GENOMIC MEDICINE: CLINICAL PRIMER
https://doi.org/10.33591/sfp.50.1.u4

Unit No. 4

GENETICS IN GLOMERULAR DISEASES AND CHRONIC KIDNEY DISEASE

Dr Koh Chee Teck, Ms Ng Jun Li, A/Prof Ng Kar Hui

ABSTRACT

Glomerular disease, manifesting as steroid resistant nephrotic syndrome and/or persistent haematuria or albuminuria, is the second most common cause of chronic kidney disease in children and adults in Singapore and worldwide. To date, there are about 500 genes known to cause monogenic kidney diseases, of which 100 are known to cause glomerular diseases. About 20-30 percent of children with steroid-resistant nephrotic syndrome (SRNS) and 10 percent of adults with focal segmental glomerulosclerosis have genetic causes; this number rises to 60-90 percent if there are predisposing risk factors like positive family history, extrarenal manifestations and/or glomerular basement membrane changes. Among these, Alport syndrome genes (*COL4A3*, *COL4A4*, *COL4A5*) are the most common genetic causes.

Genetic testing in glomerular diseases has numerous clinical impacts on the patient, such as directing immunosuppressive strategies, negate the need for kidney biopsy, kidney donor selection and cascade testing. Early introduction of renin-angiotensin-aldosterone system (RAAS) blockade can delay CKD progression especially in male patients with X-linked Alport Syndrome. Early initiation of RAAS blockade in these patients at the microalbuminuria stage or even prior to the onset of any urinary anomalies can delay kidney failure by >15 years. Such impactful treatment is possible only if there is early diagnosis based on genetic testing. Furthermore, Coenzyme Q10 (CoQ10) deficiency can also cause genetic glomerulopathy, and treatment with coenzyme Q10 supplements can decrease proteinuria and delay CKD progression.

SFP2024; 50(1): 35-40

Key Words: Genetic kidney disease, Alport syndrome, Chronic Kidney Disease, Proteinuria, Haematuria

DR KOH CHEE TECK
Senior Resident, Department of Paediatrics, Khoo Teck Puat – National University Children's Medical Institute, National University Hospital

MS NG JUN LI
Senior Laboratory Executive, Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore

A/PROF NG KAR HUI
Senior Consultant, Division of Paediatric Nephrology, Dialysis and Renal Transplantation, Department of Paediatrics, Khoo Teck Puat – National University Children's Medical Institute, National University Hospital
Associate Professor, Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore

INTRODUCTION

Singapore ranks 4th and 7th in the world for prevalence and incidence of kidney failure respectively, spending $190 million on dialysis.[1] The prevalence of Mendelian diseases among patients with chronic kidney diseases (CKD) is ~30 percent in paediatric cohorts and 5-30 percent in adult cohorts.[2] Such genetic cases are often not diagnosed in Singapore as genetic testing is not widely implemented in nephrology clinics and many patients present at late stages of CKD.[3] The underlying cause at late stages is often not apparent due to the severely scarred kidneys and lack of clinical clues. These patients are often given a diagnosis of "kidney failure of unknown aetiology". (Taken from "Trends in Chronic Kidney Failure in Singapore 2010 – 2011", Singapore Renal Registry Report No. 9 https://www.nrdo.gov.sg/docs/librariesprovider3/Publications---Kidney-Failure/trendsinrenal2010-2011.pdf?sfvrsn=0)

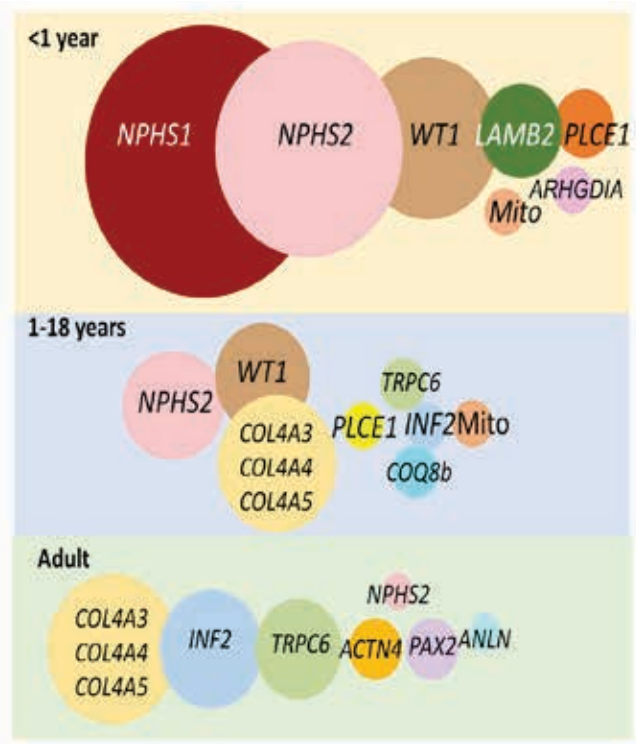
Glomerular disease is the second most common cause of chronic kidney diseases in children and adults,[4] after congenital anomalies in children and diabetic nephropathy in adults. Indications of a possible glomerular disease include persistent heavy proteinuria and/or haematuria, nephritic syndrome, or steroid-resistant nephrotic syndrome (SRNS). There are currently nearly 100 genes known to cause monogenic glomerular disease.[5,6] These include autosomal dominant, autosomal recessive, sex-linked and mitochondrial genes. Examples include *COL4A5*, *COL4A3*, *COL4A4*, *NPHS2*, *NPHS1*, *WT1*, and *TRPC6*. Monogenic causes are also known to occur in C3 glomerulopathy.

Other groups of kidney diseases that may have monogenic causes include cystic conditions (including those with increased kidney echogenicity), tubulopathies (polyuria or renal tubular loss of electrolytes, sugar, amino acids, or other metabolic findings); renal calculi or nephrocalcinosis; and congenital abnormalities of the kidney and urinary tract. Collectively, about 500 genes are known to cause monogenic kidney disorders.[7]

COMMON GENETIC CAUSES ASSOCIATED WITH GLOMERULAR AND CHRONIC KIDNEY DISEASES OF UNKNOWN AETIOLOGY

In glomerular diseases, the common genetic causes differ according to age of onset.[8,9] (refer to **Figure 1**). In those presenting in the first year of life, *NPHS1* (nephrin), *NPHS2* (podocin), and *WT1* are the most common, followed by *LAMB2* and *PLCE1*. In childhood, *NPHS2* and *WT1* appear to be important. Instead, collagen IV genes (which cause Alport syndrome) are increasingly recognised as important causes even in childhood. In adulthood, the most common causes are the collagen IV genes, followed by autosomal dominant genes like *INF2* and *TRPC6*.

Figure 1: Commonly implicated genes in glomerular diseases according to the different ages of presentation, in the absence of obvious extrarenal manifestations. The relative sizes of the circles represent the estimated prevalence within the age group of patients.



**Mito = mitochondrial*

The prevalence of NPHS2-related glomerular diseases is markedly lower in Asians with glomerular diseases compared to their non-Asian counterparts. This is shown by studies in Pakistan and India (2.6-12 percent),[10-15] as well as Japan, Korea, and China (0-3.3 percent),[16-25] in contrast to 10-30 percent in sporadic and 43-55 percent in familial cases among Caucasians and Middle East patients.[26-28]

Genetic kidney disease may also occur in tubulopathies, kidney cystic diseases, congenital anomalies of the kidney and urinary tract, or in CKD of unknown aetiologies.[7]

DIAGNOSTIC YIELD OF GENETIC TESTING IN KIDNEY DISEASES

The diagnostic yield from whole exome sequencing (WES) and panel sequencing for glomerular and, cystic kidney conditions and CKD of unknown causes range from 14-79 percent,[2] with even higher yield in those with positive family history, consanguinity, and extrarenal manifestations (refer to **Table 1**). Of note, there is no difference in diagnostic yield between adult- and childhood-onset CKD,[2] suggesting genetics testing is helpful in both paediatric and adult services.

Table 1: Diagnostic yield from exome and panel sequencing for selected kidney conditions according to paediatric or adult onset.

Types of kidney conditions according to clinical features	Childhood onset < 18 yrs	Adult onset ≥ 18 yrs	Number of genes
Glomerulopathies and Alport syndrome	67%	79%	20
Steroid resistant nephrotic syndrome or FSGS*	26%	14%	59
Cystic kidney disease	50%	17%	92
CKD of unknown cause	30%	40%	~500

Figures are adapted from a review.[2]
**FSGS = focal segmental glomerulosclerosis*

In patients with SRNS or primary focal segmental glomerulosclerosis (FSGS) and risk factors like family history or extrarenal manifestations, the likelihood of a genetic cause increases to 60-90 percent.[8,29-33] In children with asymptomatic microscopic haematuria and no albuminuria, about 30 percent may have Alport syndrome.[34] In glomerular disease, Alport syndrome is the most common culprit among children (excluding infants and adults[35-37] Among Chinese children with SRNS, Alport syndrome is present in 2.1-8.4 percent.[20,38] Additionally, 12.5 percent of Chinese families with FSGS and 2 percent of those with sporadic FSGS have heterozygous *COL4A3* mutations.[39]

Among such adults with CKD of "unclear aetiology", 17 percent have monogenic kidney diseases.[40] The two most common monogenic causes are Alport syndrome and autosomal dominant polycystic kidney disease, even though many of them do not have suggestive clinical features.[40]

INDICATIONS OF GENETIC TESTING IN GLOMERULAR KIDNEY DISEASES

Genetic testing is now recommended early in the disease course in many international guidelines.[41-43] Genetic testing can be considered in the following:

- A very young onset of disease
- Significant family history especially with late stages of CKD
- Extrarenal manifestations like neurosensory hearing loss, anterior lenticonus, fleck retinopathy, and skeletal or neurological anomalies
- Kidney biopsy shows significant glomerular basement membrane lamellation or textural changes on electron microscopy
- SRNS: Absence of initial complete remission to steroids given at adequate doses and duration (excluding secondary causes of glomerular diseases like membranous nephropathy or lupus)

- Suboptimal response to calcineurin inhibitors or other aggressive immunosuppression (with no prior complete response to isolated steroid therapy)
- Positive family history for glomerular diseases (that are not due to secondary causes like lupus, ANCA vasculitis), haematuria, proteinuria, hearing loss
- Persistent haematuria and/or proteinuria with no apparent secondary causes like hypertension, obesity, low nephron mass (e.g., ex-prematurity or very low birth weight, prior nephrectomy)
- Chronic kidney disease with no apparent cause

IMPORTANCE OF DIAGNOSING GENETIC KIDNEY DISEASES

A genetic diagnosis is crucial in the clinical management of genetic kidney diseases, such as:

- Tailoring of immunosuppressive strategies in glomerular diseases. Because genetic cases do not respond to immunosuppression,[44] international guidelines have recommended genetic testing be performed in children with SRNS[45,46] and adults with familial, syndromic, or SRNS or FSGS.[41-43] Without genetic testing, almost all SRNS adult and paediatric cases receive empirical potent second- or third-line immunosuppression. These costly drugs have significant side effects such as severe opportunistic infections and long-term malignancy.
- Allow early initiation of anti-proteinuric medications to delay CKD progression
- Use of specific management strategies
    - In patients with CoQ10 deficiency due to defects in *COQ2*, *COQ6*, and *COQ8B* genes,[47-49] oral administration of CoQ10 in individuals with a CoQ10 deficiency can lead to significant decrease in proteinuria,[50,51] potentially preventing or delaying CKD progression.[52]
    - In polycystic kidney disease, earlier diagnosis with regular surveillance for proteinuria and hypertension (using 24-hour ambulatory blood pressure monitoring) can significantly improve long term outcomes.[53,54]
    - In Fabry disease, earlier enzyme replacement therapy or chaperone therapy in genetically-diagnosed family members can improve not just kidney, but also neurological and cardiovascular outcomes.[55]
- Allow for earlier diagnosis in asymptomatic or presymptomatic family members, thereby leading to earlier interventions with larger impacts on long-term kidney outcomes.
- Allow for more targeted surveillance of extrarenal conditions like hearing loss
- Allow selection of the most suitable kidney donor (when kidney failure develops)
- Helps patients and families make reproductive decisions

In adults with CKD who had a genetic diagnosis, 73 percent had new clinical insight from the diagnosis. These included disease confirmation or reclassification, avoidance of kidney biopsies, new subspecialty referral, change in treatment, family counselling, and donor selection for transplantation.[40,56] This was echoed in Australia where the overall clinical utility of genetic diagnosis was 73 percent.[57]

ALPORT SYNDROME IS NOT RARE

The triad in Alport syndrome is glomerular disease, neurosensory hearing loss, and classic eye abnormalities, namely keratoconus and fleck retinopathy.

Depending on the presence of likely pathogenic or pathogenic variants in an individual and the gene involved (*COL4A3*, *COL4A4*, or *COL4A5*), it can be autosomal dominant, autosomal recessive, sex-linked or digenic. The kidney prognosis differs widely depending on the mode of inheritance and sex.

Alport syndrome is often misdiagnosed as IgA nephropathy, SRNS, FSGS or thin membrane disease. Individuals with Alport syndrome initially have microscopic haematuria. Children might have recurrent gross haematuria that are synpharyngitic. This eventually progresses to increasing proteinuria and worsening kidney function.

The majority of patients with Alport syndrome do not have extrarenal manifestations such as hearing loss or eye conditions, or classic glomerular basement membrane changes.

Alport syndrome is not rare and Alport syndrome is more common than expected. *COL4A5* (likely) pathogenic variants are predicted to occur in one out of 2,320 in the United Kingdom population.[58] Similarly, (likely) pathogenic *COL4A3* and *COL4A4* variants occur in one out of 106 in the population.[58]

THIN MEMBRANE DISEASE OR FAMILIAL HAEMATURIA IS NOT CONSIDERED BENIGN

People with Alport syndrome develop microhaematuria in early life and progress to proteinuria and then CKD. Persistent isolated glomerular haematuria occurs in about 1-4 percent of children and adults in the population. They are often evaluated extensively with no clear aetiology found,[59,60] and are presumed to have benign thin membrane nephropathy. This had been termed as "benign haematuria" because of the presumed good long-term outcomes.[61] Such patients are often falsely assured and discharged from follow-up. Recent studies have discovered that many of such patients have Alport syndrome (*COL4A3* and/or *COL4A4*).[62-64] An accurate genetic diagnosis is important because up to 60 percent develop CKD in later life.[64]

DISEASE TRAJECTORY OF ALPORT SYNDROME

The rate of CKD progression differs largely (refer to **Table 2**), and is dependent on the gene involved, type of pathogenic variant, sex and other contributing factors like co-existing hypertension and diabetes mellitus.[65]

Table 2: Likelihood of kidney failure (without early treatment) in different genetic forms of Alport syndrome

Type of Alport syndrome	Likelihood of developing kidney failure
Sex-linked	Males: 60% by 30 years old 90% by 40 years old 100% by 60 years old
	Females: 12% by 40 years old 30% by 60 years old 40% by 80 years old
Autosomal recessive	30% by 40 years old
Autosomal dominant	28% by 56 years old

Females with sex-linked Alport syndrome are not carriers but they can develop disease. Over 95 percent of these females have haematuria, 75 percent of them develop proteinuria, and 20-30 percent of them will experience kidney failure by age 60 years.[64] They could also develop hearing loss. Half of their sons will inherit the disease with more severe kidney phenotype that will benefit from early detection and treatment.

IMPORTANCE OF DIAGNOSING ALPORT SYNDROME EARLY

Landmark trials have established that early initiation of RAAS blockade can delay CKD progression.[52,66,67] Specifically, in male patients with X-linked Alport syndrome, early initiation of renin-angiotensin-aldosterone system (RAAS) blockade can delay kidney failure by 12-20 years.[66,67] The recent EARLY PRO-TECT trial in children with Alport syndrome suggests early initiation of ramipril at the microscopic haematuria stage can delay progression to the next stage by >40 percent.[68] Taken together with trials that established that early anti-proteinuric treatment delays kidney failure,[52] this means early RAAS blockade potentially can delay kidney failure onset by >2 decades in autosomal recessive or male X-linked Alport patients. Hence, recently revised recommendations on Alport syndrome suggested ramipril should be started at genetic diagnosis of X-linked Alport males or autosomal recessive Alport, even in the absence of urinary anomalies.[66] As RAAS blockade may have side effects, this early treatment is justifiable only at genetic diagnosis since biopsy at early stages is inconclusive.

CLINICAL IMPLEMENTATION OF GENETIC TESTING FOR KIDNEY DISEASES

Genetics testing is hardly performed in Singapore due to of various hurdles in clinical implementation. These include high costs, poor accessibility to genetic tests, lack of standard clinical algorithms, poor genetic literacy, lack of genetic training among nephrologists, lack of genetic counselling expertise, and lack of expertise among clinicians in variant interpretation, especially in dealing with uncertain or discordant genetic variants.[69-71]

A collaborative effort between nephrologists, geneticists, molecular scientists, and bioinformaticians is especially crucial in nephrology genomics clinical implementation efforts. The problems in clinical implementation are similarly encountered worldwide. However, many medical centres have successfully implemented genomics testing in nephrology though a concerted multi-disciplinary approach, as summarised by Cirillo et al.[72] Common features of these efforts are multidisciplinary genomics boards comprising of nephrologists, geneticists, genetic counsellors, bioinformaticians, and scientists; strong translational research efforts to decipher unresolved cases and defined clinical algorithms on selection and referral criteria.[73]

CONCLUSION

Despite the scientific evidence, clinical implementation of genomics testing is largely non-existent in nephrology clinics in Singapore and many parts of the world. It is likely that with more widespread implementation of genetics testing in kidney diseases, earlier diagnosis with earlier interventions will become possible, especially among family members. In the long run, the societal burden of CKD can be decreased.

REFERENCES

1. U.S. Renal Data System, USRDS 2020 Annual Data Report: Epidemiology of kidney disease in the United States. 2020.
2. Connaughton DM, Hildebrandt F. Personalized medicine in chronic kidney disease by detection of monogenic mutations. Nephrol Dial Transplant. Mar 1 2020;35(3):390-397. doi:10.1093/ndt/gfz028.
3. Asia CN. 'We're at the brink': Kidney disease crisis looms in Singapore as some doctors urge more action. Updated 22 July 2023. Accessed 23 July 2023, https://www.channelnewsasia.com/singapore/chronic-kidney-disease-failure-singapore-early-screening-nkf-dialysis-3620561?cid=internal_sharetool_androidphone_22072023_cna
4. National Registry of Diseases Office S. Singapore Renal Registry Annual Report 2019. 2019. 30 July 2021.
5. Lovric S, Ashraf S, Tan W, Hildebrandt F. Genetic testing in steroid-resistant nephrotic syndrome: when and how? Nephrol Dial Transplant. Nov 2016;31(11):1802-1813. doi:10.1093/ndt/gfv355.
6. Kopp JB, Anders HJ, Susztak K, et al. Podocytopathies. Nat Rev Dis Primers. Aug 13 2020;6(1):68. doi:10.1038/s41572-020-0196-7.
7. Hildebrandt F. Genetic kidney diseases. Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't Review. Lancet. Apr 10 2010;375(9722):1287-95. doi:10.1016/S0140-6736(10)60236-X.
8. Sadowski CE, Lovric S, Ashraf S, et al. A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome. J Am Soc Nephrol. Jun 2015;26(6):1279-89. doi:10.1681/ASN.2014050489.

9. Liu J, Wang W. Genetic basis of adult-onset nephrotic syndrome and focal segmental glomerulosclerosis. Front Med. Aug 03 2017;doi:10.1007/s11684-017-0564-1.
10. Abid A, Khaliq S, Shahid S, et al. A spectrum of novel NPHS1 and NPHS2 gene mutations in pediatric nephrotic syndrome patients from Pakistan. Gene. Jul 10 2012;502(2):133-7. doi:10.1016/j.gene.2012.04.063.
11. Dhandapani MC, Venkatesan V, Rengaswamy NB, et al. Report of novel genetic variation in NPHS2 gene associated with idiopathic nephrotic syndrome in South Indian children. Clin Exp Nephrol. Feb 2017;21(1):127-133. doi:10.1007/s10157-016-1237-0.
12. Jaffer A, Unnisa W, Raju DS, Jahan P. NPHS2 mutation analysis and primary nephrotic syndrome in southern Indians. Nephrology (Carlton). Jul 2014;19(7):398-403. doi:10.1111/nep.12241.
13. Ramanathan AS, Vijayan M, Rajagopal S, Rajendiran P, Senguttuvan P. WT1 and NPHS2 gene mutation analysis and clinical management of steroid-resistant nephrotic syndrome. Mol Cell Biochem. Feb 2017;426(1-2):177-181. doi:10.1007/s11010-016-2889-5.
14. Vasudevan A, Siji A, Raghavendra A, Sridhar TS, Phadke KD. NPHS2 mutations in Indian children with sporadic early steroid resistant nephrotic syndrome. Indian Pediatr. Mar 2012;49(3):231-3. doi:10.1007/s13312-012-0057-x.
15. Siji A, Karthik KN, Pardeshi VC, Hari PS, Vasudevan A. Targeted gene panel for genetic testing of south Indian children with steroid resistant nephrotic syndrome. BMC Med Genet. Nov 20 2018;19(1):200. doi:10.1186/s12881-018-0714-6.
16. Dai Y, Yang H, Gao P, Liu WD. NPHS2 variation in Chinese southern infants with late steroid-resistant nephrotic syndrome. Ren Fail. Oct 2014;36(9):1395-8. doi:10.3109/0886022x.2014.947515.
17. Yu Z, Ding J, Huang J, et al. Mutations in NPHS2 in sporadic steroid-resistant nephrotic syndrome in Chinese children. Nephrol Dial Transplant. May 2005;20(5):902-8.
18. Mao J, Zhang Y, Du L, et al. NPHS1 and NPHS2 gene mutations in Chinese children with sporadic nephrotic syndrome. Pediatr Res. Jan 2007;61(1):117-22.
19. Wang F, Zhang Y, Mao J, et al. Spectrum of mutations in Chinese children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. Jul 2017;32(7):1181-1192. doi:10.1007/s00467-017-3590-y.
20. Rao J, Liu X, Mao J, et al. Genetic spectrum of renal disease for 1001 Chinese children based on a multicenter registration system. Clin Genet. Nov 2019;96(5):402-410. doi:10.1111/cge.13606.
21. Nagano C, Yamamura T, Horinouchi T, et al. Comprehensive genetic diagnosis of Japanese patients with severe proteinuria. Scientific reports. Jan 14 2020;10(1):270. doi:10.1038/s41598-019-57149-5
22. Cho HY, Lee JH, Choi HJ, et al. WT1 and NPHS2 mutations in Korean children with steroid-resistant nephrotic syndrome. Sci Rep. Jan 2008;23(1):63-70. doi:10.1007/s00467-007-0620-1.
23. Furue T, Hattori M, Tsukaguchi H, et al. Clinical features and mutational survey of NPHS2 (podocin) in Japanese children with focal segmental glomerulosclerosis who underwent renal transplantation. Pediatr Transplant. May 2008;12(3):341-6. doi:10.1111/j.1399-3046.2007.00752.x,
24. Kitamura A, Tsukaguchi H, Iijima K, et al. Genetics and clinical features of 15 Asian families with steroid-resistant nephrotic syndrome. Nephrol Dial Transplant. Nov 2006;21(11):3133-8.
25. Maruyama K, Iijima K, Ikeda M, et al. NPHS2 mutations in sporadic steroid-resistant nephrotic syndrome in Japanese children. Pediatr Nephrol. May 2003;18(5):412-6.
26. Caridi G, Perfumo F, Ghiggeri GM. NPHS2 (Podocin) mutations in nephrotic syndrome. Clinical spectrum and fine mechanisms. Pediatr Res. May 2005;57(5 Pt 2):54R-61R. doi:10.1203/01.PDR.0000160446.01907.B1.
27. Weber S, Gribouval O, Esquivel EL, et al. NPHS2 mutation analysis shows genetic heterogeneity of steroid-resistant nephrotic syndrome and low post-transplant recurrence. Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Kidney Int. Aug 2004;66(2):571-9. doi:10.1111/j.1523-1755.2004.00776.x.
28. Ruf RG, Lichtenberger A, Karle SM, et al. Patients with mutations in NPHS2 (podocin) do not respond to standard steroid treatment of nephrotic syndrome. J Am Soc Nephrol. Mar 2004;15(3):722-32.
29. Trautmann A, Lipska-Zietkiewicz BS, Schaefer F. Exploring the Clinical and Genetic Spectrum of Steroid Resistant Nephrotic Syndrome: The PodoNet Registry. Front Pediatr. 2018;6:200. doi:10.3389/fped.2018.00200
30. Warejko JK, Tan W, Daga A, et al. Whole Exome Sequencing of Patients with Steroid-Resistant Nephrotic Syndrome. Clin J Am Soc Nephrol. Jan 6 2018;13(1):53-62. doi:10.2215/CJN.04120417.
31. Bierzynska A, McCarthy HJ, Soderquest K, et al. Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management. Kidney Int. Apr 2017;91(4):937-947. doi:10.1016/j.kint.2016.10.013.
32. Santin S, Bullich G, Tazon-Vega B, et al. Clinical utility of genetic testing in children and adults with steroid-resistant nephrotic syndrome. Clin J Am Soc Nephrol. May 2011;6(5):1139-48. doi:CJN.05260610 [pii] 10.2215/CJN.05260610
33. Miao J, Pinto EVF, Hogan MC, et al. Identification of Genetic Causes of Focal Segmental Glomerulosclerosis Increases With Proper Patient Selection. Mayo Clin Proc. Sep 2021;96(9):2342-2353. doi:10.1016/j.mayocp.2021.01.037.
34. Alge JL, Bekheirnia N, Willcockson AR, et al. Variants in genes coding for collagen type IV α-chains are frequent causes of persistent, isolated hematuria during childhood. Pediatr Nephrol. Jun 27 2022;doi:10.1007/s00467-022-05627-w
35. Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic Utility of Exome Sequencing for Kidney Disease. N Engl J Med. Jan 10 2019;380(2):142-151. doi:10.1056/NEJMoa1806891.
36. Lu L, Yap YC, Nguyen DQ, et al. Multicenter study on the genetics of glomerular diseases among southeast and south Asians: Deciphering Diversities - Renal Asian Genetics Network (DRAGoN). Clin Genet. Jan 22 2022;doi:10.1111/cge.14116
37. Sinha R, Ray Chaudhury A, Sarkar S, et al. High Incidence of COL4A Genetic Variants Among a Cohort of Children With Steroid-Resistant Nephrotic Syndrome From Eastern India. Kidney Int Rep. 2022;doi:10.1016/j.ekir.2022.01.1047.
38. Wang Y, Dang X, He Q, et al. Mutation spectrum of genes associated with steroid-resistant nephrotic syndrome in Chinese children. Gene. Aug 20 2017;625:15-20. doi:10.1016/j.gene.2017.04.050
39. Xie J, Wu X, Ren H, et al. COL4A3 mutations cause focal segmental glomerulosclerosis. J Mol Cell Biol. Dec 2014;6(6):498-505. doi:10.1093/jmcb/mju040.
40. Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic Utility of Exome Sequencing for Kidney Disease. N Engl J Med. Jan 10 2019;380(2):142-151. doi:10.1056/NEJMoa1806891
41. Rovin BH, Caster DJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. Feb 2019;95(2):281-295. doi:10.1016/j.kint.2018.11.008.
42. Rovin BH, Adler SG, Barratt J, et al. Executive summary of the KDIGO 2021 Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4):753-779.
43. Savige J, Storey H, Watson E, et al. Consensus statement on standards and guidelines for the molecular diagnostics of Alport syndrome: refining the ACMG criteria. Eur J Hum Genet. Aug 2021;29(8):1186-1197. doi:10.1038/s41431-021-00858-1.
44. Buscher AK, Beck BB, Melk A, et al. Rapid Response to Cyclosporin A and Favorable Renal Outcome in Nongenetic Versus Genetic Steroid-Resistant Nephrotic Syndrome. Clin J Am Soc Nephrol. Feb 05 2016;11(2):245-53. doi:10.2215/cjn.07370715.
45. Trautmann A, Vivarelli M, Samuel S, et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. Aug 2020;35(8):1529-1561. doi:10.1007/s00467-020-04519-1.
46. Kidney Disease: Improving Global Outcomes Glomerular Diseases Work G. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. Oct 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021.
47. Schijvens AM, van de Kar NC, Bootsma-Robroeks CM, Cornelissen EA, van den Heuvel LP, Schreuder MF. Mitochondrial Disease and the Kidney With a Special Focus on CoQ10 Deficiency. Kidney Int Rep. Dec 2020;5(12):2146-2159. doi:10.1016/j.ekir.2020.09.044.

48. Tan W, Airik R. Primary coenzyme Q10 nephropathy, a potentially treatable form of steroid-resistant nephrotic syndrome. Pediatr Nephrol. Nov 2021;36(11):3515-3527. doi:10.1007/s00467-020-04914-8.
49. Alcazar-Fabra M, Trevisson E, Brea-Calvo G. Clinical syndromes associated with Coenzyme Q(10) deficiency. Essays Biochem. Jul 20 2018;62(3):377-398. doi:10.1042/EBC20170107.
50. Atmaca M, Gulhan B, Korkmaz E, et al. Follow-up results of patients with ADCK4 mutations and the efficacy of CoQ10 treatment. Pediatr Nephrol. Aug 2017;32(8):1369-1375. doi:10.1007/s00467-017-3634-3.
51. Schijvens AM, van de Kar NC, Bootsma-Robroeks CM, Cornelissen EA, van den Heuvel LP, Schreuder MF. Mitochondrial Disease and the Kidney With a Special Focus on CoQ(10) Deficiency. Kidney Int Rep. Dec 2020;5(12):2146-2159. doi:10.1016/j.ekir.2020.09.044.
52. Wühl E, Trivelli A, Picca S, et al. Strict blood-pressure control and progression of renal failure in children. N Engl J Med. Oct 22 2009;361(17):1639-50. doi:10.1056/NEJMoa0902066.
53. Gimpel C, Bergmann C, Mekahli D. The wind of change in the management of autosomal dominant polycystic kidney disease in childhood. Pediatr Nephrol. Mar 2022;37(3):473-487. doi:10.1007/s00467-021-04974-4.
54. Gimpel C, Bergmann C, Bockenhauer D, et al. International consensus statement on the diagnosis and management of autosomal dominant polycystic kidney disease in children and young people. Nat Rev Nephrol. Nov 2019;15(11):713-726. doi:10.1038/s41581-019-0155-2.
55. Germain DP, Moiseev S, Suarez-Obando F, et al. The benefits and challenges of family genetic testing in rare genetic diseases-lessons from Fabry disease. Mol Genet Genomic Med. May 2021;9(5):e1666. doi:10.1002/mgg3.1666.
56. Thomas CP, Gupta S, Freese ME, et al. Sequential genetic testing of living-related donors for inherited renal disease to promote informed choice and enhance safety of living donation. Transpl Int. Dec 2021;34(12):2696-2705. doi:10.1111/tri.14133.
57. Jayasinghe K, Stark Z, Kerr PG, et al. Clinical impact of genomic testing in patients with suspected monogenic kidney disease. Genet Med. Jan 2021;23(1):183-191. doi:10.1038/s41436-020-00963-4.
58. Gibson J, Fieldhouse R, Chan MMY, et al. Prevalence Estimates of Predicted Pathogenic COL4A3-COL4A5 Variants in a Population Sequencing Database and Their Implications for Alport Syndrome. J Am Soc Nephrol. Sep 2021;32(9):2273-2290. doi:10.1681/ASN.2020071065.
59. Wang YY, Savige J. The epidemiology of thin basement membrane nephropathy. Semin Nephrol. May 2005;25(3):136-9. doi:10.1016/j.semnephrol.2005.01.003.
60. Murakami M, Yamamoto H, Ueda Y, Murakami K, Yamauchi K. Urinary screening of elementary and junior high-school children over a 13-year period in Tokyo. Pediatr Nephrol. Jan 1991;5(1):50-3. doi:10.1007/BF00852844.
61. Yuste C, Gutierrez E, Sevillano AM, et al. Pathogenesis of glomerular haematuria. World J Nephrol. May 6 2015;4(2):185-95. doi:10.5527/wjn.v4.i2.185.
62. Hirabayashi Y, Katayama K, Mori M, et al. Mutation Analysis of Thin Basement Membrane Nephropathy. Genes (Basel). Oct 2 2022;13(10)doi:10.3390/genes13101779.
63. Papazachariou L, Papagregoriou G, Hadjipanagi D, et al. Frequent COL4 mutations in familial microhematuria accompanied by later-onset Alport nephropathy due to focal segmental glomerulosclerosis. Clin Genet. Nov 2017;92(5):517-527. doi:10.1111/cge.13077.
64. Deltas C, Savva I, Voskarides K, Papazachariou L, Pierides A. Carriers of Autosomal Recessive Alport Syndrome with Thin Basement Membrane Nephropathy Presenting as Focal Segmental Glomerulosclerosis in Later Life. Nephron. 2015;130(4):271-80. doi:10.1159/000435789.
65. Deltas C, Savva I, Voskarides K, Papazachariou L, Pierides A. Carriers of Autosomal Recessive Alport Syndrome with Thin Basement Membrane Nephropathy Presenting as Focal Segmental Glomerulosclerosis in Later Life. Nephron. Jul 17 2015;doi:10.1159/000435789.
66. Kashtan CE, Ding J, Gregory M, et al. Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative. Pediatr Nephrol. Jan 2013;28(1):5-11. doi:10.1007/s00467-012-2138-4.
67. Temme J, Peters F, Lange K, et al. Incidence of renal failure and nephroprotection by RAAS inhibition in heterozygous carriers of X-chromosomal and autosomal recessive Alport mutations. Kidney Int. Apr 2012;81(8):779-83. doi:10.1038/ki.2011.452.
68. Gross O, Tönshoff B, Weber LT, et al. A multicenter, randomized, placebo-controlled, double-blind phase 3 trial with open-arm comparison indicates safety and efficacy of nephroprotective therapy with ramipril in children with Alport's syndrome. Kidney Int. Jun 2020;97(6):1275-1286. doi:10.1016/j.kint.2019.12.015.
69. Berrios C, Hurley EA, Willig L, et al. Challenges in genetic testing: clinician variant interpretation processes and the impact on clinical care. Genet Med. Dec 2021;23(12):2289-2299. doi:10.1038/s41436-021-01267-x.
70. Bland A, Harrington EA, Dunn K, et al. Clinically impactful differences in variant interpretation between clinicians and testing laboratories: a single-center experience. Genet Med. Mar 2018;20(3):369-373. doi:10.1038/gim.2017.212.
71. Gradishar W, Johnson K, Brown K, Mundt E, Manley S. Clinical Variant Classification: A Comparison of Public Databases and a Commercial Testing Laboratory. Oncologist. Jul 2017;22(7):797-803. doi:10.1634/theoncologist.2016-0431.
72. Cirillo L, Becherucci F. Genetic Testing in Nephrology: Show Your Pedigree! Kidney360. Dec 29 2022;3(12):2148-2152. doi:10.34067/KID.0002732022.
73. Pinto EVF, Prochnow C, Kemppainen JL, et al. Genomics Integration Into Nephrology Practice. Kidney Med. Sep-Oct 2021;3(5):785-798. doi:10.1016/j.xkme.2021.04.014.

LEARNING POINTS

- **Monogenic causes occur in 30 percent in children and 5-30 percent of adults with CKD.**
- **Alport syndrome and ADPKD are the two most common genetic causes of CKD.**
- **Glomerular diseases are to be suspected when a patient has persistent haematuria and/or proteinuria that is out of proportion with the stage of CKD.**
- **Genetic testing should be considered in patients with a young age of onset, positive family history especially of late CKD, presence of extrarenal conditions, and absence of complete steroid response.**
- **Clinical utility of genetic testing in kidney diseases include more tailored immunosuppressive strategies, negating the need for kidney biopsies, targeted selection of kidney donors, disease-specific therapies like coenzyme Q10, and targeted extrarenal surveillance.**
- **Alport syndrome is common in the population.**
- **The kidney prognosis in Alport syndrome differs extensively based on the modes of inheritance.**
- **Thin membrane disease can be caused by Alport syndrome and the prognosis is not so benign. Up to 30 percent of these patients can develop kidney failure by 60 years old.**
- **Early treatment of Alport syndrome with RAAS blockade can significantly delay onset of kidney failure by as much as 20-40 years in males with X-linked Alport syndrome.**