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Genetic analysis of steroid resistant nephrotic syndrome in eastern India – A single center prospective study.

Prit Pal Singh[1], Amresh Krishna[1], Harsh Vardhan[2], Brijesh Yadav[5], Abhay Kumar[4], Jayant Prakash[3], Om Kumar[1]
[1]Department of Nephrology, IGIMS, Patna, Bihar, India
[2]Department of Nephrology, PMCH,Patna, India
[3]Department of Pediatrics, IGIMS, Patna, India
[4]Department of Microbiology, IGIMS, Patna, India
[5]Department of Nephrology, Scientist, SGPGIMS, Lucknow, India

Objectives: Steroid resistant nephrotic syndrome (SRNS) occurs in 10% - 20% of nephrotic syndrome (NS) cases. Most of them progress to end stage kidney disease over the next 10-15 years. Genetic mutations are responsible for up to 30% SRNS. Knowledge of genetic mutations may lead to identification of newer mutations, avoidance of kidney biopsies and unnecessary exposure to immunosuppressants.

Methods: In this prospective cohort study, 26 sporadic SRNS patients (17 male and 9 females) aged 2 years to 25 years and five age matched individuals as control were included. Using Next generation sequencing technique, a panel of 62 genes associated with SRNS were analyzed. Ten patients underwent kidney biopsy also.

Results: We detected mutations in 12 patients (12/25) and one control (1/5). Most common mutation was in collagen genes, seen in 7/26 (27%). Mutations in Col4A3 was seen in 5/26(19.23%), Col4A4 in 1/26(3.80%) and Col4A5 in 2/26(7.69%). Other mutations detected were in membrane associated guanylate Kinase-2 gene (MAGI2) 2/26(7.70%), 1-Phosphatidylinositol-4,5-bisphosphate phosphodiesterase epsilon-1 (PLCE1) gene in 2/26(7.70%); NPHS1, Laminin β2 gene, FAT atypical cadherin-1, APOL 1, Nucleoporin 93 and Anillin actin binding protein gene in one each [1/26(3.80%)]. [Table 1] In cases where kidney biopsy was performed, most common histopathological diagnosis was FSGS seen in 6/10 biopsies (60%) followed by MCD 2 /10 biopsies (20%). All mutations were heterozygous and 'novel mutations according to American College of Medical Genetics and Genomics (ACMG) criteria. Mutation was present in 4/6 cases of FSGS (66%) and in both cases of MCD (100%) while MPGN was not associated with mutations (0/2). [Table 2]

Conclusions: SRNS is significantly associated with novel mutations, most commonly collagen genes in our cohort. Mutations frequently associated with SRNS in other studies worldwide were uncommon in our population. FSGS and MCD were commonly associated with genetic mutations.

Table 1: List of different gene mutations and its exon location of SRNS patients.

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Gene Name	Exon location	Functional classification of gene	Inheritance pattern	Gene Name	Exon location	Functional classification of gene	Inheritance pattern
COL4A3 (+)	Exon 21	VUS	AD/AR	PLCE1 (+)	Exon 3	VUS	AR
COL4A3 (+)	Exon 13	VUS	AD		Exon 1	VUS	AR
COL4A3(+)	Exon 13	VUS	AR	NUP93(+)	Exon8	VUS	AR
COL4A3 (+)	Exon 42	VUS	AR	NUP93(+)	Exon8	VUS	AR
	Exon 27	VUS	AR	APOL1 (+)	Exon 7	VUS	NA
COL4A4 (-)	Exon 27	VUS	AR	FAT1 (-)	Exon 10	VUS	NA
COL4A5 (+)	Exon 5	VUS	XLD	ANLN (+)	Exon 18	VUS	AD
COL4A5 (+)	Exon 35	VUS	XLD	CFH (-)	Exon 18	VUS	AD
MAGI2 (-)	Exon 22	VUS	AR	NPHS1(-)	Exon4	VUS	AR
MAGI2 (-)	Exon 18	VUS	AR	LAMB2 (-)	Exon 22	VUS	AR

Abbreviations: AD, Autosomal dominant; ANLN, Anillin Actin Binding Protein; AR, Autosomal recessive; COL, Collagen; FAT, atypical cadherin-1; LAMB-2, Laminin subunit beta-2; MAGI2, Membrane Associated Guanylate Kinase 2; NA, not available; NUP93, Nucleoporin 93; NPHS1, Nephrin-1; PLC1, Phospholipase C Epsilon 1; VUS, Variants of unknown significant. XLD, X-linked disorder.

Table 2. Histopathological diagnosis and associated gene mutations.

Table-2. Histopathological diagnosis and associated gene mutations.

Diagnosis in kidney biopsy	Gene mutations
MCD	MAGI2 (-), COL4A3 (+)
MCD	COL4A4 (-)
FSGS	PLCE1 (+), COL4A5 (+)
FSGS	NUP93(+)
FSGS	FAT1 (-)
FSGS	COL4A3 (+)
FSGS	-
FSGS	-
C3GN	-
DDD	-

Abbreviation: DDD, dense deposit disease; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; COL, Collagen; FAT, atypical cadherin-1; LAMB-2, Laminin subunit beta-2; MAGI2, Membrane Associated Guanylate Kinase 2; NUP93, Nucleoporin 93; PLC1, Phospholipase C Epsilon 1.