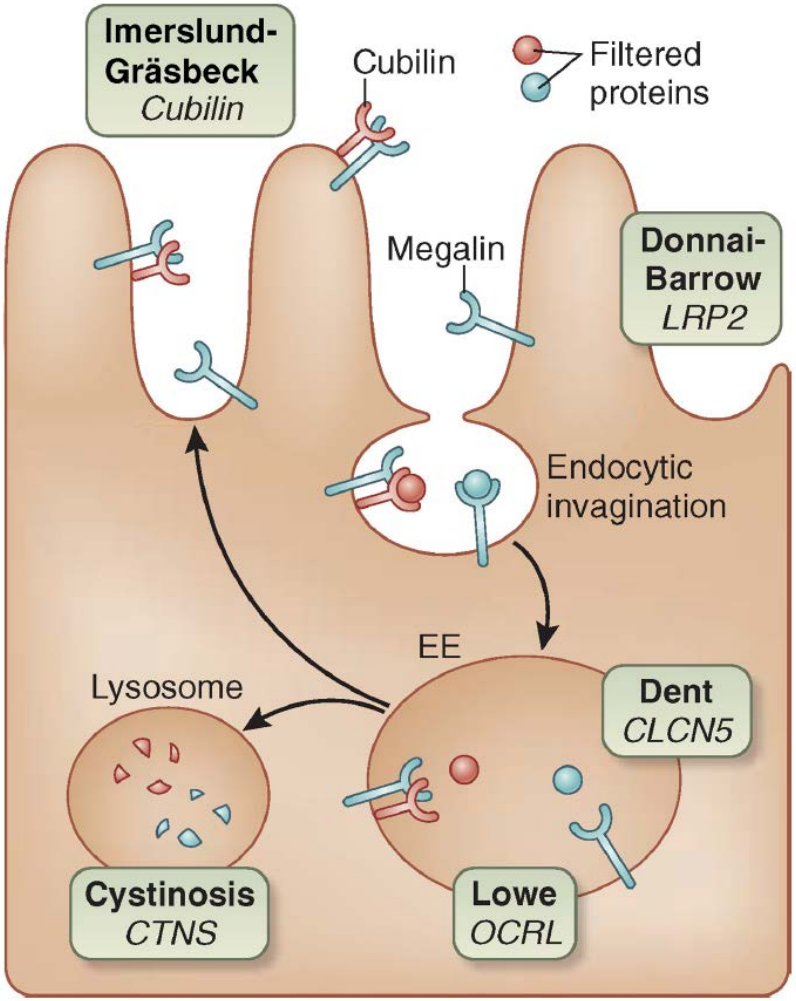
• A genetic diagnosis was established in 64% (245/384 index patients). Most common: 174 patients with Bartter/Gitelman syndrome and 76 with distal RTA.

• Genetic testing changed the clinical diagnosis in 16 cases (4%) and provided insights into the phenotypic spectrum of the respective disorders.

• Thus, genetic testing helped establish a definitive diagnosis in almost two-thirds of patients thereby informing prognosis, management and genetic counseling.

Ashton EJ et al. Kidney Int 2018; 93:961-7

Renal Fanconi Syndrome: Rare Disorders Targeting the Endolysosomal System



Willnow TE. Kidney Int 2017; 91:776-8

MUTATION UPDATE

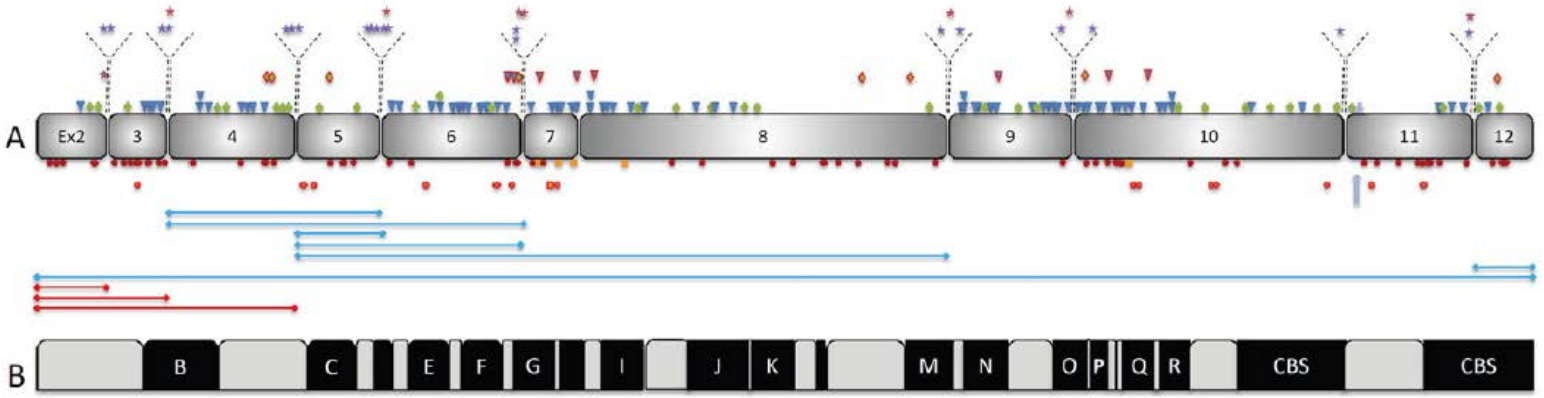
Human Mutation

HUMAN MUTATION, Vol. 36, No. 8, 743–752, 2015

Mutation Update of the *CLCN5* Gene Responsible for Dent Disease 1

Official Journal of HGV Human Genome Variation Society

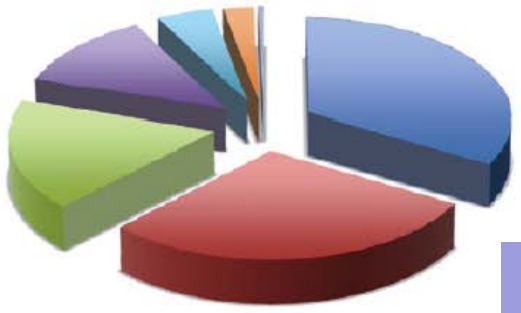
- 234 mutations
- 170 families



Type of mutation (n=234)

C

- Missense (33.33%)
- Frameshift (29.05%)
- Nonsense (17.52%)
- Splicing (12.39%)
- Large deletion (4.70%)
- Inframe (2.56%)
- Other (Alu insertion) (0.42%)
- Novel mutations



De novo mutation rate ~ 10%

Mansour-Hendili et al. Hum Mutat. 2015 Aug;36(8):743-52

Dent Disease: Renal Fanconi Syndrome & Kidney Stones

Dent's disease is characterized by manifestations of proximal tubule (PT) dysfunction associated with hypercalciuria, nephrolithiasis, nephrocalcinosis, and progressive renal failure. Low-molecular-weight (LMW) proteinuria represents the most consistent manifestation of Dent's disease, detected in almost all affected males and obligate female carriers.

Devuyst & Thakker, Orphanet J Rare Dis 2010; 5:28

Dent Disease: Phenotype Heterogeneity

Clinical data from 377 male patients belonging to 334 families

- Micro or macrohaematuria (n = 71)
- Polyuria/polydipsia (31/43)
- Proteinuria (n = 57): median value 1.28 g/24 hr
- **Proteinuria in the nephrotic range (n = 13)**
- Enuresis (n = 5)
- Hypomagnesaemia (4/30)
- Night blindness responsive to vitamin A

→ *New phenotypes: specific management and treatment*

Blanchard et al. Kidney Int 2016; 90: 430-9

BASIC RESEARCH www.jasn.org

Whole-Exome Sequencing Identifies Causative Mutations in Families with Congenital Anomalies of the Kidney and Urinary Tract

Van der Ven et al. J Am Soc Nephrol. 2018; 29: 2348-61

clinical investigation www.kidney-international.org

Whole exome sequencing frequently detects a monogenic cause in early onset nephrolithiasis and nephrocalcinosis

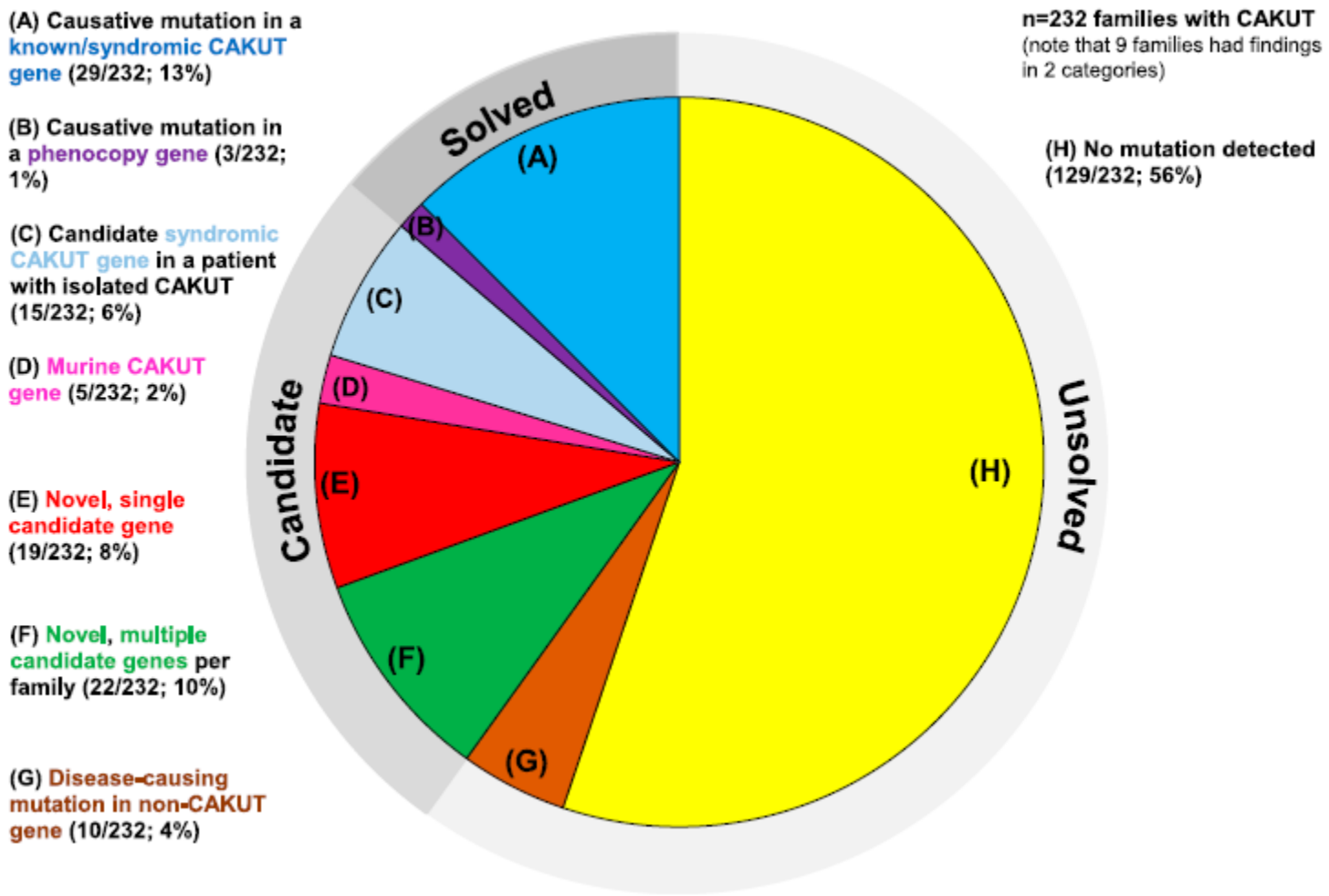
see commentary on page 15

Daga et al. Kidney Int. 2018; 93: 204-13

Whole Exome Sequencing of Patients with Steroid-Resistant Nephrotic Syndrome

Warejko et al. Clin J Am Soc Nephrol 2018;13: 53–62

Number and percentage of 232 congenital anomalies of the kidney and urinary tract (CAKUT) families in which a causative mutation in a known monogenic CAKUT gene (14%) or a candidate gene(s) (16%) was detected by whole-exome sequencing.



Amelie T. van der Ven et al. JASN 2018;29:2348-2361

Whole Exome Sequencing of Patients with Steroid-Resistant Nephrotic Syndrome

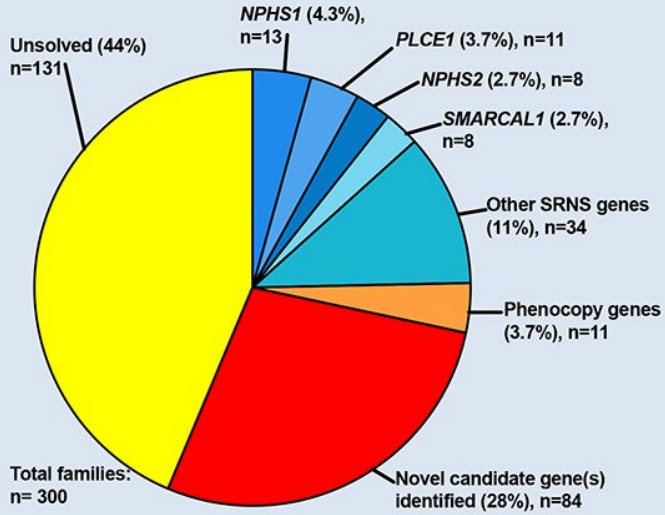
METHODS

335 individuals from **300** families with steroid resistant nephrotic syndrome

Whole exome sequencing performed

Variant calling and filtering

OUTCOMES: 25% of families had a causative mutation detected in candidate genes



CONCLUSION A potentially causative genetic mutation can be identified in many patients with steroid-resistant nephrotic syndrome.

Jillian K. Warejko, Weizhen Tan, et al. Whole Exome Sequencing of Patients with Steroid-Resistant Nephrotic Syndrome. CJASN doi: 10.2215/CJN.04120417.

ORIGINAL RESEARCH

Annals of Internal Medicine

Whole-Exome Sequencing in Adults With Chronic Kidney Disease

A Pilot Study

• Aim: To study the diagnostic utility of WES in a selected referral population of adults with CKD.

• Observational cohort in a major academic medical center. 92 adults with CKD of unknown cause or familial nephropathy or hypertension (enriched cohort).

• Whole-exome sequencing provided a diagnosis in 22 of 92 patients (24%), including 9 probands with CKD of unknown cause and encompassing 13 distinct genetic disorders.
→ *COL4A3/4/5, LMX1B, GLA, CHD7, CLCN5, HNF1B, UMOD, SCNN1G, SLC12A3, TRPC6*

• The results affected clinical management in most identified cases, including initiation of targeted surveillance, familial screening to guide donor selection for transplantation, and changes in therapy.

Whole-exome sequencing identified diagnostic mutations in 24% of adults with CKD of many causes. Promising – needs further study of the utility of WES for patients with CKD.

Lata et al. Ann Intern Med 2018; 168: 100-9

Take-Home Messages

• WES can provide a molecular-level diagnosis, supporting its utility as part of the clinical diagnostic work-up.

• Diagnostic yield varies according to the type of disorder (pediatric development, tubulopathies, …)

• Limits of WES: Not uniform coverage
→ difficulty to cover some coding segments (ex: PKD1, MUC1)
Limited ability to detect genomic imbalances, does not assess mutations in non-coding regions
Difficulties to test adults, segregation
• Incidental findings (BRCA2, …)
• Interpretation of genomic findings: ExAC, gnomAD (frequency in population)
New variant annotation algorithms

• Screening more relevant genes at once → genetic diagnosis, novel phenotypes
• Periodic reevaluation when new disease genes identified

Subtopic 2

Novel pathways in genetic disorders

State of the Art

• The complexity of glomerular and tubular structures is reflected by the large number of disease mechanisms involved in kidney disorders.

• Analysis of rare inherited kidney disorders (< 1:2,000) offers the opportunity to decipher complex mechanisms operating in various nephron segments.

• In turn, these advances may yield new therapeutic targets – with innovative compounds or repurposed drugs (already used in other indications).

• Mechanisms involved in rare diseases are often relevant for more common, complex and acquired disorders.

Devuyst et al. Lancet 2014; 383: 1844-59
Eckardt et al. Lancet 2013; 382: 158-69

A Single-Gene Cause in 29.5% of Cases of Steroid-Resistant Nephrotic Syndrome

- In young adults and children, nephrotic syndrome is classified by its response to a standardized steroid therapy as steroid-sensitive NS (SSNS) versus steroid-resistant NS (SRNS).
- SRNS constitutes the second most frequent cause of ESRD in the first two decades of life (NorthAmerican Pediatric Renal Trials and Collaborative Studies, 2008).
- For most patients, no curative treatment is available.
- Discovery of 27 recessive or dominant genes that, if mutated, cause SRNS has recently provided fundamental insights into mechanisms of this disease.

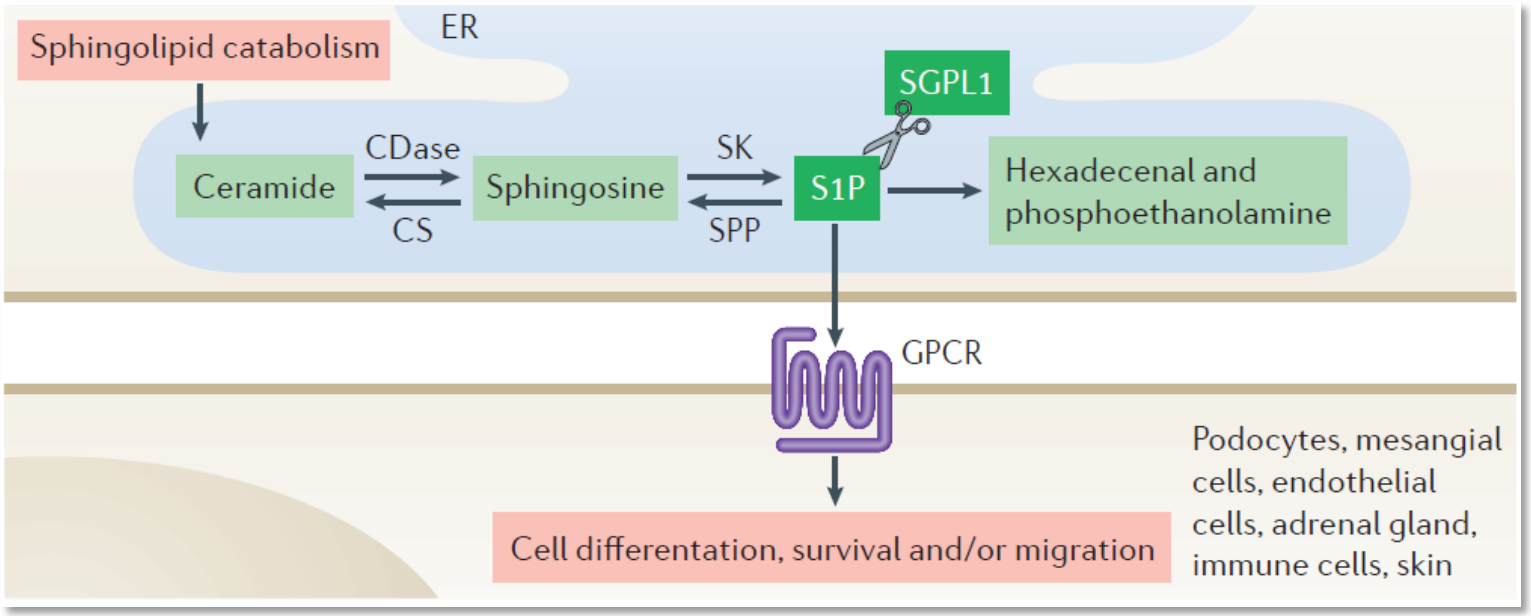
NGS in 1783 unrelated, international families with SRNS – 27 genes known to cause SRNS

→ ~30% of diagnosis: many more genes to discover

Sadowski et al. JASN 2015; 26: 1279-89

Mutations in sphingosine-1-phosphate lyase cause nephrosis with ichthyosis and adrenal insufficiency

- WES in 7 families with syndromic SRNS: Recessive mutations in SGPL1
- ER enzyme – final catabolic step of sphingolipid breakdown pathway
- Degrading sphingosine-1-phosphate (S1P) : multiple roles
- Mutation: altered sphingolipid catabolism & ceramide composition – podocytes & other cell types



Lovric et al. J Clin Invest 2017; 127: 912-28; Devuyst O. Nat Rev Nephrol 2018; 14: 80-82

ARTICLE

DOI: 10.1038/s41467-018-04193-w OPEN

Mutations in six nephrosis genes delineate a pathogenic pathway amenable to treatment

Shazia Ashraf et al.#

• WES identified recessive mutations in six different genes (*MAGI2, TNS2, DLC1, CDK20, ITSN1, ITSN2*) causing NS in 17 families with partially treatment-sensitive NS (pTSNS).

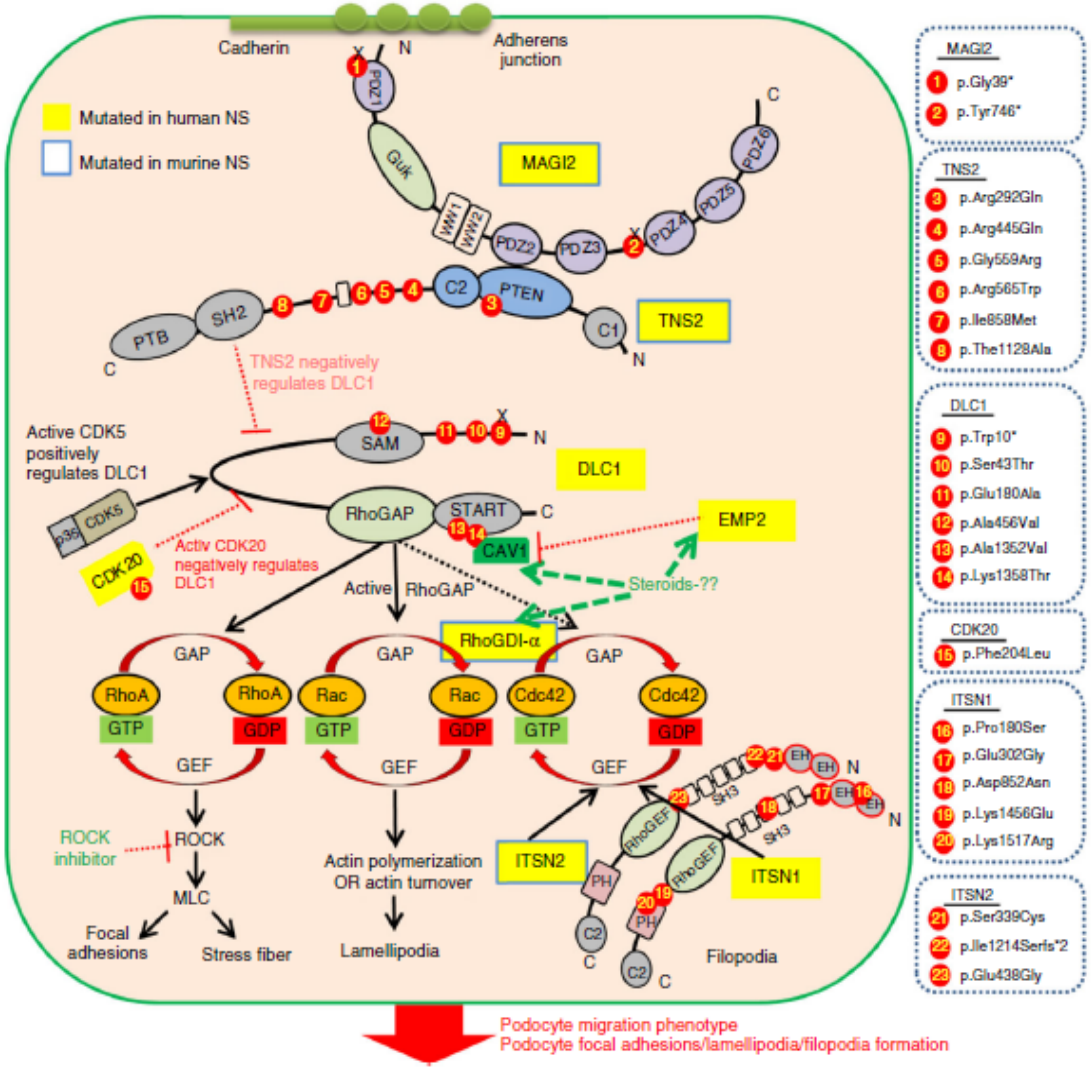
• These proteins interact and play a role in Rho-like small GTPase (RLSG) activity in podocytes. The mutant proteins are defective. They impact on the phenotype of podocytes (migration, focal adhesions, filipodia)

• Treatment with dexamethasone abolishes RhoA activation by knockdown of DLC1 or CDK20, indicating that steroid treatment in patients with pTSNS and mutations in these genes is mediated by this module.

•These data define a functional network of RhoA regulation, with potential therapeutic targets.

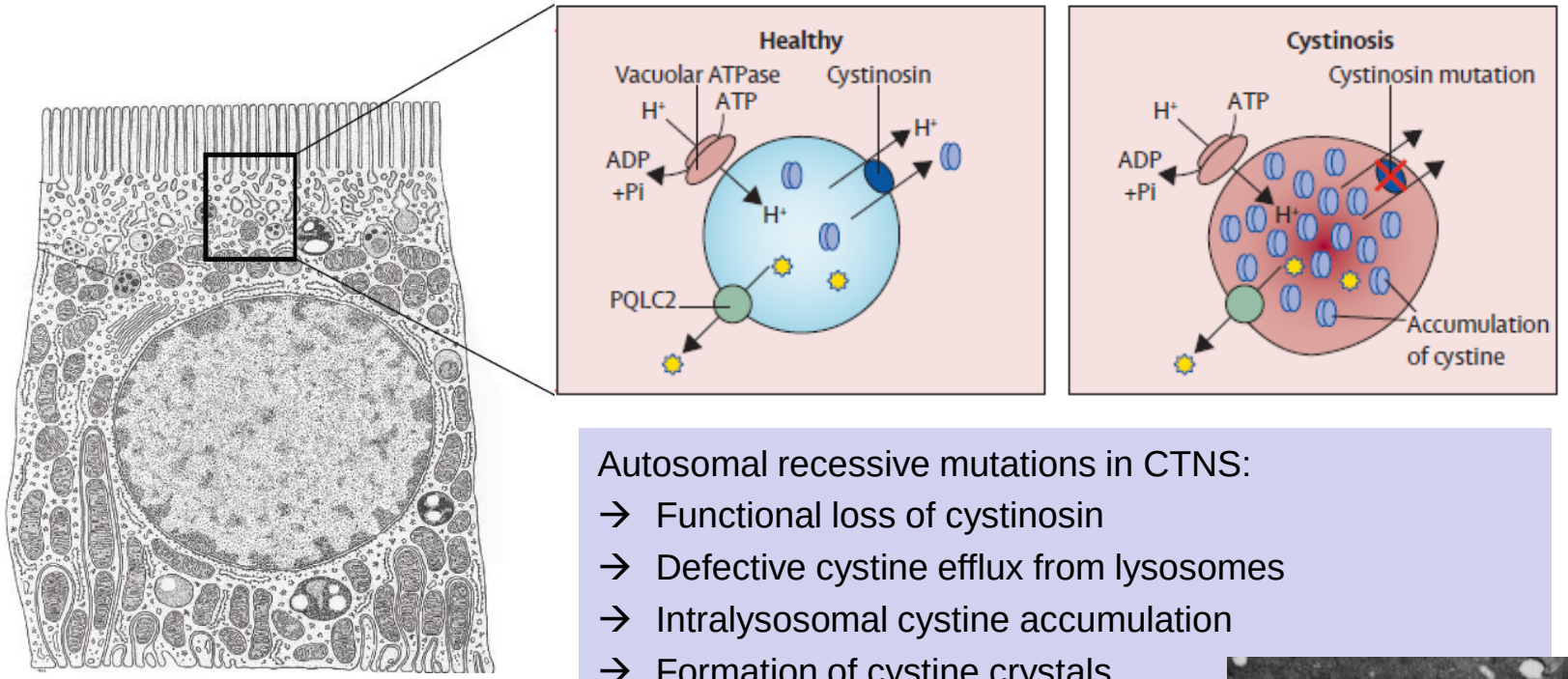
Ashraf et al. Nat Commun 2018; 9: 1960

Mutated Gene Products Interact to Regulate RhoA/Rac – Cytoskeletal Activation in Podocytes



Ashraf et al. Nat Commun 2018; 9: 1960

Cystinosis: Lysosomal Storage Disease



Autosomal recessive mutations in CTNS:

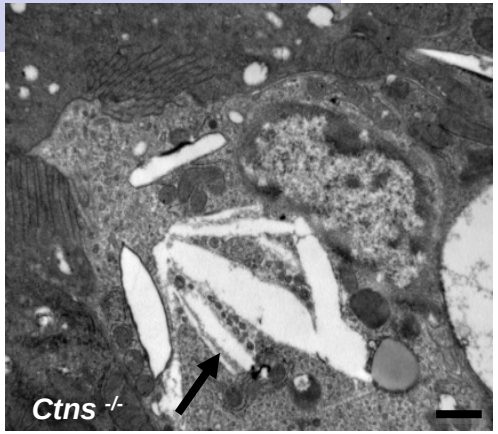
→ Functional loss of cystinosin

→ Defective cystine efflux from lysosomes

→ Intralysosomal cystine accumulation

→ Formation of cystine crystals

- Multisystemic – kidney, brain, eyes, muscles, endocrine, ...
- Cysteamine: limited effective, side-effects, poor tolerance



Devuyst O et al, Volume 383, Issue 9931, 24–30 May 2014, Pages 1844-1859

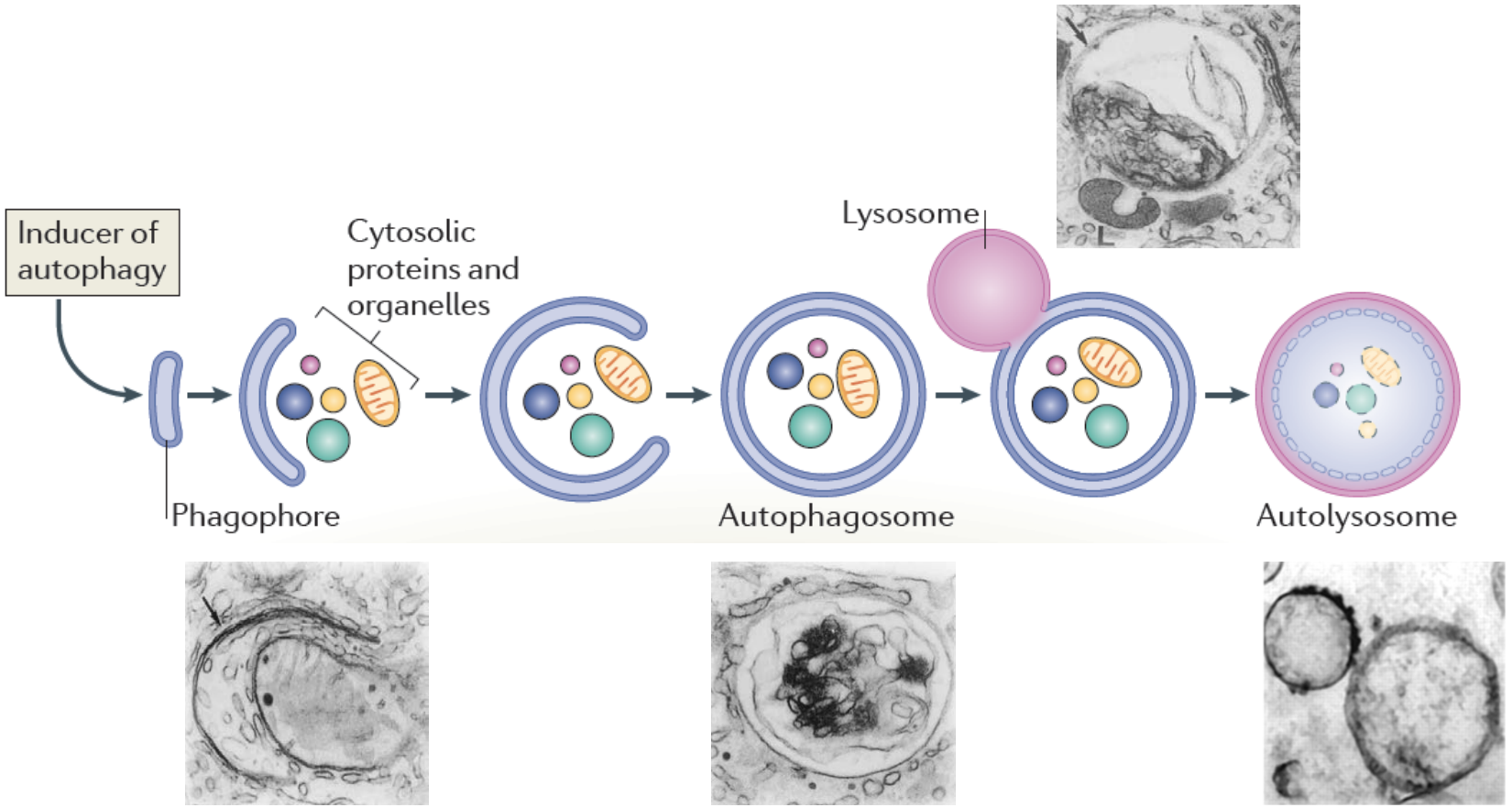
Time-course of Renal Phenotype in Nephropathic Cystinosis

Age	Symptom or Sign	Prevalence in Affected Patients
		%
6–12 mo	Renal Fanconi's syndrome (polyuria, polydipsia, electrolyte imbalance, dehydration, rickets, growth failure)	95
5–10 yr	Hypothyroidism	50
8–12 yr	Photophobia	50
8–12 yr	Chronic renal failure	95
12–40 yr	Myopathy, difficulty swallowing	20
13–40 yr	Retinal blindness	10–15
18–40 yr	Diabetes mellitus	5
18–40 yr	Male hypogonadism	70
21–40 yr	Pulmonary dysfunction	100
21–40 yr	Central nervous system calcifications	15
21–40 yr	Central nervous system symptomatic deterioration	2

Early dysfunction of proximal tubule – before renal failure

Gahl WA et al. NEJM 2002; 347: 111-21

Autophagy: a Vesicular Membrane Trafficking Targeting Cellular Materials to Lysosome

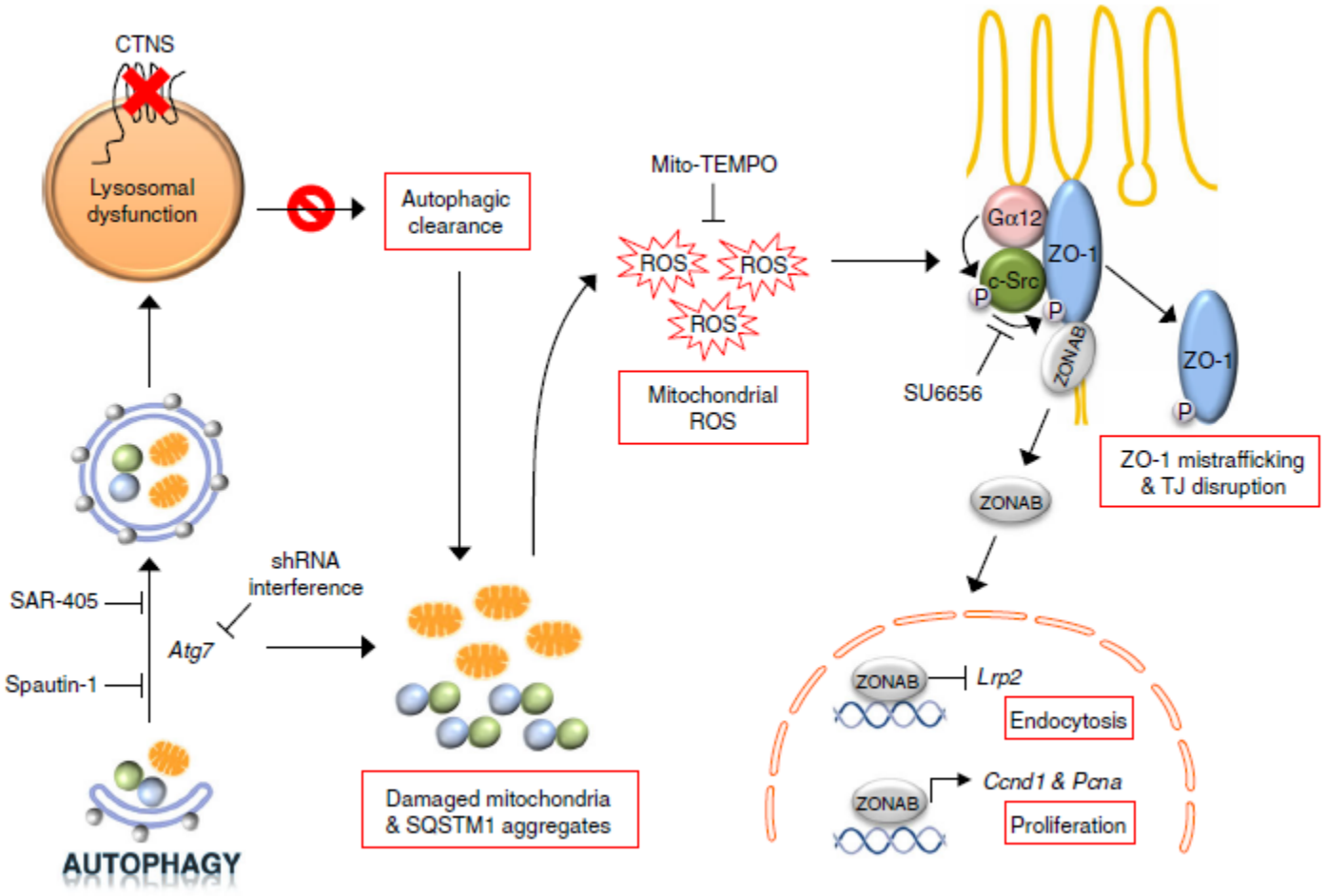


Mizushima N et al., Cell 2011; 147: 728-41

ARTICLE

DOI: 10.1038/s41467-017-02536-7 OPEN

Impaired autophagy bridges lysosomal storage disease and epithelial dysfunction in the kidney

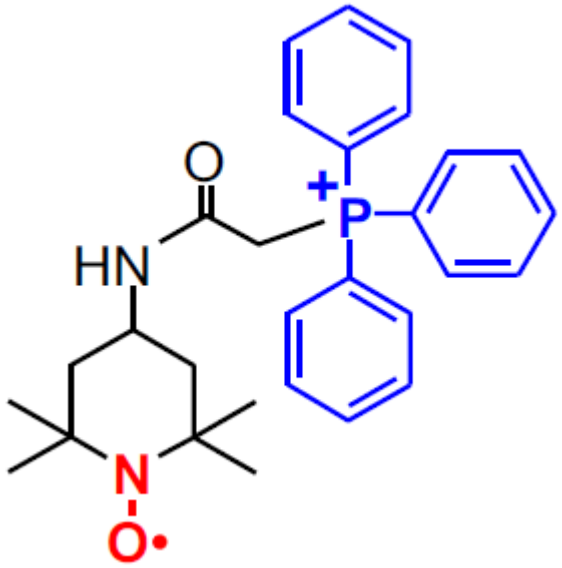


Festa BP et al. Nat Commun 2018; 9: 161

MitoTEMPO: mitochondrially targeted antioxidant, scavenger of mitochondrial superoxide

Combination of antioxidant piperidine nitroxide + lipophilic cation triphenylphosphonium

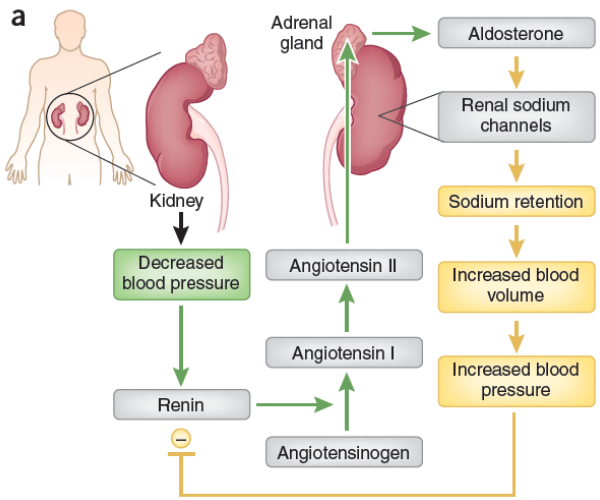
Ability to pass through lipid bilayers and accumulate several hundred-fold in mitochondria

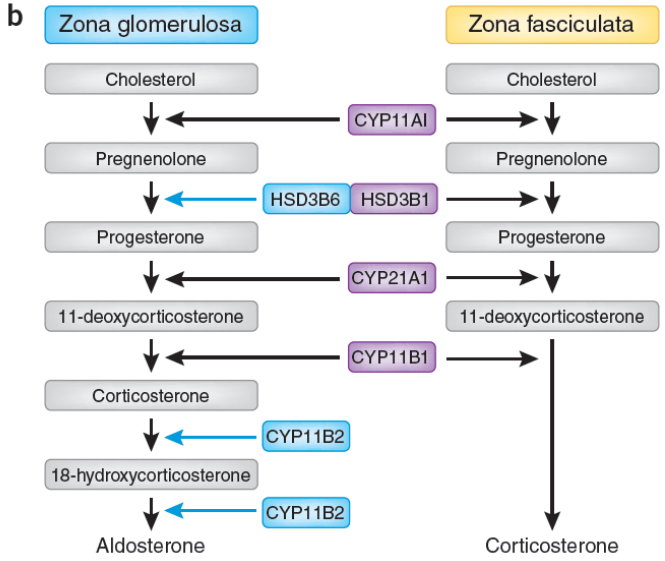


→ *Neutralizing mitochondrial ROS improves epithelial function in cystinosis.*

Festa BP et al. Nat Commun 2018; 9: 161

Mutations in Chloride Channels Cause Primary Aldosteronism





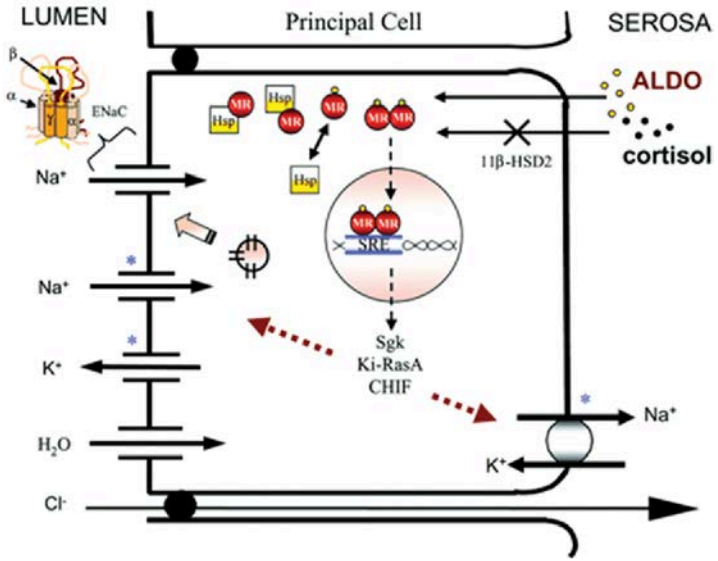
Role of aldosterone in blood pressure regulation

Primary aldosteronism:

- Autonomous aldosterone production
- Most common form of secondary hypertension
- 5% of hypertensive patients
- Increased CV risk

Mutations in genes coding for K^+ and Ca^{2+} channels, ATPases and CYP11B2 (aldosterone synthase)

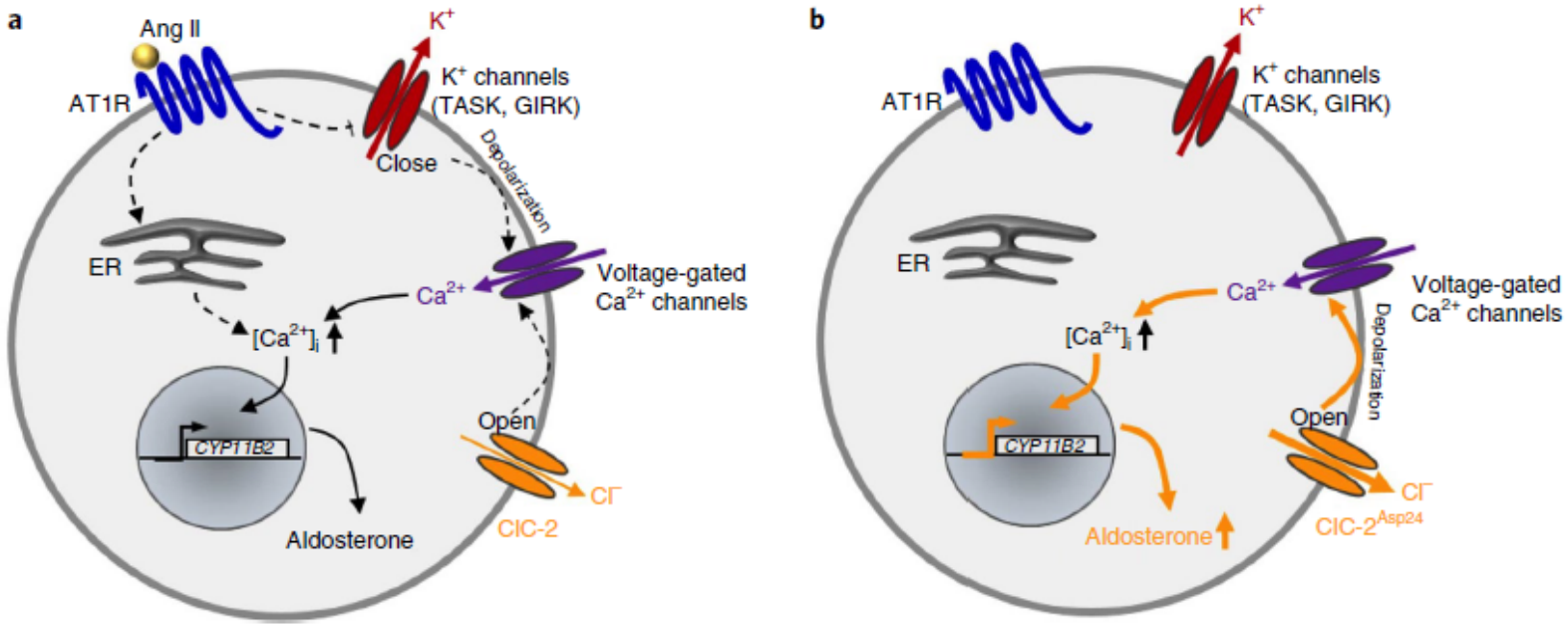
Aldosterone-producing adenomas



Rossier BC. Nat Med 2010; 16: 27-28

Scholl et al. Nat Genet 2018; 50: 349-54
Fernandes-Rosa et al. Nat Genet 2018; 50: 355-61

A gain-of-function mutation in the *CLCN2* chloride channel gene causes primary aldosteronism



Role of chloride and chloride channels in aldosterone biosynthesis – adrenal cortex

Take-Home Messages

• NGS and WES allowed to detect new pathways which operate in various cell types and cause various forms of nephrotic syndrome (steroid-response, syndromic). These pathways include altered sphingolipid catabolism & ceramide composition; and a multi-protein component of the cytoskeleton of the podocytes.

• The endolysosomal system sustains the reabsorptive activity of proximal tubule cells. Lysosomal storage diseases such as nephropathic cystinosis cause a massive losses of vital solutes in the urine. New studies show a link between defective lysosome-autophagy degradation pathways, accumulation of dyfunctional mitochondria and epithelial dysfunction. Treatment with mitochondrial anti-oxidant rescues the epithelial dysfunction.

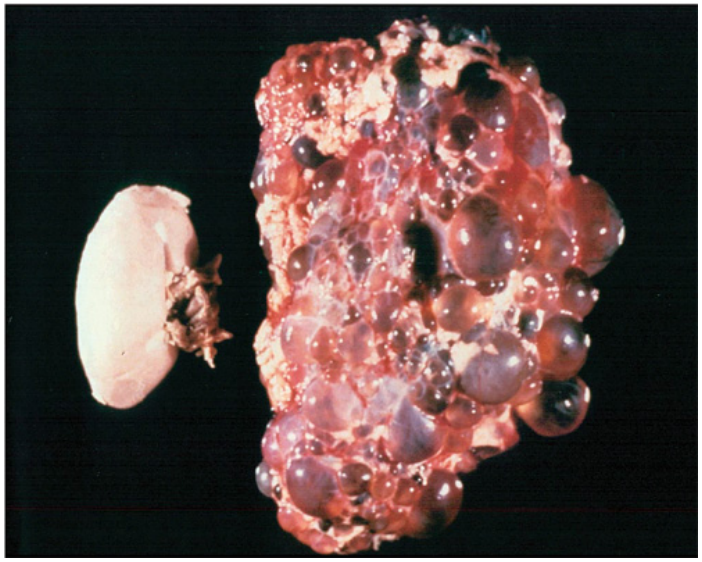
• Primary aldosteronism (PA) is the most common and curable form of secondary arterial hypertension. Heterozygous, activating mutations in the CLCN2 chloride channel operating in the adrenal glomerulosa cells have been identified in individuals with PA, increasing the expression of aldosterone synthase and causing an autonomous production of aldosterone.

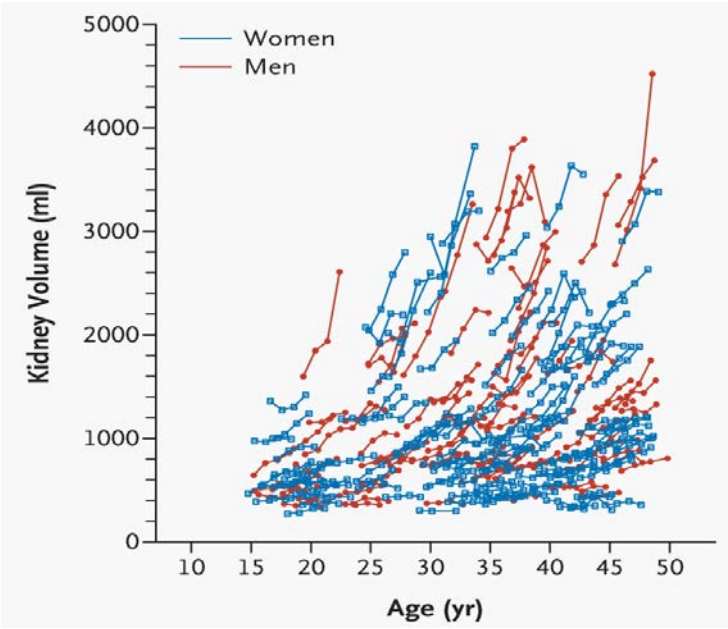
Subtopic 3

Polycystic kidney disease: New genes & treatment

Autosomal Dominant Polycystic Kidney Disease

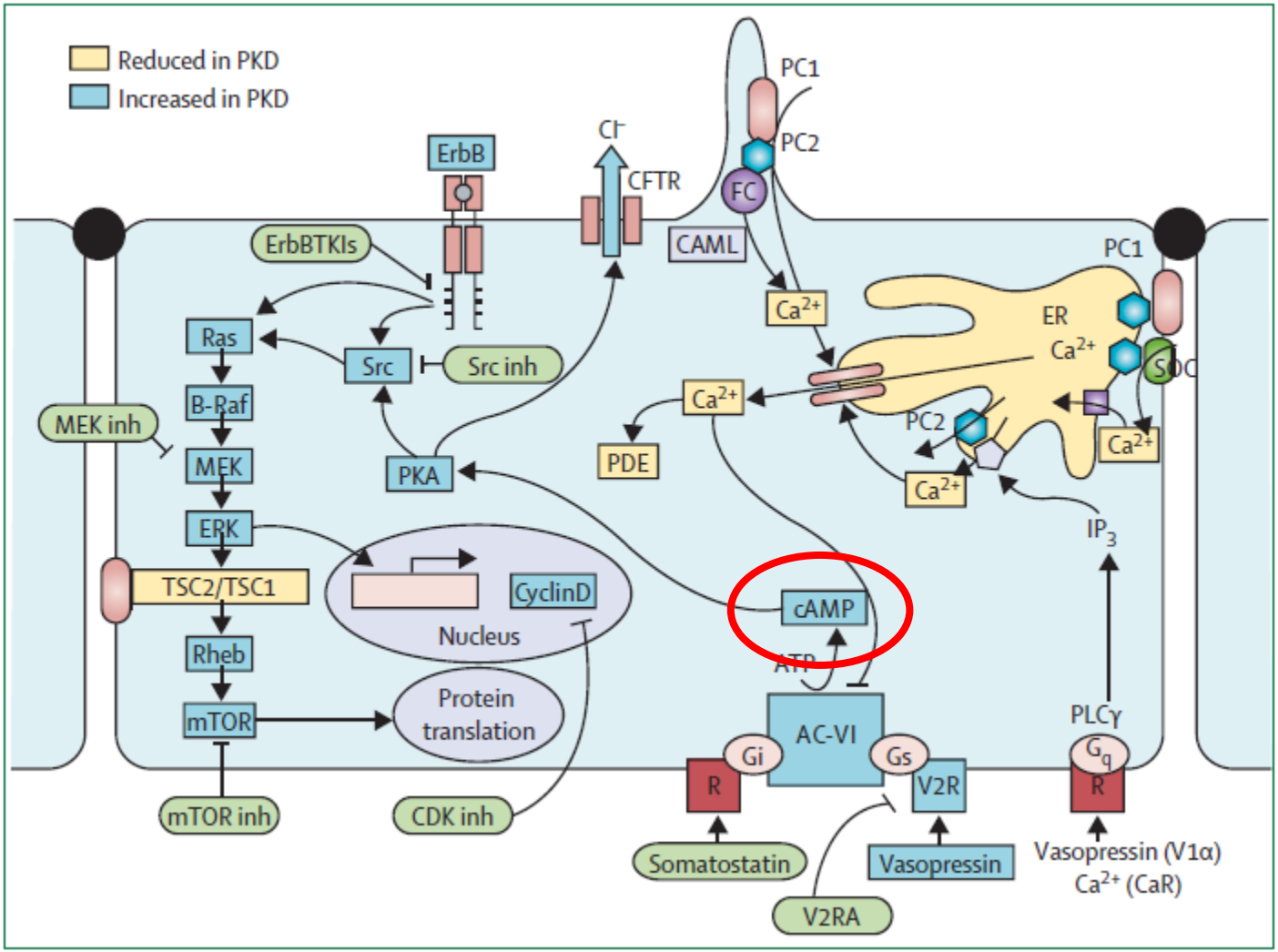
- Most frequent inherited nephropathy (1:400 - 1:1,000)
- Enlarged kidneys, multiple cysts < tubules
- Responsable for 4 - 10% of patients on dialysis – transplantation
- Genetic heterogeneity: *PKD1* (~75%) – *PKD2* (~15-18%)
- Third gene: *GANAB* – ER enzyme glucosidase II, quality control (Mild PKD – PLD)





Grantham et al. N Engl J Med 2006; 354 : 2122-30

Pathways Modulated in ADPKD

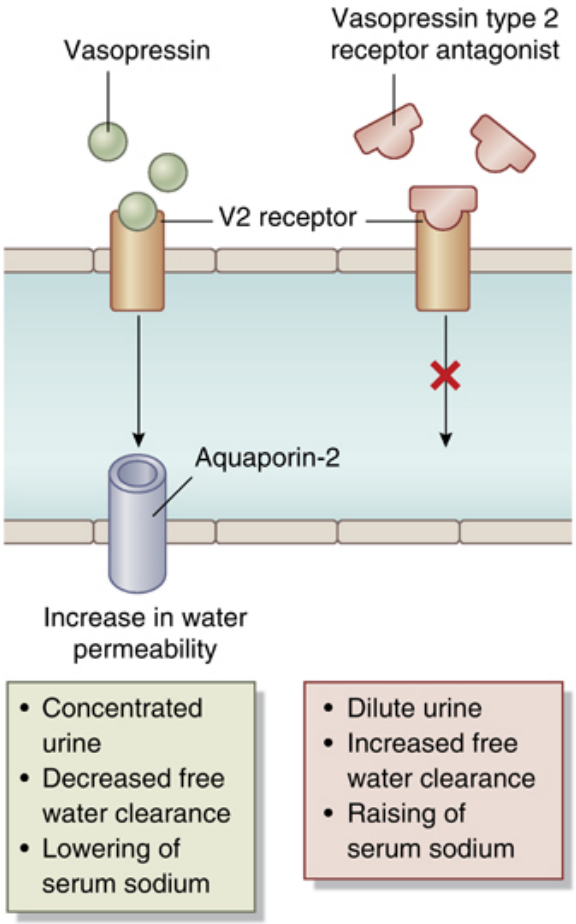


Torres VE et al. Lancet. 2007; 369: 1287-301

European Medicines Agency

Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Jared J. Grantham, M.D., Eiji Higashihara, M.D., Ph.D., Ronald D. Perrone, M.D., Holly B. Krasa, M.S., John Ouyang, Ph.D., and Frank S. Czerwiec, M.D., Ph.D., for the TEMPO 3:4 Trial Investigators*



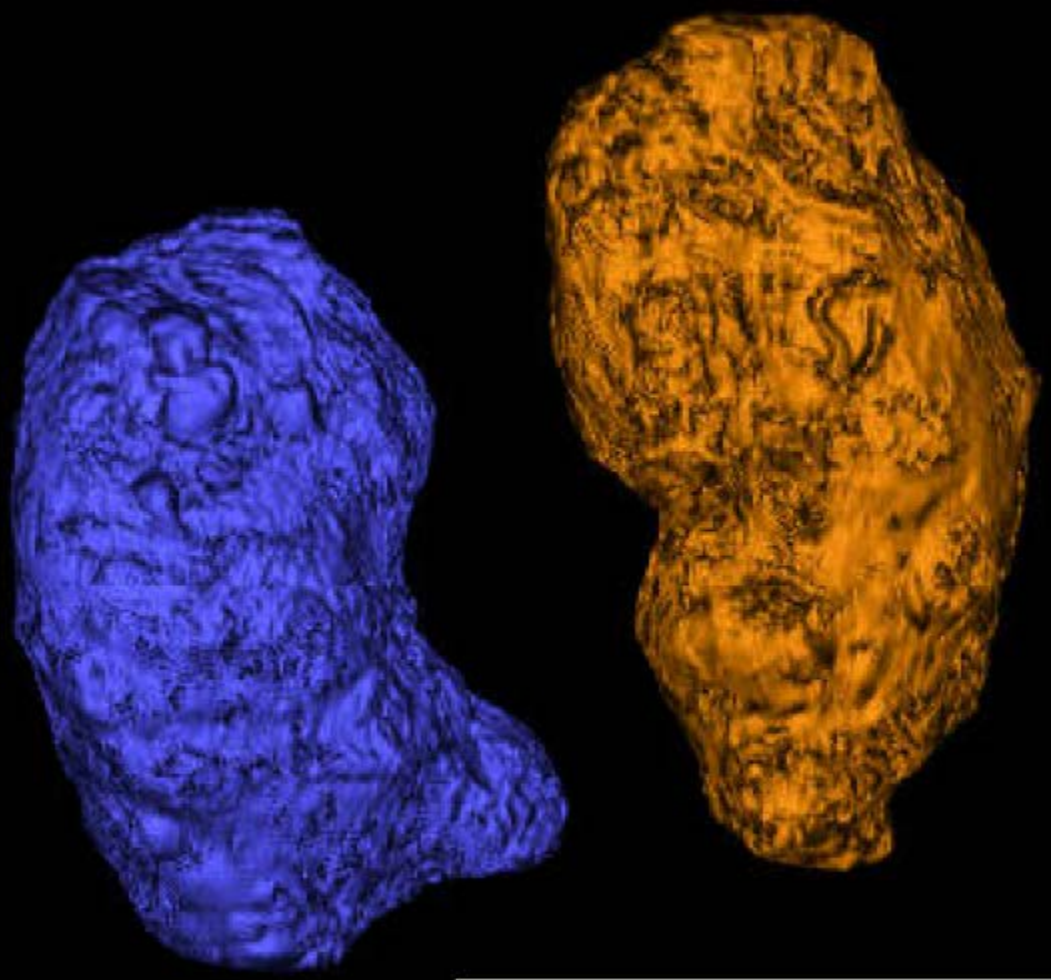
27/02/2015

Jinarc recommended for approval in ADPKD

The EMA has recommended granting a marketing authorisation to Jinarc (tolvaptan). Jinarc is indicated to slow the progression of cyst development and failing kidney function in adult patients with ADPKD.
Jinarc is for use in patients with normal to moderately reduced kidney function who have rapidly progressing ADPKD.

Torres VE et al. NEJM 2012; 367: 2407-18
Rosner MH. Kidney Int 2012; 82:1154-6

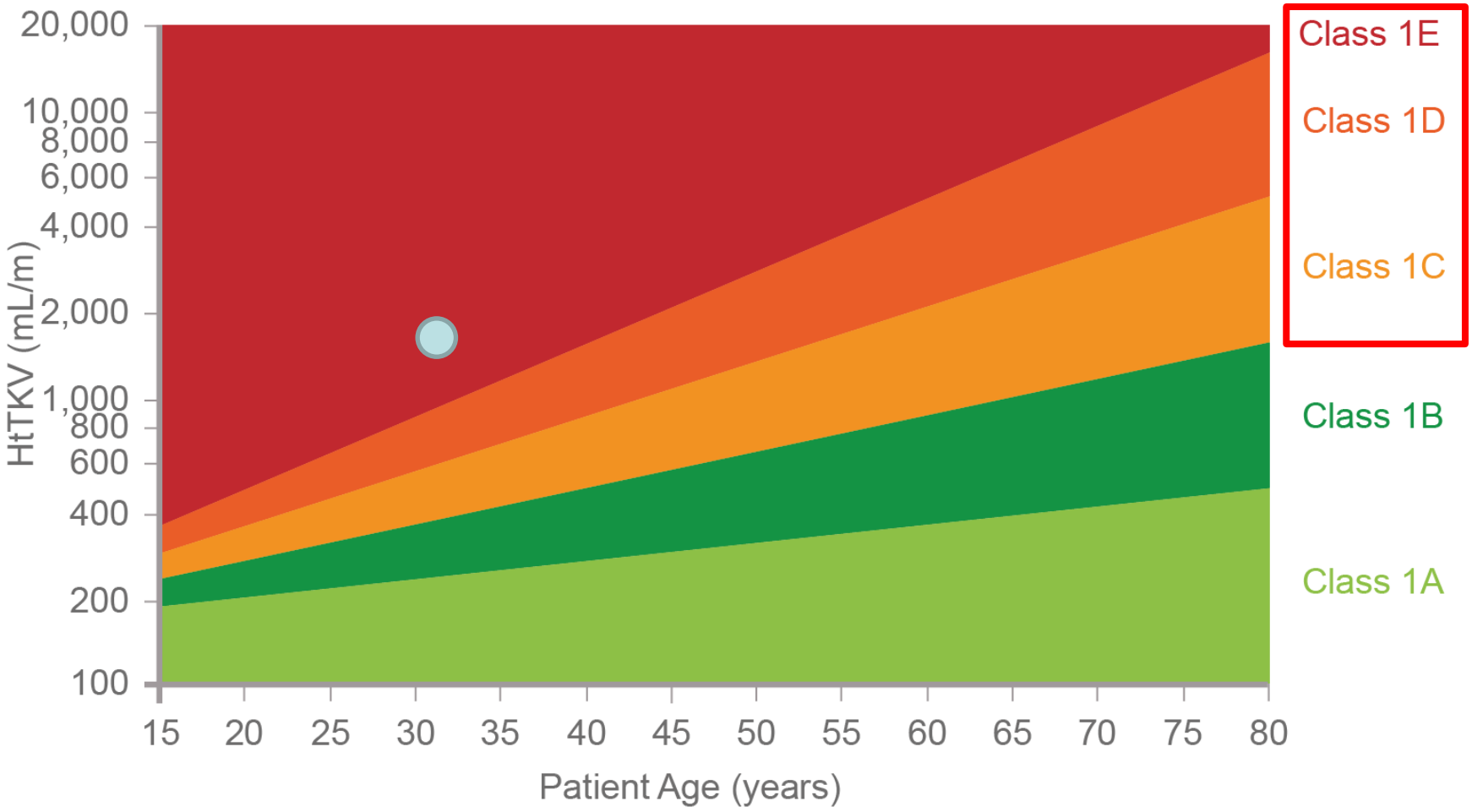
Case T. D. – 32 years-old



Region	Volume (ml)	Mean Value
REIN DRT	1266.26	38.4 ± 21.2
REIN GCHE	1545.56	52.4 ± 26.5
Total	2811.82	

MRI – TKV
Semi-auto point counting

Case T. D. – 32 years-old



Irazabal MV, et al. (2015) J Am Soc Nephrol. 26(1):160-72

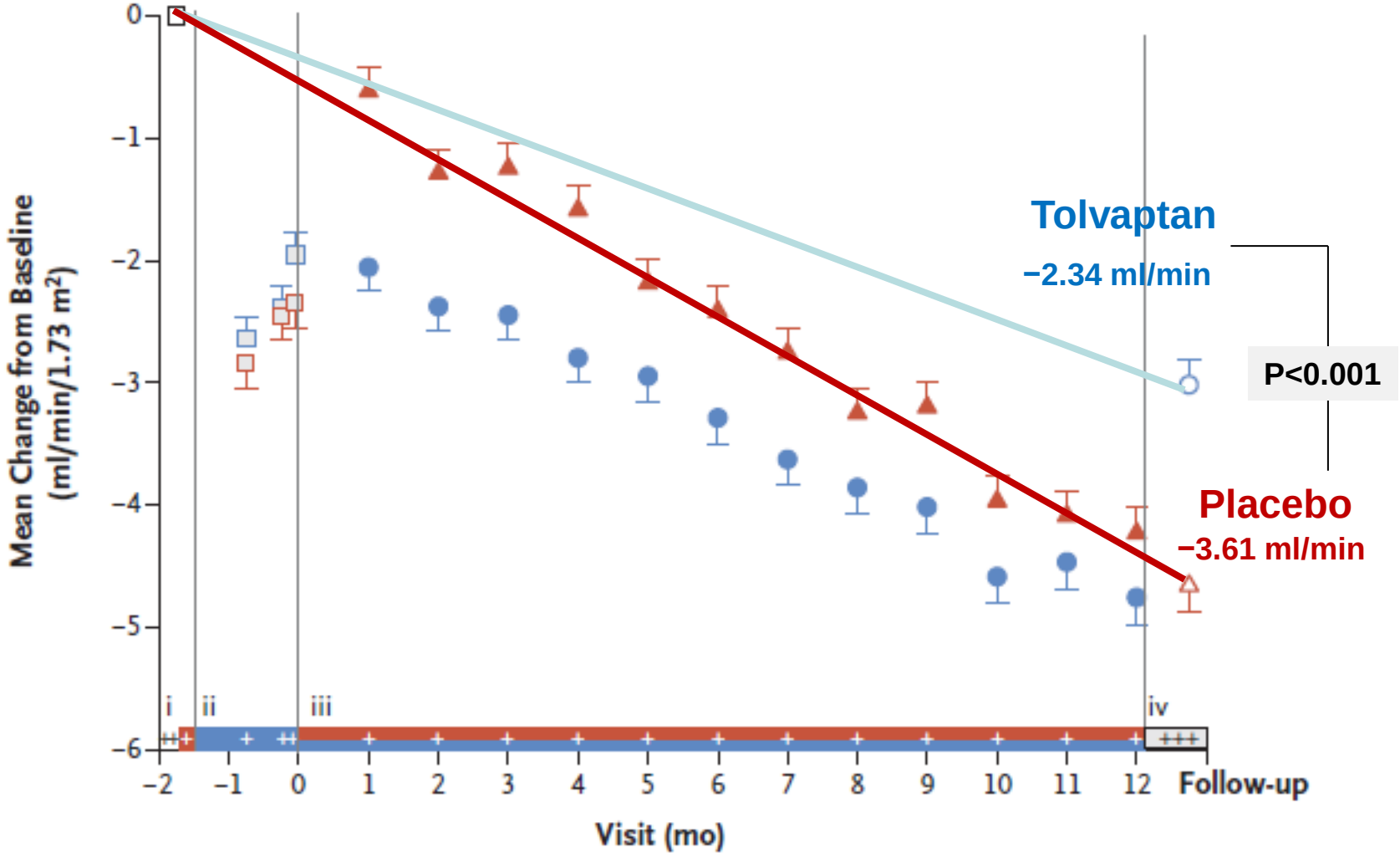
Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease

Vicente E. Torres, M.D., Ph.D., Arlene B. Chapman, M.D., Olivier Devuyst, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D., Ronald D. Perrone, M.D., Gary Koch, Ph.D., John Ouyang, Ph.D., Robert D. McQuade, Ph.D., Jaime D. Blais, Ph.D., Frank S. Czerwiec, M.D., Ph.D., and Olga Sergeyeva, M.D., M.P.H., for the REPRISE Trial Investigators*

1370 patients, 18-55 years, eGFR 25-65; 56-65 years, eGFR 25-44

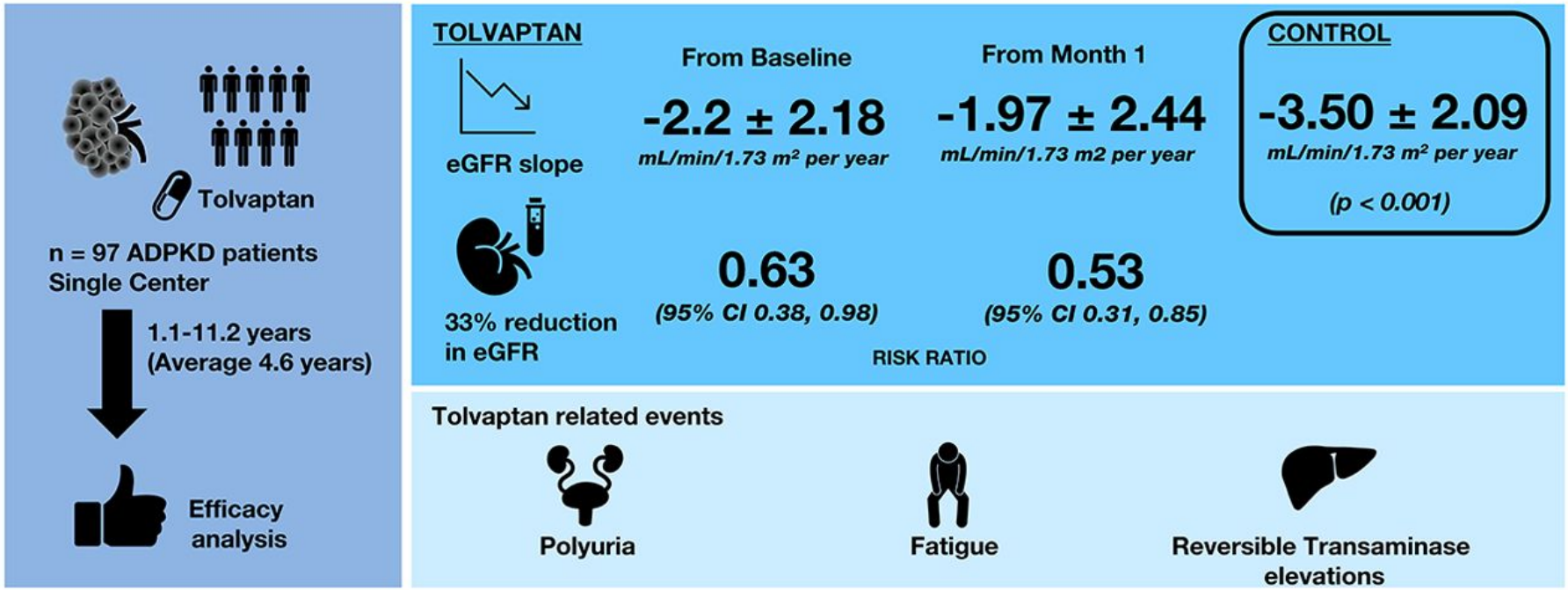
Torres et al. NEJM 2017; 377: 1930-42

Decrease of Renal Function (eGFR) during the Study



Torres et al. NEJM 2017; 377: 1930-42

Long-term administration of tolvaptan in autosomal dominant polycystic kidney disease

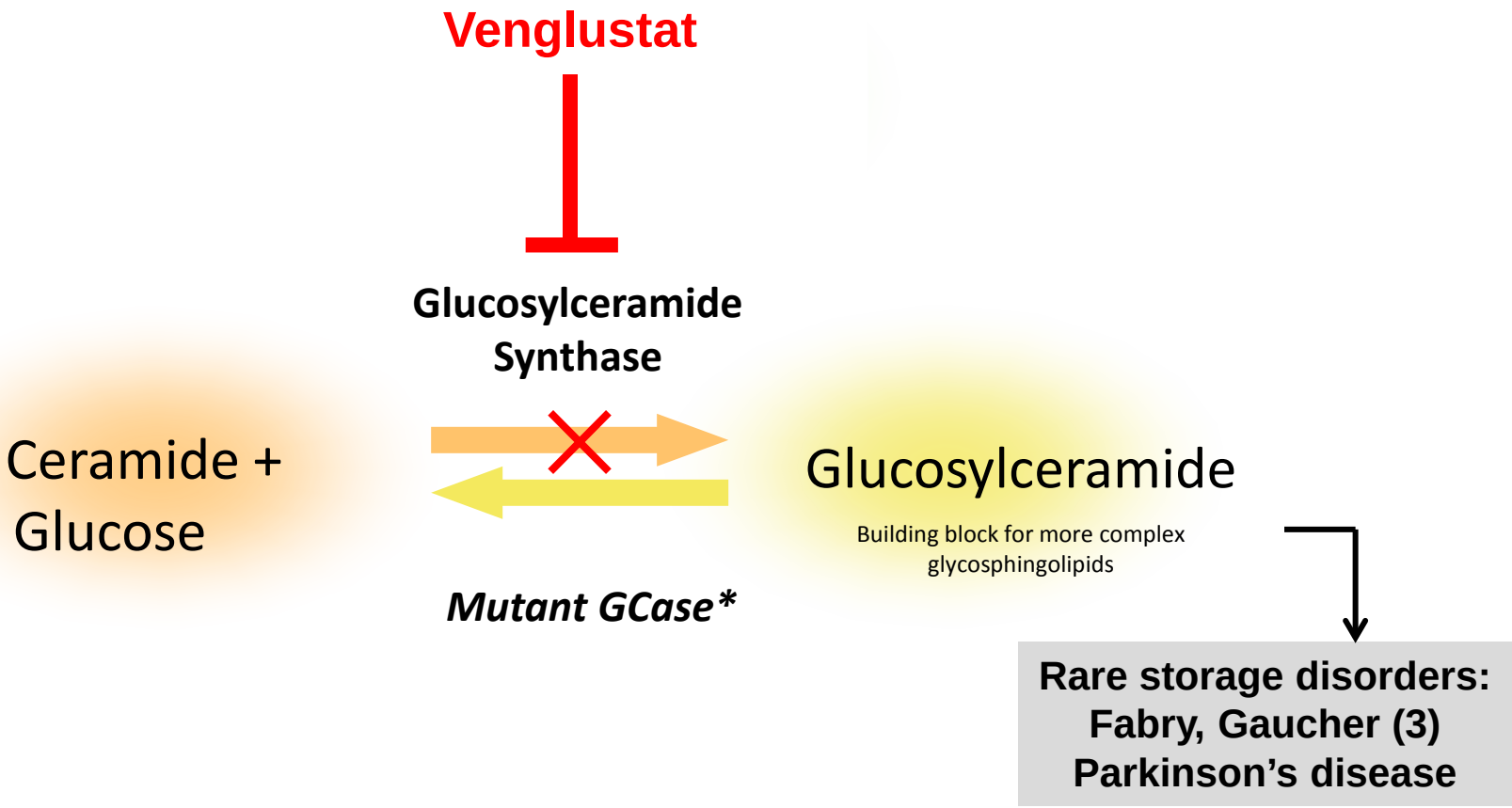


Conclusions Follow-up for up to 11.2 years (average 4.6 years) showed a sustained reduction in the annual rate of eGFR decline in tolvaptan treated patients compared to controls and an increasing separation of eGFR values over time between the two groups.

Marie Edwards, Fouad Chebib, Maria Irazabal, Troy Ofstie, Lisa Bungum, Andrew Metzger, Sarah Senum, Marie Hogan, Ziad El-Zoghby, Timothy Kline, Peter Harris, Frank Czerwiec, and Vicente Torres. ***Long-term Administration of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease.*** CJASN doi: 10.2215/CJN.01520218

Marie E. Edwards et al. CJASN 2018;13:1153-1161

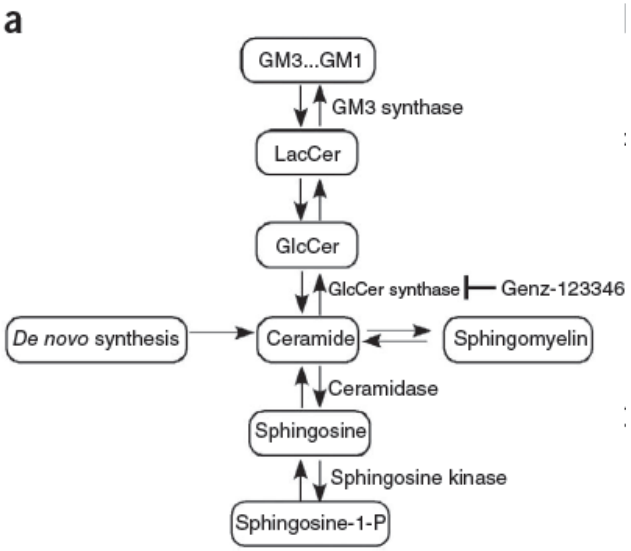
Venglustat : Mechanism of Action

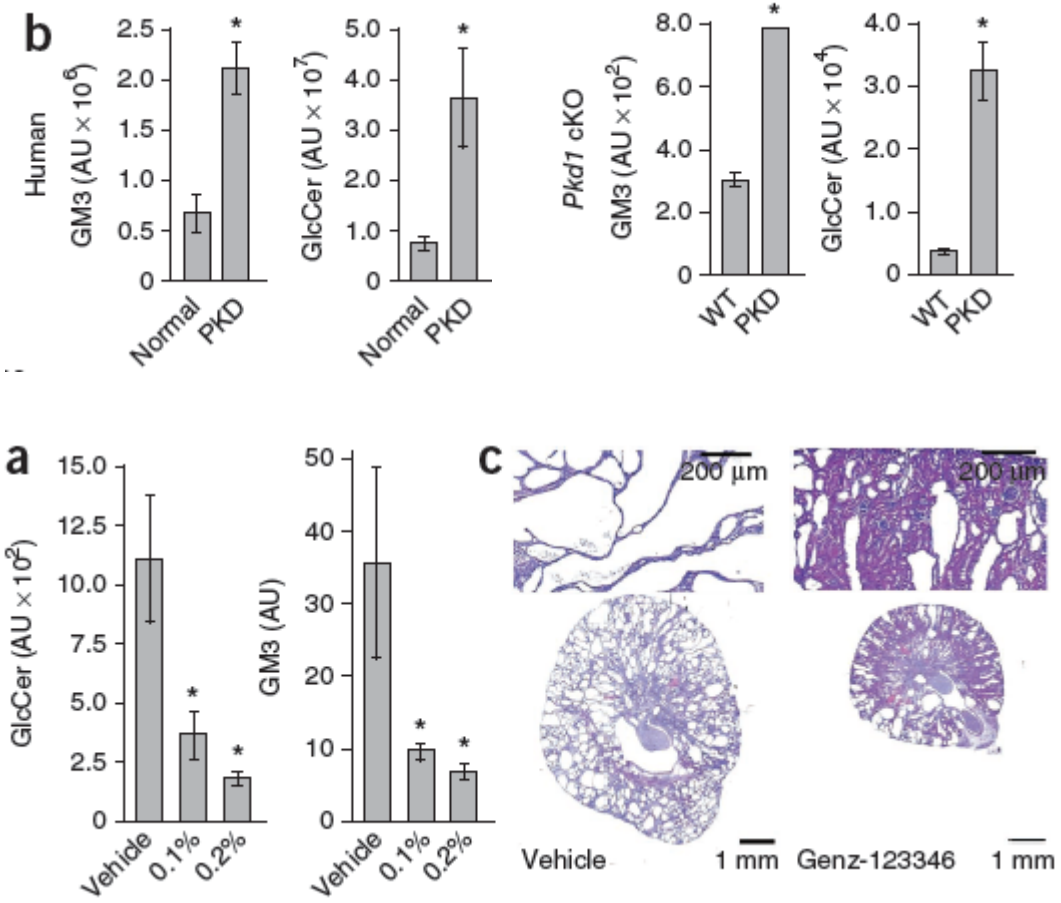


Venglustat inhibits GCS, resulting in decreased production of glucosylceramide *(GL-1, GlcCer)*

GCase, glucocerebrosidase; GCS, glucosylceramide synthase

Inhibition of glucosylceramide accumulation results in effective blockade of polycystic kidney disease in mouse models



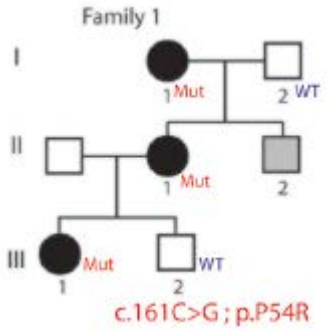


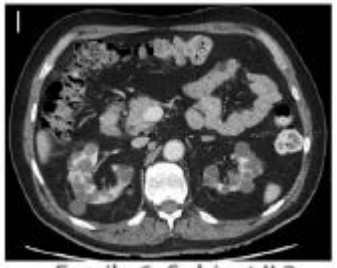
Natoli et al. Nat Med 2010; 16: 788-792

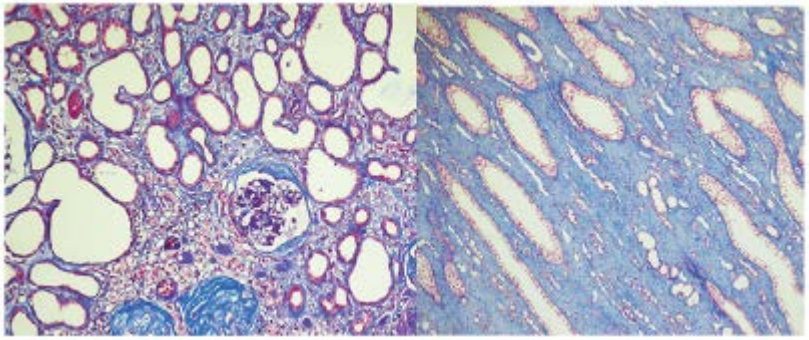
Further genetic heterogeneity in ADPKD

Cornec-Le Gall *et al.* (*Am J Hum Genet.* 2018;102:832–844; https://doi.org/10.1016/j.ajhg.2018.03.013)

Monoallelic Mutations to *DNAJB11* Cause Atypical Autosomal-Dominant Polycystic Kidney Disease







- Less than 10% of ADPKD families are negative for *PKD1, PKD2, GANAB*.
- Pathogenic variants in *DNAJB11* detected in 7/593 negative pedigrees.
- Atypical of ADPKD : cystic kidneys, not enlarged, only 7/23 subjects reached ESRD, age 59 to 89 years.
- Interstitial fibrosis: possible overlap with autosomal-dominant tubulointerstitial kidney disease (ADTKD).

- *DNAJB11* encodes a co-factor of the heat shock 70 kDa (HSP70) chaperone BiP (for binding immunoglobulin protein), which regulates the folding, oligomerization, trafficking, and degradation of proteins in the lumen of the ER; mutations cause impaired secretory/maturation of proteins.

These studies confirm the involvement of defective ER quality control mechanisms in a set of disorders associated with polycystic kidney and liver manifestations.

Cornec-Le Gall et al. Am J Hum Genet 2018; 102: 832-44

Take-Home Messages

• The REPRISE trial showed that tolvaptan resulted in a slower decline than placebo in the eGFR over a 1-year period in patients with later-stage ADPKD. Elevations in the ALT/AST occurred in 5.6% of patients. Such elevations were reversible after stopping tolvaptan.

• 128 patients with ADPKD, Mayo Clinic, tolvaptan: Follow-up for up to 11.2 years (average 4.6 years) showed a sustained reduction in the annual rate of eGFR decline in patients treated with tolvaptan compared with controls and an increasing separation of eGFR values over time between the two groups.

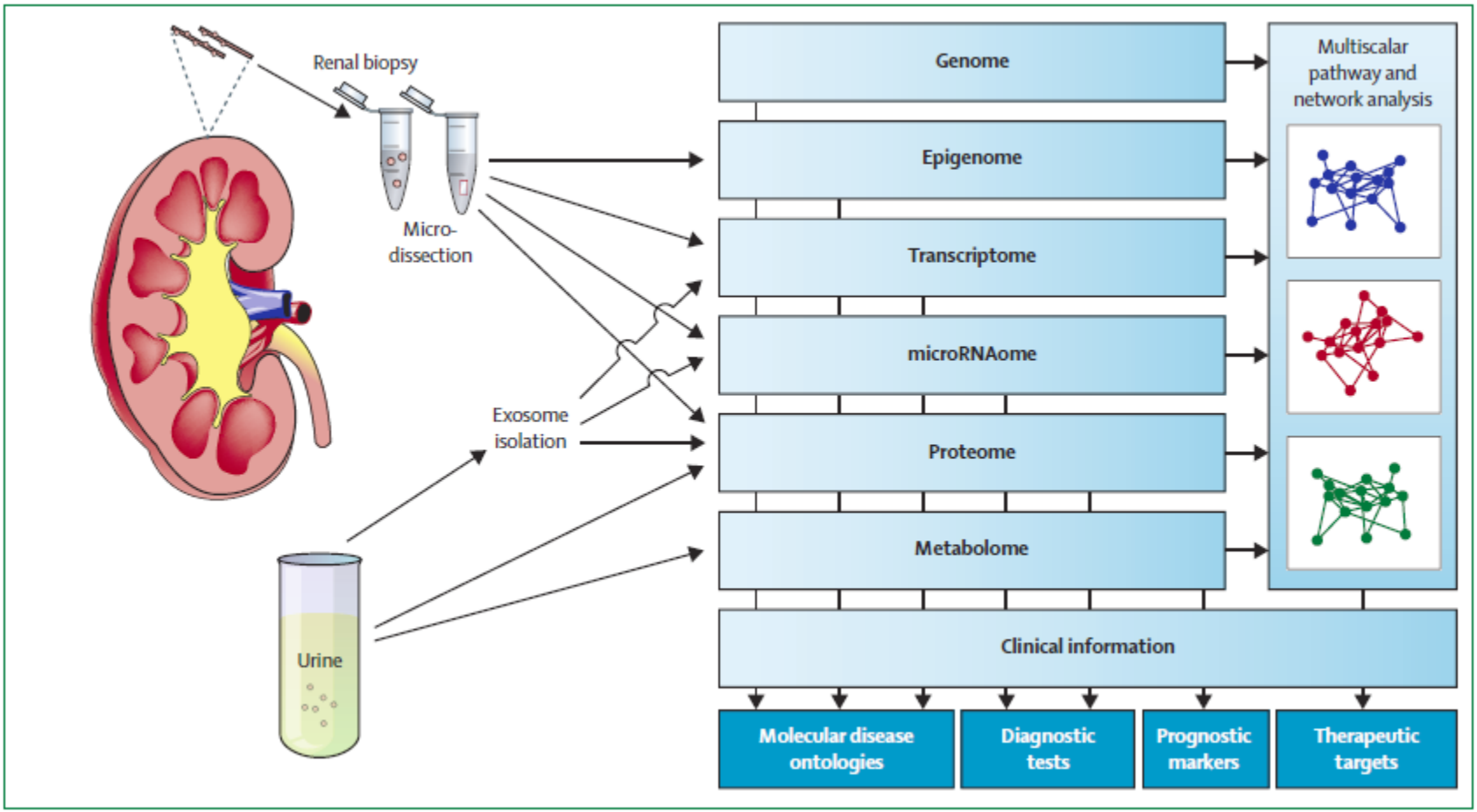
• Kidney glucosylceramide levels are higher in human and mouse PKD tissue as compared to normal tissue. Blockade of GlcCer accumulation with the GlcCer synthase inhibitor effectively inhibits cystogenesis in mouse models of human PKD. Studies will start to evaluate the therapeutic potential for glycosphingolipid modulation as a new approach to treat PKD, based on repurposing inhibitors of GlcCer synthesis (Venglustat).

• The discovery of mutations in *DNAJB11* in a small proportion of patients with (atypical) ADPKD confirms the involvement of defective ER quality control mechanisms in a set of disorders associated with polycystic kidney and liver manifestations.

Subtopic 4

New technologies

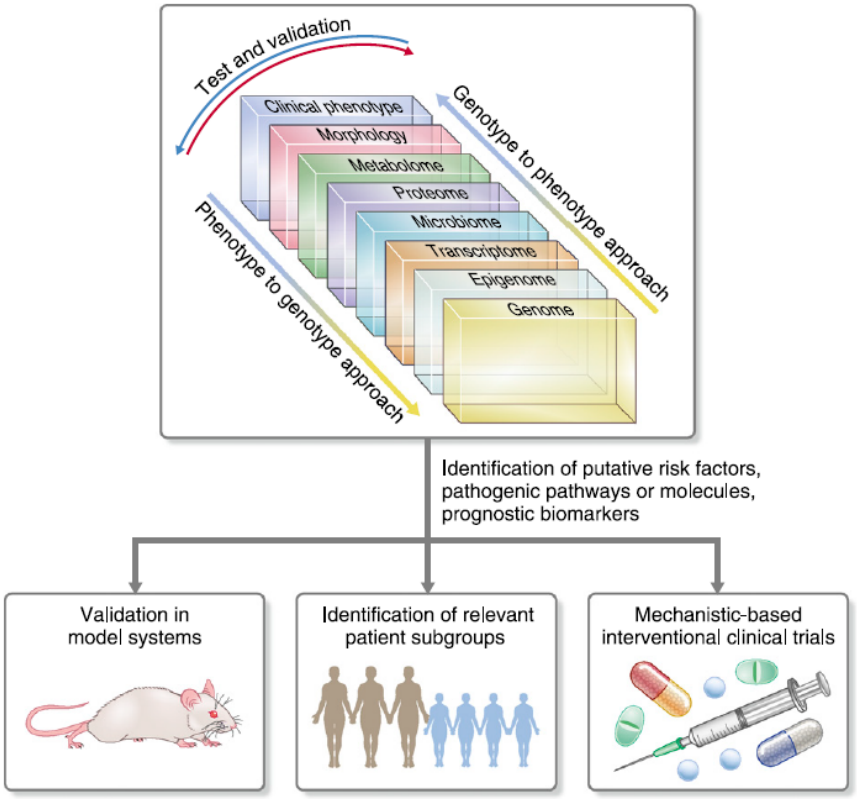
Kidney Disorders: Multi-omics Technologies



Devuyst O et al, Volume 383, Issue 9931, 24–30 May 2014, Pages 1844-1859

Defining Glomerular Disease in Mechanistic Terms: Implementing an Integrative Biology Approach in Nephrology

Laura H. Mariani, William F. Pendergraft III,† and Matthias Kretzler**

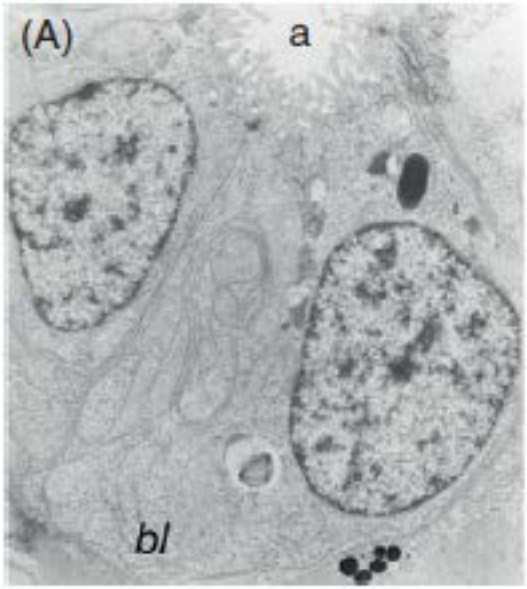


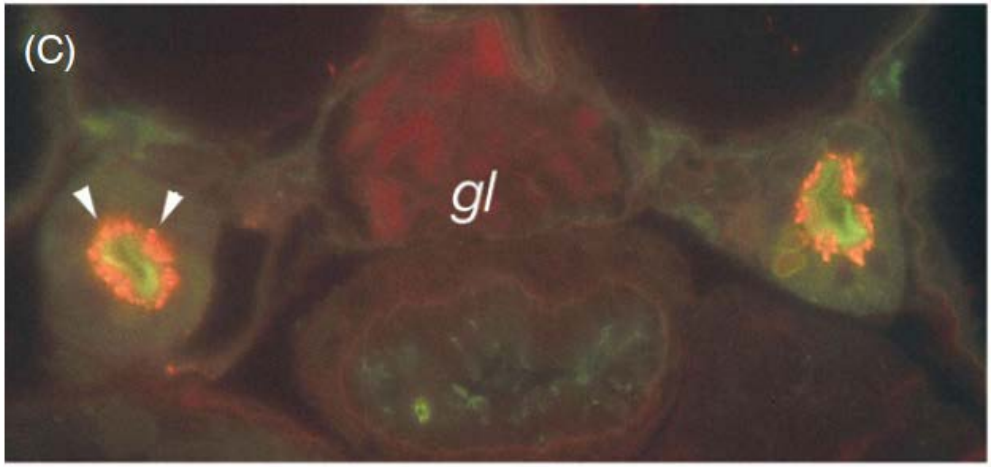
Clin J Am Soc Nephrol 11: 2054–2060, 2016.

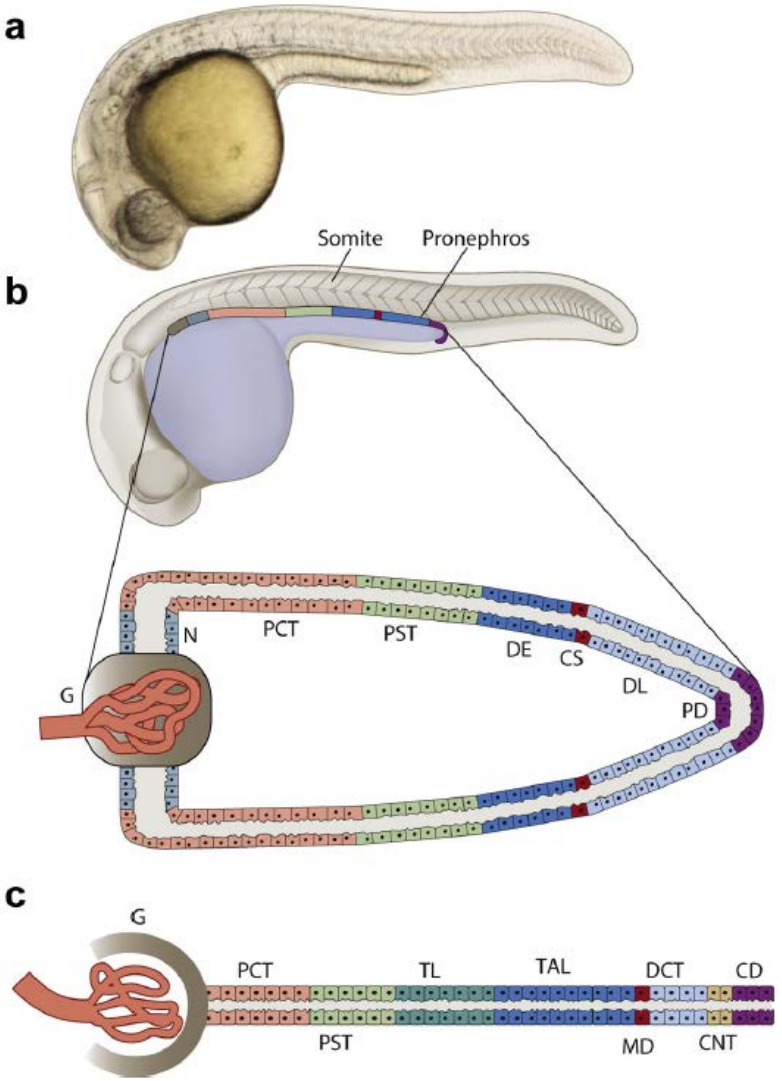
Advantages of Zebrafish as Model Organism

- *In vivo* model – whole organism (in petri dish)
- Transparent (imaging)
- Genome sequenced, easy to edit (KO, MUT)
- Transgenic lines
- Low cost for fish breeding: small size, high fertility
- No ethics concerns at embryo stage (up to 7dpf)
- Conservation of key transporters/receptors - patterning

Zebrafish: Model for Proximal Tubule



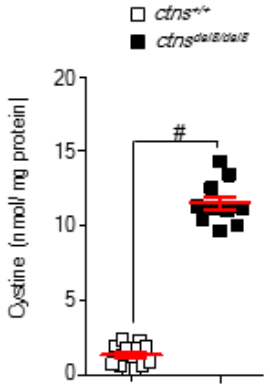




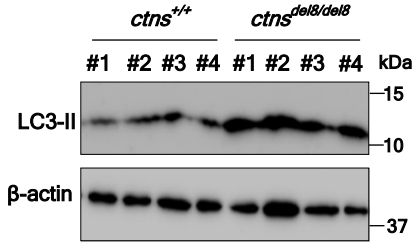
Poureetezadi et al. Kidney Int 2016; 89: 1204-10

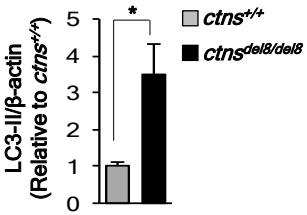
ctns KO larvae: zebrafish model of cystinosis

- Cystine accumulation (5dpf)

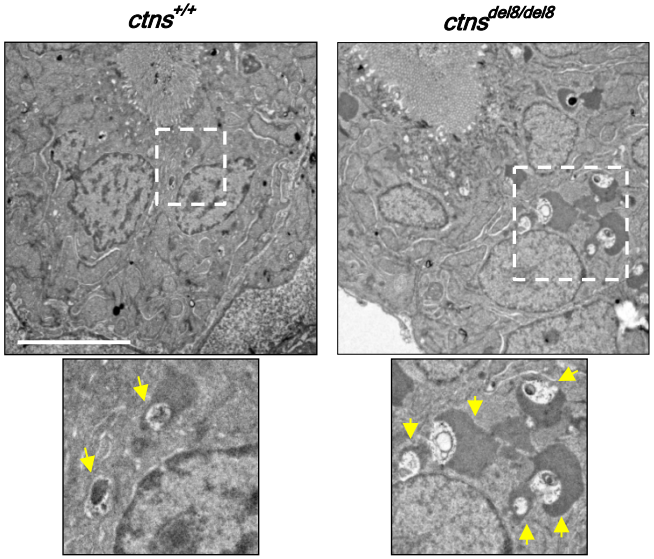


- Accumulation of autophagosomes in kidney

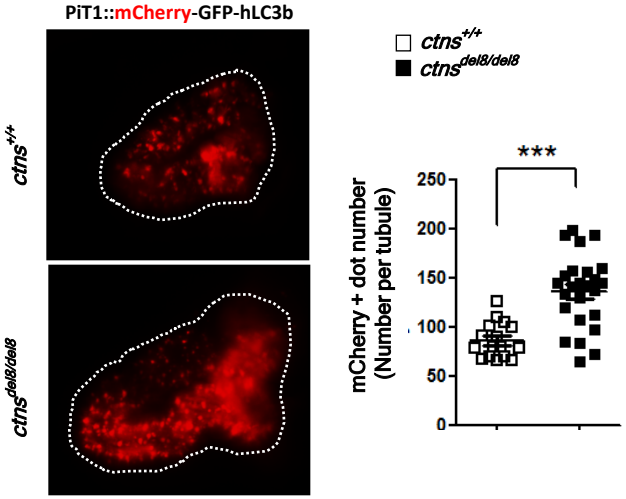




- Accumulation of autophagic vesicles

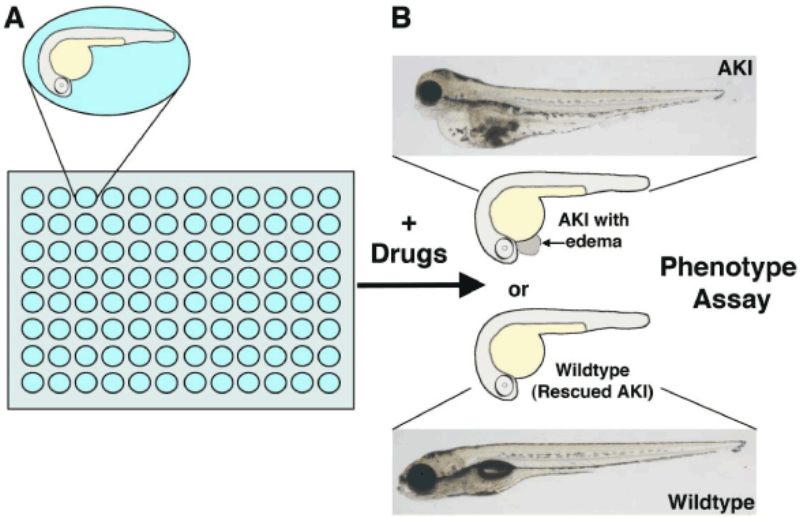


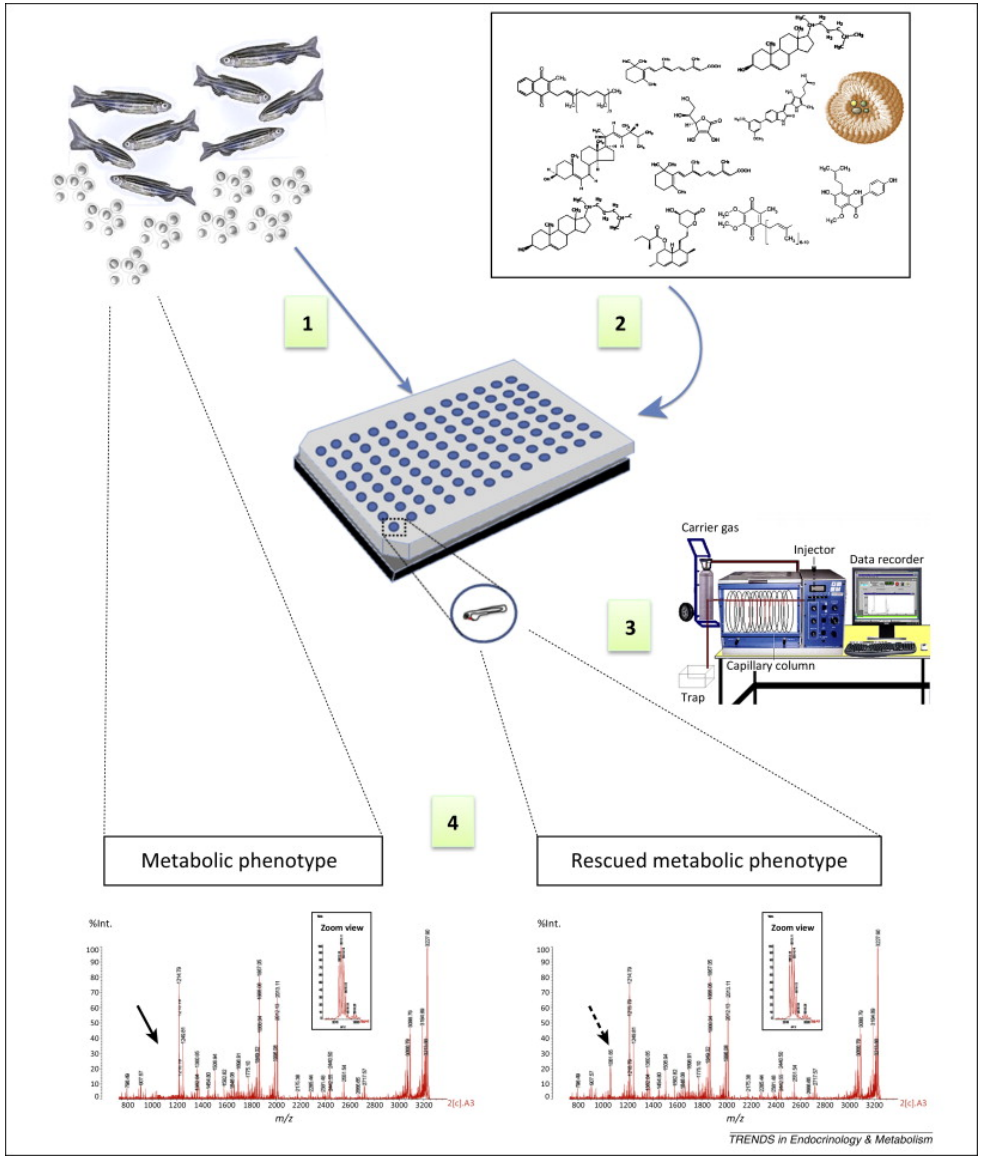
- Accumulation of autophagic vesicles



Festa BP et al. Nat Commun 2018; 9: 161

Zebrafish models: Perspectives for Drug Discovery



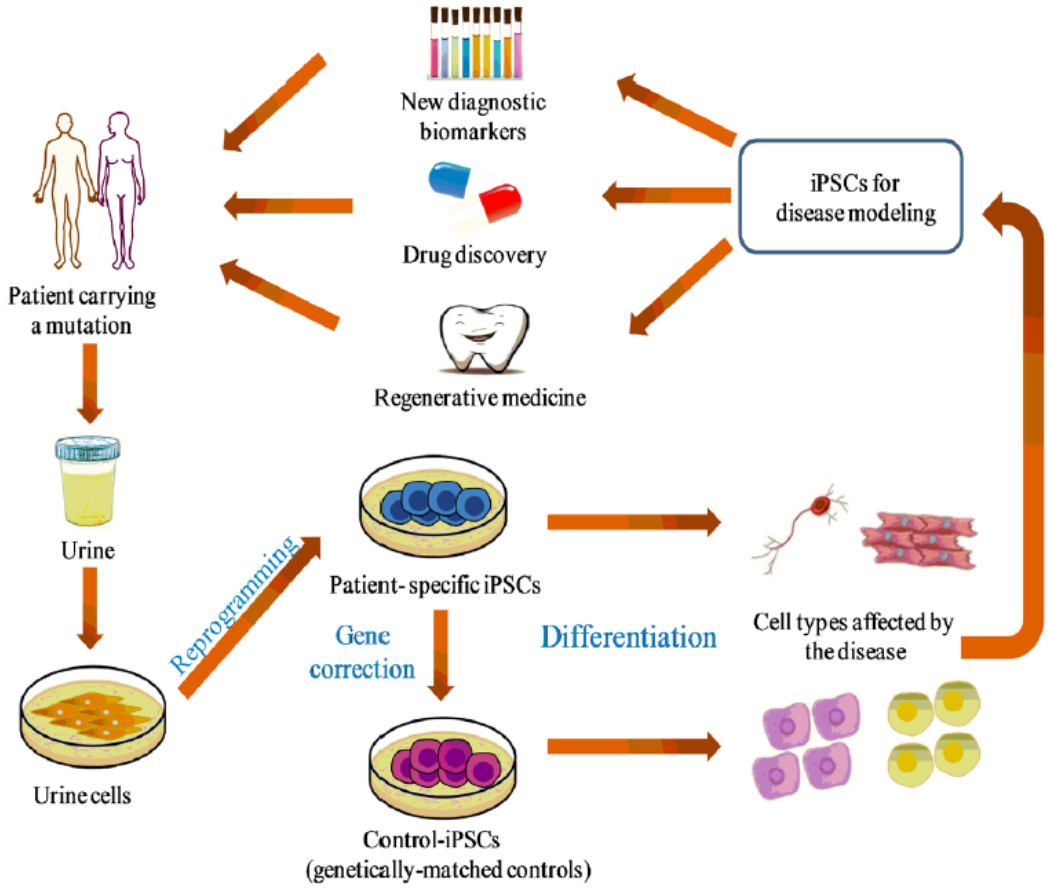


Santoro M. Trends Endocrinol Metab 2014; 25: 546-54

Review

DOI: 10.5582/irdr.2016.01062

Urine-derived induced pluripotent stem cells as a modeling tool to study rare human diseases

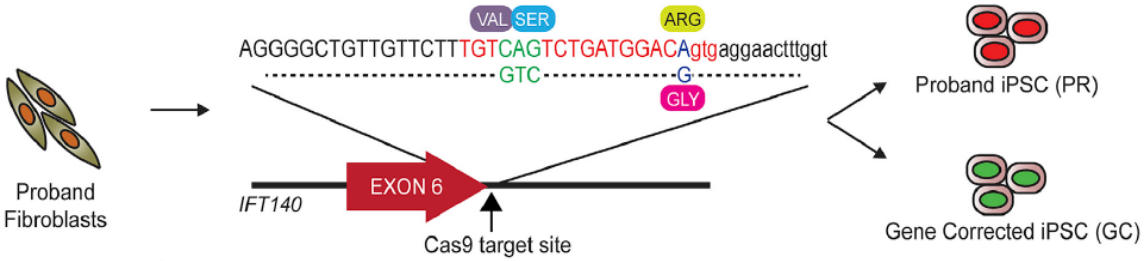


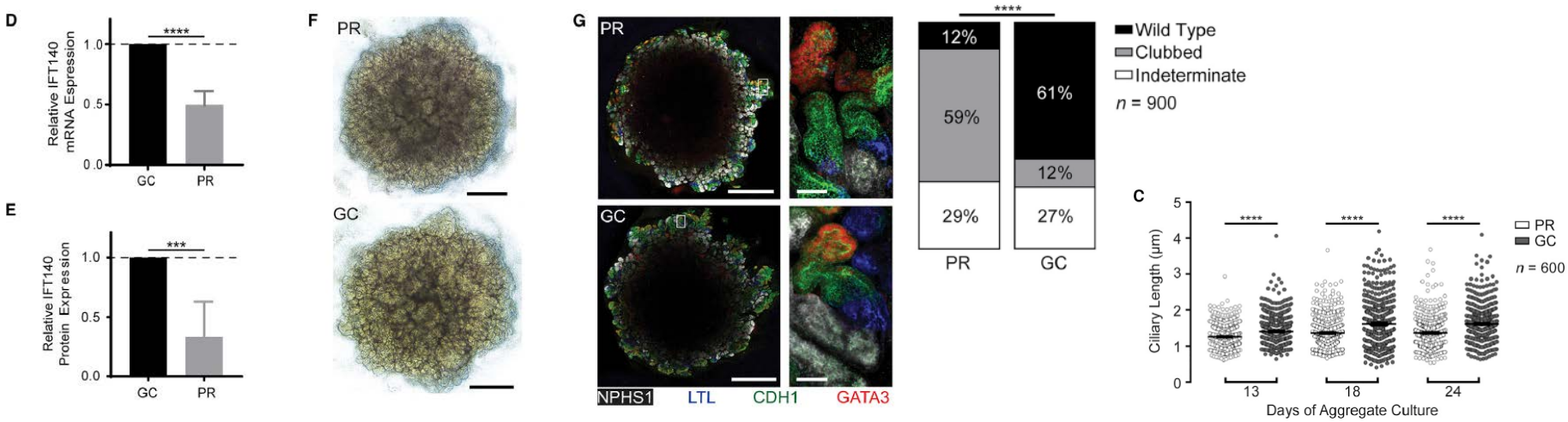
Shi et al. Intractable Rare Dis Res 2016; 5: 192-201

ARTICLE

Patient-iPSC-Derived Kidney Organoids Show Functional Validation of a Ciliopathic Renal Phenotype and Reveal Underlying Pathogenetic Mechanisms

Thomas A. Forbes,[1,2,3] Sara E. Howden,[1,2] Kynan Lawlor,[1] Belinda Phipson,[1,4] Jovana Maksimovic,[4] Lorna Hale,[1,2] Sean Wilson,[1] Catherine Quinlan,[1,2,3] Gladys Ho,[5] Katherine Holman,[5] Bruce Bennetts,[5,6,7] Joanna Crawford,[8] Peter Trnka,[9,10] Alicia Oshlack,[1,4] Chirag Patel,[11] Andrew Mallett,[10,12] Cas Simons,[8] and Melissa H. Little[1,2,*]





Forbes et al. Am J Hum Genet 2018; 102: 816-31

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Introduction and Subtopic 1: NGSin kidney disorders

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Subtopic 2: Novel pathways

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Subtopic 3: Polycystic kidney disease

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Natoli TA, et al. Inhibition of glucosylceramide accumulation results in effective blockade of polycystic kidney disease in mouse models. Nat Med. 2010 Jul;16(7):788-92.

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List of References

Subtopic 4: New technologies

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