Pediatric Nephrology (2024) 39:1421–1425
https://doi.org/10.1007/s00467-023-06223-2

CLINICAL INSIGHTS

Congenital nephrotic syndrome with diffuse mesangial sclerosis caused by compound heterozygous mutation in *LAMA5* gene

Bobbity Deepthi[1] · Ramge Ramachandran Sivakumar[1] · Sudarsan Krishnasamy[1] · Debasis Gochhait[2] · Kausik Mandal[3] · Sriram Krishnamurthy[1]

Received: 14 August 2023 / Revised: 30 October 2023 / Accepted: 31 October 2023 / Published online: 20 November 2023

Abstract

A two-and-a-half-month-old female infant presented with generalized edema for 10 days. At presentation, she had periorbital puffiness, moderate ascites, and pedal edema. Laboratory investigations revealed serum albumin 1.3 g/dL, spot urine protein to creatinine ratio (Up:Uc) 20.87 mg/mg, total cholesterol 380 mg/dL, and serum creatinine 0.31 mg/dL. Exome sequencing revealed compound heterozygous variants in *LAMA5* gene (NM_005560.6). There was a heterozygous likely pathogenic missense variant in exon 2: *LAMA5*: c.385C > A (depth 195×) and another heterozygous pathogenic variant in exon 31: *LAMA5*: c.3932_3936dup; parental segregation by Sanger sequencing proved that the variants were in trans. Kidney biopsy showed diffuse mesangial sclerosis (DMS). Our case adds *LAMA5* gene to the constellation of genes causing DMS, in addition to the classically described *WT1*, *LAMB2*, and *PLCE1* genes and to the list of genes causing congenital nephrotic syndrome (CNS).

Keywords Congenital nephrotic syndrome · Diffuse mesangial sclerosis · *LAMA5* gene

Background

LAMA5 biallelic gene variants causing congenital nephrotic syndrome (CNS) are rare entities and have recently been identified [1, 2]. Herein, we report a case of CNS with diffuse mesangial sclerosis (DMS) in a child of Indian origin due to compound heterozygous variants in the *LAMA5* gene.

✉ Sriram Krishnamurthy
drsriramk@yahoo.com

[1] Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry 605006, India

[2] Department of Pathology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India

[3] Department of Medical Genetics, Sanjay Gandhi Post-Graduate Institute of Medical Sciences, Lucknow, India

Case report

A two-and-a-half-month-old female infant presented with generalized edema for 10 days. She was born to non-consanguineous south Indian parents at term gestation with a birth weight of 2.2 kg, length 51 cm, and head circumference 35.5 cm. There was no history of fever with rash or drug intake in the antenatal period. Antenatal anomaly scans were normal with no evidence of oligohydramnios (amniotic fluid index being 13 cm at 37 weeks), intrauterine growth retardation or fetal cardiac abnormalities. There were no similar complaints in the family, and there was no history of miscarriage or fetal death in the past.

At presentation, she had periorbital puffiness, moderate ascites, and pedal edema. She was hemodynamically stable with blood pressure 82/38 mmHg (50–90th centile). The weight 4.5 kg (0.88 z), length 60 cm (1.28 z), and head circumference 39.5 cm (0.43 z) were normal. There were no features such as absent patella, hypoplastic nails, microcoria, lens abnormalities, or hypotonia. She had normal female genitalia, with no ambiguity. There was no hepatosplenomegaly. The kidney and bladder were not palpable, and no genital edema was noted.

Laboratory investigations revealed serum albumin 1.3 g/dL, spot urine protein:creatinine ratio (Up:Uc) 20.87 mg/mg, total cholesterol 380 mg/dL, and serum creatinine 0.31 mg/dL. Urinalysis showed no red blood cells (RBCs) or casts. Kidney ultrasound showed mildly enlarged kidneys (right kidney length 5.4 cm (+2.71z), left kidney length 5.1 cm (+2.43 z)) with normal echogenicity, preserved corticomedullary differentiation, with no hydronephrosis. Urinary bladder was normal, and the baby had normal female reproductive organs. Serologies for human immunodeficiency virus (HIV), hepatitis B (HBV), hepatitis C (HCV), venereal disease research laboratory test (VDRL) for syphilis, cytomegalovirus (CMV) IgM and IgG, rubella IgM, and toxoplasma IgM by ELISA were negative. Karyotype was that of a normal female (46XX). She was diagnosed with CNS. Supportive care with regular albumin infusions, enalapril, and thyroxine supplementation was continued. However, edema was unremitting along with worsening oliguria, a maximum creatinine of 1.5 mg/dL during the clinical course and electrolyte abnormalities refractory to medical management, leading to suspicion of diffuse mesangial sclerosis (DMS). The parents did not opt for kidney replacement therapy, and the child eventually expired at 6 months of age.

Postmortem kidney biopsy revealed an increase in the mesangial matrix (without an increase in cellularity) and thickened glomerular basement membrane leading to obliteration of the capillary lumen and crowding of the podocytes, consistent with DMS (Fig. 1). Exome sequencing covering around 8500 clinically relevant genes revealed compound heterozygous variants in *LAMA5* gene (NM_005560.6). Deoxyribonucleic acid (DNA) extracted from blood was used to perform targeted gene capture using a custom capture kit. The libraries were sequenced to mean depth of > 80–100 × on Illumina sequencing platform. Genome analysis toolkit (GATK) best practices framework for identification of germline variants in the sample using Sentieon was followed. The sequences obtained were aligned to human reference genome (Genome reference consortium Human build 38) using Burrows-Wheeler alignment algorithm. Sentieon haplotype caller was then used to identify variants in the sample. Clinically relevant variants in both coding and non-coding regions were annotated using published variants in the literature and a set of disease databases. Common variants were filtered, and non-synonymous variants effect was calculated using multiple algorithms such as Polymorphism Phenotyping v2 (PolyPhen-2), Sorting intolerant from tolerant (SIFT), MutationTaster2, and Likelihood ratio test (LRT). Clinically significant variants were reported. There was a heterozygous likely pathogenic variant in exon 2: LAMA5: c.385C > A (depth 195 ×) that resulted

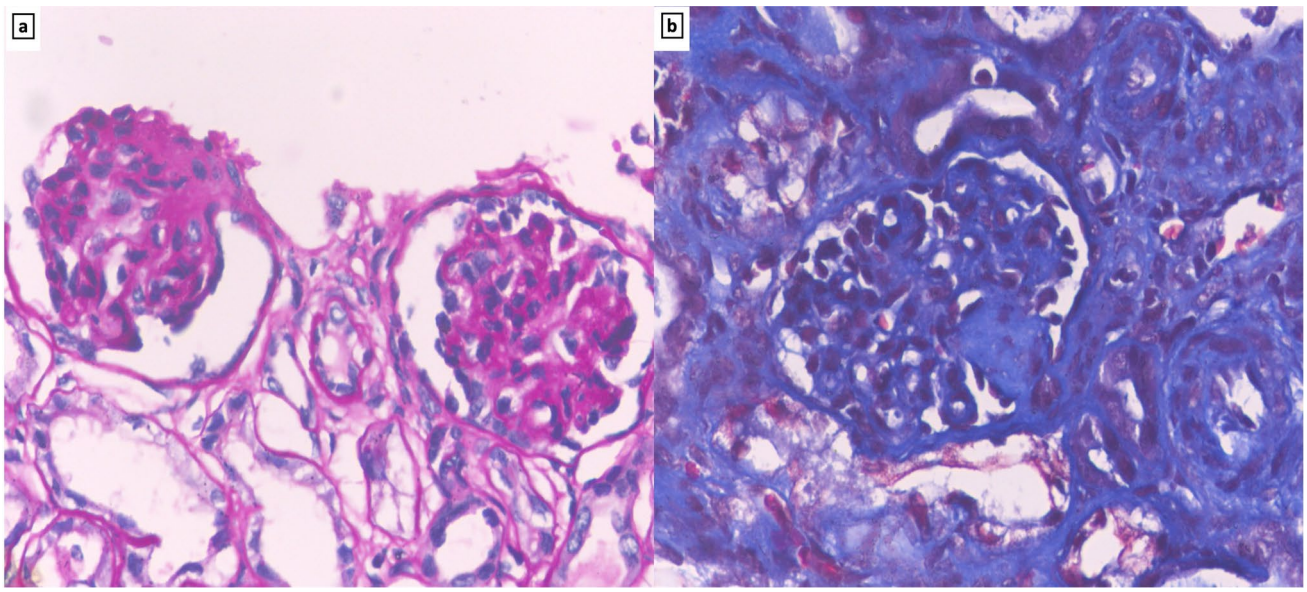

Fig. 1 **a** Light microscopy showing mesangial expansion in the absence of mesangial hypercellularity, thickened basement membrane, and decreased capillary lumen space (PAS stain). **b** Masson trichrome staining showing increase in mesangial matrix and segmental glomerulosclerosis and morphological features consistent with diffuse mesangial sclerosis

in the amino acid substitution of lysine for glutamine at codon 129 (p.Gln129Lys) and another heterozygous pathogenic variant in exon 31: *LAMA5*: c.3932_3936dup (depth 174 ×) resulting in frameshift and premature truncation of the protein 44 amino acids downstream to codon 1313 (p.Phe1313ProfsTer44). Parental segregation by Sanger sequencing proved that the variants were in trans. The parents were phenotypically healthy and had no proteinuria or hypoalbuminemia. Their serum creatinine was normal. The variants were not reported in control databases such as ClinVar, Genome aggregation database (gnomAD), Exome aggregation consortium (ExAC), Indian internal database (MedVarDb v3.0), and 1000 Genomes. The missense variant (*LAMA5*: c.385C > A) was predicted to be probably damaging by PolyPhen-2 Human divergence (HumDiv) and damaging by SIFT and LRT. Rare exome variant ensemble learner (REVEL) prediction score for the missense variant c.385C > A is deleterious (0.985). The variant prediction is deleterious by Varity (Deleterious (0.91)) and MutationTaster (Deleterious). The in silico predictions of the variant *LAMA5* (NM_005560.6):c.3932_3936dup resulting in frameshift and premature truncation of the protein 44 amino acids downstream to codon 1313 (p.Phe1313ProfsTer44) was predicted to be damaging by MutationTaster2. The reference regions were conserved across the species for both the variants (combined annotation-dependent depletion (CADD) conservation score, 26.6 for missense variant and a conservation score of 7.826 by phyloP100 for truncating mutation). The variants have been classified as likely pathogenic and pathogenic, respectively, according to the American College of Medical Genetics (ACMG) 2015 nomenclature. All the CNS/DMS genes were checked and confirmed negative for pathogenic variants (*WT1*, *PLCE1*, *NPHS1*, *NPHS2*, *LAMB2*). There were no variants noted in other CNS genes.

Discussion

DMS has been reported previously in association with *WT1*, *LAMB2*, and *PLCE1* gene mutations [1]; however, only one earlier report describes a *LAMA5* variant causing DMS and nephrotic syndrome [2].

LAMA5 pathogenic gene variants with a phenotype of steroid resistant nephrotic syndrome are rare and have been identified in five pediatric cases so far, with only one case presenting as CNS [2–5]. Table 1 summarizes the clinical characteristics of pathogenic and likely pathogenic *LAMA5* gene variants. Most of these are loss of function variants resulting in steroid resistant nephrotic syndrome or congenital nephrotic syndrome. *LAMA5* gene has a significant number of benign missense variants reported in the literature. Braun et al. [3] reported homozygous missense variants of unknown significance at highly conserved residues in five pediatric patients with nephrotic syndrome from three consanguineous families using whole exome sequencing. Three of these patients were steroid sensitive and functional studies or pathologic analyses of these variants were not performed. Hence, the pathogenic role of these *LAMA5* homozygous missense variants in causing nephrotic syndrome remains unclear.

We identified new likely pathogenic variants in the *LAMA5* gene clinically manifesting as CNS. A monogenic cause is predominant in CNS (69%). The NephQuest consortium study reports *NPHS1*, *NPHS2*, *WT1* and *PLCE1* as the commonly mutated genes in > 90% cases of CNS [1]. *LAMA5* gene is a recently identified gene for CNS [2].

LAMA5, a crucial protein of laminin trimers, mediates crosstalk between the glomerular basement membrane (GBM) and podocytes [3, 5]. Our patient had isolated nephrotic syndrome in the absence of syndromic, extrarenal, or developmental defects probably due to defects confined to the GBM, and missense variants being milder might have led to a less severe phenotype. Taniguchi et al. [2] explained this phenotype using in vitro biochemical analysis of recombinant truncated Laminin α5 proteins. DMS is a distinct histological variant of nephrotic syndrome characterized by early onset and rapid progression to kidney failure; hypertension is noted in 78.6–86% of cases. Published cohort studies have identified *PLCE* or *WT1* mutations in Isolated DMS (IDMS) [1]. Our patient is the second pediatric case of *LAMA5* variant presenting with IDMS.

Our case adds *LAMA5* gene to the constellation of genes causing DMS, in addition to the classically described *WT1*, *LAMB2*, and *PLCE1* genes and to the list of genes causing CNS.

Summary

What is new?

- Our case adds *LAMA5* gene to the constellation of genes causing diffuse mesangial sclerosis (DMS), in addition to the classically described *WT1*, *LAMB2*, and *PLCE1* genes and to the list of genes causing congenital nephrotic syndrome.

Table 1 Clinical characteristics and genetic profile of pediatric patients with *LAMA5* (NM_005560.6) gene and nephrotic syndrome in literature

ID	Author year of publication	Age at onset (mo.), gender	Clinical profile	Extra-renal features	Consanguinity	Ethnicity	Biopsy findings	Age at CKD5 (mo.)	Variant (coding nucleotide position)	Location	Protein change	Zygosity	American College of Medical Genetics (ACMG) criteria fulfilled, variant classification
1	Taniguchi et al. 2021 [2]	3, M	CNS	None	No	Japanese	ND	12	c.1282 + 1G > A, c.9232C. > T	Intron 9, Exon 68	p.Arg3078Ter	Compound heterozygous	PVS1, PM2, PP5 (#), pathogenic
2	Taniguchi et al. 2021 [2]	4, F	INS	None	No	Japanese	ND	42	c.1282 + 1G > A, c.9232C > T	Intron 9, Exon 68	p.Arg3078Ter	Compound heterozygous	#, pathogenic
3	Taniguchi et al. 2021 [2]	6, F	SRNS-IR	Cataract, Hypodysplastic kidneys	No	Japanese	DMS	39	c.1282 + 1G > A c.8158C > T	Intron 9, Exon 60	p.Arg2720Ter	Compound heterozygous	#, pathogenic
4	Jones et al. 2020 [4]	24, M	SRNS-IR	Syndromic developmental disorder	No	Italian	FSGS	24	c.857G > T	Exon 5	p.Arg286Leu	Homozygous	PVS1, PM2, PP3, PP5, pathogenic
5	Sunwoo et al. 2023 [5]	10, F	SRNS-IR	None	No	Korean	FSGS	31	c.3434G > A, c.6883C > T	Exon 27, Exon 52	p.Cys1145Tyr p.Gln2295Ter	Compound heterozygous	PM2, VUS #, pathogenic
6	*Index case 2023*	2.5, F	CNS	None	No	South Indian	DMS	6	c.3932_3936dup, c.385C > A	Exon 31, Exon 2	p.Phe1313ProfsTer44 p.Gln129Lys	Compound heterozygous	PVS1, PM2, PP3 pathogenic; PM2, PM3, PP3 likely pathogenic

M male, *F* female, *CNS* congenital nephrotic syndrome, *INS* infantile nephrotic syndrome, *SRNS* steroid resistant nephrotic syndrome, *IR* initial resistance, *LR* late resistance, *DMS* diffuse mesangial sclerosis, *FSGS* focal segmental glomerulosclerosis, *CKD5* chronic kidney disease stage 5, *ND* no data, *NP* not performed, *PD* peritoneal dialysis, *eGFR* estimated glomerular filtration rate, *RK* right kidney, *LK* left kidney, *PVS* pathogenic very strong, *PM* pathogenic moderate, *PP* pathogenic supporting, *VUS* variant of unknown significance

Author contribution BD, RRS, SK, and SK managed the patient, reviewed the literature, and drafted the manuscript. BD and RRS drafted the first version of the manuscript. DG interpreted the histopathological findings. KM interpreted the next generation sequencing results. All authors contributed to the review of literature, drafted the manuscript, and approved the final version of the manuscript. SK shall act as guarantor of the paper.

Declarations

Informed consent Written informed consent for publication of the child's clinical details was obtained from the patient's parents.

Competing interests The authors declare no competing interests.

References

1. Joshi A, Sinha A, Sharma A, Shamim U, Uppilli B, Sharma P et al (2021) NephQuest Consortium. Next- generation sequencing for congenital nephrotic syndrome: a multi-center cross-sectional study from India. Indian Pediatr 58:445–451
2. Taniguchi Y, Nagano C, Sekiguchi K, Tashiro A, Sugawara N, Sakaguchi H et al (2021) Clear evidence of *LAMA5* gene biallelic truncating variants causing infantile nephrotic syndrome. Kidney360 2:1968–1978
3. Braun DA, Warejko JK, Ashraf S, Tan W, Daga A, Schneider R et al (2019) Genetic variants in the LAMA5 gene in pediatric nephrotic syndrome. Nephrol Dial Transplant 34:485–493
4. Jones LK, Lam R, McKee KK, Aleksandrova M, Dowling J, Alexander SI et al (2020) A mutation affecting laminin alpha 5 polymerisation gives rise to a syndromic developmental disorder. Development 147:dev189183
5. Sunwoo Y, Choi N, Min J, Kim J, Ahn YH, Kang HG (2023) Case report: genetic defects in laminin α5 cause infantile steroid-resistant nephrotic syndrome. Front Pediatr 10:1054082