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GENETICS OF CHILDHOOD STEROID SENSITIVE NEPHROTIC SYNDROME (SSNS)

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Abstract

The pathogenesis of childhood-onset nephrotic syndrome (NS), disparity in incidence of NS among races, and variable responses to therapies in children with NS have defied explanation to date. In the last twenty years over 50 genetic causes of steroid resistant nephrotic syndrome (SRNS) have been identified and at least two disease loci for two pathologic variants of SRNS (FSGS and membranous nephropathy) have been defined. However, the genetic causes and risk loci for steroid sensitive nephrotic syndrome (SSNS) remain elusive partly because SSNS is relatively rare and also because cases of SSNS vary widely in phenotypic expression over time. A recent study of a well-defined modest cohort of children with SSNS identified variants in *HLA-DQA1* as a risk factor for SSNS. This article reviews what is currently known about the genetics of SSNS and also discusses how recent careful phenotypic and genomic studies reinforce the role of adaptive immunity in the molecular mechanisms of SSNS.

Keywords

Nephrotic syndrome children; Genomics; Genetic risks; GWAS

Introduction

Nephrotic syndrome (NS) is the most common glomerular disorder of childhood with an estimated incidence of two to seven cases per 100,000 children and a prevalence rate of 16 cases per 100,000 children [1]. It is defined by the clinical and biochemical constellation of massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia. Based on the pattern of response to corticosteroids, nephrotic syndrome is subdivided into steroid-sensitive NS (SSNS) and steroid resistant NS (SRNS). In children over one year of age, SSNS is responsible for 80% of all cases of the disease [2]. Among patients with SSNS, the clinical course can be variable with differing relapse rates and overall dependence on steroid administration. It is estimated that approximately 50% of patients with SSNS will have a frequently-relapsing (FR) and/or steroid-dependent (SD) course [3, 4]. The biological basis for the pattern of response to corticosteroid remains unknown.

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Etiology and pathogenesis of SSNS

The etiology of most cases of SSNS is unknown and are therefore given the label “idiopathic or primary SSNS”. The definitive reason why some patients respond to corticosteroids and others do not escapes explanation, but proposed mechanisms underlying the pathogenesis of SSNS have sought to clarify this variability in pattern of response. Shalhoub and colleagues [5] in the 1970s proposed that SSNS is the result of a primary T-cell dysfunction based on the evidence that (1) nephrotic syndrome responds to immunosuppressive agents like corticosteroids and calcineurin inhibitors which modulate T-cell function (2) there are reported cases of patients achieving remission following diseases, such as measles or malaria that are known to suppress cell-mediated immunity, and (3) there are patients who develop nephrotic syndrome as part of a paraneoplastic process in malignancies known to affect T-cell function such as Hodgkins lymphoma. Subsequent studies have explored changes in T-cell surface expression, function, and cytokine release in the setting of nephrotic syndrome, however experimental recapitulation of these findings in multiple studies have been lacking [6–10].

Another proposed mechanism of disease in SSNS includes the notion that soluble mediators play a role in altering capillary wall permeability, the so-called “circulating factor” theory. This model of nephrotic syndrome proposes that in patients with NS, normal kidneys exist in an abnormal environment [11]. Circulating stimuli provoke the glomeruli to leak protein. This theory has been particularly studied in SRNS and is supported by evidence that (1) serum from patients with SRNS when injected into normal rats has resulted in increased glomerular permeability and proteinuria, (2) some patients with recurrent SRNS post-transplant are responsive to plasmapheresis, and (3) urgent re-transplant of a kidney from a patient who had immediate recurrence of SRNS into a recipient without NS resulted in resolution of proteinuria [12–14]. While this theory has been particularly studied in SRNS, it has also been noted that a kidney allograft from a donor with biopsy-proven active SSNS into a recipient without the disease resulted in resolution of foot process effacement [15]. Several candidate circulating factors for both SRNS and SSNS have been reported in the literature including, but not limited to, hemopexin, vascular permeability factor (VPF), vascular endothelial growth factor (VEGF), reactive oxygen species, soluble urokinase-type plasminogen activator receptor (suPAR), interleukin-13 (IL-13), interleukin-18 (IL-18), tumor necrosis factor alpha (TNFα), and cardiotrophin-like cytokine factor 1 (CLC-1) [16–27]. While differential expression of these molecules have been reported during periods of relapse and remission, results have not been consistent across studies. The role of these factors in the pathogenesis of idiopathic NS was recently reviewed by Davin [19].

A third mechanism for SSNS proposes that structural defects of the podocyte and other components of the glomerular filtration barrier would explain the loss of filtration barrier integrity and resultant proteinuria. Altered expression of glomerular Podocyte B7-1 (CD80), Sphingomyelin phosphodiesterase acid –like 3b (SMPDL3b), and Angiopoietin-like 4 (Angptl4) have been reported in NS models and also addressed in the review by Darvin [19, 28–30]. This concept of structural changes is also supported by the fact that over 50 genes which localized to the podocyte and its slit diaphragm have been identified as causes of SRNS [27]. Identification of genetic defects associated with hereditary SSNS and

identification of genetic variants associated with more common idiopathic SSNS may confirm or disprove some of the disease mechanisms described in this section.

Is SSNS a genetic disease?

There is incontrovertible evidence in the literature that some forms of SRNS have strong genetic underpinnings. Depending on the population being studied, it is estimated that 2–30% of all cases of SRNS are due to a single gene defect [31, 32]. In addition, mutations in over 50 genes have been associated with SRNS [33]. Furthermore, genetic association studies have established risk alleles for some pathologic variants of SRNS. For example, using admixture linkage analysis, G1 and G2 variants in *APOL1* were identified as a risk allele for FSGS in African Americans, and variants in *HLA-DQA1* and *PLA_2R1* were found to confer a robust risk for membranous nephropathy in Europeans [34–36].

While data on the genetics of SSNS are limited, there is, however, epidemiologic evidence to suggest that some SSNS may be linked to genetic defects in one or multiple genes. Firstly, there are ethnic trends seen among patients with nephrotic syndrome. In a limited epidemiologic study out of England, Feehally and others showed that Asian children develop SSNS seven times more commonly than their non-Asian counterparts [37]. In other studies, more protracted and challenging clinical courses characterized by frequent relapses and/or steroid dependence have been seen in patients of African American or Hispanic descent [38, 39]. Secondly, it has been estimated that 3% of children with SSNS may have an affected sibling or first degree relative, and there have been numerous published case reports of familial SSNS [40–45]. In addition, in our World-Wide cohort of over 600 patients with SSNS, there are at least 30 siblings or parent-child pairs with the disease (unpublished observation). Knowing these observed ethnic trends and familial predispositions, exploring genetic explanations for SSNS follows reason.

SSNS due to single gene defects

Over 50 highly penetrant monogenic mutations cause familial SRNS [46]. However, to date, no single gene has been identified as a cause of monogenic SSNS, despite reports of multiple families with multiple generations affected by SSNS, and inheritance patterns suggestive of a penetrant single gene mutation [42, 44, 45]. Wide variability in phenotypic expression of SSNS may explain why single genes have been elusive. SSNS is a disease that is characterized by relapse and remission and tends to get better with age. It is therefore possible to obtain falsely negative family histories during evaluation. The implication of this is that ascertainment of large pedigrees with enough power for genome-wide linkage studies may be difficult. Notwithstanding, even in situations where large pedigrees have been ascertained and a definite locus defined, causative genes have not been identified. Ruf *et al.* [47] investigated a consanguineous family in which three children were diagnosed with SSNS. They identified a genome-wide significant locus on chromosome 2p, however fine mapping of the locus and candidate gene analysis has not yielded insight into a causal mutation. In addition, the locus has not been reproduced in other studies.

Given the similarities between SRNS and SSNS in clinical manifestations and changes to the glomerular filtration barrier, it is tempting to speculate that the genetic architecture of SRNS and SSNS may be similar. In some forms of familial SRNS, individuals have been identified with a SSNS phenotype. In 2006, Hinkes *et al.* [48] identified two children with truncating mutations in Phospholipase C epsilon 1 (*PLCE1*) who responded to corticosteroid and cyclosporine therapy. The reason for this is unclear, however the authors suggest that there may be a critical time window in glomerular development during which treatment with immunosuppressive medications may overcome a putative defect imposed by *PLCE1* loss of function.

More recently, Gee *et al.* [40] described an autosomal recessive form of SSNS linked to mutations in epithelial membrane protein type 2 (*EMP2*), however, a homozygous mutation in the same gene was also identified in a family with SRNS. *EMP2* gene encodes for a protein that localizes to both the podocyte and glomerular endothelial cells and regulates caveolin-1 expression [40]. Increased caveolin-1 expression has been reported in *EMP2* knock-out models and in patients with glomerular diseases [40, 49]. The mechanisms by which mutations in *EMP2* may cause SSNS and SRNS is still under investigation, however overexpression of caveolin-1 in zebrafish embryo resulted in an edema phenotype that was rescued by glucocorticoids. These findings suggest that caveolin-1 may represent a novel therapeutic target for both SSNS and SRNS [50].

Additionally, mutations in nephrin (*NPHS1*) have been reported in rare cases of SSNS suggesting a possible genetic overlap with SRNS [51, 52]. Follow up studies by the same group that reported these cases suggest that the NPHS1 variants in patients with SSNS may represent a hypomorphic mutation that confers increased vulnerability to immunogenic stimuli reversible by immunomodulation [52].

In another study, using homozygosity mapping and whole-exome sequencing, recessive mutations in *KANK 1 and 2,* genes encoding for kidney ankyrin repeat-containing protein, have been identified in two families with both SSNS and SRNS [53]. Mutations in *KANK* resulted in defective podocyte cell signaling and function [53]. Subsequent evaluation of more than 1000 individuals with nephrotic syndrome using high-throughput next generation sequencing failed to identify additional patients with mutations in the gene suggesting that single gene causes of SSNS are exceedingly rare [53].

Steroid-sensitive nephrotic syndrome may also present as part of syndromes due to single gene defects. Study of such syndromes may provide insight into the genetics and pathogenesis of SSNS. For example, Exostosin-1 (*EXT1*) mutations, which result in autosomal dominant multiple exostoses (OMIM 133700), have been associated with SSNS [54]. *EXT1* is involved in the synthesis and expression of heparan sulfate glycosaminoglycans, a key structural component of the glomerular basement membrane. Reduction in heparan sulfate under conditions of *EXT1* mutation may render the glomerulus vulnerable in situations where there is risk for further loss of heparan sulfate. Thus, nephrotic syndrome could be theorized to result in situations where heparanse activity is increased. Heparanse is expressed by peripheral T lymphocytes, thus providing a link between immune abnormalities and glomerular basement membrane changes. Increased T-

cell heparanase presence combined with structural changes to the glomerulus may explain the steroid-sensitive profile in patients with *EXT1* associated nephrotic syndrome.

In another report, patients with Immunodysregulation, Polyendocrinophaty, Enteropathy, X-Linked (IPEX: OMIM 34790), a rare X-linked recessive life-threatening disorder caused by mutations in forkhead box p3 (*FOXP3*) gene, have been known to develop nephrotic syndrome [55]. The glomerular histopathology and steroid responsiveness of NS in the setting of IPEX can vary widely. Park et al [55] described two siblings with IPEX and nephrotic syndrome. One child had steroid- and calcineurin-resistant minimal change disease, while the other child responded to combination immunomodulatory therapy. Thus, in patients with IPEX, T-cell dysregulation may be implicated in the development of nephrotic syndrome, given that *FOXP3* is required for the development of regulatory T-cells. However, the vastly different clinical courses of patients with IPEX, and the variable response to immunosuppression speaks to a more complex inheritance pattern involving environmental factors and multiple genes with highly variable penetrance in the development of SSNS.

Table 1 shows a list of genes that have been associated with mixed SSNS/SRNS phenotypes. It should be noted however that greater than 90% of individuals with monogenic NS will have a steroid-resistant disease course. Additionally, mutations known to lead to SRNS are extremely rare in patients with SSNS [56, 57]. Furthermore, genetic risk factors identified for some pathologic types of SRNS such as *APOL1* have not been associated with SSNS (Unpublished observation). Thus, the genetics of SSNS and SRNS may be more disparate than overlapping.

Complex inheritance

Whereas Mendelian traits are characterized by a strong phenotypic-genotypic correlation, complex genetic traits typically exhibit weak correlations between genotype and phenotype. Diseases arising from complex or polygenic inheritance are believed to stem from variation in multiple genes and the interaction among these genes. They are also influenced by behavioral and environmental factors. The heterogeneity of SSNS would fit with this pattern of inheritance and may be an additional reason why genes causing monogenic SSNS have been elusive. Genetic heterogeneity, small effects of disease alleles on risk, and the confounding effects of multiple interactions among genes, and between genes and the environment, make identification of genes involved in polygenic disease more challenging. While single family studies are sufficient to study genes inherited in a Mendelian pattern, genetic determinants for complex traits require larger cohorts of patients. Given the rarity of SSNS, most studies investigating the genetic risk factor have relied on small cohort of patients, which limits the ability to identify a complex inheritance pattern explaining SSNS.

Because immune dysregulation has been implicated in the pathogenesis of SSNS, most studies exploring complex inheritance have focused on determining the role of variants in Human Leucocyte Antigen (HLA) genes and loci as genetic risk factors for SSNS. In a study of class II HLA antigens in French and German children with nephrotic syndrome, Konrad et al [58] reported an association between SSNS and variants in *HLA-DQB* and *HLA-DQA*.

A study of UK children of white European descent also reported an association between SSNS and variants in *HLA-DR7* and *HLA-DQW2* [59]. Similarly, Lagueruela *et al* found an increased frequency of HLA-DQW2 and two extended haplotypes, [HLA-Al, B8, DR3, DRW52, SCO1] and [HLA-B44, DR7, DRW53, FC31] in American Caucasian children with steroid-sensitive nephrotic syndrome [60]. Also, two small Japanese studies (sample sizes 24 and 30 children, respectively) reported an association between alleles in *HLA-DQA1* and *HLA-DQB1* and risk of SSNS [61, 62]. Studies in children of Chinese descent have also reported similar association with alleles in *HLA-DQB1* and different loci on *HLA-DR* [63, 64]. One of the studies found that risk alleles may differ in children with a frequently-relapsing course compared to those with infrequent relapses [64]. A summary of studies using a candidate approach to identify genetic risk loci for SSNS is summarized in Table 2. Sample sizes in most of these studies were small and genetic analysis were limited to a few markers in the HLA locus. Of note, most of the loci associations have not been replicated in independent cohorts of patients with SSNS. It is therefore difficult to determine the significance of these risk loci on a genome-wide scale or the relevance to cohorts that differ from the discovery group.

On the other hand, genetic mapping through genome-wide association studies eliminates the need for a priori knowledge of candidate genes and provides an unbiased probe of the entire genome. In conditions where complex genetics drives inheritance, genome wide association studies (GWAS) provide hope for identifying genetic links, but require multiple cohorts to validate findings. This approach is relevant in diseases like SSNS where the phenotype is well defined and risk of misclassification is low. In GWAS on SSNS, risks for misclassification are lessened further by using a study population focused on young children who are unlikely to have been exposed to multiple environmental factors which can modify or mimic the phenotype of interest. In a recent paper, we used an exome array study to determine genetic risk factors for SSNS [65]. We hypothesized that SSNS is likely due to coding and non-coding, common and rare variants in the genome, and that these variants interact with the glomerular components, such as the podocyte, and predispose to SSNS. The discovery cohort included children from South Asia and gender-matched adult controls from the same population. We identified multiple variants in Major Histocompatibility Complex (MHC) genes, however only two *HLA-DQA1* missense variants reached significance level and were replicated in an independent cohort of children of European descent with SSNS [65]. The *HLA-DQA1* variant amino acid residues are located near the dimer interface and may disrupt the assembly of the antigen recognition domain. In silico modeling showed that the missense variants perturbed secondary protein structure and may therefore affect antigen presentation. Apart from being the first unbiased exome-wide study of genetic risk factors for SSNS, the study also confirmed previous candidate approach studies and reinforced the role of adaptive immunity in the pathogenesis of SSNS. The same locus has been replicated in a limited cohort of patients with SSNS or MCD in Europe [66]. The *HLA-DQA1* region appeared to be pleotropic for different glomerular diseases because other variants in the gene have been associated with IgA and membranous nephropathy [58, 67]. However, this locus explained only about 4.6% of the risk for SSNS in the discovery cohort suggesting that there are most likely other risk variants yet to be discovered.

In the same study, rare variants (minor allele frequency <5%) in the gene *PLCG2* encoding for the protein phospholipase c gamma 2 (PLCγ2) were found to be associated with SSNS in South Asian children. *PLCG2* is involved in adaptive immunity and B cell signaling making it another plausible risk locus for SSNS. Based on these findings, it is tempting to speculate that the pathogenesis of SSNS may be explained by the combination of variations in *HLA-DQA1* and other MHC genes, environmental factors, and rare variants in other genes such as *PLCG2* that may serve as second-hit for the disease (Figure 1). This model has been shown to be relevant in other immune-mediated glomerular disease such as IgA nephropathy (*HLA-DQA1* as the initiator and genes that are important for gut immunity as second hit) [68], membranous glomerulopathy (*HLA-DQA1* as the initiator and PLA_2R1 and thrombospondin type-1 domain-containing 7A (*THSD7A*) as second hit) [36, 69, 70], and ANCA-associated vasculitis (*HLA-DP* as initiator, and genes encoding α 1-antitrypsin (*SERPINA1*) and proteinase 3 (*PRTN3*) as second hit) [71]. However, the variants in *PLCG2* have not been replicated in other ethnic groups and future studies will determine the significance of these findings and identification of rare variants in other genes.

Conclusion

Over the last twenty years, rapid advances in genomic science and technology has improved our understanding of the molecular pathogenesis of nephrotic syndrome. Over 50 genes are mutated in SRNS and multiple risk loci have been identified for different pathologic variants of SRNS. However, monogenic causes of SSNS have remained elusive due to wide variability in the clinical course of SSNS. More recently, an exome-wide study using a carefully phenotyped cohort of children with SSNS identified human MHC gene *HLA-DQA1* as a risk allele for SSNS. These findings reinforce the role of adaptive immunity in the pathogenesis of SSNS. This locus explains only 4% of heritability of SSNS suggesting that there are other genes and loci associated with SSNS. Although we focused only on genomic studies in this review, based on findings from other studies [69], we believe utilization and integration of multiple platforms such as genomics, proteomics, metabolomics and epigenetic studies may help accelerate the discovery of further risk factors, broaden our understanding of the pathogenesis of SSNS, and identify specific and novel drug targets.

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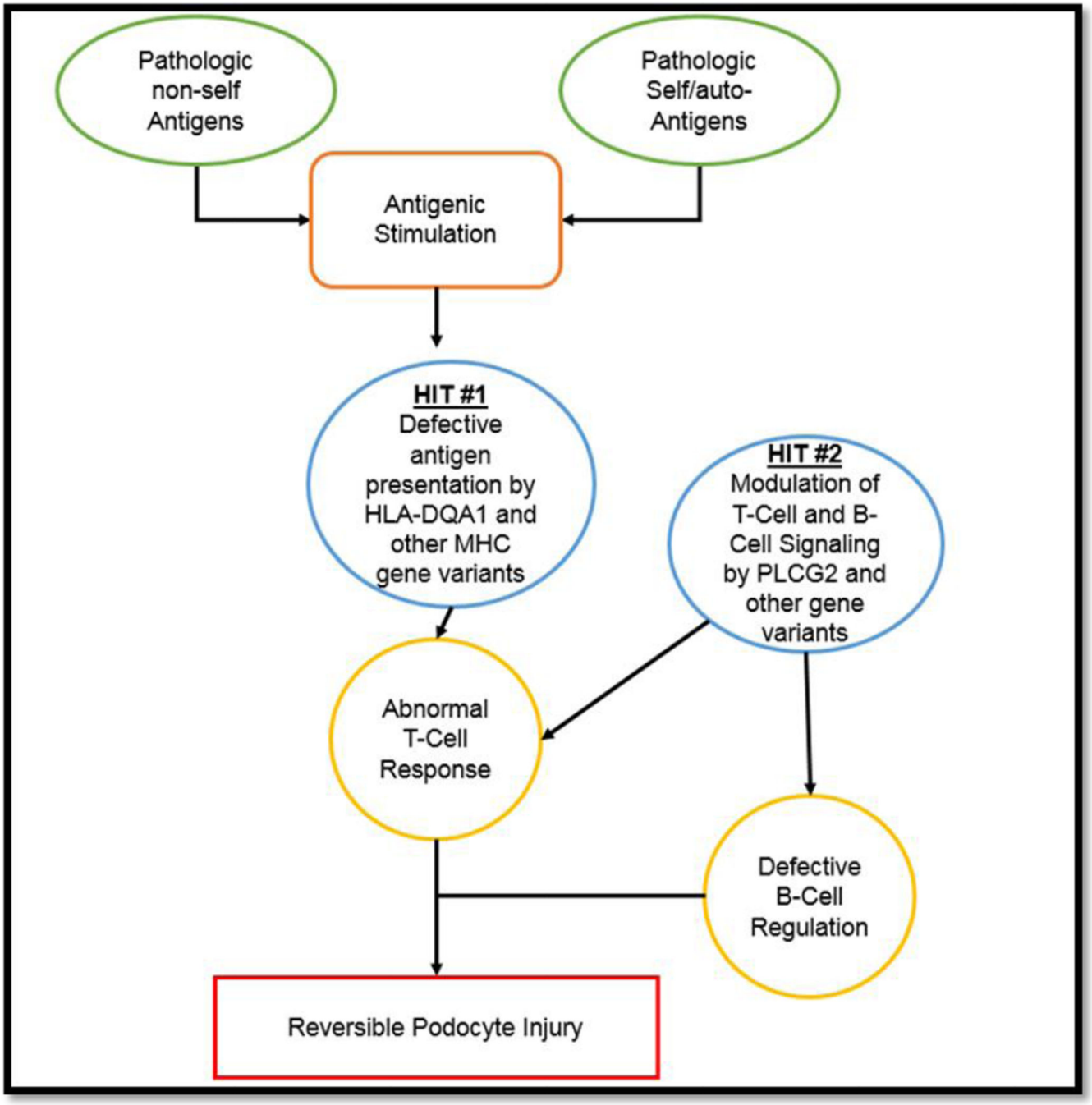

Figure 1. Proposed mechanisms for complex inheritance in SSNS

Variation in genetic make-up can predispose to a cascade towards reversible podocyte injury phenotype by aberrant adaptive immune cells, stimulation by non-self antigens such as infective agents, or self/auto-antigens.

Table 1

Mendelian disease genes associated with SSNS/MCD

GENE	LOCUS	Type of mutation	Protein localization	Associated with SRNS Y/N	Extra renal manifestations	References
EMP2	16p13	Missense Truncating	Podocyte Endothelial cells	Y	No	Gee et al [40]
EXT1	8q23	Missense	Glomerular basement membrane	N	Multiple exostoses	Robert et al [54]
FOXP3	Xp11	Missense	Immune cells	Y	Immunodeficiency Polyendocrinopathy Enteropathy	Park et al [55]
KANK1 *KANK2*	9p24 19p13	Missense	Podocyte	Y	No	Gee et al [53]
NPHS1	19q12	Missense	Podocyte and slit diaphragm	Y	No	Kitamura et al and Lahdenkari et al [51, 52]
PLCE1	10q23	Truncating	Podocyte and slit diaphragm	Y	No	Hinkes et al [48]

SSNS steroid sensitive nephrotic syndrome, *MCD* minimal change disease

Table 2

Candidate risk loci for SSNS

Study population	Cohort size	Gene	References
French and German	161	*HLA-DQB* *HLA-DQA*	Konrad et al 1995 [58]
UK Caucasian	40	*HLA-DR7* *HLA-DQW2*	Clark et al 1990 [59]
US Caucasian	32	*HLA-DQW2*	Lagueruela et al 1990 [60]
Japanese	30	*HLA-DQA1* *HLA-DQB1*	Kobayashi et al 1995 [62]
Chinese (Taiwan)	59	*HLA-DQB1* *HLA-DR*	Huang et al 2009 [63]
South Asia	76	*HLA DRB1* *HLA DQB1*	Ramanathan et al 2015 [72]
South Asia USA white	214 100	*HLA-DQA1* *PLCG2*	Gbadegesin et al 2015 [65]*

SSNS steroid sensitive nephrotic syndrome

* **Exome-wide study**