U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Lipska-Ziętkiewicz BS. Genetic Steroid-Resistant Nephrotic Syndrome Overview. 2021 Aug 26. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Genetic Steroid-Resistant Nephrotic Syndrome Overview

Beata S Lipska-Ziętkiewicz, MD, PhD[1]

Created: August 26, 2021.

Summary

The purpose of this overview is to provide clinically relevant information regarding genetic steroid-resistant nephrotic syndrome (SRNS), strategies to establish the diagnosis, management, and genetic counseling.

The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of genetic steroid-resistant nephrotic syndrome.

Goal 2

Review the genes known to be associated with genetic steroid-resistant nephrotic syndrome.

Goal 3

Provide an evaluation strategy to identify the cause of genetic steroid-resistant nephrotic syndrome in a proband (when possible).

Goal 4

Review phenocopies of genetic steroid-resistant nephrotic syndrome.

Goal 5

Review management of genetic steroid-resistant nephrotic syndrome.

Goal 6

Inform risk assessment and surveillance of at-risk relatives for early detection and treatment of genetic steroid-resistant nephrotic syndrome.

Author Affiliation: 1 Center for Rare Diseases; Department of Biology and Medical Genetics, Clinical Genetics Unit, Medical University of Gdańsk, Gdańsk, Poland; Email: b.lipska@gumed.edu.pl.

1. Clinical Characteristics of Genetic Steroid-Resistant Nephrotic Syndrome

The initial manifestation of nephrotic syndrome is severe proteinuria defined as presence of the following [Trautmann et al 2020]:

- Urine protein/creatinine ratio (UPCR) ≥200 mg/mmol (2 mg/mg) in the first morning void; OR 24-h urine sample ≥1000 mg/m^2/day corresponding to 3+ or 4+ by urine dipstick
- Hypoalbuminemia (serum albumin <30 g/L)
- Edema

About 85% of nephrotic syndrome is steroid sensitive (SSNS), defined as complete remission of proteinuria following glucocorticoid treatment. SSNS will not be discussed further in this overview.

About 15% of nephrotic syndrome is steroid resistant (SRNS), defined as proteinuria that does not remit within four to six weeks of glucocorticoid treatment. About 50% of individuals with SRNS achieve sustained remission with intensified immunosuppressive treatment, whereas the rest have multi-drug resistance and progress to chronic kidney disease (CKD) and eventually to kidney failure.

Non-genetic SRNS is defined as SRNS that is not caused by alterations in a gene known to be associated with SRNS. In contrast to genetic SRNS, non-genetic SRNS has been postulated (but not yet confirmed) to be immune mediated and associated with circulating permeability factor(s) in the plasma.

Although most non-genetic SRNS is steroid resistant at the onset, a few individuals may initially respond to standard steroid therapy but subsequently demonstrate secondary steroid resistance. About 70% of individuals with non-genetic SRNS experience rapid post-transplantation recurrence of nephrotic syndrome in the graft [Mason et al 2020].

Genetic SRNS is defined as SRNS caused by a pathogenic variant (or pathogenic variants) in a gene that affects the establishment and maintenance of the glomerular filtration barrier. The glomerular filtration barrier comprises podocytes, the glomerular basement membrane, and fenestrated endothelial cells. All genetic SRNS can be corrected with renal transplantation.

In SRNS, about 30% of individuals with childhood-onset disease and 10%-15% of individuals with adult-onset disease have an underlying genetic alteration in one of the roughly 60 genes associated with genetic SRNS (see Section 2). Genetic SRNS can be either syndromic (when associated with additional signs and symptoms) (see Table 1) or nonsyndromic (when not associated with other manifestations) (see Table 2).

2. Causes of Genetic Steroid-Resistant Nephrotic Syndrome

Tables 1 and 2 (adapted from Table 1 in Preston et al [2019] and Table 3 in Trautmann et al [2020]) summarize the genes known to be associated with genetic steroid-resistant nephrotic syndrome (SRNS).

Table 1 lists genes associated with syndromic genetic SRNS and Table 2 lists genes associated with nonsyndromic genetic SRNS.

Identification of a genetic SRNS can be particularly useful in individuals with syndromic genetic SRNS (see Table 1) in which relevant extrarenal features may escape clinical detection or may arise later in the course of disease, such as hearing loss (associated with Alport syndrome and primary coenzyme Q_{10} deficiency); Wilms tumor, gonadoblastoma, or gonadal dysgenesis (with *WT1* disorder); or chronic motor and sensory polyneuropathy (associated with *INF2*-related Charcot-Marie-Tooth hereditary neuropathy).

Note: The following genes are listed in both Table 1 and Table 2 because they can be associated with syndromic genetic SRNS or with isolated, or apparently isolated, genetic SRNS: *COL4A3/4/5*, *COQ8B* (*ADCK4*), *CRB2*, *INF2*, *LMX1B,* and *WT1*. Some individuals who present with an apparently isolated renal phenotype may have extrarenal manifestations that are not appreciated until further clinical evaluation is prompted by the identification of a pathogenic variant (or pathogenic variants) in a gene known to be associated with syndromic genetic SRNS [Knoers et al 2022].

Table 1. Syndromic Genetic SRNS: Genes and Clinical Features

Gene(s) [1]	MOI	Syndrome / Features in Addition to SRNS
ALG1	AR	ALG1-CDG: microcephaly, neurologic involvement (seizures, neurologic deterioration, cerebral or cerebellar atrophy), skeletal, cardiac, hepatic, gastrointestinal, endocrine, coagulation abnormalities (See Congenital Disorder of N-Linked Glycosylation.)
ARHGDIA	AR	Seizures & cortical blindness (OMIM 615244)
AVIL	AR	Microcephaly, short stature, retinal dystrophy, cataracts, deafness, & DD (OMIM 618594)
CD151	AR	Pretibial bullous skin lesions, SNHL, bilateral lacrimal duct stenosis, nail dystrophy, & thalassemia minor (OMIM 609057)
COL4A3 [2] *COL4A4* [2] *COL4A5* [2]	XL AR AD Digenic	Alport syndrome: ocular abnormalities (anterior lenticonus, corneal & retinal lesions), SNHL, leiomyomas (if large deletions include *COL4A6*) [3]
COQ2 *COQ6* *COQ8B* [2] (*ADCK4*)	AR	Primary coenzyme Q_{10} deficiency: neurologic involvement (encephalomyopathy, ataxia, seizures), DD, cognitive impairment, SNHL
CRB2 [2]	AR	Prenatal-onset ventriculomegaly, seizures, renal corticomedullary cysts, cardiac & congenital defects (OMIM 219730)
DGKE	See footnote 4.	C3 glomerulopathy
E2F3	AD	ID (whole-gene deletion) (OMIM 600427)
FAT1	AR	Neurologic involvement; dysmorphic features, colobomatous microphthalmia, renal tubular ectasia, hematuria [5]
INF2 [2]	AD	Peripheral neuropathy (distal muscle atrophy & weakness), SNHL (See CMT Overview.)
ITGA3	AR	Epidermolysis bullosa, congenital interstitial lung disease (OMIM 614748)
ITGB4	AR	Epidermolysis bullosa w/pyloric atresia
LAGE3	XL	Galloway-Mowat syndrome 2: facial dysmorphism, microcephaly, CNS involvement (structural brain anomalies, seizures), optic nerve atrophy, DD, cognitive impairment, skeletal abnormalities, hiatus hernia (OMIM 301006)
LAMB2	AR	Pierson syndrome: ocular malformations (microcoria, cataracts, other lens or retinal abnormalities); neonatal hypotonia, DD, cognitive impairment (OMIM 609049)
LMX1B [2]	AD	Nail-patella syndrome: limb & pelvic abnormalities (absent or hypoplastic patella, elbow abnormalities, iliac horns), absent or dystrophic nails & distal digital abnormalities, eye abnormalities including glaucoma
MAFB	AD	Duane syndrome: a non-progressive limited horizontal eye movement accompanied by globe retraction
MAGI2	AR	± neurologic impairment (OMIM 617609)

Table 1. continued from previous page.

Gene(s) [1]	MOI	Syndrome / Features in Addition to SRNS
MT-TL1	Mat	MELAS: neurologic involvement (encephalomyopathy, seizures, stroke-like episodes), exercise intolerance, SNHL, retinopathy, diabetes mellitus, hypoparathyroidism, lactic acidosis
MYH9	AD	*MYH9*-related disease: hematologic features present from birth consisting of platelet macrocytosis, thrombocytopenia, & aggregates of the MYH9 protein in the cytoplasm of neutrophil granulocytes. Most affected individuals develop ≥1 additional extrahematologic manifestations including SNHL, renal disease, presenile cataracts, &/or ↑ liver enzymes
NUP107 [6]	AR	Galloway-Mowat syndrome 7: facial dysmorphism, microcephaly, CNS involvement (structural brain anomalies, seizures), optic nerve atrophy, DD, cognitive impairment, skeletal abnormalities, hiatus hernia (OMIM 618348)
NUP85 [6]	AR	ID, short stature, microscopic hematuria (OMIM 618176)
NUP205 [6, 7]	AR	Aortic abnormalities [6, 7]
NXF5	XL	Heart block disorder [8]
OSGEP *TP53RK* *TPRKB* *WDR73*	AR	Galloway-Mowat syndrome 3: Facial dysmorphism, microcephaly, CNS involvement (structural brain anomalies, seizures), optic nerve atrophy, DD, cognitive impairment, skeletal abnormalities, hiatus hernia (OMIM PS251300)
PAX2	AD	*PAX2* disorder: eye abnormalities (retinal coloboma, optic disc dysplasia), congenital anomalies of the kidney and urinary tract, renal cysts, renal dysplasia/hypoplasia
PDSS2	AR	Primary coenzyme Q_{10} deficiency: neurologic involvement (encephalomyopathy, ataxia, seizures), DD, cognitive impairment), SNHL
PMM2	AR	PMM2-CDG: microcephaly, neurologic involvement (seizures, neurologic deterioration, cerebral or cerebellar atrophy); skeletal, cardiac, hepatic, gastrointestinal, endocrine, coagulation abnormalities
SCARB2	AR	Action myoclonus – renal failure syndrome: Neurologic symptoms (tremor, action myoclonus, tonic-clonic seizures, later ataxia & dysarthria), sensorimotor peripheral neuropathy, SNHL, dilated cardiomyopathy
SGPL1	AR	Sphingosine phosphate lyase insufficiency syndrome: varying combinations of primary adrenal insufficiency (± mineralocorticoid deficiency), testicular insufficiency, ichthyosis, neurologic involvement (DD, seizures, ataxia), immunodeficiency, skeletal abnormalities
SMARCAL1	AR	Schimke immunoosseous dysplasia: spondyloepiphyseal dysplasia resulting in short stature; T-cell deficiency

Table 1. continued from previous page.

Gene(s) [1]	MOI	Syndrome / Features in Addition to SRNS
WT1 [2]	AD	*WT1* disorder: disorders of testicular development (± abnormalities of external genitalia &/or müllerian structures) & Wilms tumor; congenital anomalies of kidney & urinary tract, diaphragmatic hernia

AD = autosomal dominant; AR = autosomal recessive; CDG = congenital disorder of glycosylation; CKD = chronic kidney disease; CMT = Charcot-Marie-Tooth disease; CNS = central nervous system; DD = developmental delay; ID = intellectual disability; Mat = maternal; MELAS = *m*itochondrial *e*ncephalomyopathy, *l*actic *a*cidosis, and *s*troke-like episodes; MOI = mode of inheritance; SNHL = sensorineural hearing loss; SRNS = steroid-resistant nephrotic syndrome; XL = X-linked

1. Genes are listed alphabetically

2. Also associated with nonsyndromic SRNS

3. Nozu et al [2017]

4. C3 glomerulopathy is a complex genetic disorder that is rarely inherited in a simple mendelian fashion. Multiple affected persons within a single nuclear family are reported only occasionally, with both autosomal dominant and autosomal recessive inheritance being described.

5. Lahrouchi et al [2019]

6. Lipska-Ziętkiewicz & Schaefer [2019]

7. Preliminary data suggest that *NUP205* may also be associated with nonsyndromic genetic SRNS [Author, unpublished data].

8. Esposito et al [2013]

Table 2. Nonsyndromic Genetic SRNS: Genes and Distinguishing Clinical Features

Gene [1]	MOI	% of All Nonsyndromic SRNS	Typical Age at Onset of SRNS	Reference
ACTN4	AD	~1%	Usually late (adult)	OMIM 603278
ANKFY1		<1%	Childhood	OMIM 607927
ANLN	AD	<1%	Mainly late (adult)	OMIM 616032
APOL1	Risk allele	No data [2]	↑ susceptibility in African Americans, Hispanic Americans, & persons of African descent	OMIM 612551
ARHGAP24	AR	<1%	Mainly late (adult)	OMIM 610586
CD2AP	AD/AR	<1%	Childhood & adult	OMIM 607832
COL4A3 [3] *COL4A4* [3] *COL4A5* [3]	XL AR AD Digenic	~10%-30% (esp if onset in/ after 2nd decade)	Mainly late (adolescent & adult)	Gast et al [2016]
COQ8B [3] *(ADCK4)*	AR	3%-5%	Childhood & adult	OMIM 615573
CRB2 [3]	AR	<1%	Childhood	OMIM 609720
GAPVD1	AR	<1%	Childhood	OMIM 611714
INF2 [3]	AD	3%	Mainly late (adolescent & adult)	OMIM 613237
LAMA5	AR	<1%	Childhood	OMIM 601033
LMX1B [3]	AD	3%-5% (esp if onset in/ after 2nd decade)	Mainly late (adolescent & adult)	OMIM 256020
MYO1E	AR	<1%	Childhood	OMIM 614131
NPHS1	AR	10%-20% (≤50% in CNS)	CNS (Finnish type) or childhood SRNS	OMIM 602716

Table 2. continued from previous page.

Gene [1]	MOI	% of All Nonsyndromic SRNS	Typical Age at Onset of SRNS	Reference
NPHS2	AR	20%-30% (≤40% in CNS)	CNS or childhood & adult SRNS	OMIM 600995
NUP133 [4]	AR	<1%	Childhood	OMIM 607613
NUP160 [4]	AR	<1%	Childhood	OMIM 618178
NUP93 [4, 5]	AR	<1%	Childhood	OMIM 616892
PLCE1	AR	3%	CNS or childhood SNRS	OMIM 610725
PTPRO	AR	<1%	Childhood	OMIM 614196
TBC1D8B	XL	<1%	Childhood	OMIM 301028
TRPC6	AD	3%	Childhood & adult	OMIM 603965
TTC21B	AR	<1%	Childhood & adult	Nephronophthisis
WT1 [3]	AD	10%-20%	CNS or childhood & adult SRNS	WT1 Disorder
XPO5	AR	<1%	Childhood	OMIM 607845

AD = autosomal dominant; AR = autosomal recessive; CNS = congenital nephrotic syndrome; MOI = mode of inheritance; SRNS = steroid-resistant nephrotic syndrome; XL = X-linked

1. Genes are listed alphabetically

2. 13% of African Americans have the *APOL1* high-risk genotype (2 risk alleles) and these individuals have a 3- to 30-fold increased risk of various forms of kidney disease; the frequency in individuals of European ancestry is unknown [Friedman & Pollak 2020].

3. Also associated with syndromic genetic SRNS.

4. Lipska-Ziętkiewicz & Schaefer [2019]

5. Preliminary data suggest that *NUP93* may also be associated with syndromic genetic SRNS [Author, unpublished data].

Nomenclature

Genetic SRNS may also be referred to as "hereditary SRNS" or "monogenic SRNS."

Nonsyndromic genetic SRNS may also be referred to as "hereditary podocytopathy/glomerulopathy." Glomerulopathy is the preferred term as a subset of individuals with a hereditary podocytopathy never receive steroids, and, thus, their renal disease cannot be classified as steroid resistant.

In the context of genetic SRNS, use of the terms "idiopathic SRNS" and "primary SRNS" is controversial as these terms may imply absence of molecularly confirmed diagnosis.

3. Evaluation Strategies to Identify the Cause of Genetic Steroid-Resistant Nephrotic Syndrome in a Proband

Establishing a specific cause of genetic steroid-resistant nephrotic syndrome usually involves a medical history, physical examination, laboratory testing, family history, and genomic/genetic testing.

The age at first disease manifestation and the rate of chronic kidney disease (CKD) progression will strongly depend on the gene affected and the type of causative pathogenic variant.

- Variants in *LAMB2*, *NPHS1*, *NPHS2*, and *WT1* account for >80% of all congenital nephrotic syndrome. See Tables 1 and 2.
- Variants in *INF2*, *TRPC6*, and the genes encoding collagen IV (*COL4A3*, *COL4A4*, and *COL4A5*) are the leading causes of adult-onset SRNS.

Medical history. A detailed medical history for renal and extrarenal manifestations should be obtained wherever possible. Possible extrarenal manifestation(s) in individuals with syndromic genetic SRNS are included Table 1.

Physical examination. Clinical examination should be performed to identify the possible extrarenal manifestations of syndromic genetic SRNS (Table 1).

Family history. A three-generation family history should be taken, with attention to parental consanguinity and to relatives with manifestations of SRNS or other renal disease with their age at onset, clinical course (including response to medications), renal function, and documentation of relevant findings through direct examination or review of medical records (including results of molecular genetic testing and/or renal biopsy). Absence of a family history of such findings does not preclude the possibility of genetic SRNS.

Molecular genetic testing can include a combination of gene-targeted testing (single-gene testing or multigene panel) and comprehensive genomic testing (exome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **Single-gene testing** can be considered if clinical findings and/or family history indicate that pathogenic variants in a particular gene associated with genetic syndromic SRNS are most likely (see Table 1).
- **A multigene panel** that includes some or all of the genes listed in Tables 1 and 2 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Some panels may not include newly discovered and/or rare genes associated with genetic SRNS. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Phenocopies of Genetic Steroid-Resistant Nephrotic Syndrome

Table 3. Phenocopies of Genetic SRNS Usually Presenting As Persistent Proteinuria

Gene [1]	MOI	Syndrome / Phenotype	Additional Features
CFH	AD Polygenic	Genetic atypical hemolytic-uremic syndrome (aHUS)	Thrombocytopenia [2]
	Complex [3]	C3 glomerulopathy	Membranoproliferative glomerulonephritis
CLCN5	XL	Dent disease 1: ± hypercalciuria & nephrolithiasis	LMW proteinuria. Other features may incl rickets or osteomalacia, growth restriction/short stature.
CUBN	AR	Albuminuria, megaloblastic anemia ± epilepsy (OMIM 618884) [4]	Imerslund-Gräsbeck syndrome 1 (OMIM 261100), intestinal malabsorption of vitamin B_{12}), LMW proteinuria

Table 3. continued from previous page.

Gene [1]	MOI	Syndrome / Phenotype	Additional Features
FN1	AD	Fibronectin glomerulopathy (OMIM 601894)	Proteinuria, type IV renal tubular acidosis, microscopic hematuria
LCAT	AR	Norum disease (Lecithin:cholesterol acyltransferase deficiency) (OMIM 245900)	Corneal opacities, target cell hemolytic anemia, proteinuria
LMNA	AD	Familial partial lipodystrophy (OMIM 151660)	Abnormal subcutaneous adipose tissue distribution, diabetes mellitus, hypertension
MMACHC	AR	Cobalamin C deficiency (See Disorders of Intracellular Cobalamin Metabolism.)	TMA, neurologic involvement; cytopenia; thromboembolism
NEU1	AR	Neuraminidase deficiency (OMIM 256550)	Progressively severe mucopolysaccharidosis-like phenotype (coarse facies, dysostosis multiplex, hepatosplenomegaly), progressive neurologic degeneration, childhood nephrotic syndrome, macular cherry-red spots, & DD/ID.
NPHP4	AR	Isolated nephronophthisis (NPH)	~80%-90% of persons w/NPH phenotype have no extrarenal features.
OCRL	XL	Dent disease 2	Proximal tubule dysfunction & LMW proteinuria, assoc w/ hypercalciuria, nephrolithiasis, nephrocalcinosis, & progressive renal failure
ZMPSTE24	AR	Mandibuloacral dysplasia (OMIM 608612)	Generalized lipoatrophy, postnatal growth retardation, dysmorphic features, mandibular & clavicular hypoplasia, other skeletal & dental abnormalities, restrictive dermopathy

AD = autosomal dominant; AR = autosomal recessive; CKD = chronic kidney disease; DD = developmental delay; ID = intellectual disability; LMW = low-molecular-weight; MOI = mode of inheritance; SRNS = steroid-resistant nephrotic syndrome; TMA = thrombotic microangiopathy; XL = X-linked

1. Genes are listed alphabetically

2. Simultaneous kidney & liver transplantation in young children w/*CFH*-aHUS may correct the genetic defect & prevent disease recurrence.

3. C3 glomerulopathy (C3G) is a complex genetic disorder that is rarely inherited in a simple mendelian fashion. In most persons with C3G, inheritance is complex and incompletely understood. For these reasons, recurrence risk to family members is not known but likely very low.

4. C-terminal variants associate with chronic proteinuria and normal renal function [Bedin et al 2020].

5. Management of Genetic Steroid-Resistant Nephrotic Syndrome

In 2020 the International Pediatric Nephrology Association developed comprehensive clinical practice recommendations for the diagnosis and management of SRNS in children [Trautmann et al 2020].

See also the detailed genetic and clinical guidelines for management of congenital nephrotic syndrome [Lipska-Ziętkiewicz et al 2020, Boyer et al 2021].

Once the diagnosis of SRNS is established, ineffective prednisolone/prednisone treatment should be avoided. Instead affected individuals should be treated with renin-angiotensin-aldosterone system inhibitors (RAASi) to reduce proteinuria.

While recent recommendations also suggest withholding calcineurin inhibitors and other immunosuppressive agents in individuals with evidence for genetic SRNS, the final decision should be made on an individual basis (for details see Trautmann et al [2020]).

Clinical management also includes the following:

- Prompt detection and treatment of hypertension
- Cautious use of diuretics, vitamin D, and thyroid hormone substitution
- Conservative management of chronic kidney disease (CKD)
- Renal replacement therapy including preemptive transplantation in selected disorders (e.g., *WT1* disorder).

6. Risk Assessment and Surveillance of At-Risk Relatives for Early Detection and Treatment of Genetic Steroid-Resistant Nephrotic Syndrome

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Screening of asymptomatic first-degree family members (see Surveillance for At-Risk Relatives) of an individual with genetic steroid-resistant nephrotic syndrome (SRNS) can allow early detection of genetic SRNS, inform the indication for and frequency of subsequent screening, facilitate prompt initiation of treatment, and thereby improve long-term outcome [Trautmann et al 2020].

Clarification of the genetic status of first-degree family members can also help to identify potential organ donors. (Note: Molecular genetic testing for the familial pathogenic variant is obligatory for genetic SRNS with autosomal dominant transmission and in certain entities with significant intra- and interfamilial variability and incomplete or age-dependent penetrance [e.g., genetic SRNS associated with pathogenic variants in *COL4A3/4/5*, *NPHS2*, or *WT1*]).

Note: Given the complexity of the genetics and surveillance recommendations for genetic SRNS, health care providers should consider referring at-risk asymptomatic relatives to a nephrology genetics center or a genetic counselor specializing in nephrology genetics (see NSGC - Find a Genetic Counselor or ABGC Find a Certified Genetic Counselor search tools).

Genetic risk assessment. Genetic SRNS can be inherited in an autosomal recessive, autosomal dominant (e.g., *WT1*-related SRNS), or, rarely, X-linked (*TBC1D8B*-related SRNS) manner. A basic view of autosomal recessive and autosomal dominant inheritance and risk assessment and surveillance for at-risk relatives of an individual with genetic SRNS is presented below.

If a proband has a specific genetic syndrome associated with SRNS (e.g., *WT1* disorder, Alport syndrome, primary coenzyme Q_{10} deficiency, Schimke immunoosseous dysplasia, or Charcot-Marie-Tooth hereditary neuropathy), counseling for that condition is indicated (see Table 1).

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., presumed to be carriers of one autosomal recessive genetic SRNS-causing pathogenic variant based on family history).
- Molecular genetic testing of the parents for the pathogenic variants identified in the proband is recommended to confirm that both parents are heterozygous for a causative pathogenic variant and to

allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
    - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
    - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.
- In some families, a parent of the proband is found to have biallelic genetic SRNS-causing pathogenic variants (rather than a heterozygous pathogenic variant). This is more likely to occur in families segregating a relatively common non-neutral variant such as the p.Arg229Gln *NPHS2* variant, which has a carrier frequency of 3% in the general multiethnic population, and carrier frequencies of 7% and 0.01% in Finnish and East Asian populations respectively. Note: A parent found to have biallelic SRNS-causing pathogenic variants is at risk of developing genetic SRNS later in life.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing autosomal recessive genetic SRNS. A parent who is heterozygous for autosomal recessive genetic SRNS may be able to serve as a kidney donor.

Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive SRNS-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder. A sib who is heterozygous for autosomal recessive genetic SRNS may be able to serve as a kidney donor.

Offspring of a proband. The offspring of an individual with autosomal recessive genetic SRNS are obligate heterozygotes (carriers) for a pathogenic variant in an SRNS-causing pathogenic variant.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an autosomal recessive SRNS-causing pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the autosomal recessive SRNS-causing pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Some individuals diagnosed with autosomal dominant genetic SRNS have an affected parent. The frequency of probands with an affected parent is highest in individuals with a heterozygous pathogenic variant in *COL4A3*, *COL4A4*, *COL4A5*, or *INF2*.
- Most individuals diagnosed with autosomal dominant genetic SRNS have the disorder as the result of a *de novo* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling. Note: Molecular genetic testing is obligatory for relatives considering organ donation.
- If the pathogenic variant identified in the proband is not identified in either parent, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].

    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with an autosomal dominant genetic SRNS may appear to be negative because of failure to recognize the disorder in family members, reduced penetrance, and/or early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the proband has a known genetic SRNS-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the pathogenic variant identified in the proband but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for autosomal dominant genetic SRNS because of the possibility of reduced penetrance in a heterozygous parent or the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant SRNS has a 50% chance of inheriting the genetic SRNS-causing pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the genetic SRNS-causing pathogenic variant, the parent's family members may be at risk.

Surveillance of At-Risk Relatives for Early Detection and Treatment of Genetic Steroid-Resistant Nephrotic Syndrome

For early diagnosis and treatment

- First degree relatives, including sibs, should be offered urine analysis for proteinuria. This testing should be offered to at-risk family members as soon as possible and should not be delayed pending molecular confirmation that the proband has genetic SRNS.

  Family members found to have proteinuria should undergo detailed clinical evaluation by a nephrologist to either confirm a diagnosis of genetic SRNS or detect any other cause of proteinuria (see Section 4). Family members who do not have proteinuria are still at risk for genetic SRNS (as genetic SRNS is characterized by variable expressivity and incomplete and/or age-dependent penetrance) and should undergo genetic testing once a molecular diagnosis is established in the proband.

- Once the genetic SRNS-causing pathogenic variant(s) have been identified in the proband, it is appropriate to clarify the genetic status of at-risk relatives to identify individuals with the familial pathogenic variant(s) as early as possible.

  Early identification of a genetic predisposition may result in successful delay of disease progression, not only by avoiding ineffective therapies and their substantial side effects, but also by the following: initiation of treatment with RAASi to reduce proteinuria; prompt detection and treatment of hypertension; cautious use of diuretics, vaccination, vitamin D, and thyroid hormone substitution; and early start of targeted treatment such as ubiquinone supplementation in COQ_{10} deficiency.

Early intervention may also include surveillance for extrarenal manifestations (e.g., endocrinologic, oncologic, immune, or neurologic; see Table 1 for particular diagnoses and associated phenotypes) [Trautmann et al 2020].

Members of the family found negative on genetic testing may be discharged from surveillance and are no longer considered at increased risk for genetic SRNS.

For family members being evaluated for living-related kidney donation

- Any relative who is a potential kidney donor should undergo molecular genetic testing to clarify the potential donor's genetic status. Screening of the potential donor with molecular genetic testing is obligatory for families segregating autosomal dominant or X-linked genetic SRNS and in certain entities with significant intra- and interfamilial variability and incomplete or age-dependent penetrance (e.g., genetic SRNS associated with pathogenic variants in *WT1*, *COL4A3/4/5*, or *NPHS2*).
- Family members who are found to have a pathogenic variant associated with autosomal dominant or X-linked genetic SRNS cannot serve as kidney donors regardless of clinical status [Lipska-Ziętkiewicz et al 2020, Trautmann et al 2020].
- Individuals who are heterozygous for a pathogenic variant associated with autosomal recessive genetic SRNS and individuals who do not have the familial genetic SRNS-related pathogenic variant can be evaluated further as possible kidney donors.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Kidney Fund**

  Phone: 800-638-8299

  www.kidneyfund.org

- **European Rare Kidney Disease Reference Network (ERKNet)**

  Phone: 49 0 6221 56-34191

  Email: contact@erknet.org

  www.erknet.org

- **Kidney Foundation of Canada**

  Canada

  Phone: 514-369-4806; 800-361-7494

  Email: info@kidney.ca

  www.kidney.ca

- **NephCure Kidney International**

  Phone: 866-NephCure; 866-637-4287

  Email: info@nephcure.org

  nephcure.org

- **Nephrotic Syndrome Study Network (NEPTUNE)**

As a research consortium of physician scientists at 26 sites in the United States and Canada, along with patient advocacy groups NephCure Kidney International and the Halpin Foundation, NEPTUNE strives to bring the latest advances in research to patients diagnosed with Focal Segmental Glomerulosclerosis (FSGS), Minimal Changes Disease (MCD), and Membranous Nephropathy (MN) with an overarching goal of utilizing precision medicine for rare diseases.

Phone: 734-615-5020

Email: NEPTUNE-STUDY@umich.edu

www.neptune-study.org

- **PodoNet Registry**

  The PodoNet Registry explores the demographics, causes and prognosis of patients with congenital and steroid resistant nephrotic syndrome.

  Clinical, Genetic and Experimental Research into Hereditary Disease of the Podocyte

  PodoNet

Chapter Notes

Author Notes

Beata S Lipska-Ziętkiewicz is the genetic coordinator at PodoNet (www.escapenet.eu/researchers/beata-lipska-zietkiewicz), one of the largest international registries of steroid-resistant nephrotic syndrome. She is a member of the Molecular Diagnostics Task Force and co-chair of the Hereditary Glomerulopathies Working Group for the European Rare Kidney Disease Reference Network (ErkNet).

Revision History

- 26 August 2021 (bp) Review posted live
- 11 January 2021 (blz) Original submission

References

Literature Cited

Bedin M, Boyer O, Servais A, Li Y, Villoing-Gaudé L, Tête MJ, Cambier A, Hogan J, Baudouin V, Krid S, Bensman A, Lammens F, Louillet F, Ranchin B, Vigneau C, Bouteau I, Isnard-Bagnis C, Mache CJ, Schäfer T, Pape L, Gödel M, Huber TB, Benz M, Klaus G, Hansen M, Latta K, Gribouval O, Morinière V, Tournant C, Grohmann M, Kuhn E, Wagner T, Bole-Feysot C, Jabot-Hanin F, Nitschké P, Ahluwalia TS, Köttgen A, Andersen CBF, Bergmann C, Antignac C, Simons M. Human C-terminal CUBN variants associate with chronic proteinuria and normal renal function. J Clin Invest. 2020;130:335–44. PubMed PMID: 31613795.

Boyer O, Schaefer F, Haffner D, Bockenhauer D, Hölttä T, Bérody S, Webb H, Heselden M, Lipska-Zie Tkiewicz BS, Ozaltin F, Levtchenko E, Vivarelli M. Management of congenital nephrotic syndrome: consensus recommendations of the ERKNet-ESPN Working Group. Nat Rev Nephrol. 2021;17:277–89. PubMed PMID: 33514942.

Esposito T, Lea RA, Maher BH, Moses D, Cox HC, Magliocca S, Angius A, Nyholt DR, Titus T, Kay T, Gray NA, Rastaldi MP, Parnham A, Gianfrancesco F, Griffiths LR. Unique X-linked familial FSGS with co-segregating heart block disorder is associated with a mutation in the NXF5 gene. Hum Mol Genet. 2013;22:3654–66. PubMed PMID: 23686279.

Friedman DJ, Pollak MR. APOL1 and Kidney disease: from genetics to biology. Annu Rev Physiol. 2020;82:323–42. PubMed PMID: 31710572.

Gast C, Pengelly RJ, Lyon M, Bunyan DJ, Seaby EG, Graham N, Venkat-Raman G, Ennis S. Collagen (COL4A) mutations are the most frequent mutations underlying adult focal segmental glomerulosclerosis. Nephrol Dial Transplant. 2016;31:961–70. PubMed PMID: 26346198.

Knoers N, Antignac C, Bergmann C, Dahan K, Giglio S, Heidet L, Lipska-Ziętkiewicz BS, Noris M, Remuzzi G, Vargas R, Schaefer F, et al. Genetic testing in the diagnosis of chronic kidney disease: recommendations for clinical practice. Nephrol Dial Transplant. 2022;37:239–54. PubMed PMID: 34264297.

Lahrouchi N, George A, Ratbi I, Schneider R, Elalaoui SC, Moosa S, Bharti S, Sharma R, Abu-Asab M, Onojafe F, Adadi N, Lodder EM, Laarabi FZ, Lamsyah Y, Elorch H, Chebbar I, Postma AV, Lougaris V, Plebani A, Altmueller J, Kyrieleis H, Meiner V, McNeill H, Bharti K, Lyonnet S, Wollnik B, Henrion-Caude A, Berraho A, Hildebrandt F, Bezzina CR, Brooks BP, Sefiani A. Homozygous frameshift mutations in FAT1 cause a syndrome characterized by colobomatous-microphthalmia, ptosis, nephropathy and syndactyly. Nat Commun. 2019;10:1180. PubMed PMID: 30862798.

Lipska-Ziętkiewicz BS, Ozaltin F, Hölttä T, Bockenhauer D, Bérody S, Levtchenko E, Vivarelli M, Webb H, Haffner D, Schaefer F, Boyer O. Genetic aspects of congenital nephrotic syndrome: a consensus statement from the ERKNet-ESPN inherited glomerulopathy working group. Eur J Hum Genet. 2020;28:1368–78. PubMed PMID: 32467597.

Lipska-Ziętkiewicz BS, Schaefer F. NUP nephropathy: when defective pores cause leaky glomeruli. Am J Kidney Dis. 2019;73:890–2. PubMed PMID: 30876747.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Mason AE, Sen ES, Bierzynska A, Colby E, Afzal M, Dorval G, Koziell AB, Williams M, Boyer O, Welsh GI, Saleem MS, et al. Response to first course of intensified immunosuppression in genetically stratified steroid resistant nephrotic syndrome. Clin J Am Soc Nephrol. 2020;15:983–94. PubMed PMID: 32317330.

Nozu K, Minamikawa S, Yamada S, Oka M, Yanagita M, Morisada N, Fujinaga S, Nagano C, Gotoh Y, Takahashi E, Morishita T, Yamamura T, Ninchoji T, Kaito H, Morioka I, Nakanishi K, Vorechovsky I, Iijima K. Characterization of contiguous gene deletions in COL4A6 and COL4A5 in Alport syndrome-diffuse leiomyomatosis. J Hum Genet. 2017;62:733–5. PubMed PMID: 28275241.

Preston R, Stuart HM, Lennon R. Genetic testing in steroid-resistant nephrotic syndrome: why, who, when and how? Pediatr Nephrol. 2019;34:195–210. PubMed PMID: 29181713.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Trautmann A, Vivarelli M, Samuel S, Gipson D, Sinha A, Schaefer F, Hui NK, Boyer O, Saleem MA, Feltran L, Müller-Deile J, Becker JU, Cano F, Xu H, Lim YN, Smoyer W, Anochie I, Nakanishi K, Hodson E, Haffner D, et al. International Pediatric Nephrology Association clinical practice recommendations for the diagnosis

and management of children with steroid-resistant nephrotic syndrome. Pediatr Nephrol. 2020;35:1529–61. PubMed PMID: 32382828.

License