

Initial Steroid Sensitivity in Children with Steroid-Resistant Nephrotic Syndrome Predicts Post-Transplant Recurrence

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ABSTRACT

Of children with idiopathic nephrotic syndrome, 10%–20% fail to respond to steroids or develop secondary steroid resistance (termed *initial steroid sensitivity*) and the majority progress to transplantation. Although 30%–50% of these patients suffer disease recurrence after transplantation, with poor long-term outcome, no reliable indicator of recurrence has yet been identified. Notably, the incidence of recurrence after transplantation appears reduced in patients with steroid-resistant nephrotic syndrome (SRNS) due to monogenic disorders. We reviewed 150 transplanted patients with SRNS to identify biomarkers that consistently predict outcome of SRNS after transplantation. In all, 25 children had genetic or familial SRNS and did not experience post-transplant recurrence. We reviewed phenotypic factors, including initial steroid sensitivity, donor type, age, ethnicity, time to ESRD, and time on dialysis, in the remaining 125 children. Of these patients, 57 (45.6%) developed post-transplant recurrence; 26 of 28 (92.9%) patients with initial steroid sensitivity recurred after transplantation, whereas only 26 of 86 (30.2%) patients resistant from the outset recurred (odds ratio, 30; 95% confidence interval, 6.62 to 135.86; $P < 0.001$). We were unable to determine recurrence in two patients (one with initial steroid sensitivity), and nine patients did not receive initial steroids. Our data show that initial steroid sensitivity is highly predictive of post-transplant disease recurrence in this pediatric patient population. Because a pathogenic circulating permeability factor in nephrotic syndrome remains to be confirmed, we propose initial steroid sensitivity as a surrogate marker for post-transplant recurrence.

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Idiopathic steroid-resistant nephrotic syndrome (SRNS), interchangeably termed by the common histologic description of FSGS, is one of the commonest causes of end stage renal failure (ESRF) in childhood and children with SRNS are the most prevalent group in the US dialysis registry (comprising 14.4% of all pediatric dialysis patients).¹ Approximately 50%–60% of children with SRNS eventually require a renal transplant. Unfortunately, this group of patients has a high incidence of disease recurrence, with rates as high as 50% reported.^{2–4} Several studies have examined possible risk factors for recurrence. To date, non–African-American race, previous

recurrence after transplantation, and time < 3 years to ESRF have been proposed to directly correlate with an increased risk of recurrence.^{5–7}

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Recent advances in our knowledge of the genetics of SRNS have highlighted the potential importance of gene mutations in helping to predict risk of disease recurrence, the majority of which cause structural/signaling changes at the filtration barrier.⁸ Specifically, a number of studies have shown that patients with autosomal recessive SRNS and either homozygous or compound heterozygous mutations in *NPHS2* (which encodes podocin, a slit diaphragm protein) have very low recurrence rates of 0%–3% after transplantation.^{6,9,10} On the other hand, haploinsufficient and apparently sporadic individuals with only a single heterozygous *NPHS2* variant (e.g., R229Q) appear to have similar recurrence rates to those with no gene mutation identified.^{6,10} However, the contribution of genetic background remains incompletely understood, because another study was unable to replicate these data and showed no recurrences in *NPHS2* haploinsufficiency.⁹ Nonetheless, the true genotype may not have been recognized with the other pathogenic SRNS mutation remaining unidentified, and additionally, digenic inheritance has been described in some forms of SRNS.¹¹ Mutations present in other key podocyte genes such as *NPHS1* or *WT1* are similarly associated with a low risk of disease recurrence. Patients with genetic mutations also appear to have a reduced response to immunosuppression (17% versus 68% in one study) and progress more quickly to ESRF.¹²

AT cell–derived circulating factor responsible for nephrotic syndrome was initially proposed in 1974.¹³ To date, a number of possible candidates have been identified, including hemopexin, cardiotrophin-like cytokine 1, and soluble urokinase-type plasminogen activator receptor.^{14,15} Subsequent work has been supportive of this circulating factor being responsible for SRNS recurrence after transplantation.¹⁶ Because the majority of patients with podocyte gene mutations appear to be resistant to immunosuppression and do not develop recurrent disease after transplantation, and the evidence suggests that the circulating factor is immunologically derived, we hypothesized that initial steroid sensitivity is a marker for circulating factor/idiopathic nephrotic syndrome, which segregates to a higher risk of post-transplant recurrence.

For idiopathic SRNS in childhood, we analyzed the following potential risk factors: young age at diagnosis, rapid progression to ESRF, young age at transplant, positive family history, and extrarenal abnormalities that might suggest an underlying syndrome (predictive of genetic mutation) versus initial steroid sensitivity, late-onset disease, lack of family history, no evidence of extrarenal features, and lack of an identified single gene mutation. We then examined whether each factor had an increased risk of disease recurrence and whether any of these parameters could be reliably identified as risk factors for post-transplant recurrence.

RESULTS

We identified 150 patients transplanted for ESRF secondary to SRNS between 1981 and 2012 in three large pediatric renal transplant centers in the United Kingdom and France. Of

these patients, 57 (38%) had documented post-transplant recurrence and 91 had no recurrence (60.7%). It was not possible to determine outcome in two patients because one became anuric after transplantation and died 1 month later, and the second patient developed irrecoverable graft thrombosis within 24 hours and required transplant nephrectomy. The first patient was initially steroid sensitive, whereas these data were unavailable for the second patient.

Patient characteristics in the recurring and nonrecurring groups are shown in Table 1. In brief, participants were classified by race as follows: 115 patients were Caucasian, 17 were North African, 6 were Afro-Caribbean, 5 were East African, 4 were Indian or Pakistani, 1 was of other Asian race, 1 was of mixed race (white and black Caribbean), and 1 was of unknown race. The median age of patients at diagnosis was 4.0 years (range, 0.3–15.5), median time to ESRF was 3.0 years (range, 0–17), and median age at first transplant was 11.5 years (range, 2.5–23.5).

The 57 patients with post-transplant recurrence had almost double the rate of complications, graft loss, and subsequent retransplantation compared with patients who did not have recurrence (28% versus 16.5%). One patient underwent three transplants; graft loss was attributed to rejection in the first two (with primary nonfunction) and recurrence in the third graft. An additional 10 patients had two transplants. Two patients had thrombosis or renal vein occlusion with the first graft, followed by disease recurrence in the second graft. The histopathologic reports of the removed grafts showed extensive necrosis in the first patient and hemorrhagic infarction in the second patient, with no evidence of recurrence in either. In eight patients, graft loss was due to disease recurrence in both transplants. Five patients lost their first graft due to recurrence and were not retransplanted. Of the 91 patients without recurrence, 15 patients lost their grafts. One patient had four transplants and 11 had two transplants; the remaining 3 patients did not have retransplants.

Genetic Mutations and Family History

Genetic testing (either by conventional Sanger sequencing or an extended gene panel by Next Generation Sequencing¹⁷) in 62 of 150 patients revealed 18 pathogenic mutations. Of the 62 tested patients, 7 had pathogenic *NPHS2* mutations, 4 had *WT1* splicing mutations (2 with Frasier syndrome and 2 with Denys–Drash syndrome), 1 had a pathogenic *NPHS1* mutation, 1 had an unbalanced chromosomal translocation between chromosomes 2 and 6, 1 had a *COQ2* mutation, 1 had a *PLCE1* mutation, 1 had a *SMARCAL1* mutation, 1 had a *TRPC6* mutation, and 1 was heterozygous for *NPHS1* and heterozygous for *NPHS2* mutations. None developed post-transplant recurrence. Of 62 patients, 3 carried heterozygous changes in *NPHS2*, but data mining using variant prediction tools and the human mutation database indicated that these were nonpathogenic. All three patients had recurrence of disease. Another patient with recurrence had a *NPHS1* heterozygous variant of unknown significance.

Table 1. Patient characteristics

Characteristic	Recurrence	No Recurrence	Unable to Determine Recurrence	P Value ^a
Patients (n)	57	91	2	
Ratio of male patients/female patients	1.02:1	1.38:1	0:2	0.40
Ethnicity				0.13
Caucasian (European/North American)	66.7	82.4	100	
Caucasian (North African)	17.5	7.7	0	
Afro-Caribbean	5.3	3.3	0	
East African	1.8	4.4	0	
Indian/Pakistani	5.3	1.1	0	
Other Asian	1.8	0	0	
Mixed race	1.8	0	0	
Unknown	0	1.1		
Deceased donor	84.2	94.5	50	0.05
Age at diagnosis (yr)	4.5 (0.7–12.5)	3.5 (0.3–15.5)	2	0.97
Time to ESRF (yr)	4 (0–17)	3 (0–16)	7	0.09
Age at first transplant (yr)	12.5 (3–23)	11 (2.5–23.5)	8.5 (7.5–9.5)	0.16

Data are presented as percentages or medians (ranges), unless otherwise indicated.

^aP value between the recurrence and nonrecurrence groups.

Of 150 children (without extrarenal abnormalities/known genetic mutations), 3 had positive family histories of a first-degree relative with isolated SRNS. Two patients were siblings. An additional four children had extrarenal abnormalities with positive family histories. Two patients were siblings with Schimke’s immune-osseous dysplasia, one had features of Galloway Mowat syndrome, and one was dysmorphic with cardiomegaly, cataracts, and learning disabilities. None of these patients had recurrence. One patient had a distant cousin with steroid-sensitive nephrotic syndrome (SSNS) who recovered; therefore, this is more likely a chance association, rather than a positive family history, because SSNS has an increased incidence in this particular ethnic group. One patient had a brother who died at age 2 years, but the cause was unknown. There were four children with extrarenal abnormalities without a positive family history or mutation. One patient had pulmonary stenosis with infertility, one had developmental delay with epilepsy and hearing impairment, one had learning disabilities, and one had sensorineural hearing loss, primary T-cell immune deficiency, growth hormone deficiency, hypothyroidism, Addison’s disease, and external ophthalmoplegia with a suspected mitochondrial cytopathy. The child with learning disabilities and no other extrarenal features had a recurrence after transplantation.

There were 25 patients with pathogenic genetic mutations ($n=18$) and positive family histories ($n=7$). None of these patients recurred after transplantation (odds ratio [OR], 0.02; 95% confidence interval [95% CI], 0.001 to 0.39; $P<0.001$). Because patients with genetic mutations are known to have a low risk of recurrence, we excluded these 25 patients from the subsequent analyses. We also excluded the two patients for whom recurrence could not be determined.

Initial Steroid Sensitivity

Initial steroid sensitivity was defined as complete remission of proteinuria (3 days of trace or negative proteinuria on dipstick

testing) on at least one episode after steroid therapy. Of 28 patients with initial steroid sensitivity, 26 developed recurrent disease after transplantation, comprising 45.6% (26 of 57) of the patients who recurred. One patient had initial steroid sensitivity but became anuric immediately after transplantation and never recovered function. Although delayed graft function is a common presentation of early recurrence, we did not include this patient as a definite recurrence because the presence of proteinuria could not be established. In 9 of 123 children, steroids were either not used initially ($n=3$) or these patients were in ESRF at presentation ($n=6$). Our results showed that 26 of 28 patients (92.9%) with initial steroid sensitivity recurred after transplantation, whereas only 26 of 86 (30.2%) of those resistant from the outset recurred. Initial steroid sensitivity at presentation was an accurate and highly significant risk factor for recurrence (OR, 30; 95% CI, 6.62 to 135.86; $P<0.001$) (Figure 1, Table 2). None of these patients had extrarenal abnormalities.

We also performed a subgroup analysis of those patients who had genetic testing and were found to have no genetic variants. This group comprised 41 patients, 37 of which received steroids initially. Of the 37 patients, 9 were initially steroid sensitive and 28 were steroid resistant. Recurrence was higher in the initially steroid-sensitive group (8 of 9; 88.9%) compared with the initially steroid-resistant group (15 of 28; 53.6%), but this difference was not significant (OR, 6.93; 95% CI, 0.76–63.05; $P=0.06$).

Donor Type

A small proportion of patients (11 of 123) had living donor transplants. Living donor transplants confer an increased risk of recurrence (OR, 6; 95% CI, 1.24–29.06; $P=0.02$).

Ethnicity

We compared African-European patients with non-African-European patients and found that there was no significant

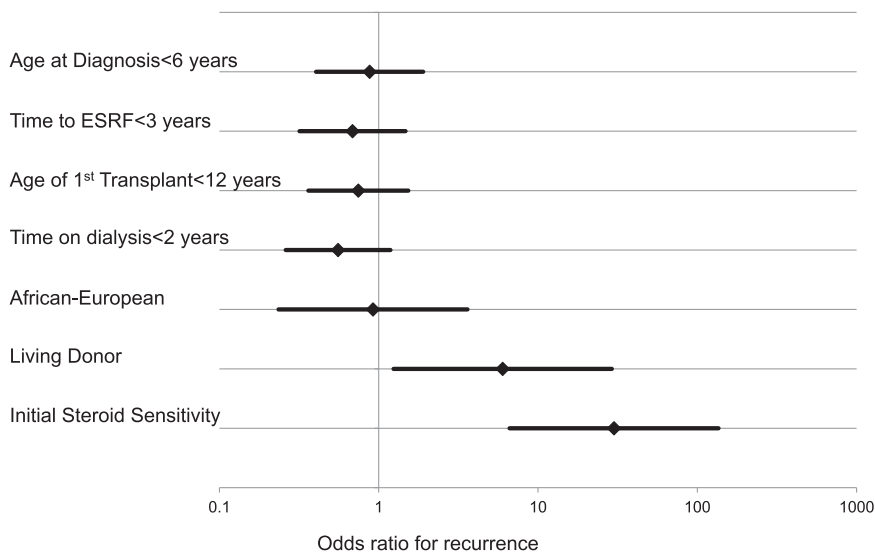


Figure 1. Forest plot of ORs for recurrence in nongenetic/nonfamilial cases. Clinical risk was calculated for each factor listed in the left column. Calculated significance is given in Results.

Table 2. ORs for post-transplant recurrence in children with nongenetic/nonfamilial SRNS

Characteristic	OR (95% CI)	P Value
Age of diagnosis <6 yr	0.88 (0.40 to 1.90)	0.84
Time to ESRF <3 yr	0.68 (0.31 to 1.47)	0.44
Age of first transplant <12 yr	0.74 (0.36 to 1.53)	0.47
Time on dialysis <2 yr	0.56 (0.26 to 1.19)	0.18
African-European race	0.92 (0.24 to 3.61)	>0.99
Living donor transplant	6.00 (1.24 to 29.06)	0.02
Steroid sensitivity	30.00 (6.62 to 135.86)	<0.001

difference in recurrence rates (OR, 0.92; 95% CI, 0.24 to 3.6; $P>0.99$). We included Afro-Caribbean and East African patients in our African-European group.

Age at Diagnosis, Time to ESRF, Time on Dialysis, and Age at First Transplant

No significant difference was detected in age at diagnosis (OR, 0.88; 95% CI, 0.39 to 1.9; $P=0.84$), time to ESRF (OR, 0.68; 95% CI, 0.31 to 1.47; $P=0.44$), time on dialysis ($P=0.18$; OR, 0.56; 95% CI, 0.26 to 1.19), or age at first transplant (OR, 0.74; 95% CI, 0.36 to 1.53; $P=0.47$) (Figure 1, Table 2) between the recurrent and nonrecurrent groups.

DISCUSSION

Our study is the first to clearly identify a highly predictive clinical feature for post-transplant disease recurrence in SRNS, and secondarily shows that the presence of genetic disease is protective.

The mechanism remains speculative, but our data keep immune-mediated pathogenicity in the spotlight. A number of lines of evidence point to a putative circulating factor being central to the pathogenic mechanisms in SSNS as well as recurrence in post-transplant SRNS.¹⁴ Although a number of candidates have been proposed, the factor has not yet been conclusively identified. This concept is supported by documented high rates of recurrence in SRNS after transplantation, response to plasma exchange, as well as supportive *in vitro* data showing the deleterious effects of diseased plasma on isolated glomeruli,¹⁶ the slit diaphragm, the actin cytoskeleton, and podocyte motility.¹⁸ Furthermore, the response of cultured podocytes exposed to SRNS disease plasma from consecutive patients is consistent, indicating that this is likely to be a discrete cellular response, caused by a specific circulating factor

rather than heterogeneous effects.^{19,20} Because there is evidence to suggest that the putative circulating factor may result from immune activation, we hypothesized that the initial response to steroids might by definition indicate the presence of a similar process and thus predict risk of recurrence after transplantation. Conversely, we predicted that steroid resistance from the outset, especially if combined with a definitive podocyte gene mutation, might be protective.

We first examined all factors including aggressive course before transplantation with a time interval between onset of the disease and CKD stage 5 of <3 years, male sex, mesangial hypercellularity in most glomeruli as well as fewer sclerotic lesions, age at diagnosis, donor type, and time to ESRF, which have been correlated with increased risk for SRNS recurring after transplantation.^{5,7,21–26} We were unable to draw conclusions on the relationship between mesangial hypercellularity because detailed histology was not available for all patients. None of the above factors were statistically significant in predicting recurrence except for donor type (Figure 1, Table 1). Patients who received a living donor transplant had a significant risk of recurrence in our study; however, there were few living donors in our study. Previous studies of living donors and recurrence risk have had inconsistent results.²¹ A recent study of 2157 children who were transplanted for FSGS demonstrated that a living donor transplant significantly increased recurrence risk but this risk became insignificant if corrected for age and race in multivariate analysis. This study, however, did not differentiate between genetic and nongenetic FSGS.²⁷ In addition, collapsing FSGS is also a well described risk factor.²⁸ This was true for the only patient in this series with collapsing FSGS (HIV-negative), who recurred immediately after transplantation and lost graft function soon afterward (patient 3, Supplemental Material).

Decreased risk of post-transplant recurrence has been previously linked to the presence of a genetic mutation, as well as to African-American race.²¹ African-American race has consistently been shown to decrease the risk of recurrence after transplantation.⁵ Our study demonstrates different results in our African-European population, in which no significant racial effect on recurrence was seen. There is some evidence that MYH9 risk alleles (for FSGS), which are more common in Africans, have differential frequencies across different countries, and there is the potential that these risk alleles might play a part in SRNS recurrence.^{29,30}

A histologic diagnosis of FSGS was traditionally thought to correspond to an increased risk of steroid resistance in childhood nephrotic syndrome. With the advent of genetic testing and the increasing rate of detection of gene mutations in SRNS, it is becoming apparent that children with monogenic inheritance of SRNS are more likely to display permanent steroid (and secondary immunosuppression) resistance.¹² Genetic mutation was confirmed as a potential protective biomarker in our series, because patients with SRNS carrying a pathogenic dominant negative, homozygous, or compound heterozygous podocyte gene mutation and/or familial disease did not develop recurrent disease. This finding also supports the concept that detection of a biallelic gene mutation might provide an appropriate biomarker of reduced risk, although more patients need to be studied. However, our data also support the notion that *NPHS2* haploinsufficiency is insufficient to prevent post-transplant disease recurrence.

In this study, none of the patients with isolated renal disease and pathogenic podocyte gene mutations recurred after transplantation; in addition, three patients had a positive family history of SRNS. Only one of eight patients with extrarenal abnormalities suffered recurrence, and these features were mild in this child (patient 5, Supplemental Material). The known exception is patients with Fin-major nephrin mutations (and an early truncation) who may develop post-transplant recurrence secondary to neoantigen exposure.³¹ We had no known Fin-major patients in our series. Notably, no patients with other nephrin mutations were recorded as developing transplant recurrence in either center during the study time period.

We found that a significant proportion of patients (19.3%) were initially steroid sensitive and only developed steroid resistance later on in the course of the disease, at times delayed by 5–7 years after onset. This initial sensitivity was strongly correlated with a complete risk of recurrence after transplantation. Posttransplant recurrence was also observed in all subsequent grafts, supportive of disease caused by the presence of a circulating factor. None of these patients had a documented gene mutation, family history, or extrarenal abnormalities, although it is possible that circulating factor nephrotic syndrome is triggered by genetic variants present within the genome together with a relevant environmental stimulus such as a viral trigger. Predictable recognition of this group might therefore facilitate accurate prognosis as well as identification of which patients to target for more intense therapy pretransplant, with strict emphasis

on better control of nephrotic relapses earlier in their course of disease to avoid secondary steroid resistance. Therapy is also currently limited by a lack of consensus for the optimal management of post-transplant SRNS recurrence, such as ciclosporin versus tacrolimus, peritransplant plasmapheresis, rituximab (anti-CD20),³² or infliximab/eterncept (anti-TNF α),³³ all strategies that have been used in attempts to control post-transplant disease with varying success.

In summary, our data highlight two identifiable clinical groups before transplant: those who are initially steroid sensitive and have a predicted high risk of recurrence and those with genetic mutations or familial disease with a low risk. There is a vigorous ongoing debate about whether steroids and calcineurin inhibitors play a direct role in stabilizing the podocyte cytoskeleton and reversing podocyte damage without any effect on the immune system. Our data suggest that this is not a significant contributor in the group of patients with steroid sensitivity, because we can link the results of immunosuppression early in the disease process to an immune-mediated recurrence after transplantation. If steroids were able to reverse podocyte damage directly, then the prediction would be that there are (genetic) patients who are steroid responsive who would then not recur after transplantation. This is evidently not the case from our data.

The presence of genetic/developmental disease was clearly protective for recurrence, because none of our patients with documented gene mutations or identifiable syndromes relapsed after transplantation. Individuals that fall into a gray area between these two phenotypes are those patients with treatment-resistant SRNS with no evidence of initial steroid sensitivity who recurred after transplantation. Notably, 31 of 57 of the patients with recurrence did not exhibit initial steroid sensitivity. This remains unexplained, although possibilities include compliance/toxicity issues or aggressive disease masking initial steroid sensitivity with subsequent resistance to other standard immunosuppression regimes. We did not analyze whether any of those 31 patients exhibited a response to more intensive immunosuppression, and clearly that would be an important parameter to follow up on in this group. On the basis of our findings, we have suggested a clinical paradigm to assist in assessing pediatric patients with progressive nephrotic syndrome who are potentially at risk of transplant recurrence (Figure 2).

In conclusion, we have detected a highly significant correlation between initially steroid-sensitive and post-transplant FSGS recurrence. We propose that this is a clinically identifiable group that is at high risk (Figure 3) and could potentially be aggressively targeted with detailed preparation and additional immunosuppression before transplantation. In addition, transplantation must be planned with extra care to maximize graft survival in these patients.

CONCISE METHODS

Patient Selection

We identified pediatric patients at the Bristol Royal Hospital for Children (Bristol, UK), the Evelina Children's Hospital (London,

clinical characteristics including sex, race, age at diagnosis, time to ESRF, age at transplant, initial steroid sensitivity at presentation, genetic mutations, family history, extrarenal abnormalities, recurrence, rejection, and graft loss.

Patients were included in the study if a positive biopsy result of FSGS was found in the patient notes (143 of 150) or, at a minimum, if SRNS was the stated diagnosis in their medical records. We excluded patients with congenital nephrotic syndrome (onset age < 3 months) or diffuse mesangial sclerosis on biopsy. Proteinuria was defined by having a urine protein/creatinine ratio of >300 mg/mmol. Steroid resistance was defined as the persistence of proteinuria (>300 mg/mmol or 300 mg/dl or equivalent on dipstick testing) after 4 weeks of daily prednisolone at a dosage of 60 mg/m² per day ± 3 daily doses of intravenous methylprednisolone at 600 mg/m². Patients were deemed to have recurred if they had persistent proteinuria of >300 mg/mmol or >1 g/d after transplantation.

Statistical Analyses

Nonparametric data were analyzed using the Mann–Whitney *U* test. Contingency tables were analyzed with Fisher’s exact test and ORs (with 95% CIs) were used to compare recurrence and nonrecurrence groups. *P* < 0.05 was considered significant. Values are reported as mean ± SEM or the median (range).

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DISCLOSURES

None.

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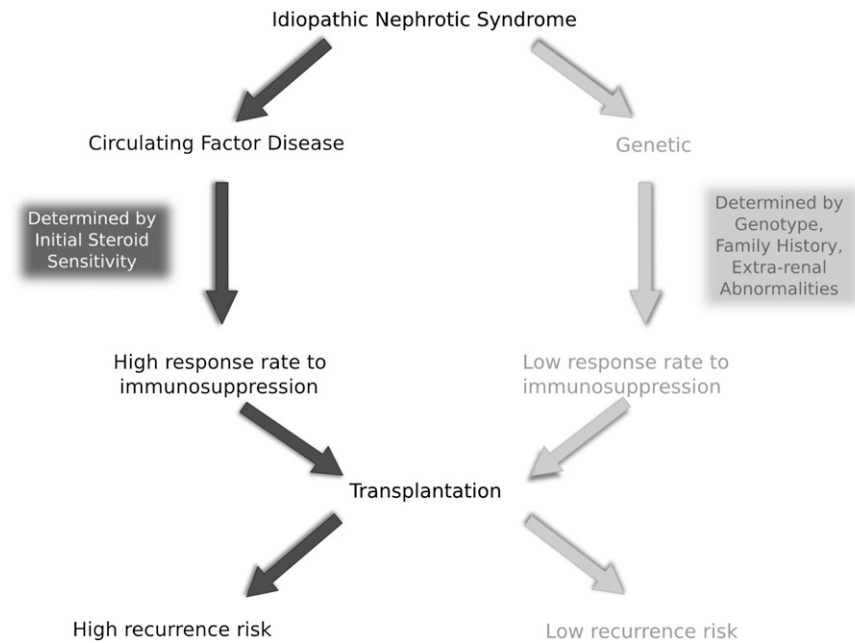


Figure 2. A suggested clinical paradigm for idiopathic nephrotic syndrome. Idiopathic nephrotic syndrome is stratified (where possible) according to clinical parameters into “circulating factor disease” and “genetic disease.” This segregates into high and low risk factors for post-transplant disease recurrence.

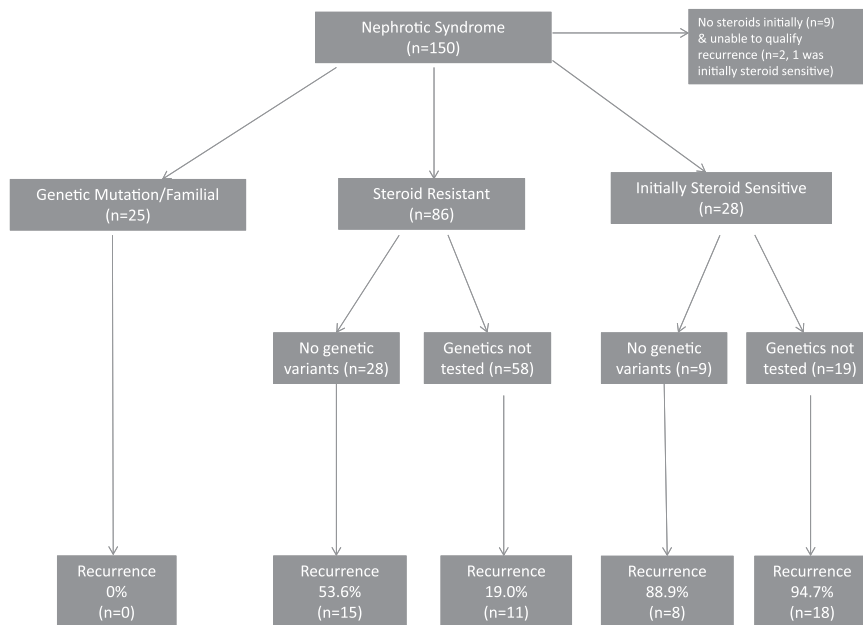


Figure 3. Stratifying patient risk according to initial steroid resistance/sensitivity. Groups are divided into genetic, steroid-resistant, and steroid-sensitive groups to give the recurrence risk of each group from this study.

UK), and the Necker Hospital for Sick Children (Paris, France) who were diagnosed with FSGS/SRNS at between 4 months and 16 years of age and who received a renal transplant between January 1, 1981, and September 1, 2012. We conducted a retrospective data collection of

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Supplementary Table 1 Patients who recurred post-transplant

Patient	Sex	Ethnicity	Age at diagnosis (years)	Initial Steroid Sensitivity	Time to ESRF (years)	Donor Type	Age at transplant (years)	Recurrence	Genetics	Comorbidities/FH
1	M	Indian	10	CRF at diagnosis	2.5	DD	15	Yes	Not tested	None
2	M	North African	6	ESRF	0	DD	8	Yes	No variants of note	None
3	M	AfroC	1.5	ESRF	0	LD	3	Yes	Not tested	None
4	M	Indian	2	ESRF	0	LD	4.5	Yes	Not tested	Distant cousin had SSNS
5	F	North African	2.5	No	2	DD	6.5	Yes	No variants of note	Learning Difficulties
6	F	Cauc	3.5	No	2	DD	7	Yes	No variants of note	None
7	M	Cauc	3.5	No	2	DD	8	Yes	No variants of note	None
8	M	North African	2.5	No	4.5	DD	8	Yes	No variants of note	None
9	M	North African	1.5	No	5.5	DD	8	Yes	No variants of note	None
10	M	AfroC	5	No	2	DD	8.5	Yes	No variants of note	None
11	F	Cauc	6	No	1.5	DD	9.5	Yes	No variants of note	None
12	F	Cauc	4.5	No	6	DD	11.5	Yes	No variants of note	None
13	M	Cauc	9	No	4	DD	15	Yes	No variants of note	None
14	F	Cauc	0.7	No	13	DD	15	Yes	No variants of note	None
15	M	Cauc	11	No	3.5	DD	15.5	Yes	No variants of note	None
16	F	Cauc	10	No	3	DD	16.5	Yes	No variants of note	None
17	M	Cauc	11.5	No	3	DD	18.5	Yes	No variants of note	None
18	M	Cauc	10	No	2.5	DD	14.5	Yes	Non-pathogenic NPHS2 variant	None
19	M	Cauc	1	No	2.5	DD	6.5	Yes	Not tested	None
20	M	North African	2.5	No	2.5	DD	7	Yes	Not tested	None
21	M	Cauc		No		DD	10	Yes	Not tested	None
22	M	Cauc	6.5	No	3	DD	10.5	Yes	Not tested	None
23	F	Cauc	7.5	No	2	DD	11.5	Yes	Not tested	None
24	F	Cauc	6.5	No	4.5	LD	11.5	Yes	Not tested	None
25	M	Cauc	3	No	7.5	DD	13	Yes	Not tested	None
26	F	Cauc	5.5	No	7	DD	13.5	Yes	Not tested	None
27	F	Cauc	11	No	0.9	DD	14	Yes	Not tested	None
28	F	Cauc	10.5	No	2	DD	15	Yes	Not tested	None
29	F	Cauc	9	No	4	DD	18.5	Yes	Not tested	None
30	M	Cauc	5.5	No	2.5	DD	9	Yes	NPHS1 single heterozygous	None
31	M	Cauc	12.5	Not used	1.5	DD	14	Yes	Not tested	None
32	F	North African	2	Yes	4	DD	7.5	Yes	No variants of note	None
33	M	Cauc	3	Yes	4	DD	8	Yes	No variants of note	None
34	F	North African	7.5	Yes	3	LD	12.5	Yes	No variants of note	None
35	F	Indian	4	Yes	10	DD	12.5	Yes	No variants of note	None
36	M	East African	4.5	Yes	9	DD	13.5	Yes	No variants of note	None
37	M	Cauc	4.5	Yes	9.5	DD	15.5	Yes	No variants of note	None
38	F	Cauc	4	Yes	10	LD	15	Yes	Non-pathogenic NPHS2 variant	None
39	M	Cauc	6.5	Yes	12.5	DD	21	Yes	Non-pathogenic NPHS2 variant	None

40	M	Cauc	2	Yes	2	DD	3.5	Yes	Not tested	None
41	M	Cauc	2	Yes	1	DD	5	Yes	Not tested	None
42	M	Cauc	2.5	Yes	3	DD	6.5	Yes	Not tested	None
43	F	Cauc	2	Yes	6	DD	8	Yes	Not tested	None
44	F	Cauc	2	Yes	6	LD	9	Yes	Not tested	None
45	M	North African	1.5	Yes	3.5	DD	10	Yes	Not tested	None
46	F	AfroC	4.5	Yes	6	DD	11.5	Yes	Not tested	None
47	F	Cauc	2	Yes	7.5	DD	12.5	Yes	Not tested	None
48	M	North African	6.5	Yes	4.5	DD	14	Yes	Not tested	None
49	F	Cauc	4.5	Yes	7	DD	14	Yes	Not tested	None
50	M	Cauc	3	Yes	9	LD	15	Yes	Not tested	None
51	M	North African	2	Yes	10.5	DD	15.5	Yes	Not tested	None
52	M	Cauc	2	Yes	11.5	DD	15.5	Yes	Not tested	None
53	M	Mixed white and black Caribbean	2	Yes	12.5	DD	16	Yes	Not tested	None
54	F	Asian	2.5	Yes	11.5	LD	17	Yes	Not tested	None
55	F	Cauc	8	Yes	7	DD	18	Yes	Not tested	None
56	F	Cauc	5	Yes	17	LD	18.5	Yes	Not tested	None
57	M	Cauc	12.5	Yes	3.5	DD	23	Yes	Not tested	None

Supplementary Table 2 Patients in whom we were unable to determine recurrence

Patient	Sex	Ethnicity	Age at diagnosis (years)	Initial Steroid Sensitivity	Time to ESRF (years)	Donor Type	Age at transplant (years)	Rejection?	Genetics	Comorbidities/FH
58	F	Cauc				LD	9.3	Poor perfusion and non function of graft & thrombosis	Not tested	Unconfirmed mitochondrial cytopathy, primary T cell immune deficiency, hypothyroidism, sensorineural hearing loss, central growth hormone deficiency, nocturnal hypoventilation, developmental delay, paralysed right diaphragm, external ophthalmoplegia, Addison's disease
59	F	Cauc	2	Yes	7	DD	7.6	Anuric from outset:	Not tested	None

Supplementary Table 3 Patients who did not recur post-transplant

Patient	Sex	Ethnicity	Age at diagnosis (years)	Initial Steroid Sensitivity	Time to ESRF (years)	Donor Type	Age at transplant (years)	Recurrence	Genetics	Comorbidities/FH
60	M	North African	1.5	Yes	3	DD	6.5	No	No variants of note	None
61	M		7.5	Yes	6	DD	16.5	No	Not tested	None
62	F	Cauc	5	Not used	8.5	DD	14.5	No	No variants of note	None
63	M	Cauc	3.5	ESRF	0	DD	4.5	No	No variants of note	None
64	F	Cauc	11.5	ESRF	0	DD	12.5	No	No variants of note	None
65	M	Cauc				DD	9.5	No	Not tested	None
66	F	Cauc	2	No	0.1	DD	3.5	No	No variants of note	None
67	F	Cauc	0.3	No	2	DD	3.5	No	No variants of note	None
68	F	Cauc	2	No	3	DD	6	No	No variants of note	None
69	M	Cauc	2	No	4	DD	6.5	No	No variants of note	None
70	F	Cauc	0.5	No		DD	7	No	No variants of note	None
71	F	Cauc	5.5	No	0.08	DD	7.5	No	No variants of note	None
72	M	Cauc	2.5	No	3	LD	8.5	No	No variants of note	None
73	M	Cauc	1.5	No	4.5	DD	10.5	No	No variants of note	None
74	M	North African	2	No	7	DD	11.5	No	No variants of note	None
75	F	Cauc	2.5	No	8.5	DD	13	No	No variants of note	None
76	F	Cauc	10.5	No	2	DD	14.5	No	No variants of note	None
77	M	AfroC	15	No	0.08	DD	16	No	No variants of note	None
78	F	East African	15.5	No	0.02	DD	16.5	No	No variants of note	None
79	M	Cauc	1	No	7.5	DD	9	No	Not tested	Brother died age 2-- cause unknown
80	M	Cauc	4	No	0.2	DD	5	No	Not tested	Developmental delay, epilepsy, learning difficulties, hearing impairment
81	M	Cauc	1.8	No	1.5	DD	5	No	Not tested	None
82	M	Cauc	3	No	1.5	DD	5.5	No	Not tested	None
83	F	Cauc	4	No	2	DD	7.5	No	Not tested	None
84	F	Cauc	1	No	2	DD	8.5	No	Not tested	None
85	F	Cauc	3.5	No	4	DD	8.5	No	Not tested	None
86	F	North African	0.8	No	7	DD	8.5	No	Not tested	None
87	F	Cauc	9	No		DD	8.5	No	Not tested	None
88	M	Cauc	6.5	No	2	DD	9	No	Not tested	None
89	F	Cauc	2.5	No	5	DD	9	No	Not tested	None
90	F	Cauc	3	No	5	DD	9	No	Not tested	None
91	F	Cauc	3	No	6	DD	9	No	Not tested	None
92	M	Cauc		No		DD	9	No	Not tested	None
93	F	Cauc	5	No	2.6	DD	9.5	No	Not tested	None
94	F	Cauc	3.5	No	4	DD	9.5	No	Not tested	None
95	F	Cauc	3	No	0.02	DD	10	No	Not tested	None

96	M	Cauc		5.5	No	1.5	DD	11	No	Not tested	None
97	F	Cauc		6	No	4.5	DD	11	No	Not tested	None
98	M	Cauc		3	No	7	DD	11	No	Not tested	None
99	F	Cauc			No		DD	11	No	Not tested	None
100	M	Cauc		5	No	3	DD	11.5	No	Not tested	None
101	M	Cauc		7	No	3	DD	11.5	No	Not tested	None
102	F	Cauc	10		No	1.5	DD	12	No	Not tested	None
103	F	Cauc		10.5	No	1.5	DD	12	No	Not tested	None
104	F	Cauc		6.5	No	4.5	DD	12	No	Not tested	None
105	F	Cauc		1.5	No	8	DD	12	No	Not tested	None
106	F	Cauc		3	No	9	DD	12	No	Not tested	None
107	M	Cauc			No		DD	12.5	No	Not tested	None
108	F	Cauc		2	No	11	DD	13	No	Not tested	None
109	F	Cauc		10	No	0.02	DD	14	No	Not tested	None
110	F	Cauc	10		No	2	DD	14	No	Not tested	None
111	F	Cauc		12	No	0.5	DD	14.5	No	Not tested	None
112	M	Cauc		2	No	12	DD	14.5	No	Not tested	None
113	M	East African		1.5	No	12.5	DD	15	No	Not tested	None
114	M	Cauc		14.5	No	0.01	DD	15.5	No	Not tested	None
115	M	Cauc			No		DD	15.5	No	Not tested	None
116	M	Cauc		13	No	3	DD	16	No	Not tested	None
117	M	AfroC		0.5	No	14	DD	16	No	Not tested	None
118	F	Cauc	8		No	7	LD	17	No	Not tested	None
119	M	Cauc		4.5	No	9	DD	17.5	No	Not tested	None
120	F	Cauc		3.5	No	12	DD	18	No	Not tested	None
121	F	Cauc		4.5	No	15.5	DD	23.5	No	Not tested	None
122	F	AfroC			No		DD		No	Not tested	None
123	M	Cauc			No		DD		No	Not tested	None
124	M	Cauc			No		DD		No	Not tested	None
125	M	Cauc	14		No	2	DD	17	No	Not tested	Pulmonary Stenosis, infertile

Supplementary Table 4 Patients with familial or genetic SRNS

Patient	Sex	Ethnicity	Age at diagnosis (years)	Initial Steroid Sensitivity	Time to ESRF (years)	Donor Type	Age at transplant (years)	Recurrence	Genetics	Comorbidities/FH
126	M	Cauc	8.5	No	2	DD	12	No	NPHS1 heterozygous mutation, NPHS2 heterozygous mutation	None
127	F	Cauc	0.9	No	14	DD	16	No	NPHS1 mutation	None
128	F	North African	0.4	No	8	DD	11	No	NPHS2 mutation	Affected mother and 1 brother
129	F	East African	1.5	No	5	DD	6.5	No	NPHS2 mutation	None
130	M	Cauc	5	No	1	DD	7.5	No	NPHS2 mutation	None
131	M	Cauc	5.5	No	1.5	DD	8	No	NPHS2 mutation	None
132	M	East African	4.5	No	7	DD	12	No	NPHS2 mutation	None
133	F	Cauc	0.3	No	11.5	DD	13.5	No	NPHS2 mutation	None
134	F	Cauc	10	No	2	DD	15	No	NPHS2 mutation	None
135	M	North African	1	No	0.02	DD	5.5	No	PLCE1 mutations	Hypospadias
136	M	Cauc	3.5	No	2.5	DD	7.5	No	SMARCAL1 mutation	Affected brother/Schimke
137	M	Cauc	6	No	0.6	DD	7.5	No	TRPC6 mutation	None
138	M	Cauc	12	No	0.8	DD	13.5	No	Unbalanced chromosomal translocation 2&6	Learning difficulties
139	M	Cauc	7	No	2	LD	11	No	WT1 mutation	Denys-Drash Syndrome
140	M	Cauc	8	No	6	LD	16	No	WT1 mutation	Frasier Syndrome
141	M	Cauc	8	No	6	LD	16	No	WT1 mutation	Frasier Syndrome
142	M	Cauc	1	Not used	1	DD	2.5	No	WT1 mutation	Denys-Drash syndrome
143	F	Cauc	2	No	0.6	DD	4.5	No	COQ2 mutation	Mild deafness
144	F	North African	0.7	No	1.5	DD	4	No	No variants of note	Affected sister and cousin, Galloway Mowatt syndrome, microcephaly, mental retardation
145	M	North African	12.5	No	0.2	DD	14	No	No variants of note	Affected sister/ cardiomyopathy, dysmorphia, cataract, mental retardation
146	M	Pakistani	0.8	No	0.4	DD	5.5	No	No variants of note	Brother with SRNS
147	F	Cauc	4	No	4	DD	8.5	No	Not tested	Brother has SRNS
148	M	Cauc	2	No	3	DD	12	No	Not tested	Sister has SRNS
149	F	Cauc	3.5	No	7	DD	10.5	No	Not tested	Schimke
150	M	Cauc	7	No	4	DD	11	No	Not tested	Schimke