Genetic aspects of congenital nephrotic syndrome: a consensus statement from the ERKNet–ESPN inherited glomerulopathy working group

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Received: 10 August 2019 / Revised: 3 March 2020 / Accepted: 10 March 2020 © The Author(s) 2020. This article is published with open access

Abstract
Congenital nephrotic syndrome (CNS) is a heterogeneous group of disorders presenting with massive proteinuria within the first 3 months of life almost inevitably leading to end-stage kidney disease. The Work Group for the European Reference Network for Kidney Diseases (ERKNet) and the European Society for Pediatric Nephrology (ESPN) has developed a consensus statement on genetic aspects of CNS diagnosis and management. The presented expert opinion recommends genetic diagnostics as the key diagnostic test to be ordered already during the initial evaluation of the patient, discusses which phenotyping workup should be performed and presents known genotype–phenotype correlations.

Introduction
Congenital nephrotic syndrome (CNS) is a heterogeneous group of disorders presenting in utero or during the first 3 months of life with marked edema and massive proteinuria [1]. In the vast majority of cases, CNS is a primary glomerular disorder due to genetic defects; occasionally it can however be caused by congenital infections or alloimmune maternal disease [2].

Originally, the disorder has been referred to as the Finnish-type nephrotic syndrome due to its high incidence in Finland (1:8.000 live births), with two NPHS1 founder mutations (i.e., Fin-major and Fin-minor) in most cases.

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Published online: 28 May 2020
content list—questions addressed in the presented recommendations:

1. Which phenotyping workup should be performed?
2. What is the preferred time-point for genetic diagnostics?
3. What is the appropriate genetic testing approach?
4. Is there a role for karyotyping?
5. What kind of samples are needed for genetic testing?
6. Is there a role for prenatal diagnosis/genetic counseling?
7. What are the phenotype/genotype correlations?
8. How to manage syndromic forms?
9. What is the inheritance pattern of a hereditary CNS?
10. Parents as kidney donors.

In addition to standard clinical care phenotypic workup in infants with CNS (Boyer et al. in prep.) we recommend additional evaluation with the aim of identifying extrarenal signs and symptoms suggestive of an underlying genetic disease.

Clinical examination should be performed to identify the possible extrarenal manifestations of a hereditary form of CNS. Table 1 summarizes possible phenotypic manifestations of syndromic forms of CNS.

Particular attention should be paid to neurological examination, including brain imaging in selected cases. Abnormal cerebral gyration or cerebellar atrophy in Galloway–Mowat syndrome (GAMOS) [17–19]; cerebral and cerebellar atrophy and stroke-like lesions in CoQ10 nephropathies [20–22]; ventriculomegaly in patients with CRB2-glomerulopathy [23] and subcortical changes in patients with SGPL1 biallelic pathogenic variants [24] have been described. Ophthalmological examination and hearing evaluation should also be performed in all cases.

2. What is the preferred time-point for genetic diagnostics?

We recommend genetic testing as a first choice diagnostic test in every CNS patient. It should be performed as part of the initial patient evaluation and should be considered prior to a renal biopsy.

Once the clinical suspicion of CNS is raised, genetic testing should be initiated. Genetic testing in CNS is a fast, non-invasive and reliable one-time diagnostic measure. Prompt genetic testing has profound effects on clinical decision making as it reduces the time for diagnosis in infants during hospital stay and may enhance the cost-effectiveness of clinical management [25, 26]. Establishing the genetic diagnosis is essential for proper patient management, facilitates the anticipation, and/or swift identification of extrarenal manifestations, informs recurrence risk counseling, and may lead to the identification of genetic defects that may represent phenocopies of nephrotic syndrome [27]. As a general rule, in genetic forms of CNS the use of immunosuppressive drugs should be avoided; instead, appropriate fluid management and proteinuria-lowering RAAS (renin–angiotensin–aldosterone system) blockade at post-neonatal age should be introduced promptly to stabilize the patient’s condition and slow renal failure progression (see Boyer et al. in prep. for further details). Particular issues around therapeutic decision making in syndromic forms are discussed further in Question 8. These include but are not limited to (1)
| Phenotypic feature | HPO code | Gene(s) associated with feature |
|-------------------|----------|--------------------------------|
| General           |          |                                |
|                   |          | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Head and neck     |          |                                |
|                   |          | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, SGPL1 |
| Dymorphic features|          |                                |
| Microcephaly      | HP0000252 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Sloping forehead  | HP0000340 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Flat occiput      | HP0005469 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Microptalmia      | HP0000568 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Hypertelorism     | HP0000316 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Epicanthal folds  | HP0000286 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Ptosis            | HP0000508 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, SGPL1 |
| Hypoplasia of the ear cartilage | HP0100720 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Microganda        | HP0000347 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Vision            |          |                                |
| Nonreactive, fixed narrowing of the pupil ('microcoria') | HP0025492 | LAMB2 |
| Aplasia or atrophy of the dilator pupillae muscle | HP0007686 | LAMB2 |
| Hypoplasia of the iris | HP0007676 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, LAMB2 |
| Hypoplasia of the ciliary body | HP0007774 | LAMB2 |
| Lenticous posterior | HP0011502 | LAMB2 |
| Corneal opacities | HP0007957 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Cataracts         | HP0000518 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Strabismus        | HP0000486 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, SGPL1 |
| Nystagmus         | HP0000639 | COQ2, WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Retinitis pigmentosa | HP0000510, HP0000547 | COQ2 |
| Optic atrophy     | HP0000648 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Cortical visual impairment | HP0100704 | PDSS2 |
| Vision loss (blindness) | HP0006618, HP0000572, HP0000505 | COQ2, LAMB2 |
| Hearing           |          |                                |
| Deafness, sensorineural | HP0000407 | COQ2, COQ6, SGPL1 |
| Neurologic        |          |                                |
| Global developmental delay | HP0001263 | COQ2, COQ6, WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, LAMB2, PDSS2, SGPL1 |
| Central nervous system |          |                                |
| Cognitive impairment | HP0100543 | COQ2, COQ6, WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, LAMB2, PDSS2 |
| Developmental regression | HP0002706 | SGPL1 |
| Cognitive decline | HP0000428 | SGPL1 |
| Impaired speech   | HP0000750 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, SGPL1 |
| Hypotonia         | HP0001290, HP0001252 | LAMB2, SGPL1 |
| Hypotonia, neonatal | HP0003139, HP0008935 | PDSS2 |
| Seizures          | HP0001250 | CRB2, COQ2, COQ6, WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, PDSS2, SGPL1 |
| Status epilepticus | HP0002133 | PDSS2 |
| Encephalopathy    | HP0001298 | COQ2 |
| Hydrocephaly      | HP0000238 | CRB2 |
| Ventriculomegaly  | HP0002119 | CRB2 |
| Focal hyperplasia of the choroid plexus | HP0007376 | CRB2 |
| Gray matter heterotopia | HP0002282 | CRB2 |
| Hypotonia, axial  | HP0008936 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Spastic quadriplegia | HP0002510 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Ataxia            | HP0001251, HP0010867 | COQ2, WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, SGPL1 |
| Dystonia          | HP0001332 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Hyperreflexia     | HP0001347 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Dilated ventricles | HP0002119 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Cerebellar atrophy | HP0001272 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Thin corpus callosum | HP0002079 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133, COQ2 |
| Cerebral atrophy  | HP00002059 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Dandy–Walker malformation | HP0001305 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Small brainstem   | HP0002365 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Pachygyria abnormal gyriabnormal sulci | HP0001302 | WDR4, WDR73, LAGE3, OSGEP, TP53RK, TPRKB, NUP107, NUP133 |
| Peripheral nervous system |          |                                |
| Areflexia         | HP0001284 | LAMB2 |
| Peripheral neuropathy | HP0001271, HP0009830, HP0000759 | SGPL1 |
| Chest             |          |                                |
| Venricular septal defect | HP0001629 | CRB2, NPH52 |
| Hypertrophic cardiomyopathy | HP0001639 | COQ2 |
| Diaphragm         |          |                                |
| Diaphragmatic hernia | HP0000776 | WT1 |
being aware of the risk of urogenital tumors and meticulous monitoring of them in WT1-associated disease; (2) promptly initiating CoQ10 supplementation in CoQ10-related nephropathies; (3) planning appropriate therapy in GAMOS individuals or subjects with CRB2 or SGPL1-associated disorders; (4) managing endocrine manifestations in individuals with SGPL1 or WT1-related syndromes.

3. What is the appropriate genetic testing approach?

We recommend one- or two-step genetic testing depending on the presenting phenotype and financial and/or technical restrictions related to the diagnostics.

Genetic screening strategies might vary depending on country specific peculiarities including availability and access to genetic testing and reimbursement policy of national healthcare systems (Fig. 1).

In CNS, basic genetic screening of NPHS1, NPHS2, WT1, and LAMB2 genes will uncover underlying genetic abnormalities in >80% of cases. Several other less commonly mutated genes account for an additional ~5% of diagnoses [6, 7, 9, 10, 28, 29]. Due to the wide range of phenotypic variability and genetic heterogeneity of the disease [6, 7, 9, 14, 28, 29] a comprehensive genetic screening comprising all SRNS-related genes is recommended as the first tier method using next generation sequencing technology.
with either an expanded gene panel or whole exome sequencing (WES). Targeted gene panels have higher depth of coverage of the genes related to a specific phenotype, which allow a higher diagnostic rate. Also, gene panels will not yield incidental findings in genes unrelated with CNS. However, the number of genes that can be examined using a gene panel approach is limited and the covered list of genes should be regularly updated as new genes are continuously identified. Conversely, WES allows detecting variants not only in an established list of known, but also in novel disease-causing genes [30]. However WES has also some important limitations. Complex rearrangements, small copy-number variants and changes within regulatory fragments (promotor, introns, enhancers, silencers etc) might be missed by standard protocols. In particular, WES may have suboptimal coverage of some clinically relevant regions: fragments with high GC content, the mitochondrial genome or duplicated regions (pseudogenes) [31]. These limitations may, to some extent, be overcome by use of hybridization-based custom target enrichment for NGS gene panels.

For patients who present a clear phenotype associated with a syndromic form of CNS, testing the particular related gene can be performed as the first step followed by comprehensive genetic testing if no pathogenic variant is detected. In populations where founder mutations or specific genetic abnormalities have already been well described such as CNS of the Finnish type (NPHS1 Fin-major and Fin-minor recessive pathogenic variants), the genetic screening strategy may be modified considering population specific features.

Informed consent should be obtained before initiating genetic studies. Informed consent forms should clearly describe the methods that will be applied, and the interpretation and handling of results and incidental findings that would have clinical and psychosocial impacts, for instance male-to-female sex-reversal related to WT1 dominant pathogenic variants.

4. Is there a role for karyotyping?

We recommend karyotype testing to be performed in each CNS patient with ambiguous genitalia and in each phenotypic female with a causative WT1 mutation.

Establishing chromosomal gender of a patient with CNS with ambiguous genitalia and/or a WT1 dominant pathogenic variant is necessary for further proper management, endocrine and oncological follow-up in particular [32, 33]. For karyotype testing, a heparin blood sample should be obtained according to local genetic laboratory recommendations.

5. What kind of samples are needed for genetic testing?

We recommend performing genetic testing on whole blood (EDTA) or umbilical cord tissue/blood sample.

A blood sample for genetic testing should be obtained as soon as possible as it informs further clinical management of a CNS patient. However, in those patients who have individual blood-sampling limitations or less than 3 months

**Fig. 1 Algorithm for genetic diagnosis in individuals with congenital nephrotic syndrome.** Asterisk [*]: applicable for populations where founder mutations have already been well described.
from a blood transfusion, buccal swabs or newborn dried blood spots may also be used [34, 35].

6. Is there a role for prenatal diagnosis/genetic counseling?

We recommend prompt genetic counseling in families with a past history or prenatal signs of CNS.

In families with a past history of CNS, recurrence risk counseling by a clinical geneticist/clinical counsellour should be promptly provided. The decision regarding pre-implantation genetic diagnosis and prenatal genetic testing should be discussed in light of the local financial, social, and legal settings [36].

7. What are the phenotype/genotype correlations?

We suggest to take the following phenotype–genotype information into account for genetic counseling:

**NPHS1**

The majority of patients in whom CNS manifests in the first week of life will harbor biallelic pathogenic variants in the nephrin gene [10, 14]. The frequency of the disorder is significantly higher in Finland with two NPHS1 founder mutations (i.e., Fin-major and Fin-minor) in most cases [3–5]. Renal pathology does not exclusively appear as “Finnish type” NS in CNS caused by recessive NPHS1 pathogenic variants [37]. There is no difference between truncating NPHS1 variants (i.e., nonsense, frameshift, and splice site) and missense NPHS1 variants in terms of age at diagnosis, proportion of age at ESKD or death, and proportion of patients who achieved at least transient albumin withdrawal [38]. A subset of patients with CNS and a milder clinical course were described associated with the NM_004646.3: c.3478C>T (p.(Arg1160Ter)) variant [10, 39].

**PLCE1**

Patients with PLCE1 (NM_016341.3) splice site recessive pathogenic variants have an earlier age of onset than patients with C-terminal truncating variants (after amino acid residue 1000) or missense variants [6]. PLCE1 pathogenic variants are mostly associated with diffuse mesangial sclerosis histopathology [6]. Anecdotally, incomplete penetrance has been reported [40, 41].

**NPHS2**

NPHS2 (NM_014625.3) biallelic pathogenic variants are the main genetic cause of CNS beginning >1 month after birth [10]. There is no correlation regarding age of onset for truncating versus missense variants [7]. The European founder mutation c.413G>A (p.Arg138Gln) is frequently detected in those CNS patients who do not have NPHS1-related disease [10]. Individuals homozygous for the c.413G>A (p.Arg138Gln) variant present NS at a median age of 2 months and generally progress to ESKD after the age of 5 years (median 79 months; range 24–159 months) [10]. Individuals with the c.779T>A (p.(Val260Glu)) variant have an earlier age at onset of nephrotic syndrome and progress more rapidly to ESKD when compared to subjects with the c.413G>A (p.Arg138Gln) variant [10].

The disease-associated allele c.686G>A (p.Arg229Gln) has variant dependent pathogenicity [42, 43]. It is considered pathogenic only when located in trans to another recessive pathogenic variant in exon 7 or 8 of NPHS2. Such compound heterozygosity generally causes late onset nephrotic syndrome (after the median age of 17 months) [6, 10, 42, 43]. However, a few subjects developed nephrotic syndrome in the first month of life; yet, progressed slowly to ESKD [10].

**LAMB2**

In LAMB2 (NM_002292.3), N-terminal truncating recessive pathogenic variants tend to manifest before 2 months of life, whereas C-terminal truncating variants later. Missense variants and small in frame deletions have a higher mean age at onset of renal disease and lack of neurologic abnormalities [6]. Diffuse mesangial sclerosis has been identified in 61% of individuals with LAMB2-associated NS [44].

**WT1**

WT1 dominant pathogenic variants are associated with a wide range of clinical phenotypes that are clearly associated with the type and location of the causative WT1 variant. More than 90% of the deleterious variants reside in the hot spot region (exons 8 and 9 and their intronic junctions) [6, 32, 45, 46].

Classically, individuals with WT1 dominant pathogenic variants have been subclassified as having Denys–Drash or Frasier syndrome, however these two syndromes may overlap phenotypically to a certain extent. A number of patients present with a milder phenotype that cannot be easily classified as one of these syndromes [32, 45, 46].

Missense substitutions affecting DNA-binding residues are associated with diffuse mesangial sclerosis, early-onset steroid-resistant nephrotic syndrome and rapid progression to ESKD. Truncating variants confer the highest risk of Wilms tumor (~80%) and congenital anomalies of kidney and urinary tact (~25%) but are typically associated with late-onset steroid-resistant nephrotic syndrome [32, 45, 46]. Intronic (KTS) variants usually present as isolated SRNS with the histological picture of FSGS and slow progression.
to ESKD. Patients with isolated SRNS are genotypic and phenotypic females.

Male-to-female sex reversal (46,XY complete gonadal dysgenesis) occurs exclusively in individuals with intronic KTS dominant pathogenic variants and exonic variants. Urogenital abnormalities have also been described in patients with all types of WT1 deleterious variants [32, 45, 46].

**CoQ10-associated CNS**

Primary CoQ10 deficiencies that stem from autosomal recessive pathogenic variants in genes involving endogenous CoQ10 biosynthesis can cause nephropathies that are collectively referred to as CoQ10-associated nephropathies. Of them, COQ2, COQ6, and PDSS2 biallelic variants have been shown to be related to CNS. As CoQ10 is essential for mitochondrial electron transport, many organs can be affected, therefore multisystemic involvement is a cardinal feature of these disorders. There are no established genotype–phenotype correlations, potentially due to the small number of patients in the literature. In addition to progressive nephropathy, COQ2 pathogenic recessive variants typically manifest with signs of progressive encephalopathy (including ataxia, generalized amyotrophy, retinitis pigmentosa, bilateral sensorineural deafness, hypotonia, and psychomotor delay), hypertrophic cardiomyopathy, as well as diabetes [20, 21]. COQ6 recessive pathogenic variants are associated with severe infantile onset progressive SRNS resulting in end-stage renal failure and sensorineural hearing loss, central nervous system involvement, congenital heart disease, and motor retardation [13, 47]. PDSS2 recessive pathogenic variants are associated with Leigh syndrome, a progressive and severe neurodegenerative disorder, which may become evident within the first months of life and may result in early death. Affected individuals usually show global developmental delay or developmental regression, hypotonia, ataxia, dystonia, and ophthalmologic abnormalities such as nystagmus or optic atrophy. Basal ganglia and/or brainstem or brain imaging show T2-weighted hyperintensities [22].

It most commonly presents as a progressive and severe neurodegenerative disorder with onset within the first months or years of life, and may result in early death. Affected individuals usually show global developmental delay or developmental regression, hypotonia, ataxia, dystonia, and ophthalmologic abnormalities, such as nystagmus or optic atrophy. The neurologic features are associated with the classic findings of T2-weighted hyperintensities in the basal ganglia and/or brainstem on brain imaging.

**Galloway–Mowat syndrome**

GAMOS is a phenotypically heterogeneous disorder characterized by neurodevelopmental defects combined with podocytopathy. Individuals with GAMOS may not present overt dysmorphic features, however pre- or postnatal microcephaly should be considered its hallmark. Central nervous system abnormalities result in severely delayed psychomotor development and propensity to seizures. Additional clinical features include skeletal anomalies and various degrees of growth retardation [18].

There is high inter- and intrafamilial variability concerning renal involvement with regard to age at onset and type of kidney disease; some individuals may not even have renal disease [17, 48].

Recessive pathogenic variants in a number of genes, including WDR73, LAGE3, OSGEP, TP53RK, and TPRKB encoding subunits of the KEOPS complex [17, 18, 48]; WDR4 encoding an enzyme required for a specific post-transcriptional modification of tRNA [49]; and NUP107 and NUP133 encoding nuclear pore complex proteins [50] have been implicated in the pathogenesis of the disorder. This significant genetic heterogeneity and extreme rarity of the disorder with less than 50 patients described so far hamper precise genotype–phenotype analyses.

**SGPL1**

Biallelic pathogenic variants in SGPL1 result in a podocytopathy and primary adrenal insufficiency. Additional features include ichthyosis, acanthosis, immunodeficiency manifesting as lymphopenia, and recurrent bacterial infections. About half had variable neurologic abnormalities including ataxia, cognitive decline, loss of motor skills, impaired speech, and sensorineural hearing loss. There was a significant variability of the extra-adrenal and extrarenal features in the ~30 individuals reported so far [24, 51, 52].

**CRB2**

Biallelic pathogenic variants in CRB2 result in a glomerulopathy with additional systemic features in a minority of cases [53]. The more severe disease manifests already prenatally with renal corticomedullary cysts and structural abnormalities of the central nervous system, ventriculomegaly in particular. In some, additional defects of the radius or postaxial polydactyly is also noted. Most affected pregnancies have been terminated [23]. No genotype–phenotype data exist due to the extreme rarity of the disorder.

**Histopathology**

Diffuse mesangial sclerosis is associated with dominant pathogenic variants in WT1 (23.1%) and biallelic pathogenic variants in PLCE1 (17.8%), LAMB2 (13.6%), and NPHSI (4.9%) [6]. CoQ10-associated nephropathies may
be associated with focal and segmental glomerulosclerosis, focal mesangial sclerosis, and collapsing glomerulopathy [20, 54]. Increased and dysmorphic mitochondria in podocytes in electron microscopy are highly suggestive for CoQ10-associated nephropathy. Yet, absence of mitochondrial abnormalities does not exclude CoQ10-associated nephropathy diagnosis.

8. How to manage syndromic forms?

In addition to standard clinical management of CNS described in detail elsewhere (Boyer et al. in prep.) we recommend that all syndromic CNS patients should be managed by a multidisciplinary team as described below.

**NPHS2**

We recommend cardiac evaluation in patients with NPHS2 biallelic pathogenic variants as cardiac anomalies have been shown in 89% of patients with the c.412C>T(p.(Arg138*)) variant [55]. Despite a few case reports describing partial or complete remission after immunosuppressive treatment, by principle patients with biallelic NPHS2 pathogenic variants respond neither to standard steroid treatment nor to intensified immunosuppressive treatment [7, 56, 57]. Therefore, we recommend not to use immunosuppressive regimens but to use RAAS blockade in such patients.

**WT1**

We recommend individuals with WT1-glomerulopathy to be evaluated for urogenital malformations. Oncological surveillance for Wilms tumor and gonadoblastoma should be applied. Subjects with exonic variants should be monitored for Wilms tumor with abdominal US performed every 3 months until the age of 7 years [58]. After reaching ESKD, bilateral nephrectomy should be considered to prevent the development of Wilms tumor, in particular in individuals carrying truncating variants [32, 59]. In subjects with a 46,XY karyotype and a female phenotype (i.e., complete gonadal dysgenesis), we recommend bilateral gonadectomy due to increased gonadoblastoma risk [32].

WT1 patients should be managed by a multidisciplinary team comprising a clinical geneticist, pediatric oncologist for Wilms tumor and gonadoblastoma surveillance, pediatric endocrinologist, pediatric surgeon, and psychologist in cases of disorders of sex development.

**LAMB2**

We recommend detailed ophthalmological examination in children with LAMB2 biallelic pathogenic variants, even though individuals with missense pathogenic variants may display variable phenotypes ranging from a milder variant of Pierson syndrome to an isolated CNS. Surviving children may have neurodevelopmental deficits and blindness [44]. Individuals with LAMB2-associated glomerulopathy need to be managed by multidisciplinary team composed of pediatric opthalmologist, clinical geneticist, pediatric neurologist and rehabilitation team.

**PLCE1**

We recommend PLCE1-related nephropathy to be included in the differential diagnosis in subjects with congenital/infantile nephrotic syndrome associated with diffuse mesangial sclerosis in particular. In general, most individuals are resistant to any immunosuppressive therapy but some selected cases may respond to steroid or cyclosporine treatment [40, 60].

**CoQ10-related mitochondriopathies (COQ2, COQ6, and PDSS2 genes)**

We recommend performing complete and repeated screening for extrarenal manifestations in patients with biallelic pathogenic variants in COQ2, COQ6, and PDSS2 or presenting phenotype suggestive of CoQ10-related glomerulopathy (hearing deficit, encephalopathy, seizures, ataxia, hypotonia, motor/intelectual disability, elevated lactate levels, and diabetes).

For diagnosis we recommend massive-parallel sequencing of the corresponding genes in the first place. In case of a non-informative genetic result, muscle or skin biopsies may be needed for measuring mitochondrial enzyme activity [61]. Renal biopsy with electron microscopy allows quantitative and qualitative analysis of mitochondria [62].

Individuals with CoQ10-related mitochondriopathy need to be managed with a multidisciplinary approach including a pediatric ophthalmologist, audiologist, clinical geneticist, pediatric neurologist, rehabilitation team, and in case of diabetes, pediatric endocrinologist.

We suggest treating the individuals with biallelic pathogenic variants in COQ2, COQ6, and PDSS2 or presenting phenotype suggestive of CoQ10-related glomerulopathy with oral CoQ10 as early as possible.

Few case reports suggest that patients with defective variants in CoQ10 biosynthesis genes treated early with oral CoQ10 have improved outcome [20, 54, 61, 63, 64]. Individuals who respond to treatment exhibit an improvement in proteinuria and sometimes in neuromuscular complaints, however, refractory encephalopathy and seizures have been reported in subjects who had a beneficial effect of CoQ10 treatment on their kidney disease [21]. As the total number of reported patients is low, the exact dose regimen to improve or reverse glomerular damage is unknown. The
initial CoQ10 dose applied in several reported cases is 15–30 mg/kg/day divided in three administrations, which might be increased to 50 mg/kg/day [47, 54, 63]. Leukocyte CoQ10 levels can be normal in these patients, and seem not to be helpful for monitoring therapy [54].

**Galloway–Mowat syndrome**

We recommend that individuals with GAMOS are managed by a multidisciplinary team including a pediatric nephrologist, pediatric neurologist, clinical geneticist, and physiotherapist. For older children psychotherapeutic, psychological and speech therapy services should be offered. Palliative care may also be considered depending on the severity of the disease.

**SGPL1-associated CNS**

We recommend patients with SGPL1-glomerulopathy to be carefully monitored for adrenal insufficiency. Individuals should be managed by a multidisciplinary team including a pediatric nephrologist, pediatric endocrinologist, pediatric neurologist, clinical geneticist, and physiotherapist. For older children psychotherapeutic, psychological, and speech therapy services should be offered. Palliative care may also be considered depending on the severity of the disease.

9. **What is the inheritance pattern of a hereditary CNS?**

We recommend that each individual with confirmed hereditary CNS will have a genetic consult performed to address the issues of recurrence risk in the family.

The majority of forms of hereditary CNS are inherited in an autosomal recessive manner. That implies a 25% risk of recurrence in subsequent pregnancies.

The exceptions are:

**WT1**—inherited in autosomal dominant manner; the recurrence risk depends whether the genetic defect is familial or occurred de novo (50% vs. <1% due to gonadal mosaicism respectively).

**LAGE3**—inherited in an X-linked recessive manner; the recurrence risk is 0% for female and 50% for male siblings.

10. **Parents as kidney donors.**

We recommend that parents undergo genetic counseling prior to kidney donation for their child who has CNS with a confirmed genetic diagnosis.

The majority of forms of hereditary CNS are inherited in an autosomal recessive (AR) manner (see #9 for exceptions). This implies that both parents are obligate carriers of one of the defective variants. An extremely rare omission to this rule would be a de novo mutation or misattributed paternity. Carriers of a heterozygous variant in an AR gene can be kidney donors.

However, it cannot be excluded that the parents actually are also homozygotes/compound heterozygotes for the pathogenic variant(s) in the gene associated with a hereditary nephrotic syndrome. NPHS2-related SRNS and WT1-associated glomerulopathy are the two forms of the disease with the most significant intra- and inter-family variability, with age-dependent penetrance reflecting defective variant type [32, 43]. Moreover, incomplete penetrance has been described in families with a WT1 pathogenic variant [65].

**Acknowledgements**

The authors gratefully acknowledge the support by the hereditary glomerulopathy working group of ERKNet, the European Reference Network for Rare Kidney Diseases, and the working group for inherited kidney disease of ESPN, the ESPN. We are indebted to Tanja Włodkowski and Giulia Bassanese from the ERKNet Central Office, who performed the systematic literature search and evidence review that formed the basis of this document. Open Access Funding provided by Projekt DEAL.

**Funding**

The development of this consensus statement was made possible by a 5000 € grant from ERKNet, the European Reference Network for Rare Kidney Diseases, and the working group for inherited kidney disease of ESPN, the ESPN. We are indebted to Tanja Włodkowski and Giulia Bassanese from the ERKNet Central Office, who performed the systematic literature search and evidence review that formed the basis of this document. Open Access Funding provided by Projekt DEAL.

**Conflicts of interest**

The authors declare that they have no conflict of interest.

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