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Editorial Review

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Genetic causes of focal segmental glomerulosclerosis: implications for clinical practice

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Abstract
Focal segmental glomerulosclerosis (FSGS) is a common cause of steroid-resistant nephrotic syndrome in children and adults. Although FSGS is considered a podocyte disease, the aetiology is diverse. In recent years, many inheritable genetic forms of FSGS have been described, caused by mutations in proteins that are important for podocyte function. In the present commentary, we review these genetic causes of FSGS and describe their prevalence in familial and sporadic FSGS. In routine clinical practice, the decision to perform the costly DNA analysis should be based on the assessment if the results affect the care of the individual patient with respect to the evaluation of extra-renal manifestations, treatment decisions, transplantation and genetic counselling.

Keywords: adults; children; focal segmental glomerulosclerosis; mutation analysis; steroid-resistant nephrotic syndrome

Introduction

Focal segmental glomerulosclerosis (FSGS) is a description of histological lesions characterized by mesangial sclerosis, obliteration of capillaries, hyalinosis, foam cells and adhesion between the glomerular tuft and Bowman's capsule [1]. In addition to the classical sclerotic lesions of FSGS, several other histological variants have been described. A group of renal pathologists redefined these histological variants and proposed a standardized pathological classification system for FSGS based entirely on light microscopic examination. The classification, also known as the Columbia Classification, defines five histological variants: the collapsing variant, the tip variant, the cellular variant, the perihilar variant and FSGS not otherwise specified [2]. In adult patients, FSGS is one of the most common patterns of glomerular injury [3], and over the last decades, the incidence of FSGS has increased significantly in Afro-Americans as well as in Caucasians [4]. In USA, FSGS now represents 35% of the renal biopsies performed in adults with a nephrotic syndrome [4]. Approximately 30–50% of adults with FSGS do not respond to steroid therapy. In children, steroid resistance is the hallmark of FSGS since a renal biopsy is only taken in children with a nephrotic syndrome when treatment fails. In the large majority of children with steroid-resistant nephrotic syndrome (SRNS), light microscopy shows FSGS (63–73%) or related forms such as minimal change disease (0–15%), diffuse mesangial sclerosis (3–15%) or IgM nephropathy (3–15%) [5, 6]. In children, these causes of SRNS are responsible for 5–20% of all cases of end-stage renal disease (ESRD) [7].

Injury to the podocytes plays a central role in the pathogenesis of SRNS/FSGS [8]. However, the aetiology of podocyte injury is quite diverse and includes B-cell and T cell-dependant factors, infections, medication and maladaptive responses that occur due to the loss of functioning nephrons or hyperfiltration [9, 10]. In addition, SRNS/FSGS can be caused by mutations in genes that encode proteins that play key roles in maintaining podocyte ultrastructure. This field of research started with the discovery that mutations in the podocytic protein nephrin were responsible for the congenital nephrotic syndrome (CNS) of the Finnish type [11]. Since then, many new genetic causes of SRNS/FSGS have been identified, the latest being the identification of mutations in *MYO1E* as cause of autosomal recessive SRNS [12].

The discovery of these genetic causes of SRNS/FSGS has underlined the role of the podocyte in SRNS/FSGS and helped to unravel the biology of podocyte function. However, it is unclear how to incorporate all this new information in clinical practice. This review will provide an overview of genetic causes of SRNS/FSGS. Specifically, we address the questions when and why genetic testing should be considered and discuss its implications.

Genetic causes of SRNS/FSGS

Table 1 lists the genes and their related proteins that cause non-syndromic SRNS/FSGS. These proteins are mainly expressed in the podocyte and are involved either directly or indirectly in the organization of the slit diaphragm and the actin cytoskeleton. FSGS caused by mutations in nephrin, podocin, *CD2AP*, *PLCε1* and *MYO1E* is characterized by an autosomal recessive pattern of inheritance. As a rule, onset of disease is in childhood (Table 1). In contrast,

Table 1. Genetic causes of non-syndromal SRNS/FSGS[a]

Gene	Gene product	Inheritance	Remarks
NPHS1 [11, 13]	Nephrin	AR	Most common cause of Finnish type CNS
NPHS2 [13, 14]	Podocin	AR	Most common cause of genetic forms of SRNS in childhood
PLCε1/NPHS3 [15]	PLCε1	AR	Associated with DMS
CD2AP [16]	CD2-associated protein	AR	Very rare. Role of heterozygous mutations unclear
MYO1E [12]	Non-muscle Myosin-1E	AR	
TRPC6 [17]	TRPC6	AD	TRPC-6 is a calcium channel; variable phenotypic expression within families. Often non-nephrotic proteinuria; incomplete penetrance
ACTN4 [18]	Alpha-actinin-4	AD	
INF2 [19]	Formin	AD	Most common identified cause of adult familial FSGS; majority of patients present with non-nephrotic proteinuria.

[a]Includes FSGS-related histologic variants in children with SRNS (minimal change disease, diffuse mesangial sclerosis, IgM nephropathy). DMS, diffuse mesangial sclerosis.

mutations in α-actinin-4, *TRPC6* and *INF2* cause autosomal dominant FSGS. In most patients, onset of disease is in adulthood, and many patients do not develop a manifest nephrotic syndrome.

FSGS can also be caused by mutations in genes that encode proteins that are not only expressed in the podocytes but also, or even more so, in other tissues and cell types. In these syndromic forms of FSGS, the extrarenal manifestations are most prominent and often diagnostic. Examples are given in Table 2. Of note, in some of these diseases, FSGS may be the only or the presenting manifestation, thus mimicking isolated FSGS. Well-known examples are mutations in the transcription factor *WT1* and mitochondrial mutations (Table 2).

Prevalence of mutations in SRNS/FSGS

Currently, mutation analysis is expensive, and single genes are analysed separately. Therefore, a cost-effective approach requires information on the prevalence of causative mutations in a given population.

Although there is a wealth of published data, it is not easy to calculate true prevalence rates. Many authors present data on cohorts with varying often overlapping patient groups with different clinical characteristics. Often, mutation analysis for a certain gene is done in patients in whom mutations in other known genes have been excluded. Thus, the real prevalence will often be much lower than predicted from the data. Lastly, most studies report the prevalence of mutations in a single gene and few attention is given to the potential role of combinations of heterozygous mutations in different genes.

Table 3 provides a summary of the prevalence of different genetic mutations in childhood and adult-onset SRNS/FSGS. It is important to realize that the prevalence is dependant on the family history, the age of the patients, the ethnicity and the histologic lesion. The family history suggests an autosomal dominant pattern of inheritance when there are diseased persons in multiple generations. An autosomal recessive pattern of inheritance is usually present when there are diseased persons in only a single generation. Obviously, there are some pitfalls. In autosomal recessive diseases, the first affected child will be considered sporadic. In this respect, an autosomal recessive inheritance should especially be suspected in children with 'sporadic' FSGS born from consanguineous parents. Autosomal dominant and recessive inheritance may be unnoticed if there is incomplete penetrance, with mutation carriers being unaffected. Mitochondrial mutations are typically characterized by maternal inheritance. However, because these mutations often follow a dominant inheritance pattern, a mutation in mitochondrial DNA (mtDNA) may be overlooked.

Several conclusions can be drawn (Table 3): almost 100% of patients with CNS have a mutation. In Finland, mutations in nephrin are the rule (>95%), whereas in other populations also mutations in other genes occur. Podocin mutations predominate in patients with infantile (4–12 months) and early childhood (1–5 years) SRNS. For podocin, ethnicity is important. Mutations are most frequently reported in studies that included patients from Western European countries. The most frequent mutation, *R138Q*, is considered a European founder mutation. Up to 16% of children will have a mutation in *WT1*. A mutation should be considered in patients with a female phenotype (important to assess genotype if a mutation is found) or males with abnormal genital development.

Most cases of adult-onset familial FSGS are inherited as an autosomal dominant disease. The most common causative gene is *INF2* (up to 17%), other mutations include *TRPC6* (up to 12%) and *ACTN4* (3.5%). However, penetrance is often incomplete with variable expression. Many adult patients with familial FSGS present with non-nephrotic proteinuria.

Mutations in podocyte genes are rarely found in adults with isolated sporadic FSGS, with the exception of compound heterozygous *NPHS2* mutations involving the common podocin *R229Q* polymorphism. The *R229Q* variant is present in 1–2.5% of Afro-Americans and in 5–10% of Caucasians [44, 50, 60–62]. There is no evidence that this variant is pathogenic in its own [62]. However, a study by Machuca *et al.* [48] suggests that FSGS develops in patients who carry the *R229Q* variant in combination with one pathogenic *NPHS2* mutation. This study mainly included Western European patients who developed nephrotic syndrome at a later age (19 years) than patients who were homozygous or compound heterozygous for pathogenic *NPHS* mutations. Of note, in cohorts of patients with sporadic FSGS not living in Western Europe, the prevalence of the combination of the *R229Q* variant and a pathogenic *NPHS2* mutation was much lower, 0–2% [14, 44, 49].

Table 2. Genetic causes of syndromal SRNS/FSGS[a]

Gene	Gene product	Inheritance	Associated conditions	Remarks
WT-1 [20–22]	WT-1	AD	Denysh–Drash syndrome: male pseudohermaphroditism, malignancies (Wilms' tumour) and progressive glomerulopathy with nephrotic syndrome. The glomerulopathy usually begins within the first months of life, with progression to ESRD by the age of 3–4 years. Renal biopsy typically shows DMS. Frasier syndrome: male pseudohermaphroditism, progressive glomerulopathy, gonadoblastoma. Proteinuria begins in childhood (usually 2–6 years) with progression to ESRD during the second or third decade of life. Histology typically discloses FSGS.	Presentation in childhood. Mutations occur in phenotypic females (may have XY genotype); or in phenotypic and genotypic males with genital development disorders such as cryptorchism, hypospadia, testicular atrophy. May present as isolated FSGS in adulthood.
Mitochondrially encoded tRNA leucine 1 [23]	$tRNA^{Leu(UUR)}$	Maternal	Most common *A3243G* mutation. Associated with MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes). Other manifestations: diabetes, deafness, visual impairment, cardiomyopathy	May present with isolated FSGS FSGS related to mitochondrial DNA mutations typically develops in adulthood.
LAMB2 [24]	Laminin β2	AR	Pierson's syndrome (microcoria and other complex ocular abnormalities, CNS, DMS)	Typically age of onset <1 year.
ITGB4 [25]	B4-integrin	AR	Epidermolysis bullosa	
CD151 [26, 27]	Tetraspanin	AR	Epidermolysis bullosa, sensorineural deafness, nail dystrophy	The only available renal biopsy of one patient did not show FSGS but thickening/fragmentation of the GBM. *CD151*-null mice develop massive proteinuria with FSGS
SCARB [28]	SCARB2/LIMP-2	AR	Action myoclonus-renal failure syndrome (progressive myoclonic epilepsy associated with renal failure)	Lysosomal membrane
LMX1b [29]	LIM HboxTF1	AD	Nail-patella syndrome (hypoplastic or absent patella, dysplasia finger- and toenails, and dysplasia of elbows and frequently glaucoma)	Renal abnormalities do occur. Mostly limited to micro-albuminuria FSGS with overt proteinuria is rare.
Non-muscle myosin IIA [30]	MYH9	AD	Non-syndromic sensorineural deafness autosomal dominant type 17 Epstein syndrome Alport syndrome with macrothrombocytopenia Sebastian syndrome Fechtner syndrome Macrothrombocytopenia with progressive sensorineural deafness.	

[a]This table provides a limited list. We have excluded FSGS associated with other kidney diseases such as nephronophtisis or Alport's syndrome. Other syndromic forms include FSGS associated with severe malformations (mandibulo-acral dysplasia; Schimke immune-osseous dysplasia, Galloway-Mowat syndrome), glycosylation disorders and mitochondrial diseases. Genes: *SMARCAL1* [31], *GMS1* [32], *PMM2* [33], *ALG1* [34], *ZMPSTE24* [35], *LMNA* [36], *CoQ2* [37], *CoQ6* [38], *PDSS2* [39]. DMS, diffuse mesangial sclerosis; GBM, glomerular basement membrane.

Table 3. Prevalence of mutations in SRNS/FSGS[a]

	Age of onset					
Genes	CNS	Infantile NS	Childhood NS	Adult FSGS (familial)	Adult FSGS (sporadic)	Remarks
NPHS1	34–90% [11, 13, 40, 41]	0–2% [13, 40]	14% [42]	n.a.	2% [42]	
NPHS2	0–51% [11, 13, 40, 43]	19–41% [13, 40]	0–18% [5, 44–47]	4–24% [48, 49]	0–11% [14, 44, 48, 49, 50]	In Western European adults, adult-onset FSGS is caused by combination of *R229Q* and one pathogenic *NPHS2* mutation. *R138Q* is considered a founder mutation in Europe. One study (US) suggested higher prevalence of *R138Q* in patients versus controls (1.2 versus 0.2%) [14]. Studies show that allele frequency of *R229Q* is higher in patients versus controls [49, 50].
LAMB2	3–9% [13, 40]	5% [13]	n.a.	n.a.	n.a.	
PLCε1	0–50% [15, 46, 51]			0% (histology: FSGS) [52]	0% (histology: FSGS) [52]	Prevalence dependent on family history and histology: Sporadic DMS 21%, familial DMS 50%, sporadic FSGS 0%; familial FSGS 12%. In most studies patients with other mutations were excluded first (e.g. *NPHS1, NPHS2, WT1, LAMB2*) [15, 51]
MYO1E	n.a.	n.a.	0–4% [12]	n.a.	n.a.	Study of Mele *et al*. excluded *NPHS1, NPHS2* and *WT1*. Up to 3.5% in familial cases of FSGS; 0% in DMS or sporadic cases of FSGS.
CD2AP	n.a.	n.a.	0–11% [16, 46, 53, 54]	0% [41, 42]	0% [42]	Role of heterozygosity discussed; Unaffected parents with heterozygous mutation described by Lowik *et al*. and Gigante *et al*. [46, 54]
WT1	0–16% [13, 40, 41]	9–13% [13, 40]	0–13% [6, 45, 50, 55]	n.a.	0% [50]	*WT1* mutations are found predominantly in phenotypic females or males with abnormal genital development.
ACTN4	n.a.	n.a.	0% [46, 53]	3.5% [18]	0% [18, 50]	
TRPC6	n.a.	5% [40]	0–6% [46, 56–58]	0–12% [17, 58]	0–2% [42, 56]	Gigante *et al*. excluded mutations in *NPHS1,NPHS2*, *WT1*, *CD2AP* and *ACTN4*. Study from Heeringa *et al*. included patients with age of onset 9–30 years [58]
INF2	n.a.	n.a.	n.a.	12–17% [19, 59]	1% [59]	In the sporadic case in Boyer *et al*. parents were not studied.

[a]Studies included with $n > 10$. DMS, diffuse mesangial sclerosis; NS, nephrotic syndrome; n.a., not available.

Genetic screening in clinical practice

The discovery of genes associated with FSGS has greatly increased our knowledge of podocyte biology and our insight in the pathogenesis of FSGS. Obviously, these studies must continue and be expanded to include well-defined cohorts of patients with FSGS. This will not only allow clinicians to detect new genes but also to describe in detail phenotype–genotype correlations. Although the identification of genetic mutations can be done relatively easily, genetic testing is expensive and results can take weeks or even months. Therefore, the relevance of genetic screening for the individual patient must be carefully considered before advising these procedures in routine clinical practice. Table 4 lists the relevant questions that should be asked when considering genetic testing in a patient with FSGS. These questions will be addressed below.

Genetic screening affects treatment decisions

Hinkes *et al.* [15] described a patient with a mutation in *PLCε1* who apparently responded to treatment with steroids. However, this example is the exception to the rule, and most studies have indicated that genetic forms of FSGS are steroid resistant [42, 63]. It is likely, although not based on firm evidence, that steroid-resistant patients also will not respond to immunosuppressive therapy with alkylating agents. Thus, the discovery of a mutation could benefit the patient by avoiding exposure to prolonged treatment with corticosteroids or cyclophosphamide. However, the latest guidelines advise not to use alkylating agents in any patient with SRNS or FSGS but rather to use cyclosporine A (CsA) [64]. The efficacy of CsA is attributed to its direct effect on the stabilization of the podocyte actin-cytoskeleton [65]. Thus, we need to know if the presence of a podocyte mutation decreases the efficacy of CsA. Some studies indeed suggested that CsA may be less effective in FSGS secondary to genetic mutations. Machuca *et al.* [48] reported that only two out of 15 patients with SRNS developed a partial remission after CsA therapy. Duration or intensity of therapy was not described. Buscher *et al.* [40] retrospectively evaluated the response to treatment with CsA in children with SRNS and reported a response rate of 17% in patients with and 68% in patients without a mutation. However, these conclusions are based on only 12 patients with a genetic mutation, and CsA was given for 6 months in a dose titrated to levels of only 80–120 ng/mL. There are many case reports of patients who have responded to CsA. These studies included patients with a mutation in podocin, *MYO1E, TRPC6, WT1* and *CoQ6* [12, 38, 43, 56, 57]. Based on the available data, results of mutations analysis should not be used to discard CsA as therapeutic agent. Mutation analysis will only affect treatment decisions if, in a given patient, one considers prolonged steroid treatment and/or the use of an alkylating agent.

Table 4. Genetic screening of patients with SRNS/FSGS: which questions to ask.

1. Does the result of genetic screening influence your treatment decisions?
2. Does the result of genetic screening affect counselling for extra-renal disease?
3. Does the result of genetic screening help in family counselling?
4. Does the result of screening affect decisions related to kidney transplantation?

Genetic screening affects care and counselling of patients

Genetic testing might be important in those conditions where the causative gene influences patient care and follow-up. The most illustrative example is a mutation in *WT1*. If mutations in the *WT1* gene are found, one should investigate the gender genotype of the female (thus excluding the XY genotype with pseudohermaphroditism), and patients with a *WT1* mutation should be screened for development of a Wilms' tumour or gonadoblastoma. In patients with mitochondrial mutations, one may consider more thorough studies of ear and vision and also regular check for diabetes. Obviously, in syndromal forms of FSGS, additional studies may be needed, guided by the underlying disease (Table 2).

Genetic screening affects counselling of the family

Genetic testing is important for genetic counselling. In children with SRNS, the prevalence of a genetic cause of the disease is high. Identification of a genetic mutation in a child can help the parents in their decision to plan new pregnancies. Also, the results can be used for prenatal genetic testing. Lastly, if a brother or a sister of a patient, with a known mutation that is associated with SRNS, develops a nephrotic syndrome, the use of steroid treatment should be questioned. The results of genetic tests can also be of help when these children are grown up and begin planning a family. In a patient with a homozygous or compound heterozygous pathogenic podocin mutation, the risk of disease transmission is 50% in case they marry a partner who is a carrier of the *R229Q* allele. In European countries, up to 10% of the people may have the *R229Q* variant. Mutations in *WT1* are also relevant. Not only is the risk of transmission high (autosomal dominant, 50% risk), the disease may also be more serious in the offspring. If a woman with isolated FSGS related to a *WT1* mutation becomes pregnant, the children can develop the more severe Denysh–Drash Syndrome or Frasier Syndrome.

Genetic testing should be considered in patients with adult-onset FSGS, who are planning parenthood. Autosomal dominant forms of FSGS will be readily identified by a positive family history, although one must keep in mind the large heterogeneity in phenotypic expression. Risk of transmission is high and should be discussed. In adults with sporadic FSGS, the relevance of genetic testing for genetic counselling has been questioned since the prevalence of finding a mutation is very low. There may be one exception, which involves the *NPHS2* gene. As mentioned, in Western Europeans, up to 10% of patients with adult-onset FSGS may be compound heterozygous for one pathogenic *NPHS2* mutation and the *R229Q* variant [48]. Half of the offspring thus will carry one pathogenic mutation, which causes no disease. However, when combined with the *R229Q* variant, these children are at high risk of developing

late-onset FSGS. This is not hypothetical since the *R229Q* variant is prevalent in the normal population (up to 10%). In these cases testing the patients for the *R229Q* variant should be sufficient.

Genetic screening and kidney transplantation

It is well known that in familial forms of FSGS, the likelihood of recurrent disease after kidney transplantation is very low. In the era before the regular use of mutation analysis, Conlon *et al.* [66] described the clinical characteristics of 26 multigenerational families (probably autosomal dominant inheritance) and 34 single generation families (probably autosomal recessive) with FSGS. In 41 patients, a kidney transplantation had been done. Only one patient developed clinical and laboratory evidence of recurrent FSGS (2.5%). In recent studies, similar conclusions were reached. Machuca *et al*. reported no recurrence in 9 patients with two podocin mutations and Jungraithmayr *et al.* reported no recurrence in 11 patients with two podocin mutations, whereas Weber *et al.* reported 1 patient with recurrence out of 32 patients with two podocin mutations [48, 67, 68]. Other studies have reported a higher incidence of recurrence (up to 38%); however, these studies have been criticized since most recurrences developed in patients with only one mutation [69, 70]. Thus, in isolated

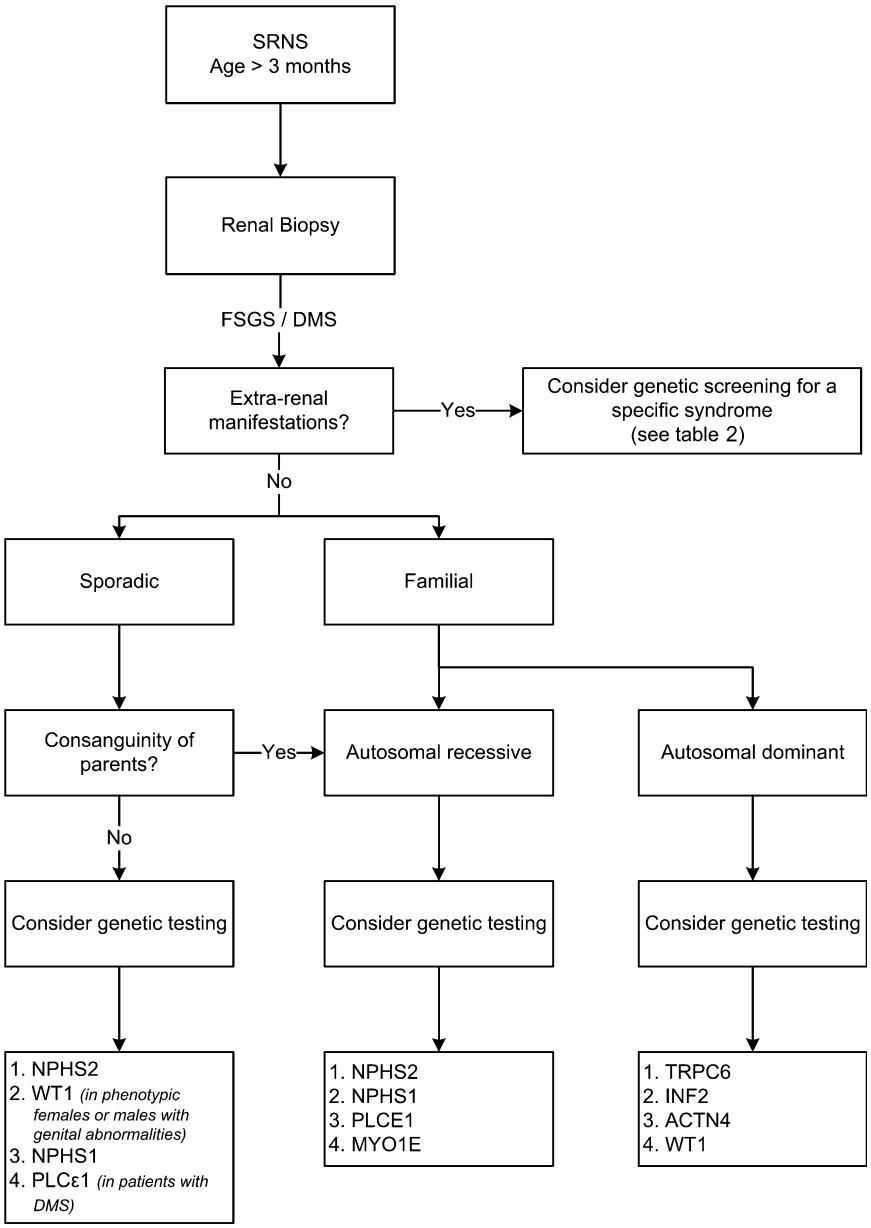

Fig. 1. Diagnostic algorithm for mutation screening in children with SRNS. DMS = diffuse mesangial sclerosis. This algorithm is suitable for patients who are evaluated for SRNS. In clinical practice, the family history should be part of the initial analysis. If in a patient with a nephrotic syndrome the family history is positive, genetic screening should be considered before starting steroid treatment. Note: in patients with SRNS, a renal biopsy should be performed to exclude other histologies such as IgA nephropathy, Alport syndrome, Dense Deposit Disease, Membranoproliferative Glomerulonephritis. Histologies compatible with FSGS include minimal change disease and IgM nephropathy.

cases of SRNS/FSGS, the detection of a homozygous or compound heterozygous mutation will predict a low risk of recurrence. Although it will not directly influence the treatment of the patient, this knowledge should be reassuring for patients and their parents. Furthermore, it may enhance the likelihood of living donor transplantation because a potential donor can be assured that the risk of graft failure due to recurrence is low.

The low risk of recurrence does not hold for patients with CNS due to *NPHS1* mutations. In these patients, the reported recurrence rate is 25% [71]. It is likely that proteinuria is caused by the development of anti-nephrin antibodies, as these antibodies were detected in almost half of the patients [70].

In patients with a family history of SRNS/FSGS, knowledge of the type of mutation will not be informative from the patient's perspective. However, mutation analysis may be more important for selection of the donor. Winn *et al.* [72] have reported two donors, who developed nephrotic syndrome after donation. The first patient was a white female, who donated her kidney to her brother who was known with FSGS. The donor remained healthy during two pregnancies after donation. Seven years after donation, she developed proteinuria due to FSGS with a nephrotic syndrome and progressed to ESRD. The second patient was a man, who donated his kidney to his brother. This involved a multigenerational family with FSGS, with most patients being non-nephrotic. Five years after donation, proteinuria developed, and 7 years later, ESRD was noted. Thus, in patients with FSGS and presumed autosomal dominant inheritance, genetic testing is advised. If a mutation is found, the donors should be analysed. Although hard data are lacking, it seems wise to exclude donors with a mutation from donating a kidney.

Guidelines for genetic screening in clinical practice

We advise genetic testing in all children with CNS since mutation detection rate is 100%, starting with *NPHS1*. Figures 1 and 2 illustrate the diagnostic algorithms for children and adults with SRNS/FSGS. We suggest that mutation analysis be performed in children with familial and sporadic SRNS. This advice is based on the fact that the prevalence of genetic causes of SRNS is high, and the results will often affect family counselling. We suggest mutation analysis in adults with a family history of FSGS.

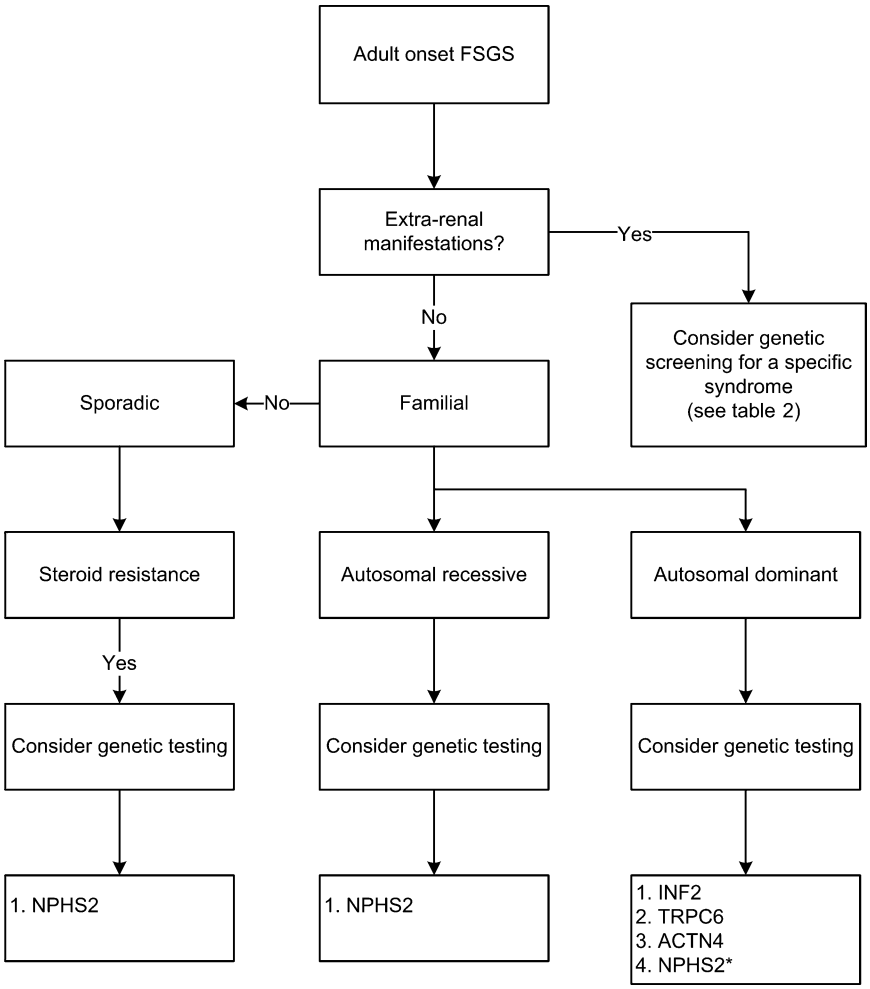

Fig. 2. Diagnostic algorithm for mutation screening in adults with FSGS. Asterisk indicates that *NPHS2* mutations can show a pseudo-autosomal dominant pattern of inheritance, e.g. one parent with a homozygous mutation in *NPHS2* and a parent with *R229Q*, the child carrying one pathogenic mutation in combination with *R229Q*.

This information can be used when discussing the prospects of a living related donor transplantation and donor selection. Genetic screening is of limited value in adult patients with sporadic FSGS, with the exception of screening for the *R229Q* in young adults, who would like to be informed of the risk that the disease develops in their offspring. The sequence of testing is dependant on the estimated prevalence, the size of the gene, and the relevance of the findings (see above).

Areas of uncertainty

Detailed genotype–phenotype correlations are lacking. No study has addressed the relation between genotype and histological classification. It is important to develop and exploit large registries of patients with SRNS/FSGS with extensive genetic screening and adequate follow-up. Only such registries can provide information on treatability of genetic FSGS, its outcome, etc.

Next generation sequencing could change our views. It is to be expected that whole exome screening will be done in the next years at very low costs; this will enable to analyse all genes related to FSGS in one array; this also will help to clarify genotype–phenotype relationships and explore the role of bigenic or multigenic heterozygous mutations.

Conflict of interest statement. None declared.

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