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# MOLECULAR BASIS OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS ASSOCIATED WITH STEROID RESISTANCE NEPHROTIC SYNDROME

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## ABSTRACT
According to the classical description, focal segmental glomerulosclerosis (FSGS) is characterized by the presence of scarring lesion in some (i.e. focal) segmental portion of glomeruli. FSGS patients generally do not respond to steroid treatment, thus despite the availability of a number of agents with variable efficacy in inducing remission, the optimal treatment of patients with steroid resistant nephrotic syndrome (SRNS) is unclear. Genetic causes can be identified in nearly 10% of affected children with highly heterogeneous disorder. Therefore it is important to know about genetic components of underlying cause of SRNS so that patients can be treated effectively before they develop end stage renal disease. This review provides potential clinical application of polymorphisms in candidate genes involved in FSGS-SRNS which may serve as markers in disease prediction. The mutant variants showing genotypic–phenotypic association can be translated to clinical practice through genetic testing. Rather, the most significant outcome of this review will be a better understanding of disease pathogenesis, which will hopefully lead in turn to novel and better treatments and more tailored drug therapy.

**KEYWORDS:** Nephrotic syndrome, Focal Segmental Glomerulosclerosis, Steroid Resistance Nephrotic Syndrome, SNPs.

**Abbreviations:** Nephrotic syndrome: NS; Focal Segmental Glomerulosclerosis: FSGS; Steroid Resistance Nephrotic Syndrome: SRNS; Steroid Sensitive Nephrotic Syndrome: SRSS; End Stage Renal Disease: ESRD; Single Nucleotide Polymorphism: SNPs; non-synonymous Single Nucleotide Polymorphism: nsSNP.

## INTRODUCTION
FSGS (Focal Segmental Glomerulosclerosis), focal stands for damage in some of the filters of glomeruli leading to sclerosis where the kidney is no more able to filter the blood properly. Focal segmental glomerulosclerosis (FSGS) is one of the most complicated and mysterious histological abrasion, rather than a disease in nephrology (Fig. 1) (Stokes et al., 2006; D'Agati, 2008b). It can happen as a primary disorder without any known cause or as a sickness, secondary to diverse problems. On the basis of the response to standard to corticosteroid therapy NS has been characterized as (1) steroid-resistant NS (SRNS) and (2) steroid-sensitive NS (SSNS). Recognition of the genetics of FSGS started with understanding the molecular composition of glomerular filtration barrier. It consists of podocytes, basement membrane and fenestrated endothelium (Klahr and Morrissey, 2003). This barrier isolates urinary space from blood under proper physiologic conditions, preventing the unnecessary escape of large molecules having molecular weight higher than 40 kDa, such as albumin and other clotting factors. In the case of NS, including FSGS this glomerular filtration barrier becomes useless and permeable (Caulfield and Farquhar, 1974; Klahr and Morrissey, 2003). Podocytes have been reported as the chief cells in the progression of FSGS (Pardon et al., 2006; Wiggins, 2007). Effacement of the podocyte foot processes is mainly caused by disrupted podocytes, this transformation in podocyte shape requires rearrangement of the actin cytoskeleton but, this is permanent and progressive process in FSGS (Zenker et al., 2009). For decades, there have been multiple broad-based studies going on to interpret probable threats that are influencing FSGS vulnerability, healing response, and development of the NS.

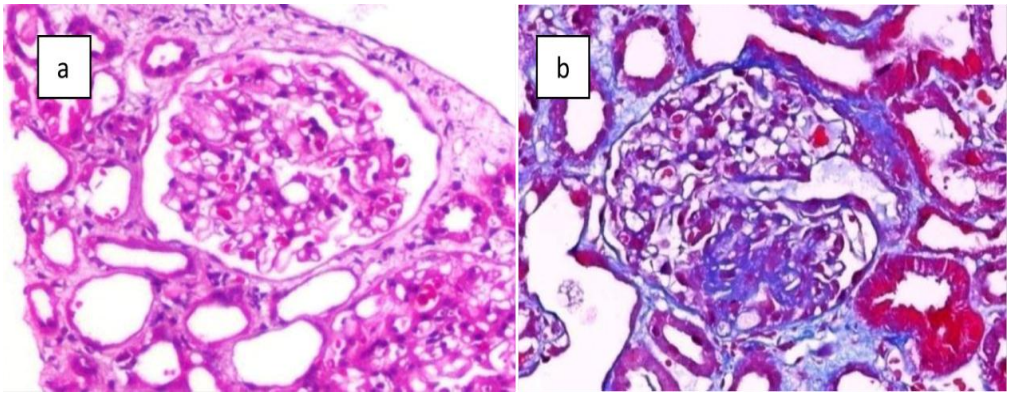


**Fig. 1: (a) Biopsy of normal glomeruli under simple light microscopy showing no sclerosis with clear cytoplasmic region. (b) Biopsy of FSCS patients stained with masson trichrome *X400, this dye* typically stains sclerosis to blue colour indicating expansion in cytoplasmic region of glomeruli (i.e. collapsing glomerulonephropathy).**

**Epidemiology of FSGS-SRNS**

The occurrence of FSGS has been growing worldwide in nearly all racial and age groups over last 20-30 years with a frequency of FSGS is 8-9 per million cases, which is 2-3 folds higher in a rate of disease findings. With the high levels of proteinuria, 50% of FSGS cases reach towards ESRD within 3 to 8 years with the recurrence rate of 20-25% even after kidney transplantation (KT) (Wiggins, 2007; D'Agati, 2008b; Kiffel et al., 2011). In USA, around 35% of renal biopsies proved to have FSGS in adults, among this, 40-50% of patients stopped responding towards steroids treatment whereas in children 63-73% SRNS were found to have FSGS. A UK study estimated the incidence of pediatric SRNS to be 0.3 per 100,000 (i.e. about 20-30 children every year). Over all there were 5-20% cases of SRNS in children leading towards ESRD (Gbadegesin et al., 2007). The male-female ratio for steroid-resistant patients is 1.2:1, which means male are more prone to this disease (Ruf et al., 2004b). The conventional studies showed that yearly occurrence rates of FSGS in African Americans were considerably higher than Caucasians (0.4 to 1.9 cases per annum, respectively), with high risk of FSGS in black persons (50%) than that of white (35%) (D'Agati, 2008b). There is 1-2 folds increase in the occurrence of FSGS-SRNS in Asian population.

**Pathogenesis of FSGS-SRNS**

In patients with FSGS-SRNS increase in protein permeability of glomerular basement membrane is caused due to various circulating agents such as the soluble form of the urokinase-type plasminogen activator receptor (uPAR), cardiotrophin like cytokines of immune cells beside the injury to podocytes due to oxidative stress (Fig. 2).

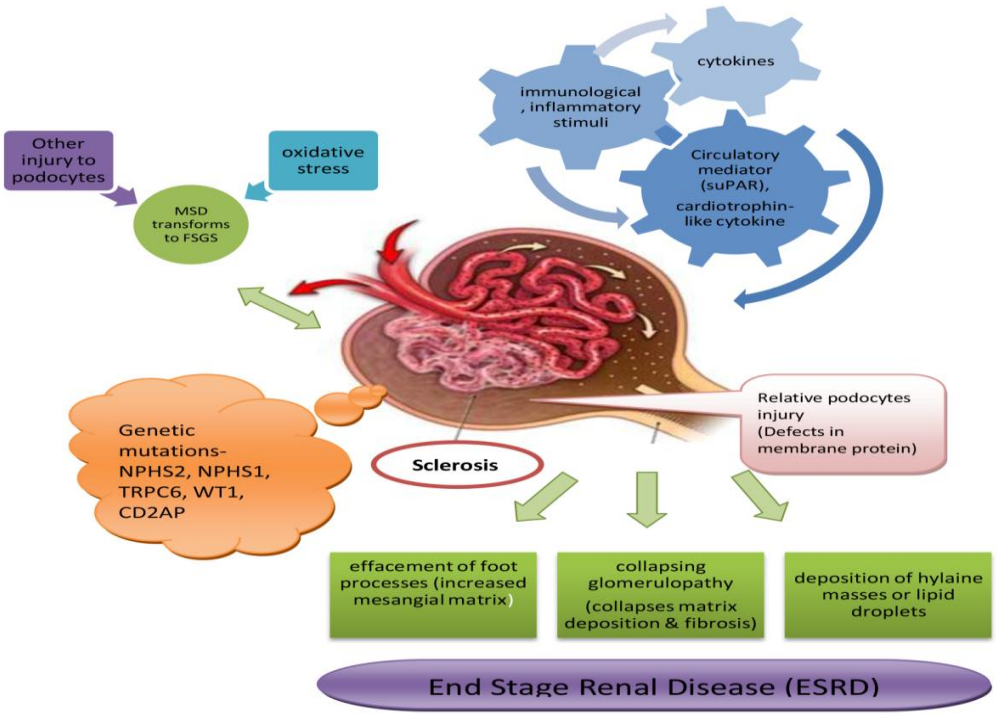


**Fig. 2: Pathogenesis of focal segmental glomerulosclerosi.**

The principal pathogenesis of FSGS-SRNS is still unidentified, but proof robustly relates the importance of genetic factors (i.e. 10%) (D'Agati, 2008b). A rising number of mutated genes have been recognized that can lead to inherited forms of idiopathic NS. These genes helps in guiding different structural proteins or enzymes that work in harmony to manage the glomerular membrane permeability and take part in various signaling events of regulating podocyte enlargement, segregation, and communications among cell-cell, cells-matrix interactions. Proteinuria results from the damage caused by these transformations in glomerular filtration barrier and in this event, podocytes require their specific epithelial cell markers such as fibroblast specific protein, nephrin, desmin, actin, collagen, and fibronectin (D'Agati, 2008a). The findings of these new podocyte proteins and their mutation study have shed light on the pathogenesis of proteinuria linked with NS and FSGS lesions.

**SNPs as biological marker**

A new type of marker, named SNPs, enlightening polymorphisms at the DNA level have recently appeared on the picture in dominating the molecular genetics field for human and animal genome studies (Cooper and Krawczak, 1989). SNP is biallelic co-dominant markers with only a single alter base present in a DNA sequence, with a common substitute of two probable nucleotides at a given location with frequency of 1% or greater within a given population (Wang et al., 1998). The probable chance of SNPs to occur is hardly one in every 1000 to 2000 base pairs, currently released SNP data projected total 160,508,575 SNPs in the human genome (dbSNP web query for build 144: Jun 08, 2015). Non-synonymous SNP (nsSNP) is a single nucleotide replacement occurring within the coding region of a gene which causes an amino acid change in the subsequent protein product which ultimately results in a structural or functional change in the protein product whose consequences may be minor or major phenotypic change accounting for the pathology of disease. Around 50-60% of induced mutations in concerned with inherited genetic disorders are due to nsSNPs (Wang et al., 1998).

**Different podocyte genes responsible for FSGS-SRNS**

All the identified genetic defects affects gene transcription and assembly of podocyte structure together with actin based cytoskeleton, and adhesion complexes (Hinkes et al., 2007). Cloning techniques were used in the identification of various genes such as NPHS1, NPHS2, TRPC6, WT1 and CD2AP which were involved in podocytes damage and were further confirmed by knockout or transgenic models (Caridi et al., 2001; Rood et al., 2012). The SNP data generated using dbSNP in different podocyte genes is graphically (Fig. 3)

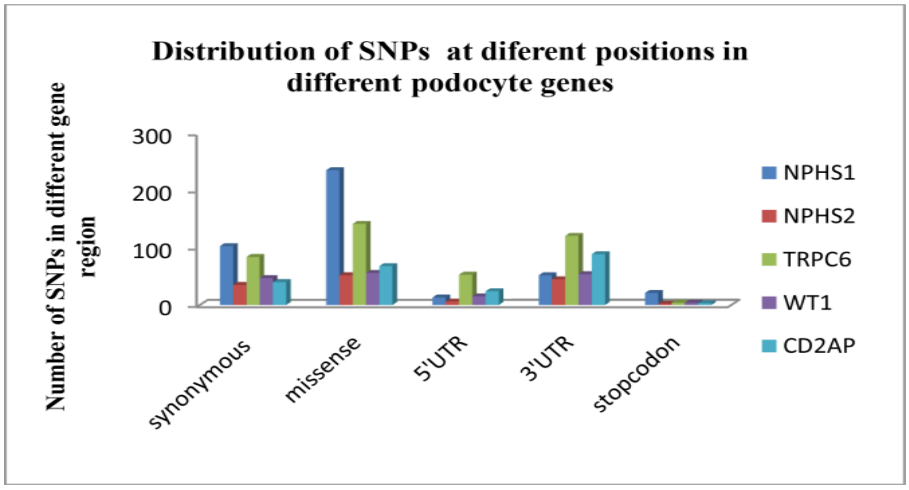


**Fig. 3: SNP data generated using NCBI-dbSNP and plotted in a form of bar graph. Targeted genes are showing distribution of SNPs in different regions excluding intronic SNPs. Highest number of SNPs was found to be missense and present in NPHS1 gene than compared to other genes.**

**NPHS1 gene**

The NPHS1gene is 26 kb in size, contains 29 exons located on chromosome 19. The NPHS1gene product is nephrin, made up of 1,241 amino acid residues and a member of cell adhesion molecules of immunoglobulin (Ig) family (Lahdenkari et al., 2004). Nephrin contains a transmembrane domain as well as eight Ig like repeated sequence, and one fibronectin III module (Beltcheva et al., 2001). Nephrin is only expressed in visceral cell of glomerular epithelial that form a network of 30 nm globular cross strands possessing elongated pores in zipper fashion (Koziell et al., 2002). Mutation in NPHS1 gene is autosomal recessive type causing congenital NS having massive uteroproteinuria from birth. Many patients with FSGS are showing mutations in overlapping genes of NPHS1/NPHS2 (Koziell et al., 2002). Reports showed 5 out of 30 patients having joint mutations in the NPHS1/NPHS2 genes, but proper phenotype/genotype correlation evidence was not yet found (Koziell et al., 2002). In 2010, overall 37 different mutations were reported from which 19 were novel in NPHS1 gene, out of those 58% of mutations were missense, whereas others included splice-site and nonsense mutations in 44 unrelated patients (Schoeb et

al., 2010). Generally majority of cases are heterozygous compared to homozygote, but the homozygous or compound heterozygous states are more lethal or linked with more severe phenotype (Beltcheva et al., 2001).

**NPHS2 gene**

The NPHS2gene size is 25 kb, made up of 8 exons that are located on chromosome 1. The gene contains 383 a.a. residues that encodes for podocin. It is an essential membrane protein that very precisely organizes and regulates structure of glomerular membrane by interacting with NPHS1, CD2AP, TRPC6 and various other genes (Reiterova et al., 2012). Podocin facilitates membrane transport of nephrin and directs podocytes intracellular signaling pathways. Boute et al. in 2000 identified NPHS2 gene as causative agent for early onset autosomal recessive SRNS. Overall 6.4-30% of sporadic SRNS were found to have mutations in NPHS2 gene in different parts of the world (Boute et al., 2000; Reiterova et al., 2012).

Even though initial reports showed recessive mutation in NPHS2 as a source of familial SRNS along with ESRD in children happening between the ages of 3 months to 5 years of age, but current data presented its association with a wide range of clinical spectrum (Franceschini et al., 2006). In many patients with 2 mutations of NPHS2 gene showing pathogenic effect develops FSGS in the early age of six years, most of these patients are not responding immunosuppressive treatment and reach towards ESRD (Hinkes et al., 2007). From the time when the NPHS2 gene got identified, various researchers in Europe, the North America and Middle East confirmed NPHS2 mutation to be a common source of sporadic SRNS, taking place in 10-30% of children with sporadic SRNS (Caridi et al., 2001). Podocin variation R229Q is one of most frequently reported one with marginally higher frequency of around 5% in SRNS as compared to healthy individuals (Ruf et al., 2004a).

**TRPC6 gene**

The TRPC6 gene is made up of 13 exons that are located on chromosome 11, having 931 amino acids encoding for the short transient receptor potential channel with a size of 106325Da (Dietrich et al., 2005). TRPC6 is a part of TRP family, expressed in many tissues that regulate intracellular Ca2+ concentration via G protein- coupled receptors (Bach, 2001; Winn et al., 2005b). Reports demonstrated 12 different mutation with familial FSGS and 4 with late onset of sporadic cases (age of 15-55 years, with a few exception at 1-9 years of age) resulting towards unpredictable rate of development to ESRD (Winn et al., 2005a).

Almost all the reported mutations were missense, except two K874X and 89fsX8 mutations. Among all missense mutations 8 (i.e. H218L, P112Q, N125S, E897K, M132T, R895L, Q889K and R895C) were gain-of-function that cause increase in Ca2+ current amplitudes where as the rest may probably showing pathogenic effect on the basis of biochemical and biophysical variations. Majority of TRPC6 mutations were dispersed all throughout N and C terminal cytosolic domains while no mutation has been observed in transmembrane domains. In European and African families, 6 families were recognized having autosomal dominant FSGS with a distinct missense variant (Gudermann, 2005; Reiser et al., 2005).

**WT1 gene**

The WT1 gene is made up of 10 exons that are located on chromosome 11p13, spanning 48 kb of genomic DNA. A number of case-control studies reported renal phenotypes related to WT1 mutations as a cause of FSGS-SRNS or related with urogenital malformations, these variants are characteristically heterozygous and germline or *de novo* in nature (Gessler et al., 1990; Kaltenis et al., 2004). Till now most of WT1 mutations are observed in 3,6,7,8 and 9 exons, but the majority of these variants were present in zinc finger domains, correspondingly coded in exon 8 and 9, thus significantly affecting NPHS1, mRNA expression levels. Bettina, et al. carried out sequencing studies taking 115 sporadic SRNS and 110 SSNS patients having WT1 mutation (exon 6-9), 6-8% SRNS patients were found with mutation in exon 8 and 9 (Hu et al., 2004; Kaltenis et al., 2004; Mucha et al., 2006). Orloff et al. demonstrated WT1 involvement with FSGS in African America population where 218 were FSGS cases and the genotyping results showed total 8 SNPs in different regions of WT1 (Orloff et al., 2005).

**CD2AP gene**

The CD2AP represents CD2-associated protein, which is a cytoplasmic ligand molecule for T-cell adhesion protein CD2 with a size of 80 kDa is generally expressed in almost all tissues excluding the brain. In kidneys, CD2AP plays a significant role in ultrafiltration processes of slit-diaphragm by interacting with nephrin and podocin (Schwarz et al., 2001; Shih et al., 2001). In animals, CD2AP mutations associated with FSGS gave rise to mesangial cell proliferation leading to glomerulosclerosis, whereas such association is less seen in humans (Shih et al., 2001). In African Americans, there has been a report on heterozygous nucleotide variant that causes CD2AP splicing resulting to FSGS (Gigante et al., 2009). In recent studies, homozygous mutation in CD2AP resulted in premature stop codon to some extent forming a truncated protein. The protein formed down regulated CD2AP expression by lymphocytes and the binding with F-actin (Shih et al., 2001; Gigante et al., 2009).

**Benefits and applications of genetic studies**

A lack of controlled studies has hindered development of effective treatment. Understanding the interaction between various factors is critical to developing new strategies for treating patients with disease. The discovery of mutation could benefit the patient by avoiding exposure to prolonged treatment with steroids

and/ or the use of alkylating agent. Genetic screening might help in making treatment decisions, patients care and counseling during their follow-up, counseling of the family. Identification of genetic mutation in a child can help the parents in their decision to plan new pregnancies and also, the results can be used for prenatal genetic testing.

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