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Rare inherited kidney diseases: challenges, opportunities, and perspectives

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Abstract

At least 10% of adults and nearly all children who receive renal-replacement therapy have an inherited kidney disease. These patients rarely die when their disease progresses and can remain alive for many years because of advances in organ-replacement therapy. However, these disorders substantially decrease their quality of life and have a large effect on health-care systems. Since the kidneys regulate essential homoeostatic processes, inherited kidney disorders have multisystem

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See Online for appendix

For more on **EURenOmics** see http://www.eurenomics.eu

For more on **Human Phenotype Ontology** website http://www.human-phenotype-ontology.org/

For the **website of the European Platform for Rare Disease Registries** see http://www.epirare.eu

For the **website of the Patient Registries Initiative** see http://www.patientregistries.eu For more on **RD-CONNECT** see http://www.rd-connect.eu

For the **International Rare Diseases Research Consortium** see http://www.irdirc.org/

For the **website of the Working Group on Inherited Kidney Diseases** see http://www.era-edta.org/wgikd/ERA-EDTA_working_group_on_ Inherited_kidney_disorders.htm

For website of **NORD** see http://www.rarediseases.org

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Contributors

All authors discussed the overall concept and plan for the review, contributed to specific sections, and reviewed and approved the final version. OD and FS integrated and edited the contributions from all authors.

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Declaration of interests

We declare no competing interests.

complications, which add to the usual challenges for rare disorders. In this review, we discuss the nature of rare inherited kidney diseases, the challenges they pose, and opportunities from technological advances, which are well suited to target the kidney. Mechanistic insights from rare disorders are relevant for common disorders such as hypertension, kidney stones, cardiovascular disease, and progression of chronic kidney disease.

Introduction

In the USA a rare disease is defined as a disease that affects fewer than 200 000 people in the country, whereas this designation is given to diseases that affect fewer than one in 2000 people in Europe,[1] fewer than one in 2500 people in Japan,[2] and fewer than one in 500 000 people in China.[3] Rare diseases are often categorised as orphan diseases to stress their severity, insufficient resources and knowledge available, and the specific conditions to develop or make drugs for them. They represent a group of 6000 to 8000 highly heterogeneous disorders that affect roughly 30 million patients in Europe.[1] About 80% of rare diseases have an identified genetic origin. The incidence of a rare disease can vary substantially between regions or ethnic groups. For example, congenital nephrotic syndrome of the Finnish type occurs more frequently in Finland (incidence of one in 8200 people) than in other parts of the world.

Rare kidney diseases constitute at least 150 different disorders and they have an overall prevalence of about 60–80 cases per 100 000 in Europe and the USA.[4–6] At least 10% of adults and nearly all children who progress to renal-replacement therapy have an inherited kidney disease, the fifth most common cause of end-stage renal disease after diabetes, hypertension, glomerulonephritis, and pyelonephritis. Because of progress in renalreplacement therapy, patients with inherited kidney disorders rarely die when their disease progresses and can live for many years. However, these patients often have compromised health with a poor quality of life. For instance, children with severe congenital nephropathies, who can be dialysed from neonatal age onwards, face many decades of life with end-stage renal disease and have a high likelihood of changes in physical, cognitive, and psychosocial development. Inherited kidney disorders have multisystem complications that add to the typical challenges for rare disorders—ie, variable phenotypes, fragmented clinical and biological data, an absence of standardisation for diagnostic procedures, and poor knowledge for disease mechanisms and natural history.[7]

In this review, we discuss the epidemiology, range, and specific nature of rare inherited kidney diseases of genetic origin and note challenges that arise in their management. We then address opportunities from technological advances and high-throughput screening approaches, which are particularly well suited to target the kidney. We particularly focus on the link between these technologies and the innovative clinical research programmes and initiatives. We show how these collaborative studies could affect the clinical management of rare kidney diseases and beyond, with mention of insights about effects of sex and ageing, the progression of chronic kidney disease, and understanding for more common disorders.

Rare inherited kidney diseases: why they are different

The kidney is a complex organ, composed of many specialised cell types, with highly regulated functions that are essential for homoeostasis.[8] The kidneys are exposed to and affect the extracellular environment more than any other organ—regulating water and electrolyte balance, acid-base homoeostasis, tissue oxygen supply, hormone and vitamin metabolism, and innate and adaptive immunity. The kidneys are also essential for metabolic clearance and secretion of drug metabolites. These functions have large quantitative effects that can directly affect body composition. Primary kidney disorders can substantially affect blood pressure, plasma composition, electrolyte and acid-base homoeostasis, cardiac excitability, growth dynamics and puberty, and CNS and cognitive functions. Various aspects of renal function can also be affected in extrarenal rare disorders or polymalformative syndromes, including mitochondrial cytopathies.[9–12]

Genetics were first used in nephrology in the 1980s with the mapping of autosomal dominant polycystic kidney disease in 1985[13] and the first identification of a causal mutation for a monogenic kidney disorder (Alport's syndrome) in 1990.[14] These breakthroughs were followed by identification of genes involved in classic disorders such as nephrogenic diabetes insipidus,[15] autosomal dominant polycystic kidney disease type 1,[16] Liddle's syndrome,[17] Dent's disease,[18] Bartter's and Gitelman's syndromes,[19,20] nephropathic cystinosis,[21] and steroid-resistant nephrotic syndrome (panel).[22] With the increased use of high-throughput and next-generation sequencing technologies, investigators have now defined the genetic basis of more than 160 rare kidney diseases (table 1, table 2). These disorders are caused by mutations in genes coding for a wide range of proteins including receptors, channels and transporters, enzymes, transcription factors, and structural components that might also have a role in extrarenal organs (bone, eye, brain, skin, etc). Figure 1 shows a functional classification of rare inherited disorders of the kidney. In addition to monogenic diseases, the combination of variants in the same genes or in genes involved in common pathways that operate in the kidney might cause variable effect sizes that cannot be explained by conventional genotype– phenotype correlations.[8,28] Careful phenotype assessments of recessively inherited kidney disorders have substantiated the effect of carrier states. For example, Gitelman's syndrome is caused by loss-of-function mutations in *SLC12A3*, which encodes the thiazide-sensitive sodium–chloride cotransporter in the distal convoluted tubule. About 1% of the general population are heterozygous carriers of *SLC12A3* mutations; such carriers have a lower blood pressure and a lower risk of hypertension than have the general population.[29]

Specific challenges

Unknown genetic cause

Despite progress in understanding of molecular causes of rare kidney diseases, the pathways for most inherited nephropathies still need identification. Known monogenic causes explain only 30–40% of cases of familial steroid-resistant nephrotic syndrome, 40–50% of cases of congenital tubulopathy, and 50–60% of cases of atypical haemolytic uraemic syndrome. Poor appreciation of genetic studies by health-care providers is of concern. Even for well defined disorders such as Alport's, Bartter's, and Gitelman's syndromes, use of genetic

testing remains rare, mainly because of high cost and long turnaround times for conventional genetic screening, the preconception that a genetic diagnosis will not affect clinical management, insufficient genetic literacy, and differences in access to genetic testing and insurance coverage.[30,31]

Absence of biomarkers

Even though routine analysis of urine samples can be helpful to indicate the origin of some disorders (figure 1), the assessment of kidney disease activity and progression is still mainly based on crude markers such as serum creatinine and proteinuria. The descriptive assessment of kidney biopsy specimens with use of light and electron microscopy, supplemented by a small set of immunological marker proteins, is still the diagnostic gold standard.[32]

Clinical heterogeneity

Many rare mendelian kidney diseases have a different prevalence in different populations and have substantial clinical heterogeneity in presence, age of onset, severity, and progression of symptoms. Different incidence rates in populations lend support to a role for genetics, and potentially the environment, in the pathogenesis of disease. Phenotypical differences can be the result of genetic (locus) heterogeneity—eg, in Bartter's syndrome, mutations in *SLC12A1* or *KCNJ1* are associated with a severe neonatal onset of disease, whereas mutations in *CLCNKB* usually result in milder and later-onset disease symptoms and mutations in *BSND* cause Bartter's syndrome plus sensorineural deafness.[33] Allelic heterogeneity might also explain disease variability. For instance, in autosomal recessive polycystic kidney disease, the presence of two truncating mutations in the disease gene, *PKHD1*, is associated with a lethal disease; at least one missense mutation is necessary for survival after neonatal age. However, the absence of two truncating mutations cannot be regarded as synonymous with a favourable prognosis.[34] Therefore, prediction of the clinical outcome for children with autosomal recessive polycystic kidney disease with one or two missense mutations remains difficult. In 2014, Tory and colleagues[25] described mutation-dependent recessive inheritance of *NPHS2*-associated steroid-resistant nephrotic syndrome. In most rare inherited kidney diseases, the mutational diversity is large and genotype–phenotype correlations are loose or absent, showing the insufficient study populations sizes and poor access to genetic testing.

Effects of modifier genes, epigenetic changes, or other modifying factors also contribute to intrafamilial variability. Sex might modify the phenotype, as it does in Gitelman's syndrome.[35] Oligogenic modifier effects, by which a second gene can modify the action of a dominant gene, play a part in genetic ciliary diseases such as nephronophthisis. For instance, in patients with homozygous *NPHP1* deletions, the presence of an additional heterozygous *NPHP6* or *NPHP8* mutation might cause additional eye or cerebellar involvement.[36,37] However evidence is in early stages for genetic and epigenetic modifiers in rare inherited kidney diseases.

Insufficient ontology

An increasing number of rare kidney diseases that were previously considered to be single disorders have been shown to be aetiologically heterogeneous. Different abnormalities can affect the same biological pathways and give rise to similar clinical, biochemical, and histopathological features. The imperfect prognostic value of traditional diagnostic nomenclatures is largely explained by its inability to differentiate underlying disease mechanisms. For instance, membranoproliferative glomerulonephritis can be caused by glomerular deposition of circulating immunoglobulins or immune complexes, by mutations in complement proteins regulating C3 convertase, and by acquired autoantibodies directed against these proteins or C3 itself.[38] Another example of heterogeneity is the generalised dysfunction of the proximal tubule (renal Fanconi's syndrome).[39] Emerging disease ontologies based on molecular pathophysiology will need prognostic validation with long-term outcomes.

Carrier state

Information on an individual's carrier status for a genetic renal disorder is not only important for genetic counselling, but might also have clinical implications for the carriers themselves. Heterozygous carriers of X-chromosome-linked disorders are usually asymptomatic or mildly affected, but in some heterozygotes, a severe disease outcome is noted. Disease severity in women with X-linked renal disorders such as Alport's syndrome and Fabry's disease is not related to the genotype, and is most probably a result of skewed X-chromosome inactivation. Therefore, women carrying an X-chromosome-linked Alport's syndrome mutation (*COL4A5* mutation), should be considered at risk to develop disease and be observed similarly to men to assess for early signs or progression to renal insufficiency. Likewise, women carrying heterozygous *GLA* mutations can be as severely affected by Fabry's disease as can hemizygous men, with progressive, multiorgan involvement, particularly nephropathy. Further research is needed to determine methods to predict the individual outcome for female carriers of these rare X-chromosome-linked renal disorders.

Carrier status might also have implications for living-related kidney transplantation. Unaffected individuals carrying a heterozygous recessive gene mutation are theoretically expected not to develop disease. Therefore, living related transplantation is usually considered suitable from patients with rare autosomal recessive renal diseases such as podocytopathies, autosomal recessive polycystic kidney disease, cystinosis, and nephronophthisis. However, whether unilateral nephrectomy in heterozygous individuals affects long-term renal function has not been determined, and studies from large registries are needed.

Insufficient model organisms

Knockout and transgenic mouse models are highly informative about the effects of genetic variation on renal phenotypes.[40] Limitations of these models include long generation time, strain effects, adaptation, and species differences in development, growth, physiology, metabolism, and adaptation to chronic kidney disease.[41,42] These obstacles mean that mouse models are of little use for rapid testing of candidate genes arising from next-generation sequencing and for drug development.

Opportunities

Omics technologies

Omics technologies provide great opportunity in research for rare renal diseases because they can probe the diseased organ directly (figure 2). Kidney biopsy samples allow investigators to study intrarenal processes ex vivo with use of transcriptomic and proteomic approaches for compartment-specific profiling of mRNA transcripts and non-coding regulatory RNA species. The European Renal cDNA Bank project has provided a reference database for gene expression profiles of microdissected kidney specimens from patients with various renal disorders and from healthy individuals.[43] Urine is a non-invasive resource to study biochemical and molecular readouts directly from the kidney. Amniotic fluid is available prenatally for studies of renal development or transport defects.[44] Exosome isolation from urine and amniotic fluid allows study of membrane and cytoplasmatic proteins and RNAs that derive from epithelial cells facing the urinary space. Although exosome isolation remains technically challenging, studies of podocyte and cystic kidney disorders indicate great potential of this analysis in the study of hereditary kidney diseases.[45–47] The possibility that application of omics approaches to such samples could identify molecular signatures and prognostic biomarkers was suggested by findings from studies in common kidney disorders such as diabetic nephropathy,[48] allograft rejection,[49] and vesicoureteral reflux.[50] Changes in urinary miRNA profile have been detected in disorders such as lupus nephritis[51] and renal fibrosis.[52] The study of the urine metabolome by nuclear magnetic resonance spectroscopy and mass spectrometry is another emerging technology that can generate molecular fingerprints of diagnostic or prognostic value,[53] as already shown in patients with Fanconi's syndrome.[54]

Next-generation sequencing

Next-generation sequencing techniques will improve diagnostic efficiency for genetic renal diseases through simultaneous investigation of all relevant genes for a given phenotype at much reduced costs and turn-around times.[24,55,56] Successful application of next-generation sequencing in diagnostic mutation screening with use of multigene panels has been shown for Alport's syndrome,[57] steroid-resistant nephrotic syndrome,[58] and nephronophthisis.[59] Beyond disease-specific next-generation sequencing panels, exome sequencing (and potentially even whole-genome sequencing) will soon become part of routine molecular diagnostics, further improving diagnostic yield. Sequencing-based technologies are also increasingly applied to individual cells, with the aim to integrate genomics, transcriptomics, epigenomics, and proteomics for multilevel analysis of cellular mechanisms. These analyses will need robust single-cell isolation, a potentially challenging task for a heterogeneous tissue such as kidney.[60]

The abundance of genetic and molecular information generated by next-generation sequencing poses a new challenge because bioinformatic capacities and analysis methods need development. The characterisation of candidate disease genes and individual mutations needs efficient model systems. Innovative strategies are also needed to integrate multilevel omics information with clinical phenotypes.[61] The European Consortium for High-Throughput Research in Rare Kidney Diseases (EURenOmics) is now working on a

cohesive bioinformatic platform for rare nephropathies. A renal phenome database is being created, using the Human Phenotype Ontology website.[62] The phenotype information will be linked to genomic, transcriptomic, proteomic, and metabolomic studies, omics datasets, and the public domain knowledge-base in a systems biology approach to identify molecular pathways associated with phenotypic features.

Model organisms

The mouse is still the major organism used to model rare kidney disorders. Cell-specific and time-specific gene-targeting methods and RNA-based technologies can manipulate gene function, which can be paralleled by targeted embryonic stem-cell clones and large-scale mutagenesis programmes.[40] The precision and number of phenotypic traits that can be tested in mice has largely increased.[42,63–65] Advances in rat genetics and genome editing, combined with robust phenotype analyses in more than 500 rat strains, pave the way for use of the rat as an alternative model organism for human diseases.[66,67]

By contrast with rodents, simple model organisms provide opportunity for higher-throughput gene manipulation and phenotype quantification. The zebrafish (*Danio rerio*) is now routinely used for study of kidney diseases and renal regeneration, based on conserved genomic organisation and nephron structure.[68] Zebrafish larvae are used to investigate kidney developmental disorders and ciliopathies,[69] glomerular disorders,[70] and tubulopathies.[71] The fruit fly (*Drosophila melanogaster*) nephrocyte combines filtration with protein reabsorption and can therefore be used as a model for podocytes and proximal tubule cells.[72,73] Although the nematode *Caenorhabditis elegans* does not possess an excretory system comparable with the mammalian kidney, conserved genes involved in formation of the primary cilium, kidney filtration barrier, or vasopressin response do exist in this organism.[74,75] Because few laboratories engage in such model studies, it is a challenge to integrate functional annotations into clinically relevant information.

Research programmes, cohorts, biorepositories

Fragmentation of patient-related information is a major obstacle for research into rare disease. Networks, registries, databases, and biorepositories have been created to overcome this issue. The European Platform for Rare Disease Registries provides instruments to develop exchange between individual registries, whereas the Patient Registries Initiative will promote interoperable patient registries. The RD-CONNECT platform will integrate rare disease projects devoted to next-generation sequencing and high-throughput approaches, and is linked with the International Rare Diseases Research Consortium (IRDiRC) which aims to deliver 200 new therapies by 2020. EURenOmics is one of the first clinical research projects of IRDiRC and RD-CONNECT. It is a consortium for omics research that integrates registries and biobanks with detailed phenotype information and biomaterials from more than 13 000 patients with rare kidney diseases. These efforts are paralleled by initiatives launched by professional and scientific societies. For instance, European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) has implemented a working group on inherited kidney diseases to promote research, care, and dissemination of knowledge.[76] Nationally, centres of excellence are being established by health authorities to improve health-care access and to help to transition patients from paediatric to adult care.[77]

Non-rare inherited kidney disorders

Rare kidney diseases exist alongside autosomal dominant polycystic kidney disease, one of the most common inherited disorders, with a prevalence of one in 1000 people (about 750 000 patients in Europe). Because of its autosomal dominant transmission and the slow progression of disease, patients with autosomal dominant polycystic kidney disease form an important pressure group that is able to drive attention to rarer inherited kidney diseases and to influence other organisations, as well as trends in research funding and drug development.

Opportunities for common diseases

Study of rare kidney diseases provides insights into more common disorders. The *UMOD* gene, in which dominantly inherited mutations can cause familial juvenile hyperuricaemic nephropathy, is an example.[23] Genome-wide association studies showed that common variants in the *UMOD* promoter were strongly associated with the risk of chronic kidney disease and hypertension in the general population.[78] Further studies showed the biological activity of these variants and how they cause hypertension.[79] The elucidation of this mechanism was helped by previous studies of genes that cause Bartter's syndrome.[20] Likewise, variants in the genes encoding the megalin (*LRP2*) and cubilin (*CUBN*) receptors that mediate tubular endocytosis of ultrafiltered proteins and are defective in rare disorders were shown by genome-wide association studies to affect renal function and risk of chronic kidney disease.[80,81] Conversely, genome studies might incidentally point to candidate genes for rare diseases. For example, the identification of *CNNM2* as the causative gene for a rare genetic disorder of renal magnesium wasting was based, among other findings, on the association between common variants in *CNNM2* and serum Mg^{2+} concentrations.[82]

Perspectives

Diagnostics

The use of next-generation sequencing is expected to increase diagnostic efficiency for rare kidney diseases. Accurate genetic counselling and carrier testing will become available for an increased number of families, with potential for early prenatal or preimplantation diagnostic testing in severe cases. A definite genetic diagnosis could have important prognostic value in some diseases. For instance, the efficacy of plasmapheresis and outcome of renal transplantation in atypical haemolytic uraemic syndrome is correlated with the type of mutation in complement genes. Patients with mutations in complement genes that encode circulating proteins (*CFH* and *CFI*) have worse outcomes than have patients with mutations in *MCP* (*CD46*), encoding a cell-associated protein.[83] Likewise, genetic testing in patients with steroid-resistant nephrotic syndrome helps to predict the response to immunosuppressive therapies and the risk of post-transplant disease recurrence.[84] In primary hyperoxaluria type 1, the Gly170Arg and Phe152Ile aminoacid changes caused by mutations in *AGXT* have been associated with responsiveness to pyridoxine supplementation.[85] As we discuss, policies to promote clinically relevant genetic testing and the adequate delivery and integration of genetic information should be implemented.

Treatment

Effective therapeutic approaches exist for some rare kidney diseases (panel). Genetic and mechanistic insights could improve existing therapies or help to develop new ones (figure 3). Cystinosis is a lysosomal storage disease caused by mutations in the *CTNS* gene resulting in intralysosomal accumulation of cystine crystals, which damage several organs, including kidney.[21] Oral administration of cysteamine, which reverses cystine accumulation via a newly described PQLC2 heptahelical protein (figure 3),[86] substantially delays renal disease progression and other complications.[89] Findings from a mouse study of cystinosis suggest that stem-cell gene therapy might also improve the multisystem complications of cystinosis.[27]

The elucidation of molecular mechanisms for disease might create opportunities for drug repositioning (ie, application of known drugs to new indications). For instance, recurrence of proteinuria after kidney transplantation in some patients with focal-segmental glomerulosclerosis has been linked to an upregulation of B7-1 (CD80), a costimulatory molecule normally expressed in T-lymphocytes, which changes foot process anchoring in podocytes.[90] The B7-1 inhibitor abatacept, approved for patients with rheumatoid arthritis, induces remission of proteinuria in both patients with post-transplant focal-segmental glomerulosclerosis and those with primary focal-segmental glomerulosclerosis.[91] Rare glomerulopathies involving podocyte integrins might also benefit from this new indication for abatacept.

Monoclonal antibodies have shown remarkable efficacy in several rare renal diseases. Eculizumab is a potent inhibitor of the terminal complement cascade (figure 3) and was first approved for paroxysmal nocturnal haemoglobinuria. Mendelian inherited forms of atypical haemolytic uraemic syndrome have been associated with changes in proteins that regulate the alternative complement pathway. The resulting excessive complement activation leads to renal and systemic thrombotic microangiopathy, which leads to high mortality, rapid progression to end-stage renal disease, and a high risk of recurrence after kidney transplantation.[87] In studies, eculizumab caused complete disease remission in most patients and investigators reported notable recovery of renal function.[92] Its highly selective mechanism of action and positive benefit–risk ratio also make eculizumab attractive for other complement-mediated diseases. Unfortunately, the prohibitive cost of eculizumab is demonstrative of the challenges that face drug development in rare diseases. The discovery that recessive loss-of-function mutations in *DGKE* causes atypical haemolytic uraemic syndrome without activation of the complement system suggests that eculizumab will not be effective for this subset of patients.[93]

Most *AVPR2* and *AQP2* mutations in nephrogenic diabetes insipidus result in retention of a normal protein within the endoplasmic reticulum (figure 3). Promising drugs include cell-permeable vasopressin-2 (V2) receptor antagonists and agonists that prevent the intracellular retention of mutated receptors in vitro.[26,88] Of note, V2 receptor antagonists might produce different effects depending on the various mutations.[94] In individuals with missense *AVPR2* mutations, a non-peptide vasopressin-1a receptor antagonist had beneficial effects on urine volume and osmolality within hours of administration.[95] Although the long-term efficacy of

this drug could not be tested (its clinical development was discontinued because of cytochrome P450 interaction) other pharmacological chaperones await further in-vivo testing. Chaperones might also become attractive for other diseases in which point mutations lead to defective folding and cellular trafficking of otherwise intact membrane proteins (eg, uromodulin-associated kidney diseases).[78] Developments in this specialty rely on high-throughput compound screening systems to reproduce mutations in individual renal-cell types.

Health policies

A major objective for the inherited kidney disorders community is to design methods so that approaches developed at highly specialised and resourced tertiary care centres (which have access to patient cohorts and diagnostic and genetic information) can be adopted in less-resource-intensive settings (which cover most of the population). Investigators should devise practical ways to promote the adoption and implementation of clinically relevant genetic testing. Changes to the medical model in many countries—increased patient empowerment, more active roles for patient organisations, possibilities of crowd-sourcing, and creation of online communities— will probably favour genetic interpretation on a personal level. Best practice guidelines for diagnosis and treatment of rare inherited kidney disorders are being established.[96] Equally important will be measures to ensure delivery and to support the effect of the genetic information on physicians, patients, and society.[30,31] These efforts are supported by numerous network and initiatives, and by organisations such as National Organisations of Rare Disorders (NORD) in the USA and Orphanet in Europe.

Research for rare diseases is expected to have important repercussions on public health policies. Measures to translate research insights into clinical benefit include creation of centres of excellence with adequate diagnostic and therapeutic capabilities, genetic counselling, early detection by global or targeted public screening programmes, and facilitated approval of novel orphan drugs.[97] Insights from research into rare diseases could also be used to modify established public health measures through identification of patients at particular risk. For instance, results of a study of children with idiopathic hypercalciuria identified mutations in CYP24A1 gene coding for the vitamin D metabolising enzyme as the underlying pathology.[98] Subsequently, investigators also detected mutations in this gene in patients who developed severe hypercalcaemia after prophylactic bolus vitamin D administration, thereby identifying a subset of individuals intolerant to this public health measure.

Finally, we stress that patient organisations have a crucial role in closing of the gap between mechanistic understanding and the development of drugs for rare diseases.[99,100] Patients work with physicians and researchers to share personal insights, provide biological samples, contact family members, and participate in clinical trials. Patient organisations can foster these activities and provide support to the community. Examples in rare kidney diseases include associations for cystic kidney disorders, primary hyperoxaluria, cystinosis, Lowe's syndrome, metabolic disorders, and so on. Coalitions of patient organisations have been important stakeholders in health policies, helping to pass the US Orphan Drug Act in 1983 and to establish the Framework Programme 7 research agenda in Europe.

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Search strategy and selection criteria

We searched PubMed and Medline for articles published in English with search terms that included, but were not restricted to, “inherited kidney disease”, “orphan disease”, “rare disease”, “nephrogenetics”, “congenital abnormalities”, in combination with “kidney” or “urinary tract”, “ciliopathies”, “tubulopathies”, “nephrolithiasis”, “glomerular diseases”, “cystic diseases”, “glomerulus”, “proximal tubule”, “thick ascending limb”, “distal tubule”, “collecting duct”, “-omics”, and “model organisms”. We identified further reports from our own experience and from references cited in relevant articles and the Online Mendelian Inheritance in Man (OMIM) database. We did not use date restrictions for searches. We did our last search in March, 2014. We modified our reference list on the basis of comments from peer reviewers.

Panel: Milestones in research of inherited kidney diseases

Milestones in nephrogenetics

1985 Mapping the first gene location for an inherited kidney disorder (autosomal dominant polycystic kidney disease, on chromosome 16)[13]

1990 First detection of a point mutation at a specific locus single-gene disorder, *COL4A5*[14]

1992 Molecular basis of nephrogenic diabetes insipidus described[15]

1993 Identification of the tuberous sclerosis gene (*TSC2*)

1994 Cloning of the *PKD1* gene, responsible for about 85% of autosomal dominant polycystic kidney disease cases; challenging due to the size (46 exons) and complex organisation (presence of six highly homologous sequences of exons 1–33) of the gene on chromosome 16p13·3[16]

1994 Liddle's syndrome reported to be due to activating mutation of the sodium channel ENaC[17]

1996 Molecular basis for inherited kidney stone diseases identified[18]

1996 Molecular basis of Bartter's and Gitelman's syndromes described[19,20]

1996 Cloning of *PKD2*, the second gene involved in autosomal dominant polycystic kidney disease

1997 First nephronophthisis gene reported on

1998 Mutations in factor H reported to cause atypical haemolytic uraemic syndrome

1998 Molecular basis of cystinosis described[21]

1999 Mutations in a paracellular protein (claudin-16) causes familial hypomagnesaemia with hypercalciuria

2000 Podocin (*NPHS2*) described as the major gene for steroid-resistant nephrotic syndrome[22]

2001 Mutations in different genes shown to cause Bardet–Biedl syndrome (digenic inheritance)

2001 Mutations in WNK kinases shown to change regulation of sodium, potassium, and blood pressure

2002 Mutations in *UMOD* (Tamm-Horsfall protein) shown to cause familial juvenile hyperuricaemic nephropathy, an autosomal dominantly inherited form of interstitial nephritis[23]

2005 Mutations in a cation channel (TRPC6) described to cause glomerular disease

2010 First success of exome sequencing in rare renal diseases (*SDCCA8* in Senior-Løken syndrome; retinal-renal ciliopathy)[24]

2011 Broad spectrum and clinical heterogeneity of *HNF1B* gene mutations shown

2013 Description of *MUC1* as the cause of medullary cystic kidney disease type 1; the gene was missed by massive parallel sequencing, showing the need for refinement of analysis methods and assessment of clinical use of whole-exome sequencing for autosomal dominant heterogeneous disorders

2014 First description of mutation-dependent recessive inheritance in the case of *NPHS2*-associated steroid-resistant nephrotic syndrome[25]

Milestones in treatment

1981 Oral cysteamine given for cystinosis

2000 Enzyme replacement therapy for Fabry's disease

2000 First in-vitro evidence that pharmacological chaperones can rescue cell-surface expression and function of misfolded vasopressin 2 receptors in nephrogenic diabetes insipidus[26]

2005 First open-label, randomised, crossover, placebo-controlled trial for the effect of somatostatin analogue octreotide longacting release in autosomal dominant polycystic kidney disease

2008 Development of mTOR inhibitors for tuberous sclerosis

2009 Eculizumab for atypical haemolytic uraemic syndrome

2009 Proof-of-principle for use of bone marrow transplantation for treatment of mouse model with cystinosis[27]

2009 Randomised, double-blind, placebo-controlled trial of the effect of somatostatin analogue lanreotide in polycystic liver disease associated with autosomal dominant polycystic kidney disease

2012 Global, randomised, double-blinded, placebo-controlled trial of the vasopressin 2 receptor antagonist tolvaptan in autosomal dominant polycystic kidney disease

2013 First randomised, single-blind, placebo-controlled, multicentre trial of octreotide longacting release for autosomal dominant polycystic kidney disease

Complete reference list included in the appendix.

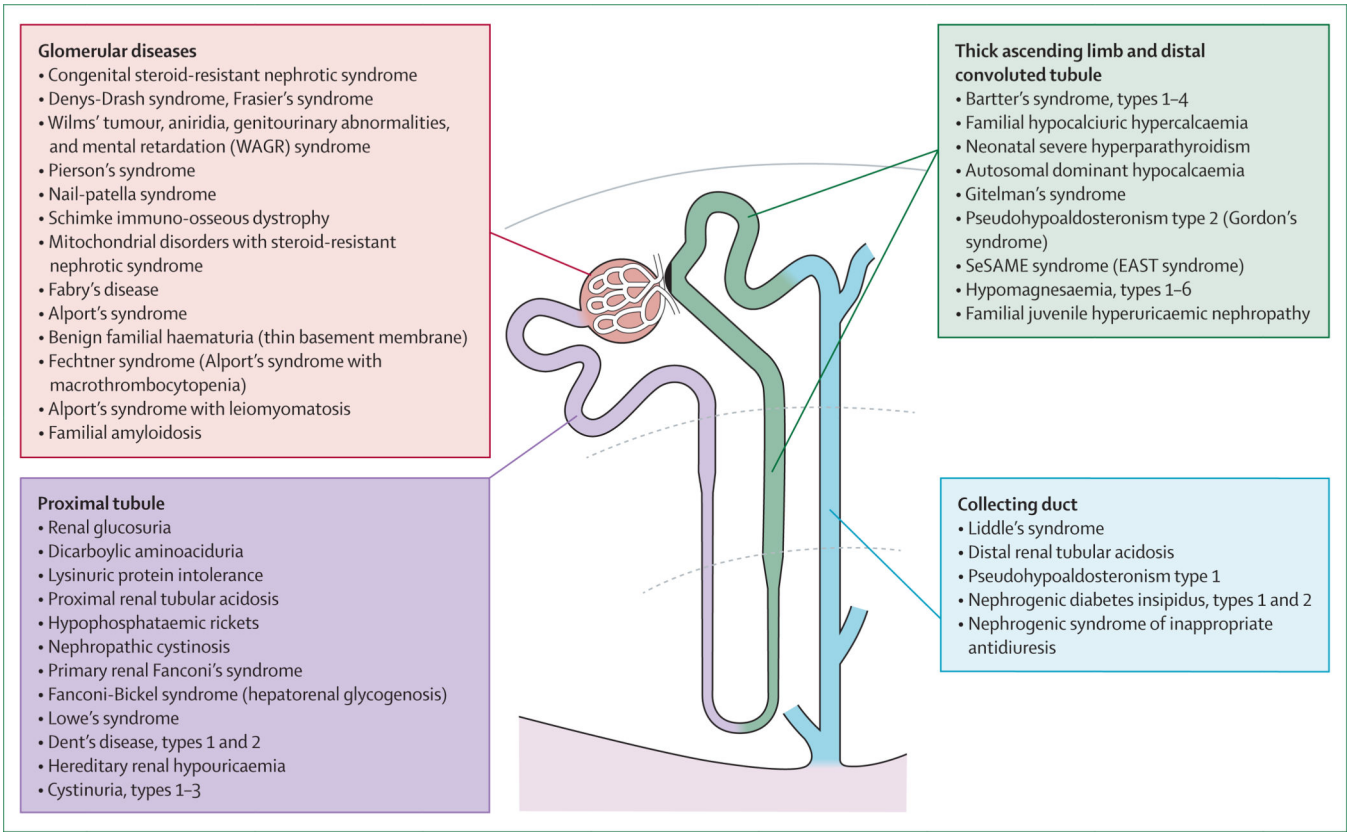

Figure 1. Inherited kidney disorders linked to nephron segments

Shows the segmental distribution of rare inherited diseases of the kidney (does not include cystic and developmental disorders). Urinalysis might point to the segmental origin of some kidney disorders. For example, glomerular diseases are usually characterised by albuminuria and dysmorphic red blood cells in urine; disorders of the proximal tubule by inappropriate urinary loss of low-molecular-weight proteins (eg, Clara Cell protein, β2-microglobulin, and vitamin D-binding protein), aminoacids, glucose, phosphate, uric acid, and calcium; disorders of the thick ascending limb by hypercalciuria and urinary concentrating defects; disorders of the distal convoluted tubule by inappropriate urinary loss of magnesium; and disorders of the collecting duct by inappropriate urinary concentration or dilution and defective potassium handling.

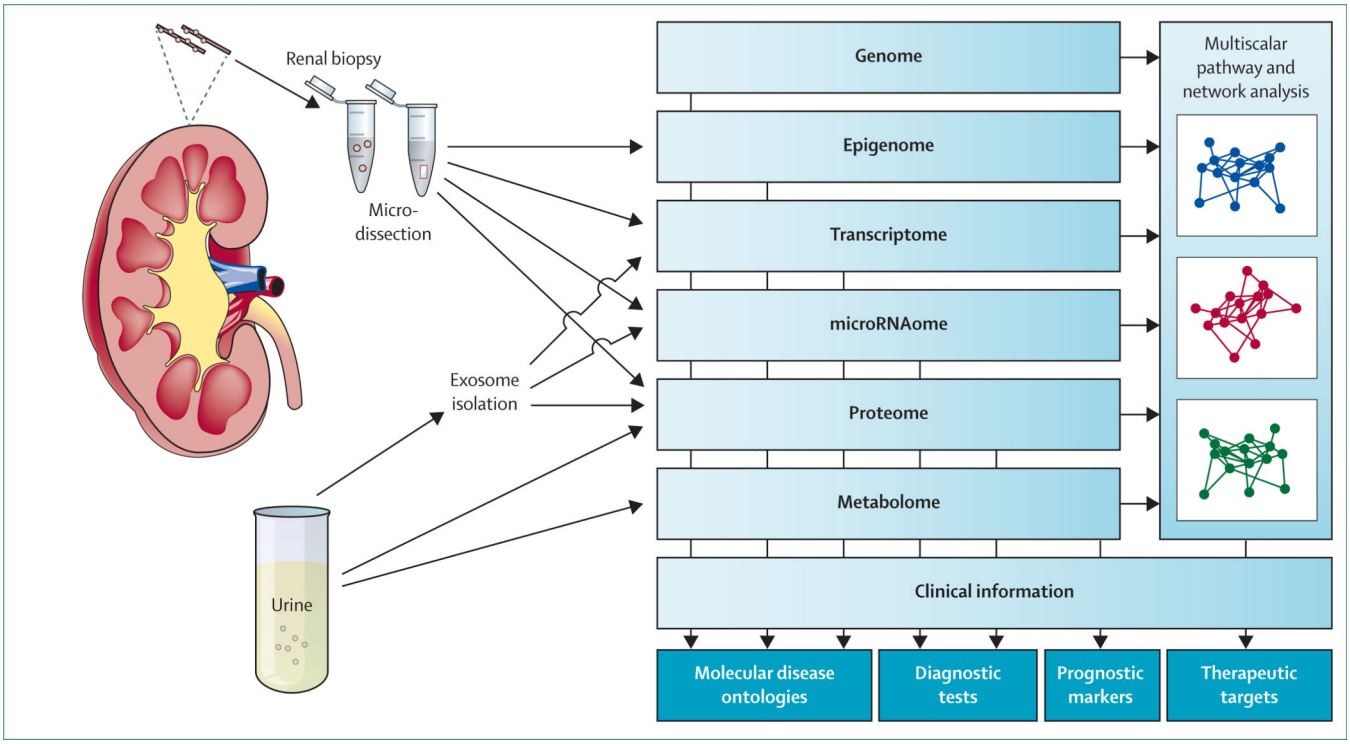

Figure 2. Application of omics technologies in rare kidney diseases

Next-generation sequencing techniques and omics technologies, which can directly probe the kidney, will improve diagnostic efficiency for genetic renal diseases. Genomic studies and molecular profiling of kidney tissues, plain and exosome-enriched urine, and multiscalar bioinformatic analysis of crucial disease pathways, will allow the development of mechanistic renal disease ontologies, diagnostic tests, biomarkers, and novel therapeutic targets.

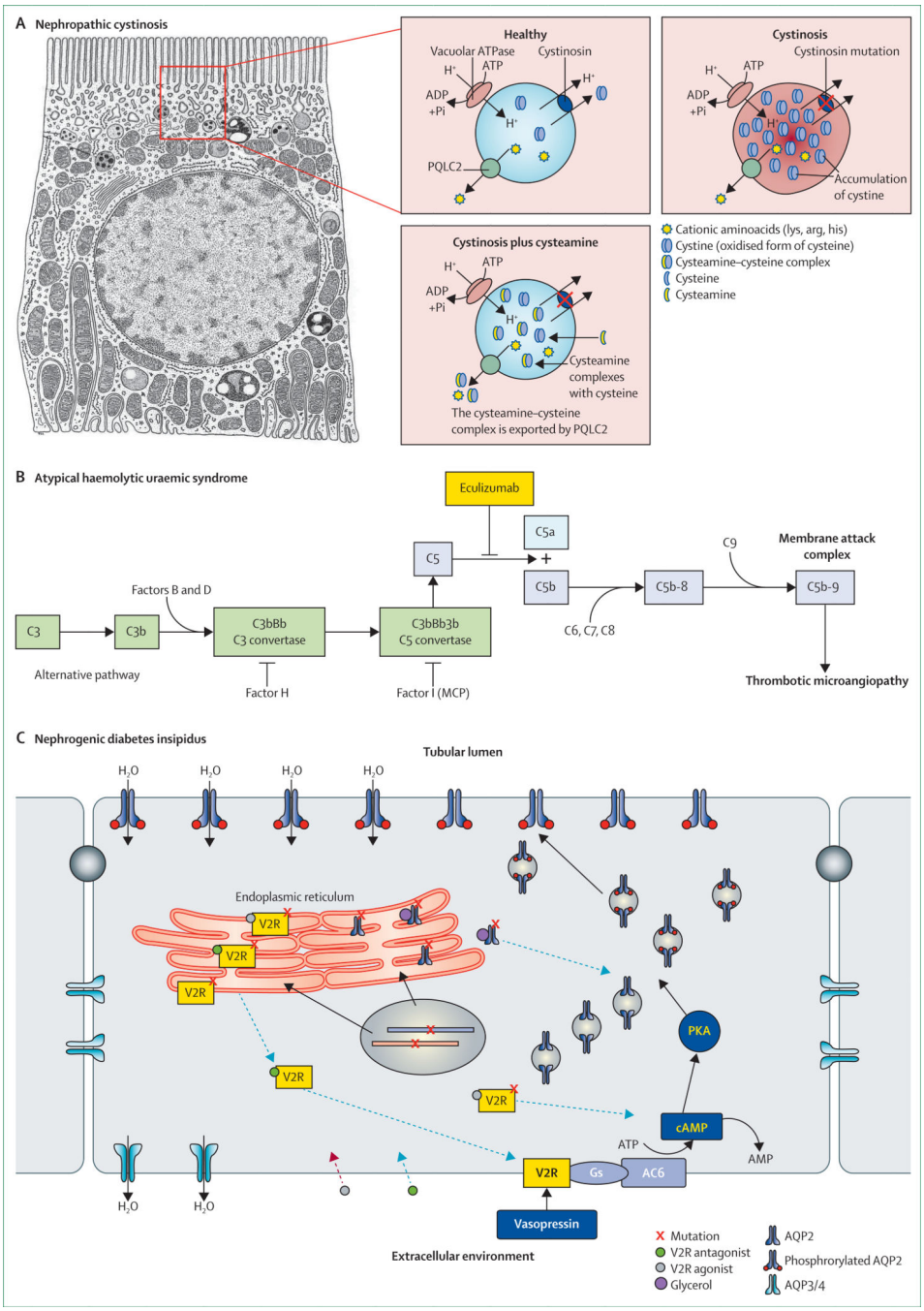

Figure 3. Examples of molecular targets in rare inherited kidney diseases

(A) Cystinosis is caused by defective cystinosin, a ubiquitous lysosomal proton-driven cystine transporter working in parallel with the vacuolar H+–ATPase. In patients with cystinosis, the loss of function of cystinosin causes cystine to accumulate in lysosomes (shown here in a proximal tubule cell). Cysteamine reduces the accumulation of cysteine by entering lysosomes and forming a cysteamine–cysteine complex, which resembles lysine and can be exported by PQLC2. Modified from Jézégou and colleagues.[86] (B) Patients with haemolytic uraemic syndrome have uncontrolled complement activation due to deficiency of

natural complement regulatory factors. Eculizumab is a humanised monoclonal antibody that inhibits the cleavage of the complement protein C5, blocking complement activation and complement-mediated thrombotic microangiopathy in patients with haemolytic uraemic syndrome. Patients with haemolytic uraemic syndrome due to recessive mutations in *DGKE*, which is not associated with activation of the complement system, do not respond to eculizumab or plasma exchange. Modified from Noris and colleagues.[87] (C) In the principal cells that line the collecting ducts, stimulation of the vasopressin-2 receptor (V2R) by vasopressin leads to an increase in cAMP, causing a protein kinase A (PKA)-mediated phosphorylation of AQP2 and their insertion into the apical plasma membrane. The resulting increase in transcellular water permeability mediates concentration of urine. Most mutations in *AVPR2* (X-chromosome-linked nephrogenic diabetes insipidus) and *AQP2* (autosomal recessive nephrogenic diabetes insipidus) result in misfolded V2R and AQP2 mutations in the endoplasmic reticulum (class 2 mutations). Pharmacological chaperones (eg, glycerol) can rescue such class 2 mutant proteins from the endoplasmic reticulum. Cell-permeable V2R antagonists stabilise the structure of mutant V2R and allow them to exit the endoplasmic reticulum and translocate to the basolateral plasma membrane. At the membrane, vasopressin will displace the antagonist and allow restoration of the cAMP cascade. This action of V2R antagonists can depend on V2R mutation. V2R agonists function similarly and might also stimulate misfolded V2R in the endoplasmic reticulum without inducing maturation. Mutant AQP2 can be rescued from the endoplasmic reticulum by glycerol. Modified from Robben and colleagues.[88]

Table 1

List and classification of genetic disorders of renal growth and structure

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
Congenital abnormalities of the kidney and urinary tract				
Renal hypodysplasia or aplasia	All autosomal recessive	RET; PAX2; UPK3A	Tyrosine-kinase receptor; transcription factor; membrane protein	191830
Vesicoureteral reflux	All autosomal dominant	ROBO2; SOX17; TNXB	Transmembrane receptor; transcription factor; extracellular matrix glycoprotein	610878; 613674
Renal coloboma syndrome	Autosomal dominant	PAX2	Transcription factor	120330
Renal cysts and diabetes syndrome	Autosomal dominant	HNF1B	Transcription factor	137920
Branchio-otorenal syndrome	All autosomal dominant	EYA1; SIX1; SIX5	Transcriptional coactivator; transcription factor; transcription factor	113650
Fraser's syndrome	All autosomal recessive	FRAS1; GRIP1; FREM2	Extracellular matrix protein; receptor interacting protein; extracellular matrix protein	219000
Urofacial (Ochoa) syndrome	Both autosomal recessive	HPSE2; LRIG2	Matrix enzyme; membrane protein	236730; 615112
Hypoparathyroidism, deafness, renal disease syndrome	Autosomal dominant	GATA3	Transcription factor	146255
Kallmann's syndrome	KAL1 is X-chromosome	KAL1; FGFR1	Adhesion-like protein, protease inhibitor; tyrosine-kinase receptor	308700;
(subtypes with renal phenotype)	linked and FGFR1 is autosomal recessive			147950
Split-hand–split-foot malformation	Autosomal dominant	Duplication of 10q24	..	246560
Townes-Brocks syndrome	Autosomal dominant	SALL1	Transcription factor	107480
Perlman's syndrome (nephroblastomatosis, gigantism) Simpson-Golabi-Behmel syndrome (gigantism, enlarged dysplastic kidneys)	Autosomal recessive	DIS3L2	Ribonuclease	267000
Type 1	X-chromosome linked	GPC3	Heparin sulphate proteoglycan	312870
Type 2	X-chromosome linked	OFD1	Centrosome protein involved in ciliogenesis	300209
Renal tubular dysgenesis	All autosomal recessive	REN; AGT; AGTR1; ACE	Endopeptidase (angiotensinogenase); secreted peptide; G-protein coupled receptor; carboxypeptidase	267430
Ciliopathies				
Autosomal dominant polycystic kidney disease, type 1 and type 2†	Both autosomal dominant	PKD1; PKD2	Both ciliary proteins, involved in mechanosensation and cell signalling	173900; 613095
Autosomal recessive polycystic kidney disease	Autosomal recessive	PKHD1	Receptor-like cilium and cytoskeleton protein (centrosome regulator)	263200
Medullary cystic kidney disease and familial juvenile hyperuricaemic nephropathy	All autosomal dominant	UMOD; REN; MUC1	Surface-bound and secreted glycoprotein (Tamm-Horsfall protein);	603860; 613092; 174000

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
			endopeptidase (angiotensinogenase); surface glycoprotein	
Nephronophthisis				
Type 1	Autosomal recessive	NPHP1	Ciliary protein, involved in organisation of apical junctions	256100
Type 2	Autosomal recessive	INVS	Ciliary protein, associates with microtubules, inhibits WNT signalling	602088
Type 3	Autosomal recessive	NPHP3	Ciliary protein, inhibits WNT signalling	604387
Type 4	Autosomal recessive	NPHP4	Ciliary protein, involved in organisation of apical junctions	606966
Type 5 (Senior-Løken syndrome 5)	Autosomal recessive	IQCB1	Centrosome protein, involved in ciliogenesis	609254
Type 6 (Joubert's syndrome 5)	Autosomal recessive	CEP290	Centrosome protein, involved in ciliogenesis	610188
Type 7	Autosomal recessive	GLIS2	Transcription factor	611498
Type 8 (Joubert's syndrome 7)	Autosomal recessive	RPGRIP1L	Centrosome protein, regulates TXA2 receptor signalling	611560
Type 9	Autosomal recessive	NEK8	Serine–threonine protein kinase, targets proteins to cilia	613824
Type 10 (Senior-Løken syndrome 7)	Autosomal recessive	SDCCAG8	Centrosome-associated protein, might be involved in ciliogenesis	613615
Type 11	Autosomal recessive	TMEM67	Ciliary protein, involved in centrosome migration	613550
Type 12	Autosomal recessive	TTC21B	Ciliary protein, involved in retrograde ciliary transport	613820
Type 13	Autosomal recessive	WDR19	Ciliary protein, involved in retrograde ciliary transport	614377
Type 14	Autosomal recessive	ZNF423	Centrosome protein, involved in DNA damage response	614844
Type 15	Autosomal recessive	CEP164	Centrosome protein, involved in DNA damage response	614845
Type 16	Autosomal recessive	ANKS6	Ciliary protein	615382
Joubert's syndrome (subtypes with renal phenotype)				
Type 1	Autosomal recessive	INPP5E	Inositol trisphosphate phosphatase	213300
Type 2	Autosomal recessive	TMEM216	Ciliary protein, might be involved in ciliogenesis	608091
Type 3	Autosomal recessive	AHI1	Basal body protein, might be involved in ciliary signalling	608629
Type 4	Autosomal recessive	NPHP1	Ciliary protein, involved in organisation of apical junctions	609583
Type 5	Autosomal recessive	CEP290	Centrosome protein, involved in ciliogenesis	610188
Type 6	Autosomal recessive	TMEM67	Ciliary protein, involved in centrosome migration	610688
Type 7	Autosomal recessive	RPGRIP1L	Centrosome protein, regulates thromboxane-A2 receptor signalling	611560
Type 9	X-chromosome linked	CC2D2A	Ciliary protein, involved in ciliogenesis and SHH signalling	612285

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
Type 10	Autosomal recessive	OFD1	Centrosome protein, involved in ciliogenesis	300804
Type 11	Autosomal recessive	TTC21B	Ciliary protein, involved in retrograde ciliary transport	613820
Type 14	Autosomal recessive	TMEM237	Ciliary protein, involved in ciliogenesis	614424
Type 15	Autosomal recessive	CEP41	Centrosome protein, required during ciliogenesis	614464
Type 16	Autosomal recessive	TMEM138	Multipass transmembrane protein required for ciliogenesis	614465
Type 18	Autosomal recessive	TCTN3	Membrane protein, required for ciliogenesis and SHH signalling	614815
Type 19	Autosomal recessive	ZNF423	Centrosome protein, involved in DNA damage response	614844
Type 20	Autosomal recessive	TMEM231	Ciliary protein, required for ciliogenesis and SHH signalling	614970
Type 21	Autosomal recessive	CSPP1	Centrosome protein, involved in spindle organisation	615636
Type 22	Autosomal recessive	PDE6D	Phosphodiesterase, involved in ciliogenesis	615665
Meckel-Gruber syndrome				
Type 1	Autosomal recessive	MKS1	Ciliary protein, regulates cilia structure and function	249000
Type 2	Autosomal recessive	TMEM216	Ciliary protein, might be involved in ciliogenesis	603194
Type 3	Autosomal recessive	TMEM67	Ciliary protein, involved in centrosome migration	607361
Type 4	Autosomal recessive	CEP290	Centrosome protein, involved in ciliogenesis	611134
Type 5	Autosomal recessive	RPGRIP1L	Centrosome protein, regulates thromboxane-A2 receptor signalling	611561
Type 6	Autosomal recessive	CC2D2A	Ciliary protein, involved in ciliogenesis and SHH signalling	612284
Type 7	Autosomal recessive	NPHP3	Ciliary protein, inhibits WNT signalling	267010
Type 8	Autosomal recessive	TCTN2	Ciliary protein, involved in ciliogenesis	613885
Type 9	Autosomal recessive	B9D1	Ciliary protein, involved in ciliogenesis	614209
Type 10	Autosomal recessive	B9D2	Ciliary protein, involved in ciliogenesis	614175
Type 11	Autosomal recessive	TMEM231	Ciliary protein, required for ciliogenesis and SHH signalling	615397
Short rib-polydactyly syndrome (Jeune's syndrome)				
Type 1	Autosomal recessive	Unknown	..	208500
Type 2	Autosomal recessive	IFT80	Ciliary protein, involved in anterograde ciliary transport	611263
Type 3	Autosomal recessive	DYNC2H1	Ciliary motor protein, involved in retrograde ciliary transport	613091
Type 4	Autosomal recessive	TTC21B	Ciliary protein, involved in retrograde ciliary transport	613819

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
Type 5	Autosomal recessive	WDR19	Ciliary protein, involved in retrograde ciliary transport	615633
Type 6	Autosomal recessive	NEK1	Centrosomal serine–threonine protein kinase, involved in ciliogenesis	263520
Type 7	Autosomal recessive	WDR35	Ciliary protein, involved in retrograde ciliary transport	614091
Type 8	Autosomal recessive	WDR60	Ciliary base protein, involved in ciliogenesis	615503
Type 9	Autosomal recessive	IFT140	Ciliary protein, involved in retrograde ciliary transport	266920
Type 10	Autosomal recessive	IFT172	Ciliary protein, involved in anterograde ciliary transport	615630
Type 11	Autosomal recessive	WDR34	Ciliary protein, involved in retrograde ciliary transport	615633
Bardet-Biedl syndrome				
Type 1	Autosomal recessive	BBS1	BBSome complex protein, required for ciliogenesis	209900
Type 2	Autosomal recessive	BBS2	BBSome complex protein, required for ciliogenesis	209900
Type 3	Autosomal recessive	ARL6	Cilium base protein, targets BBSome to plasma membrane	209900
Type 4	Autosomal recessive	BBS4	BBSome complex protein, required for ciliogenesis	209900
Type 5	Autosomal recessive	BBS5	BBSome complex protein, required for ciliogenesis	209900
Type 6	Autosomal recessive	MKKS	Chaperone, may assist folding of BBSome proteins	209900
Type 7	Autosomal recessive	BBS7	BBSome complex protein, required for ciliogenesis	209900
Type 8	Autosomal recessive	TTC8	BBSome complex protein, required for ciliogenesis	209900
Type 9	Autosomal recessive	PTHB1	BBSome complex protein, required for ciliogenesis	209900
Type 10	Autosomal recessive	BBS10	Chaperone, affects folding and stability of ciliary and basal body proteins	209900
Type 11	Autosomal recessive	TRIM32	E3 ubiquitin ligase activity	209900
Type 12	Autosomal recessive	BBS12	Chaperone, assists folding of BBSome proteins	209900
Type 13	Autosomal recessive	MKS1	Ciliary protein, regulates cilia structure and function	209900
Type 14	Autosomal recessive	CEP290	Centrosome protein, involved in ciliogenesis	209900
Type 15	Autosomal recessive	Human fritz (WDPCP; C2orf86)	Controls ciliogenesis by regulating septin cytoskeleton	209900
Type 17	Autosomal recessive	LZTFL1	BBSome regulator, involved in ciliogenesis	209900
Alström's syndrome	Autosomal recessive	ALMS1	Centrosome protein, required for cilia formation and maintenance	203800
Cranioectodermal dysplasia				
Type 1	Autosomal recessive	IFT122	Ciliary proteins, involved in retrograde ciliary transport	218330

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
Type 2	Autosomal recessive	WDR35	Ciliary proteins, involved in retrograde ciliary transport	613610
Type 3	Autosomal recessive	IFT43	Ciliary proteins, involved in retrograde ciliary transport	614099
Type 4 (Sensenbrenner syndrome)	Autosomal recessive	WDR19	Ciliary proteins, involved in retrograde ciliary transport	614378
Oral-facial-digital syndrome type 1	X-chromosome linked	OFD1	Centrosome protein, involved in ciliogenesis	311200
Renal-hepatic-pancreatic dysplasia	Autosomal recessive	NPHP3 (nephrocystin-3); NEK8 (nephrocystin-9)	Ciliary protein, inhibits WNT signalling; serine–threonine protein kinase, might target proteins to cilia	208540; 615415

MIM=Mendelian Inheritance in Man.

*HUGO Gene Nomenclature Committee symbol. †Not classified as a rare disease.

Table 2

List and classification of genetic disorders of renal function

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
Glomerular diseases				
Autosomal recessive steroid-resistant nephrotic syndrome	All autosomal recessive	NPHS1; NPHS2; PLCE1; MYO1E; PTPRO; DGKE; ARHGDIA	Podocyte adhesion receptor, component of slit diaphragm; podocyte membrane protein, links slit diaphragm to cytoskeleton; phospholipase, regulates protein kinase C pathway and small GTPases; cytoplasmic protein, regulates actin cytoskeleton functions; receptor-type tyrosine phosphatase; enzyme involved in cell signalling, activates protein kinase C pathway; cytoplasmic protein, involved in Rho protein signalling	256300; 600995; 610725; 614131; 614196; 615008; 615244
Autosomal dominant steroid-resistant nephrotic syndrome	All autosomal dominant	WT1; INF2; ACTN4; TRPC6	Transcription factor; cytoplasmic protein, severs actin filaments; F-actin cross-linking cytoplasmic protein; receptor-activated calcium channel	256370; 613237; 603278; 603965;
Denys-Drash syndrome, Frasier's syndrome	Autosomal dominant	WT1	Transcription factor	194080; 136680
WAGR (Wilms' tumour, aniridia, genitourinary anomalies, retardation) syndrome	Autosomal dominant	WT1 and PAX6	Transcription factors	194072
Pierson's syndrome	Autosomal recessive	LAMB2	Extracellular matrix glycoprotein	609049
Nail-patella syndrome	Autosomal dominant	LMX1B	Transcription factor	161200
Schimke immuno-osseous dystrophy	Autosomal recessive	SMARCAL1	Annealing helicase, catalyses rewinding of unwound DNA	242900
Mitochondrial disorders with steroid-resistant nephrotic syndrome: primary coenzyme Q_{10} deficiency, types 1 and 6	All autosomal recessive	COQ2; COQ6; ADCK4	Enzyme involved in coenzyme Q_{10} biosynthesis; enzyme involved in coenzyme Q_{10} biosynthesis; mitochondrial protein involved in coenzyme Q_{10} biosynthesis	607426; 614650; 615573
Fabry's disease	X-chromosome linked	GLA	Lysosomal enzyme, catalyses galactosyl–glycolipid moieties	301500
Alport's syndrome	X-chromosome linked; autosomal recessive	COL4A5; COL4A4; COL4A3	α5-chain of type IV collagen; α4-chain of type IV collagen; α3-chain of type IV collagen	301050; 203780; 615573
Benign familial haematuria (thin basement membane nephropathy)	Autosomal dominant	COL4A3	α3-chain of type IV collagen	141200
Fechtner's syndrome (Alport's syndrome with macrothrombocytopenia)	Autosomal dominant	MYH9	Non-muscle myosin, involved in cell shape and movement	153640
Alport's syndrome with leiomyomatosis	X-chromosome linked	COL4A5 and COL4A6 (contiguous gene deletion)	α5-chains and α6-chain of type IV collagen	308940

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
Familial amyloidosis	All autosomal dominant	FGA; LYZ; APOA1; B2M	Secreted protein; secreted enzyme; secreted lipoprotein; secreted protein	105200
Renal tubular diseases and metabolic diseases				
Renal glucosuria	Autosomal recessive and autosomal dominant	SLC5A2	Sodium–glucose cotransporter	233100
Dicarboylic aminoaciduria	Autosomal recessive	SLC1A1	Glutamate transporter	222730
Lysinuric protein intolerance	Autosomal recessive	SLC7A7	Cationic aminoacid transporter	222700
Proximal renal tubular acidosis	Autosomal recessive	SLC4A4	Sodium bicarbonate cotransporter	604278
Distal renal tubular acidosis	Autosomal dominant	SLC4A1	Inorganic anion transmembrane transport protein	179800
Renal tubular acidosis with osteopetrosis	Autosomal recessive	CA2	Enzyme involved in bicarbonate transport	259730
Hypophosphataemic rickets	X-chromosome linked; autosomal dominant; autosomal recessive; autosomal recessive;	PHEX; FGF23; ENPP1; DMP1	Endopeptidase, degrades FGF23; osteocyte hormone, inhibits tubular phosphate reabsorption; pyrophosphatase, regulates mineralisation; osteoblast transcriptional activator or osteocyte matrix regulator	307800; 193100; 613312; 241520
Nephropathic cystinosis	Autosomal recessive	CTNS	Lysosomal membrane cystine transporter	219800
Primary renal Fanconi's syndrome, types 1 and 2	Autosomal dominant; autosomal recessive	15q15.3; SLC34A1	Affected genes unknown; sodium–phosphate cotransporter	134600; 613388
Fanconi-Bickel syndrome (hepatorenal glycogenosis)	Autosomal recessive	SLC2A2	Facilitated glucose transporter	227810
Dent's disease				
Type 1	X-chromosome linked	CLCN5	Chlorid-proton exchanger	300009
Type 2	X-chromosome linked	OCRL	5-phosphatase, regulates early endosomes	300555
Lowe oculocerebrorenal syndrome	X-chromosome linked	OCRL	5-phosphatase, regulates early endosomes	309000
Hereditary renal hypouricaemia	Autosomal recessive	SLC22A12	Urate transporter	220150
Familial juvenile hyperuricaemic nephropathy; medullary cystic kidney disease type 2	All autosomal dominant	UMOD; REN; MUC1	Surface-bound and secreted glycoprotein (Tamm–Horsfall protein); endopeptidase (angiotensinogenase); surface glycoprotein	603860 and 162000; 613092; 174000
Bartter's syndrome, types 1–4	SLC12A1, KCNJ1, and BSND are autosomal recessive; CLCNKB is autosomal recessive or digenic; BSND is digenic	SLC12A1; KCNJ1; CLCNKB; CLNCKA; BSND	Sodium–potassium–chloride cotransporter; potassium channel; chloride channel; chloride channel; β-subunit of CLCNKA and CLCNKB chloride channels	601678; 241200; 607364; 613090; 602522
Gitelman's syndrome	Both autosomal recessive	SLC12A3; CLCNKB	Thiazide-sensitive sodium–chloride cotransporter; chloride channel	263800
Familial hypocalciuric hypercalcaemia, type 1; neonatal severe hyperparathyroidism; utosomal dominant hypocalcaemia (including with Bartter's syndrome)	Autosomal dominant; autosomal recessive; autosomal dominant	CASR	Calcium-sensing receptor (loss of function); calcium-sensing receptor	145980; 239200; 601198

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
			(loss of function); calcium-sensing receptor (gain of function)	
Hypomagnesaemia				
Type 1 (intestinal)	Autosomal recessive	TRPM6	Magnesium channel	602014
Type 2 (renal)	Autosomal dominant	FXYD2	Gamma subunit of sodium–potassium–ATPase	154020
Type 3 (renal)	Autosomal recessive	CLDN16	Paracellular protein, component of tight junctions	248250
Type 4 (renal)	Autosomal recessive	EGF	Epidermal growth factor	611718
Type 5 (renal, with ocular involvement)	Autosomal recessive	CLDN19	Paracellular protein, component of tight junctions	248190
Type 6 (renal)	Autosomal dominant	CNNM2	Membrane protein of unknown function	613882
Renal (associated with myokymia)	Autosomal dominant	KCNA1	Potassium channel	160120
Liddle's syndrome	Both autosomal dominant	SCNN1G; SCNN1B	γ-subunit of amiloride-sensitive sodium channel (gain of function); β-subunit of amiloride-sensitive sodium channel (gain of function)	177200
Pseudohypoaldosteronism type 1	Both autosomal recessive	SCNN1A; SCNN1G; SCNN1B	α-subunit of amiloride-sensitive sodium channel; γ-subunit of amiloride-sensitive sodium channel; β-subunit of amiloride-sensitive sodium channel	264350
Pseudohypoaldosteronism type 2 (Gordon's syndrome)	All autosomal dominant	WNK1; WNK4; KLHL3; CUL3	Serine–threonine kinase modulating sodium and potassium-coupled chloride transporters; serine–threonine kinase modulating sodium and potassium-coupled chloride transporters; structural protein mediating ubiquitination of SLC12A3; component of ubiquitin E3 ligase complex	614492; 614491; 614495; 614496
SeSAME syndrome (EAST; epilepsy, ataxia, sensorineural deafness, salt-wasting renal tubulopathy)	Autosomal recessive	KCNJ10	Potassium channel	612780
Distal renal tubular acidosis, isolated; distal renal tubular acidosis, with haemolytic anaemia; distal renal tubular acidosis, with progressive nerve deafness	All autosomal recessive	ATP6V0A4; SLC4A1; ATP6V1B1	Subunit of the vacuolar proton ATPase; anion exchanger (erythroid band 3); subunit of the vacuolar proton ATPase	602722; 611590; 267300
Nephrogenic syndrome of inappropriate antidiuresis	X-chromosome linked	AVPR2	G-protein coupled receptor for arginine-vasopressin (gain of function)	300539
Nephrogenic diabetes insipidus type 1;	X-chromosome linked;	AVPR2; AQP2	G-protein coupled receptor for arginine-vasopressin (loss of function);	304800;
nephrogenic diabetes insipidus type 2	autosomal dominant or autosomal recessive		water channel	125800
Nephrolithiasis				
Cystinuria, types 1–3	Autosomal recessive; autosomal dominant	SLC3A1; SLC7A9	Activator of cystine transporter SLC7A9; cysteine transporter	220100

	Transmission	Affected proteins*	Protein function	Phenotype MIM entry
Dent's disease type 1; Dent's disease type 2, Lowe's oculocerebrorenal syndrome	X-chromosome linked	CLCN5; OCRL	Chloride-proton exchanger; 5-phosphatase, regulates early endosomes	300009; 300555; 309000
Primary hyperoxaluria				
Type 1	Autosomal recessive	AGXT	Vitamin B6-dependent peroxisomal enzyme	259900
Type 2	Autosomal recessive	GRHPR	Peroxisomal enzyme	260000
Type 3	Autosomal recessive	HOGA1	Mitochondrial enzyme (hydroxyproline metabolic pathway)	613616
Adenine-phosphoribosyl-transferase deficiency	Autosomal recessive	APRT	Cytoplasmic enzyme forming AMP from adenine	614723
Xanthinuria type 1	Autosomal recessive	XDH	Key enzyme in purine degradation	278300

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