Kidney disease 2

Rare inherited kidney diseases: challenges, opportunities, and perspectives

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This is the second in a **Series** of two papers about kidney disease

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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 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 renal-replacement 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.

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.

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

***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.

See Online for appendix