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Genomics in the kidney clinic

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ABSTRACT

Inherited diseases are a frequent cause of end-stage kidney disease and often seen in the kidney clinic. Clinical genomic testing is increasingly available in the UK and eligible patients in England can be referred through the NHS Genomic Medicine Service. Testing is useful for diagnosis, prognostication and management of conditions such as autosomal dominant polycystic kidney disease (ADPKD), Alport syndrome, autosomal dominant tubulointerstitial kidney disease (ADTKD) and focal segmental glomerulosclerosis (FSGS). As more patients undergo genomic testing and newer technologies such as whole genome sequencing are applied, we are developing a greater appreciation of the full phenotypic spectrum of inherited kidney diseases and the challenges associated with the interpretation of clinically significant variants.

Introduction

A family history of kidney disease is reported in 10–34% of patients with advanced chronic kidney disease (CKD),[1–3] and confers an age-adjusted relative risk of end-stage kidney disease (ESKD, requiring dialysis or kidney transplantation) greater than all other common risk factors apart from type 1 diabetes.[4] Advances in genomic testing (Box 1) have demonstrated that a large proportion of progressive kidney disease can be attributed to a monogenic cause. Whole exome sequencing (WES) of a large, relatively unselected cohort of 3,315 patients with CKD/ESKD identified diagnostic variants in 9.3%, which likely sets a lower bound of monogenic kidney disease (a genetic diagnosis was made for only 24% of patients with cystic/congenital kidney disease).[3] Moreover, WES provided a molecular diagnosis for 17% of patients with clinically 'unexplained' ESKD, representative of patients with ESKD labelled as 'hypertensive' or of 'unknown aetiology' (with kidney biopsies showing only interstitial fibrosis and scarring).[3] Here, we provide an overview of inherited kidney diseases commonly encountered in the clinic and how genomic testing can be used to guide management.

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Autosomal dominant polycystic kidney disease (ADPKD)

The commonest inherited kidney disease is ADPKD, affecting 1/1,000 individuals and accounting for 10.5% of patients with ESKD.[5] 50% of affected individuals will develop ESKD by 60 years, although there is considerable variability in disease severity and extra-renal manifestations such as intracranial aneurysms (seen in ~10% patients). Approximately 30% of patients present without a family history, or with atypical cysts (Fig 1), and in these individuals genomic testing can confirm the diagnosis. Prognosis is also informed by the underlying molecular diagnosis.[6] Heterozygous variants in *PKD1* (~78%), *PKD2* (~15%) and *IFT140* (~2%, associated with a much lower risk of kidney failure) can be identified in the vast majority of patients and there is a clear correlation between disease genotype and phenotype: for example, the median age at which patients reach ESKD with a

Key points

Inherited kidney disease is a common cause of CKD, and a comprehensive family history should be sought, especially where diagnosis is uncertain.

Consider referral for genomic testing (via the nephrologist) for patients with a family history of kidney disease, young age of onset, or extra-renal features such as hearing loss or early-onset gout.

A genomic diagnosis can inform prognosis, enable predictive testing of asymptomatic relatives, and provide information on risk in future children. Genomic testing can also guide management in patients with autosomal dominant polycystic kidney disease (ADPKD), Alport syndrome (AS) and focal segmental glomerulosclerosis (FSGS) and clarify the risks of living kidney donation from relatives.

The interpretation of genomic variants is constantly evolving and there is a wider spectrum of kidney disease associated with variants in *COL4A3/A4/A5* and *UMOD* than previously thought.

The NHS Genomic Medicine service is embedding genomics into routine clinical practice in England.

KEYWORDS: Alport syndrome, ADPKD, ADTKD, FSGS, genomics

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Box 1. Genomic testing

Sanger sequencing is highly accurate and can sequence DNA segments up to 1,000 base pairs (1 kbp) but is applied to one sample at a time and is therefore slow and costly for sequencing multiple samples. It is now rarely used in clinical practice.

Next generation/massively parallel sequencing (NGS) describes technologies that allow multiple short segments of DNA to be sequenced in parallel, greatly increasing speed and allowing for scalable and high-throughput processing. Segments of ~150 base pairs are sequenced and mapped back onto a reference genome. It is used to detect single nucleotide variants (SNVs) and small insertions/deletions but is less accurate for larger structural variants and in repetitive regions of the genome.

Targeted gene panels apply NGS to a curated panel of genes associated with a phenotype. It is less expensive than whole exome or genome sequencing, with low chance of off-target discovery but is biased by the initial choice of genes.

Whole exome sequencing (WES) applies NGS to the protein coding regions of DNA (~1% of the genome) WES data can be re-analysed as new gene-disease associations come to light. It is useful for coding variant discovery but will miss non-coding regulatory variants.

Whole genome sequencing (WGS) applies NGS to the whole genome (3 billion base pairs) and thus can detect variation in non-protein coding (regulatory) DNA regions as well as structural variation. It is however still expensive (~£1,000) and the volume of generated data (200 GB) make it complex to interpret. Incidental findings (eg variants in cancer predisposition genes) can also be identified in 1–2% of individuals.

Long-read sequencing (LRS) is a technology that allows sequencing of 10–400 kbp continuous segments of DNA and can detect structural variation and variation across repetitive regions. Throughput and accuracy are lower than for NGS (though improving) and it does not routinely cover the whole genome. Powerful technologies to combine LRS and NGS are under development but at present it remains a research tool.

Multiplex ligation-dependent probe amplification (MLPA) uses pairs of probes to detect specific sections of the genome. It is currently the gold standard for copy number variant detection where a section of DNA is duplicated or deleted.

pathogenic *PKD1* variant is 58 years compared to 79 years for those with a *PKD2* variant, and those with a protein-truncating as opposed to a missense variant have worse outcomes.[7] A genomic diagnosis also has clear implications for management.

Collagen-IV kidney disease

Persistent microscopic haematuria is a common presentation in the kidney clinic. In the absence of structural or lower urinary tract disease, it is often caused by IgA nephropathy, which is not usually familial. If there is a family history of kidney disease or microscopic haematuria, or clinical or histopathological features suggestive of Alport syndrome (AS), genomic testing of collagen-IV genes is indicated. The key collagen-IV genes, *COL4A3* and *COL4A4* on chromosome 2 and *COL4A5* on chromosome X, encode the alpha–3, –4 and –5 chains of collagen-IV respectively. These chains form heterotrimers, the structural basis for basement

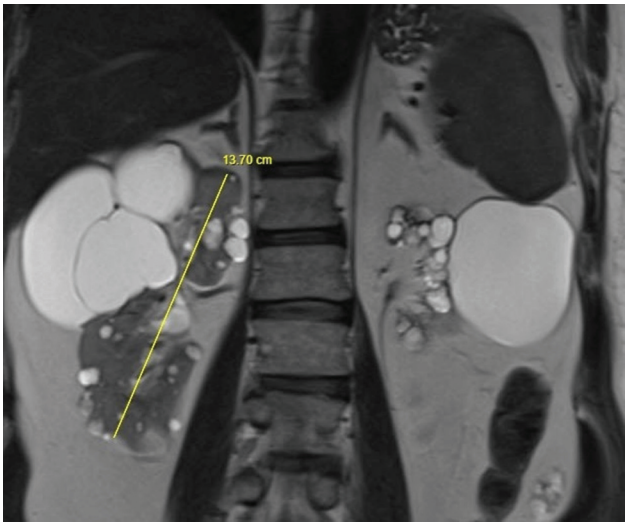

Fig 1. Magnetic resonance imaging (T2-weighted) of the kidneys of a 63-year-old man with an eGFR of 50 ml/min/1.73m^2. The right kidney has a normal polar length with irregular sized fluid filled cysts. The left kidney is atrophic with similarly irregular cysts. Genomic testing identified a truncating *IFT140* mutation.

membranes found in the glomerulus, cochlea and eye. In its classical form AS is an X-linked disease (XLAS) causing ESKD, high-frequency sensorineural hearing loss, anterior lenticonus and fleck retinopathy. XLAS very often progresses to kidney failure, occurring in >50% of males before the age of 35, with younger-onset kidney failure typical in individuals with a protein-truncating *COL4A5* variant.[8] Importantly, females with XLAS are not just 'carriers'; though they manifest less severe disease, up to 30% develop kidney failure by the age of 60.[9]

Autosomal recessive AS results from biallelic variants in *COL4A3* or *COL4A4*, but heterozygous variants in these genes can result in a milder phenotype called thin basement membrane neuropathy (TBMN). TBMN is characterised by microscopic haematuria. Some patients with TBMN will develop kidney failure, typically beyond the age of 50; as such this is sometimes referred to as autosomal dominant Alport syndrome. Although older literature suggested the lifetime risk of ESKD in heterozygotes was as high as 15–20%, more recent data indicate that such variants are so common in the general population that this risk must be greatly overstated.[10] The landscape is further complicated by the observation that likely pathogenic variants in *COL4A3/A4* are found in patients with histopathological lesions atypical for AS, such as focal segmental glomerulosclerosis (FSGS) and IgA nephropathy. This suggests an extended phenotype of collagen-related kidney dysfunction, likely with low penetrance, and forces a careful re-evaluation of the significance attached to these variants in patients without a family history of kidney disease. Nonetheless, patients with heterozygous *COL4A3/A4* variants should undergo long-term surveillance for the development of hypertension, proteinuria and kidney dysfunction.

Autosomal dominant tubulointerstitial kidney disease (ADTKD)

ADTKD is the diagnostic envelope for rarities previously known as medullary cystic kidney disease, familial juvenile hyperuricaemic

nephropathy, and uromodulin associated kidney disease. It is traditionally characterised by 'featureless', familial, progressive kidney disease with a bland urinalysis and small kidneys on imaging; however, hypertension and proteinuria may also be observed.[2] A history of early onset gout may be present. Kidney biopsy shows non-specific tubulointerstitial fibrosis with no clear glomerulopathy. It is subclassified by the underlying genetic cause, most frequently heterozygous variants in *UMOD* or *MUC1*, found in 42% and 14% of patients with ADTKD, respectively.[11]

ADTKD-*UMOD*, where pathogenic variants result in tubular epithelial accumulation of misfolded uromodulin, accounts for 2% of ESKD of unknown aetiology, excluding hypertensive cases.[2] *MUC1* variants, associated with ADTKD-*MUC1*, are difficult to detect using next-generation sequencing due to their location in a repetitive region of the gene and are found with greater frequency using long-read sequencing.[12] As with heterozygous *COL4A3/A4* variants, it is increasingly evident that *UMOD* variants are more common in the general population than previously thought and are associated with a varying spectrum of kidney disease severity.[13]

Podocytopathies

Adults with nephrotic syndrome (NS) – the triad of oedema, proteinuria and hypoalbuminaemia – or nephrotic range proteinuria (urine protein:creatinine ratio >350 mg/mmol) usually undergo kidney biopsy, and the commonest observed lesion is FSGS. Primary FSGS is considered an autoimmune disease and classically responds to glucocorticoid treatment. Subtly different FSGS-like lesions are usually considered 'secondary' to another disease process; these cases often have preserved serum albumin and do not respond to glucocorticoids, a situation sometimes referred to as steroid-resistant nephrotic syndrome (SRNS).

Studies using different genomic testing modalities have demonstrated that a monogenic cause may underlie 10–43% of FSGS cases, especially steroid-resistant cases, including where an alternative aetiology has been posited.[14,15] In adult-onset disease pathogenic variants have been identified in *NPHS2, INF2*, *TRPC6*, *ACTN4, LMXIB*, as well as the collagen-IV genes. In patients with recent African ancestry, FSGS has also been associated with common risk variants in *APOL1* which protect against trypanosomiasis but seem to render kidneys more susceptible to permanent injury from other causes including hypertension and HIV.[16]

Clinical implications of genomic findings

Genomic testing is now easily accessible for the clinician (Box 2). In patients with a known family history or classical features of AS, genomic testing can obviate the need for a kidney biopsy and allow early initiation of treatment (for patients with proteinuria) with angiotensin-converting enzyme inhibitors or sodium-glucose co-transporter-2 inhibitors. In ADPKD, genomic testing can prompt closer surveillance of patients with a protein-truncating *PKD1* variant and early initiation of tolvaptan therapy to slow cyst growth and disease progression. A higher threshold for treatment can be used for those with a lower risk genetic variant (eg *PKD2* or *IFT140*).[17] Patients with genetic FSGS may avoid prolonged courses of immunosuppression and their associated side effects. Furthermore, for individuals planning a family, pre-implantation genetic testing for monogenic disorders (PGT-M) can be used during IVF to select unaffected embryos in ADPKD, ADTKD, AS and complement factor H related-5 (CFHR5) nephropathy.[18]

Box 2. Genomic testing in the NHS

Genomic testing in England is now readily available through the NHS Genomic Medicine Service for many rare diseases and cancer, with similar services offered in the rest of the UK. Nephrologists can request testing for a range of indications including cystic kidney disease, ADTKD, familial microscopic haematuria, proteinuric kidney disease or unexplained young onset end-stage renal disease (for patients with ESKD before the age of 36 without a clear diagnosis). If a monogenic disease is suspected, the clinician can refer to the National Genomic Test Directory (www.england.nhs.uk/publication/national-genomic-test-directories) to confirm whether the patient's phenotype meets eligibility criteria for testing against expert-curated gene panels (https://nhsgms-panelapp.genomicsengland.co.uk/panels). Pathogenicity of variants is assessed and reported according to international guidelines. If eligible and after consenting the patient, EDTA blood samples are sent to the regional Genomic Laboratory Hub (GLH) with results expected in ~3 months. Further information, referral and consent forms are available on the GLH websites (www.england.nhs.uk/genomics/genomic-laboratory-hubs).

Genomic testing also has an important role in kidney transplantation. First, living donor transplantation is the best treatment option for patients with ESKD and predictive genetic testing can accurately ascertain the risk of familial disease in a prospective related donor, even when apparently unaffected. Secondly, FSGS recurs in 30–80% of transplant recipients with primary FSGS, but rarely in those with monogenic disease,[19] and a confirmed genetic variant can help guide frequency of surveillance after transplantation. Finally, while diagnostic testing for kidney disease-associated *APOL1* variants is currently not approved in the UK (as it is not a monogenic trait), the recent demonstration that *APOL1*-associated kidney disease may be targetable by a specific therapy,[20] as well as awareness that it is associated with an increased risk of kidney failure in donors and recipients, may lead to reappraisal of this policy.

Before being offered genomic testing, patients should be counselled about the consequences of a positive and negative result. Not detecting a disease-causing variant may provide relief and eliminate the need for surveillance; though the choice of sequencing modality and the genes tested may mean that the pathogenic variant goes undetected. Conversely, while a positive finding may provide warning of future kidney disease or allow earlier initiation of therapy to improve prognosis, it may also have a profound influence on the life decisions of the patient and potential implications for family members (for example, triggering cascade testing of asymptomatic relatives). Issuing an incorrect diagnosis to a patient or family (by attributing disease to a genomic variant that is not pathogenic, or by overstating risk of kidney failure) can have catastrophic consequences and should be avoided at all costs: no diagnosis is better than the wrong diagnosis.

Sequence and ye shall find

Genomic testing is becoming firmly established in the kidney clinic and is of demonstrated clinical utility. Well-chosen genomic testing can provide a diagnosis in cases where the aetiology is unclear, and can inform prognosis and guide management. As testing becomes

more widespread, the challenge will be in interpreting, for the patient in front of us, the meaning of variants and how they impact risk of kidney disease on an individual level. ■

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