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Rare diseases, rare presentations: recognizing atypical inherited kidney disease phenotypes in the age of genomics

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Abstract

A significant percentage of adults (10%) and children (20%) on renal replacement therapy have an inherited kidney disease (IKD). The new genomic era, ushered in by the next generation sequencing techniques, has contributed to the identification of new genes and facilitated the genetic diagnosis of the highly heterogeneous IKDs. Consequently, it has also allowed the reclassification of diseases and has broadened the phenotypic spectrum of many classical IKDs. Various genetic, epigenetic and environmental factors may explain 'atypical' phenotypes. In this article, we examine different mechanisms that may contribute to phenotypic variability and also provide case examples that illustrate them. The aim of the article is to raise awareness, among nephrologists and geneticists, of rare presentations that IKDs may show, to facilitate diagnosis.

Key words: ADPKD, ESRD, Fabry disease, FSGS, gene expression, inherited kidney diseases, NGS, phenotype

Introduction

Inherited kidney diseases (IKDs) are mostly rare diseases, which means, according to the European definition, that <1 in 2000 people suffer the disease, or that it affects <200 000 people in the USA [1]. Rare diseases are often categorized as orphan diseases to stress their severity, the insufficient resources devoted to them, the lack of available knowledge and the specific conditions for developing or producing drugs to treat them [2]. About 80% of rare diseases are genetic in origin and ∼50% of those affected are children [3]. Rare kidney diseases comprise at least 150 different disorders and have an overall prevalence of about 60–80 cases per 100 000 in Europe and the USA [4]. A single-gene mutation in any one of more than 200 different genes [3] can nowadays be identified in ∼20% of cases of chronic kidney disease (CKD) that manifest before the age of 25 years as well as 10% in adulthood. Nevertheless, these percentages are underestimated since there are many non-identified genes for several IKDs such as the congenital abnormalities of kidney and urinary tract (CAKUT), in which the majority of genetic causes are still unknown.

In a strict sense, some glomerular diseases also fall into the category of rare diseases, but this editorial will focus on IKDs,

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which account for around 10% of adult patients requiring renal replacement therapy. They constitute the fifth-most common cause of end-stage renal disease (ESRD) in developed countries after diabetes, hypertension, glomerulonephritis and pyelonephritis [2]. Although these figures have remained the same for decades, IKD has become a very active renal discipline only in the past two decades, and especially in the last. The number of manuscripts on IKDs has increased significantly during this period. There are many reasons for this: (i) the possibility of performing genetic testing with new genomic technologies; (ii) the development of therapies for some of these diseases; (iii) increasing awareness for IKDs triggered by educational programmes and professional societies; and (iv) improved interactions among adult and paediatric nephrologists and several healthcare professionals. As a result of this new trend, most journals and meetings now include a section devoted to IKDs.

The new genomic era, ushered in by the next generation sequencing (NGS) techniques, has facilitated the identification of the genetic basis of several IKDs. Some of the newly discovered genes are the cause of the disease in only a handful of families. This raises the question of how many more genes will be identified as being responsible for an IKD in a few families, and, consequently, what percentage of the current so-called nephropathies of uncertain origin will eventually be recognized as an IKD. Also, several IKDs are being reclassified or renamed based on their genetic cause. This has resulted in the replacement of classical nomenclature with new terminology that reflects the causative gene, such as '*UMOD*-related disease' instead of 'medullary cystic disease' [5], and 'HNF1B nephropathy' [6]. Also, focal segmental glomerulosclerosis (FSGS), which is a form of kidney disease defined by histology that usually seems to have an immunological basis, has in some patients been demonstrated to have a genetic aetiology [7–13]. Besides the more than 40 genes now described as causative of steroid-resistant nephrotic syndrome (SRNS) and/or FSGS, *COL4A3*–*COL4A5* genes have also been demonstrated to be involved in several cases of FSGS [14]. Consequently, genetics has the potential benefit of discerning diagnosis in such a heterogeneous disorder, which may help to avoid unnecessary immunosuppressive treatments.

The use of genomics in IKDs

The implementation of genomic medicine has been made possible by important advances in sequencing and bioinformatics in the last decade. NGS enables assessment of the entire genome or exome, allowing genomic medicine to take a hypothesis-free approach to genetic testing [15]. This does not mean that the nephrologist does not need to make precise clinical diagnoses, but the genomic analysis gives the power to diagnose patients with phenotypes that differ drastically from that described initially for the disease in question (Figure 1).

Targeted NGS of gene panels is improving diagnostic efficiency for IKDs through simultaneous analysis of all relevant genes for a given phenotype, at much reduced costs and faster turnaround times compared with testing sequentially one gene after another. This approach is becoming part of routine molecular diagnostics [9, 16–18]. Whole-exome sequencing (WES) is a most comprehensive approach and is often used when there are more complex clinical presentations or when gene panel testing has already proved negative [19–21]. WES has an average diagnostic yield of 20–25% but is more likely to return results of unknown significance than targeted NGS of gene panels.

Although these NGS approaches are technically feasible and relatively cheap, the amount of information that they generate

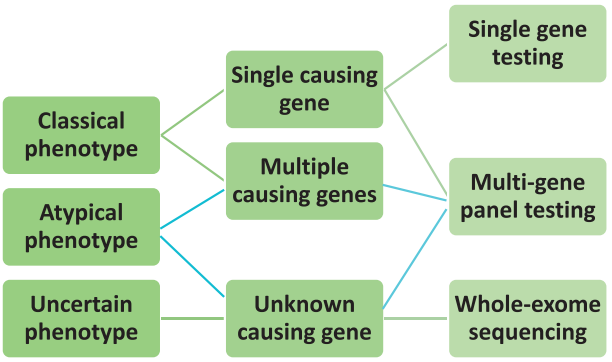

Fig. 1. Genetic testing options based on disease phenotype.

poses a new challenge due to the high number of DNA variants that each individual presents in respect to the reference sequence genome, many of which are not straightforward to interpret. Specific pipelines are used for the bioinformatic analysis of the thousands of variants identified. Determining the disease-causing mutation can be like looking for a needle in a haystack. For this purpose, variants are classified into different categories [pathogenic, likely pathogenic, variant of uncertain clinical significance (VUS), likely benign and benign]. The most widespread standards and guidelines for the classification and interpretation of sequence variants are those proposed by the American College of Medical Genetics and Genomics (ACMG) [22]. Each variant is individually assessed in the context of the variant, gene, associated disease, patient phenotype and family segregation. However, interpretations for some non-truncating variants may change over time as more information about the genetic variants and their related phenotypes becomes available in the public databases. A significant percentage of DNA variants deposited in genetic databases have falsely been assigned as disease causing. Widespread use of the ACMG guidelines [22] may result in a larger proportion of variants being classified as VUS, reducing the number of variants reported as 'causative' without having sufficient supporting evidence. Moreover, trying to interpret DNA variants in terms of phenotypic differences among patients affected by the same IKD (genetic modifiers, oligogenic inheritance, etc.) is even more complicated.

Potential causes of phenotypic variability in IKDs

Some potential explanations on why many phenotypes are so different from what would be expected are as follows (Figure 2).

Genetic heterogeneity

More than one gene causes a particular disease and, depending on the gene, the phenotype may differ. Several IKDs present with genetic heterogeneity. Examples include tuberous sclerosis complex (TSC), where patients with mutations in *TSC2* have a more severe phenotype than those with *TSC1* mutations [23], and autosomal dominant polycystic kidney disease (ADPKD), where patients with *PKD1* mutations reach ESRD about 20 years before those with *PKD2* mutations [24]. On the other hand, mutations in *UMOD*, *MUC1*, *REN* and *HNF1B* may cause similar autosomal dominant tubulointerstitial kidney disease (ADTKD) phenotypes [5], and recessive mutations in *COL4A3* and *COL4A4* cause also the same phenotype as *COL4A5* in Alport syndrome (AS) males.

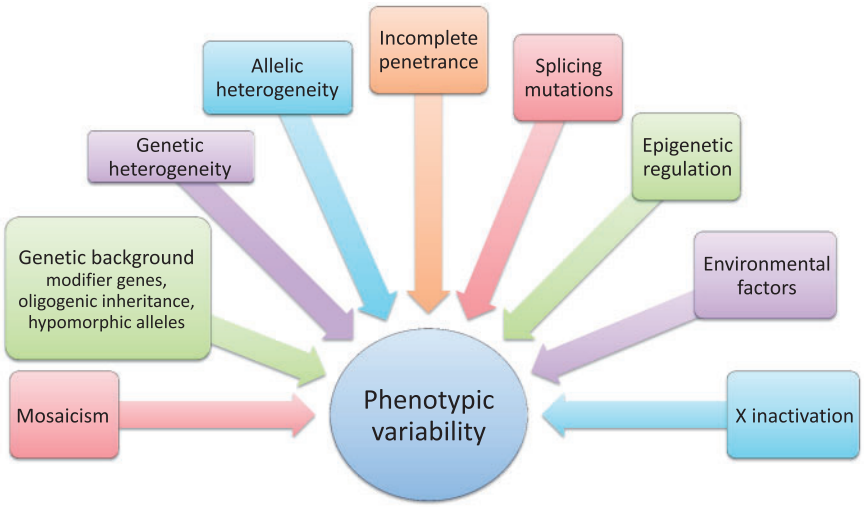

Fig. 2. Possible explanations for phenotypic variability in IKDs.

Allelic heterogeneity

Different mutations in a particular gene give rise to different phenotypes. In general, genotype–phenotype correlations are weaker for autosomal dominant monogenic disorders than for autosomal recessive diseases. For instance, carrying two truncating mutations in the *PKHD1* gene is associated with lethal autosomal recessive polycystic kidney disease (ARPKD), while the presence of at least one missense mutation is usually linked to a better outcome [25]. Similarly, the type of *PKD1* mutation influences renal outcome in ADPKD [26] since the extent of cyst formation in ADPKD is inversely correlated with the level of polycystin-1 function [27]. Mutations in the *OCRL* gene can cause Dent disease 2, which accounts for ~15% of all cases of Dent disease, or a more severe disease with extra-renal feature: Lowe syndrome. Dent disease 2 is considered, by some authors, to be a mild variant of Lowe syndrome [28]. It is unknown why some *OCRL* gene mutations cause Lowe syndrome and others cause Dent disease 2.

Incomplete penetrance

Some individuals with a given mutation do not develop the disease phenotype, which may mean that certain conditions with dominant inheritance may skip a generation in a pedigree. This is not a common situation in IKDs as most of these diseases are considered to be fully penetrant. However, patients with a single mutation in *COL4A4* or *COL4A3* can show only intermittent haematuria or even hardly ever have haematuria [29], and patients with a *MUC1* mutation can present with normal renal function in their 70s [5, 30]. The reason for incomplete penetrance may be related not only to the causative gene itself, but also to modifier genes. Also, in some sporadic cases or small families, some variants previously considered as pathogenic, but with incomplete penetrance, have nowadays been reclassified as VUS.

Oligogenic inheritance and modifier genes

The disease phenotype is determined by mutations in more than one gene. Oligogenic inheritance implies that these few genes exert an effect of comparable magnitude on the phenotype. Such inheritance has been suggested in some IKDs such as Bardet–Biedl syndrome [31], nephronophthisis [32] and AS [33]. Atypical haemolytic uraemic syndrome (aHUS) is also a very good example of oligogenic inheritance. Several families have been described with mutations in more than one gene causing aHUS, such as *DGKE*, complement genes and *THBD* among others [34–36].

In close relation to this, the concept of modifier genetic factor is used for a sequence variant that is supposed not to be a causative mutation but that contributes to the disease phenotype. Modifier variants can be located either in the causative gene, in addition to the causative mutation, or in other genes involved in common pathways.

Modifier genes probably play a relevant role in intrafamilial variability, especially in adult-onset diseases. In some cases of ADPKD, ADTKD and AS, there may be more than 30 years difference in the age at onset of ESRD in different family members. It has been reported that patients with mutations in genes known to cause SRNS and/or FSGS in combination with a heterozygous mutation in *COL4A3* may show a more severe phenotype than relatives with only mutations in SRNS genes, suggesting a modifier effect of *COL4A3* that might aggravate the phenotype of SRNS and/or FSGS [9]. Also, in studies of ADPKD families, a member presenting an early and severe disease has been found to carry an incompletely penetrant (hypomorphic) *PKD1* allele *in trans* with the familial *PKD1* mutation [37]. Hypomorphic alleles are DNA variants that by themselves give no phenotype or only a very mild one, but together with another hypomorphic allele or a mutation *in trans* worsen the severity of the disease. The role of genetic modifiers in ADPKD was particularly supported by the study from Persu *et al.*, where monozygotic twins showed significantly less clinical heterogeneity than genetically non-identical siblings [38].

Mosaicism

Mosaicism is a presence of two or more populations of cells with different genotypes in one individual. Depending on the expression of the mutated allele, in terms of both percentage and organ-specific expression, different phenotypes arise. The high-throughput nature of NGS technology allows for very high depth of coverage, with detection of a low percentage of the mutated variant in respect to the percentage of the wild-type

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allele. Mosaicism can explain mild clinical expression of the disease in a sporadic case. It also has to be taken into account during reproductive genetic counselling of the healthy parents of a *de novo* case of an autosomal dominant IKD. The parents could be counselled that there is an almost zero risk of having another affected child as the child is supposed to have a *de novo* mutation. However, this couple may conceive another affected child, and the reason is germinal mosaicism in one of the parents.

Epigenetic regulation

This is the dynamic alterations in the transcriptional potential of a cell that switch genes on and off, thereby modifying the phenotype. Examples of mechanisms that produce such changes are DNA methylation and histone modification, each of which alters how genes are expressed without altering the underlying DNA sequence. This is an open field for research in IKDs as very little is known. Most of the research on epigenetics has to date focused on cancer, but it certainly has a role to play in IKDs [39].

X inactivation

This is a process in which one of the copies of the X chromosome present in a female is inactivated. The inactive X chromosome is silenced and is transcriptionally inactive. The choice of which X chromosome will be inactivated is random in humans, but in certain cases the inactivation is skewed towards the wild-type or the mutated allele. If there is a high percentage (>90%) of cells with the wild-type allele inactivated, the disease is much more severe than would be expected for a female [40–42]. This phenomenon is organ specific; thus the findings in one cell type, or organ, cannot be extrapolated to other organs. Some examples of X-linked IKDs where this phenomenon may explain the phenotypic variability are Fabry disease (FD) [42], X-linked AS [43] and Dent's disease [44].

Splicing mutations

Clinical variability among patients carrying the same splicing mutation has been related to variable levels of aberrantly spliced transcripts [45]. This phenomenon may occur especially in splicing mutations that do not affect the intronic canonical splice sites (GT/AG). This type of splicing mutation generates a variable proportion of wild-type transcript, in addition to the aberrantly spliced transcript. The higher the proportion of the aberrantly spliced transcript, the more severe is the disease phenotype expected to be [46].

Environmental factors

Phenotype is influenced during embryonic development and throughout life by environmental factors. These factors are many and varied, and include diet, climate, drugs, illness and stress, among others. Although little is known specifically about environmental factors and IKDs [39], it is universally accepted, for example, that an inadequate diet may cause obesity, diabetes and hypertension, and that these conditions will worsen the IKDs phenotype.

Examples of atypical phenotypes in IKDs

Below we examine some examples of IKDs that highlight how atypical a rare renal disease can be, and especially how different its phenotype may be from the classical description. We also explain or speculate which of the above-described potential causes can contribute to the atypical phenotype.

AS

AS was first described by A.C. Alport in 1927 as an inherited renal disease associated with sensorineural deafness and a plethora of ocular abnormalities [47]. About 65% of patients have the X-linked form of AS [48], resulting from mutations in the *COL4A5* gene and showing a much more severe disease presentation in males than in females. In all, 15% of patients have autosomal recessive AS due to mutations in either *COL4A3* or *COL4A4*, with males and females being equally affected and showing similar disease severity. X-linked AS and autosomal recessive AS are the best-known forms of AS, but it is the so-called autosomal dominant AS, or familial haematuria or collagen IV (α3–α4) nephropathy, that is being increasingly diagnosed nowadays [29, 49]. This form is caused by heterozygous mutations in either *COL4A3* or *COL4A4*. Its prevalence is probably underestimated as some studies have shown that a significant percentage of patients with FSGS of uncertain aetiology carry a mutation in one *COL4* gene [14]. Its phenotype, which ranges from isolated haematuria to proteinuria and ESRD, suggests that a significant number of patients who reach dialysis with the hallmark of 'unknown nephropathy' or 'unspecific glomerulonephritis' may have a mutation in the *COL4A3*, *COL4A4* and *COL4A5* genes.

- A 50-year-old man presented with microhaematuria and proteinuria with a glomerular filtration rate (GFR) of 50 mL/min and without signs of hearing loss. His parents had normal urine sediment and preserved renal function. He had two daughters: a 20-year-old with haematuria and another with bland urine sediment at 25 years. Genetic testing of the patient disclosed a *COL4A5* mutation [c.3070G>A, p.(Gly1024Arg)] at an allele frequency of 30%, which revealed that he presented mosaicism. The daughter with haematuria presented the mutation in heterozygous state while the asymptomatic daughter did not carry the mutation.

After confirmation of paternity, the genetic results disclosed a gonosomal mosaicism (germinal and somatic mosaicism) in the father that explained the transmission of the X-linked AS to only one daughter (by definition a male affected by an X-linked disease will transmit it to all his daughters) as well as his mild disease presentation (due to coexistence of wild-type and mutated *COL4A5* in his kidney cells).

- A 56-year-old man was diagnosed with AS at 23 years of age after presenting with haematuria, proteinuria and hearing loss. He reached ESRD at 26 years of age and his brother reached ESRD at 28 years. Two of his daughters, with features of AS, reached ESRD at 24 and 25 years, respectively. They all have a splicing mutation *COL4A5* [c.2395 + 2T>A, p.(Gly749Valfs*20)] found to produce skipping of exon 29. It may be speculated that a skewed X inactivation of the wild-type COL4A5 allele in the females kidneys accounted for such a severe disease presentation in these women.

- A 32-year-old woman presented with SRNS and microhaematuria at 32 years of age, and her renal biopsy showed mesangioproliferative lesions with FSGS. Her renal function rapidly deteriorated, reaching ESRD at 33 years. Genetic testing identified a pathogenic splicing *COL4A3* mutation (c.4028-3C>A; r.4028_4153del) and a missense *INF2* variant [c.2065C>T, p.(Arg689Trp)] [9]. Segregation analysis in her family showed that the *COL4A3* mutation was inherited from her affected

father. He was diagnosed with non-nephrotic range proteinuria and haematuria at 39 years of age, with a renal biopsy showing FSGS; he reached ESRD at 51 years. The *INF2* variant was inherited from her asymptomatic mother. Two of the proband's uncles carried the *COL4A3* mutation, but they only presented microhaematuria at 61 and 56 years of age.

Heterozygous carriers of mutations in *COL4A3* or *COL4A4* show a very wide spectrum of disease severity, even within a family. In this family, all affected members carried a heterozygous splicing mutation in *COL4A3*, demonstrated to produce exon 46 skipping by RNA analysis and predicted to result in a protein lacking 42 amino acids [9]. Additionally, the proband also carried a missense variant in the *INF2* gene. This *INF2* non-conservative substitution, p.R689W, is located at a highly conservative domain (FH2) in the *INF2* protein and scored as highly likely pathogenic, using mutation prediction tools (SIFT, Polyphen, Mutation Taster), and because it is absent (1000 Genomes Project) or in an extremely low frequency [1 heterozygote of 118744 alleles in Exome Aggregation Consortium (ExAC)] in population databases. The arginine in the position 689 is totally conserved in mammals and a basic amino acid in all the species. In this case, we speculate that this *INF2* variant is an incomplete penetrant or hypomorphic allele, which contributes to a more severe presentation of the disease in the proband [9]. However, as no functional studies have been performed to test this hypothesis and the proband inherited it from her asymptomatic mother, this *INF2* variant has to be considered a VUS.

FD

Fabry disease (FD) is an X-linked, progressive and life-threatening genetic disease caused by deficient α-galactosidase A (α-Gal A) activity, which results in progressive accumulation of globotriaosylceramide within lysosomes in a variety of cell types [50]. This deposit causes organ damage clinically revealed as pain, angiokeratoma, cornea verticillata, proteinuria, kidney failure, cardiomyopathy, arrhythmia, transient ischaemic attacks, strokes, hypohidrosis, diarrhoea, etc. The disease, like X-linked AS, is usually more severe in males than in females. When Anderson and Fabry described FD they would never have thought that some decades later we would be able to diagnose FD patients without a single angiokeratoma, without burning pain and without cornea verticillata.

- A 45-year-old man was diagnosed with FD due to a renal biopsy done because of proteinuria. He did not show any signs or symptoms of FD, but renal biopsy disclosed the typical foam cells in the glomeruli and genetic testing showed a frameshift mutation in the *GLA* gene [c.1102delinsTTATAC, p.(Ala368Leufs*25)]. His 17-year-old daughter was an obligate carrier and was studied. Her only feature of FD was a proteinuria of 500 mg/day.
- A 52-year-old man fainted. His electrocardiogram (EKG) showed an atrioventricular (AV) block and an echocardiogram disclosed severe left ventricular hypertrophy. He was screened for α-Gal A deficiency and showed low plasma levels. Genetic testing showed a missense mutation in the *GLA* gene [c.644A>G, p.(Asn215Ser)]. He had none of the typical clinical features of FD.

These two cases are paradigmatic of what we know nowadays as renal and cardiac variants of FD. These variants are difficult to diagnose and the clinical features of these patients, once more, differ radically from those originally described by Anderson and Fabry. The missense mutation of the second patient has typically been associated with the cardiac variant of FD [51]; therefore, there is a straightforward genotype–phenotype correlation. In contrast, the frameshift mutation of the first patient has not previously been described. Although many mutation databases are in progress, most mutations do not have a clear related phenotype since they have not previously been described or have been found in patients with very different phenotypes, indicating that modifier genes or other unknown factors may also play a role.

SRNS

SRNS is clinically characterized by massive proteinuria, hypoalbuminaemia, oedema and dyslipidaemia and shows no response to steroid therapy. The underlying histological abnormality is usually FSGS. An unknown percentage of cases of SRNS are of genetic origin. To date, ∼40 genes causing SRNS have already been discovered.

- A 9-year-old female presented at the age of 7 years with oedema, >100 mg/m^2/h proteinuria and microscopic haematuria. No response to corticosteroids was observed while partial remission was obtained with cyclosporine. The renal biopsy showed FSGS. She had not developed ESRD. No members of the family (parents and two twin brothers) were clinically affected. Genetic testing identified a missense variant [c.2339T>C; p.(L780P)] in the TRPC6 gene. The father (40 years of age) and the two brothers (5 years old) had the same missense variant but had no clinical symptoms [52].

The p.L780P variant was classified as likely pathogenic because it accomplishes several criteria of pathogenicity [evolutionary conservation of the L780 residue among species, degree of physico-chemical difference between leucine and proline, pathogenic prediction by bioinformatic tools (SIFT, Polyphen, Mutation Taster), absence (1000 Genomes Project) or extremely low frequency (two heterozygotes of 121352 alleles in ExAC) in population databases]. However, since the proband has a full-blown nephrotic syndrome but her relatives show no signs or symptoms of the disease despite carrying the same mutation, the usual mentioned prediction tools are not applicable here and functional studies would be needed to ensure pathogenicity.

- A 19-year-old man had congenital-onset SRNS but his renal function remained normal. He carried a homozygous splicing mutation [c.1930 + 5G>A; r.1900_1930del31] in the *NPHS1* gene found to produce the deletion of the 31 last nucleotides of exon 14 in the messenger RNA (mRNA), which is predicted to result in a truncated protein [p.(Val634Thrfs*13)].

The mild phenotype of this patient could be explained because his splicing *NPHS1* mutation (c.1930+5G>A) does not affect the canonical GT/AG splice sites. In these cases the splicing machinery could allow the coexistence of a certain proportion of wild-type mRNA with the altered mRNA [46]. However, this is all speculation, as mRNA studies are needed to demonstrate this.

ADPKD

ADPKD is the most common IKD; it usually manifests in adulthood. Progressive cyst expansion leads to massive enlargement and distortion of the kidney architecture and, ultimately, to ESRD in most patients [53]. In ∼90% of the ADPKD families, genetic testing identifies the causative mutation in either the *PKD1* gene (85% of cases) or the *PKD2* gene (15% of cases) [54–56].

In all, 10% of cases with no identified mutation have a *PKD2*-like phenotype with the median age of onset of ESRD being 70 years or beyond. Recently, a third gene accounting for a very low percentage of cases has been identified [57]. Approximately 2–5% of patients with ADPKD present a severe form of the disease with early onset that is clinically indistinguishable from ARPKD [58].

- A 27-week-old foetus was diagnosed by ultrasound with enlarged, echogenic kidneys. At birth (36 weeks), he presented with respiratory distress and required ventilatory assistance. He had hypertension and renal insufficiency, which recovered with good control of hypertension. Eight years later the patient has enlarged kidneys containing multiple small cysts, no liver cysts and a normal estimated GFR. His sister showed a very similar phenotype. Renal ultrasounds of the parents (father, 41 years old; mother, 34 years old) showed no renal abnormalities, consistent with ARPKD. However, no mutations were found in the *PKHD1* gene while biallelic hypomorphic alleles, p.[(Arg222Trp)];[(Arg3277Cys)], were identified in the *PKD1* gene [37].

Since ADPKD is an autosomal dominant disease, one mutation is sufficient to cause disease. However, this case shows how two hypomorphic *PKD1* alleles *in trans* resembling an autosomal recessive pattern of inheritance, result in a severe ADPKD phenotype mimicking ARPKD, with asymptomatic parents being heterozygous for a hypomorphic *PKD1* allele [37].

ARPKD

ARPKD is mostly diagnosed in the perinatal period, when enlarged echogenic kidneys are observed. Histological findings consist of dilation of collecting ducts and developmental ductal plate abnormalities. Approximately 30% of ARPKD patients die in the neonatal period or within the first year of life and >50% of survivors progress to ESRD within the first decades of life [59]. ARPKD is caused by mutations in the *PKHD1* gene [60]. Almost all patients carrying two truncating mutations present a severe phenotype with peri- or neonatal death. In comparison, patients surviving the neonatal period usually bear at least one missense mutation [61, 62].

- A 50-year-old man was diagnosed with renal failure and hypertension. Ultrasound revealed some cysts in his normal-sized kidneys and also images defined as 'hepatic cysts'. In the following years, he developed portal hypertension and at 60 years of age he underwent a double liver and kidney transplant. His 'hepatic cysts' were, in fact, intrahepatic biliary dilations compatible with Caroli's disease. When his 10-years younger sister complained of the same symptoms, NGS of a cystic kidney gene panel was performed and a truncating mutation in *PKHD1* gene [c.5895dupA; p.(Leu1966Thrfs*4)] *in trans* with a missense *PKHD1* variant [c.664A>G; p.(Ile222Val)], which is likely a hypomorphic allele, was identified in both of them.

The very late onset of ESRD in this ARPKD family is probably related to the fact of carrying a likely hypomorphic *PKHD1* allele *in trans* with a truncating *PKHD1* mutation. This late presentation should encourage nephrologists to include the diagnosis of ARPKD when evaluating an adult patient with atypical features of ADPKD.

'Novel' hereditary kidney disorders

Kidney disorders that cannot be classified as purely cystic or glomerular or interstitial have been described recently. The *TTC21B* gene was initially described as causative of nephronophthisis and it has also been considered responsible for a 'new' kidney disease with FSGS and tubulointerstitial lesions [63].

- A 4-year-old girl presented with nephrotic proteinuria and myopia. She did not respond to corticosteroid and immunosuppressive therapy and reached ESRD at the age of 6 years. Her brother was diagnosed at the age of 6 years, due to his sister's disease, and presented with nephrotic proteinuria, CKD and high myopia. He reached ESRD at the age of 8 years. Both siblings received a kidney transplant with no recurrence of the disease after 8 years of follow-up. They carried compound heterozygous *TTC21B* mutations: c.626C>T (p.P209L) and c.1276C>G (p.H426D). Kidney biopsy in both siblings showed features of FSGS and tubulointerstitial lesions [64].

Conclusion

IKDs may show a phenotype that differs strikingly from that initially attributed to a particular gene. There are several potential genetic and non-genetic explanations for these unexpected phenotypes.

NGS is having a great impact on ontology, allowing the reclassification of various IKDs on the basis of knowledge of their genetic cause. This process of reclassification has various implications in terms of diagnosis, prognosis and even treatment.

NGS has also led to the identification of new genes causing rare IKDs and has broadened the phenotype of known IKDs. It is important to raise awareness among nephrologists of these atypical phenotypes, since, thanks to NGS, a diagnosis is now feasible. This opportunity should improve the diagnostic odyssey in puzzling cases, avoid unnecessary invasive diagnostic procedures such as renal biopsy, bring peace of mind to families and enable genetic counselling.

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Conflict of interest statement

None declared.

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